BRAZILIAN MEETING ON ORGANIC SYNTHESIS

18th BMOS

TIRADENTES - MG, BRAZIL

18th BMOS

Brazilian Meeting on Organic Synthesis

BOOK OF ABSTRACTS

October 17th to 21st 2022

Tiradentes – MG

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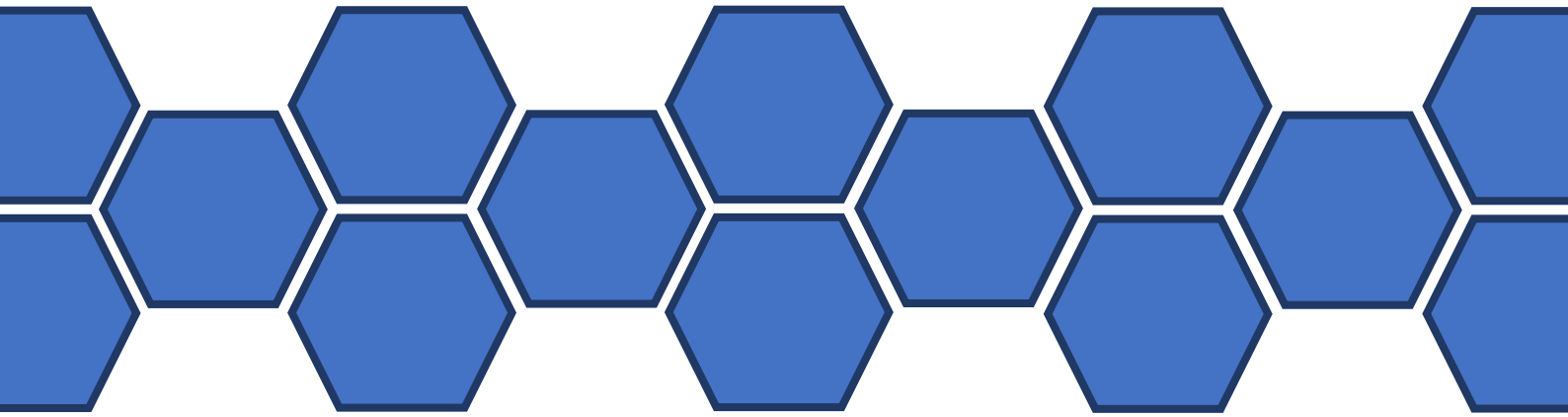

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EDITORIAL

Good evening ladies and gentlemen,

It is a great honour to say welcome to all participants on behalf of the Organizing Committee of the 18th Brazilian Meeting on Organic Synthesis, which is the most important conference of the organic synthetic community of Latin America.

It is an incredible moment for us. It is almost impossible to express the happiness and the emotion that we are feeling today in this opening ceremony after four years of expectations. When we planned this traditional and important Conference, in Minas Gerais, for the first time, we could never imagine that we would go through one of the greatest challenges ever faced by humanity, the pandemic has changed our life, our work, our values. These have been very difficult times, but we´ve faced it and, thanks to Science, we are successfully handling complex public health crisis, which we could not imagine even in our worst dreams.

In addition to the pandemic, in Brazil we have faced very troublesome times in recent years: science, scientists and universities have never been so targeted. But we are strong and we are resilient. Even at this very moment, we are still trying to find hope to look to the future with optimism. We are here today to celebrate for five days the science that inspires us every day in our lives: building molecules, discovering new methodologies, producing new and exciting knowledge, working hard to improve the world where we were born, and which we will leave for our children.

We are here today to raise a toast to life, to science, and to the art of encounter. Quoting the great Brazilian author, Guimarães Rosa: “Such is life: it warms up and cools down, it squeezes and then loosens, it calms down and then boils up. What life asks of us is courage"

I would like to thank all the participants, students, professors and researchers who came from all over the world. Also, we want to express our gratitude to the very special invited guests, who gave their best to be here in this important moment. We appreciate the essential support of the funding agencies CNPq, CAPES, FAPERJ and FAPEMIG, and the sponsors MERCK, BUCHI, SUPERLAB, ANALYTICA, ELSEVIER and IKA. Finally, a kindly thanks to the organizing and scientific committees, who worked tirelessly over the past weeks to make the event memorable, as well as the American Chemical Society, the Royal Society of Chemistry, and, especially, the Brazilian Chemical Society, which I have the immense privilege to represent here.

We wish you all an excellent congress and stay in Tiradentes, the city that was the birthplace of Brazil´s independence. Enjoy the hospitality of Minas Gerais, the spectacular conferences, the caipirinhas, and the cuisine of our region -very famous in our country. And may the words of Tiradentes always live in each of us: freedom is what guides us. Libertas quae sera tamen.

Prof. Dr. Rossimiriam Pereira de Freitas
Chair of the 18th Brazilian Meeting on Organic Synthesis

EDITORIAL

Good evening ladies and gentlemen,

Initially, I would like to thank all of you for the presence in Tiradentes, on this wonderful night in Minas Gerais.

It was destined that Brasília, the capital of the country, would be the starting point of the Brazilian Meeting on Organic Synthesis 40 years ago. Since its foundation, BMOS has grown, developed and become the largest event for Synthetic Organic Chemistry in Latin America.

BMOS is an event that has been hosted in different states over the last 40 years. Despite the importance of the state of Minas Gerais, where the Federal University of Minas Gerais is located, which is among the most important universities in the country, we have not previously hosted BMOS. Today, in October 2022, the wait is finally over. The pleasure that we are feeling in receiving all of you here in Tiradentes, Minas Gerais, is unspeakable.

The Brazilian Meeting on Organic Synthesis is the celebration of Organic Chemistry in our country. Organic Chemistry is a central area of science and its relevance was highlighted with the Nobel Prize in Chemistry in both 2021 and 2022.

Prof. Carolyn Bertozzi, who was awarded the Nobel Prize this month, said, "When the world is in trouble, chemistry comes to the rescue," whether chemistry is our Justice League, or Avengers. Organic Chemistry is the Superman or the incredible Huck.

The Brazilian organic chemistry community has been consolidating over the last 40 years. Our graduate programs are well organized and efficient, despite the lack of adequate and continuous financial support. Our meeting fortifies the union of our talents, our competences and skills for the development of our science. Today I have the honor of speaking on behalf of our community and I invite us, the Brazilian organic chemists, to remain strong, united, and dedicated to this national science. We need to promote our community, build bridges and interactions, and contribute to the education and involvement of the young generations! Together we are stronger and we will be evolving our science for the next 40 years to come.

Santos Dumont, the Brazilian inventor, was born in Minas Gerais. He was responsible for the first public flight in the world and is celebrated as the inventor of the airplane all over Europe. He reminds us of the importance of unleashing our imagination.

Carlos Chagas, born in Minas Gerais in the city of Oliveira, was responsible for the discovery of *Trypanosoma cruzi*, the agent that causes Chagas disease. To this day, he remains the only scientist in the history of medicine to completely uncover and describe an infectious disease: the pathogen, the vector, the hosts, the clinical manifestations, and the epidemiology. Carlos Chagas is honored by our scientific platform and is an example that we can achieve extraordinary realizations.

I also have to mention Darcy Ribeiro, the anthropologist and ‘mineiro’ from Montes Claros. Darcy was a well-known advocate for the rights of indigenous people,

for the rights of the people in need, and for the improvement of education in the country.

May our community fly on the wings of the 14-bis imagination, discover and synthesize intelligent molecules against neglected diseases and others, and build an inclusive, social and diverse country, because when we are in trouble, chemistry comes to our rescue!

Finally, it is with extreme happiness that I declare that BMOS is officially open. At this point, I would like to invite Professor Ronaldo Pilli from the State University of Campinas to introduce our opening speaker, Professor Janine Cossy. Professor Pilli, please, the stage is yours.

Prof. Dr. Eufrânio N. da Silva Júnior
Chair of the 18th Brazilian Meeting on Organic Synthesis

SUMMARY

MONDAY – October 17th 2022

14:00-18:00 **Registration**

18:00-18:30 **Book Release**

"Química Orgânica Sintética: Brasil 2022" – VOLUME 3

Editors:
- Prof. Dr. Fernanda Andreia Rosa (UEM)
- Prof. Dr. Fernando de Carvalho da Silva (UFF)
- Prof. Dr. Giovanni Wilson Amarante (UFJF)
- Prof. Dr. Kleber Thiago de Oliveira (UFSCar)
- Prof. Dr. Mauricio Moraes Victor (UFBA)
- Prof. Dr. Silvio do Desterro Cunha (UFBA)

Speech on behalf of FAPERJ: Prof. Dr. Vitor Francisco Ferreira (UFF)

18:30-18:40 **Presentation of BMOS: The Chemical Record Special Issue**

Editors:
- Prof. Dr. Eufrânio Nunes da Silva Júnior (UFMG)
- Prof. Dr. Angelo de Fátima (UFMG)

Speech on behalf the editors: Prof. Dr. Angelo de Fátima (UFMG)

18:40-19:30 **Opening Ceremony**

Speakers:
- Prof. Dr. Rossimiriam Pereira de Freitas (UFMG)
- Prof. Dr. Marcelo Gomes Speziali (FAPEMIG)
- Prof. Dr. Fernanda Andreia Rosa (UEM)
- Prof. Dr. Eufrânio Nunes da Silva Júnior (UFMG)

19:30-20:30 **Opening Lecture**

"The Power of Transition Metals. Construction and Functionalization of Heterocycles"

Speaker:
- Prof. Dr. Janine Cossy (ESPCI ParisTech, PARIS)

Heterocycles are present in a great diversity of natural products and/or bioactive compounds. They are also present in ligands, dyes, materials, etc. Due to the importance of heterocycles, it is important to develop efficient and versatile chemoselective methods to access these compounds. In this lecture, different methods will be presented to access functionalized heterocycles containing oxygen and nitrogen. Depending on the synthetic target to be reached, we will show that transition metals such as gold, iron, cobalt or rhodium are excellent synthetic tools to realize either the functionalization and/or the construction of heterocycles.

Introduction: - Prof. Dr. Ronaldo Aloise Pilli (UNICAMP)

20:45 Welcome reception

TUESDAY – October 18th 2022

09:00-09:40 Invited Lecture

"Carbon: The Perfect Strange"
Speaker: - Prof. Dr. Pierre Mothé Esteves (UFRJ, BRAZIL)

"Can you remember, remember my name, As I flow through your life"… This verse of the Deep Purple classic song Perfect Strangers can be applied to our core element in organic chemistry: the carbon atom. Although we may think that we know everything about its structure and pure forms, this element still brings us surprises in the XXI century. We will see that the prediction and synthesis of new carbon allotropes is possible and may represent an inspiring synthetic challenge. We show how new allotropes of carbon, containing atoms with different hybridizations and proportions, can be conceived and synthesized.

Introduction: - Prof. Dr. Fernanda da Costa Santos Boechat (UFF)

09:40-10:20 Invited Lecture

"Advances in the Synthesis and Application of Strained-ring Compounds: Catalytic & Stoichiometric Approaches"
Speaker: - Prof. Dr. László Kürti (Rice University, USA)

The synthesis of highly substituted and strained nitrogenous molecules remains a challenging task since installing substituents on small ring systems gets increasingly difficult as the degree of substitution increases. Similarly, it is difficult to install nitrogen bridges onto highly substituted and electronically diverse unsaturated systems. In this

presentation a number of synthetic routes to these valuable nitrogenous building blocks will be discussed: The direct and stereospecific synthesis of N-H- and N-alkyl aziridines from unactivated olefins using both transition metal-catalyzed and organocatalytic approaches that proceed through very different N-transfer processes; Fully-substituted N-acyl aziridines are produced in one-pot by the reaction of N-electrophilic iminomalonates with ketone enolates - this transformation is in essence an aza-quasi-Favorskii rearrangement reaction which proceeds via a 1,2-attack followed by a low-barrier intramolecular nitrenoid-insertion into a C-C bond and Structurally diverse spiro N-H azetidines are formed in a single step during the Ti(IV)-mediated reaction between oxime ethers and alkyl-Grignard reagents or via a ligand-exchange process using terminal olefins - the overall transformation proceeds via a Kulinkovich-type mechanism: a titanacyclopropane intermediate is formed and serves as a 1,2- dialkyl anion equivalent, inserting into the 1,2-dielectrophilc oxime ether substrate to ultimately give rise to the desired N-heterocyclic four-membered ring.

Introduction: - Prof. Dr. Camila Djenne Buarque Müller (PUC-Rio)

10:20-11:00 Invited Lecture

“Some chemistry using nanohybrid catalysts”
Speaker: - Prof. Dr. Eric Doris (CEA, PARIS SACLAY)

Supported metal nanoparticles are attracting increasing interest because they allow for clean, selective and efficient catalytic transformations. In addition, supporting of the metals offers the possibility to recover the active catalyst, allowing it to be reused. Numerous metals, including gold, have been assembled onto solid supports although metallic gold has traditionally been regarded as a poor catalytic species. The catalytic activity of gold is however dramatically enhanced when downsized to nanoscale. This peculiar behavior of nano-gold has recently boosted its use in fine chemical synthesis applied, for example to selective hydrogenations, carbon-carbon bond formation, or oxidations. Various materials can be used as support for nanoparticles including clays, zeolites, polymers, metal oxides, amorphous carbon, etc. Compared to other supports, carbon nanotubes (CNT) provide advantages that include chemical, thermal and mechanical stability, inertness, high specific surface area, and chemically tunable topography. Moreover, CNTs are electronically active and are likely to contribute to the stabilization of the metals. We recently reported carbon nanotube-based hybrid catalysts that were assembled using a layer-by-layer strategy. These nanohybrids, incorporating various metals, and exhibiting specific catalytic properties, were applied to a wide variety of organic

transformations. Some chemistry based on CNT-metal hybrids will be presented.

Introduction: - Prof. Dr. Leandro Helgueira de Andrade (USP)

11:00-11:40 Invited Lecture

"Controlling Catalysis with Visible Light"
Speaker: - Prof. Dr. Tomislav Rovis (Columbia University, USA)

Visible light is an abundant energy source that can also be delivered on demand. Harnessing the energy in visible light has recently been accomplished through the use of photoredox catalysis, which can generate radical intermediates by an oxidation or reduction step to initiate a bond formation followed by a return of the electron or hole to close the catalytic cycle. We have been engaged in expanding the versatility of visible light photoredox catalysis and have uncovered strategies to effect C-H activation in unactivated positions of alkanes as well as controlling catalysis spatially and temporally. Reaction development, mechanistic investigations and synthetic applications will be the subject of this lecture.

Introduction: - Prof. Dr. Brenno Amaro da Silveira Neto (UnB)

11:40-12:20 Invited Lecture

"From thiosugars and thiodisaccharides to supramolecular multivalent ligands"
Speaker: - Prof. Dr. María Laura Uhrig (Universidad de Buenos Aires, ARGENTINA)

Thioglycosides and thiodisaccharides represent a synthetic challenge for carbohydrate chemists due to their increasing importance in the Glycobiology field. In these compounds, the anomeric oxygen has been replaced by a sulfur atom, and so, they are considered carbohydrate mimetics with great potential as enzyme inhibitors or new ligands for lectins, given that this replacement does not interfere with recognition events. Moreover, this structural feature makes them more resistant towards enzymatic and acidic hydrolysis. Therefore, the development of new synthetic methods to obtain thiosugars and their use as building blocks for the synthesis of new carbohydrate-derived compounds have been an active research field over the years. In our laboratory, we are interested in developing multivalent systems with high affinity for lectins, constructed from glycomimetics such as thiosugars and thiodisaccharides. Thus, after exploring a range of covalently-constructed multivalent structures, we undertook the study of self-

assembled multivalent systems produced from amphiphilic compounds. In all cases, we have incorporated thiosugars such as 1-thiolactose, β-S-N-acetylglucosamine and even thiodisaccharides as recognition elements, which were, at the same time, the polar moiety of the amphihile. Pyrene and resorcinarene systems, as well as long chain diacyl-derived tartaric residues, have been used as hydrophobic residues. Thus, in this presentation I will refer to our latest results on the synthesis and characterization of supramolecular multivalent ligands for lectins. It will include the synthetic results regarding the construction of GlcNAc-thiodisaccharides, and also our experience on a variety of self-assembled and micellar systems, including gels, which have shown high affinity for model lectins.

Introduction: - Prof. Dr. Eduardo Eliezer Alberto (UFMG)

12:30-14:00 Lunch

14:00-14:40 Women in Organic Chemistry

Speakers: - Prof. Dr. Cintia Duarte de Freitas Milagre (UNESP)
- Prof. Dr. Fernanda Gadini Finelli (UFRJ)

14:40-15:40 Flash Presentations

Mediator: - Dr. Renato Lúcio de Carvalho (UFMG)

14:40-14:50 – "Visible-Light Mediated Carbamoylation of Nitrones via Continous Flow"
Speaker: - Pedro H. R. de Oliveira (UFSCar)

14:50-15:00 – "Investigation of the stereoselectivity in functionalization of bioactive Naringenin by dynamic kinetic resolution"
Speaker: - Eloah P. Ávila (UFJF)

15:00-15:10 – "Flat yet twisted: Towards glassy discotic LC delayed fluorescence matrices"
Speaker: - Fabrícia Nunes da Silva (UFBA)

15:10-15:20 – "Visible-Light-Promoted Synthesis of 1,3-Dicarbonyl Sulfoxonium Ylides"
Speaker: - Radell Echemendía (USP)

15:20-15:30 – "Associating cross coupling and multicomponent reactions for the synthesis of 3,5-dicyanopyridine-based AIEEgens"
Speaker: - Carolina Vesga Hernández (PUC-Rio)

15:30-15:40 – "Synthesis of Selenium-based Compounds: Promising Drug Candidates in Neglected Diseases Therapy"
Speaker: - Vanessa Nascimento (UFF)

15:40-16:20 Invited Lecture

"Nucleophilic neutralization of organophoshates: correlating promiscuity (or versatility?) with structure-reactivity-mechanistic trends"
Speaker: - Prof. Dr. Elisa Souza Orth (UFPR, BRAZIL)

Is the broad mechanistic versatility of nucleophiles towards organophosphate neutralization, that has inspired many catalysts, beneficial or a threateningly promiscuity? We have been working on unravelling this puzzle and show how varying the nature of the organophosphate can lead to N-phosphorylation or unusual N-alkylation. Also, the structure of the neutralizing nucleophile also shows an interesting trend. Should this add to their known versatility or can it be considered an unsought promiscuity? A concise understanding of the mechanism underlying organophosphates will be presented with agrochemicals and chemical warfare simulants, which isimperative for effectively applying in real destruction or monitoring systems. Several pesticides and a Tabun simulant have been efficiently neutralized with a myriad of nucleophilic neutralizing agents. Preferably, one seeks less toxic products and no side reactions. In that sense, we evidence how mechanistic studies and structure-reactivity relationships are valuable tools for modulating towards less toxic products. Moreover, we show that one monitoring system may not apply to various toxic agrochemicals, since their structure can shift the mechanism, hence lead to different products and suppress important signals or give false positives.

Introduction: - Prof. Dr. Cintia Duarte de Freitas Milagre (UNESP)

16:20-16:40 Coffee-Break

16:40-17:20 Invited Lecture

"Enantioselective C–H Insertion Reactions of Donor/Donor Carbenes for the Synthesis of Complex Natural Products"
Speaker: - Prof. Dr. Jared Thomas Shaw (University of California, USA)

Rhodium carbenes lacking electron withdrawing groups, or "donor/donor" carbenes, participate in a wide variety of selective reactions. Due to the reduced electrophilicity, these reactive intermediates exhibit remarkable functional group tolerance, enabling

access to uniquely complex organic molecules. The development of new methods and their application to the synthesis of a series of complex heterocycles, including several natural products, will be described.

Introduction: - Prof. Dr. Fernando Antônio Santos Coelho (UNICAMP)

17:20-19:00 The Royal Society of Chemistry – BMOS Early Career Investigator Award Ceremony

Mediator: - Dr. Renato Lúcio de Carvalho (UFMG)

- Prof. Dr. Eufrânio N. da Silva Júnior (UFMG)
- Dr. Elizabeth Magalhães (RSC)
- Lucas Brown (General Consul for UK, Belo Horizonte)
- Cristina Hori (Manager of the Science and Innovation Network UK)

Awardees:
- Dr. Alastair Lennox (University of Bristol, UK)
- Prof. Dr. Clare S. Mahon (Durham University, UK)
- Prof. Dr. Clarissa Piccinin Frizzo (UFSM, BRAZIL)
- Prof. Dr. Fernanda Andreia Rosa (UEM, BRAZIL)

19:00-21:00 Prize Networking drinks

WEDNESDAY – October 19th 2022

09:00-09:40 Invited Lecture

"Carbopalladation Cascades – Not only *syn*, but also *anti*"

Speaker: - Prof. Dr. Daniel Werz (Technische Universität Braunschweig, GERMANY)

A characteristic feature of carbopalladation reactions is the syn-attack of the organopalladium species LnX[Pd]-R on the reacting π-system. Such a step results in compounds bearing Pd and R on the same side of the originating alkene moiety. Embedded into longer domino sequences complex structures are efficiently obtained by a repetition of this syn-carbopalladation step. In this way, linear oligoynes were cyclized in a dumbbell-mode and led to benzene-type structures or higher oligoenes. We exploited this chemistry to synthesize not only chromans, isochromans and dibenzopentafulvalenes, but also to access the most truncated π-helicenes which only consist of a Z,Z,Z,..-oligoene chain that is fixed in an all s-cis arrangement. All these domino processes are based on a syn-carbopalladation cascade. However, a carbopalladation cascade involving formal anti-carbopalladation steps opens new

avenues to create compounds with tetrasubstituted double bonds. Such a process was realized, and mechanistically and computationally investigated. The synthetic potential was demonstrated for the preparation of various oligocyclic frameworks (including natural products) by making use of a variety of different terminating processes.

Introduction: - Prof. Dr. Arlene Gonçalves Correa (UFSCar)

09:40-10:20 Invited Lecture

"Organosilicon Chemistry for Enantioselective Synthesis, Catalyst Design and Medicinal Chemistry"
Speaker: - Prof. Dr. Annaliese Franz (University of California, USA)

The successful development of new synthetic methods and catalysts is important for the discovery and production of chiral organic molecules and materials. This talk will highlight several examples of organosilicon chemistry that provide rich opportunities and applications for methodology, mechanism and novel synthetic targets. First, the development of enantioselective synthesis and molecular recognition components involved to access chiral-at-silicon molecules will be presented with applications for the design of new catalyst systems based on siloxy compounds. Second, the unique reactivity of allylsilane and allenylsilane nucleophiles will be featured to demonstrate opportunities to develop efficient methods for the enantioselective synthesis of complex molecules such as spirooxindoles, as well as interesting opportunities to explore mechanistic features of annulation reactions and Lewis acid-catalyzed reactions. Finally, examples for the synthesis of novel organosilicon targets with medicinal applications will be presented. For all studies, results of structural, mechanistic, kinetics and molecular binding studies will be included to provide insight for catalyst activity, design and synthetic applications.

Introduction: - Prof. Dr. Luiz Cláudio de Almeida Barbosa (UFMG)

10:20-11:00 Invited Lecture

"Designing of templates to reach the distal C–H bond"
Speaker: - Prof. Dr. Debabrata Maiti (IIT - Bombay, INDIA)

Mimicking the nature has always been a coveted target for scientific communinities. A precise understanding has emerged as to how enzymes accomplish the chemical transformations. Enzymes catalyze inert C-H bond functionalization in a regio- and stereoselective manner using metal-active site. Inspired by the nature, we have developed catalytic methods to functionalize carbon–hydrogen (C–H) bonds which

provides significant economic and environmental benefits over traditional synthetic methods. Applicability of our strategies towards synthesis of various complex molecules will be discussed.

Introduction: - Prof. Dr. Emilio Carlos Lucca Júnior (UNICAMP)

11:00-12:40 **Poster Session**
GROUP A: Posters from 1 to 80

13:00-19:00 **Barbecue**

THURSDAY – October 20th 2022

09:00-09:40 **Invited Lecture**

"Benzyne Chemistry: Synthetic Methods and Total Syntheses"
Speaker: - Prof. Dr. Cristiano Raminelli (UNIFESP, BRAZIL)

The benzyne chemistry has found applications in organic chemistry, including total syntheses of natural products and preparations of functional materials. In this context, 2-(trimethylsilyl)aryl trifluoromethanesulfonates can be considered an important alternative for the generation of benzyne and derivatives, enlarging the scope of benzyne chemistry applications in preparative organic chemistry. Accordingly, in our lecture we intend to present useful synthetic methods for the preparation of heterocyclic compounds and concise approaches to the total syntheses of natural products and bioactive compounds, involving the generation of benzyne and derivatives via fluoride-induced reactions under mild conditions.

Introduction: - Prof. Dr. Warley de Souza Borges (UFES)

09:40-10:20 **Invited Lecture**

"Organocatalytic Alcohol Activation"
Speaker: - Prof. Dr. Ross Denton (University of Nottingham, UK)

"Nucleophilic substitution reactions are fundamental transformations in organic synthesis because they allow readily available alcohols to be converted into a wide variety of functional groups with predictable inversion of stereochemistry. However, they are inherently wasteful since alcohol activation is necessary and takes place at the expense of a stoichiometric reagent. The lecture will describe the design and development of organocatalytic platforms for catalytic nucleophilic

substitution reactions of alcohols and epoxides as well as applications in natural product and active pharmaceutical ingredient synthesis.

Introduction: - Prof. Dr. Amanda Silva de Miranda (UFMG)

10:20-11:00 Invited Lecture

"Tuning of neutral carbene ligands—the way to control activity, selectivity and stability of ruthenium olefin metathesis catalysts"
Speaker: - Prof. Dr. Karol Grela (University of Warsaw, POLAND)

Ruthenium-catalyzed olefin metathesis reactions represent an attractive and powerful transformation for the formation of new carbon-carbon double bonds. This area is now quite familiar to most chemists as numerous catalysts are available that enable a plethora of olefin metathesis reactions. However, formation of substituted and crowded double bonds, decreasing the amount of metal, using metathesis in medicinal chemistry, etc. still remain a challenge, making industrial applications of this methodology difficult. These limitations can be solved by designing new, more active and stable catalysts. Sometimes even a small alteration of the catalyst's structure can lead to a visible change of its properties. This was the case in the so-called Grubbs' second-generation ruthenium catalysts featuring neutral N-Heterocyclic Carbene (NHC) ligands. Such NHC ligands typically contain large N-alkyl or N-aryl groups (sometimes called "wings" or "arms" of the NHC ligand). During the lecture some examples of possible structural modifications of the NHC ligands will be presented, mostly based on adjusting the relative size of these N-groups or by limiting their free movement. Such alterations of the aromatic "wings" in the NHC ligand can be used to affect the resulted ruthenium olefin metathesis catalyst's activity, selectivity and stability.

Introduction: - Prof. Dr. Vitor Francisco Ferreira (UFF)

11:00-11:40 Invited Lecture

"Synthesis of highly functionalized 1,2,3-triazoles systems through copper- or organocatalysis protocols"
Speaker: - Prof. Dr. Diego da Silva Alves (UFPel, BRAZIL)

This presentation will provide a comprehensive overview of reported methods particularly copper- and organocatalyzed reactions - for the regioselective syntheses of high functionalized 1,2,3-triazoles systems. These chemical entities are prevalent cores in biologically active compounds and functional materials. In view of their unique properties,

substantial efforts have been paid for the design and development of practical approaches for the synthesis of these scaffolds.

Introduction: - Prof. Dr. Marco Antonio Barbosa Ferreira (UFSCar)

11:40-12:20 Invited Lecture

"Recent Developments in Carbonylation Chemistry"
Speaker: - Prof. Dr. Troels Skrydstrup (Aarhus University, DENMARK)

Carbonylation reactions represent important chemical transformations for the introduction of oxygen containing functionalities. Transition metal complexes play a key role for promoting this chemistry. In this talk, I provide a short overview on the use of CO surrogates for performing safe and stoichiometric carbonylation chemistry. Examples are given for the synthesis of pharmaceutically relevant molecules, but also for efficient late-stage introduction of carbon isotopes into bioactive molecules, aiding drug metabolism and pharmacokinetic (DMPK) studies in drug development programs. Furthermore, I will elaborate on our initial efforts to exploit this chemistry for the development of a molecular surgery strategy for extruding an embedded carbon atom within the bioactive molecule's framework, and its replacement with a carbon isotope via a sequence of C–C bond cleaving and bond forming events.

Introduction: - Prof. Dr. Anita Jocelyne Marsaioli (UNICAMP)

12:30-14:00 Lunch

14:00-15:40 Poster Session
GROUP B: Posters from 81 to 160

15:40-16:20 Invited Lecture

"Selective Functionalization of Pyridines, Diazines and Pharmaceuticals via Unconventional Intermediates"
Speaker: - Prof. Dr. Andy McNally (University of Colorado, USA)

Pyridines and diazines are ubiquitous in pharmaceuticals and agrochemicals, yet there are limits in synthetic methods that can directly functionalize the C–H bonds in these structures. We will show two distinct approaches, using phosphorus and ring-opened intermediates, that enable selective functionalization of these heterocycles into a range of valuable derivatives. A range of C–C and C–Heteroatom bond formations are viable, and the chemistry functions on structures typically encountered in drug discovery programs. Our lab has also performed

mechanistic and computational studies of the regioselectivity of these reactions and the phosphorus ligand-coupling processes involved.

Introduction: - Prof. Dr. Elson Santiago de Alvarenga (UFV)

16:20-16:40 Coffee-break

16:40-17:20 Invited Lecture

"Catalytic Chirality Generation: New Strategies for Organic Synthesis"
Speaker: - Prof. Dr. John Bower (University of Liverpool, UK)

Our group develops new catalysis platforms that enable the efficient generation of chiral building blocks and heterocyclic scaffolds. Current priority areas include: (i) the development of catalytic C-C bond activation processes and associated cycloadditions, (ii) the development of aza-Heck reactions, and (iii) the development of enantioselective alkene hydroarylation reactions. Selected recent highlights will be presented.

Introduction: - Prof. Dr. Carlos Roque Duarte Correia (UNICAMP)

17:20-18:20 Conference

ACS Session
"Exploring the new retrosynthesis tool from CAS SciFinder-n"
Speaker: - Dr. Gabriel Kaetan Baio Ferreira

"How can ACS help promote lab safety culture in the universities"
Speaker: - M.Sc. Valtair Severino dos Santos Júnior

18:20-19:00 Conference
"How to publish?"
Speaker: - Dr. Elizabeth Magalhães (RSC)

FRIDAY – October 21st 2022

09:00-09:40 Flash Presentations

Mediator: - Prof. Dr. Rosimeire Coura Barcelos (UFMG)

09:00-09:10 – "Synthesis of alpkinidine analogues"
Speaker: - Romário Ramos (UFBA)

09:10-09:20 – "Efficient synthesis of glycomimetics with potential biological activity."
Speaker: - Pierina Schiappapietra (Facultad de Química UDELAR)

09:20-09:30 – "AI-based Molecular Design and Synthesis of New Peptidomimetic Inhibitors of SARS-CoV-2 M^{pro} enzyme"
Speaker: - Pedro H. O. Borges (UFRJ)

09:30-09:40 – "Rongalite in PEG-400 as a general and reusable system for the synthesis of 2,5-disubstituted chalcogenophenes"
Speaker: - Douglas B. Paixão (UFRGS)

09:40-10:20 BMOS Award

Speakers: - Prof. Dr. Eufrânio Nunes da Silva Júnior (UFMG)
- Prof. Dr. Rossimiriam Pereira de Freitas (UFMG)

Awardees: - Prof. Dr. Alaide Braga de Oliveira (UFMG)
- Prof. Dr. Anita Jocelyne Marsaioli (UNICAMP)
- Prof. Dr. Eliezer Barreiro (UFRJ)
- Prof. Dr. Paulo Costa (UFRJ)
- Prof. Dr. Luiz Fernando da Silva Júnior (*in memoriam*)

10:20-11:00 Closing Ceremony

Speakers: - Prof. Dr. Eufrânio Nunes da Silva Júnior (UFMG)
- Prof. Dr. Paulo Henrique Schneider (UFRGS)
- Prof. Dr. Rossimiriam Pereira de Freitas (UFMG)

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A. J. S. Senna, M. T. Rodrigues Júnior, H. Santos, R. C. Gomes and F. Coelho*

Bioactive Natural Product-Based Nitrogen-Containing Lead Molecules for Total Synthesis

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Keywords: *natural products, total synthesis, alkaloids, peptides, Leishmaniasis, malaria*

ABSTRACT

Natural products are the best scaffolds for the development of new therapeutic agents.[1] Nitrogen-bearing alkaloids and peptides historically have yielded some of the most successful human medicines, such as morphine and Ziconotide®. Resulting of an extensive screening program spanning several years, we have discovered alkaloids and peptides which display sub-micromolar activity in antileishmanial and antiplasmodial assays. Large-scale isolation of such compounds provided material enough for *in vivo* bioassay investigations, with very promising results. We propose the total synthesis of the active compounds, that include large peptides (> 2,000 Da) and guanidine alkaloids. Results of large-scale isolation and both *in vitro* and *in vivo* assays will be presented, as well as the rationale to achieve the total synthesis of the active alkaloids and peptides.

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Determination of the Absolute Configuration of the Male-produced Sex Pheromone of the Stink Bug *Pellaea stictica*, (2*R*,4*R*,8*R*)-2,4,8,13-Tetramethyltetradecan-1-ol by Stereoselective Synthesis Coupled with Enantiomeric Resolution

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Keywords: *Semiochemicals, Chemical Ecology, Pentatomidae, Gas Chromatography, Chiral Derivatization Reagents, Stereoselective Total Synthesis.*

ABSTRACT

Pellaea stictica (Heteroptera: Pentatomidae) is a neotropical stink bug found in several South American countries, being a common pest of broadleaf privet, *Ligustrum lucidum* (Oleaceae). In previous work from our group, we had identified the gross structure of the male-produced pheromone of the species as the alcohol 2,4,8,13-tetramethyltetradecan-1-ol (**1**), but the stereochemistry of all methyl branches had not been determined.[1] The absolute configuration of a pheromone may be crucial to its biological activity. Therefore, the aim of this work was to identify the absolute configuration of the *P. stictica* sex pheromone in stages, by employing a series of increasingly stereoselective syntheses coupled with careful comparisons of the chromatographic and NMR spectral properties of the synthetic compounds and the natural pheromone. Here, we describe those syntheses, that culminated in the conclusive identification of the insect-produced compound as (2*R*,4*R*,8*R*)-2,4,8,13-tetramethyltetradecan-1-ol **(1)**. The key step was a coupling reaction between the phosphonium salt (**2**) and aldehyde (**3**), through a Wittig olefination.

(*R*)-**2** (2*S*,4*R*)-**3** (2*R*,4*R*,8*R*)-**1**

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Catalytic redox-neutral C-H functionalization with TEMPO in water to access aminomethyl-substituted pyrroles

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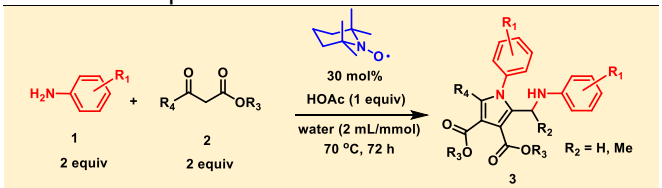
Keywords: *C-H functionalisation, In water Catalysis, TEMPO.*

ABSTRACT

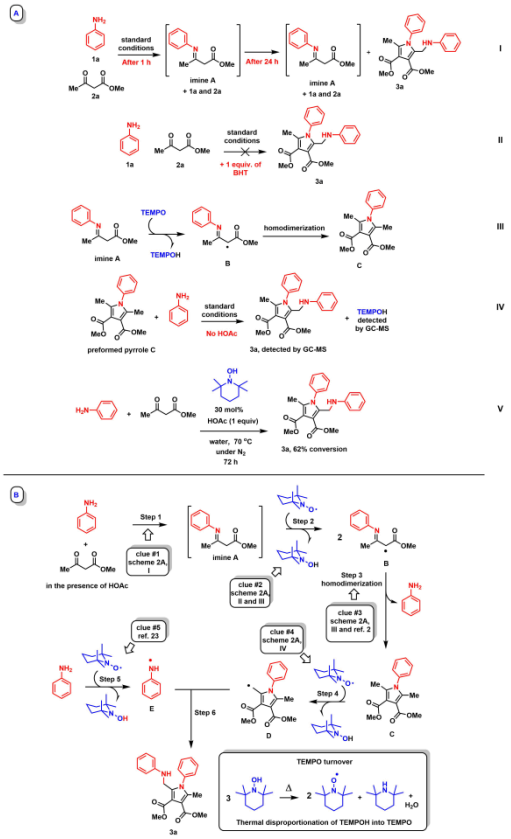
We have uncovered a straightforward method to access aminomethyl-substituted pyrroles employing redox-neutral catalysis with TEMPO in water. Our approach represents an endeavour to address redox economy in radical transformations and is fully aligned with green chemistry principles. The selective C–H functionalisation of the methyl group on the intermediate pyrrole with the N-terminus of anilines provides structural variety that is otherwise difficult to be achieved using metal-free methods. Moreover, cheap and commercial chemical feedstocks were used, thus circumventing the need for elaborated starting materials. In our view, the reported transformation is suited to prompt the development of other radical redox-neutral processes based upon TEMPO[1].

Table 1: Scope of the transformation.



Entry	R_1	R_2	R_3	R_4	Yield 3 (%)*
3a	H	H	Me	Me	89
3b	4-F	H	Me	Me	92
3c	3-F	H	Me	Me	90
3d	3-Cl	H	Me	Me	85
3e	4-Cl	H	Me	Me	86
3f	4-Me	H	Me	Me	88
3g	2-Me	H	Me	Me	84
3h	4-Br	H	Me	Me	87
3i	4-Et	H	Me	Me	90
3j	4-OMe	H	Me	Me	83
3k	4-Me	H	Me	Et	89
3l	4-OMe	H	Me	Et	86
3m	4-F	H	Me	Et	91
3n	H	H	Me	Et	92
3o	4-F	Me	Et	Et	74
3p	4-Me	Me	Et	Et	70
3q	4-Cl	Me	Et	Et	76

*Yields of isolated products.



Scheme 2: Mechanistic Insights (A) and Proposed Reaction Mechanism (B)

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The efficient Knoevenagel condensation promoted by bifunctional heterogenized catalyst-based chitosan-EDTA at room temperature

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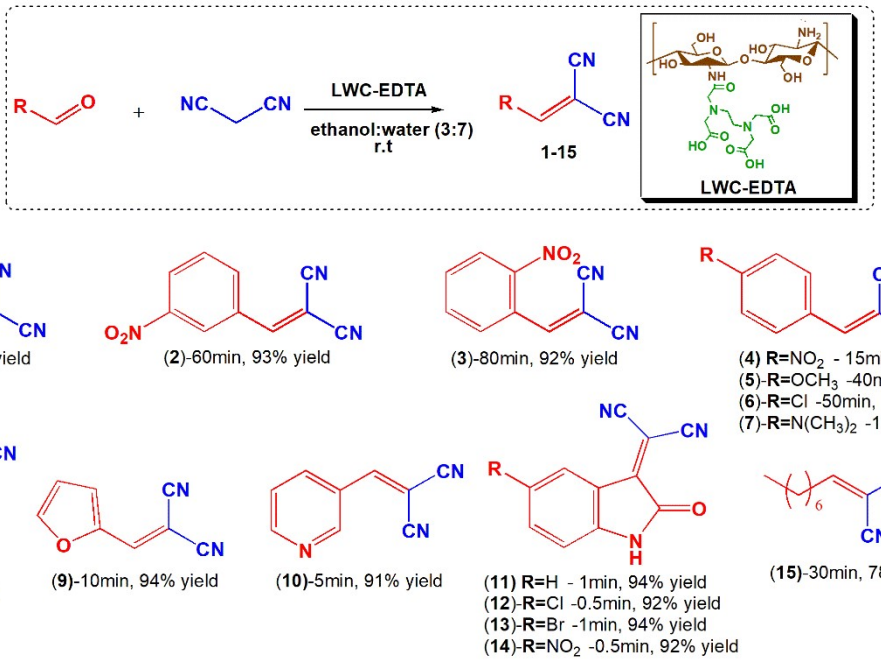
Keywords: *Heterogeneous Catalysis; Chitosan; Knoevenagel Condensation.*

ABSTRACT

The Knoevenagel Condensation is an reaction aldol-type between a carbonylated compound and active methylene compound [1]. Due to the great interest in eco-friendly processes, heterogeneous or heterogenized catalysts have been produced and employed in this reaction.

An efficient heterogeneous catalyst-based low molecular weight chitosan (LWC) modified with EDTA groups were prepared and applied as a bifunctional heterogenized catalyst in the Knoevenagel Condensation reaction, promoting fast reactions between malononitrile and aldehydes or isatins at room temperature. Chitosan-EDTA (LWC-EDTA) catalyst was synthetized by functionalization of chitosan with EDTA for 72 hours promoting the most significant modification of the matrix surface, reflecting shorter reaction times [2]. The reactions using the LWC-EDTA catalyst present excellent isolated yields (78-98%) in short reaction times (0.50-120 minutes) for different Knoevenagel compounds at room temperature (Scheme).



Additionaly, the catalyst was easily recovered and reused up to six times without significant losses of its catalytic activity (μ=89,8% of **4**).

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Application of a Diversity-Oriented Synthetic Approach to the Preparation of Natural Product-Like Compounds based on Tropolone Diels-Alder Adducts

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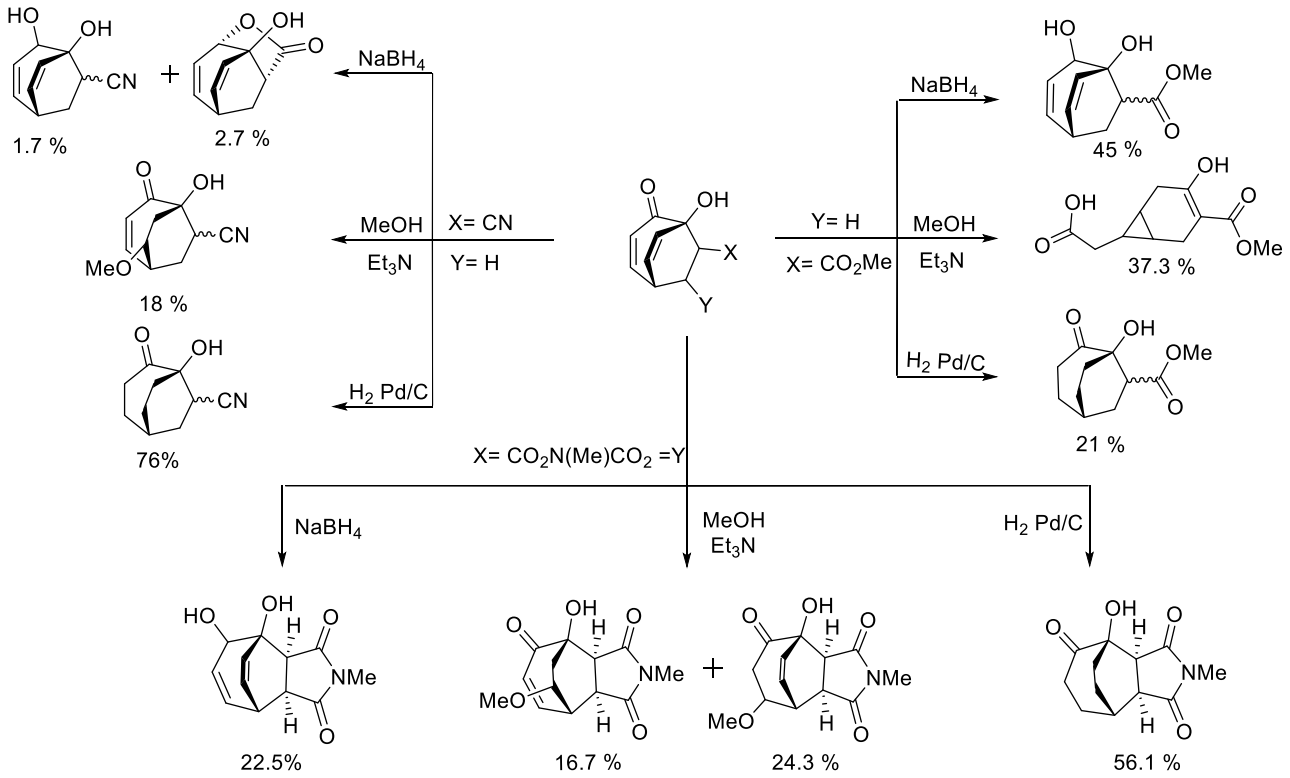
Keywords: *Diversity Oriented Synthesis, Michael Additions; Reductions*

ABSTRACT

Using a Diversity-Oriented Synthetic (DOS) approach our group has prepared a series of natural product-like compounds (NPLCs) based on a library of Diels-Alder adducts obtained from tropolone and dienophiles such as acrylonitrile, methylacrylate, and *N*-methylmaleimide. The goal of this work was to further increase the chemical space of our NPLC libraries through functional group interconversions and derivatizations of the previously synthesized adducts. Classical and robust reaction conditions, including hydrogenations with Pd/C, Lauche reductions, and Michael addition conditions, were employed to achieve this.[2] This strategy led to a collection of 10 new polyfunctionalized compounds in only two reaction steps. In addition, an interesting and previously unreported route to bicyclo[4.1.0]heptanes (norcaranes) was serendipitously discovered.



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Synthesis and Antitumoral Evaluation of Natural Product-Like Compounds Based on Tropolone and Benzotropolone Derivatives

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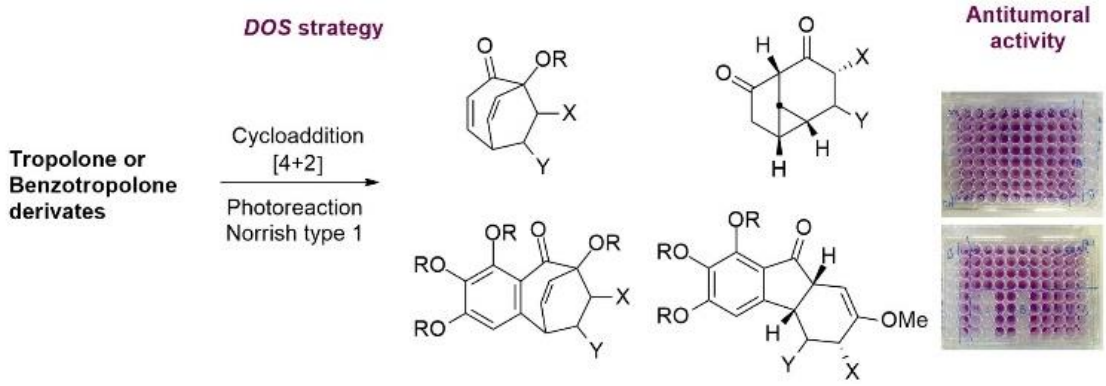
Keywords: *Diversity-Oriented Synthesis, Diels-Alder Cycloadditions, Photoisomerization.*

ABSTRACT

Diversity-Oriented Synthesis (DOS) is a strategy based on the creation of libraries of small polyfunctionalized molecules with potential biological activity. The aim of this work is the preparation of natural product-like compounds (NPLCs) using DOS, as well as their evaluation as antitumorals. For this purpose we combined [4+2] cycloadditions and photoisomerizations reactions, starting from tropolones and benzotropolones as dienes and different dienofiles, such as *N*-methylmaleimide, acrylonitrile, and methylacrilate. We obtained 14 compounds, including bicyclo[4.1.0]heptanes and hydrofluorenones. The library was evaluated against the human tumor cell lines MCF-7 (breast cancer), HT-29 (colon cancer) and NCI-H460 (lung cancer). Six of these compounds showed cytotoxicity in at least one cell line. The hits identified through this simple approach encourage us to continue our search for novel NPLCs with biological activity as antitumoral agents.



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Telescopic Synthesis of Benzo-Fused Heterocycles and Naphthalenes via Mechanochemistry and Microwave Heating-Promoted Wittig/Friedel-Crafts Reactions

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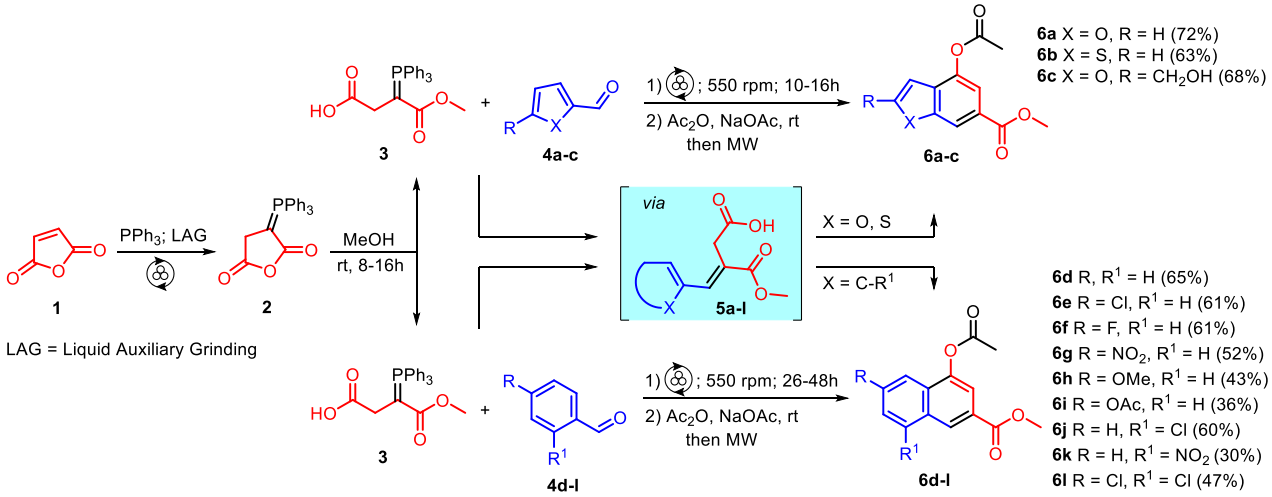
Keywords: *Solvent-free, Green Chemistry, Acylation, Itaconic half-ester.*

ABSTRACT

Mechanochemistry and microwave heating have potential to develop greener and easier organic synthesis circumventing the use of dry organic solvents and/or inert atmosphere.[1] Carboxyphosphorane **3** is a versatile building block to aromatic rings by Wittig reaction followed by Friedel-Crafts acylation of corresponding (*E*)-itaconic half-esters (**5**). This route is an alternative to the Stobbe condensation to obtain (*E*)-itaconic half-esters due to its greater stereoselectivity to this isomer in the Wittig reaction. The classical condition to this olefination employing **3** requires dry/toxic solvent and inert atmosphere. Due to the thermal instability of **3**, the Wittig olefination is carried out at room temperature resulting in long reaction time (2-10 days).[2,3,4] We developed a mechanochemical preparation of **3** and the telescopic synthesis of substituted benzo-heterocycles **6a-c** and naphthalenes **6d-l** involving a mechanochemical Wittig olefination under solvent-free condition and shorter time (1-2 days), followed by microwave heating-promoted Friedel-Crafts intramolecular acylation, Scheme 1. This telescopic approach is under investigation in the total synthesis of natural products.



Scheme 1 – Telescopic synthesis of heterocycles **6a-c** and naphthalenes **6d-l**.

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Mechanochemical Synthesis of 3-Acyl- and 3-Acyloxy-thioenaminones

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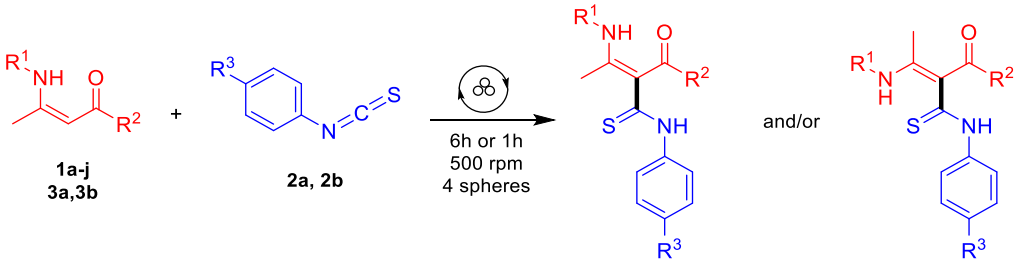
Keywords: *Thioenaminones, Mechanochemistry, Green Chemistry*.

ABSTRACT

3-Acyl- and 3-acyloxy-thioenaminones are versatile intermediates for the construction of several *N*-heterocycles with potential biological activities.[1] Several methodologies for the synthesis of this species are related in the literature,[2,3] however solvent-free methods are scarce.[4] Mechanochemistry is attractive in the synthesis of organic molecules because this technique provides greater energy efficiency, dispensing with the use of solvents, shorter reaction times and greater reproducibility.[5] In this work we using a planetary ball mill to investigating the reactivity of acyclic enaminones (**1a-j, 3a, 3b**) with arylisothiocyanates (**2a, 2b**) under solvent/catalysts-free conditions (Scheme 1). It was verified the formation of fifteen C-addition products with good yields and most of 3-acy and 3-acyloxy-thioenaminones were obtained in the form of *Z/E* isomeric mixtures. In conclusion, mechanochemistry is an efficient technique to the green synthesis of 3-acyl- and 3-acyloxy-thioenaminones.

Scheme 1 - Synthesis of 3-acyl-thioenaminones via mechanochemistry.



4a R^1: C_2H_4OH, R^2: Me, R^3: H (*E*, 84%)
4b, 4b' R^1: Bu, R^2: OMe, R^3: H (*Z*/*E*:*3*/*2*, 69%)
4c, 4c' R^1: Bu, R^2: Me, R^3: H (*Z*/*E*:*3*/*2*, 80%)
4d, 4d' R^1: $CH_2(CH_3)$-Ph, R^2: OMe, R^3: H (*Z*/*E*:*9*/*1*, 46%)
4e, 4e' R^1: i-Propyl, R^2: OMe, R^3: H (*Z*/*E*:*1*/*1*, 55%)
4f, 4f' R^1: Cz, R^2: OEt, R^3: H (*Z*/*E*:*9*/*1*, 96%)
4g, 4g' R^1: Cz, R^2: OMe, R^3: H (*Z*/*E*:*9*/*1*, 80%)
4h, 4h' R^1: CH_2-CH_2-Ph, R^2: OMe, R^3: H (*Z*/*E*:*3*/*2*, 45%)

4i, 4i' R^1: Bz, R^2: OMe, R^3: H (*Z*/*E*:*3*/*2*, 74%)
4j, 4j' R^1: Ph, R^2: Me, R^3: H (*Z*/*E*:*4*/*1*, 23%)
5a R^1: C_2H_4OH, R^2: Me, R^3: Cl (*E*, 86%)
5b, 5b' R^1: Bu, R^2: OMe, R^3: Cl (*Z*/*E*:*1*/*1*, 56%)
5c, 5c' R^1: Bu, R^2: Me, R^3: Cl (*Z*/*E*:*1*/*1*, 85%)
6a R^1: C_2H_4OH, R^2: OMe, R^3: Cl (*E*, 24%)
6b, 6b' R^1: Bu, R^2: OEt, R^3: Cl (*Z*/*E*:*3*/*2*, 80%)

ACKNOWLEDGEMENTS

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Synthesis of alpkinidine analogues

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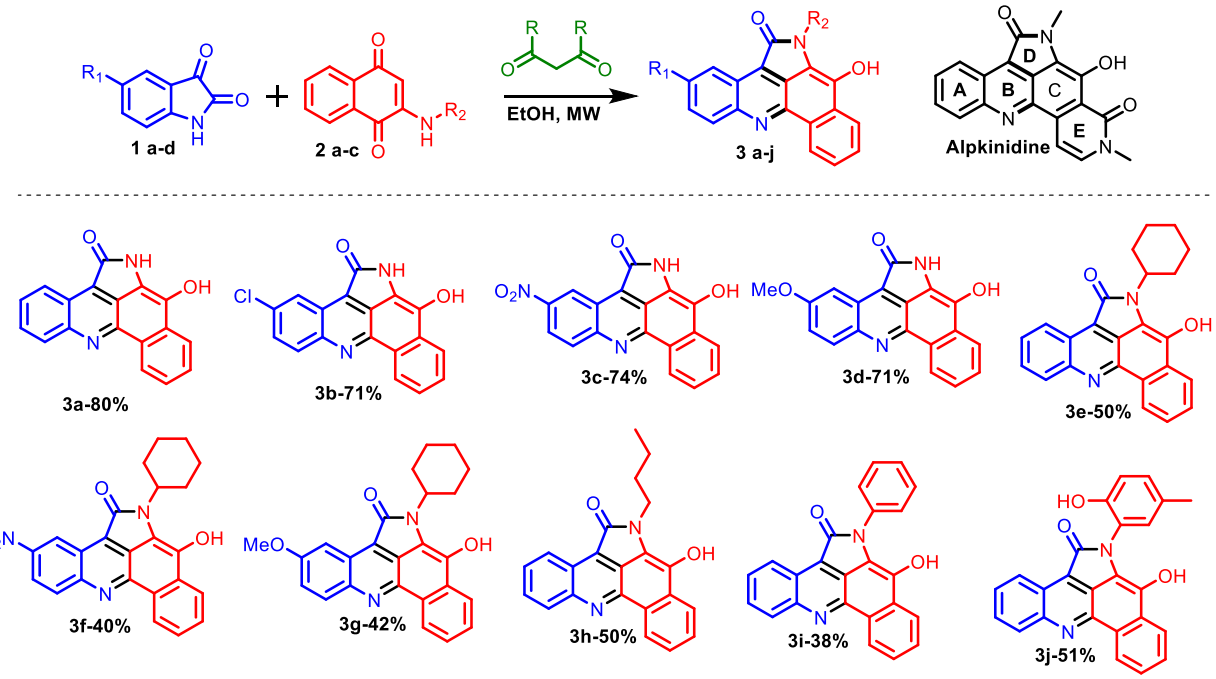
Keywords: *Microwave, Pentacycles, Heterocycles.*

ABSTRACT

Alpkinidine is a natural product obtained from marine sponge *Xestospongia carbonaria* in 2002 that shows selective cytotoxicity to solid tumor-derived cells.[1] Alkaloids members of the same family that alpkinidine exhibit a variety of biological activities such as antiviral, antiparasitic, antifungal, insecticidal, cytotoxic and antibacterial, however, the small amount obtained from the natural source makes more extensive biological studies difficult.[1,2,3] The total synthesis of alpkinidine is still a challenge and even the preparation of its derivative by modification of E-ring was described involving a multi-steps approach.[2,3] We developed a one-step methodology for the synthesis of pentacycles alpkinidine analogues using isatins and 2-amino-1,4-naphthoquinones as substrates and 1,3-dicarbonyl compounds as promoters. Several derivatives with modification in the A and E rings were obtained, Scheme1. This successful condensation is under investigation in the total synthesis of alpkinidine.



Scheme 1 – Synthesis of alpkinidine analogues **3a-j**.

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Synthesis and derivatization of ampelomins as potential radiotracers

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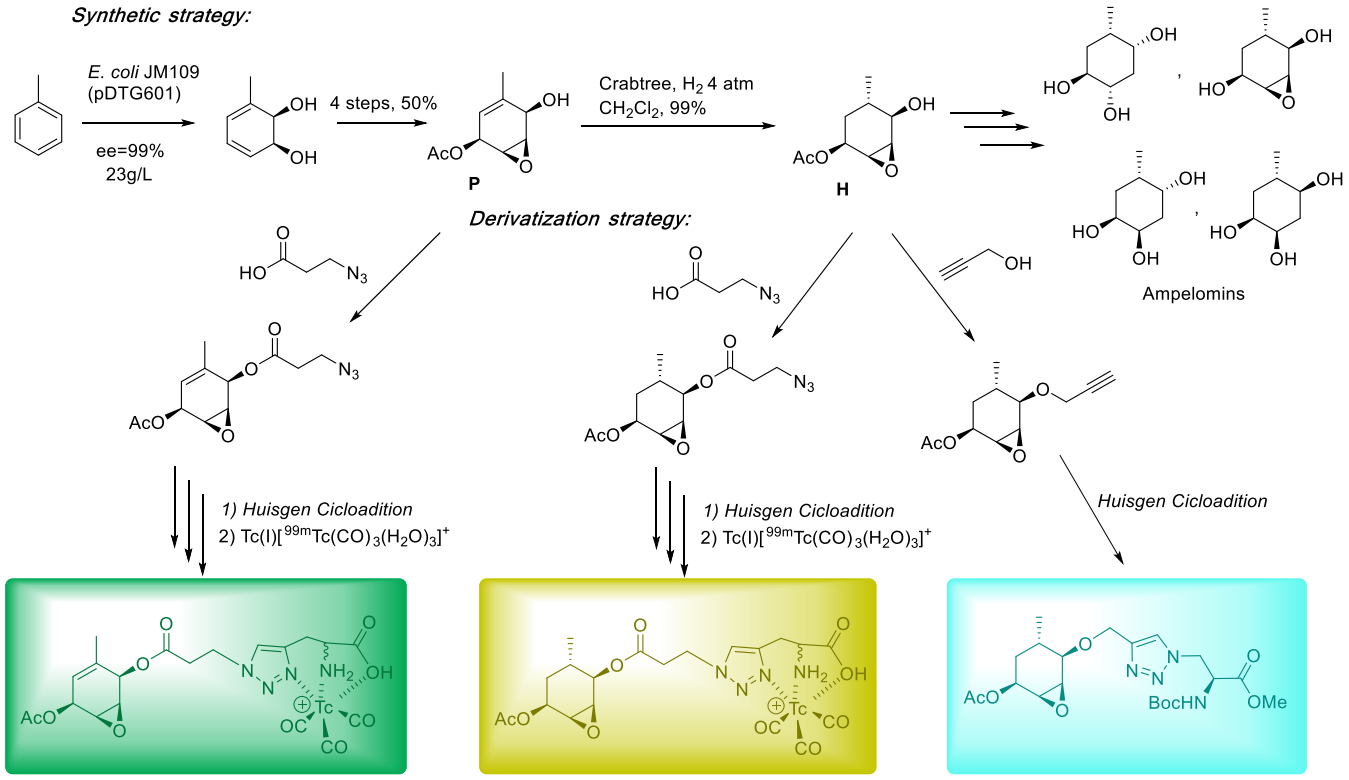
Keywords: *Ampelomin synthesis, derivatization, potential radiotracer*

ABSTRACT

Ampelomins are carbasugars with multiple hydroxyl groups that have shown the capability of selectively binding to bacterial enzymes. This confers them adequate properties for their use as radiotracers for infection foci targeting.[1] These molecules are synthesized through a common precursor (**P**) which is obtained in 5 steps from the biotransformation of toluene, with an overall yield of 50%.[2] In this work we present the synthesis and derivatization of **P** and its hydrogenated analog **H**. The derivatization is carried out with a linker containing either an azide group or a terminal alkyne. A subsequent Huisgen cycloaddition catalyzed by Cu(I) with an appropriate aminoacid provides the triazol necessary to coordinate with technetium-99m.[3] We also present the preliminary results of radiolabelling and physicochemical properties for the technetium-99m complexes.



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Diastereoselective Synthesis of Azabicyclo[3.1.0]hexenones from Chalcones

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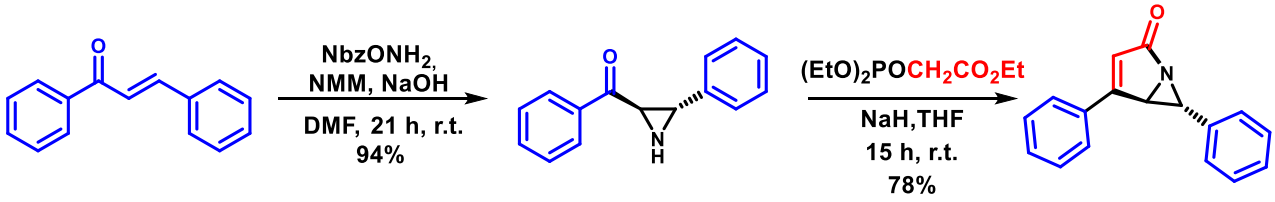
Keywords: *aziridine, γ-lactam, ring expansion*

ABSTRACT

The synthesis of 5-membered heterocyclic rings is quite interesting mainly due to the biological and pharmacological properties that these compounds present. In this context, γ-lactams stand out for being analogous to β-lactams, precursor of a wide variety of drugs and biologically active compounds.[1,2] The broad majority of methods reported in the literature to synthesize γ-lactams still start from the cyclization of a carboxylic acid and amines.[3,4]

In this work, we have developed a simple and efficient diastereoselective synthesis of new 1-azabicyclo[3.1.0]hex-3-en-2-ones from chalcones through aziridination reaction[5] followed by Horner-Wadsworth-Emmons olefination.[6] In the optimized condition, the bicyclic compound was obtained in 73% overall yield. We are now evaluating the scope and limitation using substituted chalcones as well as the asymmetric version of this new method via chiral aziridines.[7]



Scheme 1. Synthesis of 1-azabicyclo[3.1.0]hex-3-en-2-one.

ACKNOWLEDGEMENTS

Grants from CNPq (429748/2018-3 and 302140/2019-0), FAPESP (2018/23761-0, 2013/07600-3, 2014/50249-8), CAPES (001) and GSK are gratefully acknowledged.

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Novel green and more efficient reaction for the synthesis of aromatic hydrazides

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Keywords: *Aromatic hydrazides, lanthanide coordination compounds.*

ABSTRACT

Development of new lanthanide-based sensors depends on the rational design of ligands containing multiple coordination sites and planar π-delocalized systems for light reception.[1] In this work we present a novel, one-step reaction for the synthesis of aromatic hydrazides, precursors in the synthesis of the final organic ligands designed for the coordination with the lanthanide ions. The synthetic strategy implicates the reaction between a naphtoic carboxylic acid (among others) and hydrazine monohydrate, using 1,1'-carbonyldiimidazole (CDI) as coupling agent and THF as solvent.[2] We also add 4-dimethylaminopyridine (DMAP) and *N,N'*-diisopropylethylamine (DIPEA) as bases (**Figure 1**). The reaction is completed at room temperature overnight. This is a non-reported alternative to the classical two-step approach, which includes the preparation of the desired hydrazide from its corresponding carboxylic acid; which is first esterificated and subsequently treated with hydrazine monohydrate, taking up to 24 hours of reflux conditions for each reaction.[3]

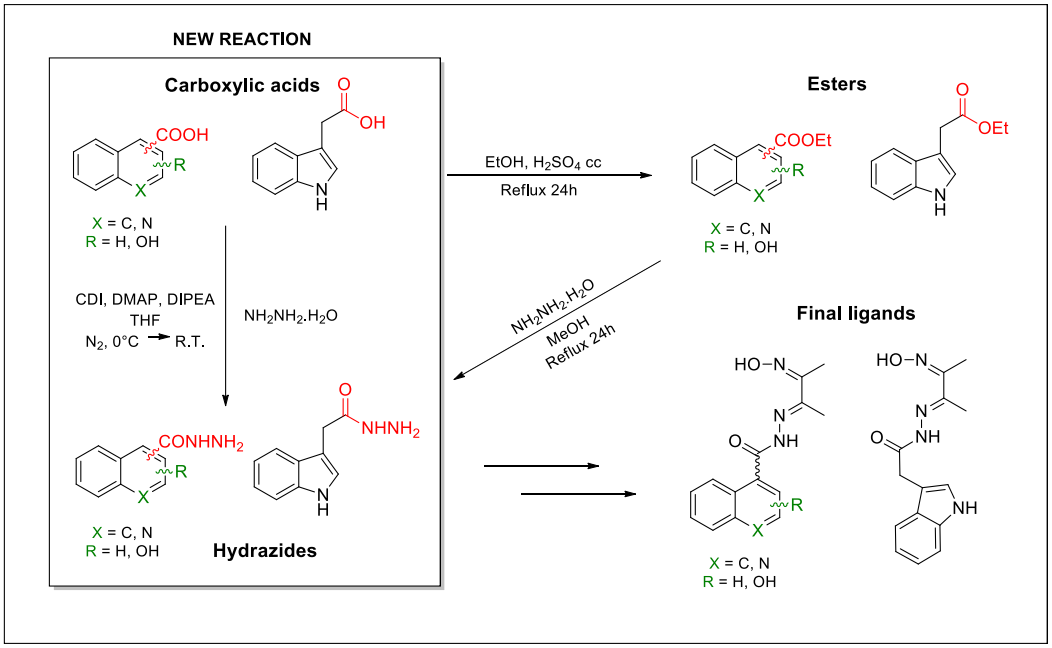

Figure 1: *New reaction for the synthesis of hydrazides and classical two-step approach*.

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Synthesis of Coumarins and Coumarin-Itaconimide Hybrid *via* Knoevenagel and Wittig Reactions

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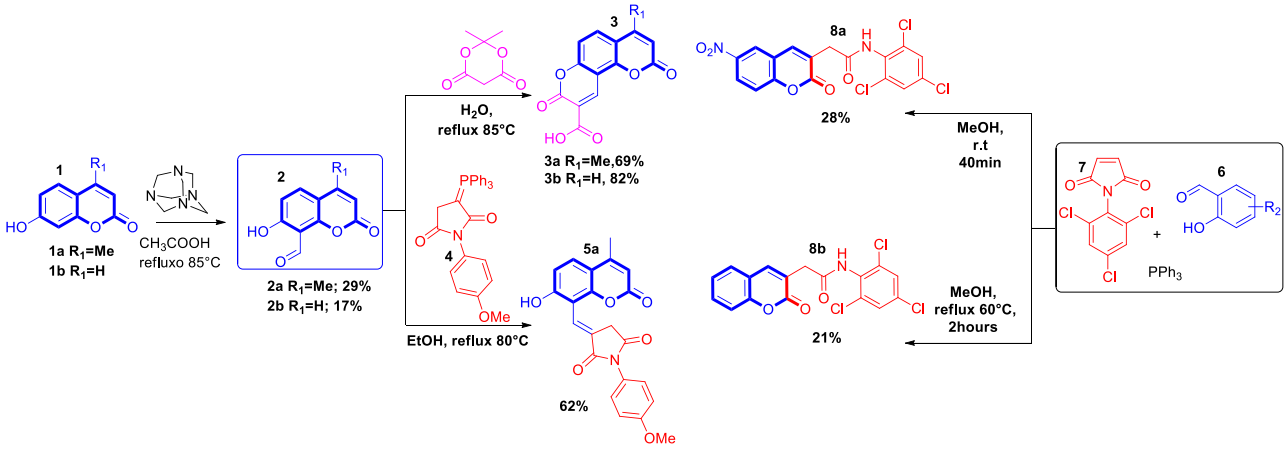
Keywords: *Coumarins, Coumarin-Itaconimide, Wittig/Knoevenagel Reaction.*

ABSTRACT

The coumarins show good biological activity and are starting materials for the synthesis of complex heterocyclic compounds.[1] In general, coumarins are obtained by classic methodologies, for example, Pechmann, Knoevenagel, Wittig or Perkin reactions.[2] Wittig reaction is the most of important reaction that promote olefination.[3] In this work, coumarins **2a-b** were obtained from Duff reaction, and then reacted with Meldrum's acid and cyclic phosphorus ylide **4** to access coumarins **3a-b** and coumarin-itaconimide **5a**, respectively. Besides, the three-component reaction of maleimide **7**, salicylaldehyde derivatives **6** and triphenylphosphine was investigated, affording coumarins **8a-b**. All products are solid compounds and were obtained adequately pure by simple filtration. Therefore, we developed a direct synthesis of new coumarins and coumarin-itaconimide with moderate to good yields through Knoevenagel and Wittig reactions.



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Synthesis of benzoquinolinetriones and bis-benzoquinolinetretraones though reaction of 2,5-diamino-1,4-benzoquinone and arylidenes derivatives of Meldrum's acid

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Keywords: *quinolone, benzoquinone, aza-annelation.*

ABSTRACT

Benzoquinolinetriones are substances that have in their skeleton benzoquinones or naphthoquinones fused to a nitrogenous heterocycle. They are valuable compounds found in molecules that exhibit remarkable physiological properties, such as antioxidant, antimicrobial, antimalarial, fungicidal, and anti-inflammatory effects.[1] Examples of this compound the naturally occurring benzoquinoline-2,5,10-triones (or fused 2-pyridinone ring naphthoquinones), Marcanine A,[2] Marcanine,[3] and Griffithazanone A.[4] In this work, novel benzoquinolinetriones and benzoquinolinetetraones were synthesized through [3+3] aza-annelation reactions of 2,5-diamino-1,4-benzoquinone and different arylidene derivatives of Meldrum's acid under microwave heating. It was observed that the nature of the substituent group in the arylidene affects the reactivity and impact in the yield of the desired product, and in the formation of bis-benzoquinolinetetraones, wherein electron withdrawing groups afford highest yields. It makes the arylidene more electrophilic, whereas electron donor groups have the lowest yield, as it causes the opposite effect. In conclusion, we have developed an efficient route to the synthesis of new 6-amino-3,4-dihydroquinoline-2,5,8-triones and bis-3,4-dihydroquinoline-2,5,7,10-tetraones.

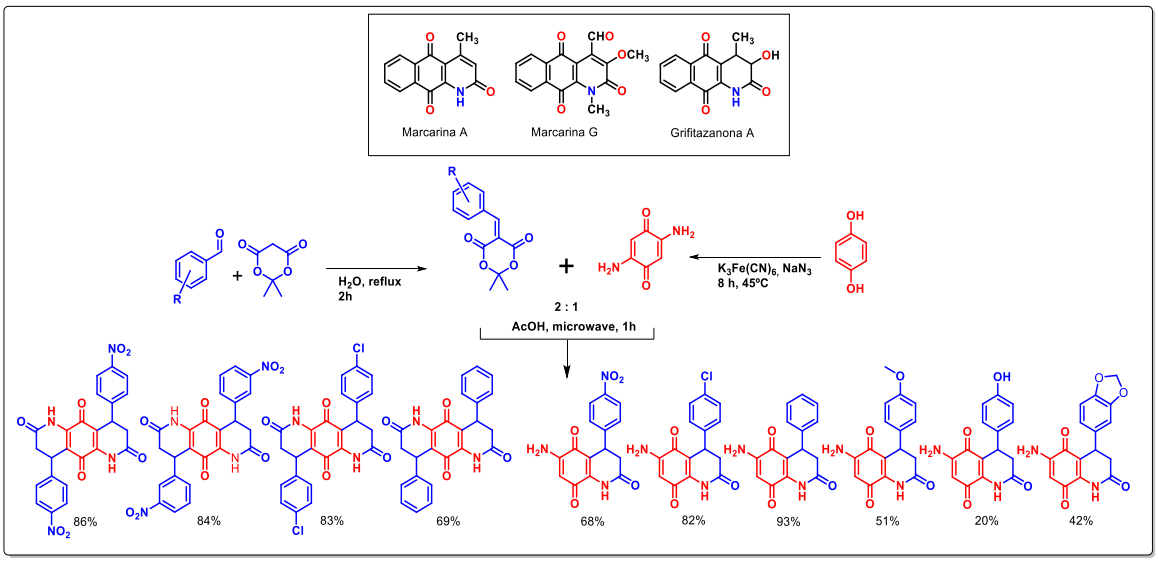

Figure 1 – Naturally occurring quinolinetriones and synthesis of 6-amino-3,4-dihydroquinoline-2,5,8-triones and bis-3,4-dihydroquinoline-2,5,7,10-tetraones

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Telescopic synthesis of *N*-arylmaleimides by combined use of mechanochemistry and microwave heating

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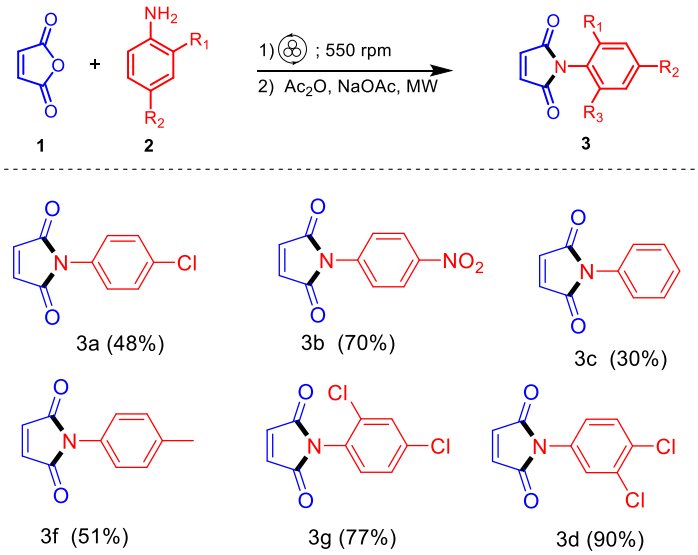
Keywords: *Microwave, Solvent-free, Green Chemistry, Maleimide, Mechanochemistry.*

ABSTRACT

The use of microwave heating and mechanochemistry have shown to be excellent green alternative for organic synthesis, since these tools minimize solvent use and reaction time. However, the combined use of these two techniques is rare. There are a variety of maleimides applications such as antibacterial[1] and as monomers to polymaleimides.[2] In this work we developed a telescopic synthesis of *N*-arylmaleimides without the use of solvent and with short reaction time when compared to the literature, using mechanochemistry for the synthesis of maleamic acid from several anilines and maleic anhydride, and subsequent microwave heating to the cyclization of maleamic acid in the presence of acetic anhydride to produce maleimides. As limitations, *orto*-anisidine, *orto*-toluidine and 2,4,6-trichloroaniline did not afford corresponding maleimides. The synthetic scope is under investigation to aliphatic amines and amino acids.



Scheme 1 – Telescopic synthesis of *N*-aryl maleimides

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New Twin Schiff Bases of Eugenol by Bidirectional Reaction

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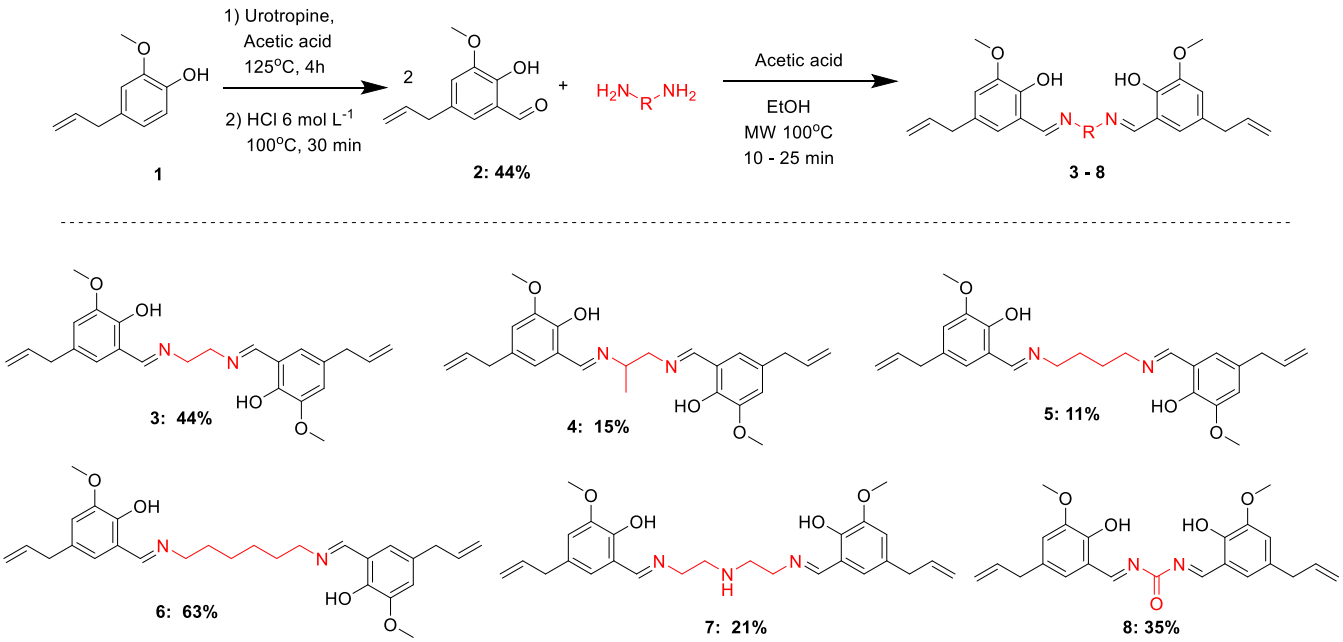
Keywords: *Eugenol, Schiff bases, Bidirectional, Bis-imines, Microwave.*

ABSTRACT

Eugenol **1** is a natural compound with biological properties such as anticoagulant, anti-inflammatory and analgesic.[1] Their Schiff bases have biological proprieties such as anti-inflammatory, anti-malarial.[2] Bidirectional reaction enables the synthesis of twin compounds. In this work, new bis-imines[3] **3-8** were synthesized with proposal to enhance biologic activity adding two eugenol molecules to further biologic study. Eugenol **1** has formylated by Duff reaction[1] affording the 5-allyl-2-hydroxy-3-metoxy-benzaldeyde **2** in 44% yield, which it was submitted of condensation with aliphatic diamines and urea **(Scheme 1)**, using microwave, ethanol as solvent in acid medium, producing bis-imines **3-8** with yield between 11-63%.



Scheme 1 – Bidirectional reaction of formilated eugenol **2** with aliphatic diamines and urea **3-8.**

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Tricomponent synthesis of *β*-enamino dicarbonyl compouds and telescopic synthesis of pyridopyrimidinone

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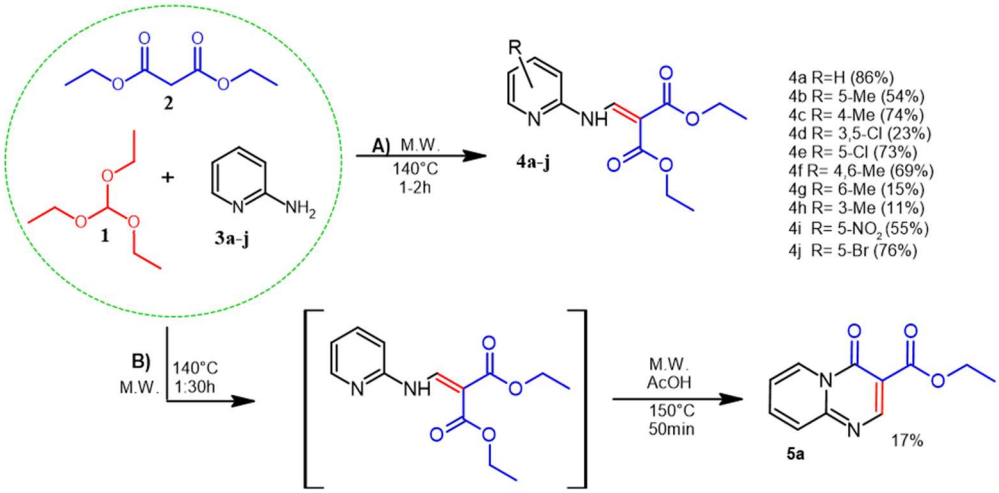
Keywords: *three-component synthesis; β-enaminodicarbonyls; pyridopyrimidinones; telescopic reaction.*

ABSTRACT

The use of multicomponent reactions, *one pot* and telescopic synthesis are desirable to the development of methodologies aiming to reach polyfunctionalized molecules in a more sustainable way.[1-3] Diethyl ethoxymethylene malonate (EMME) is an important electrophile for the synthesis of polyfunctionalized heterocycles, and can be used in different types of chemical transformations, being an attractive building block in the synthesis of dicarbonyl compounds.[5] In the present work, the reactivity of 2-aminopyridines with EMME was investigated. Thus, several *β*-enamino dicarbonyl compounds were prepared via a three-component reaction of 2-aminopyridines, diethyl malonate and triethyl orthoformate, an unprecedented condition for the synthesis of these molecules (Scheme 1A). Furthermore, pyrido-pyrimidinone could be accessed via telescopic synthesis under microwave heating (Scheme 1B).



Scheme 1 – (A) Tricomponent synthesis of β-enamino dicarbonyl **4a-j** and (B) Telescopic synthesis of pyridopyrimidinone **5a**

ACKNOWLEDGEMENTS

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Enaminones as a new amidation reagent for coumarin-3-carboxylic acids

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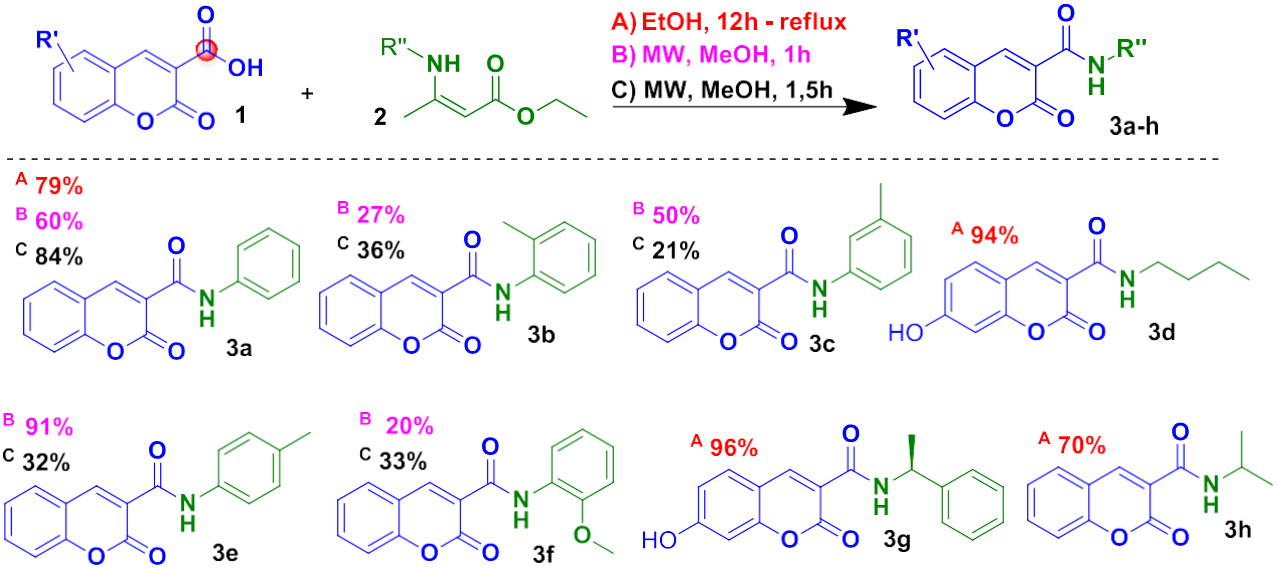
Keywords: *Amides, Enaminones, Coumarin-3-carboxylic acids*

ABSTRACT

The synthesis of amides has attracted attention in organic synthesis and biochemistry, because compounds containing amide bonds are important for medicine, agricultural chemicals and polymer materials[1]. In this way, several methods have been developed[2], most of them applying hard reaction conditions, and, most of them employing coupling reagent. Amides of 3-Carboxy-coumarins exhibit activities such as anticancer[3] and are fluorescent probes.[4] Therefore, 3-carboxy-coumarins can be employed as starting material to synthesizing new amides with improved properties.[5] Enaminones is a theme of ongoing interest because this class of compound is a versatile intermediate in organic synthesis.[6] In this work, we investigated the reactivity of 3- carboxy-coumarins **1** with enaminones **2**, and amides **3** were obtained under three conditions: A, B and C. Allproducts are solid compounds and were obtained adequately pure by simple filtration. Therefore, we developed a new methodology to the synthesis of amides from enaminones and 3-carboxy-coumarins with good yields without the use of traditional coupling reagents.



Scheme 1 – Synthesis of amides **3a-h** via three different conditions.

ACKNOWLEDGEMENTS

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Synthesis of new adenine and triazole derivatives with potential antibacterial activity

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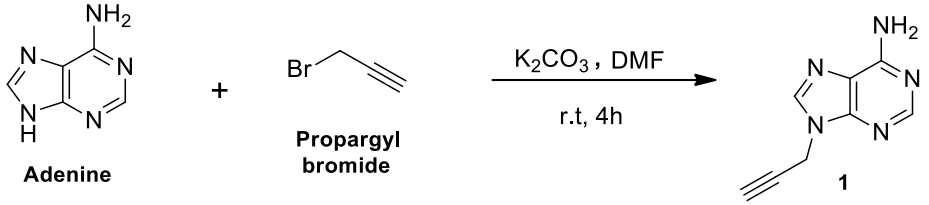
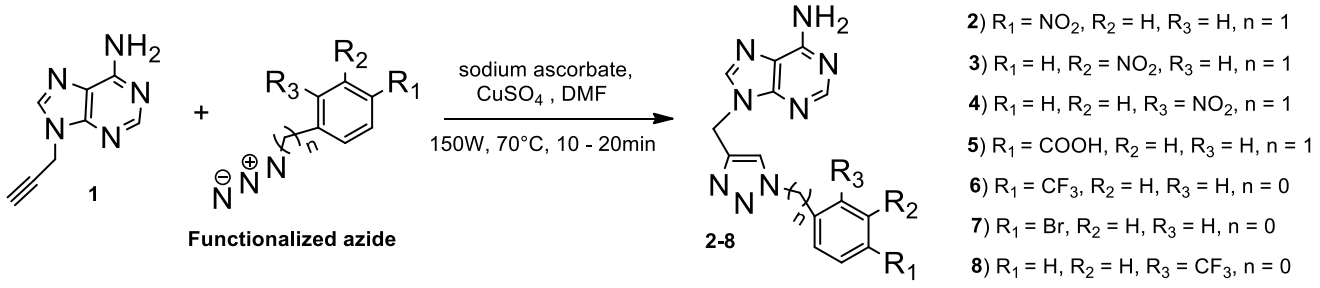
Keywords: *Heterocyclic. 1,3-dipolar cycloaddition. Staphylococcus epidermidis.*

ABSTRACT

New adenine derivatives were synthesized, characterized, and evaluated for their antibacterial activity against Gram-positive (*Staphylococcus aureus* and *Staphylococcus epidermidis)* and Gram-negative (*Escherichia coli)* bacteria. Initially, the alkynyl-adenine compound (**1**) was prepared via bimolecular nucleophilic substitution (S_N2), between adenine and propargyl bromide (Scheme 1).[1] The precursor (**1**) was reacted with several azides functionalized to give seven new adenine derivatives (**2**-**8**) containing the 1,2,3-triazole ring. The reactions were conducted by 1,3-dipolar cycloaddition of Huisgen, in the presence of Cu(I) as a catalyst under microwave irradiation (Scheme 2).[1,2,3] All the products were obtained with good yields (75% to 99%) and were characterized by NMR, Infrared spectroscopy, and mass spectrometry. Antimicrobial activity of the derivatives (**1**-**8**) was assessed by the disc diffusion and broth microdilution method. Derivatives **1** and **2** showed antimicrobial activity against *S. epidermidis* at a concentration of 200 µg/mL. None of the compounds was active against Gram-negative bacteria.



Scheme 1: Reaction conditions to obtain alkynyl-adenine derivative (**1**).



Scheme 2: Reaction conditions to obtain adenine and triazole derivatives (**2**-**8**).

ACKNOWLEDGEMENTS

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Visible-Light Mediated Carbamoylation of Nitrones via Continous Flow

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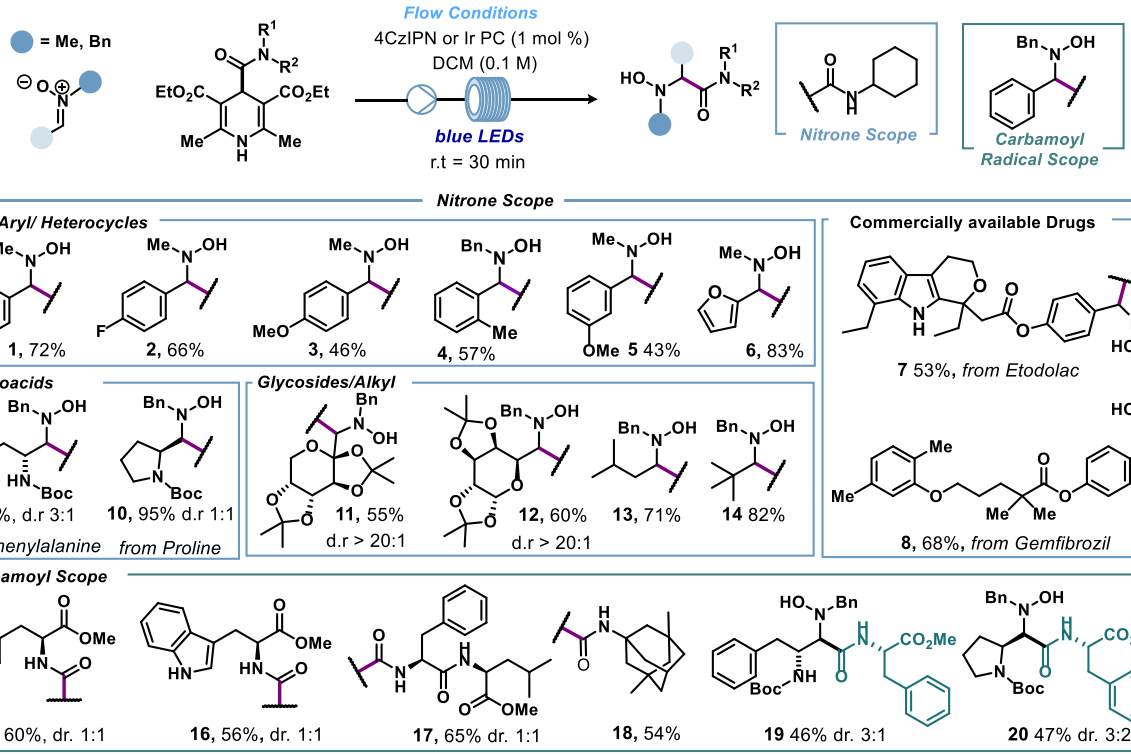
Keywords: *Photoredox Catalysis, Continuous Flow, Nitrones.*

ABSTRACT

Nitrones are important starting materials for the synthesis of biologically relevant nitrogen-containing scaffolds. Among established synthetic protocols, the selective addition of nucleophilic species to nitrones stands as a straightforward route for accessing *N,N*-disubstituted hydroxylamines. Although appealing, some of these strategies require harsh conditions that significantly hedge its applicability and functional group tolerance.[1] More recently, photoredox catalysis has emerged as an important trend in the context of amide preparation, given its milder reaction conditions and compatibility with a wide range of substrates.[2,3] Considering these aspects, we developed an efficient time-economical and easy-to-scale photocatalytic strategy for the amidation of nitrones using 1,4-dihydropyridines (DHPs) as carbamoyl radical sources under continuous flow regime. The optimized protocol showed better yields compared to batch conditions and allowed the preparation of a wide library of compounds comprising pharmaceutical active ingredients, amino acids, peptides, and glycosides, requiring only 30 minutes of residence time.



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Synthesis of 4-*O*-Propargyl-resveratrol as a Pharmacological Platform for Diversity-Oriented Synthesis

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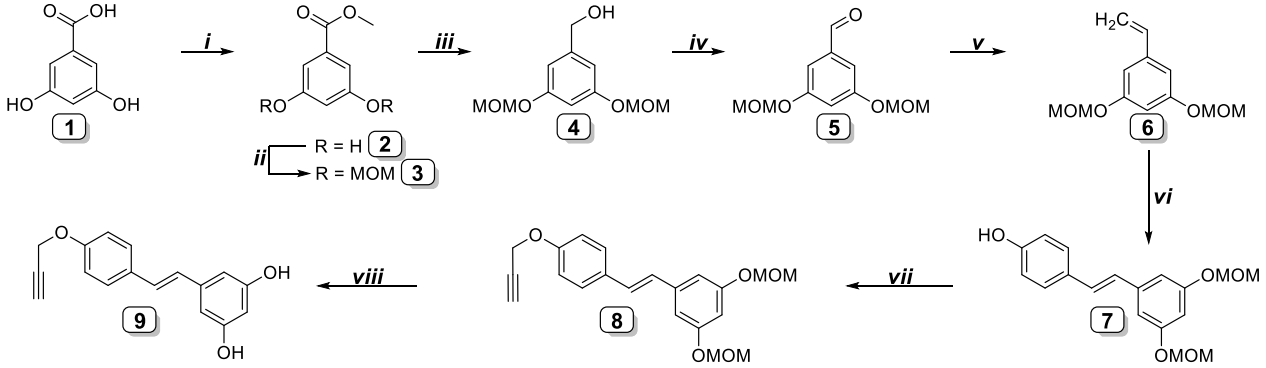
Keywords: *Resveratrol, total synthesis, diversity-oriented synthesis.*

ABSTRACT

Trans-resveratrol, a natural stilbenoid, displays a myriad of biological activities – from cardioprotector to metabolic modulators and neuroprotection[1]. Due to its low bioavailability, the *in vivo* effects are due to metabolites, mainly D-glucopyranouronates[2], such as the 3-*O*-*β*-D-glucuronate-4'-*O*-methyl derivative, credited for neuroprotection against Alzheimer's disease[3]. With this in mind, we proposed 4'-*O*-propargylated resveratrol as a bioisostere, with a possibility of further *in vivo* or preparative glycosylation at phenolic positions; annulations or *C*-*C* couplings at the alkyne – being a platform for diversity-oriented modifications. The synthesis started with low-cost *α*-resorcylic acid, **1**, followed by Fischer esterification, ***i***, and protection of phenolic OHs, ***ii***. Reduction of carboxylate group followed by partial reoxidation with subsequent Wittig olefination afforded the olefin, **6**, in 70% yield over 5 steps. The stilbenoid **7** was obtained through a Mizoroki-Heck coupling in 86% yield, with successive propargylation and deprotection of phenolic groups, affording the proposed 4'-*O*-propargyl-resveratrol in 30% overall yield (8 steps).



i) H_2SO_4, MeOH, reflux, overnight. 99%. ***ii)*** MOMCl, DIPEA, THF, r.t., 24h. 94%. ***iii)*** $LiAlH_4$, THF, r.t., 1h. >99%. ***iv)*** $[Cu(MeCN)_4]BF_4$ (5mol%), bipy (5mol%), NMI (10mol%), TEMPO (5mol%), air, r.t. 1h, 93%. ***v)*** Ph_3PMeI, K_2CO_3, 1,4-dioxane, reflux, 72h, 82%. ***vi)*** $Pd(OAc)_2$ (5mol%), AcONa, BTEAC, 4-iodophenol, DMF, 110°C, 3h, 86%. ***vii)*** K_2CO_3, propargyl bromide, MeCN, r.t., 22h, 73%. ***viii)*** HCl, MeOH, 60°C → r.t., 4h, 61%

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From Biomass to Biflavonoids: Synthetic Studies Towards Synthesis of Amentoflavone

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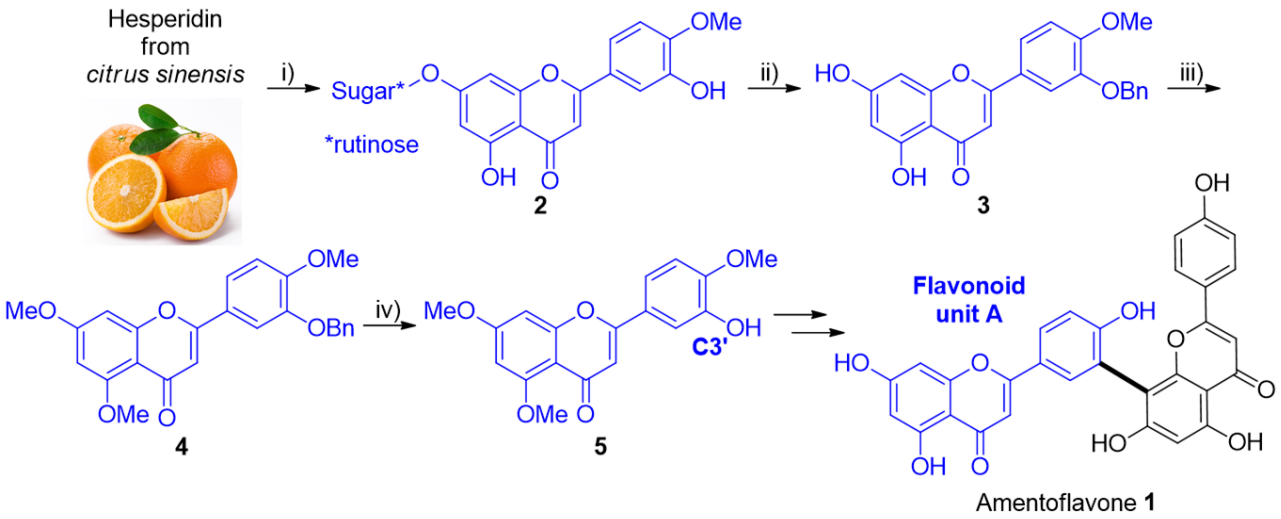
Keywords: *Total Synthesis, Amentoflavone, Biomass, Flavonoid*

ABSTRACT

Biflavonoids are natural products from class of polyphenols. The syntheses found in the literature are biomimetic, reported to initiate from hydroxylated acetophenone and a substituted benzaldehyde[1] by condensation, in a long and expensive route. Here we described synthetic studies to total synthesis of amentoflavone **1** from biomass. The biflavonoid is divided into flavonoid units A (from hesperidin) and B (from naringin). For the synthesis of part A (Scheme 1), hesperidin was extracted from albedo of *Citrus sinensis*[2]. The glycosylated flavone was oxidized to diosmin **2**, which suffered the following sequence of transformations: benzylation and sugar hydrolysis, methylation, and then debenzylation reaction. In this way was possible to obtain **5** with a 14% yield from hesperidin (5 steps). Following transformations will include triflate synthesis at C3' and coupling with a boronic flavonoid unit B by palladium C-C coupling, leading to a total synthesis of amentoflavone only from natural and renewable resources.



Conditions: i) I_2, pyridine, reflux, 74%; ii) BnCl, $KHCO_3$, DMF, then EtOH, H_2SO_4, reflux (52% over 2 steps); iii) MeI, K_2CO_3, DMF, 69%; iv) Ni-Raney, H_2, EtOH, 52%.

Scheme 1: Synthetic studies towards the total synthesis of amentoflavone from biomass

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Synthesis of functionalized cyclohexenones by formal [3+3] cycloaddition reaction of 3-carboxycoumarins and acyclic enaminones

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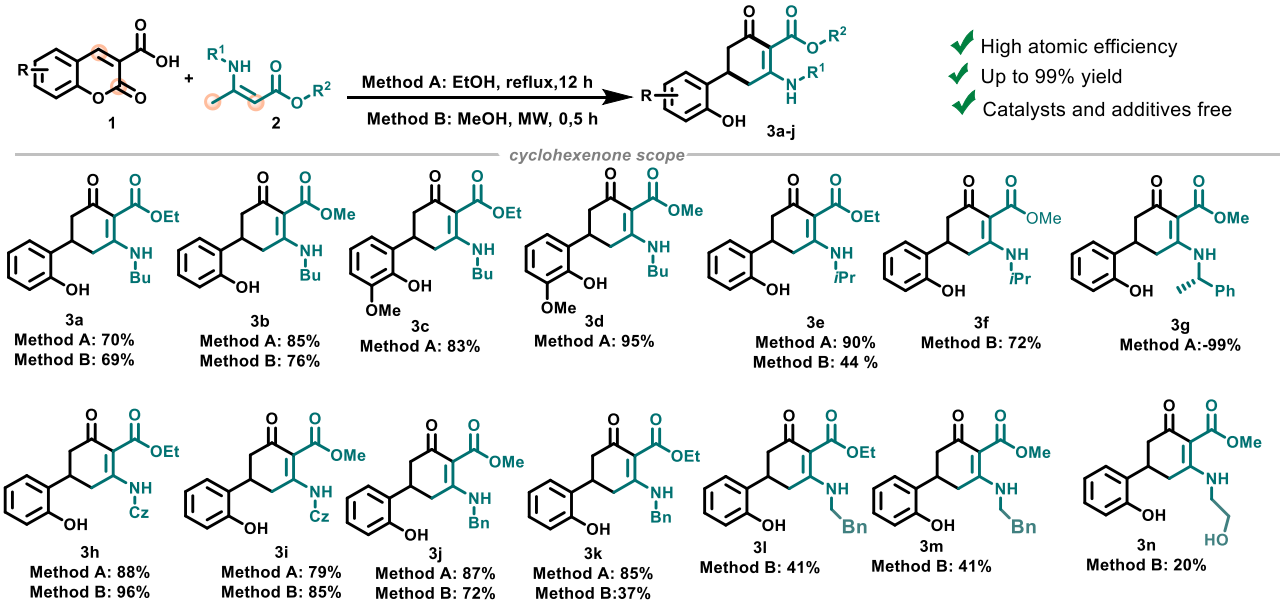
Keywords: *Cyclohexenone derivatives, enaminones, cycloaddition reaction.*

ABSTRACT

The cyclohexenone core is an attractive target for synthetic organic chemists due to its significance in current medicinal chemistry[1] and constitutes a substructural component of several natural compounds.[2] Traditionally, cyclohexenones are prepared using the well-known Robinson annulation, which combines a tandem process of Michael addition, intramolecular Aldol condensation, and dehydration within a one-pot operation.[3] However, these methods still have many disadvantages, such as excessive synthetic steps, the use of expensive catalysts, and difficulty in obtaining reaction substrates.[4] Here, we developed a direct synthesis of novel functionalized cyclohexanone derivatives via formal [3+3] cycloaddition reaction of coumarino-3-carboxylic acids and acyclic enaminones. Different substituent groups were tolerated forming desired product in good yields with high atomic economy (Scheme 1). The cyclohexanones are formed via Michael addition, followed by decarboxylation. Posteriorly, an intramolecular *C*-acylation occurs resulting in the opening of the coumarin ring with a subsequent proton shift. Therefore, we developed a simple, inexpensive, and regioselective synthesis of highly functionalized cyclohexanone derivatives.



Scheme 1. Synthesis of novel functionalized cyclohexanone derivatives.

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Regiosselective directing-group free C(2)-arylation of indoles through photocatalysis

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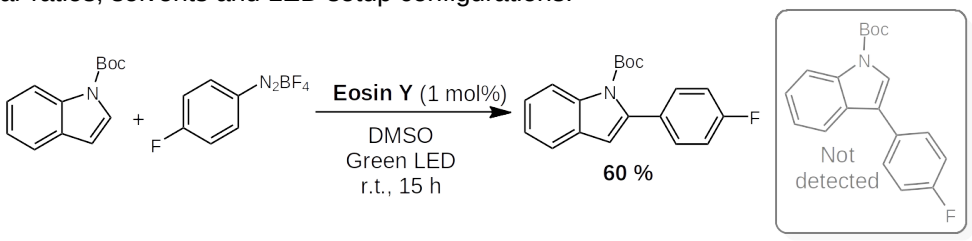
Keywords: *photocatalysis, indole, aryldiazonium salts.*

ABSTRACT

The indole motif is a versatile pharmacophore found in many biologically active substances and 2-arylindoles have been attracting attention of our group due to its promising activity against some cancer types.[1] The selective C(2)-arylation of an indole moiety is interesting for late stage modification. It is usually performed with precious metal catalysts and/or the use of directing groups or harsh conditions.[2] Regarding photocatalysis, two works report the arylation of indoles,[3-4] but none has attached much attention to the regiosselectivity.

In this work, we present a C(2)-selective arylation of indoles. We envisioned a model reaction between *N*-Boc-Indole, 4-fluorobenzenediazonium tetrafluorborate and Eosin Y as photocatalyst, and have tested it in different molar ratios, solvents and LED setup configurations.



Scheme 1: Model reaction

The optimized conditions provided the C(2)-arylated product in 60% yield. We are moving forward to an unprecedented evaluation of the effect of indole electronics in the regiosselectivity of this reaction.

ACKNOWLEDGEMENTS

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Palladium-Catalyzed Carbonylative Synthesis of Aryl Selenoesters Using Formic Acid as an Ex Situ CO Source

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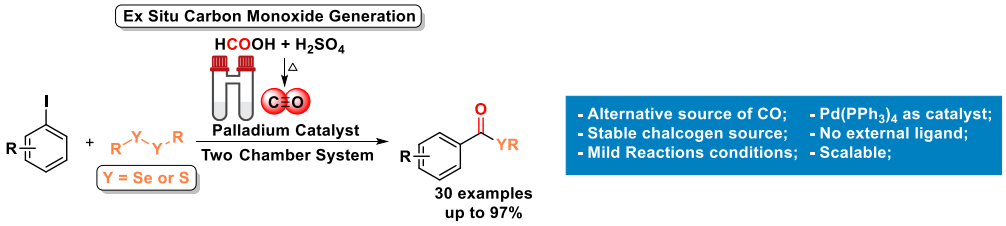
Keywords: *Selenoesters, carbonylation reactions, carbon monoxide, palladium.*

ABSTRACT

Selenoesters, play a significant role in synthetic organic chemistry, acting as important mild acyl-transfer agents in the synthesis of different compounds.[1] Consequently, significant effort has been devoted to the development of more efficient protocols for the synthesis of selenoesters.[2] Furthermore, the aryl selenoesters have gained even more importance after the development of an alternative chemoselective diselenide−selenoester ligation technique for chemical protein synthesis.[3] The nucleophilic acyl substitution of acyl chlorides with a nucleophilic selenium source is the simplest strategy and by far the most explored protocol.[4] Nevertheless, this strategy encounters unavoidable drawbacks, such as the need to use environmentally dangerous reagents for the preparation of acyl halides, their low chemical stability and harsh conditions for the selenylating reagent, use of strong bases, and strong moisture-sensitive reducing agents. On the other hand, carbonylation reactions have become an important synthetic tool for the insertion of the carbonyl group into organic molecules.[5] Despite the current relevance of carbonylation reactions, limited examples concerning the use of carbon monoxide as a building block for the synthesis of selenoesters can be found in the literature. In this context, a new catalytic protocol for the synthesis of selenoesters from aryl iodides and diaryl diselenides has been developed, where formic acid was employed as an efficient, low-cost, and safe substitute for toxic and gaseous CO (Scheme 1). This protocol presents a high functional group tolerance, providing access to a large family of selenoesters in high yields (up to 97%) while operating under mild reaction conditions, and avoids the use of selenol which is difficult to manipulate, easily oxidizes, and has a bad odor. Additionally, this method can be efficiently extended to the synthesis of thioesters with moderate-to-excellent yields, by employing for the first time diorganyl disulfides as precursors.[6]



Scheme 1.

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Diastereoselective Passerini reactions using Cyrene

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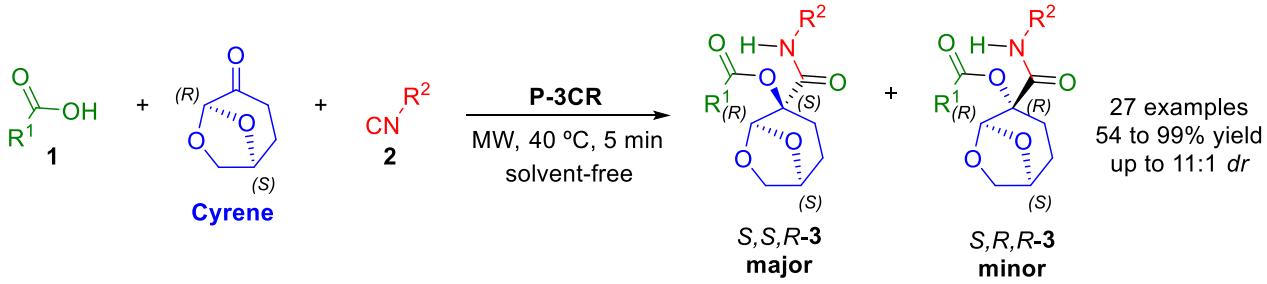
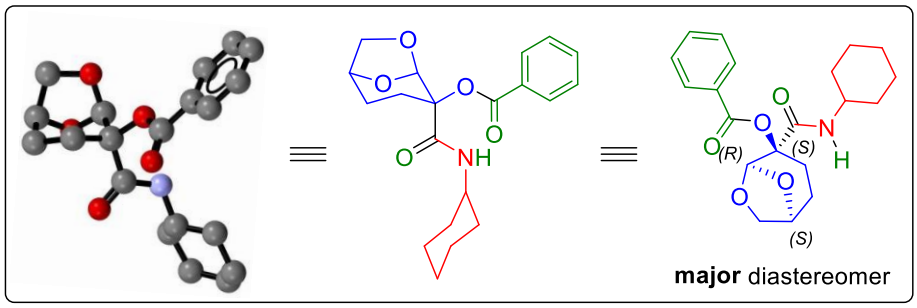
Keywords: *Cyrene, microwave, Passerini reaction.*

ABSTRACT

Cyrene is a bio-based material made from a renewable resource (cellulose waste)[1,2] and has been used as an alternative green and sustainable polar aprotic solvent for organic reactions in place of toxic DMSO, DMF, DMA and NMP.[3,4] Herein we describe its use as a sustainable source of carbonyl group in the Passerini three-component reaction (P-3CR) with a variety of carboxylic acids and isocyanides yielding new acyloxyamide derivatives in solvent-free conditions under microwave heating. The exceptionally high reactivity of the carbonyl group of cyrene allowed a fast reaction rate (control experiments showed that it is more reactive than common aldehydes like benzaldehyde and even paraformaldehyde). This catalyst- and additive-free method provided high product yields (up to 99%) with diastereoselectivities ranging from 2:1 to 11:1. The stereochemistry of the major diastereomer was confirmed by X-ray analysis of one of the products. Theoretical calculations are being carried out to explain these results.





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A new method for the preparation of *N*-alkyl-1-phenyl-1*H*-tetrazole-5-amines using trichloroisocyanuric acid

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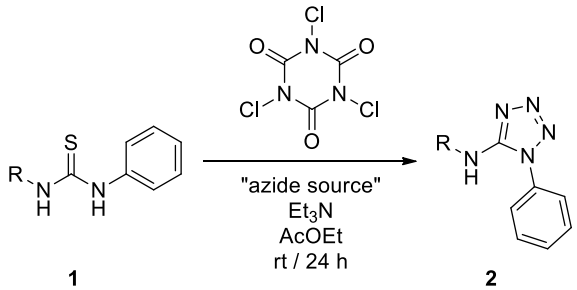
Keywords: *Trihaloisocyanuric acids, tetrazoles, azide.*

ABSTRACT

A new and efficient methodology for the synthesis of *N*-alkyl-1-phenyl-1*H*-tetrazole-5-amines **2** was developed by the reaction of different alkyl-phenyl thioureas **1** with trichloroisocyanuric acid, trimethylsilyl azide and triethylamine in ethyl acetate. These tetrazoles were initially obtained in low to moderate yields (22-57 %) by a previous optimized methodology with sodium azide and some results were improved changing the azide source to trimethylsilyl azide (37-64 %). Although the yields were not as expected when compared to literature[1], trichloroisocyanuric acid proved to be an efficient, not toxic and safe source for the oxidative desulfurization of thioureas to obtain this important class of heterocycles using a green solvent.



1 **2**

Product	R	Azide source	Yield (%)
2a	iPr	NaN_3	57
		$TMSN_3$	37
2b	Bu	NaN_3	34
		$TMSN_3$	64
2c	Cy	NaN_3	35
		$TMSN_3$	37
2d	Bn	NaN_3	22
		$TMSN_3$	49

ACKNOWLEDGEMENTS

The authors thank IQ-UFRJ and CNPq.

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Application of *Click Chemistry*, via CuAAC reaction, in the synthesis of 1,3-bis(1,4-disubstituted-1,2,3-bistriazole)-propanones

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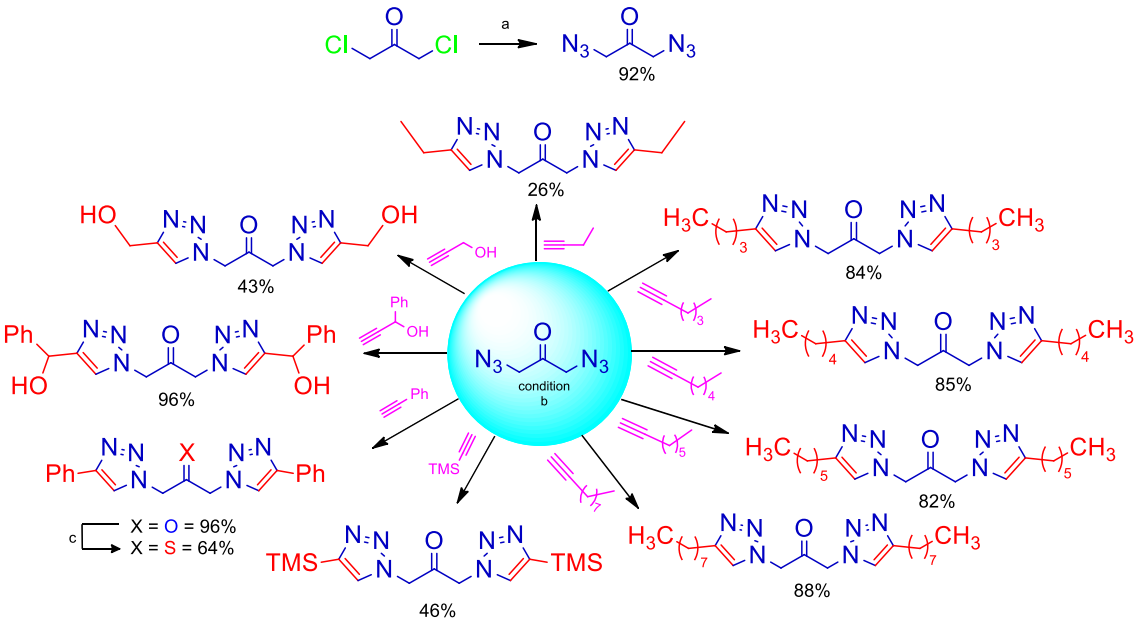
Keywords: *click chemistry, bistriazoles, CuAAC reaction*

ABSTRACT

The application of *Click Chemistry*, via 1,3-dipolar cycloaddition between a terminal alkyne and an organic azide catalyzed by copper Cu(I), is of great importance in Organic Synthesis. This methodology allows the synthesis of 1,4-disubstituted-1,2,3-bistriazoles with high selectivity, purity and with good yields. This work addresses the synthesis of 1,3-bis(1,4-disubstituted-1,2,3-bistriazole)-propanones, not yet described in the literature,[1] containing alkyl, aryl, and hydroxylated substituents. Our synthesis started with 1,3-diazido-propanone, obtained from 1,3-dichloroacetone in 92% yield, which was used in the *CuAAC* reaction providing keto-bistriazole products (ranging 26-95% yield), by the use of $Cu(OAc)_2$ as a source of copper in the presence of sodium ascorbate.[2] To expand our investigation, the phenyl derivative was successfully transformed to the sulfur derivative (64% yield), using the Lawesson reagent, expanding a class of heterocyclic compounds synthesized with great interest for materials and medicinal chemistry.



Conditions: a) $ClCH_2(C=O)CH_2Cl$, NaN_3 (3 eq.), acetone, rt, 15 h; b) alkyne (2.5 eq.), $Cu(OAc)_2$/NaAsc (1:2), *t*-BuOH/H_2O (1:1), rt, 15 h; c) bistriazole (1 eq.), Lawesson reagent (1.5 eq.), toluene, reflux, 48 h.

Scheme 1: Synthesis of 1,4-disubstituted-1,2,3-bistriazoles via *CuAAC*.

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One-pot synthesis of benzoxazines using fluorinated anilines

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Keywords: *Benzoxazine, one-pot reaction, cascade reaction.*

ABSTRACT

3,4-dihydro-1,4-benzoxazines are common scaffolds in many biologically active and medicinally significant compounds.[1,2] There are several procedures described in the literature to synthesize this moiety of molecules using halogen containing starting materials, however it is not common to synthesize them using one-pot reactions in the absence of metal catalyst.[3,4] In the present work, we present a one-pot procedure starting from fluorinated anilines and cyclohexene oxide to obtain the benzoxazine ring, illustrated with a number of examples, with yields up to 50%. These results are promising and show great potential as a new synthetic route for benzoxazines.

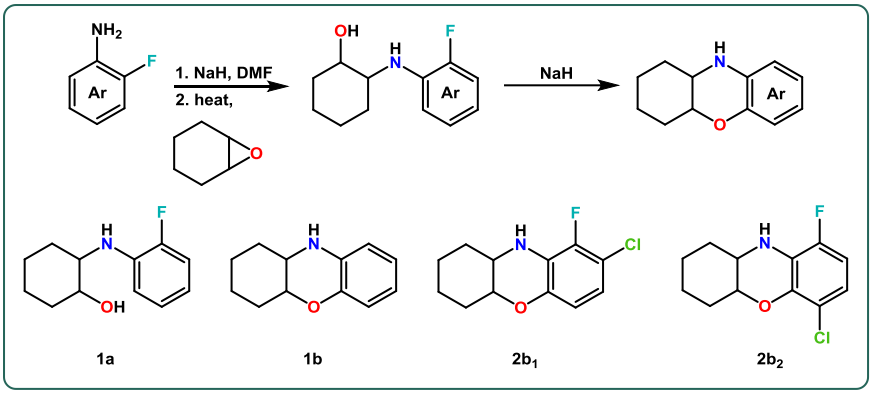

Figure 1. Synthesis of benzoxazines scaffolds using fluoro-anilines as starting materials.

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Rh(III) catalyzed C-H activation at the C-2 position of indoles with nitroolefins

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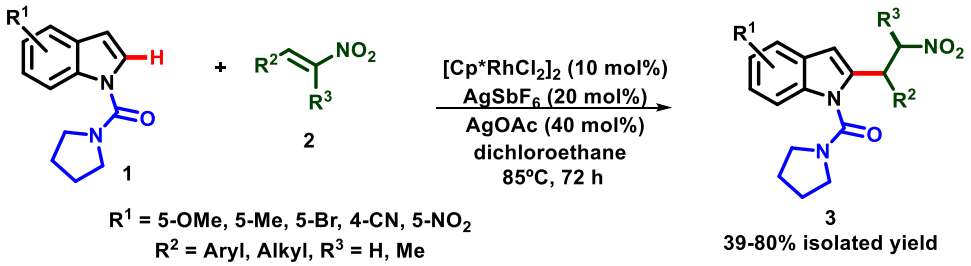
Keywords: *indole, C-H activation, nitroolefins, homogeneous catalysis*

ABSTRACT

Indole derivatives have several biological activities, such as antiviral, anti-inflammatory, and anticholinesterase.[1] As a result, the investigation of new methods of synthesis/functionalization of this ring has attracted the attention of the chemical community.[2] C-H activation is an efficient synthetic process, whose mechanism, in general, involves the cleavage of the C-H bond and the formation of a C-Metal bond coordinated by directing groups, resulting in a process of cyclometalation followed by insertion of the functional group.[3] Here, we describe the synthesis of novel indole derivatives using nitroolefins via Rh(III)-catalyzed C-H activation. To obtain the desired product 3, several reaction conditions were explored. When $[Cp^*RhCl_2]_2$ and $AgSbF_6$ were employed,[4] compound 3 was obtained in moderate yield. After screening for different parameters, compound 3 was obtained in 80% yield. With the optimized condition established, we started the scope and limitation study, and 18 indole derivatives were synthesized with yields between 39 and 80%.



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DABCO-promoted photocatalytic C-H functionalization of aldehydes

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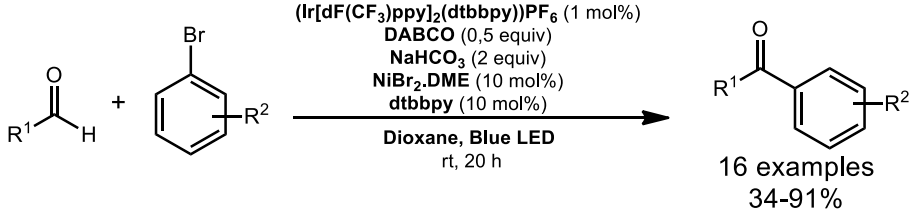
Keywords: *photocatalysis, indirect HAT, arylketones.*

ABSTRACT

The development of photocatalysis allowed several methodologies for mild C-H funciontalization, the Hydrogen Atom Transfer (HAT) strategies being the most used and attractive ones.[1] In the indirect HAT, the abstractor, once activated by a photocatalyst, can promote a selective cleavage of C-H bonds, Quinuclidine and analogues being the most explored nitrogenated structures for this purpose.[2]

This work presents the first application of DABCO as HAT abstractor in a photocatalytic strategy for aldehyde C-H activation. We achieved several aryl ketones in good yields through the nickel-catalyzed cross coupling of aryl bromides and the radicals generated in the HAT step. We also performed computational calculations and determined that the HAT step between aldehydes and DABCO is a mildly endergonic but sufficiently fast step.



Scheme 1: Synthesis of arylketones from C-H funciontalization of aldehydes

After our publication,[3] other DABCO-related structure was reported as HAT catalyst for C-H substrate activation,[4] proving to be an interesting tunable catalyst.

ACKNOWLEDGEMENTS

The authors thanks CAPES and FAPERJ for financial support.

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Continuous-flow synthesis of amphetamines towards the certified reference materials production

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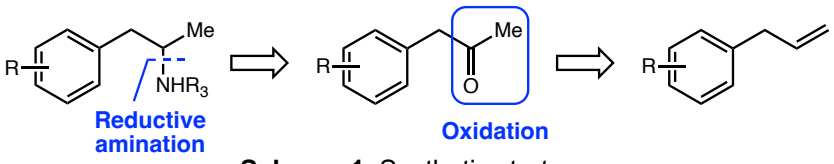
Keywords: *amphetamines, Wacker-Tsuji oxidation, ozonolysis, reductive amination*

ABSTRACT

Amphetamines are substances of synthetic origin that have CNS stimulant and are widely commercialized as illegal drugs. The identification of drugs in seized samples is performed by comparing chromatographic and MS analyses with certified reference materials. Herein we intend to develop an efficient synthetic strategy for this class of compounds aiming at the production of CRM.
The synthetic strategy consists of reductive amination of the appropriate ketones obtained by oxidation of the corresponding olefins.



Scheme 1. Synthetic strategy

We have studied this route under batch and continuous flow conditions for large-scale production. The oxidation of olefins providing the corresponding ketones in 50% yield for the best condition. Since the purifications of this product were very laborious and we could not reach higher yields, another strategy to prepare the ketones is under investigation.[1,2] The reductive amination led to desired amines in excellent yields under batch and flow conditions, reaching a very short time in flow.[3]

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Intramolecular Pd-catalyzed cross-coupling reaction for the synthesis of cyclic sulfoxonium ylides and their application in C-H functionalization of indoles

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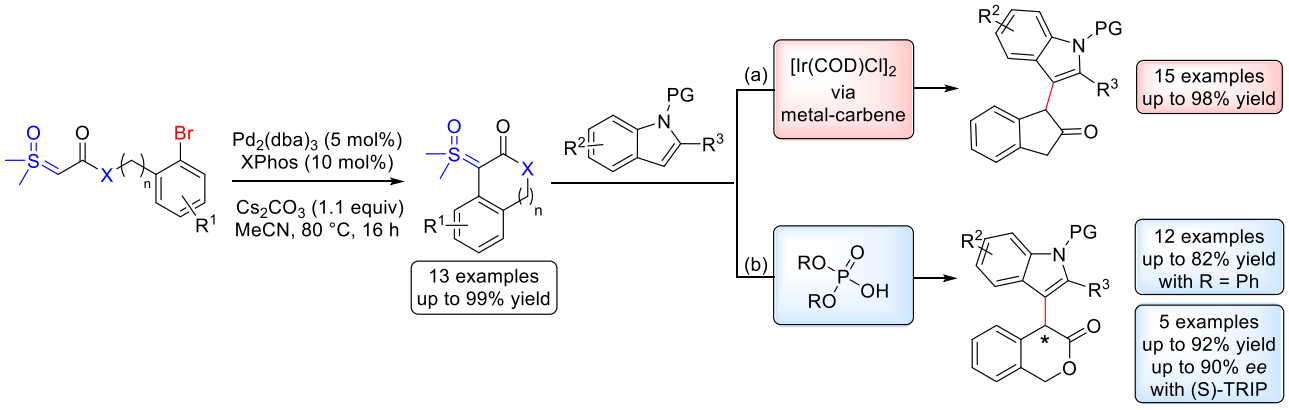
Keywords: *sulfoxonium ylides, C-H functionalization, asymmetric transformation, metal-carbene, organocatalysis*

ABSTRACT

In recent years, the versatility of sulfoxonium ylides in organic synthesis has been widely explored in numerous chemical transformations, going far beyond the classical Corey-Chaykovsky reactions usually associated with sulfur ylides. Their highly desirable structure features and inherent properties, such as the thermal stability, low toxicity, ease of use and long shelf life, have made these compounds suitable for large scale reactions and very attractive to be applied in industrial processes.[1] As a consequence, the disclosure of efficient protocols to achieve new sulfoxonium ylides has also become a very active topic of investigation and, with these new structures accessible, some authentic applications have emerged in the literature.[2] Specifically, asymmetric transformations from α-carbonyl sulfoxonium ylides for X-H insertions and C-H functionalization reactions have been carried out with high enantioselectivity using organocatalysts and metal complexes.[3]

In this work, we present an intramolecular version of Pd-catalyzed cross-coupling reaction to synthesize cyclic α-carbonyl-α-aryl sulfoxonium ylides. The applicability of these new compounds was demonstrated in C-H functionalization of indoles by two different methodologies; a) formation of iridium-carbene complex intermediate; b) organocatalyzed protonation by phosphoric acid. We also demonstrated that under the influence of an asymmetric phosphoric acid the reaction provides good levels of enantiocontrol in up to 90% *ee.*



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Chiral precursors for intermolecular Diels-Alder reactions.

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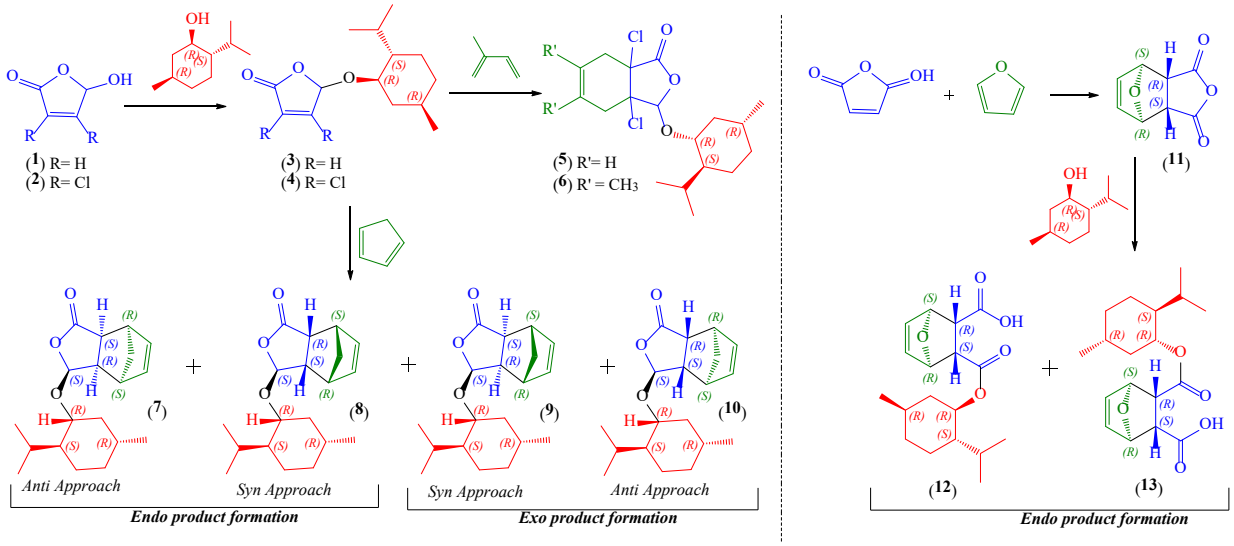
Keywords: *Diels-Alder, furan-2(5H)-one, maleic anhydride, menthol, mucochloric acid*

ABSTRACT

Menthol is a terpene alcohol widely used to obtain ethers and esters because it has three chiral centers and four stereoisomers with different biological properties.[1–4] Chiral precursors for the intermolecular Diels-Alder reaction using furan, isoprene and cyclopentadiene as dienes have been prepared by enantioselective addition of menthol to 5-hydroxyfuran-2(5*H*)-one (**1**) and mucochloric acid (**2**). Addition of menthol to (3aR,4S,7R,7aS)-3a,4,7,7a-tetrahydro-4,7-epoxyisobenzofuran-1,3-dione (**11**) was performed and two diastereoselective products were isolated (**12**-**13**). Reaction of compound (**3**) with cyclopentadiene provided four diasteroisomers (**7**-**10**) which were separated by column chromatography. Compounds (**7**-**10**) were characterized by the spectrometric methods assisted by theoretical calculations. Reaction of compound (**4**) with isoprene provided two stereoisomers which were separated by column chromatography.



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Copper-catalysed one-pot hydroboration/azidation/cycloaddition reaction of alkynes

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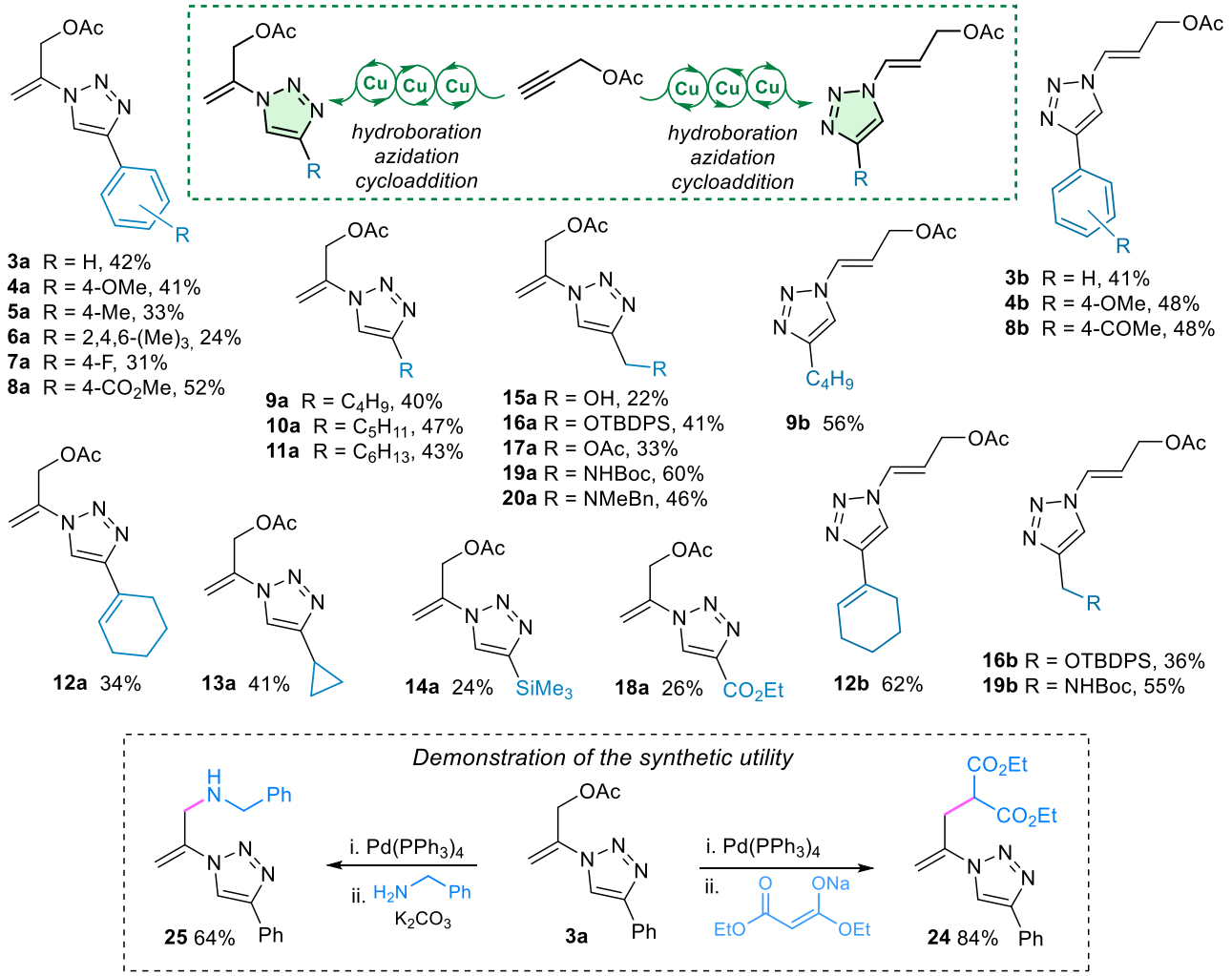
Keywords: *Copper catalysis, alkynes, vinyl triazoles.*

ABSTRACT

Herein we report our study on the development of a catalytic one-pot process, regioselective, environmentally friendly, and operationally simple method to explore the reactivity of functionalized propargylic alkynes through a series of three copper-catalysed reactions in a single reaction vessel. The sequence consisted in a hydroboration, azidation, and 1,3-dipolar cycloaddition and led to the regioselective formation of vinyl 1,2,3-triazoles in good yields (yields reported for the 3 steps).



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Knoevenagel reaction: reactional profile monitored by NMR spectroscopy

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Keywords: *Knoevenagel, kinetic, NMR.*

ABSTRACT

The Knoevenagel reaction is a condensation between methylene and carbonyl compounds in the presence of a catalyst (usually an amine), forming tri- or tetra-substituted alkenes.[1,2] This work aims to study the effect of the catalyst on the reaction mechanism by NMR, using 4-nitrobenzaldehyde, 4-methoxybenzaldehyde or benzaldehyde as carbonyl compound, dimethyl malonate as methylene compound, and piperidine or triethylamine as catalyst. The experimental data show that the reaction occurs when piperidine was used for all carbonyl compounds. However, the reaction doesn't occur when triethylamine was used (Figure 1). According to pKa values,[3] the amines used aren't strong enough to form the enolate anion, suggesting that the formation of the iminium intermediate is responsible for the reactivity observed in the case of piperidine and the absence of any reaction in the case of triethylamine, suggesting that the amine acts only as nucleophile, instead of dual action (as base and nucleophile) as suggested.[2]

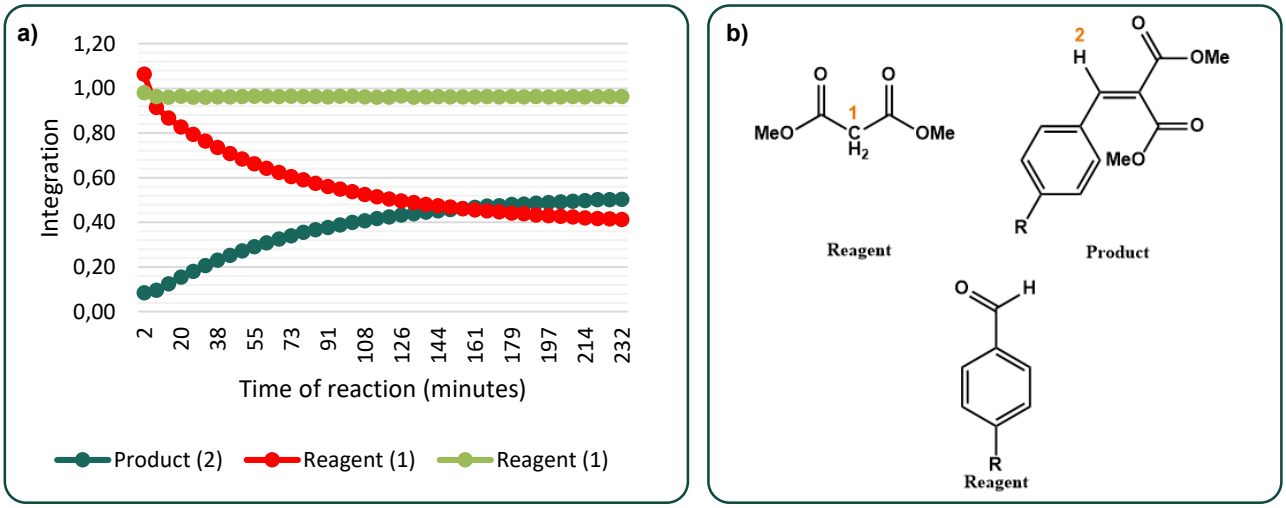

Figure 1. a) Kinetic profile of reactions performed in CD_3CN at 45ºC, using piperidine (red and dark green) or trimethylamine (light green), both with benzaldehyde and dimethyl malonate. **b)** Reagents and product structures.

ACKNOWLEDGEMENTS

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Copper-catalyzed cycloaddition for the synthesis of Imidazo[1,2-α] pyridine-based hybrids

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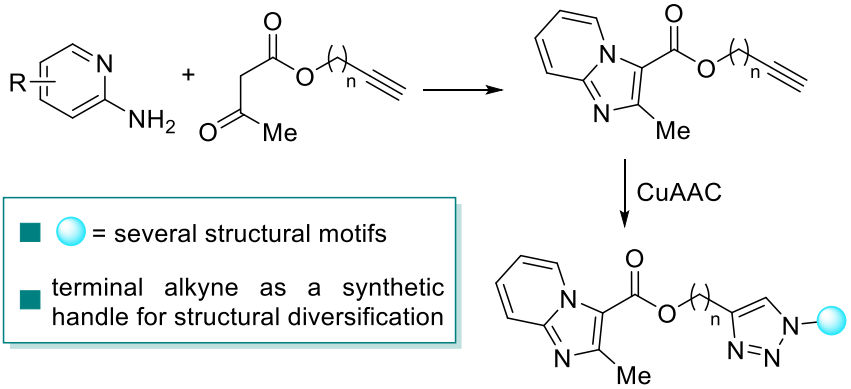
Keywords: *Imidazo[1,2-a]pyridine hybrids, CuAAC, Natural product derivatization.*

ABSTRACT



Imidazo[1,2-α]pyridines are well known for their usage as pharmaceuticals, such as zolpidem, or alpidem.[1] There are several ways to synthesize this motif.[2] However, the scope variation is restricted to the moiety connected to the amino pyiridine ring or at the C2 position of the imidazole core. For this reason, we aimed to expand the versatility of this substrate by attaching a terminal alkyne to the molecule via a keto ester cycloaddition. Thus, we report the connection between imidazo[1,2- α]pyridines with several biologically relevant molecules. The strategy used to build these connections was based on copper-catalyzed cycloaddition, where different azides and imidazo[1,2- α]pyridine core bearing an alkyne were used in this transformation. In total, 8 imidazo[1,2- α]pyridines bearing a terminal alkyne could be synthesized, thus, allowing for the synthesis of 27 new hybrid molecules connected by a triazole ring. In addition 17 imidazo[1,2- α]pyridines connected to either carbohydrate or natural originated molecules were also prepared.

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To the funding agencies CAPES, CNPq. To UFRGS, PPGQ and LAMOCA.

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Thermal O-H Insertions of Phosphates into Aryldiazoacetates Followed by Substitution Reactions with Arenes: a Formal Metal-Free C-H Insertion Strategy Leading to α,α-Diaryl Esters

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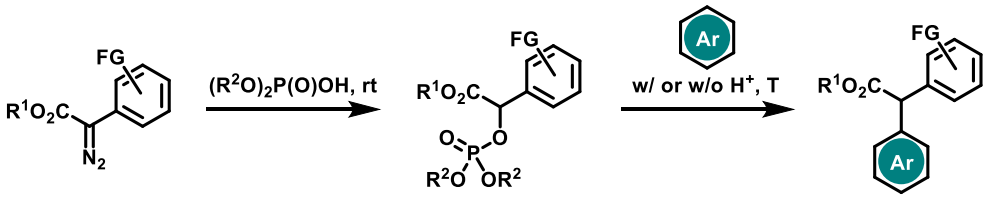
Keywords: *Diazo Compound, Phosphate, O-H insertion, Nucleophilic Substitution.*

ABSTRACT

Insertion reactions involving diazo compounds have been extensively explored in past years. Several important advances have been achieved in pure metal-catalyzed, thermally-promoted,[1] and pure visible light-mediated transformations.[2]

Due to our interest in this field,[3] we decided to study O-H insertions of phosphates into aryldiazoacetates and synthetic applications of the obtained phosphonates. Arenes were found to successfully displace the phosphate moiety, as leaving group, within the intermediate phosphonates containing a *para*-substituted electron-donor group at the aryl ring in a spontaneous fashion, while non-activated intermediates could only undergo the reaction by the additional activation of the leaving group with a Brønsted acid.

The reaction sequence in this work demonstrates that phosphates can be inserted into aryldiazoacetates without any promoter; and can be used as viable leaving groups in substitution reactions with arenes. This approach is complementary to other previous strategies; and represents a formal metal-free C-H insertion strategy of arenes into aryldiazoacetates.[4]



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Facile synthesis of highly fluorescent BORANIL dyes in solution and solid-state

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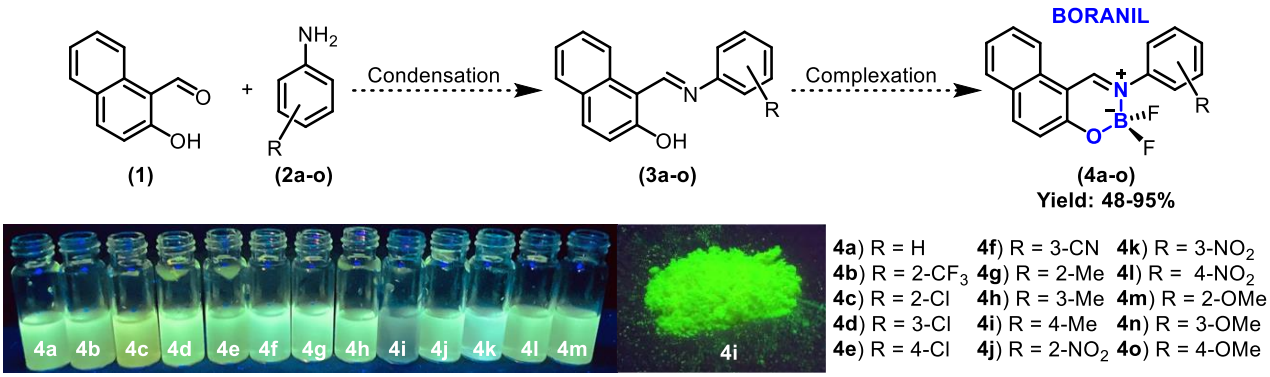
Keywords: *BORANIL, fluorophores, Organic fluorescent dyes.*

ABSTRACT

Organic fluorescent dyes are high potential materials as they have a wide application in several fields, covering organic light-emitting diodes (OLED), such as dye-based solar cells (DSSC), chemosensors, bioimaging, lasers and medicinal and pharmacies.[1] The luminescent compounds formed by Boron complexes have obtained an interesting attention over the last few years due to their promising properties such as near infrared emission (NIR), fluorescent quantum yields and large absorption coefficients.[2-4]

The synthesis of the new BORANIL fluorophores **4a-o** we initially obtain the imine intermediate **3a-o**, from the condensation reaction of 2-hydroxy-1-naphthaldehyde **1** with substituted aromatic amines **2a-o**. Subsequently, the imine intermediate **3a-o** were complexed with $BF_3.OEt_2$ (*Scheme 1*). The compounds **4a-o** were obtained 48-95% yields after chromatographic column and confirmed by IR and NMR analysis. All the compounds showed vivid emission colors in the solid state. The luminescence of the compounds in solution and in the solid state will be studied.



Scheme 1: Synthesis for obtaining the new fluorophores BORANIL (**4a-o**). Compounds under the UV lamp (365 nm) in acetonitrile solution.

ACKNOWLEDGEMENTS

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Difluoroacetylation and Difluoroamidation of Tryptophan-Containing Peptides Through Photocatalysis

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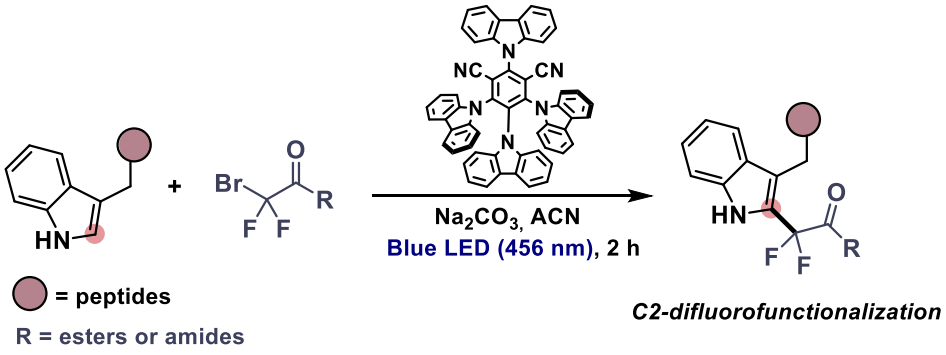
Keywords: *α-gemdifluoro radicals, Tryptophan, Peptides, Photocatalysis*

ABSTRACT

Modifications on tryptophan (Trp) residues became an attractive alternative to peptide or protein functionalization due to its unique reactivity and low abundance in living system which enables chemoselective transformations.[1] The Trp core were frequently functionalized through polar reactions[2] and recently, photocatalytic selective C-H functionalization of Trp have also been reported.[3] In view of the unique proprieties and applications of fluorine-containing scaffolds in medicinal and agrochemistry, Chen's,[4] Chiang's[5] and Beier's[6] groups developed, independently, the insertion of fluoroalkyl or perfluoroalkyl radicals to the indole ring of Trp. Inspired by these previous works and viewing the relevance of fluorine-containing compounds, we herein present an alternative protocol for the insert α-gemdifluoro radicals - generated through the reduction of bromodifluoroacetates and bromodifluoroamides - to Trp-containing peptides. These radicals were coupled with different peptides and a wide range of fluorinated compounds could be obtained. So far, some experimental evidences point to a reductive quenching followed by a radical-radical coupling between oxidized Trp and α-gemdifluoro radicals.



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Synthesis of new bioactive hydroxycoumarin derivatives

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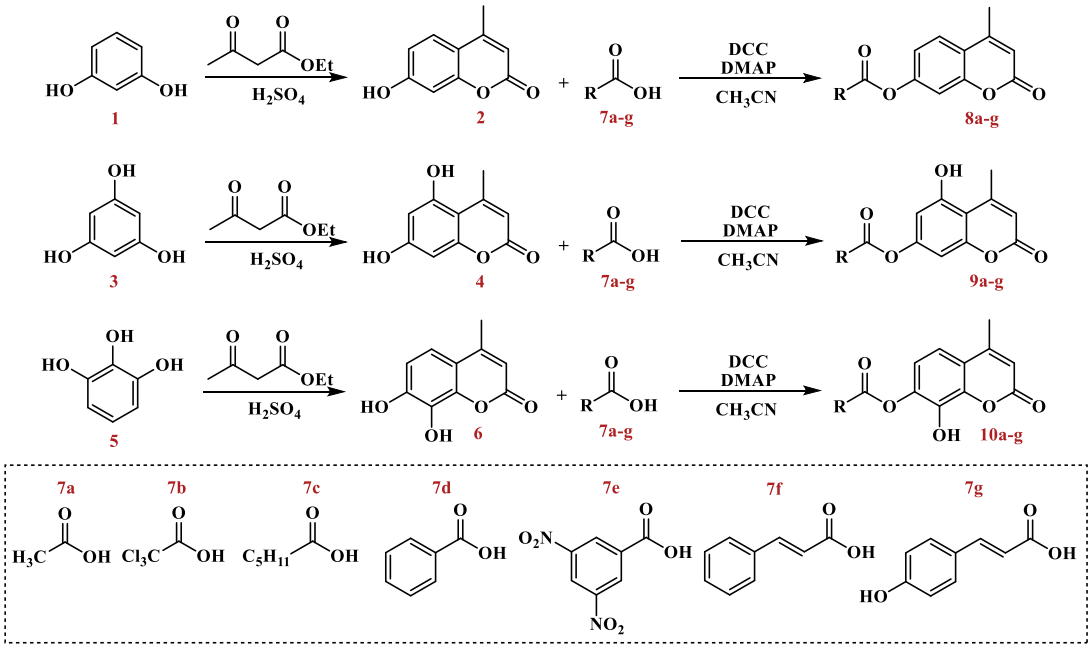
Keywords: *Coumarin, AChE inhibition, O-H functionalization.*

ABSTRACT

Coumarins are an important class of natural products widespread in different plant families' roots, flowers, and fruits. They also have already been biosynthesized by some fungi and bacteria species. As specialized metabolites, coumarin derivatives deserve great interest because various biological activities are attributed to them. Herein, we present the synthesis of new coumarins esters (**8a-g, 9a-g,** and **10a-g**) as potential antioxidants and inhibitors of acetylcholinesterase enzyme (AChE). The building blocks are the hydroxycoumarins **2**, **4,** and **6**, which were synthesized with high yields (77-82%) from simple-structured phenols (**1**, **3,** and **5**) through Pechmann reactions. The ester derivatives were accessed by Steglich esterification of **2**, **4,** and **6**, changing the carboxylic acids (**7a-g**). The products were obtained with moderate to good yields (14-84%). All final products (**8a-g, 9a-g, and 10a-g**) were characterized through spectrometric techniques and evaluated as AChE inhibitors, with promising results.



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UFBA Universidade Federal da Bahia

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Synthetic studies on Stemona alkaloids. Construction of the tricyclic frameworks of Tuberostemospiroline, Stemo-lactam R and Stemoamide

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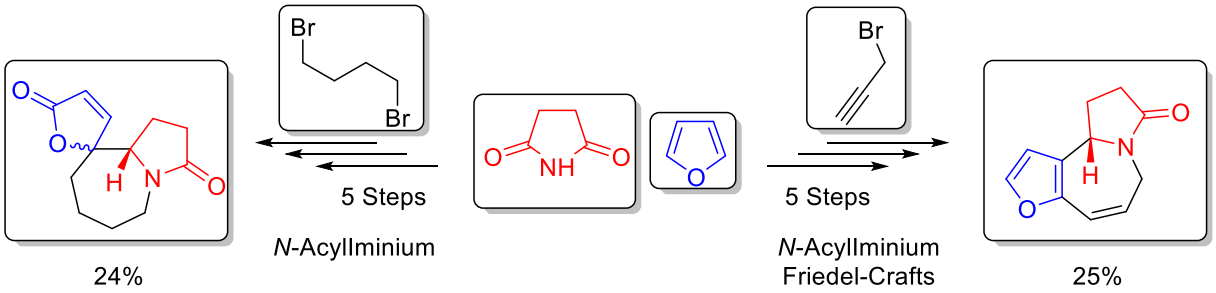
Keywords: *Stemona Alkaloids; Stemoamide; Tuberostemospiroline; Stemo-lactam R; N-Acyliminium Ion*

ABSTRACT

The tricyclic cores present in the Stemona alkaloids tuberostemospiroline, stemo-lactam R and stemoamide were formed in 5 steps each. A cationic cyclization was used as a key step, an intramolecular reaction between furan derivatives and *N*-acyliminium ions. For the stemoamide core (right) an intramolecular Friedel-Crafts alkylation of a furan was made possible in the presence of a *Z* double bond tethered to a precursor of a *N*-acyliminium ion. For the tuberostemospiroline and stemo-lactam R (left), the cyclization was performed in the presence of a bromo substituted furan.



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Direct electrophilic fluorination of amino acids and proteins

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Keywords: *fluorination, amino acids, proteins.*

ABSTRACT

Fluorine is an interesting nucleus for labeling biological systems since it is not naturally present in biomolecules and is easily traced in NMR experiments. Although synthetic fluorine-containing amino acids have already found applications in structural and dynamic studies of biomolecules, their preparation involves multi-step routes and low-yield reactions. Despite its applicability, direct fluorination of wild-type proteins has never been reported. This work presents studies on the fluorination of amino acids under mild conditions of biocompatibility and its application in the direct fluorination of specific residues in proteins. Preliminary results showed that L-tyrosine is fluorinated under electrophilic fluorination conditions in a buffered medium (pH = 7), while L-phenylalanine remains unreacted. Cyanovirin and GB1 are proteins with three and four tyrosine residues, respectively, and furnished very promising results under the same conditions of the amino acids. Selectivity and kinetic NMR studies of fluorination reactions are ongoing.

Scheme 1. 3D structure of GB1 (left) and Cyanovirin (right)

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Synthesis of chalcone derivatives through aromatic acylation

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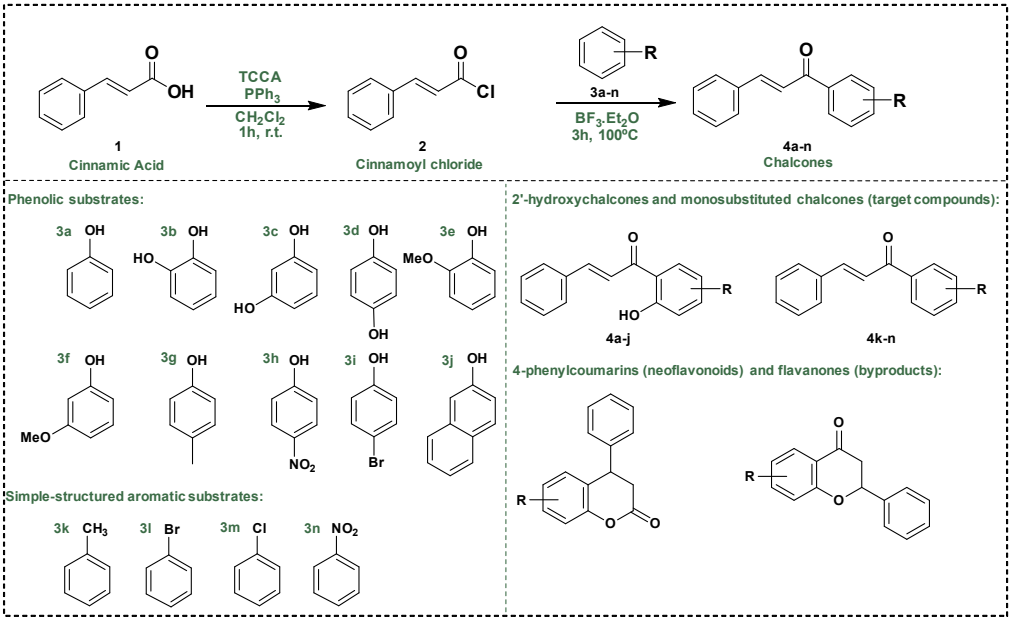
Keywords: *Chalcones, Neoflavonoids, Aromatic acylation.*

ABSTRACT

Chalcones are specialized metabolites widespread in vegetal families, such as Leguminosae, Compositae, and Moraceae. In addition, chalcone derivatives are known due to their potential pharmacological activities and great chemical versatility since they are building blocks for synthesizing novel compounds with higher biological activities. This work describes the synthesis of new chalcones through aromatic acylation. The synthetic route starts by converting cinnamic acid into acyl chloride using trichloroisocyanuric acid (TCCA) and triphenylphosphine (TPP). Then, accessible aromatic compounds were acylated using boron trifluoride etherate ($BF_3.OEt_2$) as Lewis acid. Some common compounds, such as toluene and chlorobenzene, were tested to investigate if the reaction occurred and the regiochemistry involved. Particular phenol substrates resulted in 2'-hydroxychalcones, which will be building blocks for further steps. In some cases, neoflavonoids (4-phenylcoumarins) and flavanones were also identified as byproducts. The target chalcones were achieved with yields between 20 and 72%; some yields are higher than reported through Claisen-Schmidt chalcone synthesis.



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Synthesis of New Quinoline-DHPM Hybrids

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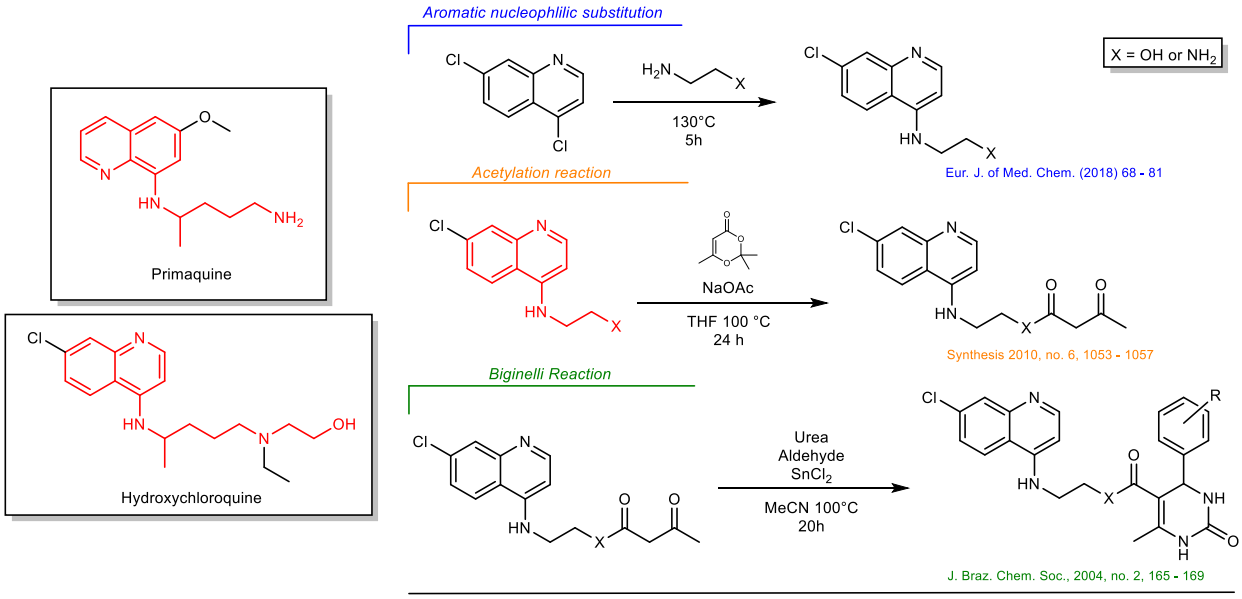
Keywords: *Antimalarial, Multicomponent Reaction, Quinoline derivatives*

ABSTRACT

The development of drug analogues aims to increase its effectiveness against their primary targets or eventually create new responses to other diseases[1]. It is known that chloroquine and primaquine have a history of antimalarial activity, but the growth in resistance of the *P. falciparum* to conventional treatment[2] and the 241 million cases of malaria reported in 2021[3] prompted the scientific community to research for new compounds with enhanced capabilities. Concerning this development, the hybridization concept, in which two or more bioactive molecule scaffolds are united, has been used to create new molecules in the past decades[2]. Specifically in this work, the already known activity of quinoline derivatives and dihydropyrimidinones as antimalarial[2] and antimitotic[4], respectively, inspired the synthesis of new hybrids with potential bioactivities. These molecules where obtained with a 3-step linear synthesis and further studies will apply the primaquine substrate directly at the second step.



Quinoline-based analogue synthesis

ACKNOWLEDGEMENTS

The authors are thankful for fellowships from CAPES and CNPq, financial support from PPGQ-UFPR and LabRMN for the ^{1}H and ^{13}C spectral data.

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Use of organocatalysis for the synthesis of phenyl-hydroxylated-butyric acids

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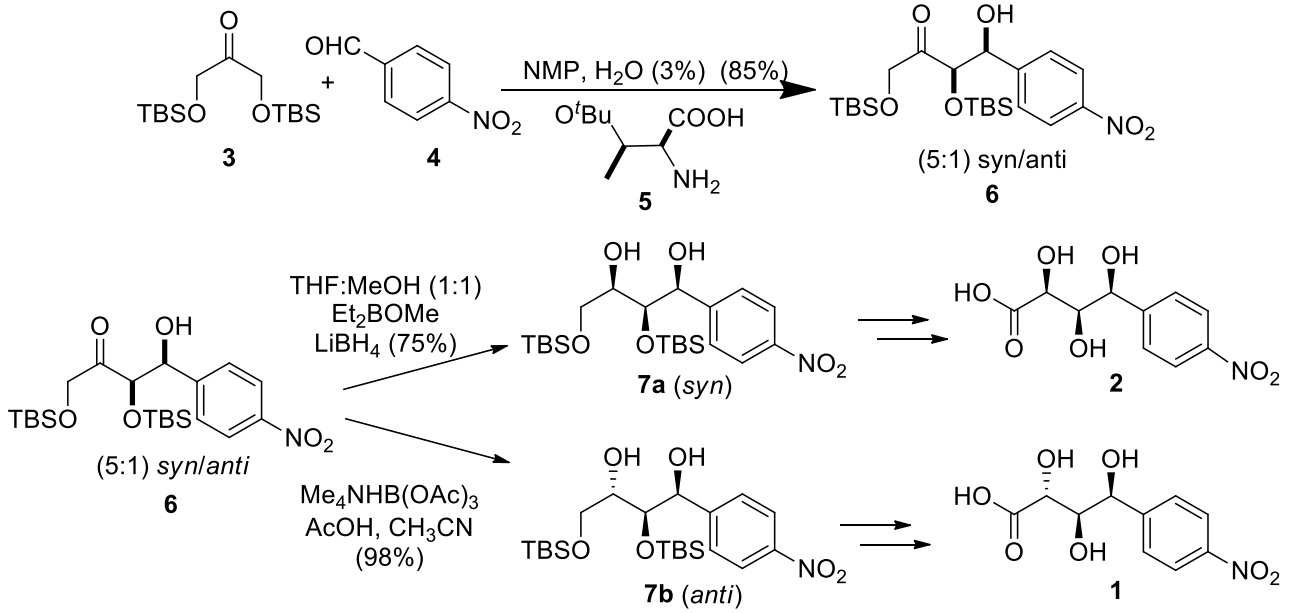
Keywords: *Total Synthesis, organocatalysis, aldol reaction, asymmetric reactions*

ABSTRACT

Organocatalytic reactions are becoming powerful tools in the construction of complex molecular skeletons. In 2021, Benjamim List and David MacMillan were awarded the Nobel Prize in Chemistry for the development of asymmetric organocatalysis. In this work we used the organocatalysis reaction as key step to get the 4-(*p*-nitro)-phenyl-hydroxylated-butyric acids. The acids **1** (2,3-*anti*-3,4-*syn*) and **2** (2,3-*syn*-3,4-*syn*) were synthesized from TBS-dihydroxyacetone (TBS-DHA) **3** and *p*-nitrobenzaldehyde **4** using an organocatalyzed aldol reaction as the key step. The stereoselectivity of the *syn*-aldol coupling was suggested as resulting from a transition state including a low energy *anti*-Z enamine, derived from the condensation of TBS-DHA and O-^{t}Bu-*L*-threonine. Selective *anti*- and *syn*-carbonyl reduction of the carbonyl adducts led to 2,3-*anti*-3,4-*syn* and 2,3-*syn*-3,4-*syn* hydroxy compounds, respectively, which underwent the same sequence of transformations (ketal synthesis, primary TBS-deprotection, oxidation and deprotection) to afford 4-(*p*-nitro)-phenyl-hydroxylated-butyric acids **1** and **2** in seven steps and 22% and 24% overall yield, respectively.



Scheme 1: Use of organocatalysis for the synthesis of phenyl-hydroxylated-butyric acids.

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Double halofluorination of alkynes using trihaloisocyanuric acids and Olah's reagent

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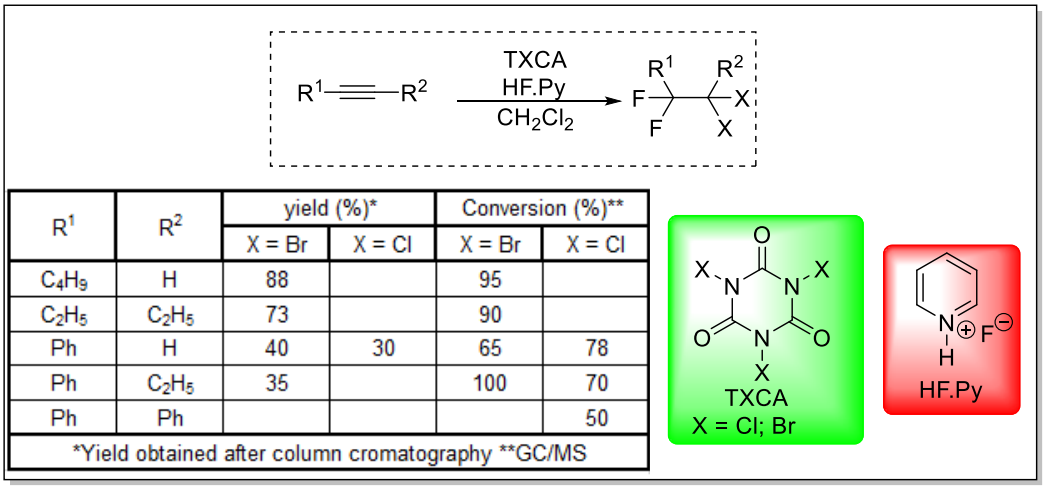
Keywords: *halofluorination, Olah's reagent, trihaloisocyanuric acid.*

ABSTRACT

The introduction of fluorine into organic compounds causes a series of changes in their physicochemical properties;[1,2] therefore methods of obtaining these compounds are widely desirable[3,4]. In this context, the present work aimed to develop a methodology for double halofluorination of alkynes, using trihaloisocyanuric acids (TXCA: TCCA for chlorine, TBCA for bromine)[5] as electrophilic reagents. The methodology developed to carry out the double halofluorination reaction was the use of alkyne (3 mmol), TXCA (2.5 mmol) and HF.py complex (Olah's reagent, 10 mmol) in dry dichloromethane (20 mL), under argon atmosphere. The alkynes used were 1-hexyne, 3-hexyne, phenylacetylene, 1-phenyl-1-butyne and diphenylacetylene, obtaining, mainly, the desired products in 30-88% yield. TBCA presented the best yields and the most selective reactions compared to TCCA that obtained more by-products, for the cases studied.



R^1	R^2	yield (%)*		Conversion (%)**	
		X = Br	X = Cl	X = Br	X = Cl
C_4H_9	H	88		95	
C_2H_5	C_2H_5	73		90	
Ph	H	40	30	65	78
Ph	C_2H_5	35		100	70
Ph	Ph				50

*Yield obtained after column cromatography **GC/MS

ACKNOWLEDGEMENTS

Authors thank CNPq, FAPERJ and CAPES for financial support

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The 2nd generation of *In Tandem* enantioselective Heck-Matsuda reaction directly from anilines

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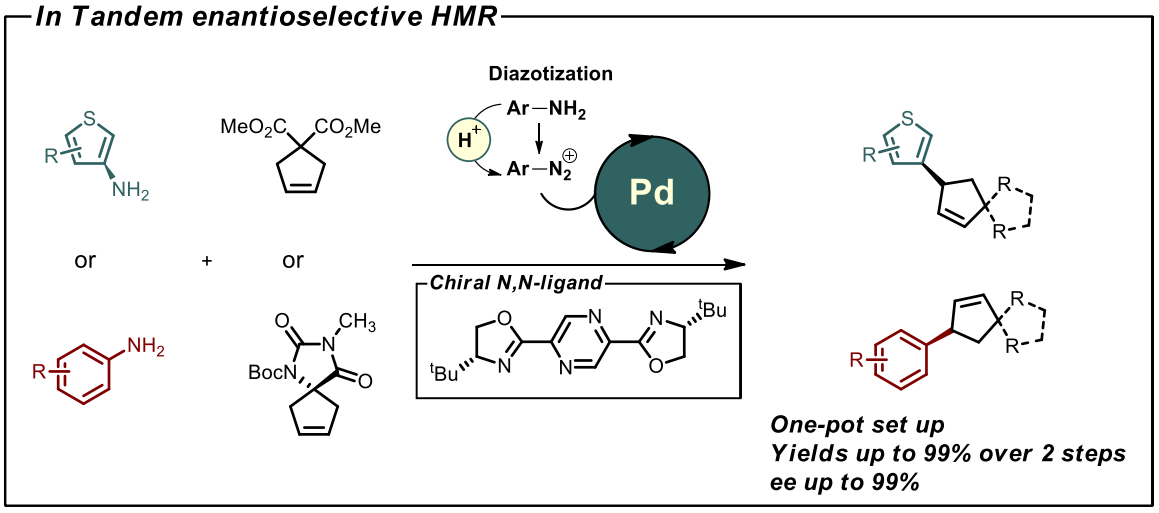
Keywords: *Palladium catalysis, enantioselective desymmetrization, in situ diazotization.*

ABSTRACT

The enantioselective Heck-Matsuda reaction (HRM) is a robust methodology to access enantioenriched building blocks and complex molecules in organic synthesis. Due to its robustness and vast applicability, considerable advances have been stablished in the past years.[1] Among other features, the mild, open-flask and greener conditions stand as desirable aspects for a reaction. Despite its operational simplicity, some safety issues regarding diazonium salts must be taken into account while preparing, dealing with and storing these salts.[2] Recently, our group reported the first *in Tandem* enantioselective HMR under almost neutral conditions.[3] Moving beyond this important proof of concept, new studies has been carried out to make this protocol even more practical and to expand its synthetic scope. Herein, we present the 2nd generation of the *in situ* enantioselective HMR accomplishing the desymmetrization of unactivated olefins with high tolerance to group functionalities in yields up to 99% and *ee* up to 99%.



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VERSATILE APPLICATIONS OF CYANOACETIC ACID IN ORGANIC CHEMISTRY: ACTIVATED METHYLENE COMPOUND FOR THE KNOEVENAGEL CONDENSATION AND EFFICIENT ORGANOCATALYST FOR THE BIGINELLI REACTION

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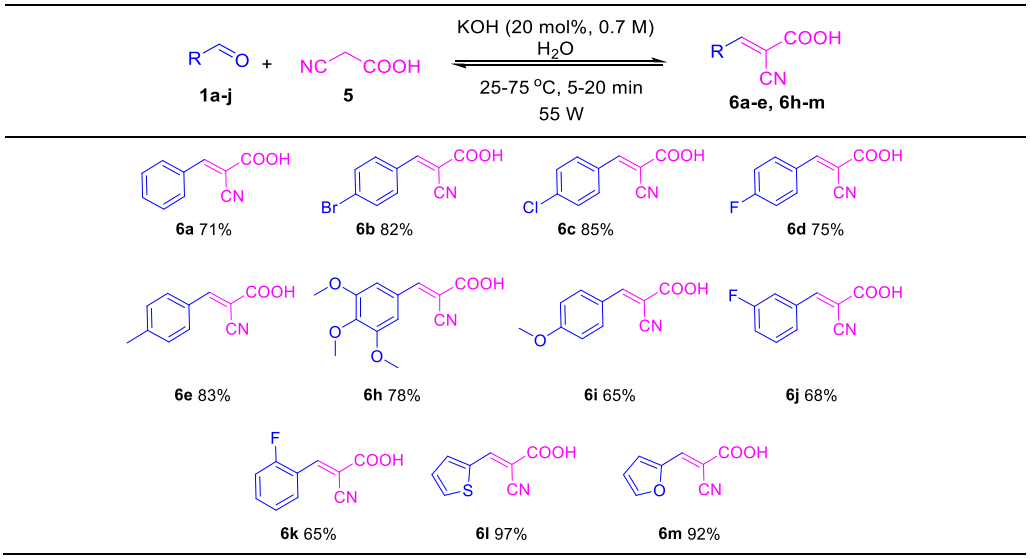
Keywords: *Knoevenagel Condensation, Biginelli Reaction, Organocatalyst.*

ABSTRACT

The application of cyanoacetic acid (CA) as a catalyst for the Biginelli reaction and as an active methylene compound for the Knoevenagel condensation reaction was evaluated. Using CA as Brønsted acid catalyst, after a synthetic optimization process, it was possible to synthesize eight dihydropyrimidinones with good yields 80-99% using ethanol as solvent. It is the first time that the use of CA is reported in the synthesis of this class of compounds, which have a wide bioactive potential. As well, CA was used as a reagent in the Knoevenagel condensation reaction, through which polyfunctionalized olefins are obtained and can be used as building blocks for structurally complex molecules. Using KOH as a catalyst, eleven Knoevenagel adducts were synthesized with good yields 65-97%, using microwave irradiation as heating source in water. These compounds were used to *Aedes aegypti* larvicides essays showing good valuables of IC_{50} (14.48 µg/mL - 64.81 µg/mL).

Scheme 1. Scope of Knoevenagel adducts **6a-e**, **h-m** using cyanoacetic acid and aromatic aldehydes derivatives under MW irradiation.



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Meyer-Schuster-Type Rearrangement for the Synthesis of α–Iodo-α,β-Unsaturated Thioesters

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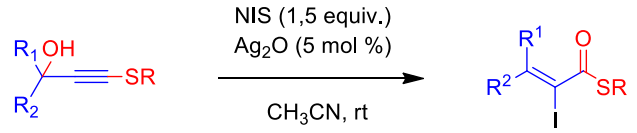
Keywords: *α-iodo-α, β -unsaturated thioesters, Meyer-Schuster-type rearrangement, synthesis.*

ABSTRACT

α, β-unsaturated thioesters steadily gaining strong attention in organic synthesis not only as an important biological active group, but also as an useful intermediate building block for new bond formation.[1,2] Due their application in several areas, numerous methods for their preparation were developed, such as aldol reaction and olefinations.[2,3,4] However, many of these methods present regioselectivity problems and form complex mixture of products. In this context, Meyer-Schuster rearrangement became valuable alternative, as it favors the formation of α, β-unsaturated carbonyl compound.[5,6] Herein, we developed new approach of Meyer-Schuster rearrangement for access α-iodo-α,β-unsaturated thioesters from propargyl thioalkyne using silver catalyst, *N*-iodosuccinimide as electrophilic iodine source in acetonitrile at room temperature. The present protocol demonstrated to be highly efficient for wide range of propargyl thioalkyne. Symmetric substrate were successful converted to tetrasubstituted olefins that are considered as a challenger to synthesize. Moreover, asymmetric substrate gave Z-isomers exclusively.



Mild conditions
High selectivity
100 % atomic economy

32 examples (40-94 %)
exclusively Z - isomers, if
R = aryl; R^1,R^2 = H, aryl

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Direct synthesis of markers for forensic analysis from *C. sativa* extracts

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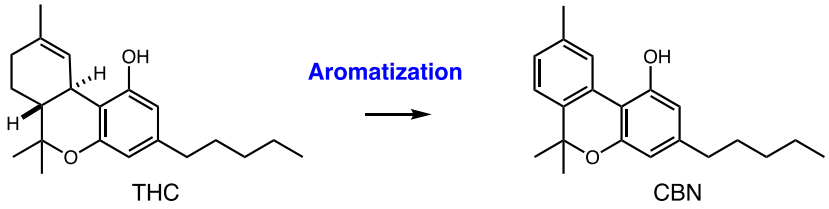
Keywords: *tetrahydrocannabinol, cannabinol, aromatization, qNMR analysis*

ABSTRACT

Cannabis is the most used drug worldwide and the main responsible for legal violations. In this concern, the detection of abuse is extremely important and involves a high level of analytical complexity, since biological samples such as hair, blood, and urine must be analyzed in different contexts. Among the main markers associated with the use of cannabis, we find cannabinol (CBN), also known for its medicinal relevance.[1] In this work, we intend to synthesize CBN from the direct aromatization of *C. sativa* extracts enriched with Δ^9-tetrahydrocannabinol (THC).



Scheme 1. Synthesis of CBN from *C. sativa* extracts

Isolated THC was submitted to iodine-promoted aromatization providing CBN at 52% yield after optimization.[2] Six different extracts of *C. sativa* were treated under the optimized conditions and analyzed by ^{1}H qNMR using electronic references, from a method developed at INMETRO. Studies employing other oxidant agents are ongoing.

ACKNOWLEDGEMENTS

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Scaled up and telescoped synthesis of propofol under continuous-flow conditions

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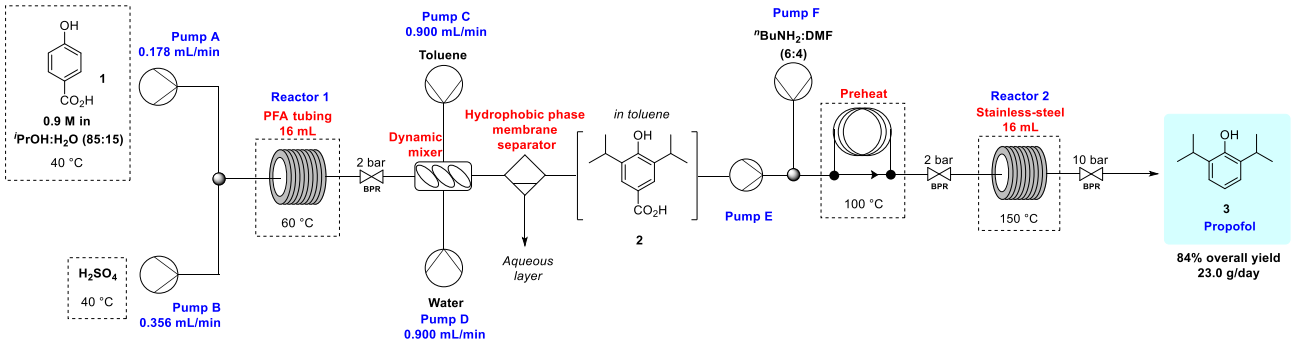
Keywords: Continuous Flow Synthesis, Active Pharmaceutical Ingredient, Propofol, Anesthetic, Covid-19

ABSTRACT

Herein we report a machine-assisted and scaled-up synthesis of propofol, a short-acting drug used in procedural sedation, and which is in high demand during this COVID-19 pandemic. The continuous-flow protocol proved to be efficient, with great potential for industrial translation. We demonstrate success in the telescoped continuous flow approach, proving the robustness of the method in both separated and telescoped modes.

The synthesis of active pharmaceutical ingredients (APIs) using enabling technologies has become an active research field. The use of continuous flow technologies for this purpose is now prominent in both academia and industry, showing great advantages over traditional batch processes.[1,2] Propofol is marketed, for example, as Diprivan® (AstraZeneca). It is a fast-acting intravenous anesthetic agent with worldwide demand, being applied for the induction and maintenance of anesthesia and sedation for medical procedures in adult and pediatric patients.[3,4]

Initially, the optimization of the synthesis of 4-hydroxy-3,5-diisopropylbenzoic acid (**2**) and propofol (**3**) was performed in batch conditions to explore initial reaction conditions which are compatible with microflow reactors, which means the highest possible concentrations with no evidence of precipitation. Tests applying continuous flow were then carried out in two stages. The first step is a Friedel–Crafts alkylation of 4-hydroxy-benzoic acid (**1**), which produced the *bis*-isopropylated **2** in up to 43.8 g (real 24 h experiment), using a 16 mL PFA reactor. An improvement was achieved by using purification via acid-base extraction without the need for tedious column chromatography. The second step is a decarboxylation reaction, in which applying relatively mild conditions and short reaction times, propofol (**3**) was obtained in up to 71.6 g/day (real 24 h experiment) using a continuous flow 16 mL stainless steel reactor. The telescoped continuous flow protocol was performed in up to 6 h, thus affording 5.74 g (32.2 mmol) of propofol (**3**) with a productivity of 23.0 g/day, demonstrating innovation and attractiveness for industrial application (Scheme 1).



Scheme 1. Telescoped protocol for propofol synthesis under continuous-flow conditions.

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Carbamoylation of Morita-Baylis-Hillman Adducts via Visible-Light Photoredox Catalysis

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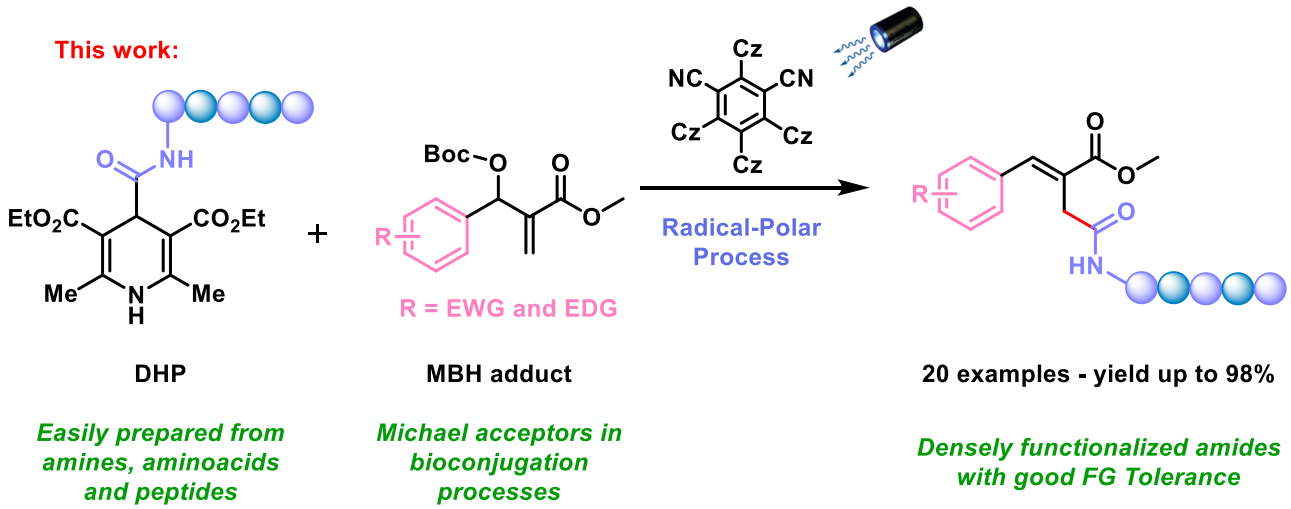
Keywords: *Photoredox Catalysis, Morita-Baylis-Hillman Adduct, Carbamoyl.*

ABSTRACT

Amide-containing structures are extremely important in pharmaceuticals and biologically active compounds. Traditional amidation strategies are mostly based on the C-N bond formation. Although very useful and widely employed, those protocols normally use stoichiometric coupling reagents, and require harsh conditions when bulky or less nucleophilic/electrophilic coupling partners are employed. Over the last years, photoredox catalysis has emerged as a promising alternative in this field. Besides its mildness, wider FG tolerance and sustainability, photocatalysis also offers the possibility of accessing amides via C-C couplings involving carbamoyl radicals. In this regard, dihydropyridines (DHPs) have shown an impressive performance as carbamoyl radical sources, being employed in a diverse set of transformations.[1-3]
Herein, we demonstrate that photocatalytic generated carbamoyl radicals can be incorporated to Morita-Baylis-Hilman (MBH) carbonates, widely known and versatile synthetic building blocks,[4-5] to afford a family of densely functionalized amide scaffolds, using the carbazolic organophotocatalyst 4CzIPN.



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Tribromoisocyanuric acid as a versatile oxidant in the synthesis of 1,3,4-oxadiazoles in solid-state or organic solution *medium*

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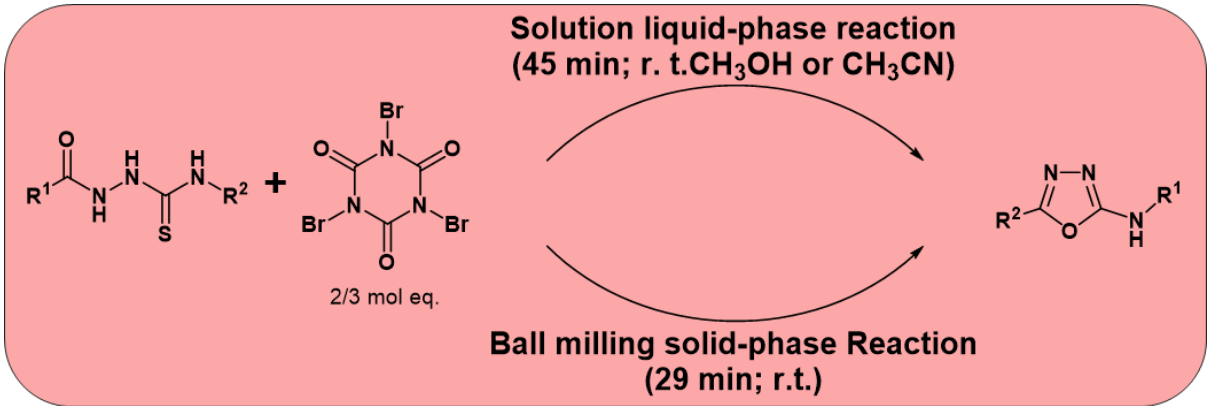
Keywords: *oxidative cyclization, mechanochemical reaction, heterocycle.*

ABSTRACT

Efficient synthetic methodologies involving the formation of 1,3,4-oxadiazole heterocycle are desirable whereas this class of substances exhibits a privileged biological scaffold.[1] Furthermore, the synthesis of 2-amino-1,3,4-oxadiazol was recently achieved *via* oxidative cyclization of *N*-acylthiosemicarbazides promoted by tribromoisocyanuric acid in a polar organic solvent medium, enabling the synthesis of diverse substituted 2-amino-1,3,4-oxadiazole in mild conditions.[2] The use of trihaloisocyanuric acids in solid-state mechanochemical reactions was reported as an efficient neat alternative to the employment of organic solvents,[3] this is mainly advantageous since it provides the reduction of organic solvent waste in the product obtention process.

Herein we report the oxidative cyclization of *N*-acylthiosemicarbazide with tribromoisocyanuric acid using mechanochemical solid-state set up in an automated ball milling *apparatus*.



R^1	R^2	Yield (%) Solution[a]	Yield (%) Mechanochemical[b]
4-Py	Ph	73[b]	84
Ph	Ph	94[b]	39[d]
Ph	Bn	92	24
4-Py	Bn	92	61[d]
4-Py	Ph	71	87

[a] reaction in a solution of CH_3OH. [b]CH_3CN is used as solvent instead. [c]Product obtained using an IKA ULTRA-TURRAX® Tube Drive ball milling reactor. [d]Yield determined by ^1H NMR using 1,4-dimethoxy benzene as internal standard

ACKNOWLEDGEMENTS

The authors are grateful to the CAPES and CNPq for the funding and support.

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Selective Oxidations in the Synthesis of Complex *ent*-Kauranes

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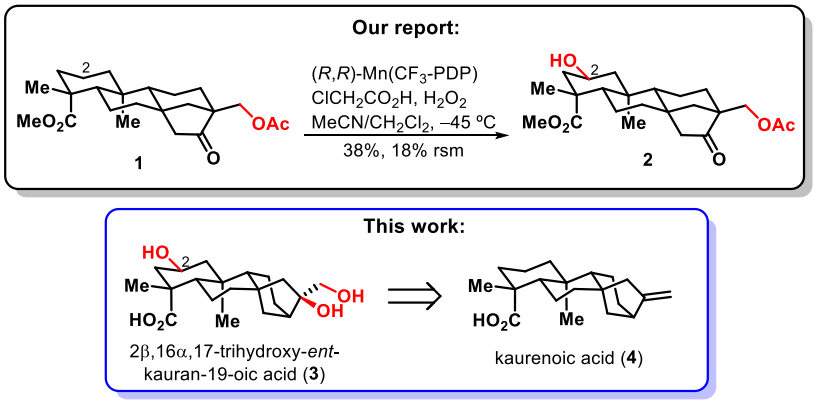
Keywords: *Catalysis, diterpenes, C-H oxidation.*

ABSTRACT

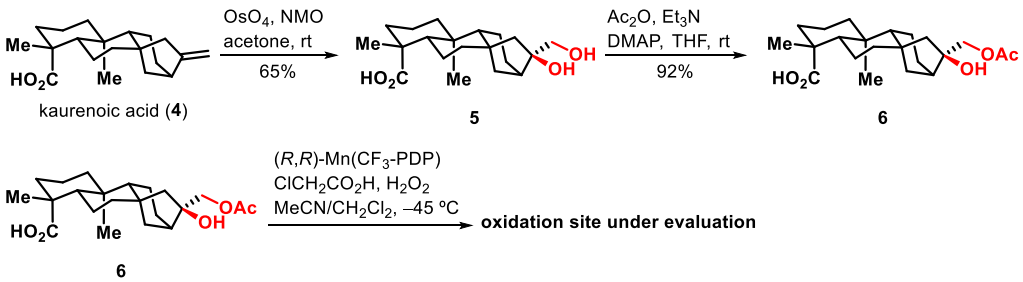
Incorporation of oxygen atom in organic molecules may cause significant changes in chemical and biological properties. In this way, we aim to synthesize natural products by increasing the oxidation level of the *ent*-kaurane kaurenoic acid (**4**). In view of our recent report for the site-selective C2 oxidation of the *ent*-beyerane **1** using Mn(CF_3PDP) as catalyst,[1] we envisioned synthesizing the natural product **3**, isolated from *Mikania hirsutissima*, after a olefin dihydroxylation followed by the oxidation at the C2 site (Scheme 1).[2]

Scheme 1



Our synthesis began with the dihydroxylation of kaurenoic acid (**4**) with OsO_4 and NMO, delivering the diol **5** in 65% yield as the only diastereoisomer. The diol was selectively acetylated with Ac_2O to furnish the natural product **6** in 92% yield.[3] After, the compound **6** was submitted to our oxidation protocol and the oxidation site is currently under evaluation (Scheme 2).

Scheme 2



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Efficient synthesis of glycomimetics with potential biological activity.

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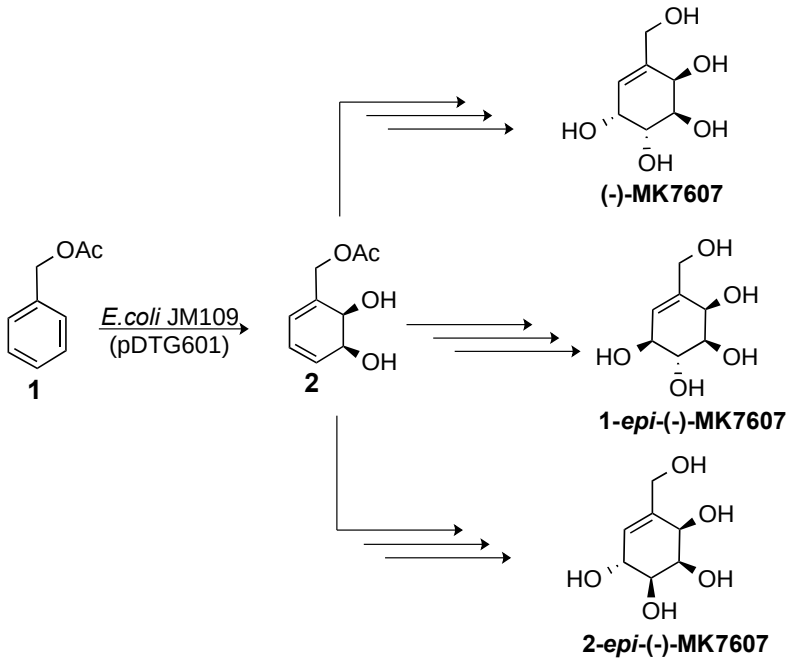
Keywords:*glycomimetics, stereoselective synthesis*

ABSTRACT

Glycomimetics are compounds structurally analogous to natural sugars,whichhave shown better metabolic stability and greater selectivity for target proteins. Particularly, carbasugars are glycomimetics in which the oxygen atom in the closed form of the carbohydrate, is replaced by a carbon atom.

Here, we present aconcise synthesisof the carbasugar (-)-MK7607 and two of its epimers (1-*epi*-(-)-MK7607 and 2-*epi*-(-)-MK7607), stereoisomers of the natural herbicide isolated from *Curvulariaeragrostidis* D2452,(+)-MK7607.[1]

Cis-cyclohexadienediol (**2**), obtainedby enzymatic dihydroxylation of benzyl acetate with the recombinant strain *E. coli* JM109 (pDTG601) which expresses a toluene dioxygenase (TDO),[2] was used as starting material.



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BIOMIMETIC OXIDATION USING SECOND AND THIRD GENERATION OF MANGANESE PORPHYRINS: EVALUATION OF THE CATALYTIC SYSTEM ON THE OXIDATION OF RHODAMINE B

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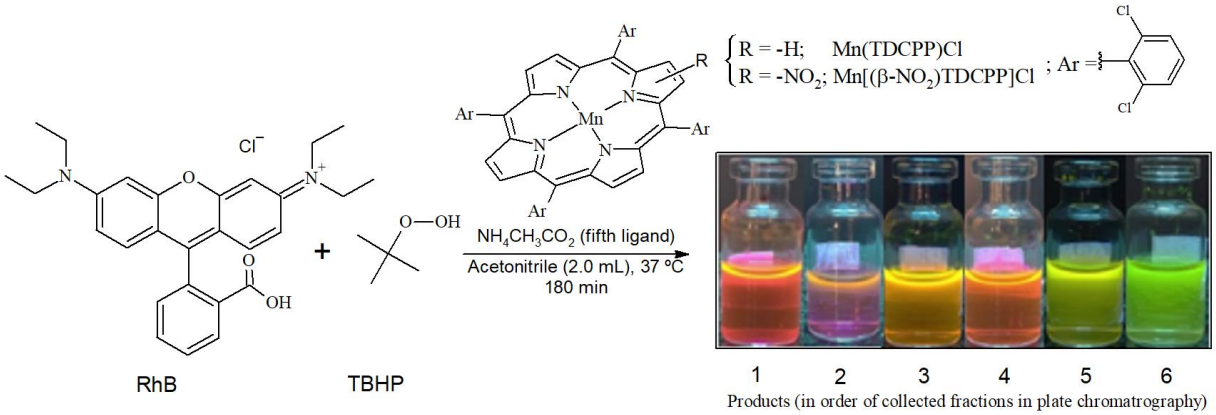
Keywords: *Synthesis; Metalloporphyrins; Catalysis.*

ABSTRACT

Porphyrins and their derivatives are naturally occurring chemical compounds that perform essential functions for the maintenance of life, as they participate in diverse biological processes[1]. This work investigates the application of second and third generations of manganese porphyrins, the well-kown Mn(TDCPP)Cl and its β-nitro derivative Mn[(β-NO_2)TDCPP]Cl as biomimetic catalysts in the degradation of the synthetic dye Rhodamine B (named as RhB).

The best reaction conditions for RhB conversion were found in the presence of *tert*-butylhydroperoxide as oxygen donor and ammonium acetate as fifth ligand. The reactions were carried out in acetonitrile in ratios catalyst/substrate/oxidant as 1:75:75, whose condition were adjusted from previous reports[2, 3] The Reaction Scheme shows the catalytic scenario and products obtained.



In this reaction condition, the best substrate conversions were 23.17% and 21.57% with the catalysts Mn(TDCPP)Cl and Mn[(β-NO_2)TDCPP]Cl, respectively.

The chromatographic analysis of the catalytic reactions showed the formation of at least six products (Reaction Scheme), which are still being elucidated via ^{1}H NMR.

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Click cyclooligomerization of azidocyclitols and their host-guest chemistry studies

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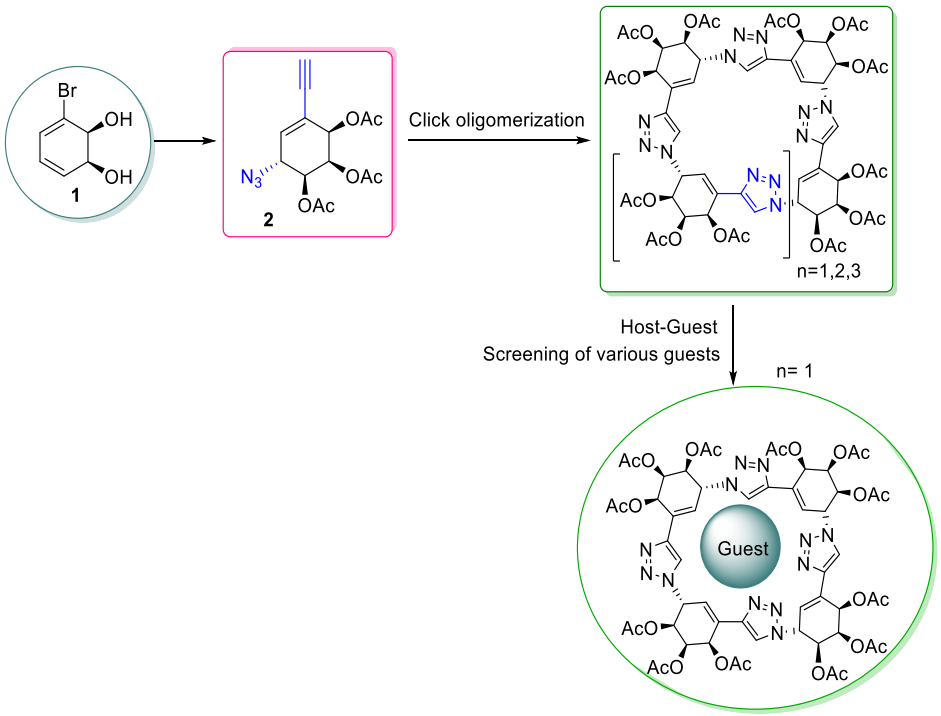
Keywords: *Click chemistry, Polyoxygenated macrocycles, Host-guest chemistry.*

ABSTRACT

The Cu-catalyzed alkyne-azide cycloaddition is arguably the most used reaction in "click chemistry".[1] It is so efficient that it has been used as a polymerization method. Among the monomers used, polyoxygenated compounds, such as sugars, are relevant. They oligomerize by a click reaction to give linear or cyclic structures.[2]

We have experience on the synthetic applications of *cis*-cyclohexadienediols derived from microbial oxidation of arenes. In this context, the polyoxygenated azidoalkyne monomers can be prepared using chiral diols derived from the enzymatic dihydroxylation of monosubstituted benzenes mediated by the recombinant strain *E. coli* JM109(pDTG601).[3]

Herein we present the synthesis and click oligomerization of monomer **2** starting from diol **1** as shown in scheme A. Finally, the host-guest chemistry of the protected tetramer macrocycle is presented using different molecules ranging from neutral organic aromatic compounds to anions such as halides, sulfate, nitrate, and others.



Scheme A

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Synthesis and trypanocidal bioactivity evaluation of butenolides bearing 1,2,3-triazole fragments

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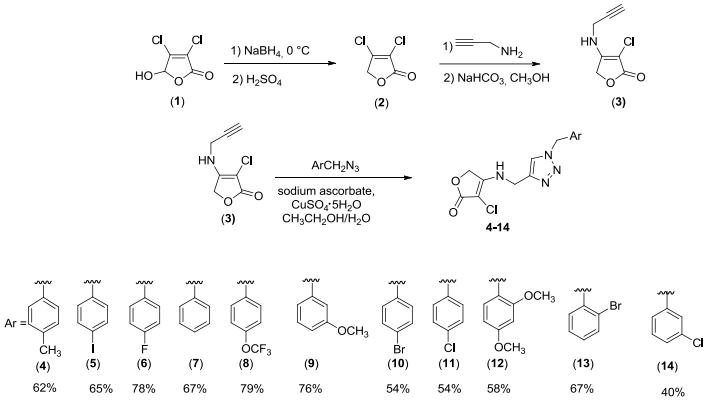
Keywords: *Butenolide, CuAAC reaction, Trypanocidal activity*

ABSTRACT

The present investigation describes the synthesis and trypanocidal bioactivity evaluation of a series of butenolides bearing 1,2,3-triazole moieties. To prepare the compounds, the mucochloric acid (**1**) was reduced with sodium borohydride affording the butenolide **2** with 89% yield.[1] Then, the conjugated addition of propargylamine to compound **2** gave terminal alkyne **3** with 49% yield.[2] Finally, the CuAAC reaction[3] between terminal alkyne **3** and benzylic azides resulted in the preparation of compounds **4**-**14** with yields ranging from 40-79% (Scheme 1).



Scheme 1 – Synthetic steps involved in the preparation of butenolides **4**-**14**.

Since butenolides showed trypanocidal activity in previous report[4], we performed the screening of the activity of compounds **4-14** on Vero cells infected with *T. cruzi* Dm28c tagged with luciferase [5]. Compound **10** inhibited parasite proliferation at 36+8.8% at 20 μM, with EC_{50} for the host cell of 380 μM. Specific IC_{50} determination for *T. cruzi* will be carried out.

ACKNOWLEDGEMENTS

We are grateful to CAPES and FIOCRUZ for financial support.

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Synthesis of quinolone/naphthoquinone/triazole hybrids with antitumor profile

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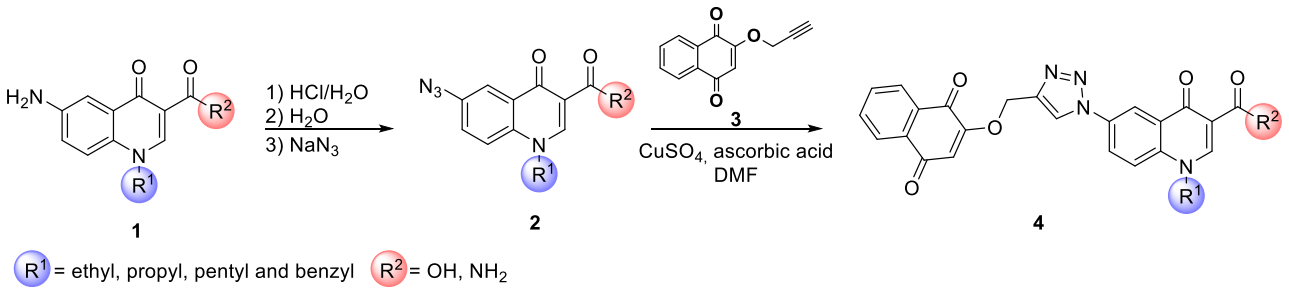
Keywords: *quinolone, naphthoquinone, triazole.*

ABSTRACT

The conjugation of structural fragments, present in substances with known biological activity, in the structural design of new drugs, is a strategy of medicinal chemistry, which aims at the development of new, more effective bioactive agents, in relation to the original prototypes.[1] Studies indicate that the 4-quinolone, 1,4-naphthoquinone and 1,2,3-triazole nuclei are important in the design of new substances with diverse biological activities, such as anticancer, for example.[2-4] Thus, the objective of this work is the synthesis of new hybrids designed from the conjugation of 4-quinolone, 1,4-naphthoquinone and 1,2,3-triazole fragments to obtain substances with a potentiated anticancer profile. The proposed substances were synthesized from 6-amino-4-quinolone (**1**) by means of a diazotization reaction followed by treatment with sodium azide and a subsequent copper(I)-catalyzed cycloaddition reaction with 2-propargyloxy-1,4-naphthoquinone (**3**). The hybrids (**4**) obtained had their structures confirmed by spectroscopic analysis methods.



Scheme 01 - Synthetic route to obtain derivatives **4**.

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Synthesis of derivatives of (Z)-masticadienoic acid with potential bioactivity

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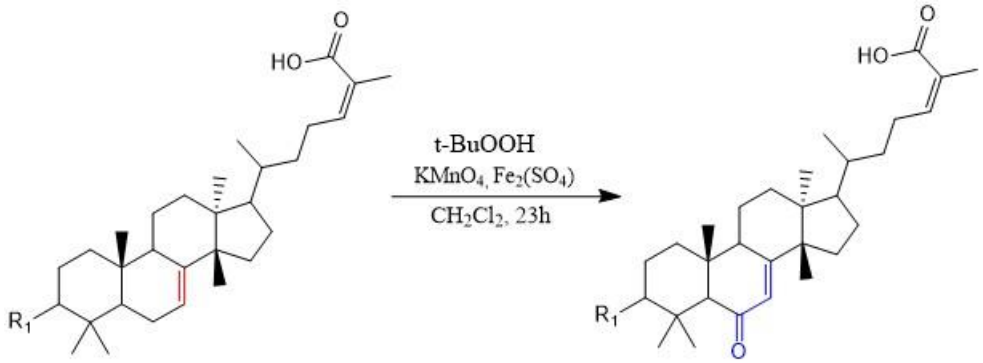
Keywords: *Allylic oxidation, triterpene derivatives, masticadienoic acid.*

ABSTRACT

The synthesis of natural product derivatives allows correlating chemical structure and biological activities, despite limitations in terms of efficiency, chemo-, regio- and stereoselectivity, due to these substances' structural and characteristic diversity.[1] Allylic oxidation in an activated position can proceed selectively to provide moderate to high yields of the desired product and allow its use in the synthesis of natural products.[2] Derivatives of triterpenes have shown potential biological activity as antibacterials,[3] however, with moderate to low yields, this is the main challenge in their preparation. The triterpenes (*Z*)-masticadienoic acid **(1)** and (*Z*)-schinol **(2)** were isolated from the hexane extract of the berries of *Schinus terebinthifolius* (Anacardiaceae), previously reported for this species. They present moderate antimicrobial activities against *Staphylococcus aureus* and *Pseudomonas aeruginosa* with a MIC of 250µg.mL^{-1}. From these compounds, oxo derivates were synthesized by allylic oxidation and the products were also evaluated in bioassays of acetylcholestarase and pathogenic microorganisms.



(1) R_1: =O

(2) R_1:OH

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CAPES

CNPq Conselho Nacional de Desenvolvimento Científico e Tecnológico

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Synthesis of new fluorescent chalcogen-tripyrranes derivatives

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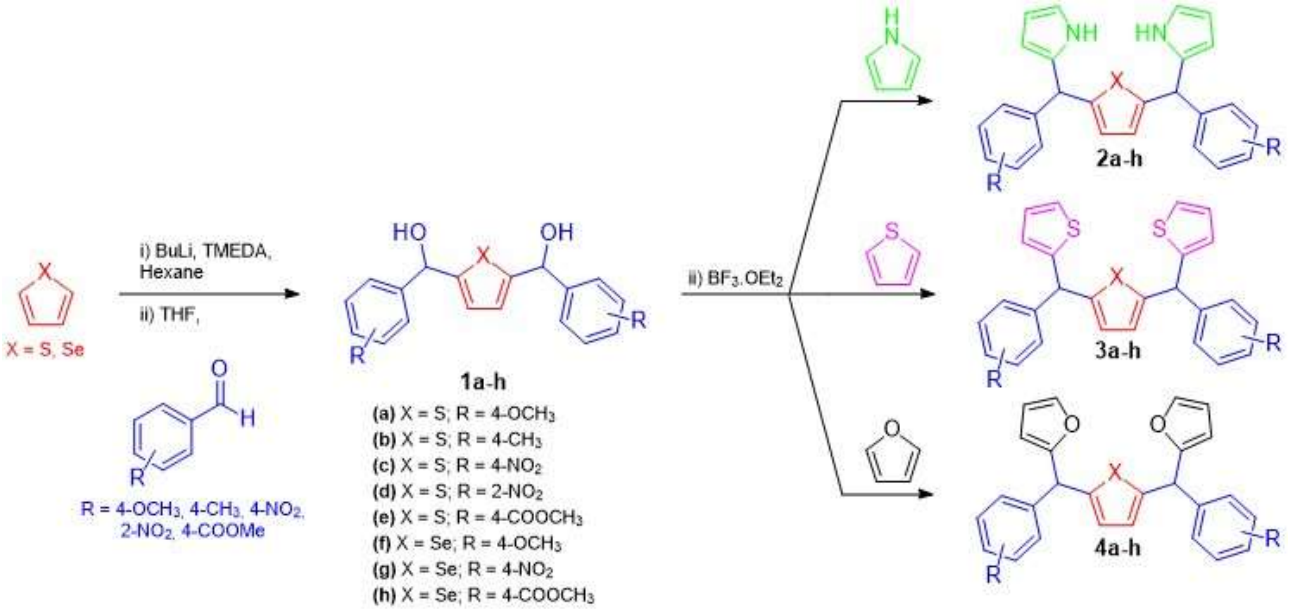
Keywords: *Chalcogenophenes, Synthesis, Photophysical*

ABSTRACT

The tripyrranes (**2**) are intermediates in the synthesis of porphyrins, whose oxidation products are the tripyrrins. Usually the focus of tripyrrins is the coordination chemistry;[1] and no reports concerning the tripyrranes. This work presents the synthesis of **2**, **3** and **4** (Figure 1). The synthesis of the compounds **1** and **2** have been reported in the literature.[2] On the other hand, there are few or no examples of chalcogen-heteroaryl substituted compounds (**3** and **4**, Figure 1) synthesis, which represents a great challenge. The compounds **1** were obtained by thiophene lithiation, followed by aldehyde addition and resulting in diols (**1a-h**, Figure 1). The step of chalcogenophene catalyzed by Lewis acid ($BF_3.OEt_2$) results into compounds **2-4(a-h)**. Structural elucidation was confirmed by High-Resolution Mass Spectrometry (HRMS) and characterized by 1D and 2D Nuclear Magnetic Resonance (NMR), IR and UV spectroscopy. The HOMO/LUMO energies have been calculated by M062X/cc-pvdz method. The photophysical study was performed with compounds **2a** and **3a** in four solvents (ACN, Dioxane, EtOH and CH_2Cl_2) at $1x10^{-4}$ mol/L concentration. Both compounds presented a similar absorption profile, showing absorption in the violet to blue region at 440-470 nm. The sort of solvent and substituent (R or X) no affect the ground state of the HOMO/LUMO energy. The compound **2a** produced a dependence of the emission wavelength with the excitation wavelength. It is associated to non-traditional intrinsic luminescence and could explain the optical properties of these compounds.[3]



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Amphetamine chiral intermediates obtained by reductive amination of prochiral ketones

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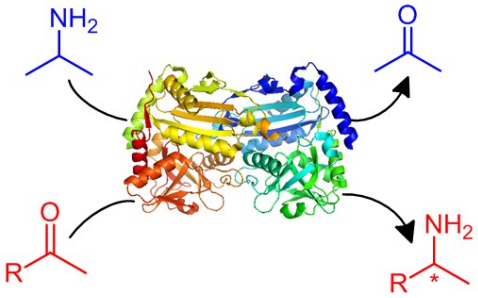
Keywords: *Biocatalysis, transaminases, chiral amines.*

ABSTRACT

ω-transaminases are pyridoxal-5-phosphate (PLP)-dependent enzymes that catalyze the transfer of an amino group from an amino donor to an aldehyde and/or ketone. The present work studied the asymmetric synthesis of primary amines from prochiral ketones to produce important synthetic intermediates, such as amphetamines. Two different substrates were evaluated for ten commercial enzymes, five of which are R-selective and five S-selective, and eight heterologously expressed ω-transaminases in *E. coli*, four R- and four S-selective. The preliminary results regarding the substrate scope and absolute configuration assignment are promising. Out of seven commercial ω-transaminases showed conversions from 51 to 99%, and *ee* varying from 39 to >99% for both R- and S-selective ones.



ACKNOWLEDGEMENTS

Financial support of the Sao Paulo Research Foundation – FAPESP [grants number 2014/50249-8; 2019/15230-8]; National Institute of Science and Technology – INCTBioNat [CNPq grant number 465637/2014-0; FAPESP grant number 2014/50926-0]; This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001.

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Synthesis of the Brivaracetam API Employing Asymmetric Photocatalysis and Continuous Flow Conditions

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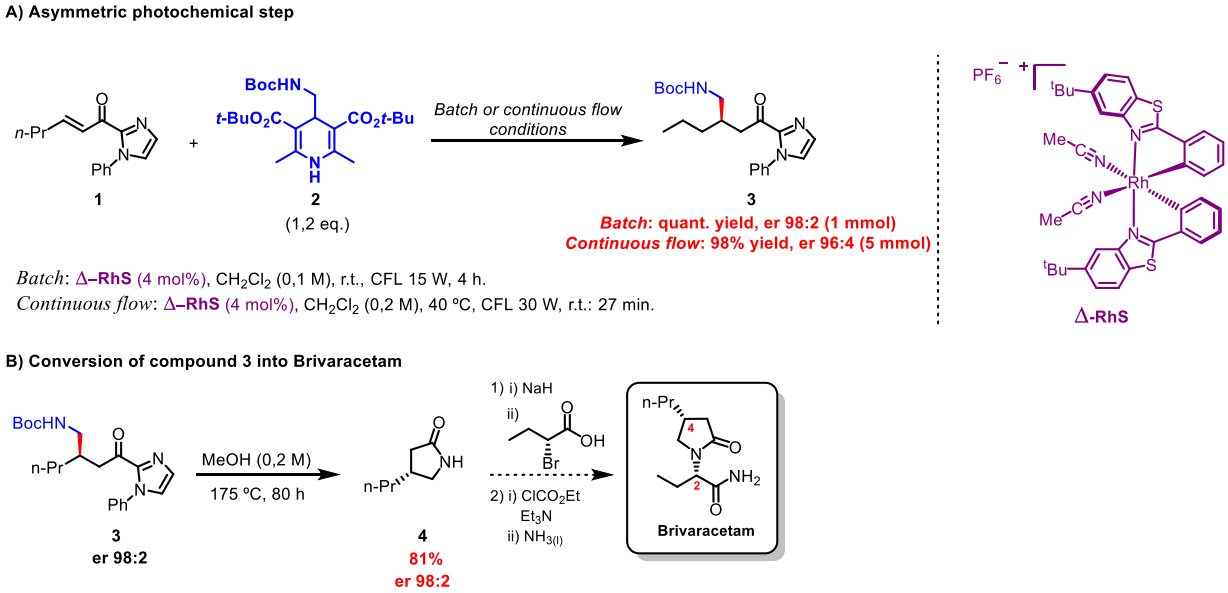
Keywords: *Asymmetric Photocatalysis, API Synthesis, Continuous Flow.*

ABSTRACT

Brivaracetam is an Active Pharmaceutical Ingredient (API) used to produce a medicine that treat seizures in patients with a condition known as drug resistant epilepsy (DRE).[1] Brivaracetam is an enantiopure drug (2*S*/4*R* stereoisomer) and the biggest challenge for its synthesis is the stereocontrolled installation of the *n*-propyl substituent at C-4 position. The use of asymmetric catalysis remains quite unexplored in the synthesis of this API, thus, in this study we report a new synthesis of Brivaracetam making use of asymmetric photocatalysis and continuous flow conditions. The synthesis starts with α,β-unsaturated acylimidazole **1** and Hantzsch ester **2**, which were prepared according reported procedures.[2] Compounds **1** and **2** were reacted in the presence of the chiral catalyst **Δ-RhS**, developed by the Meggers group, and the experiments were performed using visible light (blue LEDs). Optimization studies in batch and continuous flow conditions were performed and we identified the best conditions for obtaining the aminoketone **3** in terms of yield and enantiomeric ratio. The continuous flow set up allowed us to scale up the reaction in up to 5 mmol of **1** without losses in yields or e.r. (Scheme 1).



Scheme 1. Synthesis of brivaracetam.

After stablishing the best conditions for the preparation of compound **3** we conducted a study concerning its conversion into lactam **4**. Our initial approach involved 3 distinct steps, however, we were able to accomplish this transformation in just one step with very good yield (81%) and no loss of enantiomeric purity (Scheme 1). With the intermediate **4** in hand we accomplished the formal synthesis of Brivaracetam while the conversion of lactam **4** into our desired API is currently ongoing in our laboratory.

ACKNOWLEDGEMENTS

We thank to FAPESC (2020/TR1451) and FAPESP (2019/27176-8), CAPES and CNPq for the financial support and also to UFSC and UFSCar for the facilities.

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Synthesis of Fentanyl under Continuous (Photo)Flow Conditions

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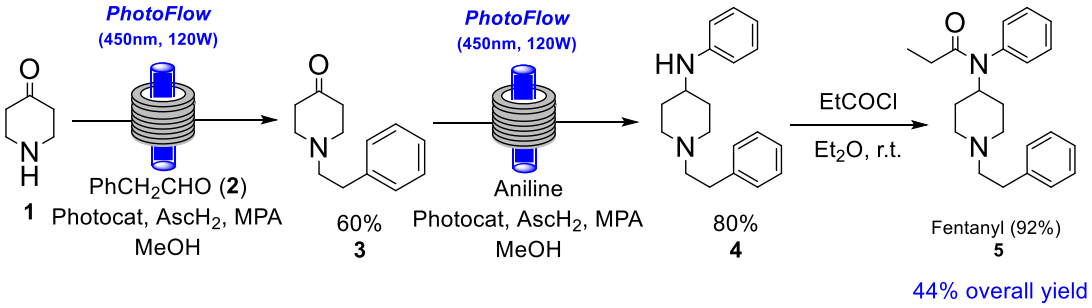
Keywords: *Photocatalysis, Flow Chemistry, Fentanyl, Synthesis*

ABSTRACT

Fentanyl is an FDA-approved analgesic used to treat persistent, moderate to severe chronic pain and intraoperative analgesia[1], with an increasing global market registered for the period of 2015 to 2019[2]. The current literature on its synthesis frequently includes the use of toxic reagents, halogenated solvents, long reaction times, and high temperatures. Therefore, effort must be made to develop new synthetic routes that attend to the current demands of the pharmaceutical industry. For this reason, we envisaged a protocol that uses the latest technologies in synthetic chemistry – flow chemistry – associated with photocatalysis to create an efficient and concise route to this active pharmaceutical ingredient (API). The synthesis is composed of three steps, in which compounds **3** and **4** are accessed by a photocatalysis continuous flow set-up under blue light irradiation (450 nm), while the product fentanyl (**5**) is generated by acylation. Thus, phenylacetaldehyde (**2**) was reductively aminated with piperidin-4-one (**1**), in the presence of a hydrogen donor and a photocatalyst, under blue light irradiation, to produce the intermediate **3** in 60% yield. Intermediate **3** was then reductively aminated with aniline, following the same procedure, to afford diamine **4** in 80% yield, and finally, fentanyl (**5**) was obtained via acylation with propionyl chloride in diethyl ether in 92% yield. Scale-ups of the first and second steps were evaluated; compound **3** was obtained in 9.5 g (52% yield, 47 mmol scale) and compound **4** was produced in 4.7 g (84% yield, 20 mmol scale) in 24h experiments. In conclusion, we have developed an efficient protocol for the synthesis of fentanyl using photocatalysis and flow chemistry technologies, that are under implementation in the pharmaceutical industry, providing an effective and concise route to produce fentanyl.



ACKNOWLEDGEMENTS

The authors are grateful for the financial support received from FAPESP (process n°2020/06874-6 and 2021/06110-9), CAPES, CNPq and UFSCar.

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Synthesis and i*n vitro* biological evaluation of triazole pyrimidinones as antiviral agents against Chikungunya virus

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Keywords: *triazole pyrimidinone, arboviruses, Chikungunya.*

ABSTRACT

Chikungunya fever is a disease that generates severe and debilitating arthralgia, often chronic. There are still no vaccines and drugs for the treatment, in Brazil there is a 93.7% increase in cases when comparing the years 2021 and 2022[1]. Synthetic pyrimidine derivatives were reported with promising results against Chikungunya virus[2,3,4]. We carry out the synthesis of seven unpublished compounds of triazole pyrimidinone derivatives (1a-g, Fig 1) and evaluated their cytotoxic activities in fibroblast cell line Baby Hamster Kidney cells (BHK-21). All compounds showed a very low cytotoxic activity since the concentration that reduced the proliferation of BHK-21 by 50% (CC_{50} were above >500 μM). Of the seven compounds synthesized, six of them exhibited cell viability above 80% for all concentrations studied (62,5; 125; 250; 500 μM, Fig 2). Antiviral activity assay against Chikungunya virus (CHIKV) are ongoing.

GRAPHICAL ABSTRACT

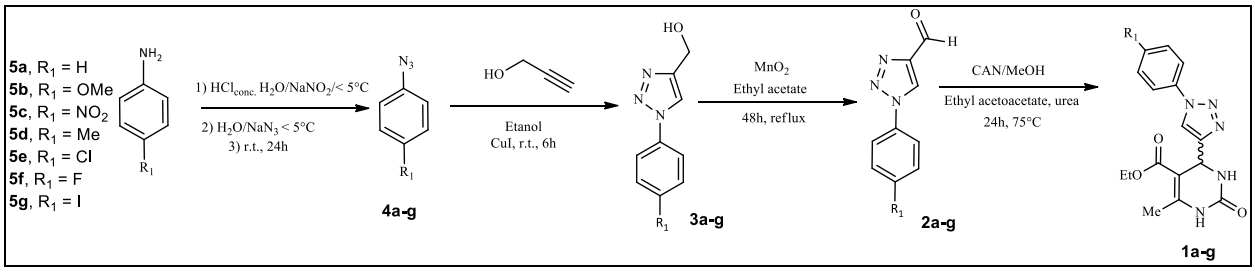

Figure 1: Synthetic route of triazole pyrimidinone.

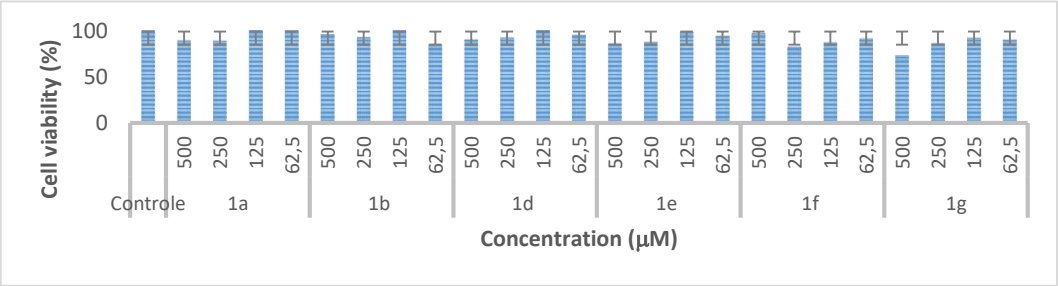

Figure 2: Cytotoxic activities of 1a-g against BHK-21.

ACKNOWLEDGEMENTS

This work is supported by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ) grants.

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One-Pot Two-Step Chemical Synthesis of Molnupiravir

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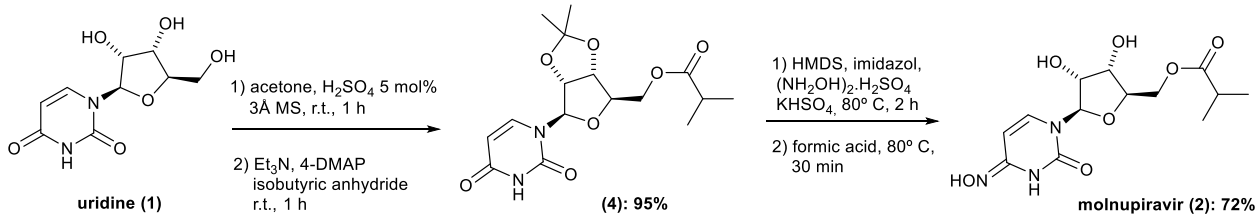
Keywords: *Molnupiravir, One-pot synthesis, Covid-19.*

ABSTRACT

Molnupiravir is an orally available antiviral drug recently approved for emergency use against Covid-19 in many countries worldwide.[1] Hence, there is a high interest in developing an efficient and cost-effective synthesis route for its production to ensure a readily available global supply chain.[2] Given the importance and inherent limitations of all existing uridine-based approaches for molnupiravir synthesis,[3-6] more efficient and inexpensive routes still need to be developed. Therefore, herein, we report a one-pot two-step chemical synthesis of molnupiravir starting from uridine (**1**) (Scheme 1). The first one-pot step consists of acetonide protection using acetone under acidic conditions followed by esterification process. After only extraction and pH-control, the intermediate (**4**) was obtained with 95%. Then, second one-pot procedure was oxyamination and deprotection to give molnupiravir (**2**) on a multigram scale (10 g scale) with a 68% overall yield and >99% purity as shown by HPLC analysis. Advantages are available commodity reagents and simple pH-controlled extractions and crystallization purification procedures.



ACKNOWLEDGEMENTS

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Synthesis of piperine linked with 1,2,3-triazole and evaluation of the inhibition of efflux pumps

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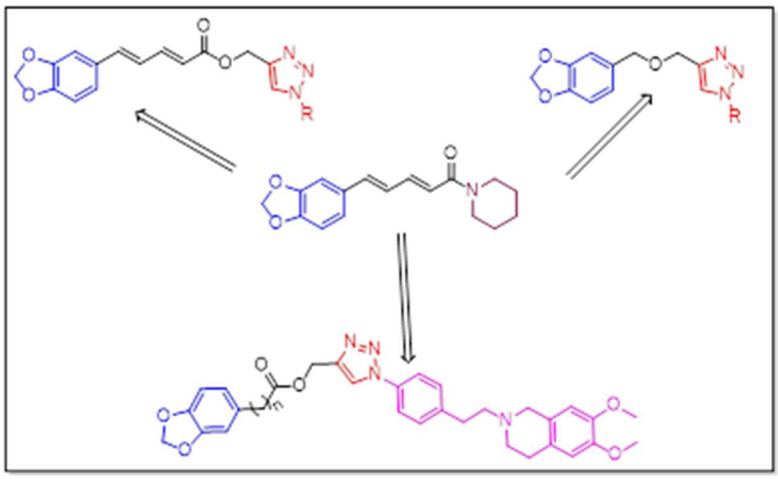
Keywords: carbohydrate, *piperine, 1,2,3-triazole, efflux pumps, Schistosoma mansoni*

ABSTRACT

Efflux mechanisms are widely recognized as major components of resistance to many classes of chemotherapeutic as well as anti-infective agents. Multidrug resistance (MDR) has expanded dramatically across a wide range of organisms from bacteria to humans, resulting in a global increase in life-threatening infections and deaths[1]. That makes it a serious threat to public health around the world and needs action in all government sectors. An example of a natural product described in the literature with efflux pump inhibitory activity is piperine[2]. This work aims to synthesize piperine hybrids containing the 1,2,3-triazole moiety, starting from the terminal alkynes of piperine with carbohydrates and aromatic azides. To obtain the piperine coupled to triazole, the click chemistry concept was used, the Cu (I) -catalyzed 1,3-dipolar cycloaddition reaction using terminal alkynes with organic azides[3]. Compounds are being screened for their inhibition activity on human and the *Schistosoma mansoni* parasite efflux pumps.



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2,1,3-Benzothiadiazole-based bis-silylated compounds as precursors in the preparation of highly fluorescent organic-inorganic hybrid materials

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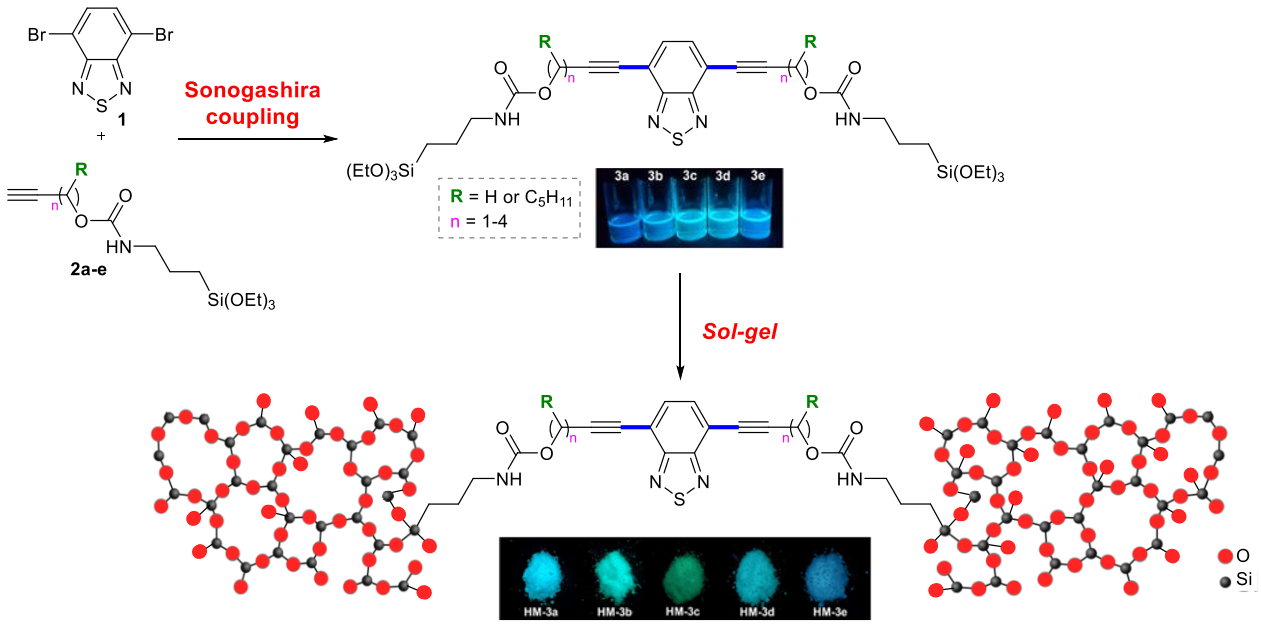
Keywords: *Silsesquioxanes, benzothiadiazole, hybrid materials, fluorescent compounds, fluorescence.*

ABSTRACT

The benzothiadiazole (BTD) is a heteronuclear structure with great synthetic interest due to its electron-withdrawing and electronic delocalization capacities, with highly fluorescent derivatives, applied in many areas, such as OLEDs, donor-acceptor polymers, dye-sensitized solar cells and sensors.[1] In this sense, the insertion of silicon atoms in BTD compounds make it possible to obtain organic-inorganic hybrid materials via reaction of hydrolysis and polycondensation, combining the versatility of organic compounds and the stability of inorganic silica matrix.[2]

In this work, we report the synthesis of silylated BTDs compounds by the Sonogashira coupling of dibromo BTD **1** and previously prepared silylated alkynes **2a-e**. The obtained products **3a-e** presented fluorescence emission in the blue region with high quantum yields and were applied in the synthesis of organic-inorganic hybrid materials via sol-gel method. The BTD loading and aging time were optimized; the studies were realized in duplicates in order to obtain a better reproducibility in the method. The prepared hybrid materials presented absorption in the visible region, highly intense fluorescence emission in the blue-cyan-green regions with relatively high quantum yields and low content of BTD precursors.



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Synthesis and application of new chalcogen-pillar[n]arenes as catalysts in aqueous media

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Keywords: *Catalysis, macrocycle, nitrile, selenium, tellurium.*

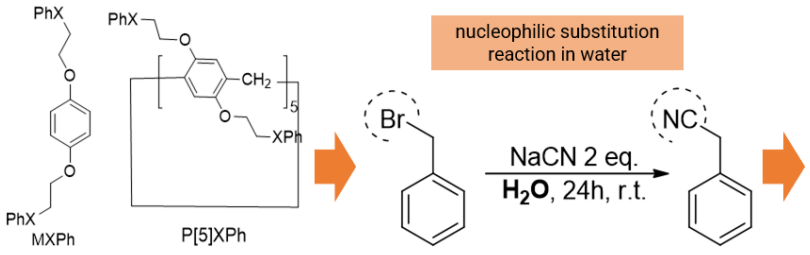
ABSTRACT

The pillar[n]arenes are macrocycles that showing different applicability, one of them is as organic reaction catalyst. [1] In that regard, chalcogen also are a class of substance that has aroused interest in this area. [2] The objective of this work is to synthesize these calcogen-pillararene hybrids and evaluate their catalytic potentials.

All synthesized molecules (P[X]Ph and MXPh) were tested as catalysts in the reaction, having water as solvent, to obtain 2-phenylacetonitrile and the results can be seen in the graphical abstract.

It's observed that without catalyst the reaction isn't completed, with P[5]TePh as the best catalyst, with yield of 96%. This excellent result highlights Te as the best chalcogen and the action of the macrocycle cavity, since its monomer proved to be inferior. With that, new studies continue to be carried out to explore the scope of the reaction, such as its scalability and catalyst recovery.

GRAFICAL ABSTRACT



	Catalyst	Yields
1	-	15%
2	MSePh – 5% mol	29%
3	MTePh – 5% mol	45%
4	MSPh – 5% mol	5%
5	P[5]TePh – 1% mol	96%
6	P[5]SePh – 1% mol	55%
7	P[5]SPh – 1% mol	22%

catalyst choice results

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FAPERJ, CNPq, CAPES, PPGQ-UFF

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Reactivity of the (*S*, *E*)-*γ*-aminated nitroalkene derived from L-(-)-phenylalanine in [4+2] cycloadditions: Synthesis of conformationally constrained 1,3-nitroamines

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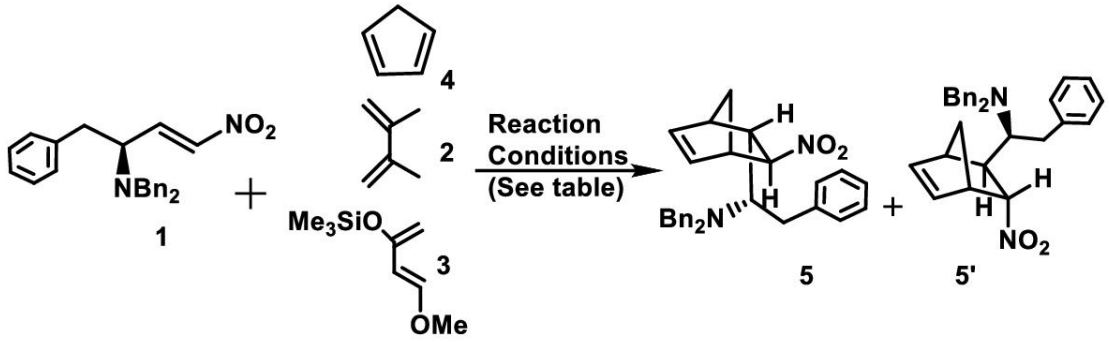
Keywords: *Diastereoselective synthesis, chiral nitroalkenes*, [4+2]-Cycloaddition

ABSTRACT

Nitroalkenes constitute an important class of organic compounds that exhibit exceptional synthetic versatility[1] We synthesized, for the first time, chiral nitroalkenes[2a] bearing a nitrogenated stereogenic center in the *γ*-position and investigate their stabilities, reactivities and diastereoselectivities in conjugate addition with various nucleophiles[2a] and in [4 + 2]/[3 + 2] cycloadditions, promoted by $LiClO_4$, to provide aminated nitroso acetals.[2b] Now, we describe the reactivity of the dienophile chiral **1**, synthesized from L-(-)-phenylalanine (88% global yield; 5 steps)[2a,b] in [4+2]-cycloadditions, with different dienes, aiming at the synthesis of 1,3-diamines conformationally constrained.[3] Thus, the enantiopure ϒ-aminated dienophile **1** was reacted with 2,3-dimethyl-hexadiene (**2**), *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (**3**) (Danishefsky's diene) and cyclopentadiene (**4**), see table. The diene **2** was not reactive despite the use of Lewis acid (Entries 1, 2). The Danishefsky's diene (**3**), also did not lead to desired cycloadduct (Entries 3,4). Using the more reactive and more stable diene **4**, a 2.8:1 mixture of the diastereomers **7**+**7'** was formed in 50% yield (Entry 5). Aiming to improve the yield, **1** and **4** were heated to 140^{O}C in sealed tube, without solvent, producing **5**+**5'** in 65% yield in the 3:1 ratio (Entry 6). The use of 20% $Yb(OTf)_3$, as a Lewis acid did not significantly improve the reaction (Entry 7). The structure of **5** and **5'** was unequivocally elucidated by NMR-^{1}H, NMR-^{13}C and HRMS.

Table 1: Reactivity **between t**he chiral γ-aminated dienophile **1** and the dienes **2-4**.



Entry	Diene	Reaction Conditions	Yield (%)[b]	Adduct[c]
1	2	$AlCl_3$ or $Yb(OTf)_3$ 20%/ Toluene /110^{O}C/ 48h	a	-
2	2	$Yb(OTf)_3$ 20%/Toluene/170^{O}C sealed tube/24h	a	-
3	3	$Yb(OTf)_3$ 20%/ CH_2Cl_2 /rt/ 48h	a	-
4	3	$AlCl_3$ or $Yb(OTf)_3$ 20%/ CH_2Cl_2 /70^{O}C/ 24h	a	-
5	4	Toluene refluxe/110^{O}C/ 48h	50%	5:5`(2.8:1)
6	4	Solventless/24h/140^{O}C in seal tube	65%	5:5`(3.0:1)
7	4	Toluene refluxe/$Yb(OTf)_3$ 20%/ 110^{O}C/48h	55%	5:5`(2.8:1)

a) Complex mixture of products. b) Measured after purification on silica gel chromatography c) d.e. measured by NMR.

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Synthesis of Novel 1,4-disubstituted 1,2,3-triazolic esters

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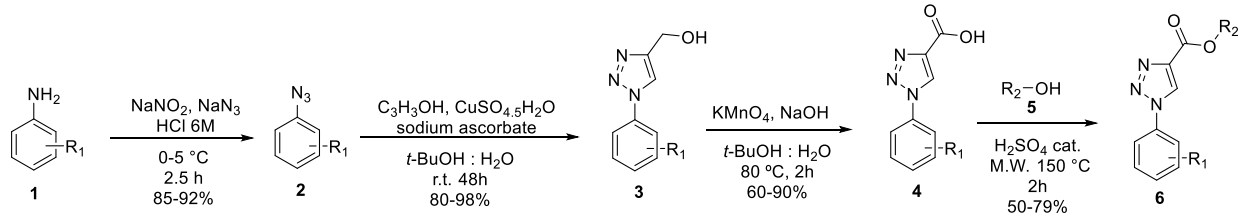
Keywords: *1,2,3-triazolic esters, click chemistry, Fischer esterification.*

ABSTRACT

Heterocyclic compounds containing the 1,2,3-triazole nucleus have received special attention in the field of synthetic chemistry since there are many possibilities of application as starting materials and in material and biological areas, like antimicrobial[1] and antichagasic action[2]. In this scenario, the objective of this work is the synthesis of 1,4-disubstituted 1,2,3 triazolic esters with novel structures. The 1,2,3-triazolic esters (**6**) were obtained through a four-step linear synthesis (Scheme 1). Firstly, functionalized anilines (**1**) underwent a diazotization reaction in the presence of sodium nitrite ($NaNO_2$), hydrochloric acid (HCl) and sodium azide (NaN_3) at 0 °C to generate the corresponding azides (**2**)[3] in 85-92% yield. Then, the azides and the propargyl alcohol reacted in a Copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction to build exclusively the 1,4-disubstituted 1,2,3-triazole ring with a primary alcohol (**3**) in *tert*-butanol and water at room temperature[4] with 80-98% yield. The carboxylic acids (**4**) were obtained in 60-90% yield through total oxidation of primary alcohols using $KMnO_4$ and NaOH in *tert*-butanol and water at 80 °C[5]. Finally, the 1,2,3-triazolic esters were synthetized through Fischer esterification between the carboxylic acids and commercial alcohols (**5**) under microwave radiation[6] at 150 °C using sulfuric acid as catalyst in 50-79% yield. The structures of novel compounds were confirmed by infrared, ^1H and ^{13}C NMR spectroscopy. These new esters (**6**) will be evaluated with trypomastigote and epimastigote forms of *Trypanosoma cruzi* in biological tests.



R_1 =H, 4-CH_3, 4-Cl, 4-F, 3,5-F or 3,5-CF_3

R_2 = CH_3, C_2H_5, $CH(CH_3)_2$ or C_4H_9

Scheme 1 – Synthesis of 1,4-disubstituted 1,2,3-triazolic esters

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Associating cross coupling and multicomponent reactions for the synthesis of 3,5-dicyanopyridine-based AIEEgens

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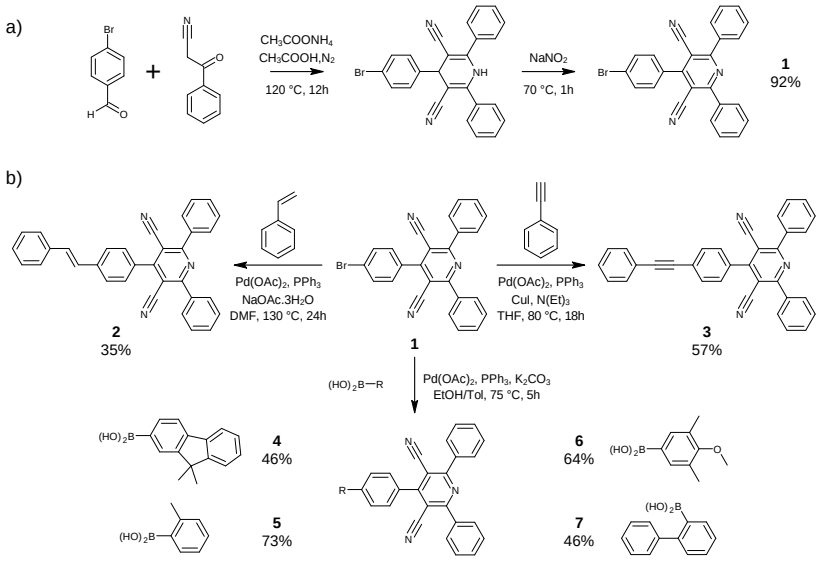
Keywords: *AIEE, fluorescence, dicyanopyridine, multicomponent reactions, cross-coupling reactions.*

ABSTRACT

The design of donor-acceptor structures has led to compounds with interesting photophysical properties. Among them Aggregation Induced Emission (AIE) and Aggregation Induced Enhanced Emission (AIEE) which are present when having rotation and vibration restrictions in a non-planar conformation, preventing energy dissipation and favoring radiative decays over non-radiative decays, increasing the luminescence of the aggregated states [1].Aiming AIEE, a series of donor-acceptor substituted 3,5-dicyanopyridines derivatives were synthetized using a two-step methodology. The multicomponent Hantzsch reaction[2] was employed for the construction of the acceptor moiety, 2,6-diphenylpyridine-3,5-dicarbonitrile, followed by C-C cross coupling reactions (Suzuki, Heck and Sonogashira), to add the donor units. Photophysical characterization was performed in solution, and the compounds showed absorption in the ultraviolet region and fluorescence emission ranging from ~425-525 nm in different solvents. Some compounds displayed enhancement of luminescence in THF solutions containing water fraction (f_w) from 70% up to >90%, which indicate AIEE properties.



Scheme 1. Synthesis of compounds 1- 7. **(a)** Multicomponent Hantzsch reaction to obtain the 2,6-diphenylpyridine-3,5-dicarbonitrile unit. **(b)** Coupling reactions to obtain compounds 2 (Heck), 3 (Sonogashira) and 4-7 (Suzuki).

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Leveraging complex experimental data from olefin metathesis reactions with the aid of data science and DFT modeling

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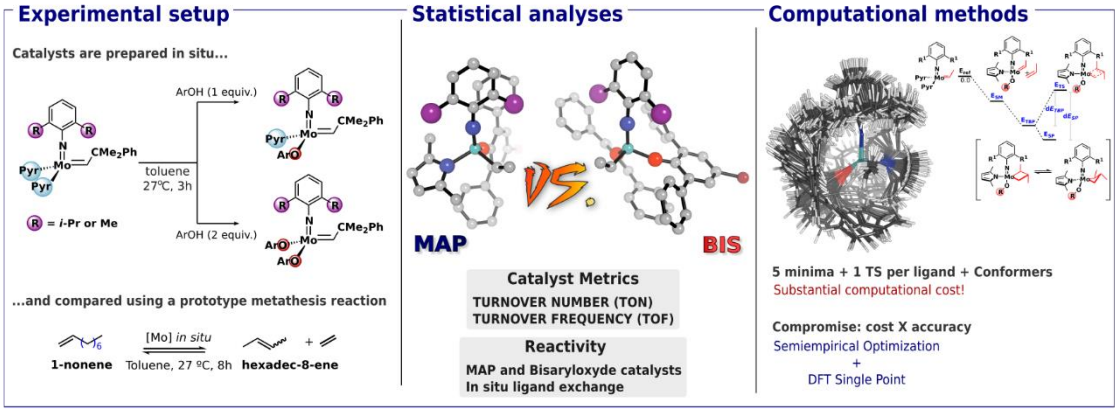
Keywords: Statistics, Schrock Catalysts, Olefin Metathesis, Computational Chemistry, Chemical Space

ABSTRACT



The catalysis literature is experiencing a great increase in publications that employ data science to describe reaction partners and experimental conditions in terms of parameters that capture relevant steric and electronic aspects of the reactions under investigation.[1] The underlying statistical analyses involved in these protocols empowers researchers to create predictive models for different kind of selectivities, experimental outcomes such as yield, and even theoretical-based activation energies at a fraction of DFT cost.[2] More recent approaches take advantage of classification methods to characterize a chemical space using these same descriptors, from which the most diverse molecules can be identified for innovative chemical design.[3] Besides being a platform to select promising catalysts for further testing, these statistical models can also act as a guide to mechanistic investigations by indicating which are the important factors correlated with the desired response. Here, we describe how data science can help the rationalization of the distinct reactivities observed for several Schrock catalysts employed in the wide-known olefin metathesis reactions. We report our ongoing studies to understand how different phenolic ligands can impact the Mo-alkylidene catalysts performances as measured by their Turnover Number (TON) and Turnover Frequency (TOF). Our dataset consists of carefully curated kinetic data from 140 reactions employing 35 ligands in two different concentrations.[4] A remarkable characteristic of this dataset is that all catalysts are prepared *in situ* by ligand exchange from a common precursor. Besides the complicated equilibria associated with the metathesis pathway itself, this experimental design provides an additional layer of complexity as the ligands can furnish monoaryloxy (MAP) catalysts, bisaryloxy catalysts, or even both.[5] We employed data analysis tools to aid the deconvolution of this complex experimental data and also guide the development of the catalysts scope by means of predictive models. Additionally, extensive DFT calculations were employed to further identify promising ligands in terms of the relative energy between relevant intermediates and also their intramolecular interactions.

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RATIONAL DESIGN AND SYNTHESIS OF NEW INDOLYZINES WITH SYNTHETIC AND MEDICINAL INTEREST

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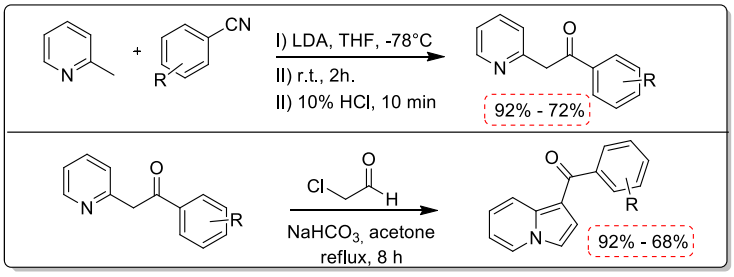
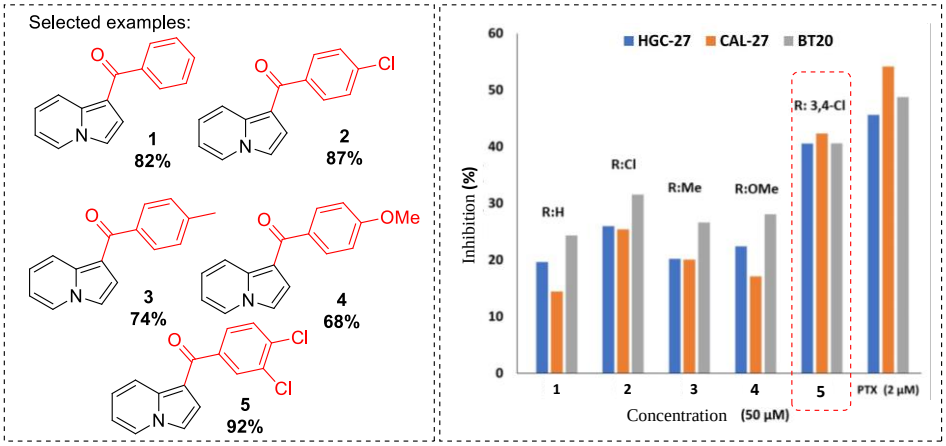
Keywords: *Indolizine, antitumoral, TopLiss Batchwise protocol.*

ABSTRACT

In medicinal chemistry, the indolizine nucleus have been described for its potential against anti-inflammatory, anticancer, larvicidal, antituberculosis, antioxidant, among others (1). This nucleus is treated as an indole bioisostere, considered a privileged ring, causing it to attract attention from medicinal chemists due to its great versatility. Inspired by an indole prototype undergoing clinical trials, indolizines with aryl ketone groups in the pyrrole ring showed interesting antitumor activity (2). In this sense, the work seeks the synthesis of a class of substituted indolizines with different structural patterns, following the TopLiss Batchwise protocol. For this, the cyclization and formation of the first series of indolizines was performed using 2-methylpyridine with yields ranging from 68 - 92%, with the substituents of interest for the medicinal study. These molecules were submitted to the evaluation of antitumor activity and based on the results obtained another class of indolizines is being prepared, in order to optimize the activity previously observed.





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Design and synthesis of new 3-thio-1,2,4-triazole derivatives as glutaminase inhibitors.

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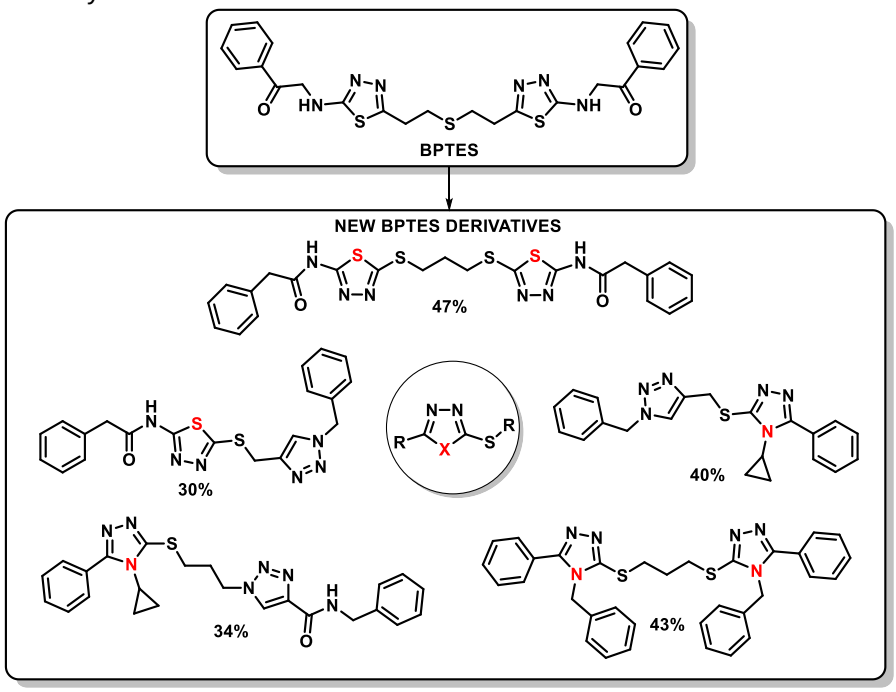
Keywords: glutaminase inhibitors, 3-thio-1,2,4-triazoles, BPTES.

ABSTRACT

Chemistry of 1,2,4- and 1,2,3-triazoles has been extensively investigated by chemists looking for a further application in medicinal chemistry, since these scaffolds present relevant biological activities as pharmacophoric groups.[1] These compounds showed good activity in different types of as cancer.[2] Insertion of those scaffolds can be done by different procedures, such as Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC)[3] or *via* basic cyclization of thiosemicarbazides. Newcomb *et al.*[4] synthetized a symmetric molecule with 1,2,4-thiadiazole scaffold (named BPTES), which exhibited good glutaminase inhibition. Glutaminase is overexpressed in tumor cell lines and is considered a promising therapeutic target for treating cancer. BPTES acts at allosteric site of glutaminase, presenting a different method of inhibition. Thus, in this work we designed and synthesized new derivatives of BPTES with the 1,2,4- and 1,2,3-triazole as scaffolds for new glutaminase inhibitors. Five derivatives were prepared in 30-47% overall yield in 3-5 steps, and their evaluation against glutaminase is underway.



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Ruthenium-catalyzed Metathesis Toward Trisubstituted Olefins – A Parameterization Approach

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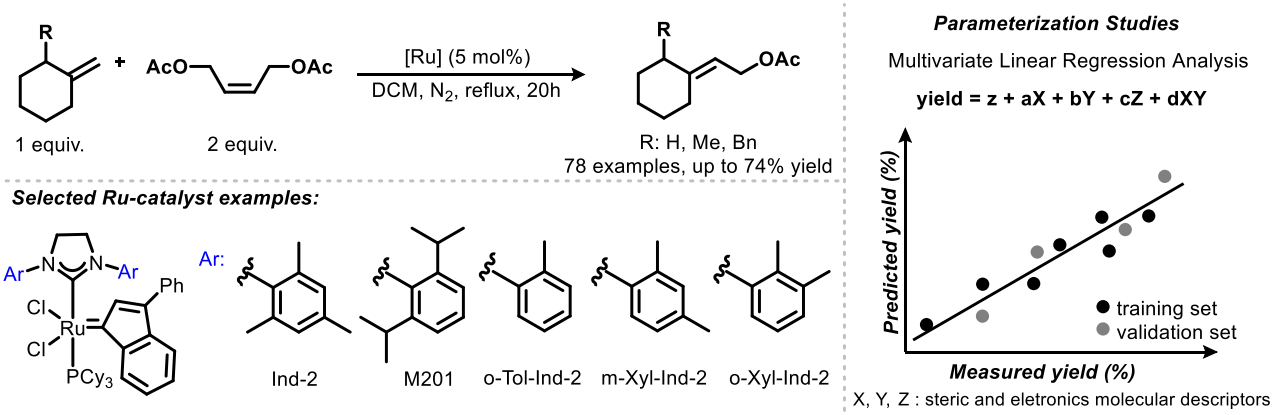
Keywords: *Catalysis, Olefin Metathesis, Parameterization.*

ABSTRACT

Olefin metathesis is a synthetic transformation in which two olefins are transformed into two new olefins. This reaction first observed in 1950 found wide application in industrial processes and natural product syntheses and was honored with the Nobel Prize in Chemistry in 2005.[1] To date, however, some challenges remain for the synthesis of highly substituted olefins or general control over product stereochemistry.[2-5] We present a predictive modeling approach to advance the design of new catalysts to address these challenges. Herein, we report on our efforts to integrate data science and computational chemistry tools to guide, predict, and explain the development of synthetic catalysts in the context of ruthenium-catalyzed trisubstituted olefin metathesis. In order to investigate substrate reactivity towards catalysts, we performed reactions with 3 methylenecyclohexane derivatives (challenging substrates), *cis*-1,4-diacetoxy-2-butene and 26 Ru-based catalysts. These experimental results were integrated with steric and electronic molecular descriptors obtained for the Ru complexes to parameterize the catalyst structure in respect to reaction yield. Our current results indicate that although the general structure of ruthenium-based olefin metathesis pre-catalysts is highly modular, the use of carbenes as one of the neutral ligands has the greatest impact in the performance of these reactions. Variation in the substitution pattern of the aromatic ring connected to the NHC nitrogens comprises the major variability of results for the challenging substrates, however, was not possible to observe a clear correlation. Thus, by means of the catalyst parameterization we expect to find correlations and predict new structures to expand the scope of catalyst used in these important reactions.



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Organic Synthesis applied to Advanced Materials: Organic Electronics

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Keywords: *donor-acceptor hybrids, functionalized nanotubes, carbazole, thiophene, Zinin reduction, electrochromism*

ABSTRACT

"Organic Electronics" with advanced organic materials are at the core of the organic light emitting devices (OLED). Our research group has been investigated novel molecular hybrid electroluminescent agents using the donor-acceptor (**D**-**A**) approach[2]. Herein we report the synthetic preparation of quaternary molecular nanohybrids **A**-**D**-**A**-**D** (Fig. 1) based on covalent conjugated amide bonds between oxidized multiwalled carbon nanotubes (**A**), amino-nitro-carbazole (**D**), 3-carboxy-thiophene (**A**) and poly(3-hexyl/dodecyl thiophene) (**D**). The initial synthetic step is the chemical modification of the nanotubes.[3] **1a** was prepared (Scheme 1) from dinitration and selective reduction with Zinin reaction[4]. The next step is the preparation of MWCNTCO-NHCbzNO$_2$ and "*in situ*" reduction with $SnCl_2$. The binding of 3-carboxythiophene was achieved through a microwave-assisted amidation yielding MWCNTCO-NHCbz NH-COTh (Scheme 2). Finally, the hexyl/dodecyl-thiophene quaternary hybrids **A**-**D**-**A**-**D** were obtained using the grafting technique. This poly-functionalized nanotubes showed outstanding optical contrast, coloration efficiency, fast switching times and electrochromic cyclability being promising electrochromic agents.

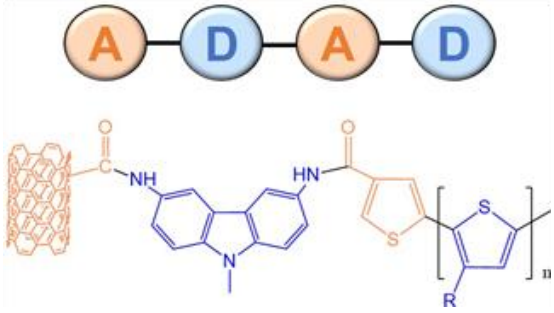
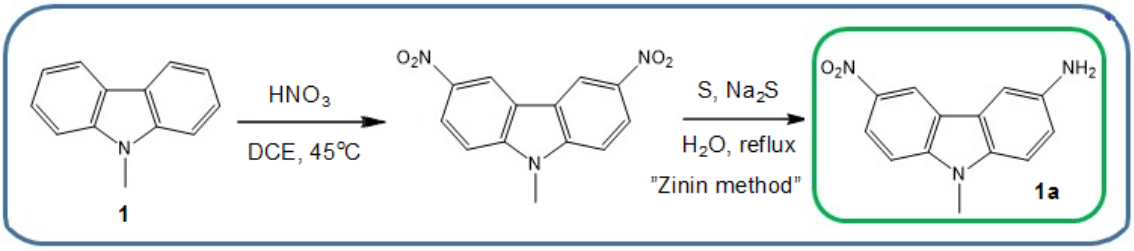
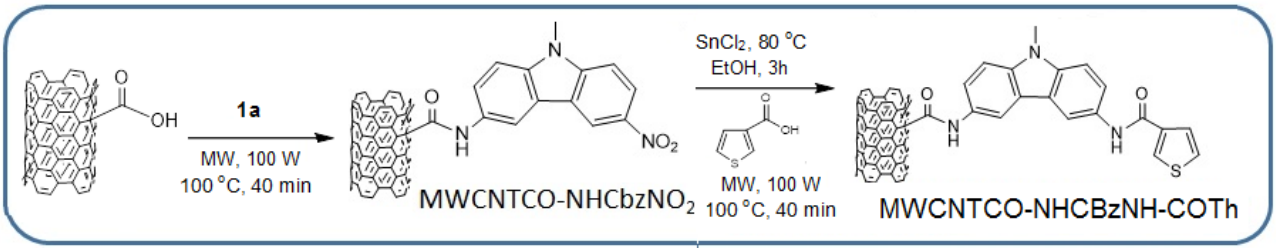


Fig. 1. Quaternary molecular nanohybrid **A**-**D**-**A**-**D** (R = C_6H_{13}, $C_{12}H_{25}$)



Scheme 1. Synthetic route for the preparation of 3-amino-9-methyl-6-nitro-carbazole (**1a**)



Scheme 2. Functionalization of MWCNT-ox with **1a**, "*in situ*" reduction and reaction with 3-carboxythiophene

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AI-based Molecular Design and Synthesis of New Peptidomimetic Inhibitors of SARS-CoV-2 M^{pro} enzyme

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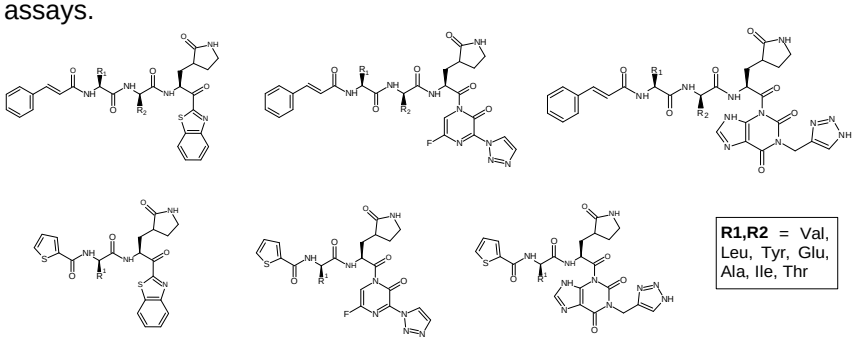
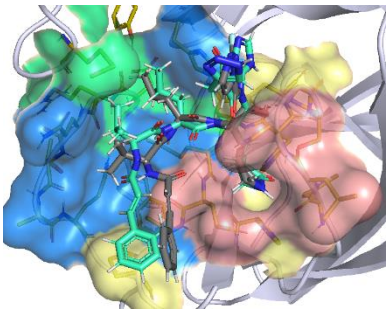
Keywords: *SARS-CoV-2, artificial intelligence, MPro inhibitors.*

ABSTRACT

The COVID-19's pandemic caused by the SARS-CoV-2 virus has caused several impacts across the world, being responsible for over 6 million deaths[1]. Inhibitors of the main protease (M^{pro}), which is essential for the viral replication, are an effective choice.[2]. Application of computational approaches derived from the artificial intelligence (AI) field, allow us to quickly propose new and potentially effective molecules based on a dataset of known inhibitors. Our work focused on the use of generative deep learning methods to develop inhibitors against M^{pro}. Compounds proposed by our group's AI model[3] were studied through molecular docking and are currently being synthesized for subsequent validation on biological activity assays. New peptidomimetic compounds will be coupled with different warhead groups as novel M^{pro} inhibitors. The synthesis was carried by conventional solution-phase peptide coupling methods with different aminoacids. Compound characterization was performed by NMR, IV and EI-MS. Compounds will be screened for biological activity assays.





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Synthesis of Near-Infrared Fluorophore Squaramides

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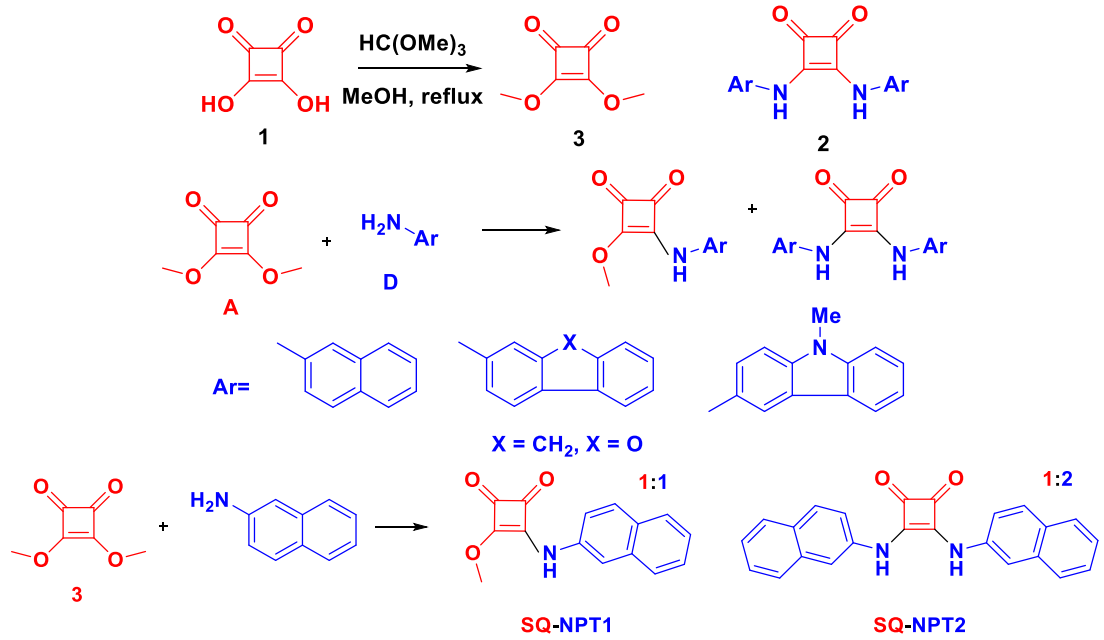
Keywords: *donor-acceptor molecular hybrids, squaramides, near-infrared fluorescence*

ABSTRACT

The squaric acid (**1**) is a very versatile organic building block used for the synthesis of advanced molecular agents with remarkable applications in a variety of fields in organic and inorganic chemistry[1-6]. The condensation between electrophilic squaric derivatives with the electron-acceptor unit (**A**) as squarate ester for instance, and aromatic amines (electron-donating unit, **D**) generate electron donator-acceptor (**D-A**) hybrid molecular systems known as squaramides (**2**) that can exhibit near-infrared fluorescence (NIRF)[5-6]. Herein, we report the efficient synthetic route for the preparation of some **D-A** molecular hybrid squaramides. The dimethylsquarate (**3**) was prepared treating **1** with trimethylorthoester[7] and the fluorescent amines were synthesized through the corresponding nitroaromatic derivatives. Using this approach, we obtained 2-naphtyl- (**SQ-NPT**), fluorene- (**SQ-NFLU**), dibenzofuran- (**SQ-NDBF**) and 9-methylcarbazole- (**SQ-NCBZ**) substituted squaramides. The mono- (**SQ-NPT1**) and di-(**SQ-NPT2**) naphtylsquaramides presented fluorescence in the near-infrared region. Monosquaramides and disquaramides might be selectively obtained in according to the corresponding molar ratios[8].



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Synthesis of Bis-N-Acyl-Hydrazones as New Promising Antifungal and Anticonvulsant Chemical Entities

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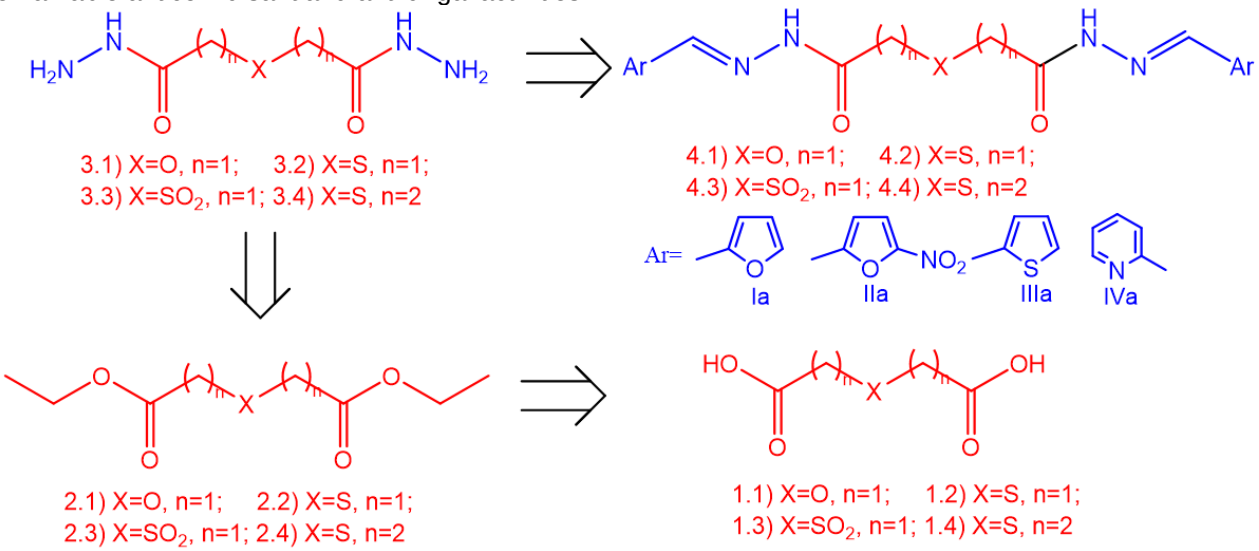
Keywords: synthesis of aromatic bis-N-acyl-hydrazones, microwave irradiation, antifungal, anticonvulsant

ABSTRACT

N-acylhydrazone (NAH) has been proven to be a versatile and promising small-molecule scaffold for the development of new, effective and safe therapeutically useful bioactive chemical agents.1-2 The present work reports the synthesis of novel aromatic NAH molecular hybrids Ar-CH=N-NH(C=O)-(CH2)n-X-(CH2)n-(C=O)NH-N=CH-Ar (X=O,n=1; X=S,SO2 n=1,2; Ar= 2-furan (I), 5-nitrofuran (II), 2-thiophene (III) and 2-pyridine(IV)) as possible antifungal and anticonvulsant agents. The planned retrosynthetic analysis (Scheme 1) to prepare these bis-N-acylhydrazones have diglycolic (1.1), thiodiglycolic (1.2) and its analogous sulfone (1.3), and 3,3-thiodipropionic (1.4) acids as starting materials. These dicarboxylic acids were submitted to Fisher esterification (ethanol/H_2SO_4) yielding the diethyl ester intermediates (2.1-2.4). The bis-hydrazides (3.1-3.4) were obtained by a very effective reaction with hydrazine hydrate using ultrasound irradiation in an unprecedented way. Finally, the desired NAHs (4.1-4.4) were obtained through the reaction of each of the hydrazides with the corresponding aromatic aldehydes (Ia-IVa). These new bioactive chemical entities exhibit remarkable anticonvulsant and antifungal activities.



Scheme 1. Synthetic Approach to functionalized furan- (**I**), 5-nitrofuran- (**II**), 2-thiophene- (**III**) and 2-pyridine- (**IV**) bis-N-acylhydrazones

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Highly selective fluorescent sensor for cysteine based on Seleno-BODIPY

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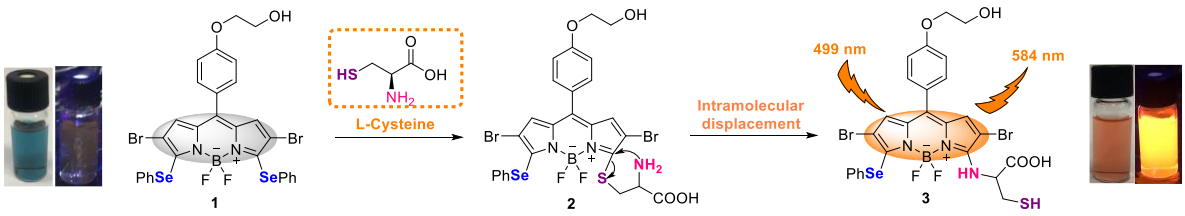
Keywords: *Chalcogen, Cysteine, Fluorescent probe, Selenide, Seleno-BODIPY*

ABSTRACT

Biothiols, such as cysteine (Cys) and glutathione (GSH), carries an important function in the maintenance of redox homeostasis in living organisms. Their excess or deficiency in biological systems may be associated with disorders like cardiovascular and immune dysfunction, and diseases such as cancer, among others.[1] Thus, biothiols intracellular visualization and quantification are very important. There are already fluorescent sensors able to distinguish biothiols from several other amino acids, however, it's still a great challenge for scientists the distinction between biothiols, GSH, and Cys due to their structural similarities. As these analytes are involved in pivotal roles in the biological systems, selective fluorescent sensors for Cys have been gaining a lot of prominence.

In this work, we present a new fluorescent probe (di-seleno-BODIPY - boron dipyrromethene, **1**) for selective detection of Cys, over GSH and amino acids. Compound **1** was synthesized starting from a BODIPY nucleus substituted by an ethylene glycol moiety, followed by a bromination (NBS) step, ending with a selenilation (PhSeH, generated *in situ*).[2] The seleno-BODIPY **1** was fully characterized (NMR, HRMS) and submitted to extensive photophysical properties measurements (λ_{abs} = 594 nm, λ_{em} = 628 nm).

Searching for biological applications, a screening with different analytes was performed in which it was possible to verify that compound **1** reacts selectively with Cys, comparatively to GSH and 11 amino acids (THF/H_2O 50% v/v pH = 7), showing a color change from blue to orange, in a turn-on fluorescence process (orange fluorescence). Absorption and emission spectra of compound **1** were obtained in the presence of the analytes and a hypsochromic shift with an isosbestic point were observed for Cys (λ_{abs} = 499 nm, λ_{em} = 584 nm). A kinetic study was carried out using Cys (50 eq.), in 25 minutes. MS analysis revealed (m/z = 760.20) that Cys reacts with BODIPY **1** leading to **3**, through an unexpected SePh substitution. A mechanistic investigation led to the conclusion that the reaction is driven by an initial sulfur attack, followed by a *N*-rearrangement. (Scheme 1). The occurrence of similar mechanisms has already been reported in the literature for halogenated BODIPYs.[3]



Scheme 1: Proposed mechanism for detection of Cys with BODIPY **1**.

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Bismuth(III)-Catalitic Synthesis of Cyclic Guanidines

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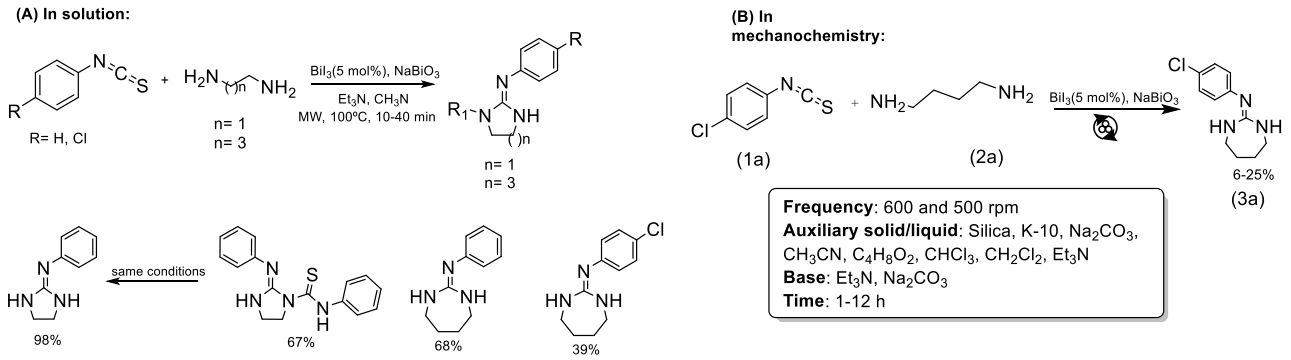
Keywords: *Cyclic guanidine, Mechanochemistry, Solvent-free.*

ABSTRACT

Heterocyclic guanidines are building blocks for the synthesis of natural, pharmaceutical and agrochemical products, among others[1]. They are usually prepared by means of halocyclization reactions with intramolecular displacement, hydroamination and carboamination of metal-catalyzed alkenes and alkynes[2]. However, these methodologies have disadvantages, employing conditions with the use of protective groups, requiring later steps of deprotection, catalysts that are difficult to access, in addition to the use of toxic solvents, such as toluene, and in some cases the need to use an inert atmosphere[3,4]. Two methodologies have been developed for the synthesis of cyclic guanidines: in solution[5] and via mechanochemistry. Both using the domino reaction, without the need to isolate their intermediates, in which amine nitrogen is added to the thiourea formed in situ. In this work, seven-membered guanidine synthesis was employed. Mechanochemistry proves to be efficient and attractive for the synthesis of this molecule, proving its reactivity. After optimal solvent-free condition, the scope will expand, as will your synthetic applications.



Scheme 1 – Synthesis of cyclic guanidines.

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Hybrid Amides as Molecular Building Blocks for Emerging Near-Infrared Fluorophores

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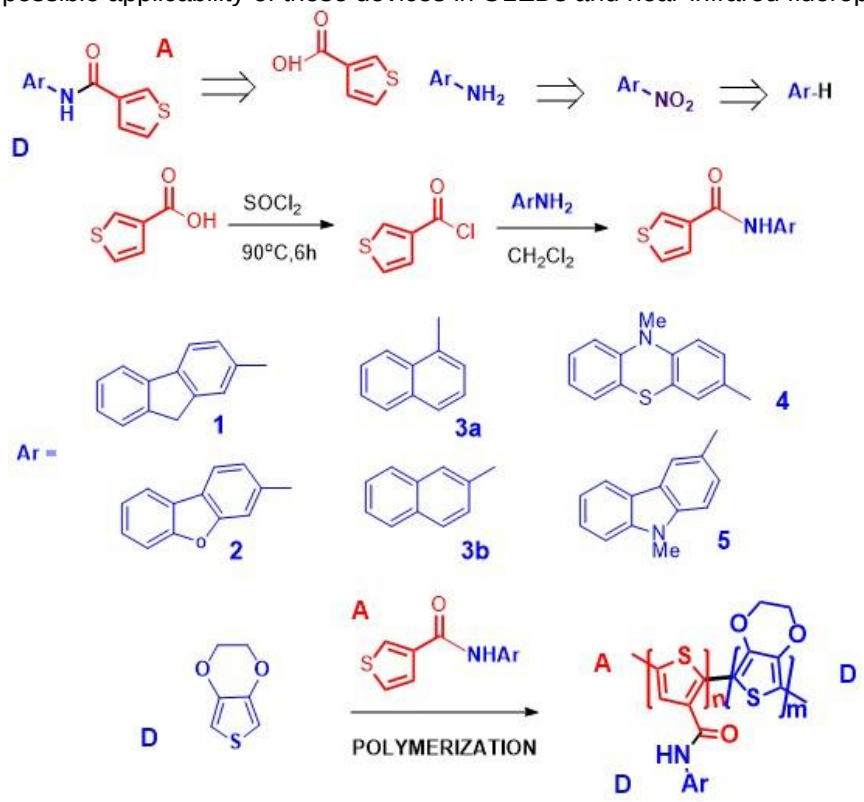
Keywords: *fluorescent amines & hybrid amides, carboxythiophene, donor-acceptor, PEDOT, near-infrared fluorophores*

ABSTRACT

The development of advanced electroluminescent agents with electron donor-acceptor (**D-A** or **D-p-A**) hybrid/ambipolar molecular systems is a very promising approach to achieve high quantum efficiency.[1] In this work, the synthetic key-step is the rational planned chemical connection **D-A** through an amide bond between an acceptor carboxy-thiophene moiety (**A**) with donating fluorescent amino-aromatic based units (**D**) (**ArNH$_2$**, **Ar =** 2-fluorene(**1**), 2-dibenzofuran (**2**), 1-/2-naphthyl (**3a,3b**), N-methyl-3-phenothiazine (**4**) and 3-N-methylcarbazole (**5**)). These binary hybrids can be transformed into the tertiary systems **D-A-D** (through electro- or chemical copolymerization with 3,4-ethylenedioxythiophene (EDOT, **D**) the most useful polythiophene to achieve good photometric and electrochromic properties due to the high quantum yield (PL), thermal stability, and easy preparation.[2] In fact, the thermal, optical and electrochemical properties of some of these novel semiconductive materials ever showed themselves as better when compared to the PEDOT film and highlighted a possible applicability of these devices in OLEDs and near-infrared fluorophores.



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The acylation of sulfoxonium ylides by a non-radical pathway from *N*-hydroxyphthalimide esters

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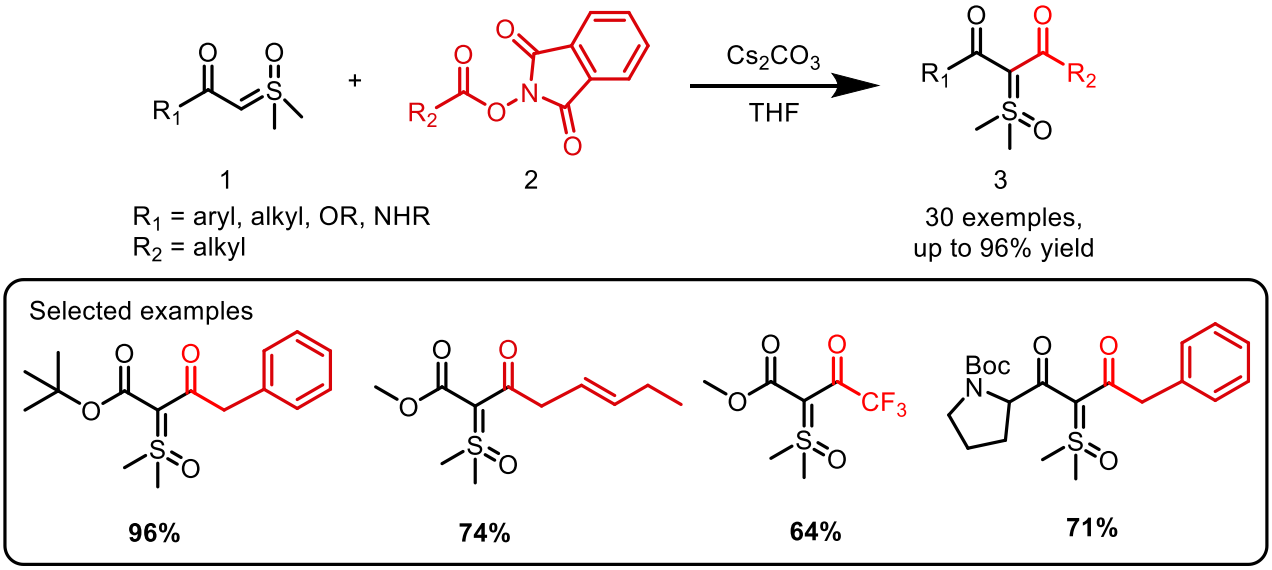
Keywords: *Sulfur ylide, C-C bond formation, coupling reaction.*

ABSTRACT

Sulfoxonium ylides are important building blocks in organic synthesis and have gained increased attention in recent years[1]. The synthesis of disubstituted sulfoxonium ylides, however, rely on the use of diazo compounds via rhodium catalysis, coupling of ylides with arynes and coupling of ylides with aryl halides/triflates via palladium catalysis[2,3]. These methods are limited to aryl groups only. Triethylsulfoxonium ylides can also be used but are limited to methyl substituents. Here we describe an unusual, transition metal free, reactivity of sulfoxonium ylides with *N*-hydroxyphthalimide esters affording alpha substituted sulfoxonium ylides with acyl groups. The reaction works with sulfoxonium ylides with different functional groups in mild conditions (scheme 1). *N*-hydroxyphthalimide esters are known to react forming radical species in photochemical conditions or in the presence of transition metals such as Ni and Fe.[4] Mechanistical studies, however, suggest that the reaction takes an ionic pathway.

Scheme 1. General methodology for the synthesis of substituted sulfoxonium ylides.



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A new thioglycolic ester β-cyclodextrin/$PdCl_2$ complex as an accessible catalyst for aqueous Suzuki-Miyaura coupling reaction. Investigation of mechanism and exploration in the synthesis of biflavonoids.

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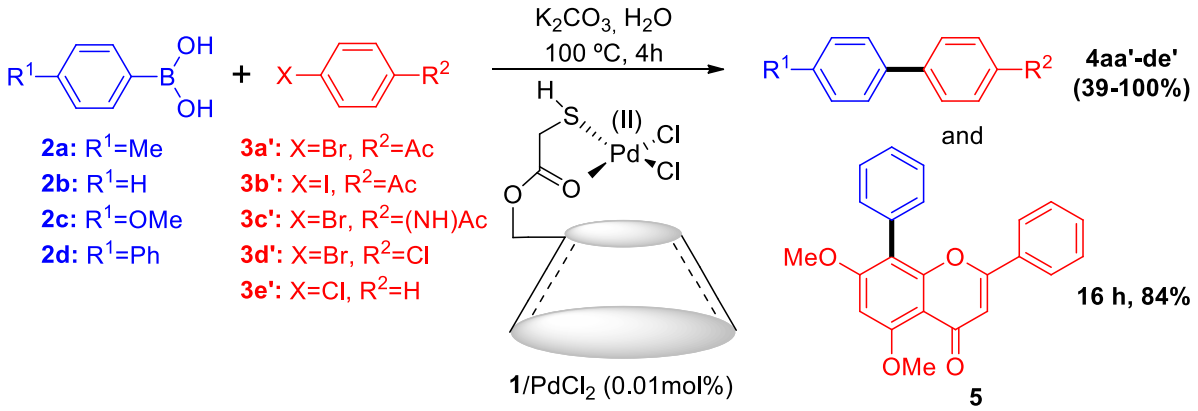
Keywords: *β-cyclodextrin, Suzuki-Miyaura coupling reaction, bioflavonoids*

ABSTRACT

We designed and synthesized the first examples of novel thioglycolate β-CD derivatives complexed to $PdCl_2$ and its application as an efficient catalyst for aqueous Suzuki-Miyaura reaction[1] in an open-air flask. The ligand **1** afforded the best catalytic performance when complexed with $PdCl_2$. The **1**/$PdCl_2$ catalyst showed excellent activity in the SM reaction of boronic acids **2a-d** and aryl halides **3a'-e'**, furnishing coupling products **4aa'-de'** from moderate to excellent yields (39-100%). The advantages shown were easy and simple preparation and storage, catalytic efficacy (0.01 mol%) under mild reaction conditions, and environmental benefits due to the use of water as solvent. Meanwhile, a mechanism was suggested,[2] based on the controlled experiments with bulky aryl halide, which allowed the synthesis of biaryl flavonoid **5** in 84% yield. Consequently, these novel thioglycolic β-CD derivatives as ligands will open novel challenging designs of new water-soluble catalyst systems with potential synthetic utility in cross-coupling reactions.



Scheme 1: aqueous Suzuki-Miyaura coupling reaction with modified β-cyclodextrin catalyst

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A new protocol for the synthesis of carbamates from CO_2 employing immobilized DBU

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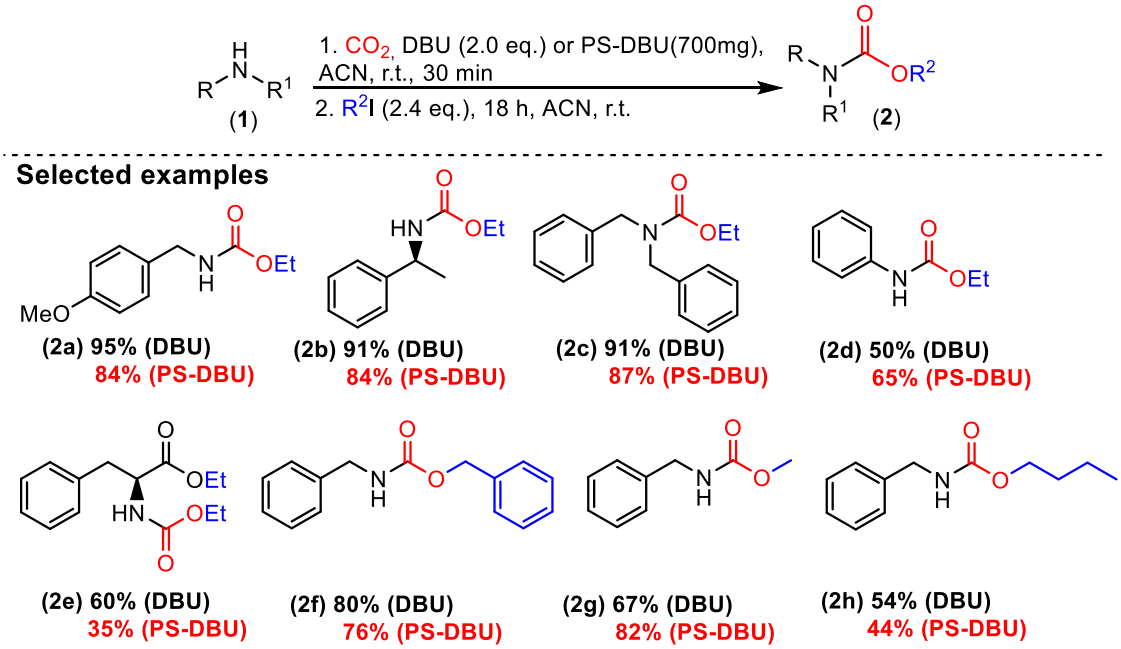
Keywords: *Carbon dioxide, heterogeneous and homogeneous catalysis, carbamates.*

ABSTRACT

Carbon dioxide has proven to be an important source of a one-carbon building block in organic synthesis since it is a renewable raw material, economical, abundant, and with low toxicity. Physiochemically, CO_2 is a thermodynamic and kinetic stable molecule, however, it can be transformed into value-added compounds using a suitable chemical environment.[1-3] In addition, carbamates are important amine-protecting groups and platforms in the synthesis of isocyanates. The work presented herein showcases the synthesis of carbamates from CO_2 and amines (**1**) using mild reaction conditions. We evaluated different solvents, reaction times, and catalytic systems (homogeneous and heterogeneous) for the capture and subsequent transformation of CO_2 into **2**. We found that in a one-pot, two sequence steps, the carbamic acid intermediate formed between **1** and CO_2 can be transformed into **2** using alkyl halides as the alkylating agents at room temperature in good yields (up to 95%) and DBU or PS-DBU as catalysts.



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Disclosing Another Face of Sulfoxoniun Ylide's reactivity: Synthesis of *Gem*-Difluorinated Sulfoxides

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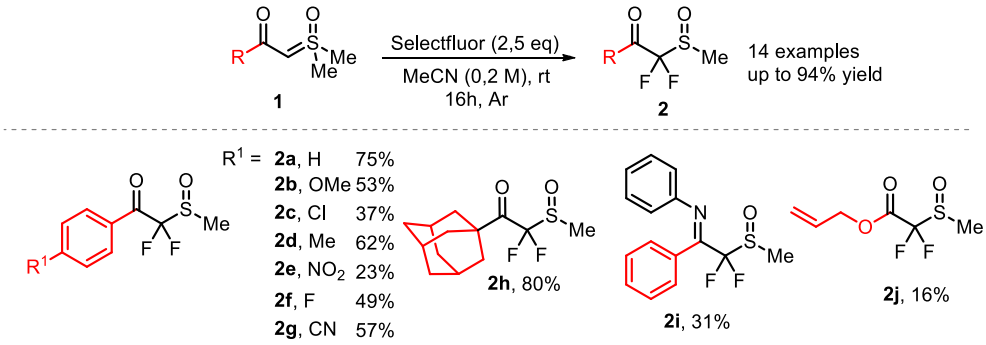
Keywords: *Sulfoxonium Ylide, Gem-Difluorination, Sulfoxides*

ABSTRACT

The exchange of hydrogen atom to fluor represents an important topic in medicinal chemistry, as they can alter properties, as metabolic stability and lipophilicity, among others.[1] In this context, *gem*-difluorinated compounds are important building blocks in fluorine-containing pharmaceuticals and materials.[2]

Our group research has focused in *α*-functionalization of carbonyls from sulfoxonium ylides, with representative examples obtaining *α* -fluorine carbonyl compounds.[3] Herein, we present the synthesis of *gem*-difluorinated *β*-keto sulfoxides from sulfoxonium ylides, in an unexpected reactivity. This reaction occurs in a simple procedure, without any additives. After initial discovery, studies in optimization were carried out, with optimized conditions depicted below (**Scheme 1**). Aromatic ketones were tolerated under these conditions (up to 94% yield), and adamantyl group was obtained in 80% yield. Imine was evaluated, with 31% yield in **2i**. Ester, although in lower yield, was obtained in 16% in **2j**. Studies in mechanism and applications of this methodology are under investigation.



Scheme 1. Scope of gem-difluorination of *β*-keto sulfoxides with selected examples

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Alkylation of α-carbonyl sulfoxonium ylides

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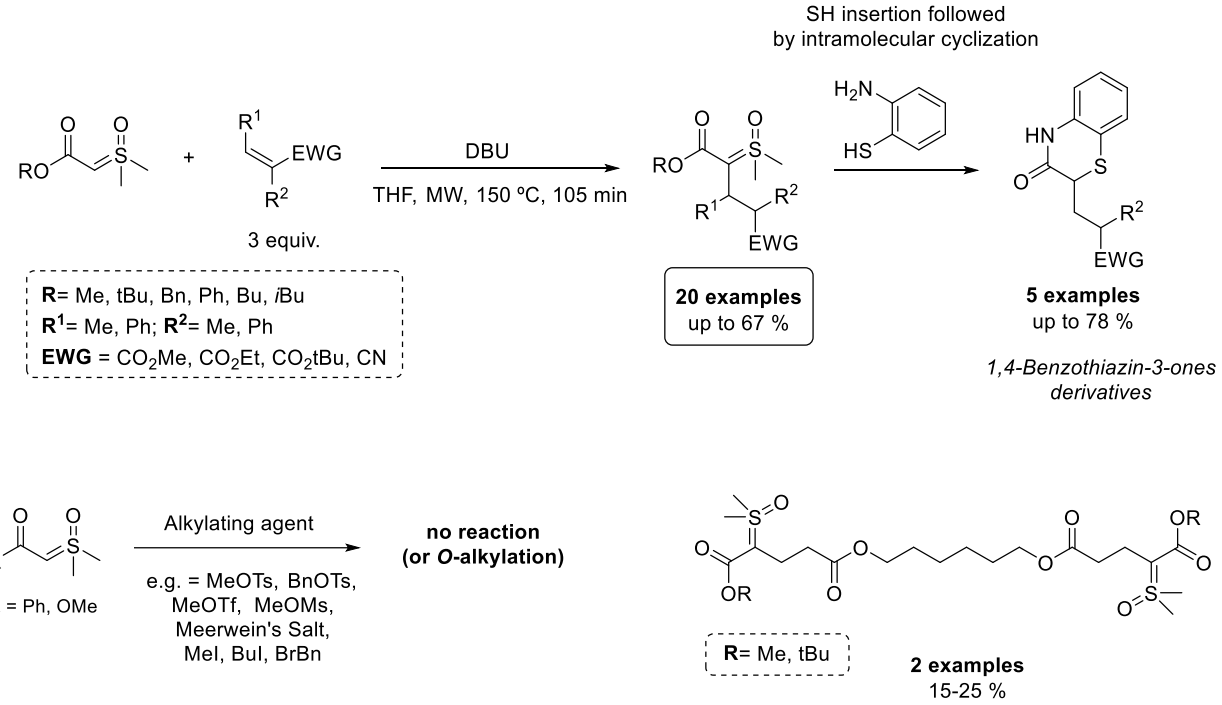
Keywords: *Sulfoxonium Ylides, Alkylating Agents, Michael Additions, 1,4-Benzothiazin-3-ones, Sulfur Bis-Ylides.*

ABSTRACT

Sulfur ylides represent an important synthetic tool for organic chemists since they are used as building blocks in total synthesis, in material chemistry, and in the production of drugs. However, there is a great difficulty associated with the alkylation of α-carbonyl sulfoxonium ylides. No method describes the insertion of any group different from aryl, which limits its application[1,2]. In this context, a series of alkylating agents was investigated to obtain the alkylated ylides via nucleophilic substitution reactions. However, this strategy was ineffective. Interestingly, the synthesis of these ylides was only possible when Michael acceptors were employed. In this case, 21 alkylated sulfoxonium ylides were obtained in 2-67 % yields and without any competition with cyclopropane formation. To demonstrate an application, 1,4-Benzothiazin-3-ones, a class of compounds with great pharmaceutical importance, were synthesized. In addition, a diacrylate was used in the studies, furnishing sulfoxonium bis-ylides in 15-25 % yields and which were employed in S-H insertion reactions, providing the corresponding β-ester di-thioethers in 25-40 % yields.



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Synthesis of New Photodegradable Antimicrobial Agents

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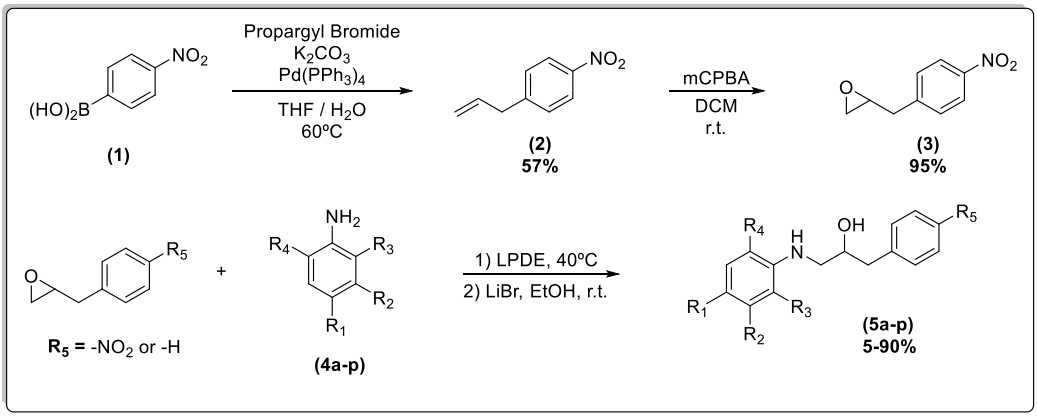
Keywords: *Antibiotics, Photodegradation, synthesis*

ABSTRACT

Multi-drug resistant (MDR) bacteria are currently a severe public-health problem due to the extensive and indiscriminate overuse of antimicrobial agents. MDR bacteria lead to a problematic situation, where the treatments for infectious diseases are becoming less effective and increasing medical costs and mortality.[1] One of the reasons for the growth of MDR bacteria cases is the high levels of antibiotics residues in bodies of water, leading to a demand to develop new antimicrobial agents, which scaffolds could degrade under ambient light, preventing accumulation in the environment.[2,3] The present work describes the synthesis, characterization and photodegradation of 16 new compounds with potential biological application as photodegradable antimicrobial agents based on our previously reported scafold.[4,5] The synthesis, photodegradation, and biological activity will be presented.



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Rongalite in PEG-400 as a general and reusable system for the synthesis of 2,5-disubstituted chalcogenophenes

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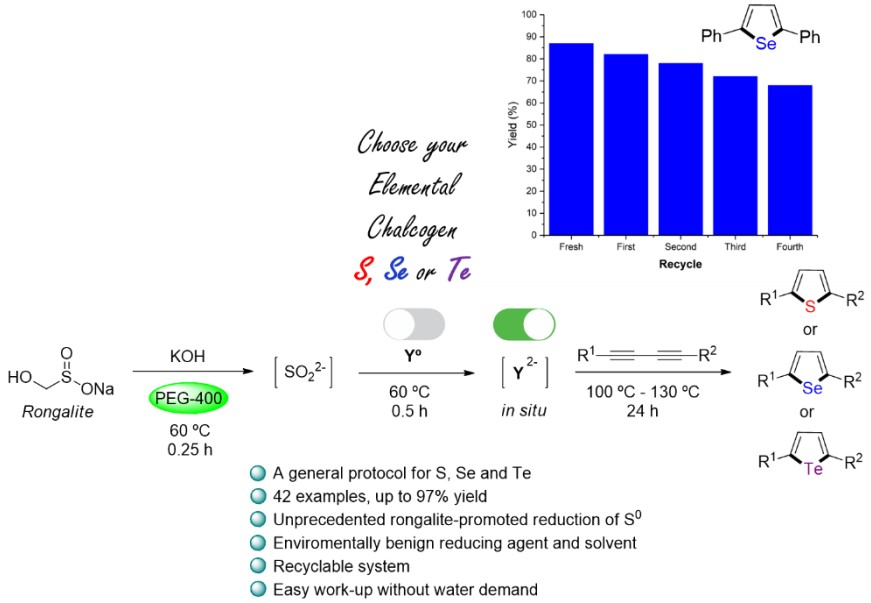
Keywords: *Organochalcogen, Cyclization, Rongalite.*

ABSTRACT

In this work, we report the use of rongalite in PEG-400 as a general, reusable, efficient, inexpensive and environmentally benign reductive system for elemental chalcogens and its use for the synthesis of 2,5-disubstituted chalcogenophenes (S, Se, Te) from 1,3-butadiynes. Using this method, a wide range of symmetrical and non-symmetrical 1,3-butadiynes were successfully employed for the synthesis of the desired chacogenophenes. This protocol benefits from many sustainable features; it is catalyst-free, safe to carry out, and uses cheap reagents and non-toxic chemical reaction media. Furthermore, the operationally simple reaction conditions and easy product separation allowed the reuse of PEG-400 in up to four successive reactions for the synthesis of 2,5-diphenylselenophene.



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Selective alkynylation of cyclic amines via Ruthenium C-H activation bond under visible light

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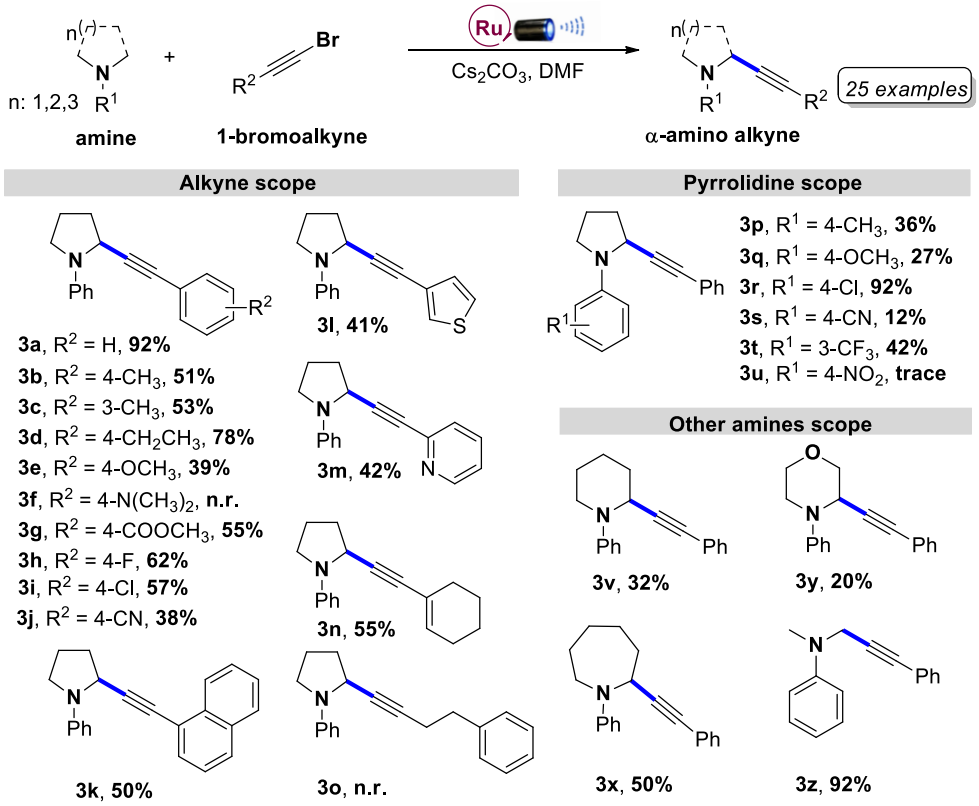
Keywords: *Photocatalysis, C-H activation, Ruthenium, Alkynylation*

ABSTRACT

Functionalization through C-H activation bond involves the use of non-prebuilt substrates that are converted into more complex molecules.[1] At the same time, transformations involving photoredox catalysis can promote the formation of new carbon-carbon bonds through an alkyl radical. These radical reactions driven under mild conditions, using visible light as cheap and sustainable energy source emerges as an efficient alternative for conventional methods.[2] From this perspective, we presented an selective alkynylation of cyclic amines mediated by a photoredox process with blue LEDs irradiation and $[Ru(bpy)_3]Cl_2$ as the catalyst. To evaluate the substrate scope of this approach for the synthesis of substituted α-amino alkynes, various 1-bromoalkynes and cyclic amines were used. In summary, was developed an elegant, efficient atom economy protocol for the synthesis of α-amino alkynes through C-H activation bond, assisted by Ruthenium catalyst resulting into 25 examples with moderate to good yields under mild conditions.



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High Throughput Screening (HTS) Applied to the Synthesis of APIs' Impurities

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Keywords: *Microscale, Parallelization, Screening.*

ABSTRACT

High-throughput methods were developed in the 1980s to improve the efficiency of drug discovery. High-throughput screening (HTS) was conceived to rapidly develop the best synthetic conditions to effect a specific transformation.[1] Parallelization of experiments and the work in microscale (2.5–10 µmol) are attractive features of this technology.

As a case study, we selected *the synthesis of Ibuprofen Impurity C (**1**)*. In 2017, 89% yield was reported for **1** using $K_2S_2O_8$ in water.[2] However, we could not reproduce these results and obtained low yields and conversions.

To find suitable synthetic conditions for **1**, we used microscale HTS (Figure 1). 96 reactions were performed in 1 mL vials exploring different bases, solvents, additives and temperatures in the presence of $K_2S_2O_8$ and found a reactive combination rendering **1** in 37.5% yield.

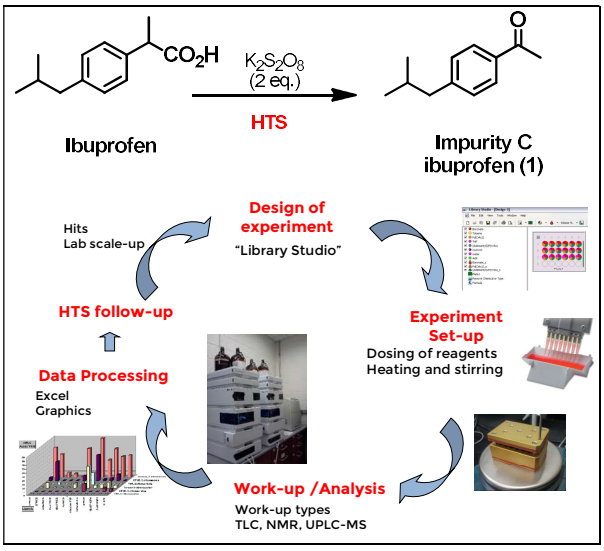

Fig. 1: Oxidative decarboxylation of ibuprofen to compound **1** using HTS.

Further screen to explore the oxidant role is currently on-going.

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Nitration and reduction of (hetero-)aromatics for electroluminescence: deacetylation, oxidation and Zinin method

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Keywords: *selective nitration methods, fluorescent aromatic amines, Zinin reduction*

ABSTRACT

Aromatic nitro/amino compounds are versatile synthetic building blocks for useful molecular functionalization.[1,2] In our research group the synthesis of nitro/amino dibenzo-fused compounds (Fig.1) is the key-step for synthesis of new binary (**ArNH-Ar^1**) and ternary (**Ar^1-NHArNH-Ar^1**, **Ar^1-NHArNH-Ar^2**) electroluminescent hybrids[3]. The classical nitration (nitric/sulfuric acids) is the most applied method, such as for N^5,N^{10}-dioxide-phenazine **PNZNOX (1).** Nevertheless, for **PTZ-Ac(2.1)** an intramolecular deacetylation rearrangement arises, even with acetic acid media[4] or any other milder/"green" conditions[1]. Nitric-acetic acids[4,5] is an efficient mono-nitration method for **OXA(5), FLU-6.1/6.2** and **DBF-7** (**R^2**=NO_2), however for **2.1**, **PTZ-Bz (2.2)**, **PTZ-Me (2.3)**, **OXTH (3)**, **THIA (4)** and **DBT (8)** the oxidation to the sulfoxide also occur. Mono-(**R^2**=NO_2)/di-nitration (**R^2=R^4=**NO_2)[6] can be obtained with different reaction conditions.[5] Nitric acid in 1,2-dichloroethane is better for mono-/di-nitration (**R^1=**NO_2/ **R^1=R^3=** NO_2) of **CBZ (9)**[7]. The new mononitro-monoamino compounds **NO_2-Ar-NH_2** (**R^1=**NO_2**,** **R^3=**NH_2 or **R^2=**NO_2**,** **R^4=**NH_2) can be selectively prepared from the dinitro analogs using the Zinin reaction[8]. The monoamino/diamino derivatives were obtained with classical reduction (iron/tin/zinc).

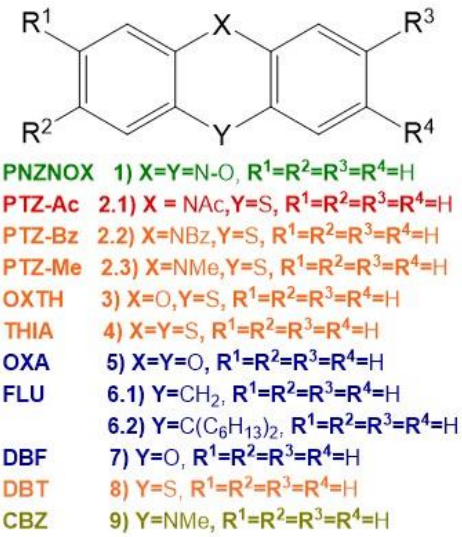
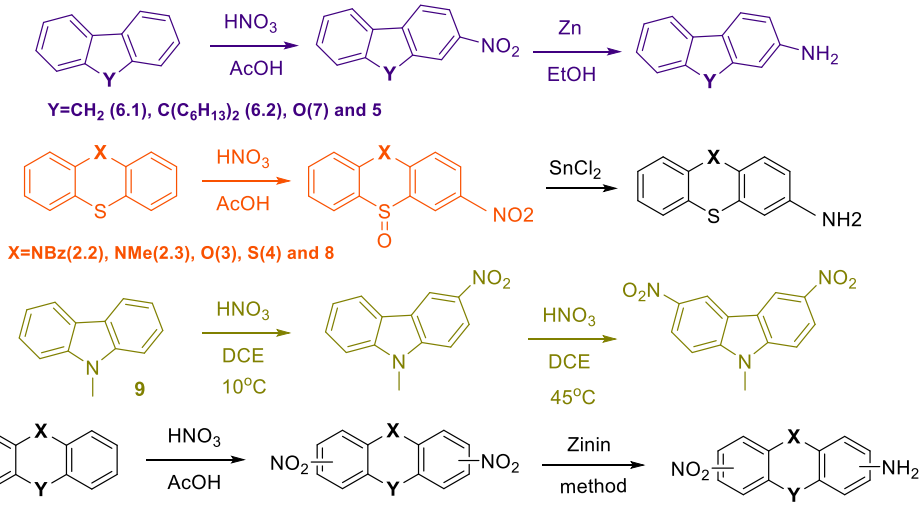


Fig.1 – Molecular aromatic scaffolds for synthesis of nitro- and amino-electroluminescent builging blocks



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Nucleophilic Fluorination using Potassium Fluoride, Crown Ethers, Bulky Alcohols and Diols Based on Simulations of Molecular Systems

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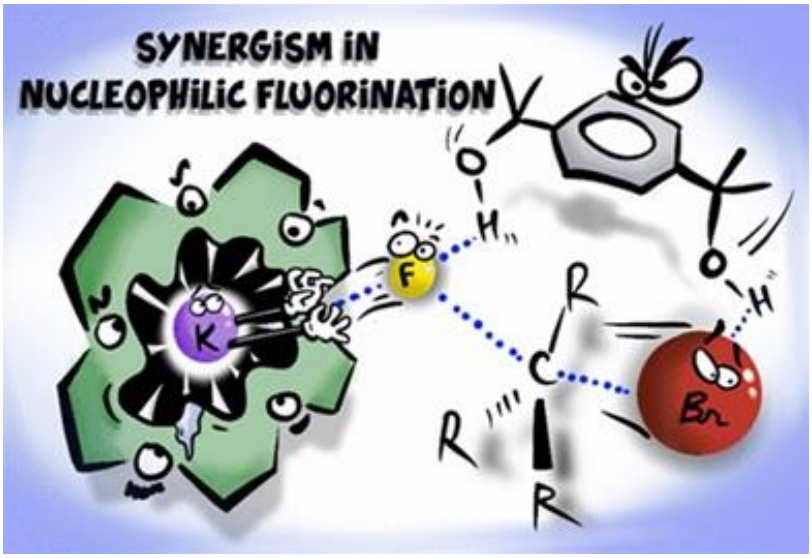
Keywords: *fluorination, phase transfer catalysis, bulky diols*

ABSTRACT

The organic chemistry of fluorine has gained notoriety in recent years due to the many properties that this element adds to bioactive organic compounds.[1] However, complex reagents are still used for nucleophilic fluorination in general as fluorine source. The use of potassium fluoride could be a best choice for this purpose because this is cheap and simple to manipulate, but the difficulty in obtaining organofluorinated compounds by this way is partly due to its low solubility in organic solvents. Another challenge is controlling the competition between nucleophilic substitution reactions and elimination. In this work, the use of bulky alcohols and diols in catalytic quantities is discussed and tested to increase the selectivity and yield of the reaction.[2,3] New methods of synthesis were developed based on theoretical calculations, followed by experimental studies of nucleophilic fluorination reactions. We have investigated the influence of bulky alcohols combined with phase transfer catalysis. The experiments show the efficacy of bulky alcohols containing two hydroxyls when combined with crown ether 18-crown-6 using acetonitrile as a solvent, with yield of 46% at moderate temperature of 82 ^{o}C and only 24 hours of reaction. Longer reaction time could lead to higher yield and minimal formation of E2 product.



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Synthesis of azole derivatives targeting a promising antimicrobial activity.

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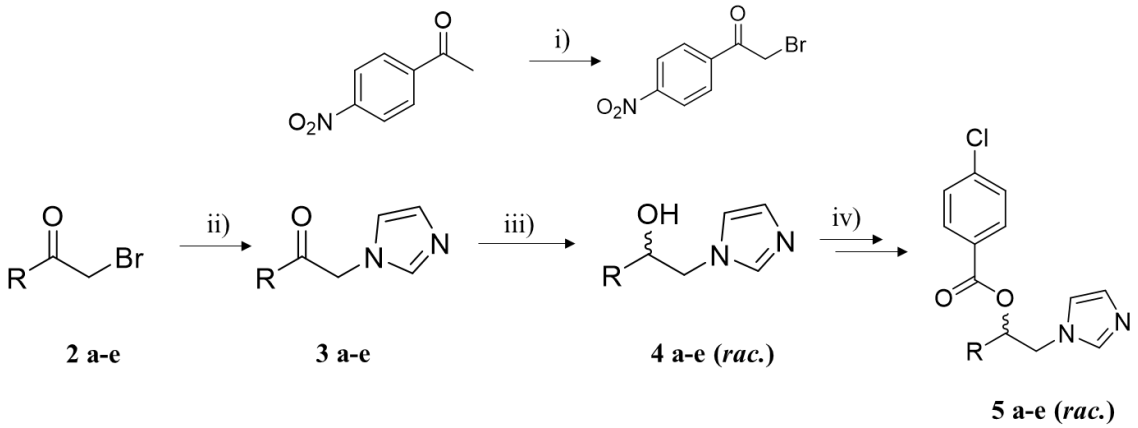
Keywords: *Stereoselective synthesis, biotransformation, Steglich esterification*

ABSTRACT

The interest in azole derivatives is due to their promising antimicrobial activity, which emerges from the combination of their functionalized groups. There are reports of the high activity of reduced imidazo-ketone derivatives in the inhibition of heme oxygenase-1 in rodent and human spleen cells, on micromolar scales.[1] It was possible to find studies with molecules with a similar chemical skeleton, modified by esterification, which showed excellent results in antituberculosis agent[2] and as antifungal activity[3]. Some azole derivatives esterified with 4'-chlorobenzoic acid showed excellent antifungal activity against *C. albicans* and *C. tropicallis*[3]. In order to expand the investigation on this class of compounds, new azole derivatives were synthesized (Scheme 1) to explore their antimicrobial activity. Besides, we comparing racemates to enantiomerically enriched compounds via the biotransformation step, given that the application of microorganisms as catalysts has been increasing, making the processes organics become cleaner[4], as well as their stereoselectivity.



R = a. phenyl; b. 4'-chlorophenyl; c. biphenyl; d. β-naphtyl; e. 4'-nitrophenyl

Conditions: i) NBS, TsOH, $CHCl_3$, r.t., 82%; ii) imidazole, acetone, r.t., ranging 82%-87%; iii) $NaBH_4$, MeOH, ranging 70%-86%; iv) 4'-chlorobenzoic acid, DCC, DMAP, CH_2Cl_2.

Scheme 1: Synthesis of azole derivatives.

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Synthesis, toxicity and preliminary anti T. cruzi activity of arylated thiazole derivatives

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Keywords: Chagas disease, thiazole, Suzuki reaction, *in vitro* model.

ABSTRACT

Chagas disease is a parasitic infection caused by Trypanosoma cruzi. The investments in research of drugs/medicines and control of this disease are small, even affecting more than 6 million people, especially in Latin America. The reference drug, in Brazil, is benznidazole, which is effective in the acute phase, but limited in the chronic phase, which makes essential the search for candidates who acts in all stages[1]. According to the literature, thiazole derivatives may present trypanocidal properties[2-3]. Based on this review, a synthetic route was developed to obtain arylated thiazole derivatives. The synthesis was based on Suzuki reaction (Figure 1). These molecules had their preliminary trypanocidal activity and toxicity evaluated *in vitro* models, most of them presented LC_{50} values greater than 400µmol.L^{-1}. The compound 4c showed the best results in trypanocidal activity, reducing 76% of the infection in host cells in a concentration of 20µmol.L^{-1}.

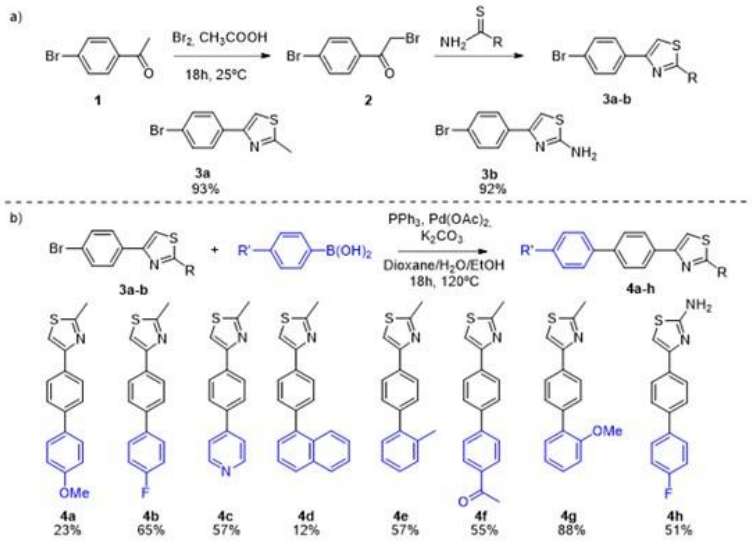

Figure 1 - Synthesis and structures of thiazoles **4a-h**

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Synthesis and iodination of *N*-phenylcarbamates

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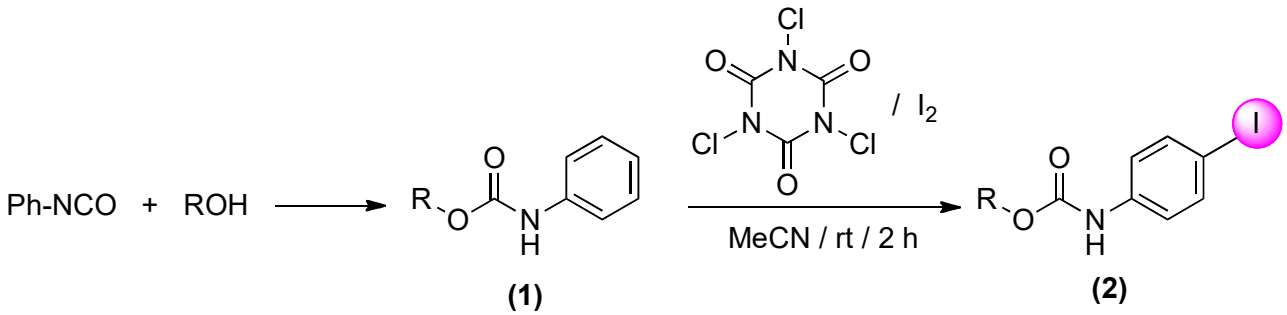
Keywords: *halogenation, iodination, regioselective synthesis, carbamates.*

ABSTRACT

The *N*-phenylcarbamates (NPC) group is present in many commercial and biological active molecules. Halogenated NPC can present new or increased biological activity when compared to analogue non-halogenated NPC.[1]

NPC are commonly synthesized by reacting phenylisocyanates with alcohols. The direct halogenation of NPC is desirable since it decreases the need of expensive halogenated phenylisocyanates. Our group has previously developed new methodologies to halogenate *N*-phenylureas. [2] Due to its similarity to NPC, in this work we expanded the scope of those methodologies to obtain halogenated NPC.

The NPC (**1**) were obtained by condensation of phenylisocyanate with water and alcohols. The reaction of (**1**) with trichloroisocyanuric acid (0.34 equiv.) / I_2 (1 equiv.) produced the corresponding *N*-(4-iodophenyl)carbamates (**2**) in 73 – 100 % yield and high selectivity.



(1) **(2)**

R	**(1)** (%)	**(2)** (%)
H	-	95
Me	83	84
i-Pr	45	89
octyl	65	98
benzyl	48	99
Ph	73	73

In summary, we developed a very convenient methodology to prepare *N*-(4-iodophenyl)carbamates in mild conditions.

ACKNOWLEDGEMENTS

The authors would like to thank CNPq and CAPES for financial support.

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Kinetic resolution of propargyl tertiary alcohols by *Candida antarctica* lipase A

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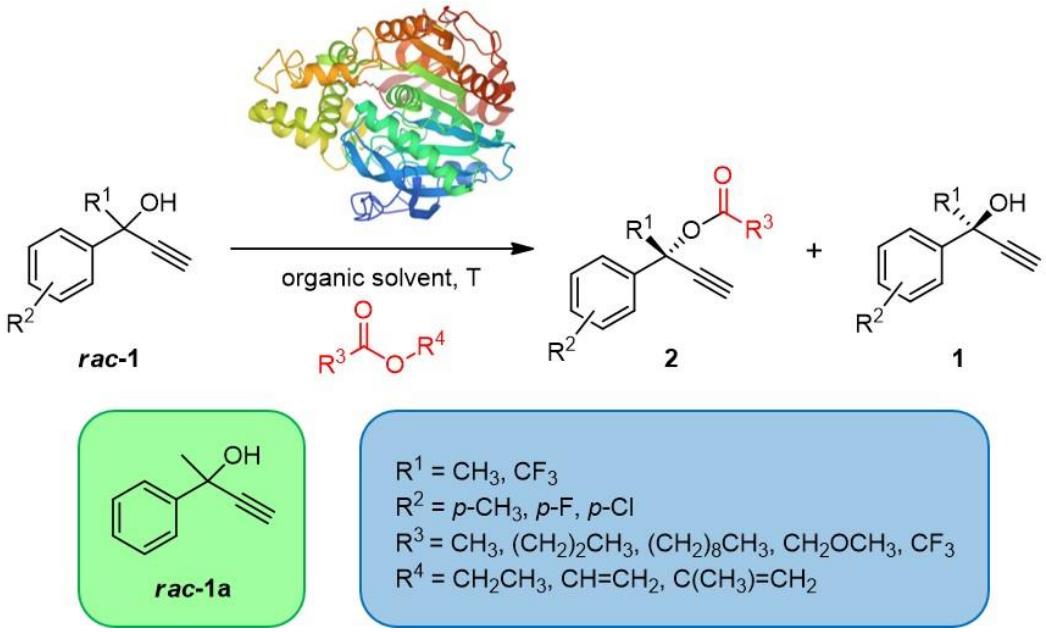
Keywords: *Kinetic resolution, lipase, propargyl tertiary alcohols.*

ABSTRACT

The enzymatic kinetic resolution of tertiary alcohols is still a great challenge for organic chemists due to the steric hindrance of these substrates, which are essential building blocks for the pharmaceutical industry.[1] The few examples reported in the literature for the kinetic resolution of these compounds utilize *Candida antarctica* lipase A (CAL-A), which requires only an acyl donor and organic medium for an enantioselective transesterification reaction.[1-3] The present work focuses on developing a new methodology for the kinetic resolution of propargyl tertiary alcohols using immobilized CAL-A as the chiral catalyst. Several reaction conditions were investigated, evaluating the effect of temperature, solvent, acyl donor, and reactants concentrations for the transesterification of 2-phenyl-3-butyn-2-ol (***rac*-1a**), obtaining a conversion of 33% and an *ee* of 94% in only 48 hours of reaction, what is unprecedented for this substrate using a wild-type enzyme. The substrate scope is in ongoing development.



ACKNOWLEDGEMENTS

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001; Financial support of the Sao Paulo Research Foundation – FAPESP [grants number 2019/15230-8].

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An efficient route for the synthesis of *rac*-1,2,3-triazole-dihydropyrimidinone compounds and an asymmetric biocatalytic application to obtain an enantiomerically enriched phenolic derivative

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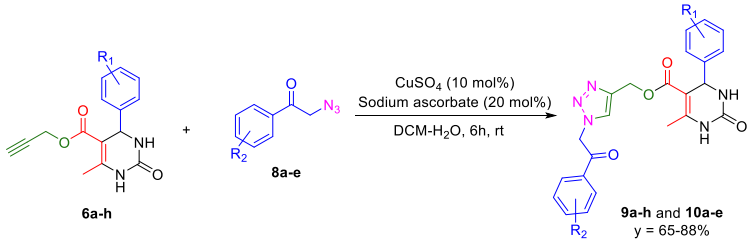
Keywords: *multicomponent reactions; heterocycles; 1,3-dipolar cycloaddition; enzymatic kinetic resolution; lipase; biocatalysis.*

ABSTRACT

The dihydropyrimidinone (DHPM) and 1,2,3-triazole nuclei are two heterocycles extremely relevant in organic chemistry due to its several synthetic and biological applications. Taking into account, the purpose of this study was to develop a synthetic route that incorporates these two portions in the final structure of the formed products. For this, the initial step was the synthesis of a β-dicarbonyl compound containing a terminal alkyne moiety. From that reagent, a scope of propargylic-DHPM compounds was developed with yields up to 99%. In addition, a scope of azidoketones synthesized from bromoketones was developed (90-99% yield), which after reaction optimization steps, were used in the synthesis of *rac*-1,2,3-triazole-DHPM derivatives with moderate to good yields 65-88% (Scheme 1). As well, from a biocatalytic route developed by our research group, it was possible to perform the asymmetric synthesis of a target compound with 92% enantiomeric excess.



Scheme 1. Scope of *rac*-1,2,3-triazole-DHPMs.

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Synthesis of new Ugi adducts from 2-*N*-heteroaryl acetic acids

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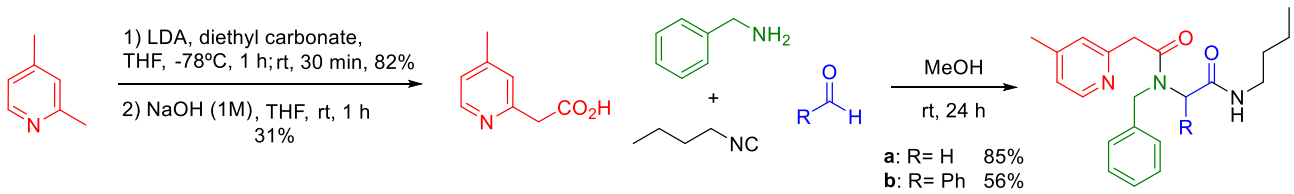
Keywords: *carboxylic acids, Ugi reaction, multicomponent reaction*

ABSTRACT

Multicomponent reactions are considered excellent synthetic tools for construction of drug-like compounds, in view of their atomic economy, high efficiency and simple operation.[1] The Ugi reaction (U-4CR) is one of the most studied multicomponent reactions, as it allows access to peptidomimetics with potent biological activity and high structural diversity.[2]

In this work, new Ugi adducts have been synthesized from 2-*N*-heteroaryl acetic acids. Initially, the direct carboxylation was evaluated by using the conditions reported for photochemical functionalization of benzylic positions using CO_2,[3,4] however, to date, the desired products were not obtained. Alternatively, carboxylation with LDA and diethyl carbonate,[5] followed by hydrolysis with NaOH afforded the corresponding 2-*N*-heteroaryl acetic acids in moderate overall yields.

In order to obtain the Ugi adducts, the 2-(4-methylpyridin-2-yl)acetic acid was reacted with two different aldehydes, benzylamine and *n*-butylisonitrile leading to the desired peptidomimetics. We are now exploring other azaarenes and testing new carboxylation reactions using CO_2.



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Palladium-catalysis enables near-stoichiometric CO_2 use for isotopic labeling

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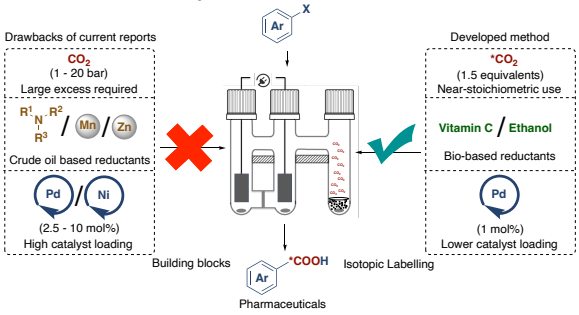
Keywords: *Catalysis, Palladium, Electrochemistry, Carboxylation, Aryl electrophiles.*

ABSTRACT

The conversion of carbon dioxide into bulk chemicals is attracting considerable attention from the chemical industry, but besides scarce examples, this still needs further advances for cost reduction.[1] On the other hand, value-added chemicals could build the bridge between this academic venture to widespread use in the chemical industry. Within the studied reactions, the catalytic reductive carboxylation (CRC) of aryl electrophiles caught our attention for being previously investigated but with major limitations such as the need to use metallic or crude oil-based reductants, high catalyst loadings, and a large excess of carbon dioxide.[2] Although carbon dioxide is cheap and widely available gas, the use of near-stoichiometric amounts of CO_2 could facilitate the ^{13}C and ^{14}C isotopic labeling of pharmaceuticals. Thus, we turned our efforts on developing a method for the efficient isotopic labeling of aryl carboxylic acids. Based on previous literature we first optimized a photo redox-mediated method in which an organic dye was used in tandem with the palladium catalyst.[3,4] Due to the presence of a side product that could not be avoided after extensive optimization, we attempted to transpose the catalytic system for an electrochemical system.[5] After further optimization of the electrocarboxylation reaction, we efficiently performed the CRC reaction with only 1.5 equivalents of $^{13}CO_2$ released from barium carbonate, which enables the labeling with $^{14}CO_2$. Furthermore, the developed method could use bio-based reductants and a lower catalyst loading. Currently, 27 scope entries are presented with 23 different products between aryl and heteroaryl electrophiles with yields from 25 to >95%. Additionally, the reaction mechanism is being studied by both experimental and computational methods.



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Methanol as Syngas Surrogate for Low-Pressure Hydroformylations

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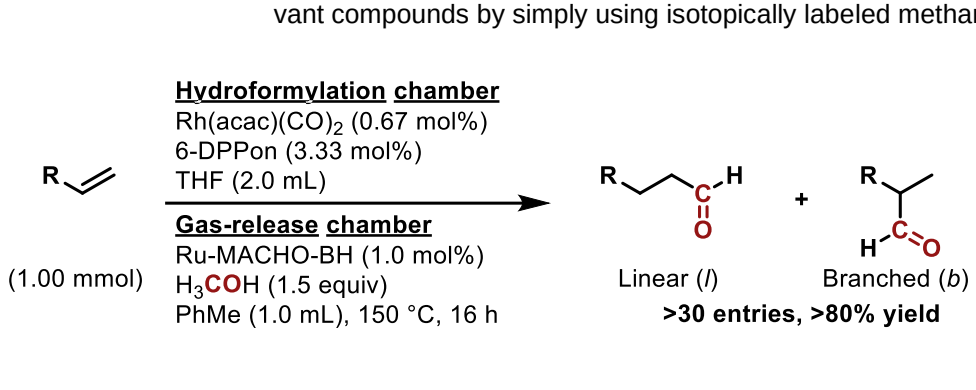
Keywords: *Catalysis, Hydroformylation, Syngas release*

ABSTRACT

In industry, hydroformylation of alkenes with syngas (CO + H_2) to aldehydes using transition metal-based catalysts is carried out on million-ton scale annually. However, on laboratory scale handling toxic and flammable syngas is often avoided due to the requirement of costly equipment and maintenance, resulting in the sought for syngas surrogates.

In this work we report, which to the best of our knowledge, is the first methodology utilizing methanol as a syngas surrogate for hydroformylation of olefins. The reaction is performed in a developed two-chamber setup, which allows for separating the ruthenium-catalyzed dehydrogenation of methanol to syngas and the rhodium-catalyzed hydroformylation of olefins to aldehydes. The system uses fully commercially available catalysts and ligands, Ru-MACHO-BH and Rh(acac)$(CO)_2$ + 6-DPPon, for the dehydrogenation of methanol and the hydroformylation, respectively. A broad substrate scope containing >30 entries from aliphatics, styrenes, and allylbenzenes containing electron withdrawing and donating groups to natural products and drug precursors with yields between 80 to >95% is presented. In addition, the use of stoichiometric methanol (1.5 equivalents) further enables the methodology for cheap stable isotope labeling of pharmaceuticals and relevant compounds by simply using isotopically labeled methanol.



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Statistical tools applied to lignin models oxidation through Co(salen) catalysis

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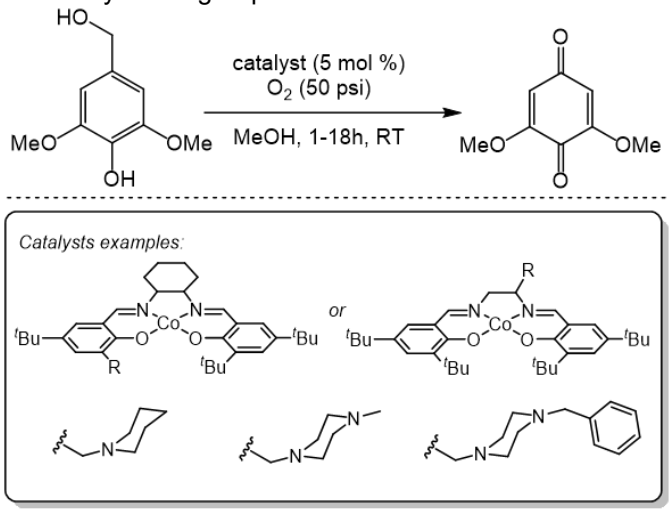
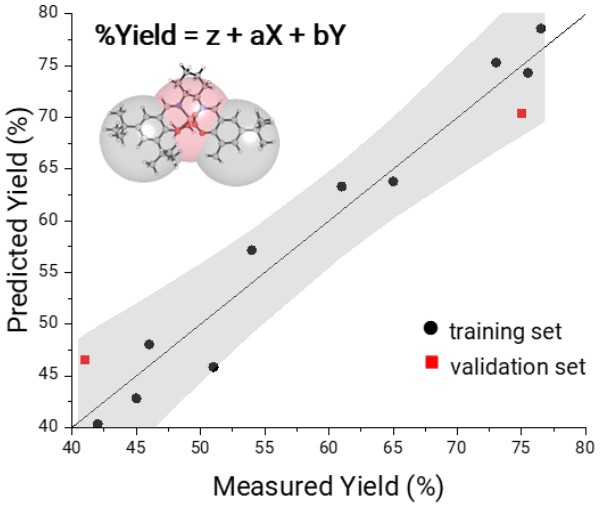
Keywords: *Lignin depolymerization, Co(salen) catalyst, regression models.*

ABSTRACT

Catalysts based on the Co-Salen framework stand out for its high performance, low price and environmentally friendly properties for depolymerization and valorization of lignin. These important transformations are promising candidates for renewable production of aromatic feedstock, which importance cannot be overstated. Lignin is an amorphous and highly functionalized polymer, making the design of robust and efficient catalysts an incredibly complex problem. This work combines statistical tools with computational chemistry to generate predictive models, based on the catalysts developed by Bozell and collaborators between 1995 and 2020, to provide insights into important parameters that could affect the depolymerization reaction and rationalize the process of ligand design.[1-3] The models generated from the molecular descriptors indicated dominant steric trends influencing catalytic regeneration and deactivation processes, with no significant tendency from electronic descriptors due to literature limitations. New approaches for study the electronic influences are underway in our group.





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Predictive models in aldol reactions catalyzed by chiral enamines

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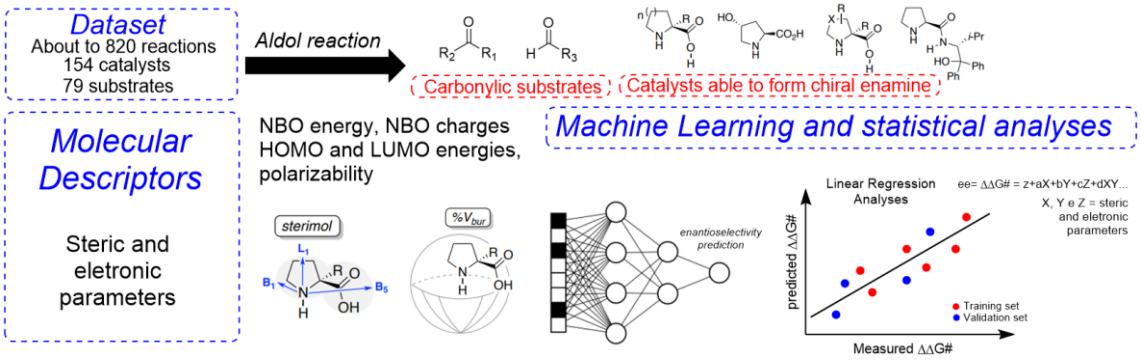
Keywords: *Organocatalisys, aldol reaction, chiral enamines.*

ABSTRACT

High selective catalytic processes are of paramount industrial importance, as their applications in the manufacture of products used in our whole society, such as polymers and drugs, are manifold. Historically, the development of selective catalytic chemical reactions has been based on trial-and-error protocols in which expert knowledge guides experimental decisions. An important point refers to the existing bias in the choice of experimental conditions or specific substrates[1]. A transformation that stands out is the aldol reaction, given the great relevance of selectively forming carbon-carbon bonds[2] from the reaction of two carbonyl compounds. The enantiocontrol of aldolic reactions is a multifaceted challenge, for which cleaver solutions have been developed such as the use of chiral auxiliary or silane-enolates. However, in many of these protocols a covalent bond must be formed between some activating molecule, which is, generally, discarded in further synthetic steps. In this context non-covalent catalysis with chiral molecules can induce the enantioselectivity of the product, even in the presence of multiple stereocenters in the starting material[3]. In particular, the use of proline derivatives leads to a simpler catalysis since this molecule have a small structure and can form selectively an enamine due to its chiral center. Considering the importance to identify and control this type of selectivity, and also the relevance of aldol reactions, the present work aim, through computational and data science tools, to establish a general framework of the catalysts and substrates typically employed in organocatalyzed aldol reactions in order to rationalize the main factors that affect their associated enantioselectivity. About 820 aldol reactions were carefully cataloged from the literature, and the structures present involve catalysts derived from L-proline, and substrates for the aldol reaction. Additionally, catalysts with more than one selectivity-inducing site in the enamine, by hydrogen bonding, were included. Regarding the substrates, different benzaldehyde derivatives were cataloged, as well as cyclic ketones and acetone itself. These structures were parameterized using molecular descriptors that capture electronic and steric effects. Our preliminary results show that the models have a bigger representation from the catalysts terms and also has variation elements from the aldehydes. This terms intercorrelate eletronic and steric aspects of the reaction components. Thus, it was possible to build linear correlation models to predict the enantioselectivity of the cataloged reactions.



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Application of flow chemistry strategies for the N-alkylation of amines of synthetic and medicinal interest

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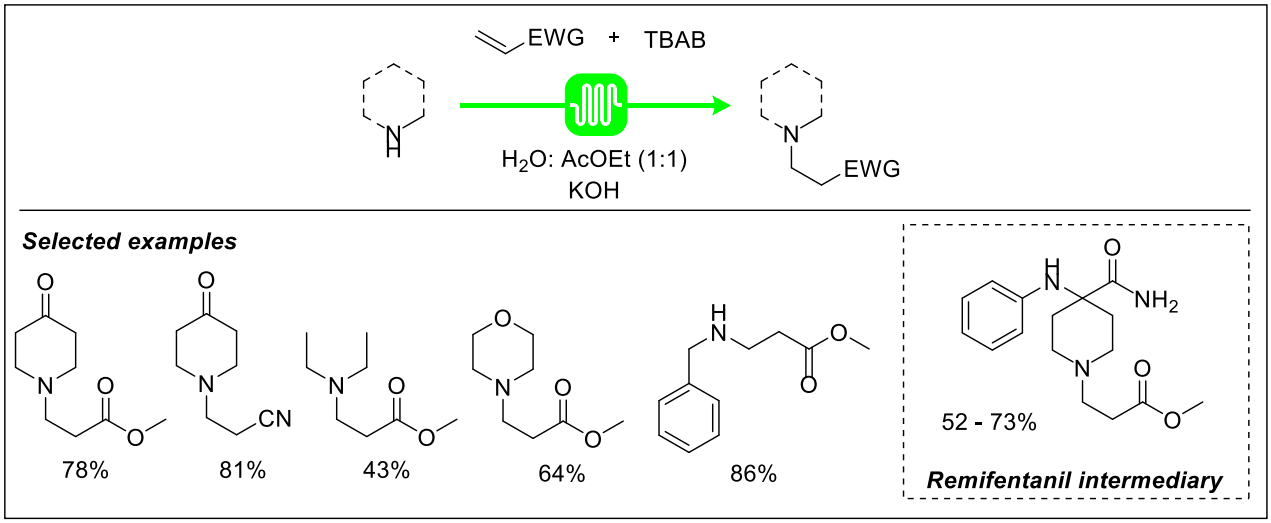
Keywords: *Flow chemistry, green chemistry, piperidines.*

ABSTRACT

With the growing concern about the impacts that human actions have caused on nature, sustainable alternatives are sought.[1] In chemistry, the concept of green chemistry was created which directly impacts organic synthesis. This project makes use of this concept to promote the N-alkylation of amines, mainly piperidines, through the use of phase transfer catalysts (PTC) and flow chemistry. Fentanyl-like compounds, which present the piperidine moiety in their structures,[2] can be configured as a model encouraging these studies. The incorporation of flow chemistry takes advantage of the sustainable characteristics of this technology.[3] After a screening of conditions, through a Michael reaction, employing TBAB as the PTC and methyl acrylate, a number of functionalized derivatives could be produced in modest to high yields in 10 min of residence time. The screening also included different bases and PTC's. Application of the methodology for the synthesis of a remifentanil intermediary has also been achieved.



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Ligand parametrization in Co(salen) to catalytic depolymerization of lignin

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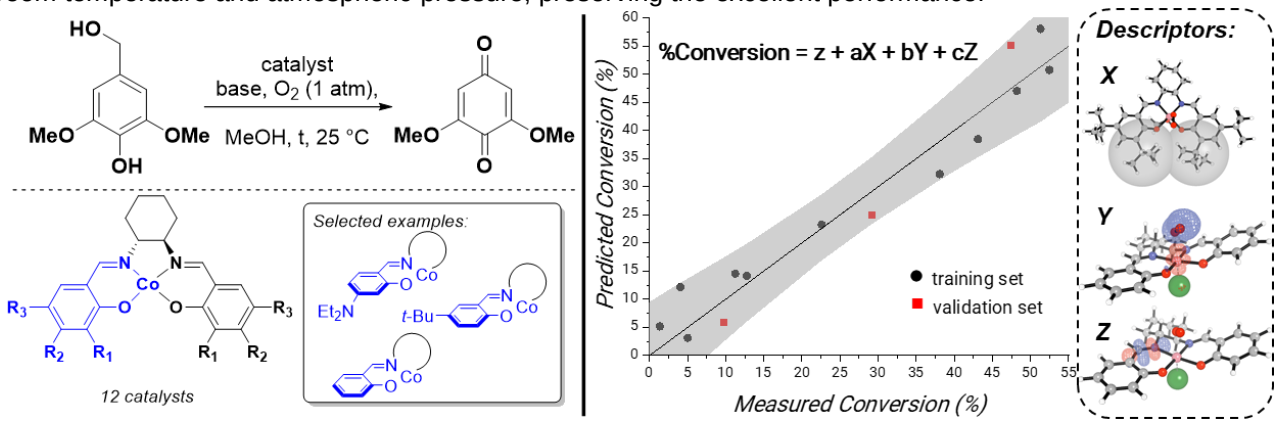
Keywords: *Catalysis, Lignin, Cobalt.*

ABSTRACT

Biomass valorization is one of the promising paths to decrease the oil dependency and to achieve valuable compounds, such as chemical feedstocks, demand efficient and low-cost transformations. Lignin is the only source of renewable aromatic compounds and the second largest component of biomass, in this study we investigated the depolymerization of lignin models toward high value-added compounds like benzoquinone via Co(salen) oxidative catalysis.[1] This work was based on the systematic variation of salen substituents to explore electronic and steric effects that could affect the oxidation efficiency in terms of conversion and yield, integrating statistical tools we were able to develop a predictive multivariate linear regression model, which also indicates the relevant parameters that maximize aimed responses.[2,3] The best catalyst was efficient to convert the lignin models in a cheap and green way, using less catalytic and reagent amounts, short time, room temperature and atmospheric pressure, preserving the excellent performance.



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Synthesis of thionaphthoquinone and triazole hybrids with antineoplastic potential

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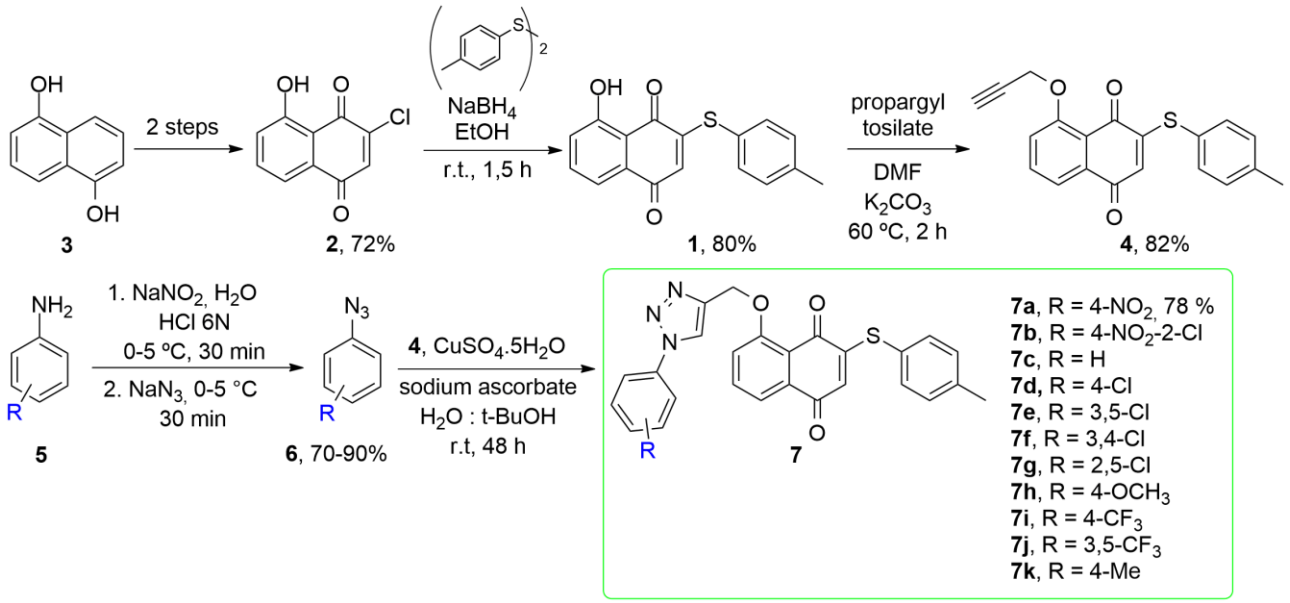
Keywords: *naphthoquinones, regiospecific synthesis, triazole*

ABSTRACT

Naphthoquinones are a class of substances widely studied in the literature due to their wide variety of biological activities. Thionaphthoquinones have recently demonstrated excellent antineoplastic activity and selectivity against leukemia cell lines, especially thionaphthoquinone **1**.[1] Likewise, the 1*H*-1,2,3-triazole moiety is of great importance due to its plurality of biological activities. In this context, this work aims at the synthesis of hybrids of thionaphthoquinones and 1*H*-1,2,3-triazole rings. The synthetic route starts with the regiospecific synthesis of **2** starting from **3**. The chlorine atom was then replaced by a *p*-thiocresol producing thionaftoquinone **1**,[1-3] which was then propargylated on the aromatic ring providing **4**. In parallel, anilines **5** underwent diazotization followed by nucleophilic aromatic substitution forming azides **6**. Finally, **4** reacted with **6** through a click reaction producing hybrids **7**.[4] The developed synthetic route proved to be efficient and other analogues, varying the substitution pattern, are still being synthesized.



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New iboga analogs by selective functionalization of C_{19} of voacristine

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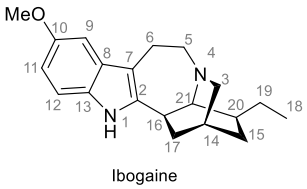
Keywords: *Semisynthesis, Late-Stage Functionalization, iboga alkaloids*

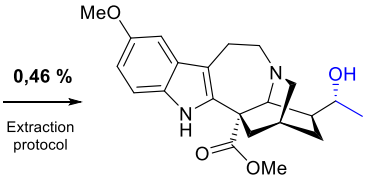
ABSTRACT

Ibogaine is a monoterpene indol alkaloid (MIA), known for its psychedelic and antiaddictive effects.[1] Clinical applicability is limited due to its cardiotoxicity.[2] Chemical efforts are required to generate safer iboga-analogs; for this purpose, we employed a semisynthetic strategy starting from natural occurring compounds (voacangine and voacristine) to obtain a chemical library of analogs.[3] Our current work focus on functionalizing positions C_{18}-C_{19} of the iboga skeleton (see Figure.A) for which the 19-hydroxyl group present in voacristine emerges as a key feature. We developed a synthetic strategy that allows the obtention of C_{19} modified analogs (Figure.B), based on this system's particular reactivity. After the generation of a good leaving group in position 19, a spontaneous internal cyclization takes place to afford an azetidonium salt, which can be further re-opened upon treatment with suitable nucleophiles in the appropriate solvent, producing the desired products. This compounds will be assay as inhibitors of monoamino-transporters and the hERG channel.

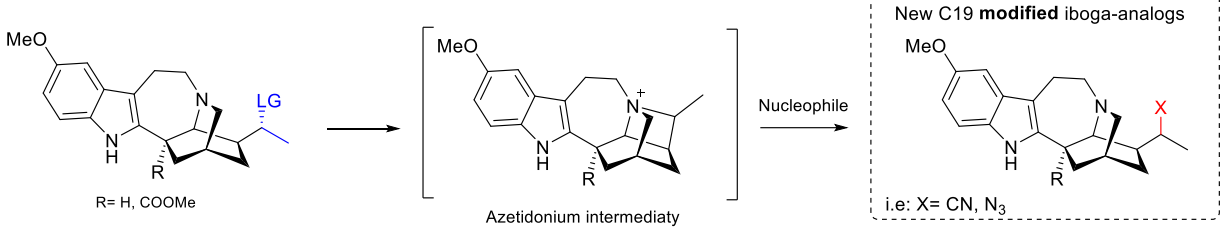
A/ Natural ocurring alkaloids




Voacanga africana



B/ C_{19} synthetic modification strategy



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α-Xyloidone as a synthetic platform: a new approach to direct synthesis of thioethers

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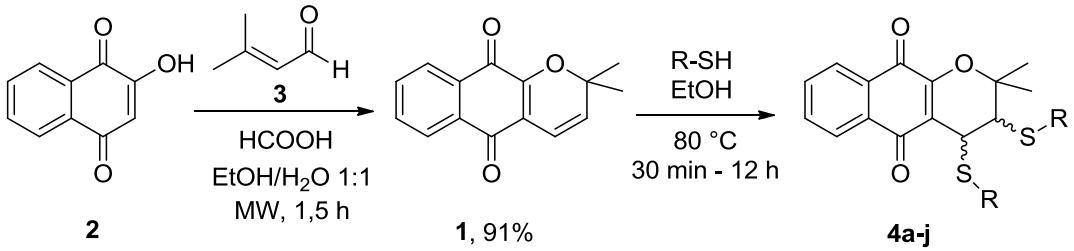
Keywords: *α-xyloidone, direct addition, thioethers.*

ABSTRACT

Pyranonaphthoquinones class are abundant in nature and, because of its diverse biological profile, they are explored in the literature, especially xyloidones and lapachones.[1] Although the functionalization of these compounds is mainly based on modifications using lapachones as precursors, xyloidones can also be used as synthetic platforms. However, this approach is still restricted to hydrogenation reactions, diol, halohydrin or epoxide formation, which, initially, leads to formation of simpler lapachones.[2] In order to obtain structurally complex derivatives, subsequent reactions are necessary. Thus, the objective of this work is to obtain new thioethers, from the direct functionalization of α–xyloidone. The synthetic strategy starts by obtaining α–xyloidone **1** through the Knoevenagel condensation between lawsone **2** and α,β-unsaturated aldehyde **3**, followed by an intramolecular cyclization.[3] Then, the thioethers **4** were obtained through the direct addition of different commercial thiols to **1** resulting in ten new type **4** derivatives with moderate to good yields.



4a: R= Ph, 12 h, 29 %; **4b:** R= 2-CH_3-Ph, 12 h, 41 %; **4c:** R= 3-CH_3-Ph, 12 h, 40 %
4d: R= 4-CH_3-Ph, 12 h, 42 %; **4e:** R= 4-OCH_3-Ph, 12 h, 68 %; **4f:** R= 4-F-Ph, 12 h, 35 %
4g: R= 4-SCH_3-Ph, 4 h, 60 %; **4h:** R= 4-Cl-Ph, 12 h, 34 %; **4i:** R= 4-OH-Ph, 12 h, 32 %
4j: R= 2-Naphtil, 30 min, 40 %

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The use of biomass and Click Chemistry against Chagas Disease

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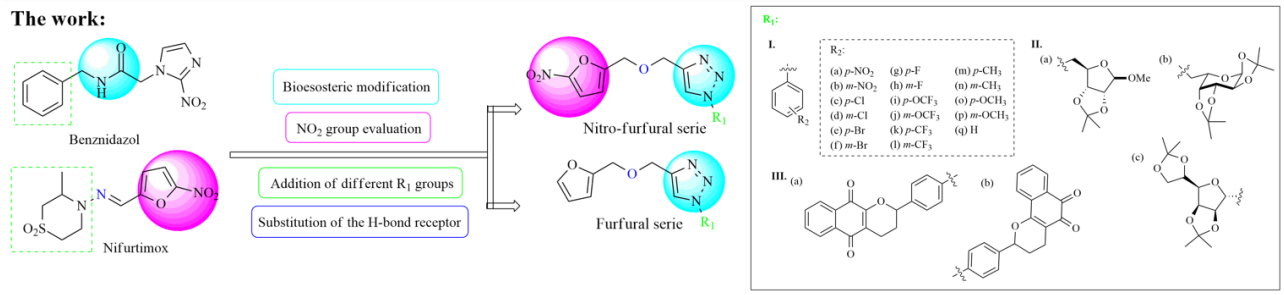
Keywords: *Chagas Disease, furfural, biomass, 1,2,3-triazole, Click Chemistry*

ABSTRACT

The 'Kissing bug' represents the main transmission route of Chagas disease, an anthropozoonosis caused by the protozoan *Trypanosoma cruzi*. Considered by WHO a tropical neglected disease, this American trypanosomiasis is a potentially life-threatening illness responsible for estimated 75 million people at risk of infection and 10.000 deaths per year, more than any other parasitic disease. The current treatments, benznidazole and nifurtimox, were both discovered half a century ago, although their safety and efficacy profile are far from ideal.[1,2] In this work, we report the use of furfural and nitro-furfural scaffolds derived from the sugar cane biomass as building blocks for the synthesis of novel 1,4-disubstituted 1,2,3-triazoles carried out by copper-catalyzed 1,3-dipolar cycloaddition.[3,4] The biological evaluation of the compounds against *T cruzi* intracellular forms, toxicity on mammalian cells and the study of a structure-activity relationship based on the outcomes will be presented.



The progress:

Furfural serie	I												II			III	
	(a)	(b)	(c)	(d)	(e)	(f)	(g)	(m)	(n)	(o)	(p)	(q)	(a)	(b)	(c)	(a)	(b)
Synthesis and caracterization	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	○	○
Biological evaluation	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	○	○

Nitro-Furfural serie	I												II			III	
	(a)	(b)	(c)	(d)	(e)	(f)	(g)	(m)	(n)	(o)	(p)	(q)	(a)	(b)	(c)	(a)	(b)
Synthesis and caracterization	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Biological evaluation	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○

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Synthesis of new fluorene-1,2,3-triazoles pottencially bioactives

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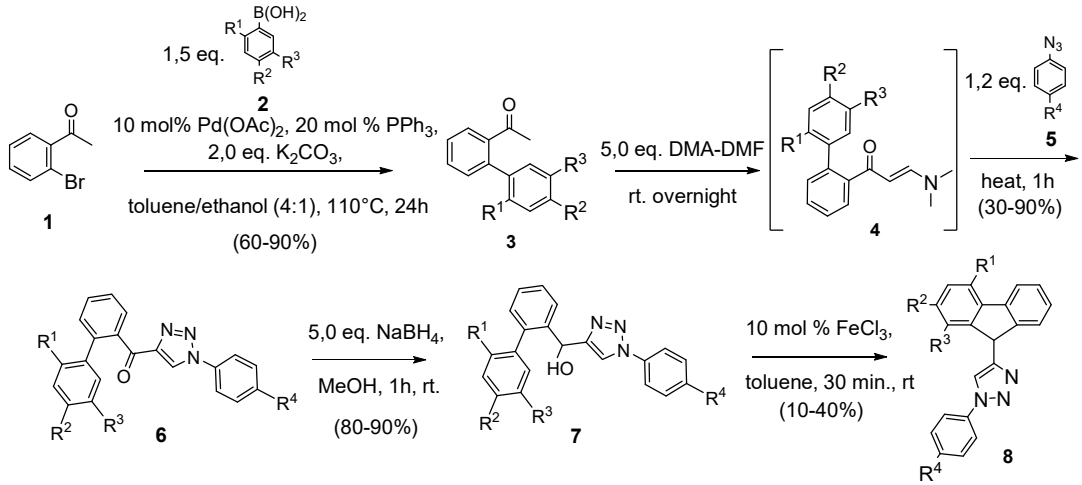
Keywords: *fluorene-triazoles, Suzuki, 1,3-dipolar cycloaddition.*

ABSTRACT

Fluorenes are polysubstituted derivatives of benzene, with an important role in medicinal chemistry and materials science[1,2]. 1,2,3-triazoles are 5-membered heterocyclic with broad biological activity and have attracted the attention of our research group due to their pharmacological versatility and synthetic practicality[3]. The copper-catalyzed alkyne-azide cycloaddition reaction (CuAAC) has been extensively applied at LabSint to explore the pharmacological potential of a series of hydroxy-1,2,3-triazoles and the fluorene 1,2,3- triazoles **8 a-c**[4]. In this work, the fluorene 1,2,3- triazoles **8d-h** were obtained by the synthetic route presented in the scheme below. This synthetic route presents as keys steps the Suzuki reaction between 2'-bromoacetophenone (**1**) and boronic acids **2**, the 1,3-cycloaddition reaction between enaminones **4** and aryl azides **5**[5] and the intramolecular Friedel-Crafts reaction using iron[III] chloride in the last step. From this step, the new fluorene 1,2,3-triazoles **8a-h** were obtained in 10-40% yields and are being optimized.



8a: R^1, R^2 e R^3= CH; R^4= F (40%); **8b**:: R^1, R^2 e R^3= CH; R^4= OMe (30%); **8c**: R^1, R^2 e R^3= CH; R^4= CHO (25%); **8d**: R^1, R^2 e R^3= CH; R^4= Br (50%); **8e**: R^1= OMe; R^2 e R^3= CH; R^4= NO_2 (25%); **8f**: R^1 e R^3= CH; R^2= SCH_3; R^4=Br (10%); **8g**: R^1=CH; R^2 e R^3=  ; R^4= Br (10%); **8h**: R^1 e R^3= CH; R^2= CN; R^4=Br (20%)

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Sodium bisulfite and microwave irradiation promote the synthesis of 2-styrylbenzimidazole and 2-styrylbenzothiazole derivatives

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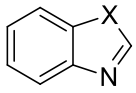
Keywords: *Sodium bisulfite, 2-styrylbenzothiazoles, 2-styrylbenzimidazoles.*

ABSTRACT

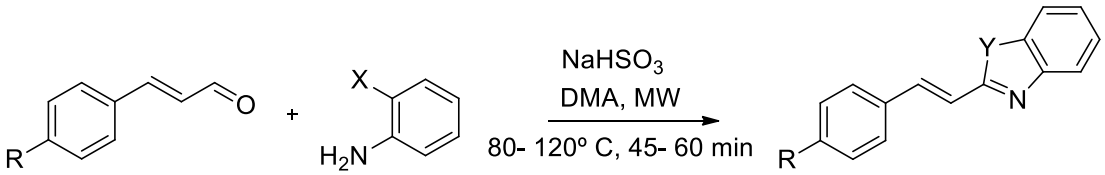
The benzimidazole (X=NH) and benzothiazole (X=S) skeletons (Figure 1), are present in the chemical structure of a variety of natural products, in most cases constituting the structural part of the substances responsible for the observed biological activities.[1,2]



X= S or NH

Figure 1. Benzimidazole (X=NH) and benzothiazole (X=S) nuclei.

Similar to benzimidazoles, benzothiazoles are commonly synthesized using methods that exhibit long reaction times, low yields, and the use of expensive and difficult-to-handle reagents or catalysts.[3,4,5,6] Seeking to obtain a series of compounds derived from 2-styrylbenzimidazoles and 2-styrylbenzothiazoles, a new synthetic method was developed and tested.[7] The reactions were conducted under microwave irradiation (MW) conditions. Reactions were carried out between different *α,β*-unsaturated aldehydes and 2-aminothiophenol or 2-phenylenediamine in the presence of sodium bisulfite ($NaHSO_3$) as catalyst in *N,N*-dimethylacetamide as solvent (Figure 2). The yields obtained ranged from 54 to 98% for both classes of compounds.



R= H, R = NO_2, R = CH_3O, X= S or NH_2, Y=S or NH.

Figure 2. Synthesis of 2-styrylbenzothiazole and 2-styrylbenzimidazole derivatives.

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Investigation of the stereoselectivity in functionalization of bioactive Naringenin by dynamic kinetic resolution

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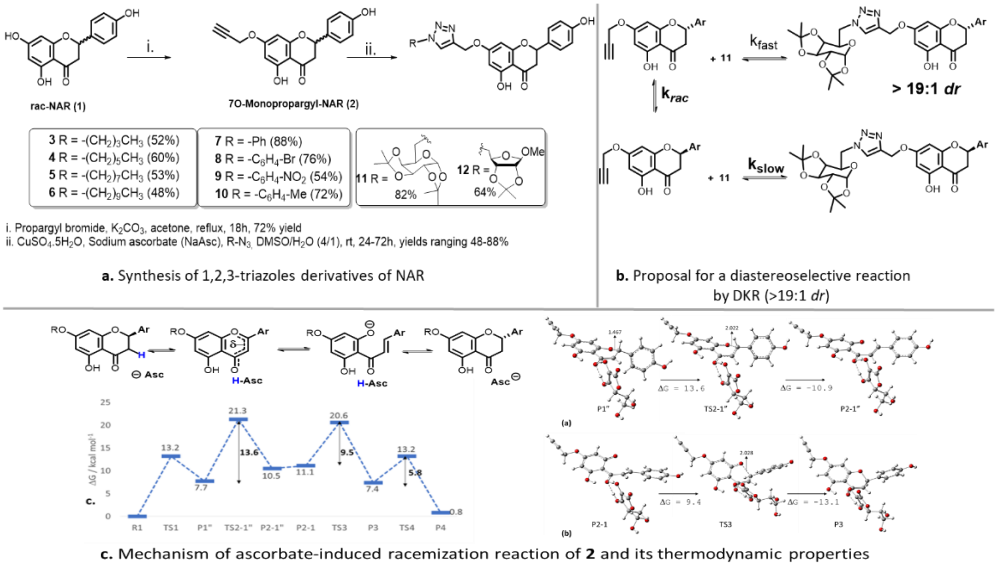
Keywords: *Flavanone functionalization, stereoselective synthesis, DFT calculations*

ABSTRACT

Naringenin (NAR,**1**) is a source of new candidates for drug prototypes.[1,2] Herein we reported the stereoselective functionalization of racemic NAR skeleton with different groups linked by 1,2,3-triazole pharmacophoric moiety performed by copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) (Scheme 1a).[3] The reaction between **2** and enantiopure azide **11** was diastereoselective (>19:1 *dr*). It concomitantly allowed the complete conversion of the racemate, in which (*S*)-NAR was the reactive species indicating a possible dynamic kinetic resolution (DKR).[4] The racemization (k_{rac}) is proposed through ring-opening/intra-molecular Michael reactions and the first step is the rate-limiting step, with ΔG^{a}= 13.6 kcal mol^{-1} (Scheme 1b).[5]

Scheme 1. Synthesis 1,2,3-triazole NAR derivatives and DKR studies



Mechanistic studies by DFT are in progress to elucidate the origin of stereoselectivity of kinetically favored step (k_{fast}) and the role of NAR as chiral ligand as stereoinducting species. This strategy could allow new paths for the development of asymmetric reactions to obtain enantiomerically pure flavonoids.

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Chemoselective Synthesis of Mannich Adducts of 1,4-Naphthoquinones Obtained via Multicomponent Reactions

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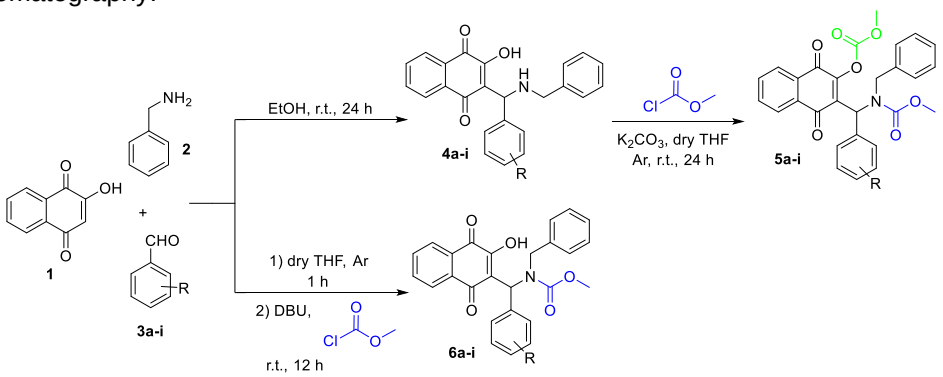
Keywords: *Naphthoquinone, lawsone, Mannich Reaction.*

ABSTRACT

One of main focuses of organic synthesis has been the search for new drugs capable of reducing or eliminating the morbimortality and suffering rates of patients affected by different diseases. The studies of new biomolecules begin with its relevance in the literature, such as 1,4-naphthoquinones which have numerous bioactivities. In addition, synthetic methodologies that involve multicomponent reactions are sought. In this sense, this work aimed to synthesize new 1,4-naphthoquinones.
1,4-Naphthoquinones **5** were obtained in two sequential steps. First, a reaction was carried out using three components – lawsone (**1**), benzylamine (**2**) and different aldehydes **3**, resulting in Mannich adducts **4**. Then, adducts were reacted with methyl chloroformate. The final products were obtained in good yields (55-97%). To obtain monosubstituted derivatives, the same three components were initially added and after 1 hour, DBU and methyl chloroformate were added. The products **6** were obtained in good yields (37-87%) after purification by column chromatography.



ACKNOWLEDGEMENTS

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Direct aldehyde arylation for unnatural amino acids synthesis

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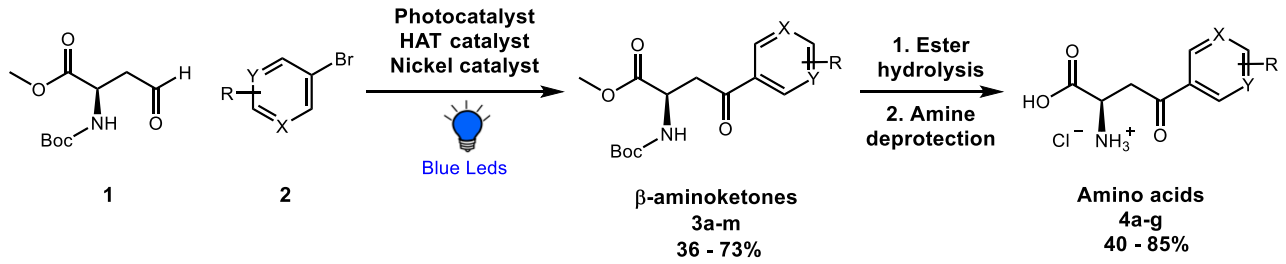
Keywords: *Photocatalysis, Hydrogen Atom Transfer, amino acids.*

ABSTRACT

Unnatural amino acids play crucial roles in biological processes and are important building blocks for modifying and improving the properties of pharmaceutical peptides and complex molecules.[1–3] Traditionally, these amino acids are obtained from Friedel Crafts reactions[4], Michael additions[5], asymmetric Stetter reactions[6] or Mannich reactions[7,8]. Despite being well established and efficient, several of these reactions suffer scope limitations due to harsh conditions.

In this context, we envisioned the unnatural aspartate derivatives **4a-g** synthesis through direct arylation of aldehyde **1** via metallaphotoredox and HAT catalysis as the key step.[9] After optimization studies, aryl bromides scope was evaluated, furnishing β-aminoketones **3a-m** in 36 to 75% yields. Subsequently, **3a-m** were submitted to ester hydrolysis and amine deprotection, affording the desired products **4a-g** in 40 to 85% yields. In conclusion, we developed a mild and efficient route, which is compatible with a variety of functional groups.



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Microbial Metabolism of Hydroxychloroquine and Cytotoxicity of its Metabolite

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Keywords: *hydroxychloroquine, fungi biotransformation, cytotoxicity.*

ABSTRACT

Drugs suffer several metabolic reactions by the action of a wide array of body enzymes. In humans, the metabolism of xenobiotics may result in metabolic bioactivation producing toxic chemical species, and their involvement in causing adverse drug reactions has been extensively studied and reported[1]. Some microorganisms can produce enzymes similar to the human body and are used in studies to mimic human drug metabolism[2]. In the present study, *Cunninghamella echinulata* var. *elegans* ATCC 8688a efficiently biotransformed hydroxychloroquine (HCQ) into one main derivative identified as the new 4-(1,2,3,4-tetrahydroquinolin-4-ylamino)pentan-1-ol (HCQ-M) in 36% yield at 28°C using water as solvent. The microbial transformation occurred through N-dealkylation, 7-chloro-elimination, and reduction of the two conjugated double-bond from the quinoline system of HCQ, generating a new stereogenic center. Product characterization was obtained by high resolution mass spectrometry. Cytotoxic assays against human fibroblast showed that HCQM displayed higher toxicity than HCQ.

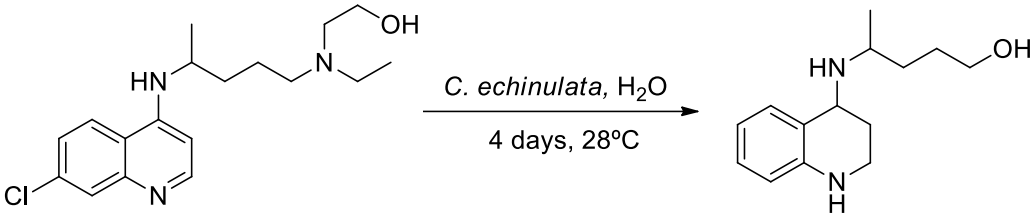

Figure1: Representation of biotransformation of hydroxychloroquine (HCQ) into its main metabolite (HCQ-M) by *Cunninghamella echinulata* var. *elegans* ATCC 8688a for four days.

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UFBA Universidade Federal da Bahia

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Synthesis of hydroxychloroquine analogs by Knoevenagel reaction

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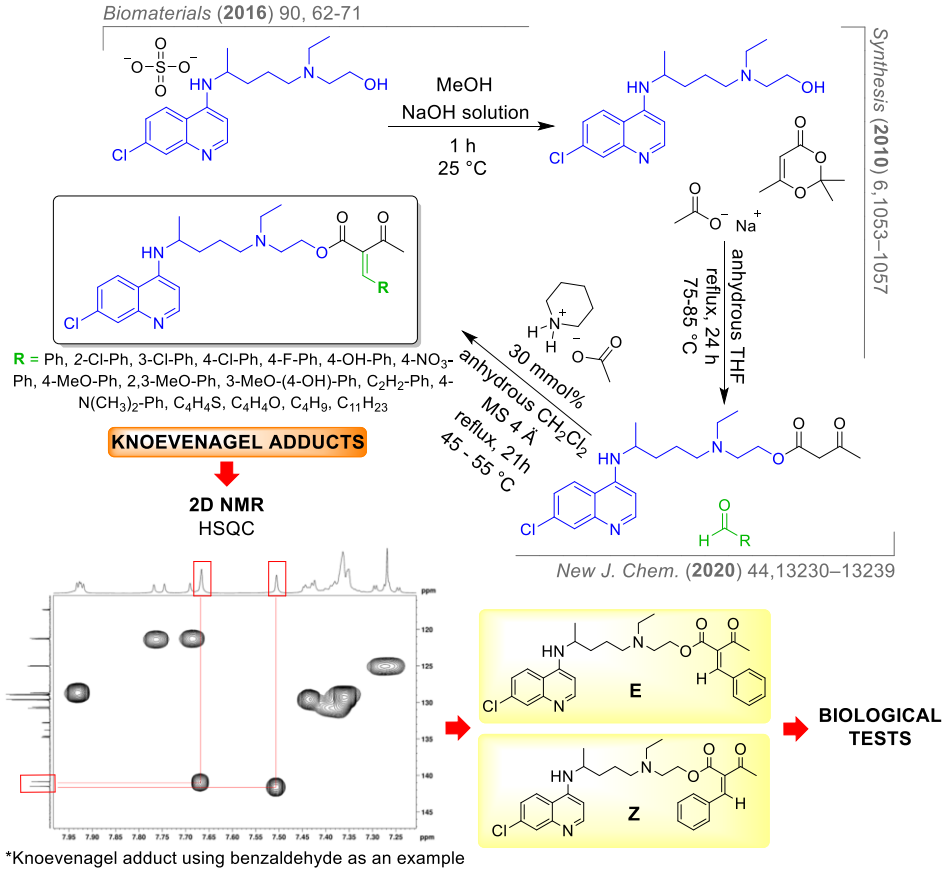
Keywords: *Hydroxychloroquine analogs, Knoevenagel adducts, and E/Z isomers.*

ABSTRACT

Knoevenagel condensation is widely used in the pharmaceutical industry to obtain biologically active compounds[1]. Hydroxychloroquine (HCQ) is a heterocycle belonging to the 4-aminoquinoline family. HCQ is an antimalarial drug and is also prescribed for treating inflammatory rheumatic diseases, mainly rheumatoid arthritis, and systemic lupus erythematosus[2]. In addition, HCQ was recently proposed as a possible Coronavirus (Covid-19) treatment[3]. Therefore, the present work synthesized a new HCQ analogous to Knoevenagel condensation. Initially, the hydroxychloroquine acetoacetate was previously obtained by reaction using TMD (2,2,6-trimethyl-4*H*-1,3-dioxin-4-one). After, the Knoevenagel condensation was investigated using the classic protocol with several aldehydes for the synthesis of the alkylidenes. The results demonstrated the formation of Knoevenagel adducts in moderate yields, proving the efficiency of the established methodology. The correlation between the olefinic hydrogen and the respective carbon in the bidimensional (2D) NMR analysis by the HSQC experiment showed the presence of E/Z isomers observed in the alkylidenes.



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Flat yet twisted: Towards glassy discotic LC delayed fluorescence matrices

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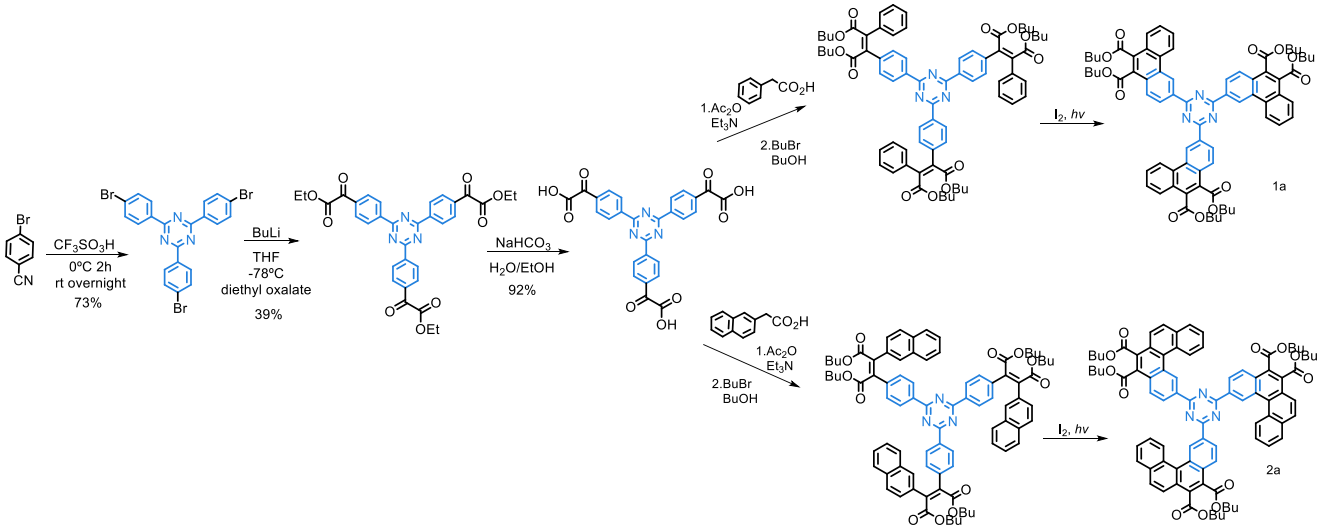
Keywords: *Triphenyl-triazines, Liquid Crystal, TADF.*

ABSTRACT

Alignable anisotropic columnar liquid crystals have great potential for light-emitting devices, because by aligning the emitting dipoles with respect to the device surfaces, losses due to inefficient light coupling can be significantly reduced. To achieve this alignment, the liquid crystalline order must be present in a glassy state around room temperature. To function as a matrix for third generation delayed fluorescence emitting materials, the energy of the T1 state must be about or greater than 3eV[1].

We identified triphenyl-triazine (Scheme 1) as a large T1 energy core with triple symmetry to enable the elaboration of crystalline liquid derivatives, and alkyl-carboxylic ester groups as suitable substituents to induce high viscosity and glassy behavior[2]. The core has rotational flexibility due to its single-bonded phenyl substituents, formed from perkin bonds between oxalic and glyoxalic acids, followed by a photoreaction forming phenanthrene and helicene in each case.



Scheme 1. Synthesis of triazine derivatives designed as glass matrices for anisotropic emission from delayed fluorescence emitters.

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Design, synthesis and study of novel luminescent and liquid crystalline aza-heterocycles

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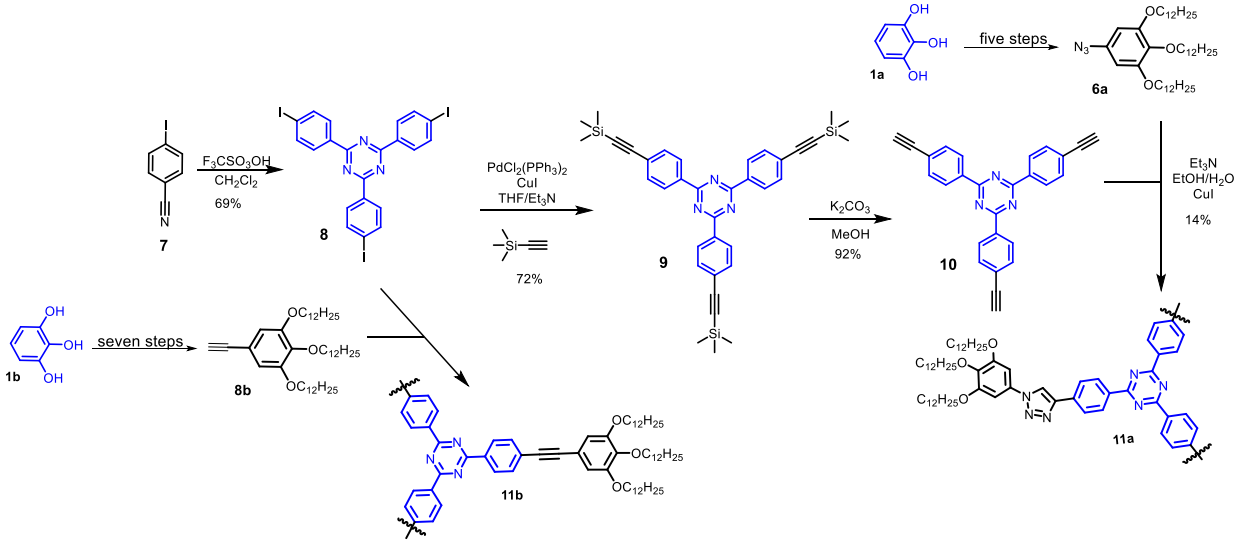
Keywords: *Liquid Crystal, 2,4,6-triphenil-1,3,5-Triazines, Star Shape*.

ABSTRACT

Columnar liquid crystals (CLC) are functional materials that deserve special attention due to their abilities to form highly ordered one-dimensional (1D) superstructures and because they are widely used for charge and ion transport, and photonic applications[1].

The investigation of dynamic and anisotropic properties in conjugated molecules with hybrid electron acceptor-donor (D-A)[2,3] characteristics is recurrent. In this sense, the molecules synthesized in this work are derived from 2,4,6-triphenyl-1,3,5-triazine. Because of the C3 symmetry of this nucleus the synthesized molecules are star-shaped, the Click and/or Sonogashira reactions built the bridges between the molecule nucleus and the halogenated compounds or aromatic azides, which vary according to the amount of alkyl chains and their position. Scheme 1 shows the structure of the molecules synthesized in this work.



Scheme 1. Synthesis of star-shaped molecules derived from 2,4,6-triphenyl-1,3,5-triazine

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UFBA, UFSC, CAPES and FAPESB.

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Visible-Light-Promoted Synthesis of 1,3-Dicarbonyl Sulfoxonium Ylides

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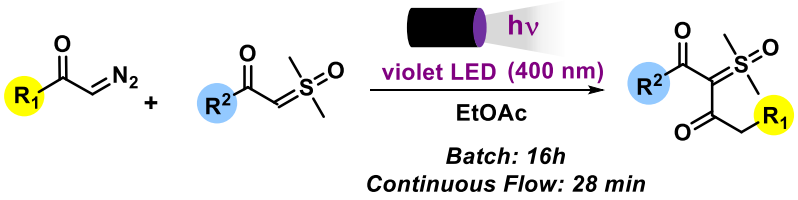
Keywords: *1,3 dicarbonyl sulfoxonium ylides, diazoketones, visible-light.*

ABSTRACT

α-Mono-carbonyl sulfoxonium ylides can be readily prepared from the acylation of reactive dimethyl sulfoxonium methylide or congeners.[1] However, the synthesis of 1,3-dicarbonyl sulfoxonium ylides[2] is still limited once a second acylation from a α-carbonyl sulfoxonium ylide with acyl chlorides or anhydrides is not efficient. In this work we present a novel visible-light-promoted coupling of diazoketones with sulfoxonium ylides, employing violet led, in both batch and continuous flow conditions. This transformation permits the direct synthesis of synthetically useful 1,3-dicarbonyl sulfoxonium ylides (33 examples, 21-85% yields), by means of an acylation reaction from the *in situ* and selective generation of ketenes. The reaction performed under flow conditions proved to be very efficient, providing the 1,3- dicarbonyl sulfoxonium ylides with higher yields and shorter reaction times.



Batch: 16h
Continuous Flow: 28 min

- **broad substrate scope**
- **novel sulfoxonium ylides**
- **catalyst-free synthesis**
- **33 examples up to 90% yield**

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Direct Synthesis of 4-Acyl-1,2,3-Triazoles From Acetophenones: A Green-Chemistry Approach

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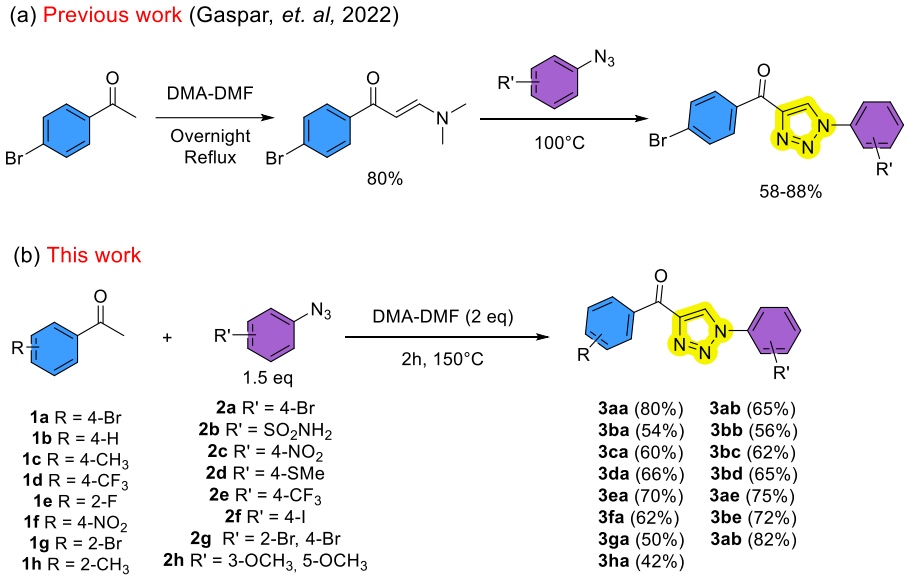
Keywords: *4-Acyl-1,2,3-Triazoles, 1,3 dipolar-Cycloaddition, Green Chemistry.*

ABSTRACT

4-acyl-1,2,3-triazole are an important scaffold due to their wide applicability, primarily as precursors of bioactive 1,2,3-triazoles.[1,2] In 2022 our group reported the cycloaddition between enaminone and aryl azides obtaining new 4-acyl-1,2,3-triazoles in a solvent-free methodology.[3] From this study it was possible to elucidate key points of this proposed reaction: concerted and asynchronous mechanism, electron-withdrawing groups increase the reaction rate, and the 1,4-disubstituted triazole is the major regioisomer. This work aims to improve the previously reported synthesis in order to obtain new 4-acyl-1,2,3-triazoles direct from acetophenones in a solvent and metal-free one-pot reaction. After the optimizations, the best condition was determined using acetophenone **1a**, DMA-DMF and azide **2a** at 150 °C for 2 hours obtaining compound **3aa** in 80% yield. New triazoles were obtained from different acetophenones and aryl azides with 42-93% yields (Scheme 1). With this, a straightforward methodology is shown to obtain new 4-acyl-1,2,3-triazoles.



Scheme 1: (a) Solvent and metal-free synthesis of 4-acyl-1,2,3-triazoles from enaminones and azides; (b)Direct metal and solvent-free one-pot synthesis of 4-acyl-1,2,3-triazoles from acetophenones and azides.

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A direct and mild approach to α-hydroxy amides through oxalic acid decarboxylation in Passerini reactions

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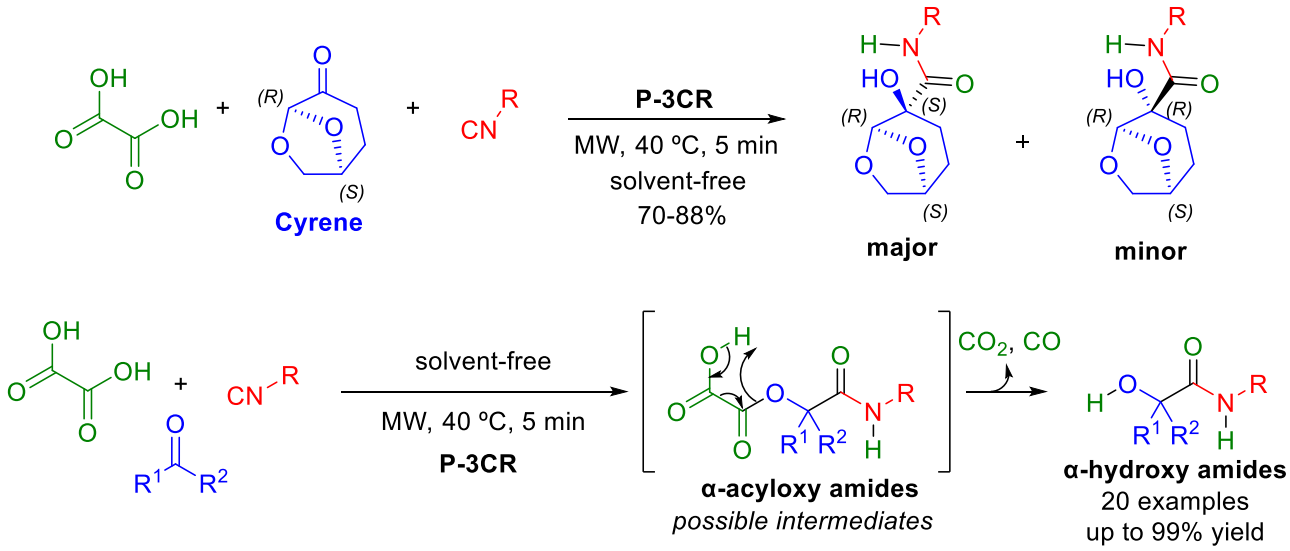
Keywords: *α-hydroxy amides, microwave, Passerini reactions, decarboxylation.*

ABSTRACT

α-Hydroxy amides are an important class of compounds found in natural products and bioactive molecules of drug candidates.[1–4] During our ongoing studies on the Passerini three-component reactions (P-3CR) using cyrene,[5] we found out that upon reaction with oxalic acid in solvent-free conditions under microwave heating, a decarboxylation process was taking place leading directly to an α-hydroxy amide in high yield and good selectivity. Herein we report the scope of this reaction with a variety of aldehydes and ketones. This convenient methodology provides the free hydroxyl group possibly through an intramolecular concerted decarboxylation process from the α-acyloxy amide intermediates. The efficiency of the decarboxylation process is very dependent upon the type of carbonyl compound used, and higher yields were observed for cyrene and 6-membered ring ketones, such as cyclohexanone and 4-^{t}butylcyclohexanone. Aldehydes also furnish α-hydroxy amides, albeit in lower yields.



ACKNOWLEDGEMENTS

The authors thank Universidade de Brasília (Edital DPG 001/2022), FAPDF (Edital 03/2021) and CAPES for financial support.

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(5) Unpublished results.

Diasteroselective Synthesis of 1,2,3,4-Tetrahydroquinolines via an Intramolecular Ugi-Smiles Reaction

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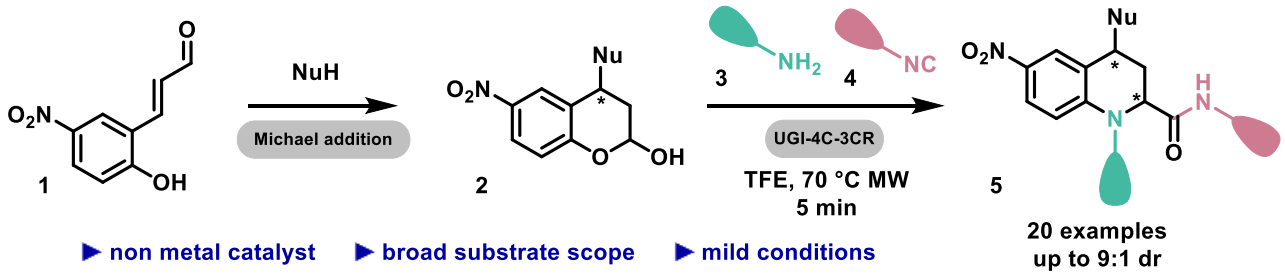
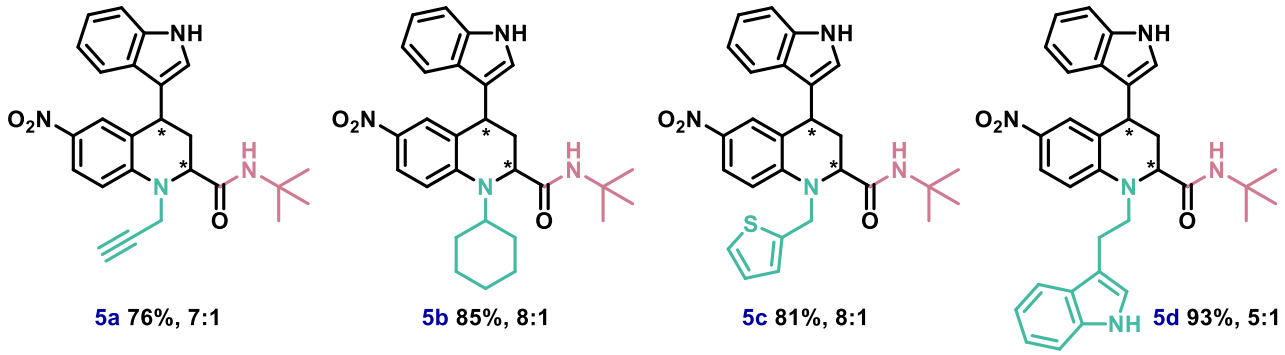
Keywords: *Organocatalysis, multicomponent reactions, diasteroselective synthesis.*

ABSTRACT

Tetrahydroquinolines (THQ) are a group of nitrogen heterocycles that has attracted considerable attention from organic and medicinal chemists due to their widespread presence in biologically active natural products and pharmacologically relevant therapeutic agents.[1,2] For these reasons, the development of more sustainable methodologies for the synthesis of tetrahydroquinoline derivatives still is a very interesting field of research.[3,4] In an effort to develop efficient synthetic routes for the synthesis of highly substituted tetrahydroquinolines derivatives, we herein describe an organocatalytic Michael Addition followed by an Ugi-Smiles reaction. This approach takes advantages of the simplicity and high diversity generation of both the organocatalytic step and the multicomponent reaction to provide a diasteroselective route for the synthesis of a library of 1,2,3,4-tetrahydroquinoline derivatives in a sequential approach. Under the optimal reaction conditions 20 examples with a high yield and d.r. up to 9:1 could be smooth obtained.



Selected examples:



ACKNOWLEDGEMENTS

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Continuous-flow kinetic resolution of bicyclic tertiary alcohol using lipase as catalyst

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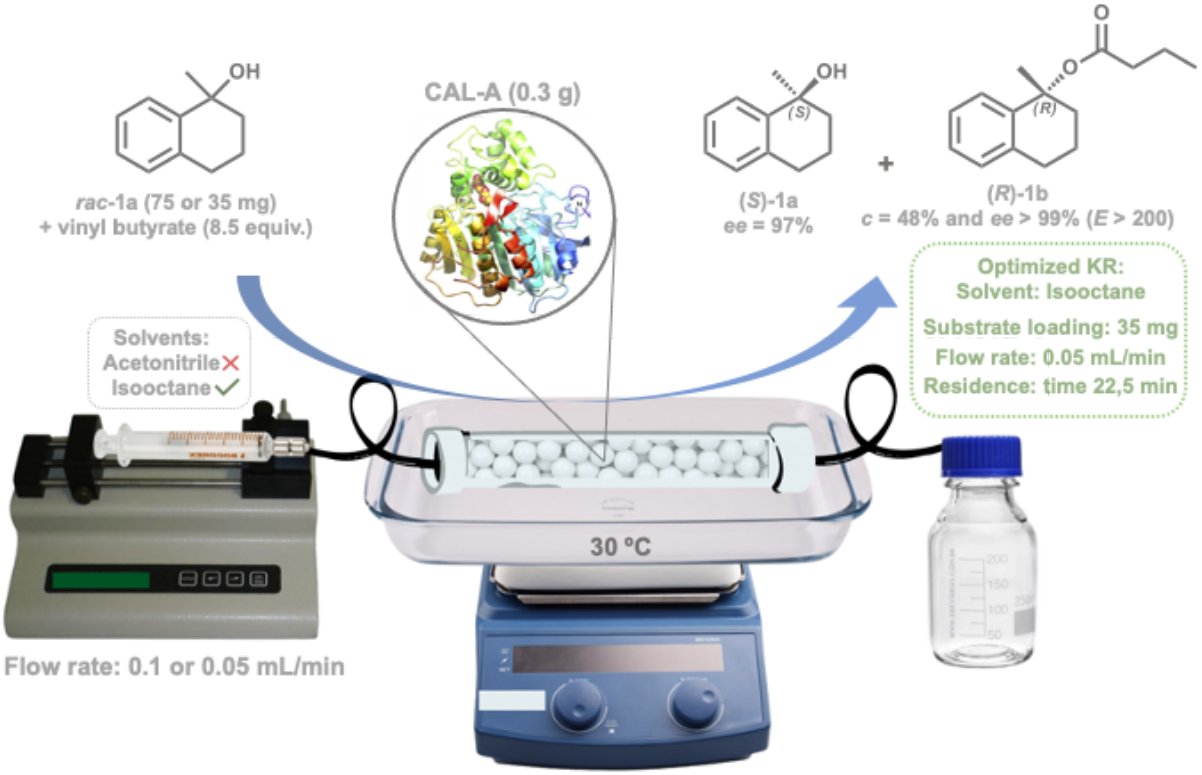
Keywords: *chemoenzymatic resolution, packed bed flow system, tertiary bicyclic alcohols*

ABSTRACT

Kinetic resolution (KR) is a well-established approach to produce enantiopure alcohols. The KR of *sec*-alcohols usually uses enzymes – especially hydrolases – as catalysts, however, most hydrolases have no activity for tertiary alcohols (TAs).[1] Considering that optically active TAs are important synthons for the pharmaceutical and natural products industry, the search for better strategies for their production is eminent.[2] In this work, we report the first continuous-flow KR of the bicyclic TA 1-methyl-1,2,3,4-tetrahydronaphthalen-1-ol (*rac*-**1a**), using immobilized *Candida antarctica* lipase A (CAL-A) as biocatalyst and vinyl butyrate as acyl donor. After screening solvent, substrate concentration and flow rate, we obtained an optimized KR leading to the (*R*)-product only in 1 hour at a flow rate of 0.05 mL/min (c = 48%, $ee_{product}$ > 99%). Due the potential of flow system with heterogeneous catalysts[3], this study may allow an efficient combination of KR with a racemization, providing a desired dynamic KR (DKR) for TAs.[4]



ACKNOWLEDGEMENTS

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (**CAPES**) – Finance Code 001. This work was also funded by the grants #2019/15230-8 from São Paulo Research Foundation (**FAPESP**).

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Exploitation of ultrasound and flow chemistry for the one-pot synthesis of new *N*-fused indoles

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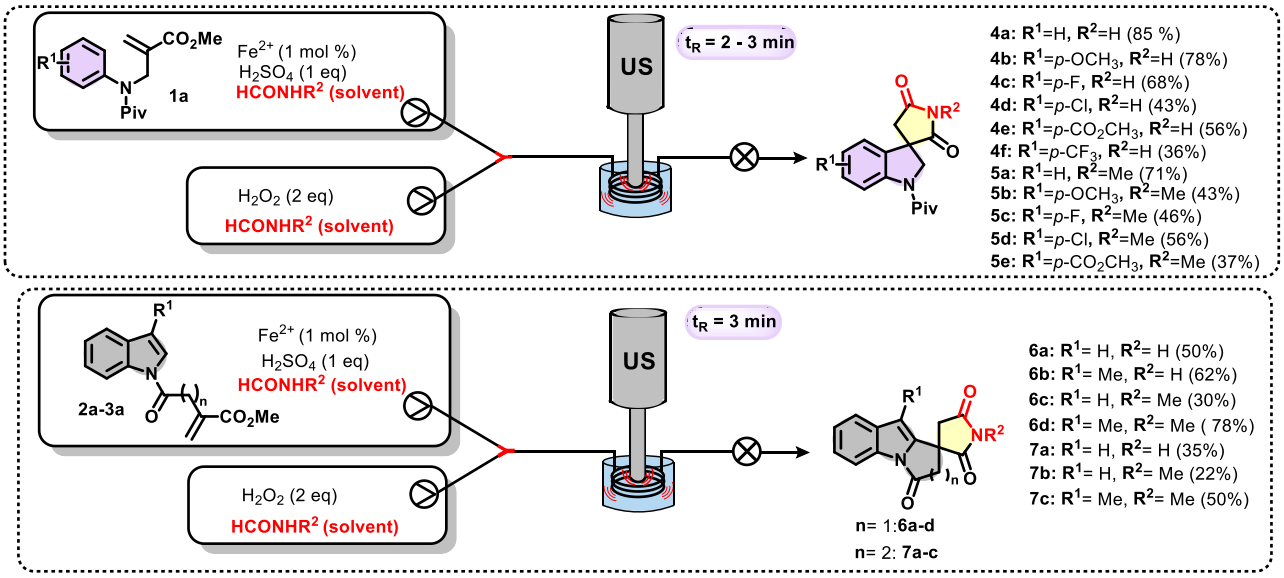
Keywords: *Indole, flow reactors, sono-Fenton, spiro, formamides.*

ABSTRACT

Indole is a privileged *N*-heterocycle found in nature,[1] as well as the *N*-fused polycyclic indoles are a motif present in a wide range of natural and synthetic products which exhibits important biological activities.[2] There are some few reports about the use of ultrasonic flow reactors for organic synthetic applications [3] and it is known from the literature that the sono-Fenton process can enhance the formation of radicals.[4] In this work an ultrasonic flow reactor was applied to promote the one-pot synthesis of new spiro-fused indoles through the application of formamides and sono-Fenton process. Compound **1a** was applied as a model to evaluate the one-pot synthesis of the spiroimide **4a**, a 3 minutes residence time was ideal to get full conversion to the spiro[indoline-succinimide]. We applied the reactor for the synthesis of new spiro[indoline-succinimide] (**4a**-**f**, **5a**-**e**), spiro[-pyrrolo-indole-succinimide] (**6a**-**d**), and spiro[pyrido-indole-succinimide] (**7a**-**c**), in excellent to moderate yields, as shown in **Scheme 1**.



Scheme 1: Reaction scope for the synthesis of spiro-fused indoles.

ACKNOWLEDGEMETS

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Exploitation of formamide reactivity towards renewable vinylic esters to produce novel biobased polymers

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Keywords: *Biobased polymer, formamide, catalysis, continuos flow.*

ABSTRACT

Considering the great relevance of polymers for both industry and academia, this work aims to develop a new synthetic approach for the production of biopolymers in which all the carbons come from renewable sources, having the exploration of formamide reactivity as a key step. The first step of this work proposes the fast continuos flow synthesis of monomers from formamide ($HCONH_2$) – that can be produced from carbon dioxide (CO_2)[1] – and renewable vinylic esters. Initially, the synthesis of these monomers was carried out in continuous flow by amidation the unsaturated esters with the carbamoyl radical ($\bullet CONH_2$), which is generated from formamide in a system irradiated by UV light containing the photocatalyst TBADT.[2] In the second stage, the monomer **3a** was used as a model and a new structurally diversified polymer was obtained through polymerization with diols.[3]

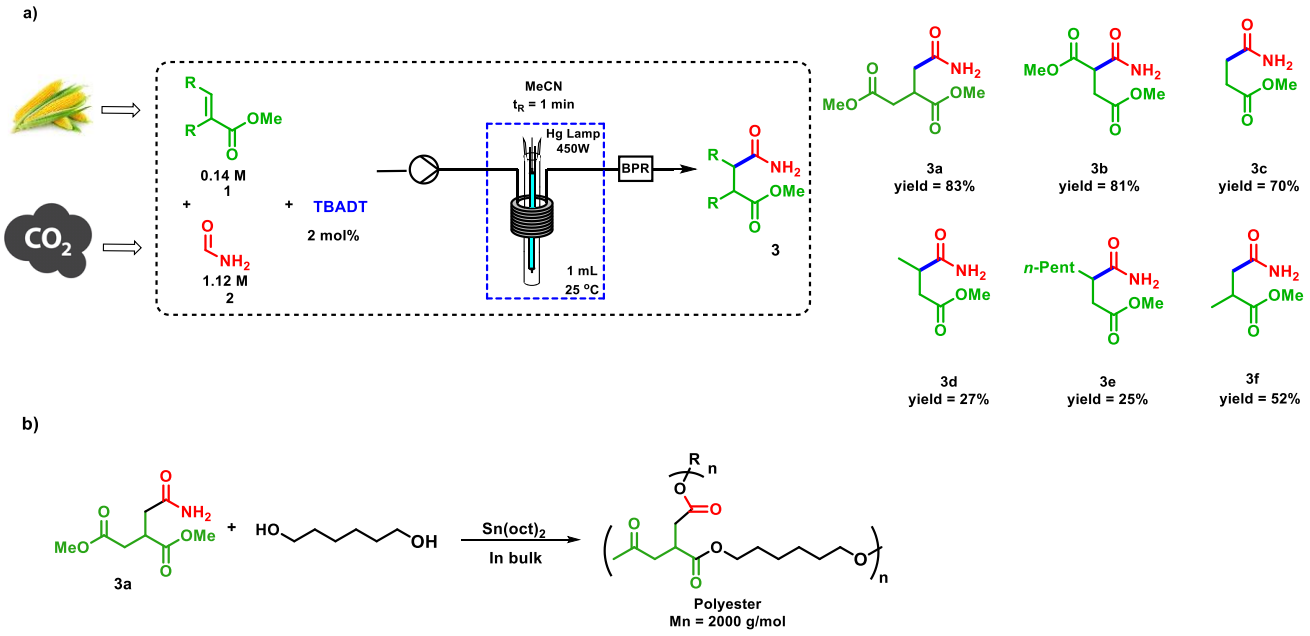

Figure 1: Synthetic route for biopolymers synthesis: a) Synthesis of the monomers, b) Reaction of Polymerization.

ACKNOWLEDGEMENTS

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Design and synthesis of new selenium-functionalized naphthoquinones with potential antitumor activity

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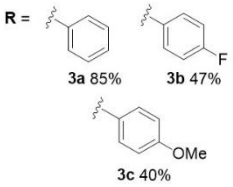
Keywords: *lawsone, organoselenium, cancer.*

ABSTRACT

Cancer is the major public health problem worldwide and, in Brazil, the estimate for each year of the triennium 2020-2022 indicates that there will be 625 thousand new cases.[1] The main treatments, such as chemotherapy and radiotherapy, can have several side effects and are not effective in advanced stages of the disease.[2,3] So, the need for the development of substances with better anticancer activity and safety profiles is evident. Thus, organoselenium and naphthoquinones stand out for having excellent activity against several tumors.[4] Therefore, this work aims to combine these two scaffolds through a ligand that has also been shown to be efficient for this disease when combined with other structures.[5]

To obtain the best condition for obtaining the desired product **3a**, the reaction parameters were varied. Before that the reactions were carried out under 0.9 equivalent of **2**, free of bases and at room temperature (Figure 1).



	$(PhSe)_2$	Base	Temperature (°C)	Yield (%)
1	0,6	-	rt	43
2	0,6	-	50	38
3	0,6	-	80	41
4	0,5	-	rt	54
5	0,4	-	rt	50
6	0,5	$NaHCO_3$ (1,5)	rt	70
7	0,7	-	rt	64
8	0,8	-	rt	72
9	0,9	-	rt	85
10	1,0	-	rt	81
11	0,9	$NaHCO_3$ (1,5)	rt	64
12	0,9	-	rt	85

Figure 1. Synthetic route and optimization of obtaining **3a-c** products.

ACKNOWLEDGEMENTS

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Fluorophores containing the 1,3,5-triazine core with BODIPY and organophosphorus substituents for application as molecular sensors

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Keywords: *Organophosphorus, Fluorescence, 1,3,5-triazine*

ABSTRACT

We have been working to develop a new class of molecular sensors (IV) that gathers, in the same molecule, one fluorescent BODIPY block (I), one phosphoramidate block (II) and one auxiliary 2-aminoethylpyridine block (III), all connected to the 1,3,5-triazine nucleus. (Figure 1) At this stage of our research we are searching the best stepwise substitutions of the three Cl atoms from the starting cyanuric chloride.

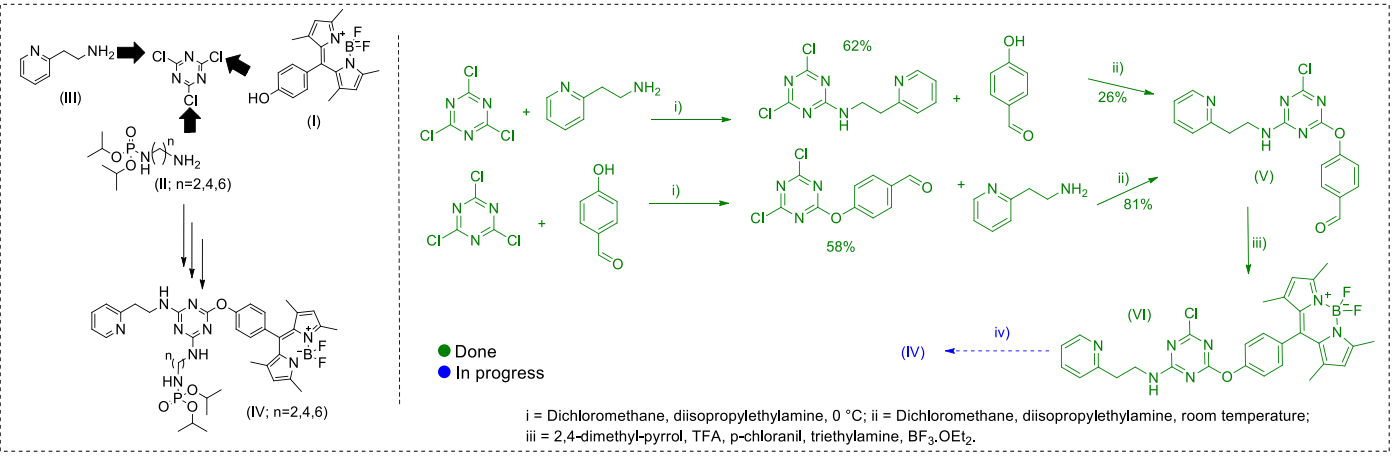

Figure 1: Schematic pathway to fluorophores IV.

Among the nucleophiles I, II and III, 2-aminoethylpyridine showed the best result as the first substituent on cyanuric chloride. Attempts to react BODIPY (I) failed as the second substituent. Alternatively, we developed the new aldehyde intermediate (V) by two ways, in order to construct the BODIPY nucleus through the subsequent reaction with 2,4-dimethylpyrrole and $BF_3.Et_2O$. In addition, we are looking for the best conditions to introduce the phosphoramidate II, to complete the triad. (Figure 1)

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Synthesis and application of selenoxide-pillar[5]arene as catalysts in nucleophilic reactions in water

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Keywords: *Catalysis, macrocycle, pillar[n]arene, selenium.*

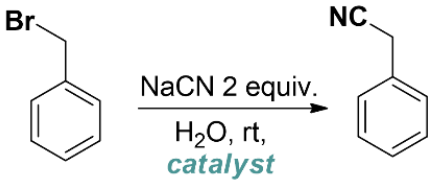
ABSTRACT

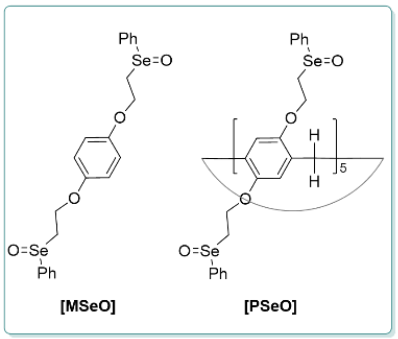
Because of the singular electron-rich cavity and easy functionalization, pillar[n]arenes have been extensively studied for several applications.[1] Besides, selenium compounds are highlighted in different fields, including catalytic potential in promoted organic reactions.[2] Therefore, the objective of this work is to promote the synthesis of C-C bond, in a green reactional media through the use of pillar[5]arenes combined with organochalcogens.

Thus, a selenoxide-pillar[5]arene (PSeO) and its monomer (MSeO) were synthesized and tested as catalysts. The results are shown in the graphical abstract. Noticeably, the best reactional condition and catalyst was PSeO in entry 3, which provided the product with 75% yield. Through the higher yield of the PSeO comparatively to MSeO, indicates that macromolecule cavity acts positively during the reaction.

From these promising results, further studies are being carried out to explore the scope of the reaction and catalyst recovery, as well as the mechanism by which the reaction is processed.

GRAPHICAL ABSTRACT





catalysts

	Catalyst	Time (h)	Yield (%)
1	-------	24	17
2	[MSeO]	16	41
3	[PSeO]	16	75
4	[PSeO]	6	30
5	[PSeO]	12	22
6	[PSeO]	24	55

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Synthesis of 4-oxoquinoline ribonucleosides and screening as ligands for *Ld*NH inhibition

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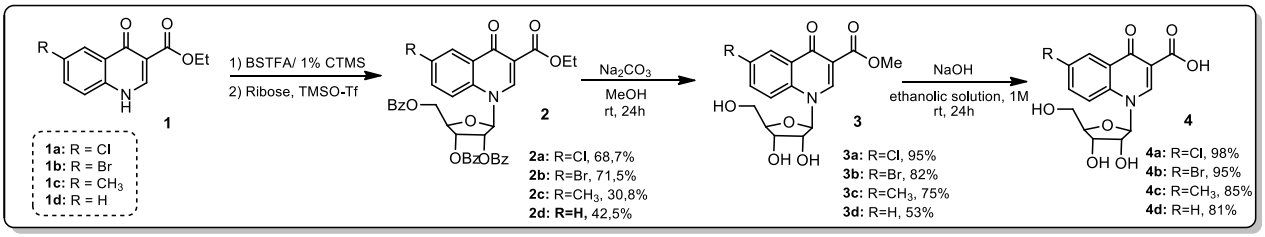
Keywords: *Leishmania, Biocromatography, Ribonucleosides,4-oxoquinolines*

ABSTRACT

Leishmaniasis is a serious disease due to its worldwide reach and high lethality. Drugs used in clinic for leishmaniasis treatment are expensive and highly toxic. So, it is necessary to develop new leishmanicidal agents and investigation of new therapeutic targets, in the search for more effective drugs. Herein we report the synthesis of a library of 4-oxoquinoline ribonucleosides as potential LdNH inhibitors, a key enzyme in the salvage pathway of Leishmania donovani, considered as target for drug design. First, 4-oxoquinolines **1** were previously silylated with BSTFA/1% CTMS, followed by the addition of ribose and TMSO-Tf, leading to 4-oxoquinoline ribonucleosides **2**. Selective deprotection reaction provided the methyl ester **3**, which was subjected to basic hydrolysis to obtain carboxylic acid ribonucleosides **4**. These derivatives were evaluated as ligands for *Ld*NH inhibition, in a range of 82 to 99%. Preliminary studies indicate that **4a** inhibts *Ld*NH, with IC_{50}= 2,66 µmol.$L^{-1.}$



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The use of aldoximes as directing groups in oxidation reactions of C−H bonds

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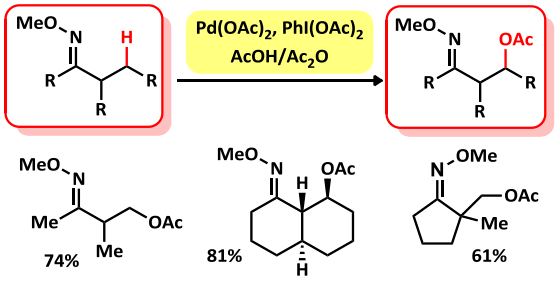
Keywords: *C−H activation, Directing groups, Palladium, Oxidation, Catalysis.*

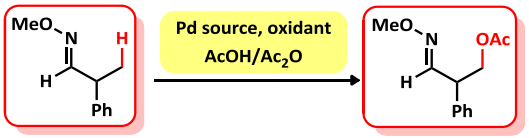
ABSTRACT

The oxidation of C−H bonds is of interest for organic synthesis, but achieving high sitioselectivity is still a challenge. In 2004, Melanie Sanford and coworkers developed a methodology for acetoxylation of βC—H bonds to ketone oximes catalyzed by $Pd(OAc)_2$ (Scheme 1).[1]



Scheme 1. Palladium-catalyzed acetoxylation of C−H beta bonds to oximes.

Several substrates were successfully oxidized in good to optimal yields. The selectivities for (i) βC—H bonds to the oxime are due to the preferential formation of the five-membered paladacycle and (ii) C—H bonds of primary carbons are due to the minimization of the steric demand around the palladium atom.[2,3]
This work proposes to develop a palladium-based catalytic system capable of acetoxylate C—H bonds in beta position to aldehyde oximes, which is unprecedented in the literature. Some oxidant and palladium sources have already been tested (Scheme 2).



$Pd(OAc)_2$, BAIB: 0%	Oxone, $Pd(OAc)_2$: 0%
$Pd(TFA)_2$, BAIB: 0%	$K_2S_2O_8$, $Pd(OAc)_2$: 0%
$Pd(acac)_2$, BAIB: 0%	Benzoyl peroxide, $Pd(OAc)_2$: 0%
$(MeCN)_2PdCl_2$, BAIB: 0%	$PhI(OAc)_2$, $Pd(OAc)_2$: 0%
Na_2PdCl_4, BAIB: 0%	*m*CPBA, $Pd(OAc)_2$: 0%

Scheme 2. Some oxidants and palladium sources tested.

ACKNOWLEDGEMENTS

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Continuous flow photochemical synthesis of 3-methyl-4-arylmethylene isoxazole-5(4H)-ones and investigation of their larvicidal activity

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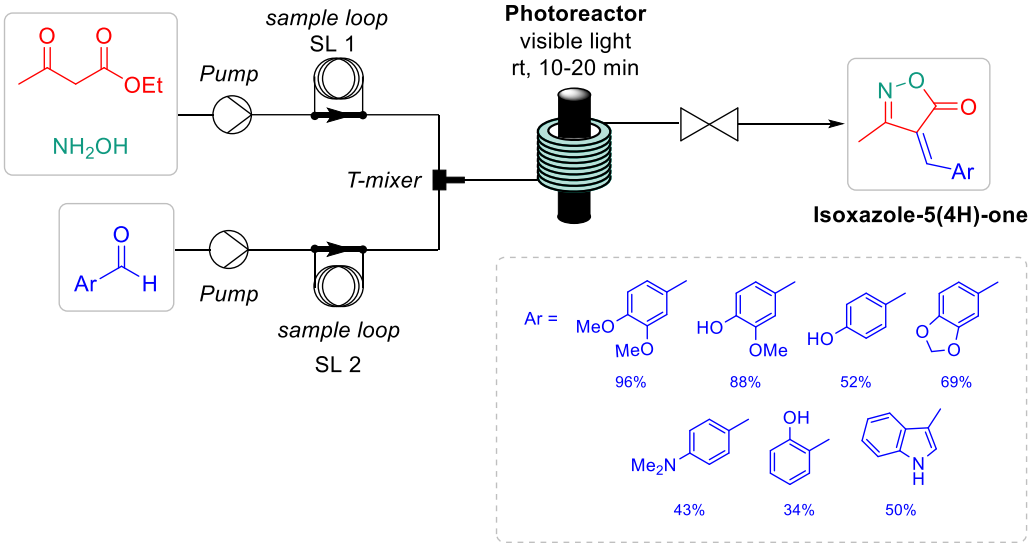
Keywords: *Isoxazolone, phochemistry, multicomponent reaction.*

ABSTRACT

Isoxazole-5(4H)-ones are heteropentacycle compounds found in several bioactive molecules with pharmaceutical and agrochemical properties.[1-2] A well-known multicomponent reaction between β-ketoester, hydroxylamine and aromatic aldehydes leads to 3-methyl-4-arylmethylene isoxazole-5(4H)-ones, in mild conditions.[3] The initial purpose was to investigate whether the reaction might be induced by light, as described in previous works.[4-5] Remarkable results were obtained using a high-power lamp, reducing reaction times compared to methodologies that used heating or catalysis. Since there are many examples of successful continuous flow heterocycle synthesis, including photochemical reactions,[6] the study evolved to run the reaction in flow conditions and scale up the synthesis of isoxazolones using a photochemical reactor set-up for the first time. Seven different compounds were successfully obtained and, among them, five showed larvicidal activity on immature forms of *Aedes aegypti* in tests that investigated their growth inhibitory character.



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Methylated imidazoles in reactions with organothiophosphates: reactivity as a tool for safe detoxification

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Keywords: *Catalysis, organophosphates, pesticide, nucleophile, degradation*

ABSTRACT

Due to the high toxicity of organophosphate pesticides (OP's), different forms of degradation of these pesticides have been reported.[1] Imidazole (IMZ) has catalytic properties in dephosphorylation reactions, attacking preferably the phosphorus atom of OP's in contrast to pathways via the aromatic/aliphatic carbon .[2,3] Seeking the detoxification of these OP's, this study evaluated the reactivity of organophosphates that contain the P=O bond and the P=S bond, against imidazole (IMZ) and its methylated derivatives (x- MEI: 1-MEI, 2-MEI and 4(5)-MEI). It was observed that the reactivity increases with increasing pH and is higher for the attack on aliphatic carbon than for phosphorus. Furthermore, for species that contain the P=S group, the reaction occurs more slowly and the mechanism can be modulated through variations in pH and the difference in pKa of the x-MEI (Figure 1), which highlights the importance of understanding the reactivity for efficient degradation of these OP´s.

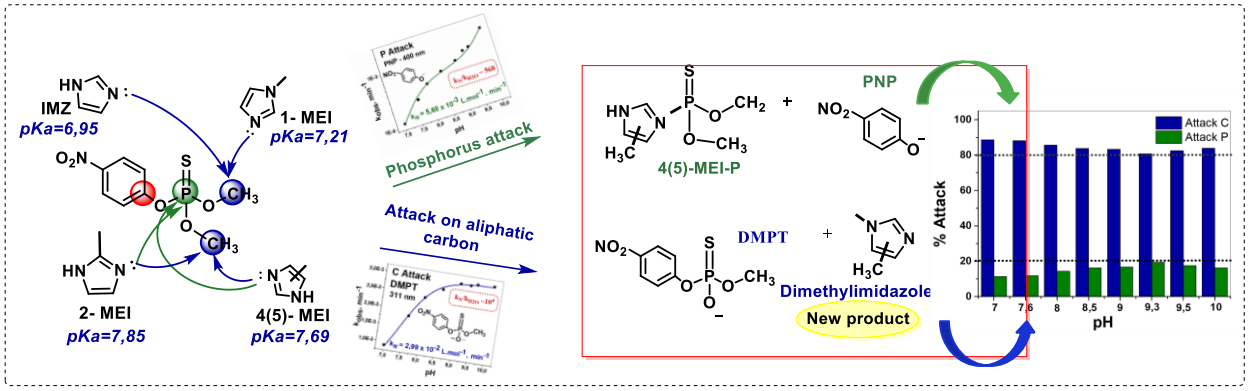

Figure 1 – Scheme of the reaction of methyl-parathion with IMZ, 1-MEI, 2-MEI and 4(5)-MEI and the percentage of attack on aliphatic carbon and phosphorus atom.

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Ultrafast transition metal-free synthesis of functionalized oxindoles under microwave irradiation

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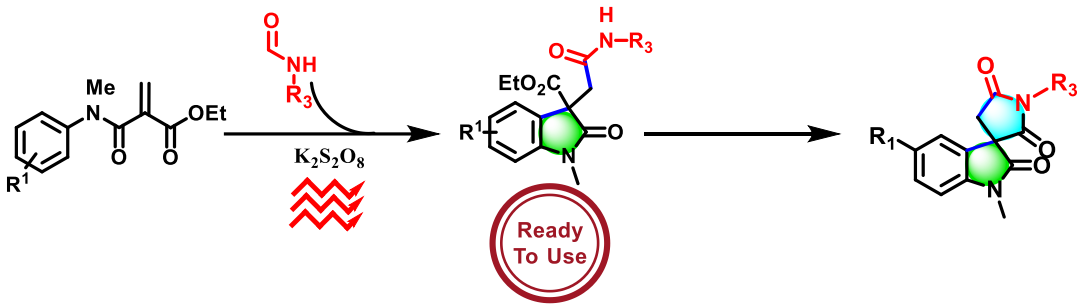
Keywords: *Ultrafast synthesis, metal-free, formamide, oxindoles, microwave, spiro-coumponds.*

ABSTRACT

Oxindoles are a class of endogenous aromatic heterocyclic organic compounds with a bicyclic structure that are found in body fluids and tissues of mammals, bacteria, invertebrates, and as natural products of some plants.[1,2] Due to their diverse pharmacological profile with noteworthy effectiveness, industry and academia have shown great interest in the development of novel synthetic oxindole derivatives with biological activities. The installation/construction of oxindole cores still relly on ring-closing strategies that usually depend on methodologies catalyzed by transition metals and long reaction times.[3-5] Seeking to decrease reaction times and greener reagents, we decided to explore a methodology with formamide (reagent/solvent) and potassium persulfate (radical initiator) under microwave irradiation in the presence of *N*-phenyl-*N*-acrylamide substrate, which resulted in an ultrafast reaction of 10 s. Using this ultrafast transition metal-free synthetic methodology a broad scope of highly functionalized oxindoles was obtained. The produced functionalized oxindoles allowed us to readily access spiro[oxindole-imides].



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Hydroxamic acids derived from cinnamic acid as urease inhibitors

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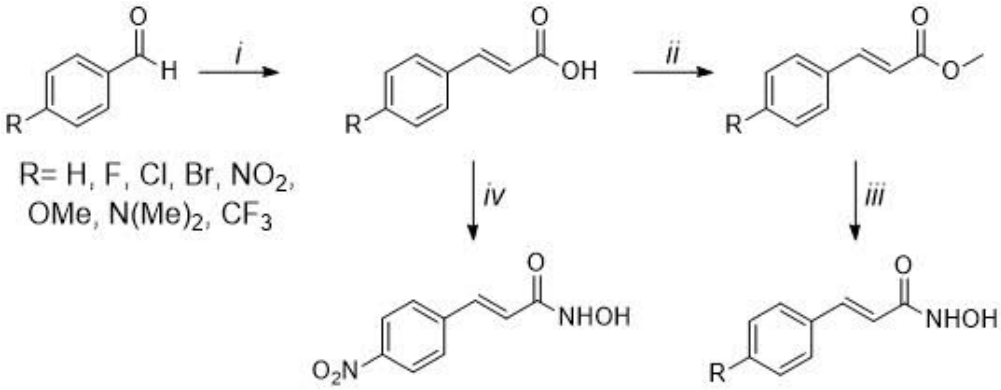
Keywords: *Urease inhibitor, hydroxamic acids, H. pylori.*

ABSTRACT

Urease is a nickel metalloenzyme responsible for the hydrolysis of urea to ammonia and carbamic acid. This enzyme is mainly present in plants, bacteria and fungi.[1] In human health, the activity of ureases is an important virulence factor in infections caused by ureolytic pathogens, for example *H. pylori*, since urea is the major nitrogenous metabolic product in humans.[2] The ureolytic activity also impacts agricultural productivity, considering that urea is the main nitrogen fertilizer used in the world.[1] The negative effects of urease activity and the absence of safe and effective inhibitors in the market motivate the development of new urease inhibitors. In this context, hydroxamic acids are an important class of compounds to be investigated, given that acetohydroxamic acid (AAH) has well-established inhibitory properties.[3] In this work, eight hydroxamic acids derived from cinnamic acid were synthesized (**Scheme 1**) and had their urease inhibitory activities evaluated *in vitro*. The hydroxamic acids were obtained in 47-90% yields and preliminary tests showed inhibitory activities 10 times higher than to AAH.



Scheme 1. Synthetic route of hydroxamic acids. *i)* Malonic acid, piperidine, ethanol, 70ºC, microwave irradiation, 45 minutes. *ii)* Trimethylsilyl chloride, methanol, reflux, 24 h. *iii)* Potassium hydroxide, hydroxylamine hydrochloride, methanol, room temperature. *iv) N,N'*-carbonyldiimidazole, hydroxylamine hydrochloride, anhydrous tetrahydrofuran, inert atmosphere, room temperature, 48 h.

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Synthesis and Characterization of a new Fluorescent Probe for Cell Imaging based on Digoxin-BODIPY Conjugated system

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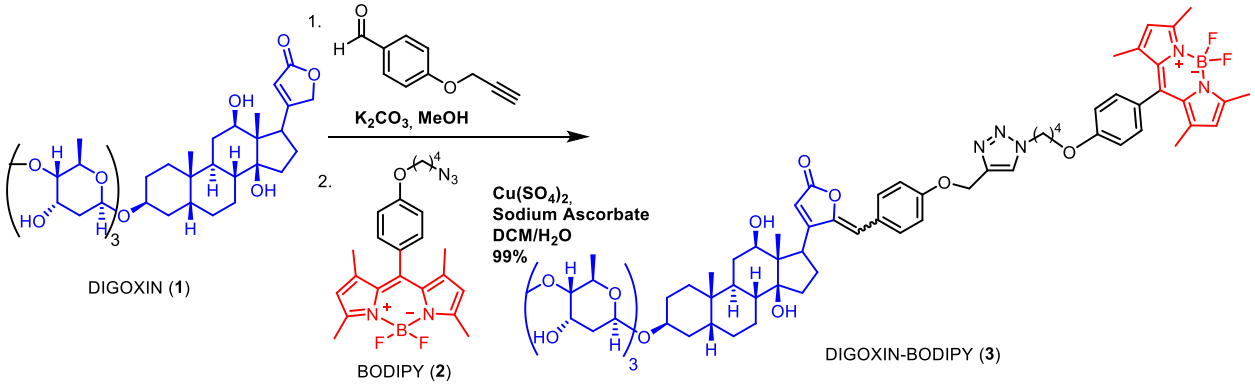
Keywords: *fluorescent probe, BODIPY, benzylidene digoxin.*

ABSTRACT

Digoxin (**1**) is an important cardiotonic steroid[1]. Condensation reactions between the lactonic portion of digoxin with commercial or synthesized aldehydes leads to the formation of digoxin derivatives called benzylidenes digoxin[2], which have already demonstrated biological activities *in vitro* studies[3,4]. The mechanism of action of these compounds is still unknown. One way to determine could be the use of a fluorophore probe, such as those of the BODIPY class, since these compounds have good photophysical properties[5]. The objective of this work was the synthesis and characterization of a new benzylidene digoxin, as well as coupling this compound to a BODIPY probe. Thus, a new benzylidene digoxin-BODIPY probe was synthesized (**Scheme 1**). The synthesized compounds were characterized by mass spectrometry, ^{1}H and ^{13}C NMR. Finally, studies concerning its photophysical proprieties were performed and are depicted in **table1**.



Scheme 1. Synthesis of DIGOXIN-BODIPY (**2**).

Table 1. Photophysical properties of BODIPYs in acetonitrile

Compound	l_{abs} (nm)	e (L.mol^{-1}.cm^{-1})	l_{Fluo} (nm)	DI (nm)[a]	F_{fluo}[b]
BODIPY (2)	497	110454.09	508	11	0.245 ± 0.020
DIGOXIN-BODIPY (3)	497	73659.41	508	11	0.208 ± 0.021

[a]Stokes shift, [b]Fluorescence quantum yields were calculated using Fluorescein (excitation at 460 nm, in NaOH 0.1 M) as reference. The standard deviation (SD) was calculated from 3 measurements. The BODIPYs were dissolved in acetonitrile.

ACKNOWLEDGEMENTS

UFSJ, USP, CAPES, CNPq and FAPEMIG

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Selective C-H functionalization of relevant N-heterocycles using organometallic intermediates

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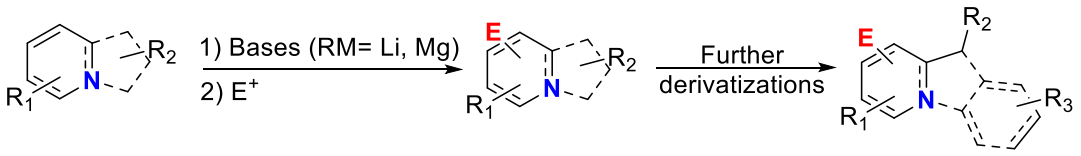
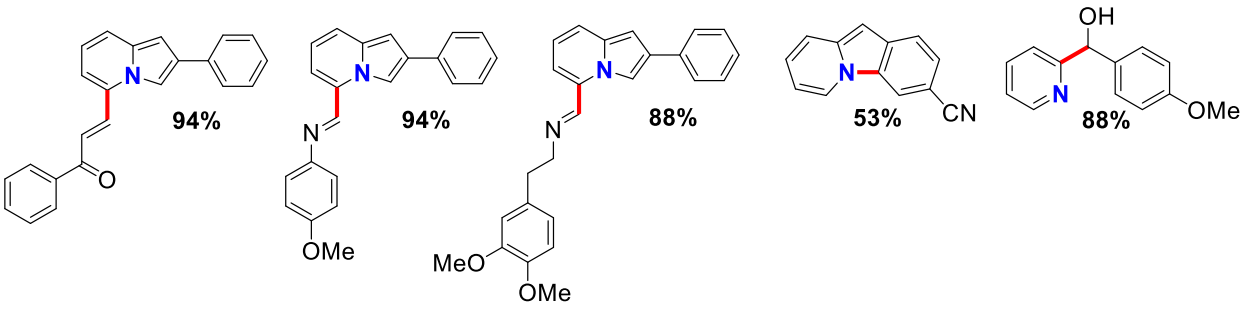
Keywords: *pyridoindole, indolizines, photophysical properties, cyclization.*

ABSTRACT

N-heterocycles that contain a fused ring indole, pyridine or pyrrole have been attracting interest from researchers due to its biological activities and different areas of application, such as medicinal chemistry and photophysical materials, with important luminescent properties. Many synthetic strategies have been developed for the synthesis of novel pyridoindoles and indolizines.[1] In this work, we have performed a C-H functionalization study of 2,5-disubstituted indolizines to obtain an aldehyde intermediary and through further derivatizations generate a number of compounds which showed significant fluorescence. Also, we functionalized different cyanopyridines using metallic bases to obtain alcohols. These building blocks have been used in cyclization studies using different strategies, among them modern photocatalysis techniques, acid catalysis or cyclization promoted by metal, allowing the synthesis of pyridoindoles derivatives.[2] We are employing photocatalysts such as TBADT or Eosin Y and different sources of light to develop the a new photoredox methodology.



Selected examples



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Studies on Enzymatic Ammonolysis of fatty esters and vegetable oils under continuous flow conditions

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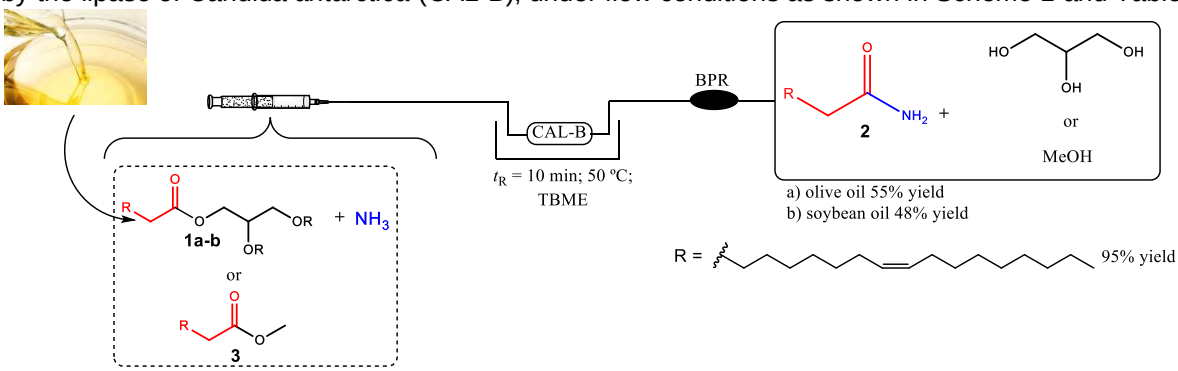
Keywords: *Biocatalysis, lipase, fatty esters, ammonolysis, flow conditions.*

ABSTRACT

Fatty amides are compounds that have a wide application in industry, being used as surfactants in detergents and personal care products [1]. These amides are normally obtained from their respective fatty acids or esters. However, the synthesis of these amides, when performed under batch conditions, takes a long time to reach high or satisfactory yields. To overcome this problem and based on work done by our research group [2], we propose the study of the ammonolysis reaction of vegetable oils (1a-b) and fatty esters (3), promoted by the lipase of Candida *antarctica* (CAL-B), under flow conditions as shown in Scheme 1 and Table 1.



Scheme 1. Ammonolysis of vegetable oils and fatty esters under flow conditions.

Table 1. Optimization of enzymatic ammonolysis of methyl oleate (3)[a].

Entry	t_R (min)	T (ºC)	Conversion (%) [b]
1	5	50	80
2	10	50	95
3	15	50	96
4	20	50	98
5	10	30	78
6	10	RT	41

a) Continuous-flow operation: methyl ester (0.02 M) and ammonia (sat) in MTBE; temperature (T): room temperature (RT) - 50 °C; residence time (t_R): 10–20 min; lipase: CAL-B (270 mg) was packed into a stainless steel tubing (1/4 in × 4.6 mm × 5 cm; reactor volume with lipase beads: 0.7 mL); back pressure regulator (BPR): 75 psi.

b) Conversion was determined by GC–MS analysis.

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Suzuki coupling in Tröger's bases: overcoming challenging substrates through aqueous micellar catalysis

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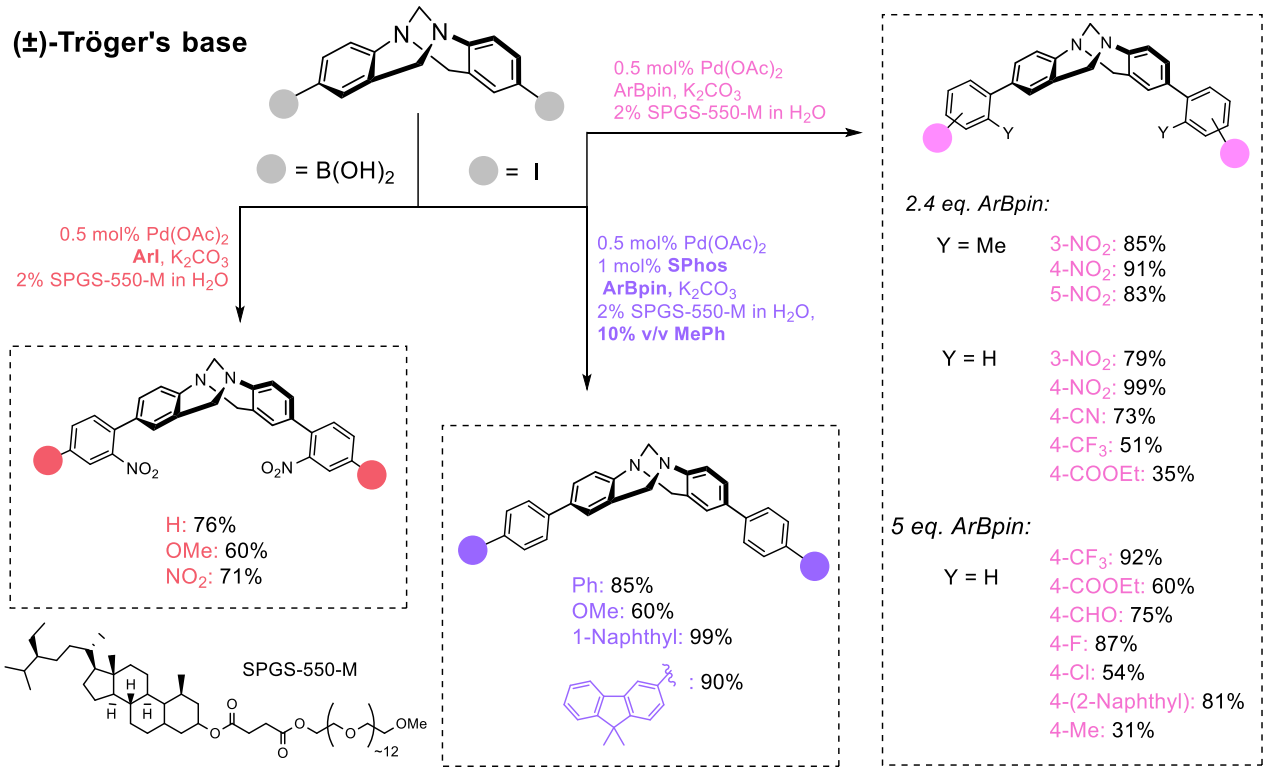
Keywords: *Micellar catalysis, Tröger's bases, Suzuki coupling*

ABSTRACT

An enormous collection of techniques developed by modern organic synthesis can lead to winsome non-natural products with unique attributes. Tröger's base emerges as an example regarding the uncommon geometry that cannot be found in nature. This compound has two aromatic planes, at an angle about 90°, being an inflexible structure displaying noteworthy two stereogenic centers at the nitrogen atoms. Despite the technological advances promoted by this scaffold, for example microporous membranes, molecular recognition, and quantification of weak interactions in solution, literature has been scarcer with respect to metallic catalysis methods. There are limited examples employing classical $Pd(PPh_3)_4$ catalyst and reports aiming optimization of reactions suggest unstable and sensitive ligands, like alkylphosphines. On the other hand, micellar catalysis provides a singular environment that modifies kinetic and thermodynamic profile of the reaction. In this work is reported a simple and efficient method with functional group tolerance to promote arylation in Tröger bases.



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Exploring the reactivity of iminomalonates with photogenerated radicals

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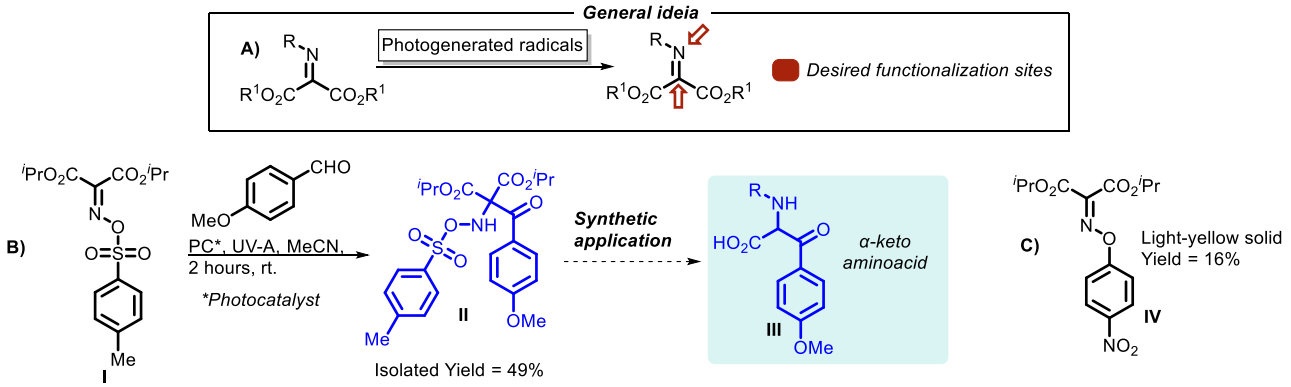
Keywords: *photocatalysis, iminomalonate, electrophilic amination, photogenerated radicals.*

ABSTRACT

The construction of new C-N bonds is of wide application considering the high number and diversity of nitrogen-bearing pharmaceuticals.[1] In this scenario, the common synthetic approaches comprise the use of nucleophilic nitrogen sources to promote substitution reactions, reductive amination,[2] and transition-metal-catalyzed cross-couplings.[3] A modern strategy relies on the use of electrophilic aminating agents including iminomalonates.[4] Inspired by the growing importance and suitability of photocatalyzed processes[5] and the work of Prof. Kürti and co-workers regarding the exploration of iminomalonates upon hard and soft diverse nucleophiles,[6] this work envisages the design and application of iminomalonates with photogenerated radicals to achieve alfa-position and nitrogen direct functionalization (**Scheme 1A**). Concerning our preliminary results, we have successfully promoted the acylation of iminomalonate **I** by an in situ generated acyl radical under UV-A (**Scheme 1B**), and the optimization of this reaction is underway. Additionally, we have synthesized the new iminomalonate **IV** (**Scheme 1C**) whose reactivity is under investigation.



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Large-scale and fast synthesis of monodispersed gold nanorods using a commercial grade natural phenolic compound.

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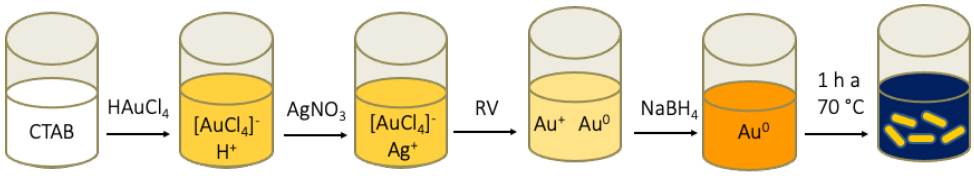
Keywords: *gold nanorods, large scale synthesis, monodispersion.*

ABSTRACT

Gold nanorods (GNRs) have great potential in biomedical fields[1] (development of new diagnostic tests, drug delivery, vaccines formulations) which require the synthesis of GNRs in high yields, adjustable aspect ratio, size monodispersity, easy surface decoration and in a scale up procedure. The seedless syntheses described[2] have a typical volume of 10-100 mL and use analytical grade (AG) reagents. In this work we report a fast (1 h) and large scale (1 L) seedless synthesis of GNRs using commercial resveratrol as a weak reductant (Scheme 1). This natural product can be purchased in regular pharmacies and are suitable for use after a simple recrystallization. The use of non-AG reagents reduces the cost of the process and makes it attractive to industrial applications.



Scheme 1 – Seedless synthesis of GNRs using: CTAB, $HAuCl_4$, $AgNO_3$, resveratrol (RV) and $NABH_4$.

GNRs were synthesized with high quality, reproducibility, yields and longitudinal localized surface plasmon resonance between 650 – 850 nm. Characterizations were made by Ultraviolet-Visible Spectrophotometry, DLS and TEM (Figure 1).

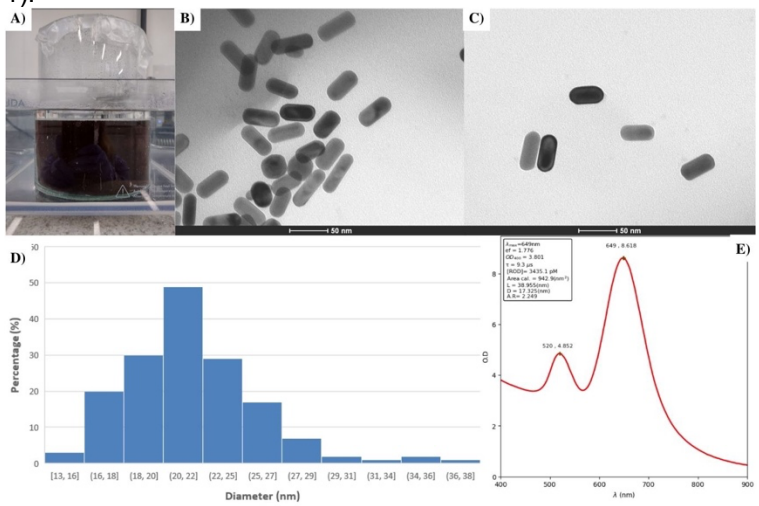


Figure 1 – Photograph of the gold nanorods synthesized by one time (A) and the corresponding TEM (B) e (C). Images with dimensions of 47(±9) × 22(±4) nm (D). UV-Vis spectrum (E).

ACKNOWLEDGEMENTS

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Synthesis of fentanyl triazole derivatives and their affinity for μ opioid and σ_1-receptor

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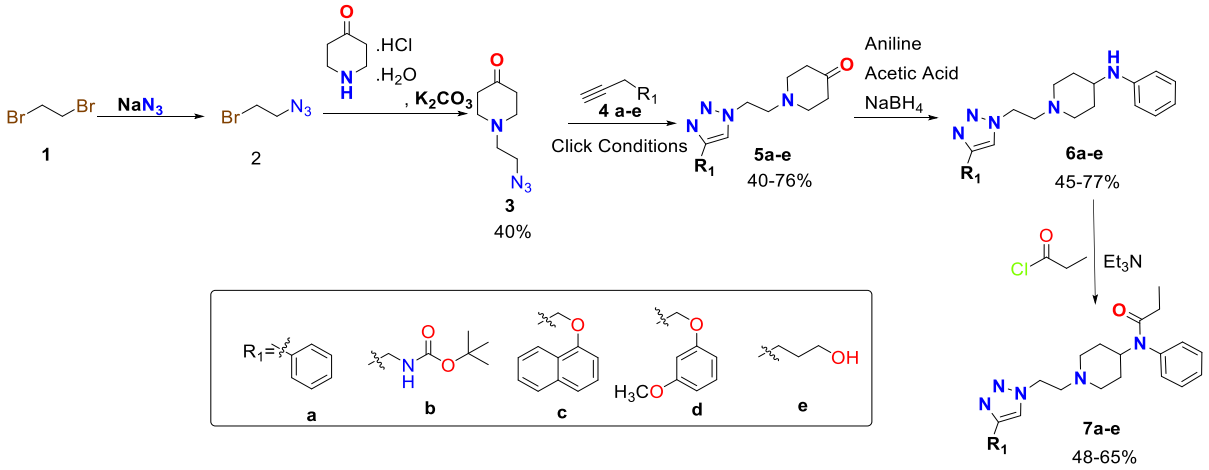
Keywords: *Opioids, click reaction, triazole analogues.*

ABSTRACT

Fentanyl is a synthetic opioid used primarily to control severe pain. [1] However, fentanyl has serious side effects such as respiratory depression, emesis, constipation, and causes physical dependence. Several fentanyl analogues have already been synthesized aiming to modulate its pharmacological properties, but there is still a search for an ideal opioid, which maintain its high analgesic property with minimal side effects.[2]

Thus, the objective of this work was to prepare new fentanyl triazole analogues (Scheme 1), where the affinity of the compounds towards the Mu (μ) opioid receptor (MOR) and the sigma 1 (σ_1) receptor were evaluated. The σ_1 receptor is unique and shares no homology to other receptor classes and their activity is related to addiction, pain and analgesia, memory information, etc.[3] The compounds **6d** presented the best affinity for both receptors (MOR IC_{50} = 1.9 ± 0.4; σ_1=6.9 ± 0.6). The route of synthesis consisted of the alkylation of 4-piperidone with halide **2**, producing the intermediate **3** via an one pot methodology, from dibromide **1**. The reaction of **3** with **4a-e** alkynes led to the formation of novel triazole piperidones, via CuAAC reaction . These intermediates were subjected to reductive amination to produce type **6** compounds. The acylation of these amines secondary yields generated new triazole derivatives of the fentanyl, with yields ranging from 48-65% in this step.

Scheme 1. Synthetic route used to obtain new triazole derivatives of fentanyl



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Ni(0)-Catalyzed Stereoselective Monotranposition of Alkenes

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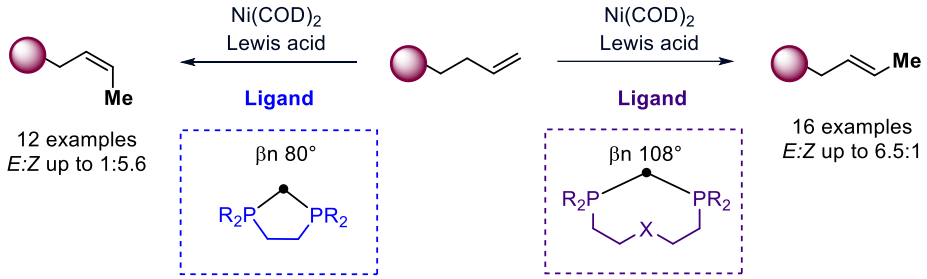
Keywords: *Catalysis, Olefin Isomerization, Nickel, Lewis Acid.*

ABSTRACT

The combination of Ni(0) and Lewis Acid (LA) successfully allowed the transposition of terminal double bonds to yield 1,2-alkenes. Interestingly, only one migration was observed, even when further migrations would lead to a more stable, conjugated isomer .[1] Careful ligand choice allowed the stereocontrol for this reactions. While wide bite bisphosphines produce *E*-products, small bite angle phosphines produce *Z* isomers.



Scheme 1. Stereoselective monotransposition of double bonds.

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A Simple Access to α-Ketoamide Peptide Pyrazoles as SARS-COV-2 Main Protease Inhibitors

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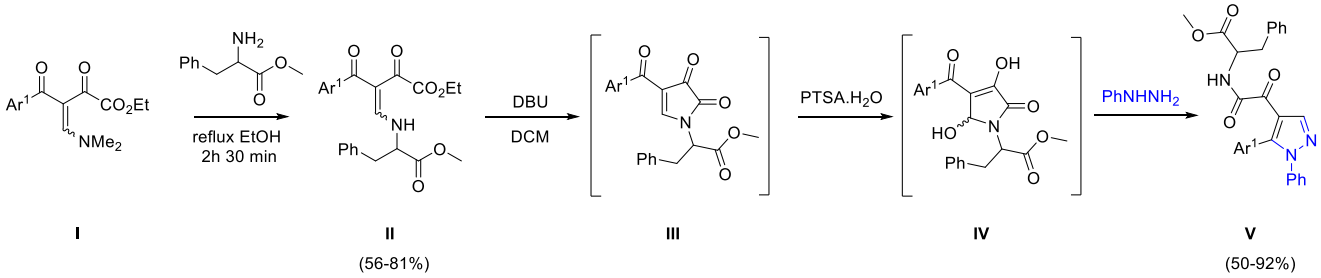
Keywords: *Synthesis, α-ketoamides, aza-heterocycles, pyrazoles.*

ABSTRACT

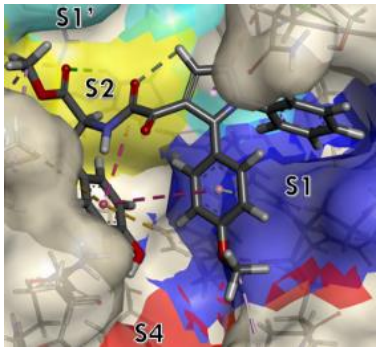
Since the start of the COVID-19 pandemic, which is caused by SARS-COV-2, significant effort has focused on the design of M^{pro}-specific inhibitors for developing effective drugs.
In this context, we performed a virtual screening of the SINTHET collection containing 744 polyfunctionalized aza-heterocycles on M^{pro}. Pyrazoles containing the *α*-ketoamide moiety derived from amino ester were predicted as binders of M^{pro}. Thus, the synthesis of the target compounds was envisioned employing the *β*-enamino diketones derived from amino ester and hydrazine, based on the methodology reported by us. Then, the reaction of the respectively *β*-enamino diketones with DBU furnished in situ formation of the cyclic intermediate pyrrole-2,3-dione, which underwent a ring-opening reaction by phenylhydrazine, providing the *α*-ketoamide pyrazole derivatives with yields of 50 to 92%. This strategy provides efficient and simple access to *α*-ketoamides containing amino ester residues. The synthesized compounds will be further evaluated against SARS-COV-2 M^{pro}.

Scheme 1. Formation of Polyfunctionalized *N*-Phenylpyrazole V from the *β*-enamino diketones



Ar^1= (a) C_6H_4-4-NO_2, (b) C_6H_4-4-Br, (c) C_6H_4-4-Cl, (d) C_6H_4-4-F, (e) C_6H_5, (f) C_6H_4-4-OCH_3

Figure 1. MPro-ligand complex formed to the best ranked ligand in molecular docking



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Molecular hybridization of 2-aminophenoxazin-3-one and dihydropyrimidinone

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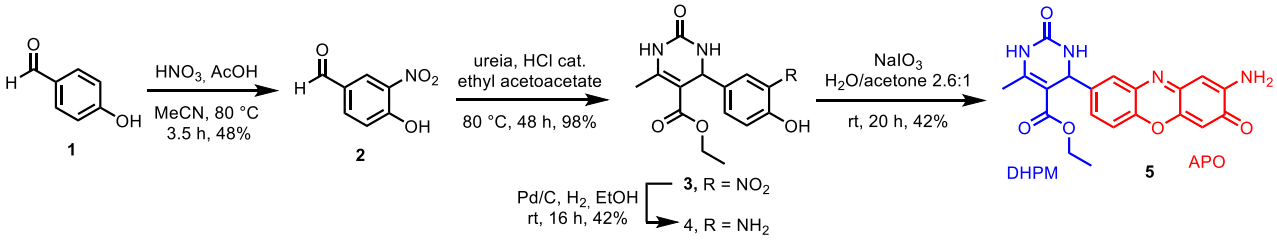
Keywords: *2-aminophenoxazine-3-one, dihydropyrimidinone, molecular hybridization.*

ABSTRACT

Molecular hybridization is a strategy used to synthesize new compounds with improved features based on the combination of nuclei with already known pharmacological activity.[1] The aim of this work was to put together in the same molecule two different pharmacophoric nuclei: 2-aminophenoxazin-3-one (APO) and dihydropyrimidinone (DHPM) and study the activities of the resulting compound. APO has anticancer activity,[2] DHPM has anti-inflammatory and antibacterial activities,[3] and both have antitumor and phytotoxic activities.[4,5] Nitration of *p*-hydroxybenzaldehyde **1** was followed by Biginelli reaction with urea and ethyl acetoacetate to furnish compound **3**, which was then hydrogenated. The resulting aminophenol **4** was oxidized with $NaIO_3$, yielding the target compound **5**. Preliminary phytotoxicity tests of this compound in wheat coleoptile bioassays[6] did not indicate significant activity, probably due to its low solubility in water and organic solvents. Pharmacological tests of this compound as well as of its thio derivative (prepared from thiourea) will follow.



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Enzymatic synthesis of Mangiferin adducts

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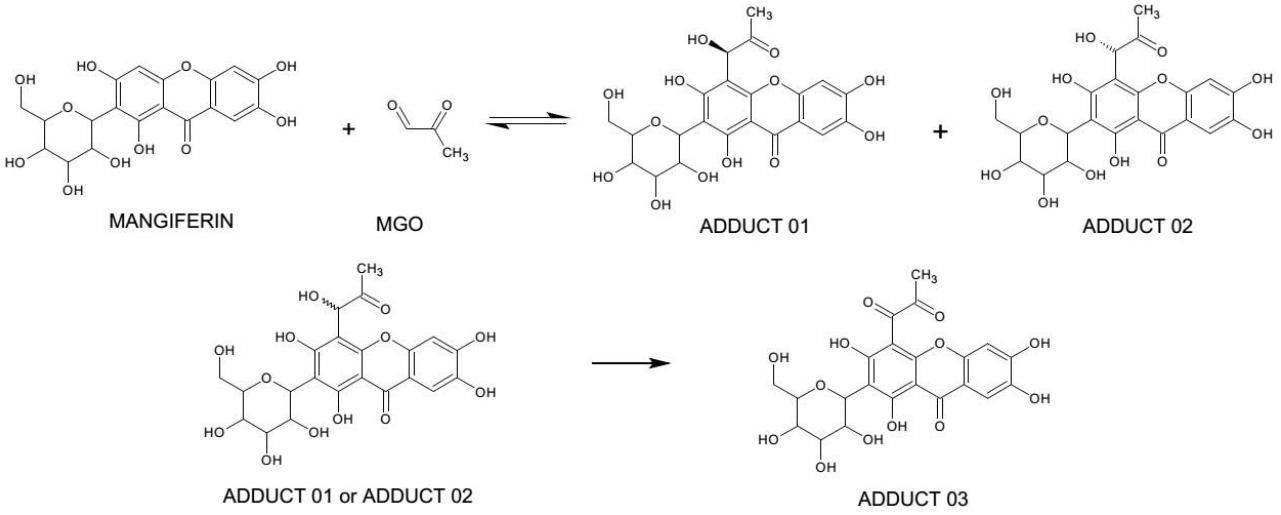
Keywords: *Mangiferin adducts, stereoselective synthesis, enzymatic catalysis*

ABSTRACT

Mangiferin can generate adducts with methylglyoxal.[1,2] For the synthesis of the adducts, BSA(0.0285mM), Methylglyoxal(158mM), Mangiferin(3.078mM) and phosphate buffer [KH_2PO_4/K_2HPO_4,(0.1M,pH=6.6)] associated with the hypoxanthine(0.301mM)/xanthine oxidase enzyme system, responsible for the rapid *in situ* generation of radicals[3] were used. Reaction conditions: incubation for 3h and 24h, absence of light, 37°C, agitation and analysis by HPLC/UV-Vis and NMR. Within 3h incubation, two diastereoisomer adducts (01 and 02) were produced. At 24h, a third adduct (03) was evidenced. The experiment was scale-up, with 48h incubation, for kinetic monitoring. After analysing the aliquots that were withdrawn every 1h, it was possible to conclude that diastereoisomer adducts were formed in the first 8h. After that, adduct 03 begins to be produced with a simultaneous decrease in the quantity of diastereoisomers adducts. The formation of these adducts depends on the prochiral face to which mangiferin attaches to methylglyoxal. The oxidation of diastereoisomer adducts generates adduct 03.



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Microwave/flow synthesis of thiazolidinedione derivatives and their larvicidal activity against *Aedes aegypti*

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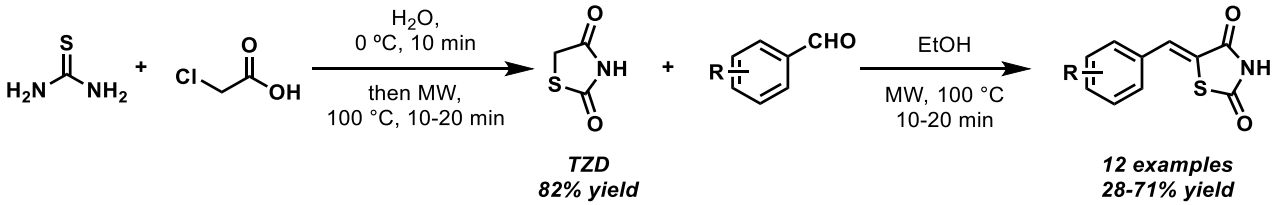
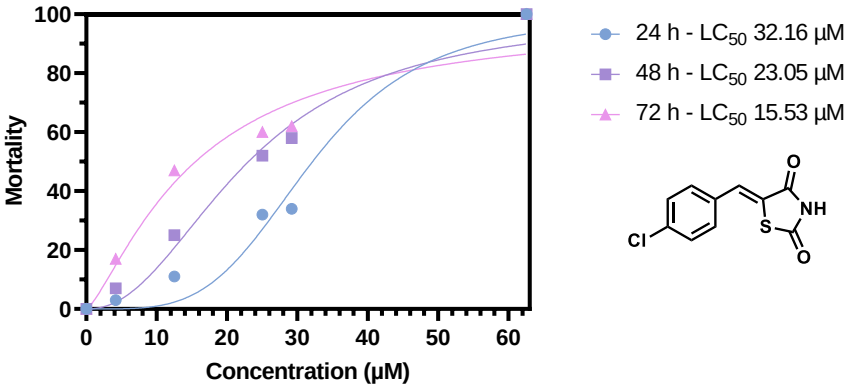
Keywords: *thiazolidinediones, microwave, continuous flow, Aedes aegypti.*

ABSTRACT

Thiazolidinediones (TZDs) are a class of compounds that have been studied for quite a long time to treat type II diabetes.[1] In the course of our studies to prepare TZD derivatives, we found that some of these compounds possess a good profile of larvicidal activity against *Aedes aegypti*. These compounds were prepared in good yields by condensation of the TZD moiety with 12 different aldehydes under microwave heating. To scale up the synthesis, the reactions are currently being carried out under flow conditions as well.[2] The target compounds were tested in larvicide trials and those who responded well got its concentrations lowered for LC_{50} computation.[3] The most promising molecule so far showed an IC_{50} of 32 μM in 24 h.





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Benzyl chalcogenocyanates synthesis: non-catalyzed and catalyzed systems with phase-transfer catalysts.

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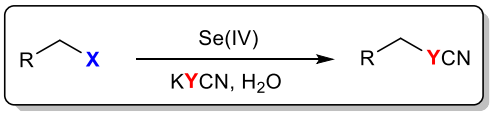
Keywords: O*rganocatalysis*, phase-transfer catalyst*, organochalcogenocyanates,* benzyl thiocyanates, benzyl selenocynates*.*

ABSTRACT

Organochalcogenic compounds have been the focus of study in recent years due to their pharmacological importance, their anticancer properties and their use as building blocks in different transformations. Herein we describe the synthesis of organochalcogenic compounds, more specifically benzyl thiocyanates and benzyl selenocyanates from two methodologies. At first, it involves the nucleophilic attack of potassium thiocyanate on benzyl bromines in a homogeneous reaction system, without the need for purification. 18 thiocyanates with yields between 50% and 93% and 8 selenocyanates with yields between 69% and 86% were obtained. The second strategy, still under development, involves a heterogeneous reaction system, where H_2O has been used as solvent and Selenium (IV) species as organocatalysts have been shown to be efficient as phase transferors. Both methodologies try to reduce the environmental impact, producing less waste and using polluting fewer solvents.



ACKNOWLEDGEMENTS

This study was financed in part by CNPq and CAPES. The authors are grateful to FAPEMIG for financial support of this research.

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Ru(II)-catalyzed asymmetric transfer hydrogenation of chalcones in water: application to the enantioselective synthesis of flavans BW683C and tephrowatsin E

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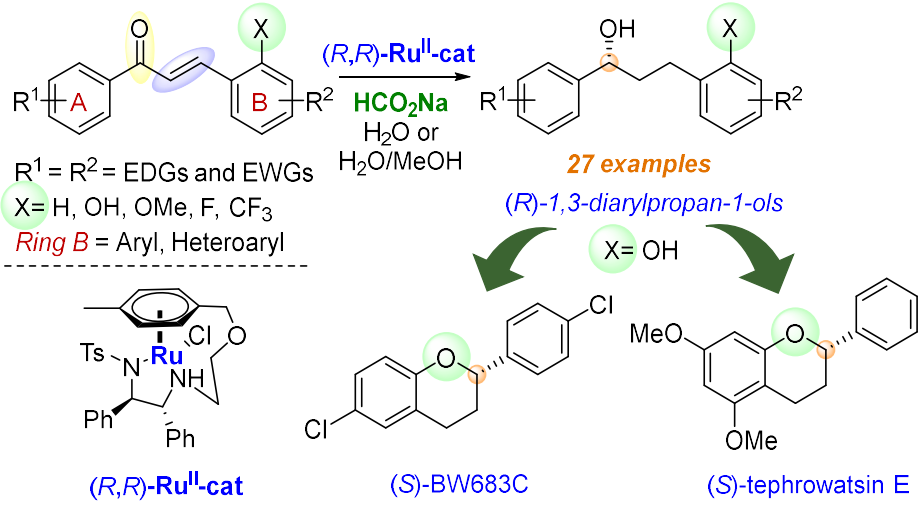
Keywords: *Asymmetric catalysis, Ruthenium, Reduction, Total synthesis, Flavonoids.*

ABSTRACT

The oxo-tethered-Ru(II) precatalyst [(*R*,*R*)-Ru^{II}-cat] promoted the one-pot C=C/C=O reduction of chalcones using sodium formate as the hydrogen source in water through asymmetric transfer hydrogenation (ATH). Our group had previously reported the enantioselective synthesis of natural homoisoflavonoids and isoflavonoids through ATH of enones.[1–3] Now, the procedure has been tuned to allow the ATH of acyclic substrates in water. Twenty-seven 1,3-diarylpropan-1-ols were obtained in good to excellent yields (up to 96%) and enantiomeric purities (up to 98:2). Our data suggested that the enones are firstly reduced to the corresponding dihydrochalcones (1,4-selectivity), and then into the 1,3-diarylpropan-1-ols (C=O reduction). The stereoelectronic effects of electron-donating and electron-withdrawing groups at the *ortho*, *meta* and *para* positions of both aromatic rings were evaluated over the reaction outcome. The 2-OH group at the B ring was well-tolerated, allowing a straightforward enantioselective synthesis of two flavans through the Mitsunobu cyclization, the antiviral (*S*)-BW683C and the natural flavan (*S*)-tephrowatsin E.



ACKNOWLEDGEMENTS

We gratefully acknowledge the financial support from CAPES, CNPq, FAPERJ and UFRJ.

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Synthesis of new paeonol derivatives for the treatment of neglected parasitic diseases

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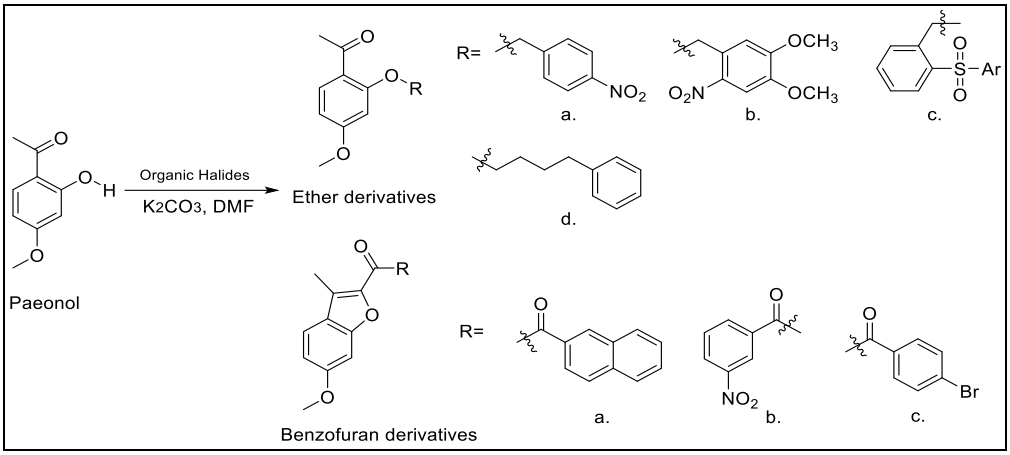
Keywords: *paeonol derivatives; parasitic diseases; organic synthesis.*

ABSTRACT

Today, thousands of people die all over the world from parasitic diseases neglected by the government, the pharmaceutical industry, no medicine has managed to eliminate the parasites in their entirety, and they are only used as treatments. As a consequence, there is an increase of studies to obtain new drugs through research in the synthesis of natural products and their derivatives, new methodologies have been developed in the area of organic synthesis using nucleophilic substitution reactions. Paeonol has been a widely studied natural product due to its diverse biological activities, as well as its derivatives. A new paeonol ethers and benzofuran derivatives were obtained using a nucleophilic substitution reaction, which where determined by NMR. Four of these derivatives are crystals and where studied by X-rays. All the synthesized compounds are being evaluated as possible actives in the treatment of neglected parasitic diseases and the results will be discussed later.



Scheme 1. General syntehis for paeonol ether and benzofuran derivatives

ACKNOWLEDGEMENTS

This study was funded by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001, by the National Council of Scientific and Technological Development - CNPq (Process 305190/2017–2) and the Foundation of Support to Research and Innovation of Espírito Santo (FAPES PPE-Agro n° 76418880/16 and 76419363/16). We would also like to acknowledge LabPetro (UFES, Brazil) for performing RMN measurements (Technical Cooperation Agreements n°. 0050.0022844.06.4), and FAPESP (Process 2017/15850-0 and 2021/10066-5).

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Electrochemical Synthesis of Functionalized 1,4-naphthoquinones: Selenofunctionalization of Potential Antitumor Compounds

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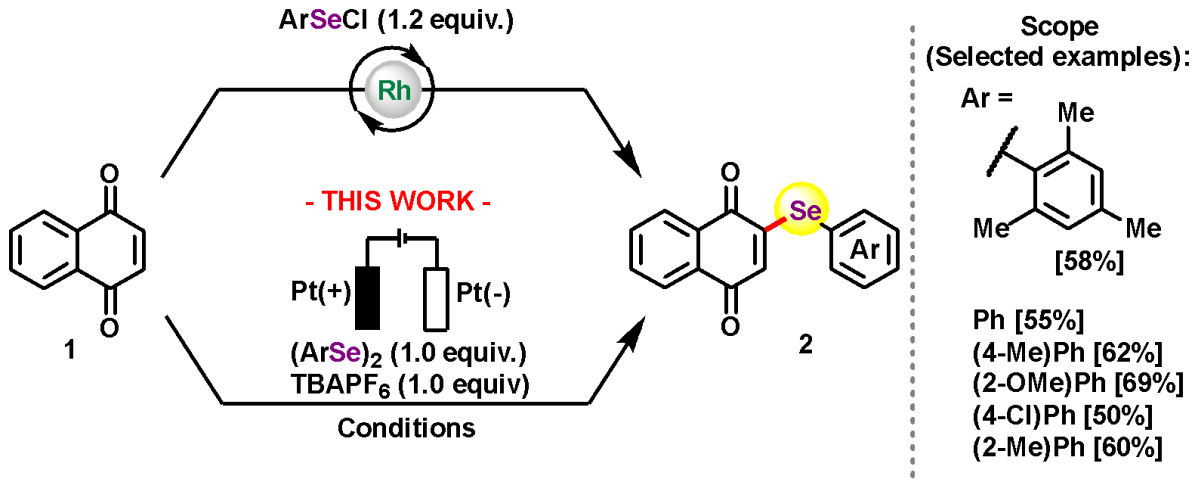
Keywords: *Quinones, electrosynthesis, C−H activation, selenation.*

ABSTRACT

Quinones are known to present valuable anticancer properties,[1] as for example doxorubicin (**1**), a widely used quinoidal anticancer drug (**Scheme 1**).[2] Our research group have been exploring the benefits of double redox-centered quinones as ROS-modulating agents, obtained through a rhodium-catalyzed C–H activation procedure (**Scheme 1**).[3] From these studies, a limited scope of selenated naphthoquinoidal compounds were obtained *via* a rhodium-catalyzed C–H functionalization.

Although this previous methodology led to the successful obtention of C–H-selenated quinones with important anticancer activities, the use of an expensive catalyst such as rhodium-Cp^t chloride dimer compromises the applicability of the method. Encouraged by this limitation, here we report the direct access of selenated naphthoquinones *via* a metal-free reaction, using favorable electrochemical conditions (**Scheme 1**). From this developed method, a set of twenty-five molecules were achieved, which will later be evaluate against the HL-60 (human leukemia) cell line.



Scheme 1. Previous and current obtention of C–H selenated quinones.

ACKNOWLEDGEMENTS

This research was funded by grants from CNPq, CAPES, FAPEMIG and INCT-Catálise.

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Synthesis of novel fluorescent lapimidazoles as candidates for Hydrogen Sulfite Probes

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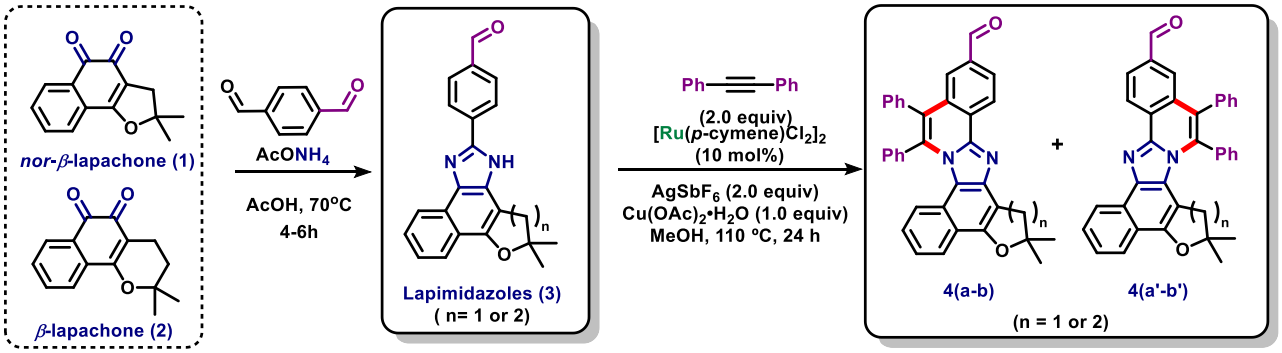
Keywords: *Catalysis, imidazoles, C–H activation, fluorescent sensor.*

ABSTRACT

Bisulfite and sulfite are widely used as a preservative for beverages and food to prevent oxidation and bacterial growth.[1] However, HSO_3^-/ SO_3^{2-} is toxic in high doses, which is associated with allergic reactions and food intolerance symptoms.[2] Therefore, the sensing of these species has enormous importance for human healthy. Imidazoles derivatives, such lapimidazoles, display special luminescent properties and have been applied as sensors for different purposes such anion sensor[3] and mitochondrial staining[4]. In search of new fluorescent molecules for bisulfite sensing, this work provides the synthesis of lapimidazole **3** as a potential fluorescent sensor and also its usage as substrate for an elegant protocol of a ruthenium-catalyzed C–H/N–H annulation with diphenylacetylene. This method allows to access new π-extended lapimidazoles **4(a-b)** and **4(a'-b')**, which probably will have extraordinary luminescent properties, being also candidates for application as fluorescent sensors. Studies about the photophysical properties and its application as hydrogen sulfite probes are being carried out in our laboratories.



Scheme 1. Synthesis of proposed new fluorescent lapimidazoles.

ACKNOWLEDGEMENTS

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Synthesis of Large Stokes Shift 2,6-Sulphur-Disubstituted BODIPYs

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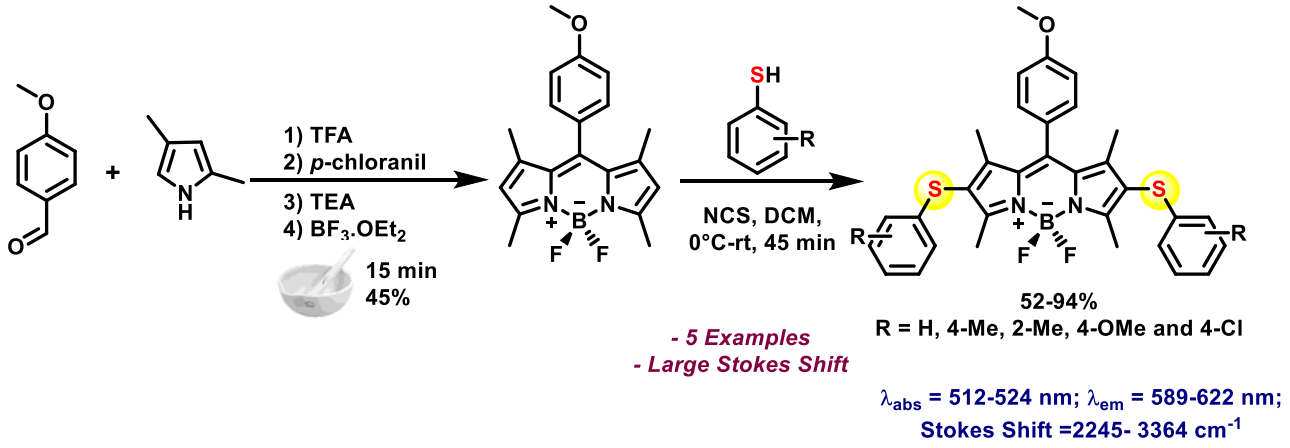
Keywords: *BODIPY, Boron-dipyrromethene, Fluorophores, Thioarylation.*

ABSTRACT

Compounds containing chalcogen elements have wide applications in many areas of science. Importantly, they can act as redox centers and modulate the activity of biomolecules. Boron-dipyrromethene (BODIPY) derivatives has been extensively employed in many research fields, including chemosensors, photosensitizers and OLEDs. Synthetic methods for the insertion of sulphur atoms into the basic architecture of BODIPYs can strategically modulate the photophysical properties of BODIPY. Therefore, we designed new 2,6-sulphur-disubstituted BODIPYs based on thiophenol derivatives (**Scheme 1**). The straightforward and selective functionalization of the BODIPY by thiophenol chloride prepared *in situ* from *N*-chlorosuccinimide and commercially available thiophenols allows for easy modification and addition of targeting moieties.[1] Analysis of the photophysical properties shows that 2,6-thioaryl-BODIPY derivatives display large Stokes shifts.



Scheme 1. Synthesis of 2,6-thioaryl-BODIPY fluorophores.

ACKNOWLEDGEMENTS

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Ruthenium-catalyzed C–H activation as a powerful tool for annulation of nonsymmetric imidazoles: A new avenue towards fluorescent compounds

Luana A. Machado,[1,2] Esther R.S. Paz,[1] Maria H. Araujo,[1] Leandro D. Almeida,[1] Ícaro A. O. Bozzi,[1] Gleiston G. Dias,[1] Cynthia L. M. Pereira,[1] Leandro F. Pedrosa[2], and Eufrânio N. da Silva Júnior[1,*]

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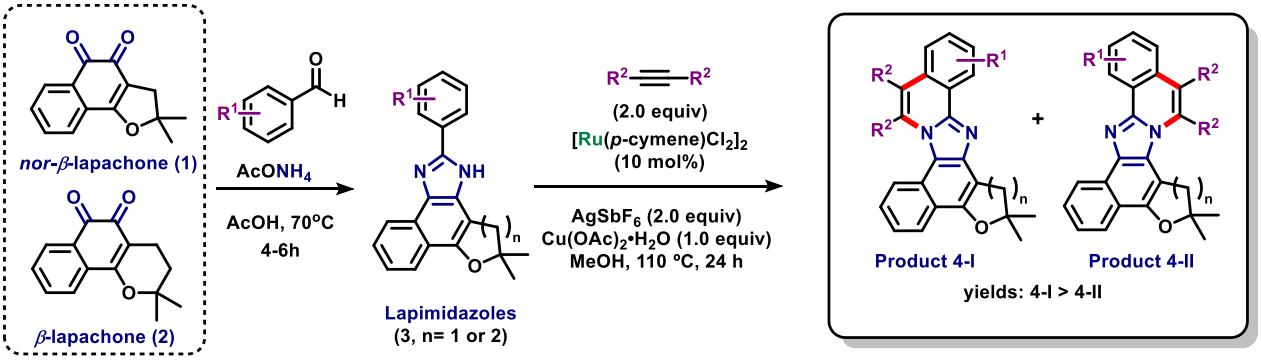
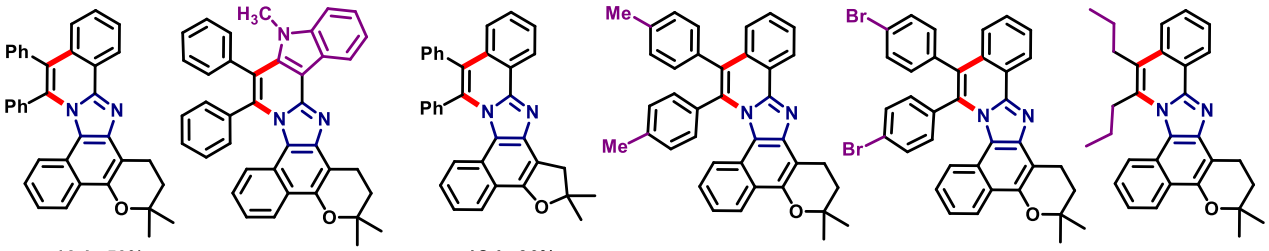
Keywords: *Annulation, C–H Activation, Lapachones, Ruthenium Catalysis, Fluorescence.*

ABSTRACT

Imidazoles constitute an important class of heterocyclic compounds with extensive potential use, from pharmaceuticals to optoelectronics. Amongst the imidazoles class, lapimidazoles has attracted significant interest. Starting from *nor*-*β*-lapachone **1** and *β*-lapachone **2**, several arylated lapimidazoles **3** can be obtained, and subsequently used as substrates on the C–H activation process. In this work, several modified polycyclic lapimidazoles **4** are described *via* a C–H/N–H ruthenium-catalyzed annulation reaction with internal alkynes.[1] With this protocol was possible to directly obtain a large variety of compounds with different substituents, valuable for the construction of important fluorescent compounds. A certain regioselectivity was observed, due to steric effects originated from the structure of the substrate. Further investigations about their fluorescent properties are being carried out in our laboratories.



Achieved scope (examples):



Scheme 1. General overview of the developed ruthenium-catalyzed C–H annulation on lapimidazoles.

ACKNOWLEDGEMENTS

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A practical iodination of BODIPY fluorophores using iodine and iodic acid

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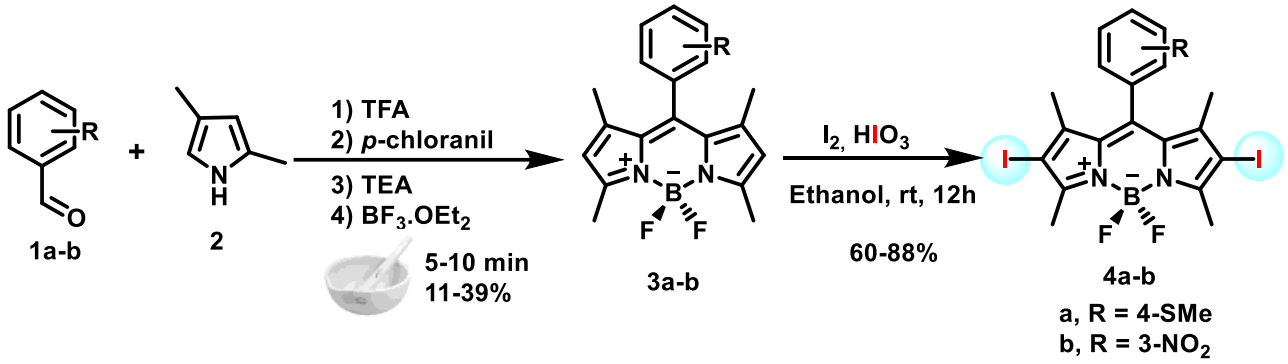
Keywords: *BODIPY, , Boron-dipyrromethene, Fluorophores, iodination.*

ABSTRACT

Over the past decades, there is increasing interest in the design, preparation, and functionality of BODIPY (4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene) dyes due to their outstanding chemical, thermal, and photophysical properties. In this sense, new synthetic methods for the preparation of BODIPYs are widely investigated and commonly reported in the literature. Iodination of BODIPYs is one of the most useful approaches to the photodynamic therapy reagents and a good platform for the construction of extended π-electron conjugation affording red-shifted BODIPY derivatives through the transition-metal catalyzed reactions. Herein, two new iodinated-BODIPYs fluorophores (**4a-b**) were synthesized by replacing the β-pyrrole hydrogen by iodine atoms through aromatic electrophilic substitutions using iodic acid and iodine (**Scheme 1**). This method provides an easy access to a wide range of potentially valuable BODIPY derivatives. Afterwards, these compounds will be tested as potential fluorescent sensors in biological applications.



Scheme 1. Synthesis of iodinated BODIPY fluorophores.

ACKNOWLEDGEMENTS

This research was funded by grants from CNPq, CAPES, FAPEMIG, FAPERJ and INCT-Catálise.

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Multicomponent Synthesis of SAHA-Monastrol hybrids

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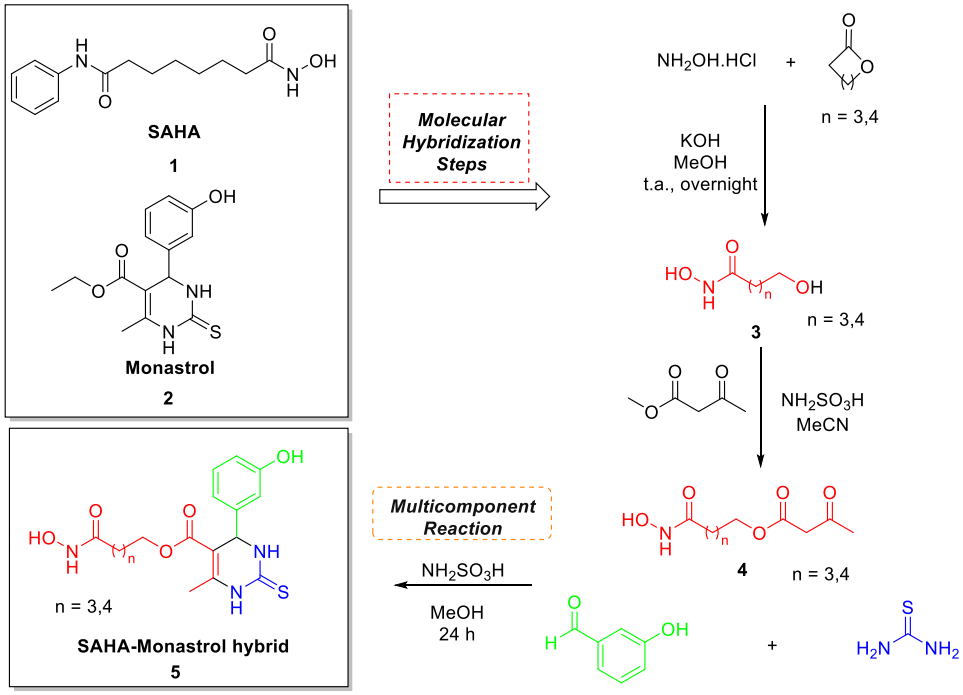
Keywords: *Monastrol, SAHA, Multicomponent Reaction.*

ABSTRACT

Molecular hybridization is a relevant tool for new compounds with biological activity.[1,2] Considering the antitumor activities present in Monastrol (**1**), obtained from the multicomponent Biginelli reaction, that acting on the inhibition of kinesin,[3] and of suberoyl hydroxamic acid, SAHA (**2**), active substance (hit) present in the drug Zolinza®, histone deacetylases inhibitor,[4] the aim of this work was to investigate the synthesis of new SAHA- Monastrol hybrids (**5**). The incorporation of hydroxamic acid was explored from 6- and 7-membered lactones via ring-opening reaction in the presence of $NH_2OH.HCl$.[5] Alcohol **3** was used in the transesterification reaction to access the 1,3–dicarbonyl precursor (**4**), which, in conjunction with the other components, were submitted to Biginelli MCR (Scheme 1). The new dihydropyrimidinones were obtained in good yields, and the use of 3-hydroxy benzaldehyde provided the proposed SAHA-Monastrol hybrid (**5**).



Scheme 1. Molecular Hybridization provided SAHA-Monastrol hybrids (**5**) through Biginelli MCR.

ACKNOWLEDGEMENTS

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Synthesis of amphiphilic compounds exposing *S*-linked β-N-acetylglucosamine

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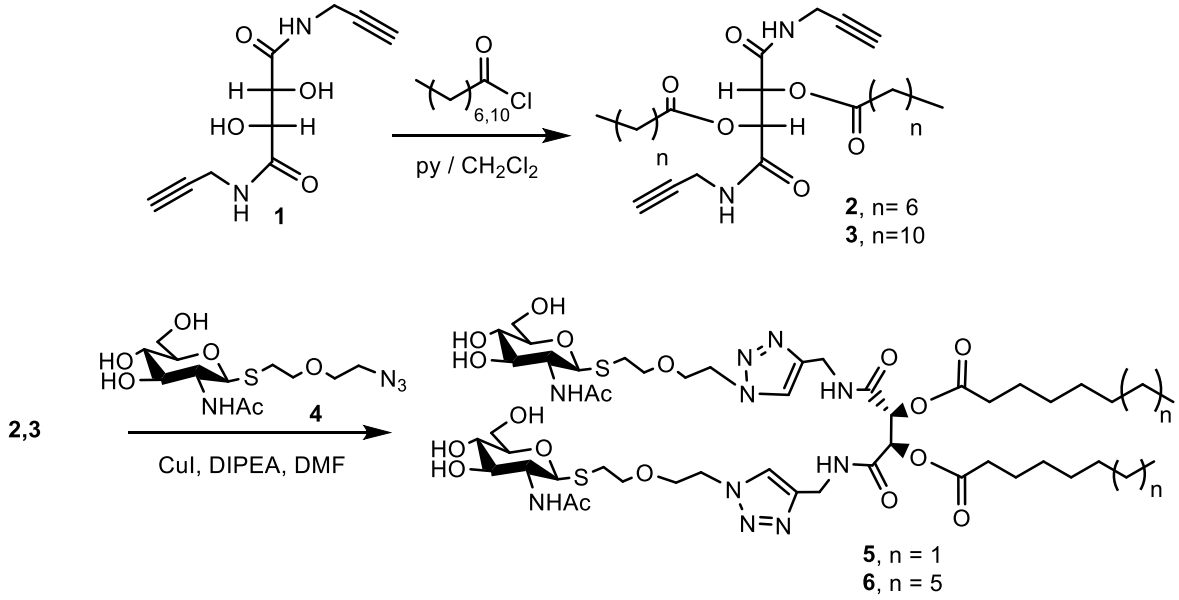
Keywords: *Amphiphiles, L-tartaric acid, carbohydrates, self-assembly*

ABSTRACT

Previous results obtained in our group showed that L-tartaric acid could be used a convenient scaffold for the access to amphiphilic compounds with good self-assembly properties.[1] Thus, as part of our ongoing project on the development of sugar-containing multivalent ligands by supramolecular approaches, we extended this methodology to incorporate *S*-linked β-N-acetylglucosamine residues. Starting from the *N*,*N*'-dialquinyl-diamide **1**, we obtained the diacyl derivatives **2** and **3** by treatment with octanoyl and dodecanoyl chloride respectively. On the other hand, derivative **4** was prepared by a one-pot protocol from 1,3,4,6-tetra-*O*-acetyl-2-acetamidoglucose with thiourea in the presence of BF_3, followed by reaction with 1-azido-2-(2-bromoethoxy)ethane.[2] Finally, click reaction of the hydrophobic platforms **2** and **3** with **4** led to the pursued products **5** and **6** in 73% and 77% yields, respectively. Compounds **5** and **6** showed a strong tendency to form self-assembled systems in water. Compound **5** led to a stable hydrogel having a Tg = 52ºC.



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Synthesis of new heterocycles arrangements from Morita-Baylis-Hillman adducts.

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Keywords: *Heterocycles, C-C bond formation, Morita-Baylis-Hillman, Organocatalysis.*

ABSTRACT

The use of the imidazolic bicyclic alcohol as catalyst has proved to be effective and robust in a variety of di-carbonilic compounds in Morita-Baylis-Hillman (MBH) reaction[1]. Acenafthenequinone (**1a**) and phenanthrene-9,10-dione (**1b**) are possible precursors of heterocycles[2]. These molecules were used as eletrophiles in aqueous MBH reactions using cyclopentenone and cyclohexanone as nucleophiles[3] to provide the corresponding new MBH adducts in moderate to excellent yields. Then, adduct **4d** was acetylated giving a better leaving group for the next step (Figure 1). Finally, to validate the use of these MBH adducts in the synthesis of new heterocyclic arrangements, acetylated compound **5** was reacted with primary amines, using methanol as solvent, at room temperature, for 12 hours. The acenaphtho[1,2-b]indol-11(8H)-one derivatives were obtained in good yields (up to 86%). Studies are ongoing in our laboratory aiming at exploring this methodology in the synthesis of new heterocyclic arrangement.

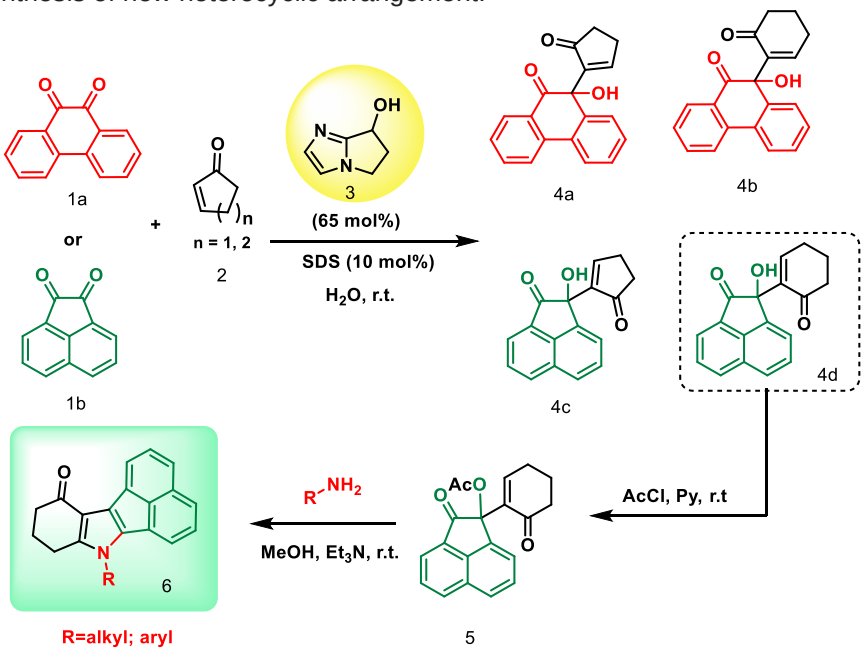

Figure 1 – Synthesis of acenaphtho[1,2-b]indol-11(8H)-one derivatives from MBH adducts.

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1,6-addiction of Indolizines in *para*-Quinone Methides with Indium Chloride as Catalyst

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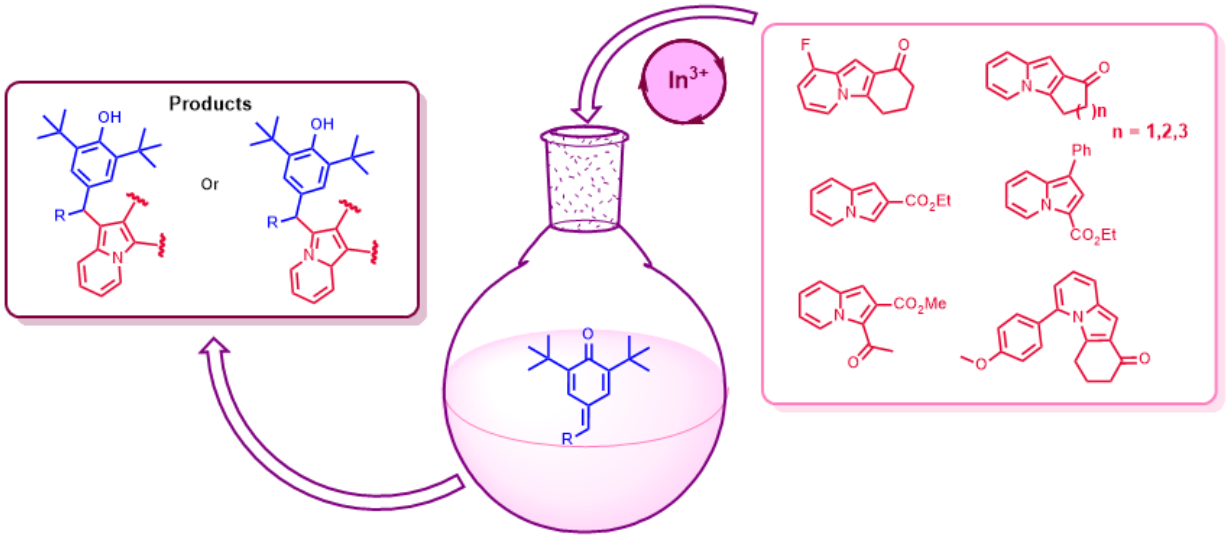
Keywords: *Catalysis, Indium Chloride, p-quinone methides, indolizines.*

ABSTRACT

para-Quinone Methides (*p*-QM's) are a variety of compounds characterized by a reactive intermediate that contains an electrophilic site[1,2]. They can be used as 1,6-Michael acceptors in the presence of Lewis acids as catalyst[3,4]. In this work, we explored the use of $InCl_3$ as catalyst to enhance the reaction between *p*-QM's and indolizines. The optimal reaction conditions were found after an optimization step with 2 mol % of $InCl_3$ using DCE as solvent, at room temperature. In these conditions we were able to synthesize 17 analogues with excellent yields (up to100%) **(Figure 1)**.

Figure 1 – Scheme of the reaction between *p*-QM's and indolizines with indium chloride as catalyst.



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