http://dx.doi.org/10.5935/0103-5053.20140056

J. Braz. Chem. Soc., Vol. 25, No. 5, 887-889, 2014.
Printed in Brazil - ©2014 Sociedade Brasileira de Química
0103 - 5053 $6.00+0.00

Article

Microwave-Assisted Synthesis of *N*-Heterocycles and Their Evaluation Using an Acetylcholinesterase Immobilized Capillary Reactor

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Os etenoditioacetais polarizados são conhecidos como importantes intermediários em muitos processos de síntese. Neste trabalho, reporta-se a anelação livre de metal de transição de 1,1-bis(tiometil)-2-nitroetileno com hidroxilalquilaminas e alquildiaminas. Esta metodologia permite a síntese direta de *N*-heterociclos tais como imidazolidinas, oxazolidinas e benzoxazóis sob irradiação de micro-ondas. Estes compostos foram avaliados como inibidores da acetilcolinesterase usando um reator capilar contendo a enzima imobilizada acoplado a um espectrômetro de massas.

Polarized ketene dithioketals have been recognized as useful building blocks in many synthetic operations. In this work, a transition-metal-free annulations of 1,1-bis(thiomethyl)-2-nitroethylene with hydroxylalkylamines or alkyldiamines have been reported. This methodology provides a directed approach to *N*-heterocycles, e.g., imidazolidines, oxazolidines and benzoxazoles under microwave conditions. These compounds were evaluated as acetylcholinesterase inhibitors by using an enzyme immobilized capillary reactor-tandem mass spectrometry.

Keywords: dithioketals, oxazolidines, imidazolidines, benzoxazoles, microwaves, green technology

Introduction

Association of biological activity with heterocyclic motifs is well known and is an important strategy in drug discovery programs. In this way, the development of new, easy and fast environmental benign strategies to the formation of these scaffolds have been receiving great attention.[1] Over the past several years, polarized ketene dithioketals **1** (Figure 1) have been recognized as useful building blocks in many synthetic transformations. They can be converted into the corresponding *S*,*N*- and *N*,*N*-ketals, **2** and **3**, respectively, making them important as precursors for a large variety of functionalized ketals.[2]

Furthermore, the ketene dithioketals have also been employed as intermediates for the synthesis of several

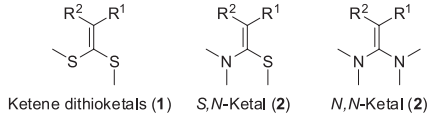

Figure 1. Ketene dithioketals **1**, *S*,*N*- and *N*,*N*-ketals **2** and **3**, respectively.

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N-heterocycles, which present different biological properties, such as enzyme inhibition,[3,4] insecticides,[5] and tuberculostatic activity.[6] More recently, the bis-vinylic substitution of 1,1-bis(methylthio)-2-nitroethylene with diamines or hidroxylamines has been reported for the synthesis of 5-member or 6-member nitrovinyl derivatives.[7]

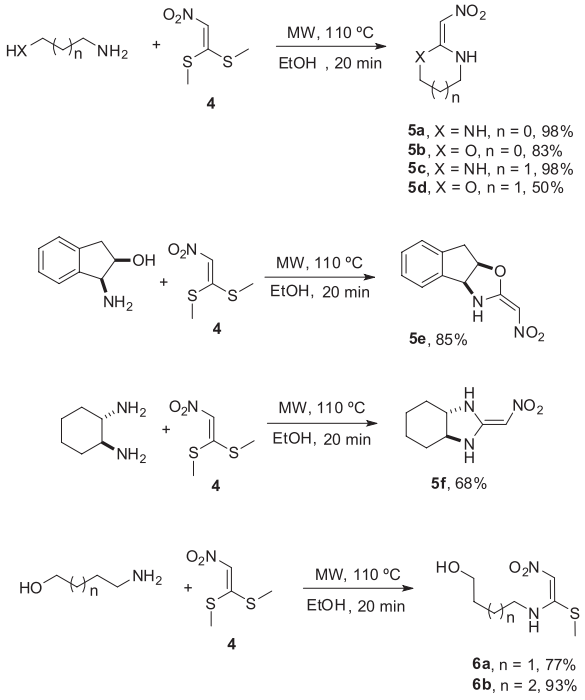
In general, the reaction conditions employed for the bis-vinylic substitution include reflux in ethanol for several hours,[4,8] in presence of catalysts such as *p*-toluenesulfonic acid (PTSA).[3,5] As part of our studies on ketene dithioacetal for the synthesis of heterocycles, we have found that microwave irradiation accelerates the vinylic substitution of nitroketene *S,S*-acetals with anilines and amines using ethanol as solvent.[9] Employing this method, we have synthesized a new class of hydrogen bond donor organocatalysts which was applied to the activation of trans-β-nitrostyrenes toward reactions with a range of carbon-based nucleophiles, affording the corresponding adducts in excellent yields.[10]

In this work, we report the microwave-assisted metal-free-annulation reaction of hydroxylakylamines and alkyldiamines to the formation of several heterocycles, such

as imidazolidines, oxazolidines and benzoxazoles, and their evaluation as acetylcholinesterase inhibitors.

Results and Discussion

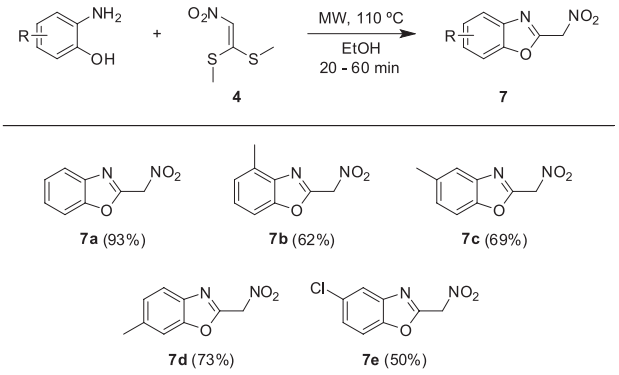
We have started our studies with the reaction of 1,1-bis(thiomethyl)-2-nitroethylene (**4**) with a range of alkyldiamines and hidroxylalkylamines (Scheme 1). Irradiation of a suspension formed by nitroethylene **4** with the corresponding amines in ethanol afforded five and six membered *N*-heterocycles **5a**-**f** in good yields.[11] However, when 4- or 5-aminopentanol were employed, only mono-substituted acyclic products **6a**-**b** were obtained. Furthermore, the same reactions were performed under solvent free conditions and comparable yields could be obtained in a shorter reaction time. Only ten minutes were able to finish the monosubstitution, however maintaining the irradiation for more time, double substitution products were not produced.



Scheme 1.

Benzoxazoles are an important class of heterocyclic compound that can be applied to diverse therapeutic areas.[12] Therefore, to our delight, by applying the same methodology, a series of benzoxazoles **7a**-**e** could be easily synthesized using 1,1-bis(thiomethyl)-2-nitroethylene **4** and substituted 2-aminophenols as start materials (Scheme 2).

Icopezil, a benzisoxazole derivative, is a very potent and selective acetylcholinesterase (AChE) inhibitor with an IC_{50} = 0.33 nM.[10] Carreiras *et al.*[13] described



Scheme 2.

the anti-cholinesterase activity of 5-amino-4-cyano-1,3-oxazoles. Recently, Zhu *et al.*[14] reported the synthesis of 2-aminobenzimidazoles and their activity as novel inhibitors of AChE.

The enzyme AChE acts in the central nervous system and rapidly hydrolyzes the active neurotransmitter acetylcholine into the inactive compounds choline and acetic acid.[15] Low levels of acetylcholine in the synaptic cleft are associated with a decrease in cholinergic function characterizing Alzheimer's disease, which is the most common cause of dementia among the elderly. As AChE inhibitors are currently one of the few therapies approved for the treatment of Alzheimer's disease, the identification of novel ligands that could modulate AChE activity is of great therapeutic importance.[16]

Recently, we have reported the screening of a small library of coumarins using acetylcholinesterase from *Electrophorus electricus* immobilized onto a fused silica capillary enzyme reactor (*ee*lAChE-ICER) in a liquid chromatograph-tandem ion-trap mass spectrometer (LC-IT-MS/MS).[17] Employing this method, we were able to identify a new competitive inhibitor of AChE, as potent as tacrine, with an IC_{50} = 0.356 μM.

In order to contribute with the structure-activity relationship study, we evaluated the *N*-heterocycles **5a**-**f** and **7a**-**e** using *ee*lAChE-ICER in the LC-IT-MS/MS system and tacrine was employed as a standard inhibitor. Among the tested compounds, the benzoxazoles showed the best inhibition profile, being **7c** and **7d** the most potent with 53.5 and 70.0% inhibition at 200 μM, respectively (Table 1).

Conclusions

We have shown that the double nucleophilic substitution between hydroxylalkylamines or alkyldiamines with 1,1-bis(thiomethyl)-2-nitroethylene **4** employing microwave heating furnished the corresponding nitroketene *N,O*-aminoacetals and *N,N*-aminals with moderate to

Table 1. Inhibition percentage of *N*-heterocycles **5** and **7** against *ee*lAChE

Compound	Inhibition at 200 μM / %
5a	17.7
5b	12.8
5c	35.3
5d	26.8
5e	0.0
5f	27.5
7a	15.3
7b	19.5
7c	53.5
7d	70.0
7e	0.0
tacrine	99.3

good yields, in very short reaction time. A small library of benzoxazoles was also obtained with moderate to good yields. The activity of these heterocycles against AChE was evaluated and benzoxazole **7d** showed the best inhibition profile. Further enzymatic studies of this new class of benzoxazole will be reported in due course.

Supplementary Information

Supplementary information is available free of charge at http://jbcs.sbq.org.br as PDF file.

Acknowledgements

The authors are grateful to FAPESP (grants 2009/07281-0 and EMU 2009/54040-8 for HRMS analysis), CNPq (INCT-INBEQMeDI), CAPES and GSK Trust in Science Program for financial support and fellowships.

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Submitted: January 7, 2014
Published online: March 21, 2014

FAPESP has sponsored the publication of this article.