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Green Chemistry

ARTICLE

Niobium-promoted reaction of α-phenylglyoxylic acid with *ortho*-functionalized anilines: synthesis of 2-arylbenzothiazoles and 3-aryl-2*H*-benzo[*b*][1,4]benzoxazin-2-ones

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A new and general method to prepare 2-arylbenzothiazoles and 3-aryl-2*H*-benzo[*b*][1,4]benzoxazin-2-ones by the reaction of α-arylglyoxylic acid with *o*-aminothiophenol and *o*-aminophenol respectively is described. The use of ammonium niobium oxalate (ANO) as the catalyst and PEG-400 as the solvent were crucial to afford the title compounds in good yields and selctively. The reaction time can be reduced from hours to few minutes when ultrasound was used as an alternative energy source.

Introduction

Heterocyclic compounds are widely found in natural products and are important in the pharmaceutical industry, being present on the structure of different drugs consumed worldwide.[1] Among them, 2-substituted benzothiazoles have attracted great interest, since they are the core motif of many bioactive molecules. For instance, 2-arylbenzoxazole **A** has anti-cancer activity,[2a] benzo[*d*]thiazole-2-thiol **B** is an anti-oxidant,[2b] and the amide-functionalized benzothiazole **C** presents antibacterial activity (Figure 1).[2c] This important structural unity is present in commercially available drugs, such as the Riluzole® **D**, used in the treatment of the amyotrophic lateral sclerosis[2d] and a sort of materials, such as dyes and agrochemicals.[3] These compounds are usually prepared through the condensation of 2-aminothiols with aldehydes or acyl chlorides.[4] They also can be obtained by the direct C-H activation promoted by the transition metal-catalyzed cross-coupling of benzothiazoles with aryl halides,[5] aromatic carboxylic acids,[6] aryl boronic acids,[7] aryl silanes,[8] aldehydes[9] or by the double C-H activation of arenes.[10]

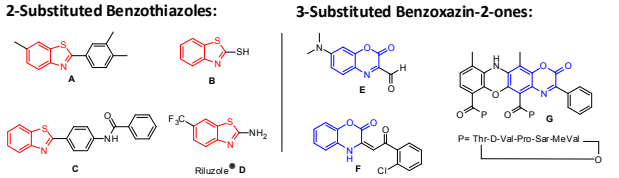

Figure 1: Bioactive 2-substituted benzothiazoles (**A-D**) and 3-substituted benzoxazin-2-ones (**E-G**).

Another important class of the heterocyclic compounds are the 1,4-benzoxazines, which has been receiving attention due to the pharmacological and biological activities associated to these compounds.[11] For instance, Ofloxacin®, which has on its structure a benzoxazine center, is a commercially available drug used in the treatment of acute bacterial exacerbations of chronic bronchitis and against several bacterial infections.[12]

An interesting and still scarcely studied class of benzoxazine derivatives are the 2*H*-benzo[*b*][1,4]benzoxazin-2-ones, which are known to have photoactive properties, as the aldehyde **E**,[13a] or antibacterial activity, as the aryl ketone **F** (Figure 1).[13b] Besides that, the actinomycin D analogue **G** presented antitumor activity.[13c] The current methods to prepare benzoxazin-2-ones involve the use of Pd or Cu catalysts,[14b] volatile solvents,[14b] strong oxidizing agents[14d] and usually large reaction times.[14] Due the potential application of this class of compounds in material and medicinal chemistry, the development of efficient and green methodologies to obtain 3-substituted 2*H*-benzo[*b*][1,4]benzoxazin-2-ones is very attractive.

Since it was firstly described by Fontana and co-workers in 1991,[15a] α-phenylglyoxylic acid (PGA) has aroused the interest of organic chemists as a versatile acyl transfer reagent in the synthesis of a diversity of compounds (Scheme 1).[15,16] Among the green features in using PGA as acylating are the high atom economy and the formation of CO_2 as the only waste in the reaction. Despite the high potential of PGA as a green acyl transfer in organic synthesis, it is still far from being a popular reagent. This is due probably to the peculiar or nontrivial reaction conditions required for the metal-catalyzed decarboxylative coupling, which include the use of expensive palladium and ruthenium catalysts, equivalent amounts of strong oxidizing agents, volatile solvents and large reaction times (Scheme 1).[16-18]

Recently, a visible-light-mediated decarboxylative/oxidative amidation of PGAs catalyzed by Ru-complex to prepare aromatic amides from anilines was described.[17] The strategy was extended to the construction of heterocyclic compounds, including benzimidazoles, benzoxazoles and benzothiazoles, when the *ortho* position of the starting aniline was substituted with NH_2, OH and SH groups respectively. However, the use of expensive reagents, oxidizing solvent and long reaction times together with the restrict number of studied examples (only one benzothiazole was prepared) are some disadvantages of this protocol. More recently, Wang and Huang described an electrochemical method for the

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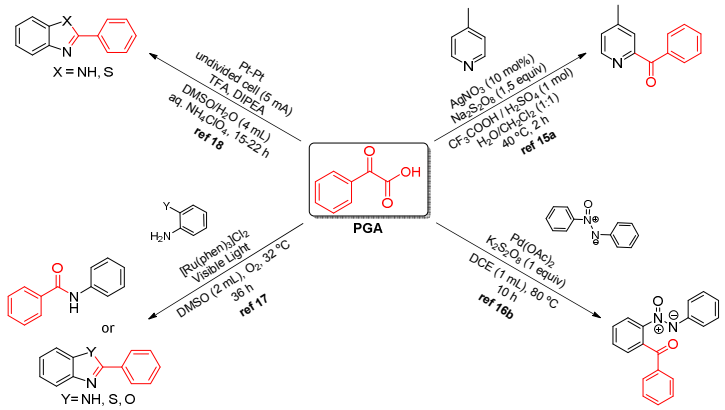
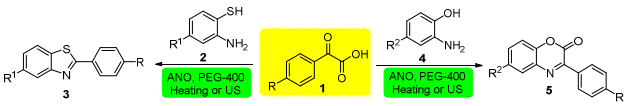
decarboxylative coupling of PGA with *ortho*-phenylenediamines and 2-aminothiophenols to afford 2-substituted benzimidazoles and benzothiazoles, respectivey.[18] Besides a special apparatus, this protocol requires the use of 3 equiv of 2-aminothiophenol, over equiv amounts of TFA, DIPEA and the highly reactive oxidant NH_4ClO_4 for up 22 h to afford good yields of the respective 2-substituted benzimidazoles (Scheme 1). Thus, the development of mild and green methodologies to apply PGA and its derivatives in organic synthesis remains an endeavour for synthetic organic chemists.



Scheme 1: PGA as an acylating agent.

Ammonium niobium oxalate (ANO), $NH_4[NbO(C_2O_4)_2(H_2O)_x]\bullet nH_2O$, is used as precursor in the preparation of important materials, such as ceramic, optical lenses, highly pure niobium oxides, tin films and catalysts.[18] Besides that, ANO is not air- or moisture-sensitive, it is easy to handle, cheap and has a low toxicity.[19,20] Recently, we described the first use of ANO as a catalyst in the reaction between aldehydes and indoles, leading to bis-indolylmethanes under ultrasound irradiation only in few minutes of reaction, showing the possibility of using these Nb species as a cheap and available catalyst.[21]

In continuation to our studies in the development of greener approaches to efficiently synthesize bioactive compounds, we describe herein a new methodology to obtain 2-substituted benzothiazoles **3** and 3-substituted 1,4-benzoxazin-2-ones **5** starting from α-arylglyoxylic acid **1**. The method involves the use of ANO as a catalyst and PEG-400 as a green solvent under both, conventional heating and ultrasound (US) irradiation as an alternative energy source (Scheme 2).



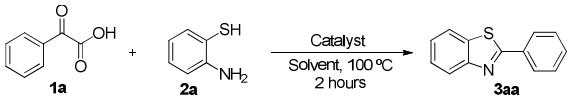
Scheme 2: General scheme of the reactions.

Results and discussion

Initially, our study was focused on determining the optimum condition to obtain 2-arylbenzothiazoles **3aa** using a niobium-based catalyst under conventional heating (Table 1).

Thus, firstly we chose α-phenylglyoxylic acid **1a** (0.6 mmol) and 2-aminothiophenol **2a** (0.5 mmol) as standard substrates for the optimization study (Table 1).

Table 1: Optimization study to obtain 2-phenylbenzothiazole **3a**.[a]



1a **2a** **3aa**

Entry	Catalyst (mol%)	Solvent	Yield of **3a** (%)[b]
1	ANO (10)	PEG-400	85
2	Nb_2O_5 (10)	PEG-400	84
3	$Nb_2O_5{\cdot}H_2O$ (10)	PEG-400	46
4	ANO (5)	PEG-400	62
5	ANO (15)	PEG-400	70
6	-	PEG-400	30
7	ANO (10)	Glycerol	50
8	ANO (10)	H_2O	44
9	ANO (10)	DMSO	45
10	ANO (10)	DMF	NR
11[c]	ANO (10)	PEG-400	73
12[d]	ANO (10)	PEG-400	NR

[a] Reactions were performed using α-phenylglyoxylic acid **1a** (0.6 mmol), 2-aminothiophenol **2a** (0.5 mmol), the catalyst (mol%), solvent (1.0 mL) at 100 °C for 2 h. [b] The product 3a was isolated by chromatography column. [c] Stoichiometry of the reagents = 1:1. [d] The reaction was proceeded at 60 °C.

The performance of the reaction was studied using three different niobium catalysts at 100 °C in PEG-400, for 2 h (Table 1, entries 1-3). This time and temperature were chosen based on our previous works on the use of Nb oxide as catalyst. Among the tested catalysts, ANO and anhydrous Nb_2O_5 (10 mol%) provided the expected benzothiazole **3aa** in 85 and 84% yields, respectively. Because ANO is cheaper, bench stable and easier to manipulate compared to Nb_2O_5,[19] it was chosen as the catalyst for the following optimization studies. In order to evaluate the ideal catalyst amount, the reaction was performed using 5 and 15 mol% of ANO, leading to the formation of 62 and 70% yields respectively, showing that 10 mol% is enough (Table 1, entries 4-5 vs. entry 1). When the reaction was performed in the absence of ANO, only 30% yield of **3aa** was obtained, confirming the importance of the ANO as the catalyst of the reaction (Table 1, entry 6).

After the best catalyst and catalyst amount were determined, it was performed a study in order to evaluate the effect of the

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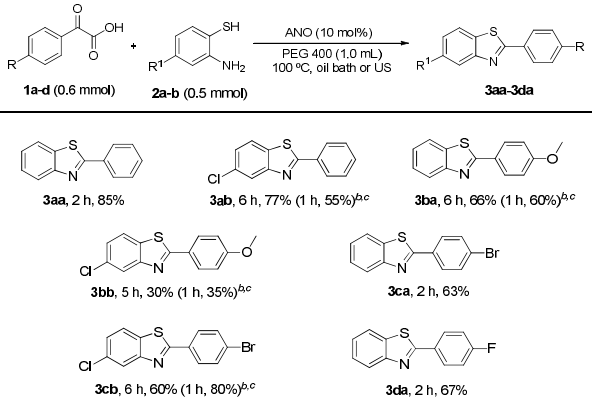
solvent in the reaction medium. Changing the solvent for glycerol, H_2O and DMSO gave **3aa** in modest yields of 50, 44 and 45%, respectively (Table 1, entries 7-9), while with DMF no reaction was observed and the starting materials were recovered (Table 1, entry 10). Thus, PEG-400 showed to be the best solvent for this reaction. Changing the reagents' stoichiometry to 1:1 led to a decrease in the yield (73%), showing that a little excess of **1a** is mandatory in order to obtain better results (Table 1, entry 11). Finally, the reaction was performed at 60 °C for 2 h, but no reaction occurred at this temperature (Table 1, entry 12). Thus, our best reaction condition to prepare 2-phenylbenzothiazole **3aa** was using α-phenylglyoxylic acid **1a** (0.6 mmol), 2-aminothiophenol **2a** (0.5 mmol), ANO (10 mol%) as the catalyst and PEG-400 (1.0 mL) as the solvent under conventional heating (oil bath) at 100 °C for 2 h, affording the product in 85% yield (Table1, entry 1).

With the optimal reaction condition in hands, it was performed a study in order to examine the scope of the reaction, evaluating the behaviour of substituted 2-aminothiophenols and α-arylglyoxylic acids and confirm the efficiency and generality of the methodology.

Table 2: Reaction scope of the niobium-catalyzed synthesis of 2-substituted benzothiazoles **3**.[a]

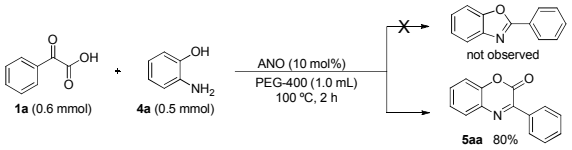


[a] Reactions were performed using α-arylglyoxylic acids **1a-d** (0.6 mmol), 2-aminothiophenols **2a-b** (0.5 mmol), ANO as the catalyst (10 mol%), PEG-400 as the solvent (1.0 mL) at 100 °C under stirring in air atmosphere. [b] The mixture was submitted to ultrasound irradiation (60% of amplitude) instead using an oil bath. [c] The final reaction temperature was 110 °C. The yields were determined after isolation by chromatography column.

Besides that, the reaction was performed using 2-amino-4-chlorobenzenethiol **2b** and α-arylglyoxylic acids **1a-c**, in order to evaluate the behaviour of an electron withdrawing group (EWG) in the aromatic ring of the 2-aminothiophenol. As expected, it was observed an increase in the reaction time (up to 6 h) and the respective products **3ab**, **3bb** and **3cb** were obtained in 77, 30 and 60% yields, respectively. This is due to the deactivation of the aromatic ring, decreasing the nucleophilicity of the NH_2 and SH groups in both important reaction steps, the formation of the imine by the NH_2 attack and the cyclization from the SH.[22] Aiming to reduce the reaction time while increasing the yields of benzothiazoles **3ab**, **3ba**, **3bb** and **3cb**, the reaction was performed under sonication with an ultrasound probe.

Thus, when a solution of PGA **1a** and 2-amino-4-chlorobenzenethiol **2b** in PEG-400 was sonicated (60% of amplitude) for 1 h in the presence of ANO, the respective product **3ab** was obtained in 55% yield (Table 2, values between parentheses). If the US irradiation is continued, several co-products are formed, with predominance of bis(4-chloro-2-aminophenyl) disulfide, the oxidation product of the starting thiol **2b**. Similarly, the reaction time to prepare **3ba** and **3bb** could be reduced to 1 h under sonication, while the yields were essentially the same that those under conventional heating (Table 2).

Based on the successful results using 2-aminobenzenethiols **2**, we investigated the applicability of the protocol in the reaction between α-phenylglyoxylic acid **1a** and 2-aminophenol **4a** instead 2-aminothiophenol **2a**, in order to obtain the correspondent 2-phenylbenzo[*d*]oxazole. However, instead the benzoxazole, 2*H*-benzo[*b*][1,4]benzoxazin-2-one **5aa** was the only observed product, obtained in 80% yield (Scheme 2).



Scheme 3: Synthesis of 2*H*-benzo[*b*][1,4]benzoxazin-2-one **5aa**.

A study on the scope of the reaction showed that this is a general protocol which can be extended to several α-arylglyoxylic acids **1a-c** and 2-aminophenols **4a-c**, affording the respective 3-substituted 2*H*-benzo[*b*][1,4]benzoxazin-2-ones **5aa-cc** in moderate to good yields after 1-2.5 h of reaction (Table 3).

Similarly to the observed for 2-aminothiophenol **2a** (Table 2), the reaction of 2-aminophenol **4a** with 4-methoxyphenylglyoxylic acid **1b** (R= CH_3O) afforded lower yield of the respective product **5ba** (65% after 2 h). On the other hand, when 4-bromophenylglyoxylic acid **1c** (R= Br) was used, the reaction time decreased from 2 to 1 h, affording the respective product **5ca** in 70% yield. The effect of the presence of EWG and electron releasing group (ERG) bonded to the aromatic ring of the 2-aminophenol **4** was also evaluated. Products **5ab** and **5bb**, prepared by the reaction of 2-amino-4-methylphenol **4b** (R^1= CH_3) with arylglyoxylic acids **1a** (R= H) and **1b** (R= CH_3O) were obtained in 87 and 86% yields respectively, in 2 h of reaction.

When 2-(4-bromophenyl)-2-glyoxylic acid **1c** (R= Br) was used, the respective benzoxazin-2-one **5cb** was formed in 93% yield after 1 h. In this case, electronic effects in both, the acid **1c** and the aminophenol counterpart **4b** were evidenced, promoting the acceleration of the reaction.

The reaction of 2-amino-4-chlorophenol **4c** (R^1= Cl) with acids **1a-c** afforded the respective products **5ac**, **5bc** and **5cc** in 70, 70 and 66% yields, respectively in 2-2.5 h. The electron-withdrawing effect exercised by the chloro in the ring of the 2-aminophenol **4c** is considerable, causing a significant decreasing in the yield.

In order to improve the efficiency on the synthesis of 3-substituted 2*H*-benzo[*b*][1,4]benzoxazin-2-ones **5**, since this class of compounds is underexploited in materials and medicinal chemistry, it was performed a study on the use of ultrasound irradiation, similarly to that for the synthesis of benzothiazoles **3**.

Fortunately, excellent results were obtained, leading to the formation of the products between 83 and 96% yields in only a few minutes of reaction (Table 3, values between parentheses). This is a very promising result, once the energy efficiency in using US irradiation contributes to improve the greenness of the reaction.[23]

Table 3: Reaction scope of the niobium-catalyzed synthesis of 3-substituted 2*H*-benzo[*b*][1,4]benzoxazin-2-ones **5**.[a]

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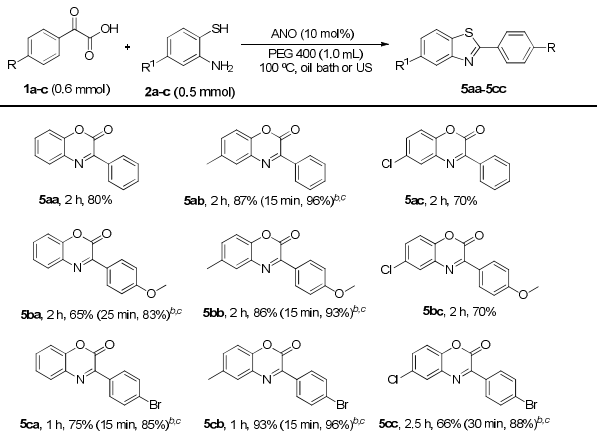
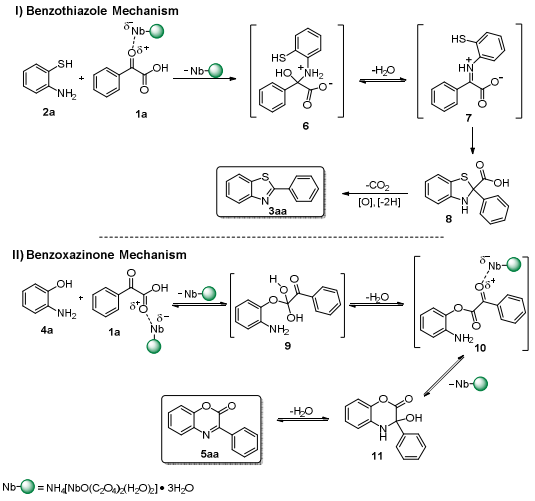


[a] Reactions were performed using α-arylglyoxylic acids **1a-c** (0.6 mmol), 2-aminophenols **4a-c** (0.5 mmol), ANO as the catalyst (10 mol%), PEG-400 as the solvent (1.0 mL) at 100 °C (oil bath) under stirring in air atmosphere. [b] The mixture was submitted to ultrasound irradiation (60% of amplitude) instead using an oil bath. [c] The final reaction temperature was 110 °C. The yields were determined after purification by column chromatography.

Based on our results and in previously described works,[14d,22] plausible mechanisms for the synthesis of 2-substituted benzothiazoles **3** and 3-substituted benzoxazin-2-ones **5** are depicted in Scheme 4, for **3aa** and **5aa**. The first step in the synthesis of benzothiazole **3aa** (Scheme 4, mechanism I) is the condensation between 2-aminothiophenol **2a** and PGA **1a**, which is catalysed by ANO, leading to the formation of the intermediate zwitterion **6**. In the sequence, elimination of water occurs to give the iminium **7**, which after the intramolecular attack of SH group affords **8**, that in a step of decarboxylation and after a *N*-Csp^3 bond oxidation, deliver the product **3aa**.

On the other hand, in the synthesis of the 3-phenyl benzoxazin-2-one **5aa** (Scheme 4, mechanism II), the first step involves an ANO-catalysed esterification reaction between the 2-aminophenol **4a** and PGA **1a**, following by water elimination, leading to the intermediate **10**. After that, an ANO-catalysed cyclization by attack of the remaining NH_2 group leads to the cyclic intermediate **11**, which after water elimination is converted to the product **5aa.**



Scheme 4: Proposed reaction mechanisms.

Conclusions

Ammonium niobium oxalate (ANO), $NH_4[NbO(C_2O_4)_2(H_2O)_x]\bullet nH_2O$, proved to be an excellent catalyst in promoting the reaction of 2-aminothiophenols and 2-aminophenols with α-arylglyoxylic acids, leading to the formation of 2-aryl benzothiazoles and 3-aryl 2*H*-benzo[*b*][1,4]benzoxazin-2-ones in good to excellent yields. The protocol is selective, producing CO_2 as the only co-product and it can be accelerated by ultrasound irradiation, reducing the reaction time from hours to few minutes, while increasing the product yields. The use of PEG-400 as a green, cheap and available solvent allowed a good solubility of reagents and catalyst and enabled the sonication of the reaction mixture. Taken together, the features of this alternative protocol make it a green and robust alternative to prepare 2-substituted benzothiazoles and 3-substituted 2*H*-benzo[*b*][1,4]benzoxazin-2-ones.

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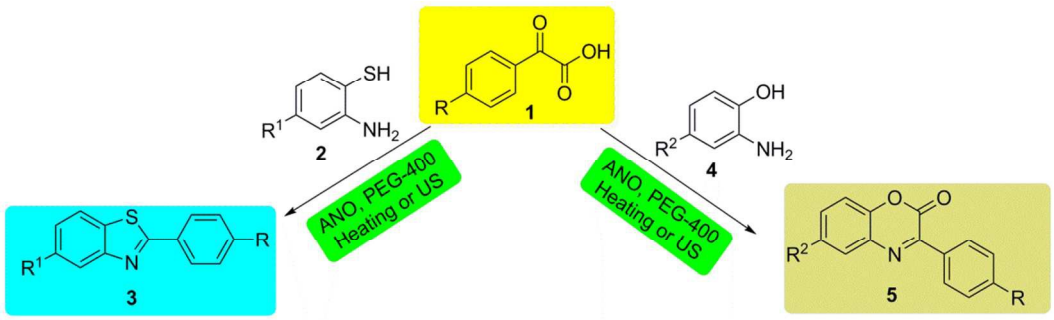

Ammonium niobium oxalate promotes the reaction of α-phenylglyoxylic acid with *o*-functionalized anilines for the synthesis of benzothiazoles and benzoxazin-2-ones.