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Synthesis of bis(indolyl)methanes using ammonium niobium oxalate (ANO) as an efficient and recyclable catalyst†

Samuel R. Mendes,*[a] Samuel Thurow,[b] Filipe Penteado,[b] Maitê S. da Silva,[a] Rogério A. Gariani,[a] Gelson Perin[b] and Eder J. Lenardão*[b]

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A green and efficient procedure was developed for the synthesis of bis(indolyl)methanes using ammonium niobium oxalate (ANO) $NH_4[NbO(C_2O_4)_2(H_2O)_x]\cdot nH_2O$ as the catalyst and water or glycerol as the solvent. Products were obtained in good to excellent yields under conventional heating (water, 50 °C) or under sonication (glycerol, 110 °C). In the reaction in water, the catalyst was easily reused for further reactions without loss of activity.

Introduction

Indoles and their derivatives are important compounds which are present in a variety of natural products.[1] In addition, bis(indolyl)methanes (BIMs) and their analogues present various important biological and pharmacological activities, such as antifungal, anti-inflammatory, antibacterial, antibiotic and analgesic properties.[2] Recently, BIMs were shown to exhibit anticancer activity, inhibiting the growth of cancer cells,[3] including prostate,[3a,b] colon,[3c] pancreatic[3d,e] and lung.[3f] One of the metabolites of indole-3-carbinol, the dimeric 3,3′-bis(indolyl)methane (also called DIM), has an important role in preventing breast cancer.[3g,h]

Due to the important pharmacological properties of BIMs, there are in the literature many methods to prepare this class of compound. Generally, the acid promoted electrophilic substitution of indoles with carbonyl compounds is the method of choice.[4] Although highly atom-efficient, the use of toxic reagents, high temperature and volatile organic solvents are among the drawbacks of most of these protocols.[4] Thus, the search for methodologies which decrease the environmental impact of the preparation of BIMs is of great interest to the pharmaceutical industry. The use of green solvents[5] or solvent-free[6] conditions, non classical energy sources such as microwaves,[7] ultrasound[8] and infrared,[9] eco-friendly reagents and catalysts[10] are among the alternatives to improve the greenness of the synthesis of BIMs.

In this sense, ultrasonic irradiation is a useful technique to increase the energy efficiency in organic synthesis.[11] Short reaction times, and the formation of pure products in high yields under mild reaction conditions are among features that put this technique as a green tool for organic synthesis. One of the twelve Principles of Green Chemistry, principle #6, ‘design for energy efficiency’, is strongly covered by sonochemistry.[12]

On the other hand, the use of niobium compounds as catalysts has emerged in recent years as an alternative to both Lewis and Bronsted acid catalysts.[13] The use of niobium pentoxide and niobic acid (hydrated Nb_2O_5) as catalysts in organic synthesis is well described.[13a–e] Ammonium niobium oxalate (ANO), $NH_4[NbO(C_2O_4)_2(H_2O)_x]\cdot nH_2O$, in turn, is used as a niobium precursor in the preparation of functionalized materials including ceramic, optical lenses, high purity niobium oxides, tin films and catalysts.[14] Besides, in contrast to the more famous derivative $NbCl_5$, ANO is cheap, easy to handle and is not sensitive to air or moisture.[14,15] The relatively low toxicity of niobium,[16] allied to its solubility in water,[14] make ANO a very attractive compound to be explored in organic synthesis.

In the last few years we have developed greener methodologies to prepare bioactive molecules and fine chemicals combining two or more of the Green Chemistry Principles, including the use of green solvents,[17] cheap and available catalysts[18] and energy-efficient protocols.[19] In this line, we describe herein the first use of $NH_4[NbO(C_2O_4)_2(H_2O)_x]\cdot nH_2O$ as a catalyst to promote the electrophilic substitution of indoles with carbonyl compounds to prepare bis(indolyl)methanes

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[a] Grupo de Análise, Preparação e Aplicação de Materiais – GAPAM – Departamento de Química – Universidade do Estado de Santa Catarina – UDESC, 89219-710 Joinville, SC, Brazil. E-mail: samuel.mendes@.udesc.br; Tel: +55 (47)4009-7840
[b] Laboratório de Síntese Orgânica Limpa - LASOL - Universidade Federal de Pelotas - UFPel, P.O. Box 354, 96010-900 Pelotas, RS, Brazil. E-mail: lenardao@ufpel.edu.br; Tel: +55 (53) 3275-7533

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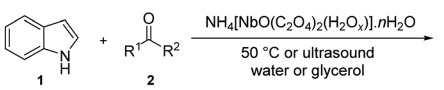


Scheme 1 General scheme of the reaction.

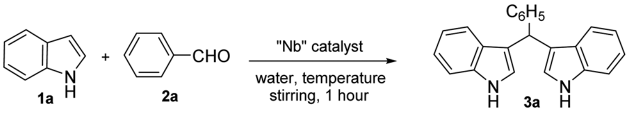
under green reaction conditions (Scheme 1). A detailed study on the use of water and glycerol as a solvent, as well as on thermal and ultrasonic irradiation as energy sources, was also performed.

Results and discussion

Our initial studies were focused on the development of an optimum set of reaction conditions to the synthesis of BIMs using ANO in aqueous media (Scheme 1).

Initially, indole **1a** (1.0 mmol) and benzaldehyde **2a** (0.6 mmol) were chosen as starting materials (Table 1). Firstly, the reaction was performed in H_2O (1.0 mL) using 1 mol% of ANO as the catalyst under constant stirring at room temperature for 1 h and open atmosphere. Under these conditions, the desired product **3a** was obtained in 11% yield (Table 1, entry 1). Looking for a higher yield, the amount of catalyst was increased and, gratifyingly, when 5 and 10 mol% of ANO were used, **3a** was obtained in 65% yield (Table 1, entries 2 and 3). By increasing the reaction temperature to 50 and 100 °C (oil bath), product **3a** was obtained in 85 and 82% yield, respectively (Table 1, entries 4 and 5). Finally, we observed that when the reaction time was increased to 2 h, **3a** was obtained in 97% yield (Table 1, entry 8). Because ANO is usually used as a niobium oxide precursor, we also tested the use of Nb_2O_5 as the catalyst for the reaction; however, no satisfactory result was obtained (Table 1, entry 6). Thus, the best reaction conditions to prepare BIMs under conventional heating was the use of indole **1** (1.0 mmol), aldehyde **2** (0.6 mmol), H_2O as solvent (1.0 mL) and ammonium niobium oxalate complex (ANO) as the catalyst (5.0 mol%) at 50 °C under air atmosphere for 2 h (Table 1, entry 8).

Table 1 Optimization studies using indole **1a** and aldehyde **2a** in water and under conventional heating[a]

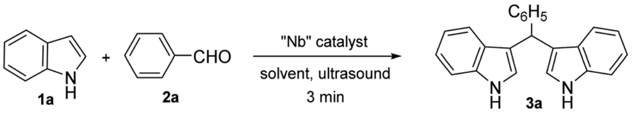


Entry	Catalyst (mol%)	Temperature (°C)	Yield of **3a** [b] (%)
1	ANO (1.0)	25	11
2	ANO (5.0)	25	65
3	ANO (10.0)	25	65
4	ANO (5.0)	50	85
5	ANO (5.0)	100	82
6	Nb_2O_5 (5.0)	50	12
7	ANO (5.0)	25	85[c]
8	ANO (5.0)	50	97[c]

[a] Reactions performed with indole **1a** (1.0 mmol), benzaldehyde **2a** (0.6 mmol), H_2O as the solvent (1.0 mL) and the niobium species at the indicated temperature for 1 h. [b] Yields of pure **3a** were isolated by column chromatography (hexanes/AcOEt). [c] Reaction time was increased to 2 h.

Aiming to verify the effect of ultrasound in accelerating the reaction, an ultrasonic probe sonicator with a processor power of 130 W and frequency of 20 kHz operating at 60% of ultrasonic amplitude was used. The first experiment was performed using our best conditions determined above under conventional heating using ANO (water as the solvent at 50 °C). The temperature of the reaction was monitored (with an I.R. thermometer) and it was observed that after 3 min of sonication, the reaction temperature was 47 °C, remaining at around 50 °C over a total time of 30 min under sonication. Unfortunately, after 3 min, 4% of indole **1a** was converted to product **3a** and after 30 min of sonication in water, the conversion was only 23% (Table 2, entries 1 and 2). Then, an investigation was performed to find a better solvent for the reaction. Fortunately, it was revealed that glycerol, a biobased solvent, afforded **3a** in 99% yield after only 3 min (Table 2, entry 3). At the final time of sonication in glycerol, the temperature of the reaction mixture was 110 °C. Toluene, DMSO, DMF and CH_2Cl_2 were ineffective in promoting the reaction under sonication for 3 min, with conversion rates of 1.0, 0.05, 1.0 and 2.0% respectively (Table 2, entries 4–7). Bioethanol was a reasonable solvent for this reaction, affording the desired product **3a** in 49% yield after 3 min (Table 2, entry 8). We decided to also explore the use of anhydrous and hydrated Nb_2O_5 in glycerol;

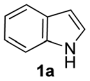
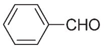
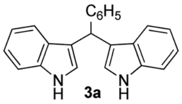
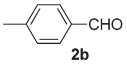
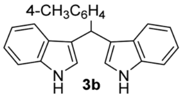
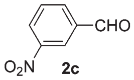
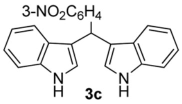
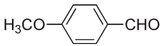
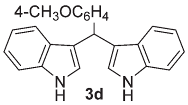
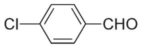
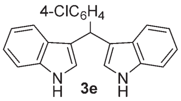
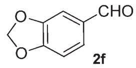
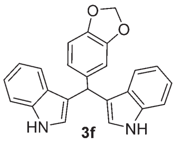
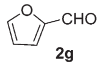
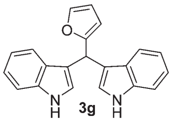
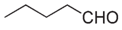
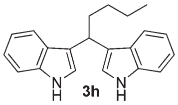
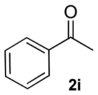
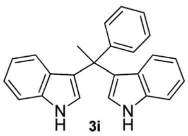
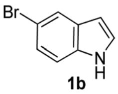
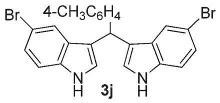
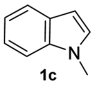
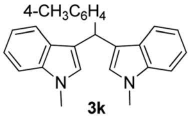
Table 2 Optimization studies using indole **1a** and aldehyde **2a**, under ultrasound irradiation[a]



Entry	Catalyst[b] (mol%)	Solvent (1.0 mL)	Conversion to **3a** [b] (%)
1	ANO (5.0)	Water	4
2	ANO (5.0)	Water	23[c]
3	ANO (5.0)	Glycerol	99[d]
4	ANO (5.0)	Toluene	1
5	ANO (5.0)	DMSO	NR
6	ANO (5.0)	DMF	1
7	ANO (5.0)	CH_2Cl_2	2
8	ANO (5.0)	EtOH	49
9	Nb_2O_5 (5.0)	Glycerol	27
10	$Nb_2O_5{\cdot}H_2O$ (5.0)	Glycerol	32
11	ANO (3.0)	Glycerol	92
12	ANO (10.0)	Glycerol	95
13	ANO (15.0)	Glycerol	97

[a] Reactions performed with indole **1a** (1.0 mmol), benzaldehyde **2a** (0.6 mmol) and the solvent (1 mL) under ultrasonic irradiation (20 kHz, 60% sonic amplitude) for 3 min. [b] Determined by GC, based on the amount of indole **1a**. [c] The reaction was sonicated for 30 min (final temperature = 50 °C). [d] The final temperature was 110 °C.

Table 3 Scope and generality of the niobium-catalyzed synthesis of bis(indolyl)methanes **3a–k** using indoles **1a–c** and carbonyl compounds **2a–i** [a]

	Indole	Carbonyl compound	Product	Conventional[b]		Ultrasound[c]	
Entry	1	2	3	Time (h)	Yield[d] (%)	Time (min)	Yield[d] (%)
1	 **1a**	 **2a**	 **3a**	2.0	97	3	99
2	**1a**	 **2b**	 **3b**	1.0	92	5	92
3	**1a**	 **2c**	 **3c**	3.0	89	8	82
4	**1a**	 **2d**	 **3d**	2.0	99	15	90
5	**1a**	 **2e**	 **3e**	1.0	89	5	92
6	**1a**	 **2f**	 **3f**	3.0	83	2	88
7	**1a**	 **2g**	 **3g**	1.0	96	1	88
8	**1a**	 **2h**	 **3h**	3.0	60	20	35
9	**1a**	 **2i**	 **3i**	3.0	68	15	20
10	 **1b**	**2b**	 **3j**	8.0	99	5	90
11	 **1c**	**2b**	 **3k**	3.0	65	2	93

[a] Amounts used: indole **1** (1.0 mmol) and carbonyl compound **2** (0.6 mmol). [b] H_2O (1 mL) as the solvent at 50 °C (oil bath) and stirring under air atmosphere. [c] Glycerin (1 mL) as the solvent under ultrasonic irradiation (20 kHz) and air atmosphere. [d] Yields of pure products isolated by column chromatography (hexanes/AcOEt) and identified by GC-MS and ^{1}H and ^{13}C-NMR.

however, lower yields of **3a** were obtained in both cases (Table 2, entries 9 and 10). Higher amounts of ANO did not improve the reaction performance (Table 2, entries 11 and 12), while the use of a lower amount led to a decrease in the product yield (Table 2, entry 10).

In order to explore the scope and limitations of the niobium-based catalysis, the protocol was extended to other examples, under the optimized conditions in water (conventional heating) and in glycerol (under sonication).

Firstly, various aromatic aldehydes (**2a–g**) were reacted with indole **1a** under conventional heating in water, affording BIMs **3a–g** in good to excellent yields after 1–3 h (Table 3, entries 1–7). No remarkable differences in reactivity were observed when electron-withdrawing or electron-donor groups were present in the aromatic ring. An exception was the electron-rich 1,3-dioxole benzaldehyde **2f**, which gave the respective BIM **3f** in lower yield (82%) compared to other benzaldehydes (Table 3, entry 6). Under our best conditions, the hetero-aromatic furaldehyde **2g** was converted to **3g** in 96% yield after 1 h (entry 7). It is noteworthy that the reaction worked also with aliphatic valeraldehyde **2h**, giving the alkyl substituted BIM **3h** in 60% yield after 3 h (Table 3, entry 8). It was also possible to apply our niobium-catalyzed procedure to the reaction of indole with acetophenone **2i**; in this case, tetrasubstituted BIM **3i** was obtained in 68% yield after 3 h (Table 3, entry 9).

Next, the behavior of different indoles (**1b–c**) on the Nb-catalyzed electrophilic substitution was evaluated (Table 3, entries 10–11). Thus, 5-bromo-1*H*-indole **1b** produced, after reaction with 4-methylbenzaldehyde **2b**, the bromo-containing BIM **3j** in 99% yield. A longer reaction time was necessary in this case, probably due to the deactivation of the indole by the bromo atom (Table 3, entry 10). *N*-Methyl substituted indole **1c** was equally converted to the respective BIM **3k** in 65% yield after 3 h (Table 3, entry 11).

Following this, the reaction between indoles and carbonyl compounds was performed using our previously optimized protocol with glycerol and ultrasound. In most cases, the BIMs were obtained with similar yields to those obtained by the in water reactions under conventional heating. The reaction times, on the other hand, were reduced from hours to a few minutes (Table 3). Valeraldehyde (**2h**) and acetophenone (**2i**) afforded the respective BIMs in 35 and 20% yields respectively, which are inferior to those obtained using water and conventional heating (Table 3, entries 8 and 9). In contrast, a better yield of **3k**, derived from *N*-methyl indole **1c** and 4-methylbenzaldehyde **2b**, was obtained using glycerol/ultrasound compared to the in-water protocol (93% *vs.* 65%, Table 3, entry 11).

Furthermore, a study regarding the reuse of the ANO was also performed. It was observed that the aqueous solution of the catalyst could be successfully reused up to 5 times without any pre-treatment, with good results. Thus, after the completion of the reaction, the crude product **3a** was simply extracted with ethyl acetate (3 × 5 mL) and the aqueous catalyst was reused directly in a new reaction. The product **3a** was obtained in yields between 97 and 95% after successive cycles (Fig. 1).

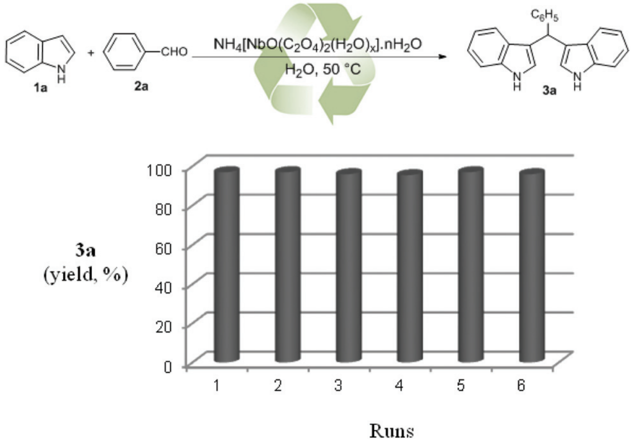
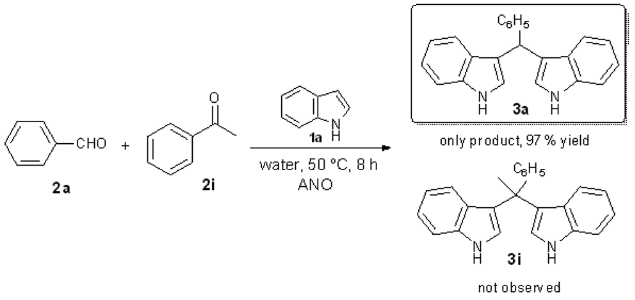


Fig. 1 Reuse of ANO/water in the synthesis of **3a**.



Scheme 2 Chemoselectivity of the reaction.

We also studied the reuse of the catalyst and solvent in the glycerol-mediated reaction of **1a** with **2a**. We observed, however, that the catalyst was inactive after the first reaction and more ANO was required for the next reaction. The same solvent (glycerol) was used in four reactions, giving **3a** in 99, 92, 89 and 70% yields. Besides the need to add a new ANO for each reaction, a large amount of AcOEt was necessary for an efficient extraction of **3a** (6 × 3 mL); these features make the recycling of glycerol in this case somewhat unattractive.

The chemoselectivity of the reaction in water was also investigated. Thus, a mixture of benzaldehyde **2a** (0.6 mmol), acetophenone **2i** (0.6 mmol) and indole **1a** (1.0 mmol) was subjected to the reaction under conventional heating conditions for 8 h. The only product obtained was **3a**, derived from benzaldehyde **2a**, in 97% yield, while acetophenone remained unreacted and could be recovered (Scheme 2). This result shows the high chemoselectivity of our method.

Conclusions

Ammonium niobium oxalate (ANO), $NH_4[NbO(C_2O_4)_2(H_2O)_x]\cdot nH_2O$, proved to be an effective, selective and reusable catalyst for the green synthesis of bis(indolyl)methanes under conventional heating in water or under ultrasonic irradiation in glycerol. Besides being a simple procedure, the niobium catalyst was easily reused in the reaction in water. The use of glycerol allows the use of sonication to accelerate the reaction from hours to only a few minutes. The low toxicity of niobium allied to an atom-economic reaction, and the use of green solvents and sonication are features which make this new, Nb-based protocol, a green alternative to access bis(indolil) methanes selectively.

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