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$TiCl_3OTf$-[bmim]Br: a novel and efficient catalyst system for chemoselective one-pot synthesis of thioamides from arylaldoximes

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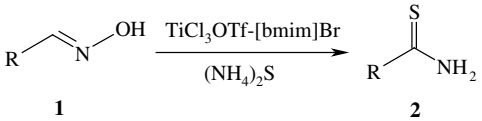
ABSTRACT

The combination of $TiCl_3OTf$ with 1-butyl-3-methylimidazolium bromide is found to be an efficient and novel catalytic system for chemoselective one-pot transformation of arylaldoximes to their corresponding thioamides in high to excellent yields.

One of the strategies for combination of economic and environmental aspects is one-pot reactions. This process consists of two or more synthetic steps, which are performed without isolation of any intermediates, thus reducing time, and saving energy and raw materials.[1] Recently, thioamides and their derivatives have received considerable attention due to their utility as synthons in organic chemistry, for example, the synthesis of a variety of heterocycles such as thiazoline or thiazole derivatives,[2] betaines,[3] mesoionic rhodanine,[4] and other heterocyclic compounds.[5] In addition, thioamides such as 6-mercapto-purine show antitumor activity in their own right.[6] Thus, the development of facile and environmentally friendly synthetic methods toward thioamides constitutes an active area of investigation in organic synthesis. The most well-known method for the preparation of these compounds is limited to nitriles or amides as precursors.[7,8] Therefore, expansion of this method to a number of substrates for the preparation of new thioamide derivatives is highly desirable.

One of the practical methods for clean and efficient chemical synthesis is combination of Lewis acids with ionic liquids.[9] This ionic catalytic system has led to much higher reaction rates than those performed in classical organic solvents.[10] These results, in combination with our recent studies on the design of new synthetic methodologies,[11] especially in ionic liquids,[12] led us to develop a new, simple, chemoselective, and efficient procedure for the one-pot conversion of oximes to their corresponding thioamides in the presence of a catalytic amount of $TiCl_3OTf$[13] on 1-butyl-3-methylimidazolium bromide (Scheme 1).[14]

Further examination of this transformation illustrated that two paths can be considered for the conversion of oximes to their thioamides: Path 1 (traditional manner), that is, (1) conversion of the oxime to the corresponding nitrile; (2) isolation of the nitrile; (3) purification of the nitrile, and (4) conversion of the nitrile to the thioamide. However, in path 2, these steps can be performed in a one-pot manner, and the intermediate nitrile trapped without isolation. This procedure alleviated the necessity of isolating the intermediate nitrile and vastly improved the yield. To investigate the utility of $TiCl_3OTf$-[bmim]Br in one-pot reactions, benzaldoxime was treated with $TiCl_3OTf$-[bmim]Br followed immediately by the addition of ammonium sulfide at 80 °C. Regardless of reaction times, no thioamide was obtained. However, treatment of the oxime with $TiCl_3OTf$-[bmim]Br in the traditional manner gave the corresponding thioamide in 44% yield (path 1). On further investigation, we found that a true one-pot reaction was possible. 4-Chlorobenzaldoxime was treated with $TiCl_3OTf$-[bmim]Br, and allowed to react at 80 °C. Once conversion to the nitrile was complete, as determined by TLC, ammonium sulfide was added



1 2

Scheme 1.

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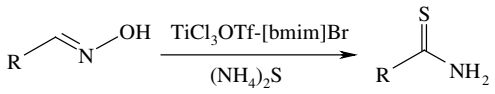
Table 1
Influence of catalyst and solvent on the synthesis of **2b**

Entry	Catalyst[a]	Solvent[b]	Time (h)	Yield[c] (%)
1	ZrO_2	[bmim]Br	24	40
2	$ZrCl_4$	[bmim]Br	24	82
3[b]	$ZrO(OTf)_2$	[bmim]Br	8	63
4	$Zr(OTf)_4$	[bmim]Br	12	59
5	$TiCl_3OTf$	[bmim]Br	1	90
6	—	[bmim]Br	1	0
7	$TiCl_3OTf$	[bmim]Cl	1	50
8	$TiCl_3OTf$	[bmim]OTf	1	26
9	$TiCl_3OTf$	[bmim]PF_6	1	19
10	$TiCl_3OTf$	$[(MIM)_2(CH_2)_6Cl_2]$[d]	1	30
11	$TiCl_3OTf$	Bu_4NBr	1	8
12	$TiCl_3OTf$	CH_3CN	1	0
13	$TiCl_3OTf$	DMSO	1	0
14	$TiCl_3OTf$	$CHCl_3$	1	0
15	$TiCl_3OTf$	CH_2Cl_2	1	0
16	$TiCl_3OTf$	—	1	5

[a] 15 mol %.
[b] Ionic liquids and organic solvents were used, 1.5 mmol and 2 ml, respectively.
[c] Isolated yield.
[d] 1,6-Bis(3-methylimidazolium-1-yl)hexane chloride.

Table 2
$TiCl_3OTf$-[bmim]Br catalyzed one-pot conversion of aldoximes to thioamides[a]



1 **2**

Entry	R	Time (h)	Yield[a] (%)
a	C_6H_5	1	87
b	4-ClC_6H_4	1.2	90
c	2-ClC_6H_4	2.2	85
d	2,4-$Cl_2C_6H_3$	3.2	82
e	4-BrC_6H_4	0.8	89
f	2-BrC_6H_4	2.3	84
g	4-FC_6H_4	0.4	90
h	3-$NO_2C_6H_4$	1.2	88
i	4-Pyridyl	0.7	80
j	2-Pyridyl	1	86
k	2-Furyl	1.25	88
l	4-CH_3-Furyl	2.7	85
m	3-$CH_3OC_6H_4$	1.2	89
n	5-$CH_3OC_6H_4$	4.25	67
o	4-$BnOC_6H_4$	4.3	62
p	2,4-$(CH_3O)_2C_6H_3$	7	0

[a] Yields refer to isolated pure products characterized by ^1H NMR, ^{13}C NMR, IR spectroscopy and CHNS analysis.

and the reaction mixture was allowed to stir at 80 °C (path 2). This one-pot procedure led to a dramatic almost doubling of the yield of the thioamide (90%) as compared to the overall yield obtained in the traditional process.

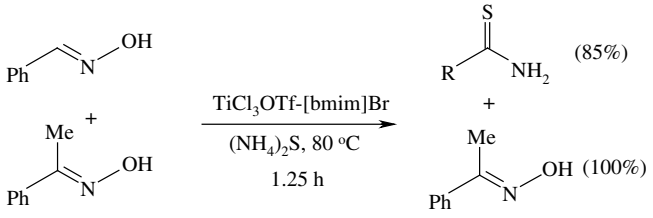
To explore the scope and versatility of this method, the one-pot reaction of 4-chlorobenzaldoxime (1.0 mmol) and ammonium sulfide (1.2 mmol) was chosen as a model, and the role of various catalysts and solvents on the reaction system was investigated. The results are summarized in Table 1.

The reaction using $TiCl_3OTf$-[bmim]Br gave the best result (Table 1, entry 5). Interestingly, we observed that combination of $TiCl_3OTf$ with [bmim]Br was essential for this transformation; attempts to carry out the reaction in the absence of each of these substrates gave virtually no product (Table 1, entries 6 and 16). To further optimize the reaction, the procedure was carried out at temperatures ranging from 30 to 100 °C. It was found that, as the reaction temperature was increased, the yield of **2b** was improved, and the reaction time was shortened. The yields plateaued when a temperature of 80 °C was reached.

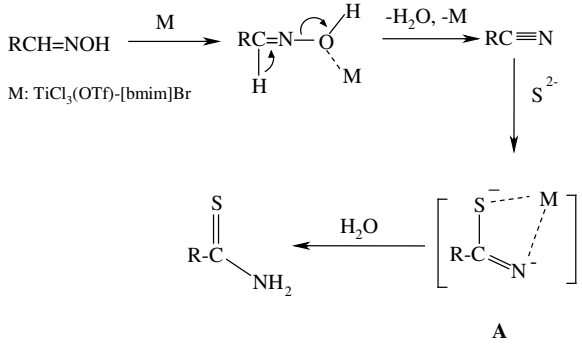
With these results in hand, we turned our attention to investigate the scope of various aldoximes in the reaction. The results are summarized in Table 2. To the best of our knowledge, no report is available in the literature using oximes as precursors for one-pot thioamide synthesis in ionic catalytic systems. The experimental procedure for this transformation is remarkably straightforward, and does not require the use of toxic organic solvents or inert atmospheres.

As shown in Table 2, aldoximes bearing either electron-withdrawing or electron-donating groups such as nitro, chloro, or methoxy underwent transformation to the corresponding thioamides, successfully. We observed minor electronic effects; for example, aldoximes with electron-withdrawing groups (Table 2, entries **b**–**j**) reacted rapidly, while the presence of electron-rich groups (Table 2, entries **n** and **o**) decreased the reactivity, requiring longer reaction times. 1,3-Benzenedialdoxime could also be transformed to the corresponding dithioamide in 88% yield after 1 h (Scheme 2).

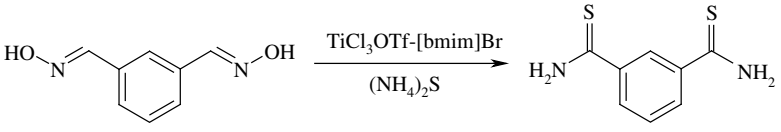
Moreover, heterocyclic aldoximes such as 4- or 2-pyridylaldoximes (Table 2, entries **i** and **j**) and 2-furyl or 5-methyl-2-furylaldoxime (Table 2, entries **k** and **l**) displayed high reactivity under these conditions. It should be pointed out that benzaldoximes with increased numbers of electron-donating groups such as



Scheme 3.



Scheme 4.



Scheme 2.

2,4-dimethoxybenzaldoxime did not react with ammonium sulfide under the present reaction conditions even after 8 h. On the other hand, we found that aliphatic aldoximes were stable under these reaction conditions. This method was also highly chemoselective. In a mixture of an aldoxime and a ketoxime, the aldoxime was converted to the corresponding thioamide in high yield while the ketoxime remained intact and was recovered quantitatively (Scheme 3).

Such selectivity has not been reported previously, and can be considered a useful practical achievement in thioamide synthesis. Although the mechanistic details of the reaction are not known exactly, a plausible rationalization may be advanced to explain the product formation (Scheme 4).

Presumably, in the first step, interaction between the catalyst and the oxime furnishes the corresponding nitrile. In the next step, intermediate **A** is produced by attack of ammonium sulfide on the nitrile and finally, this intermediate is hydrolyzed to the desired product.

In summary, we have described a new and efficient protocol for the chemoselective one-pot synthesis of primary thioamides from arylaldoximes using $TiCl_3$(OTf)-[bmim]Br as a novel catalytic system. The simple experimental procedure combined with the ease of work-up makes this method convenient for the synthesis of functionalized primary arylthioamides.

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13. $TiCl_3$OTf was prepared according to the literature, see: Iranpoor, N.; Zeynizadeh, B. *Synth. Commun.* **1999**, *29*, 2747.
14. *Typical procedure for the synthesis of 2-furanthioamide:* To a mixture of 2-furylaldoxime (1 mmol) in [bmim]Br (1.5 mmol), $TiCl_3$OTf (0.15 mmol, 45.7 mg) was added. The reaction mixture was stirred at 80 °C for 1 h. Following complete consumption of the aldoxime (TLC), ammonium sulfide (1.2 mmol) was added, and the mixture was stirred at 80 °C for 15 min (the progress of the reaction was followed by TLC). When the reaction was complete, it was quenched with ice-water (10 ml) and stirred at room temperature for 10 min. The mixture was extracted with ethyl acetate (3 × 5 mL), and the organic layers were combined and washed with brine. After drying ($MgSO_4$) and concentration in vacuo, the residue was chromatographed on silica gel (*n*-heptane/ethyl acetate, 4:1 as eluent) to afford the pure product in 88% yield.
Data for 2-furanthioamide (Table 2, *entry* ***k***): yellow solid, mp 103–105 °C; ν_{max} (KBr) 3329, 3275, 3157, 1624 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 9.48 (s, 1H, NH), 9.25 (s, 1H, NH), 7.56 (d, J = 4.8 Hz, 1H), 7.48 (d, J = 3.2 Hz, 1H), 6.93 (dd, J = 4.4, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.0, 165.2, 152.7, 141.9, 134.6. Anal. Calcd for C_5H_5NOS: C, 47.23; H, 3.96; N, 11.01; S, 25.22. Found: C, 46.96; H, 4.10; N, 11.17; S, 25.67.