A Thiophosphoryl Chloride Assisted Transformation of Arylaldoximes to Thioamides

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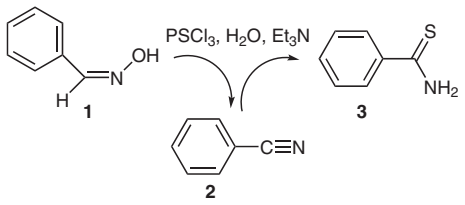
Abstract: Primary benzothioamides were accessed from benzaldoximes (benzaldehyde oximes) via benzonitriles in a sequential tandem approach utilizing thiophosphoryl chloride as a dehydrating and thionating agent.

Key words: primary thioamides, oximes, thiophosphoryl chloride, nitriles

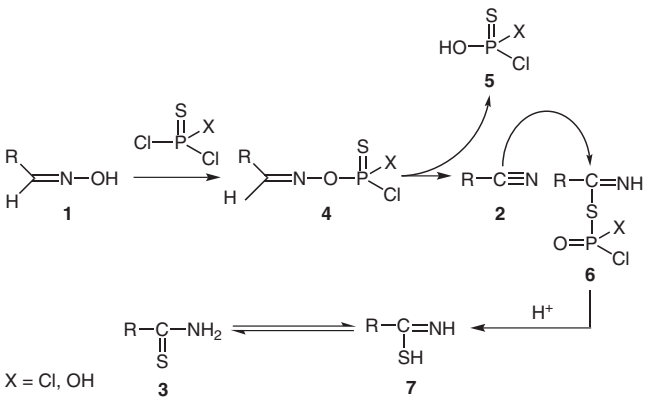
The significance of primary thioamides and their impact on the development of chemistry is constantly growing due to their great pharmaceutical and synthetic applicability.[1] In particular they are useful building blocks in the Hantzsch thiazole synthesis for the preparation of a wide variety of substrates.[2] Although, various methods have been reported in the literature for the preparation of thioamides, the majority of procedures are limited to nitriles or amides as the precursors.[3] Therefore, the development of novel synthetic approaches from alternative substrates for the preparation of thiocarbonyl compounds,[4] in particular thioamides, constitutes an active area of investigation in contemporary organic synthesis.

We wish to develop a method for thioamide formation from aldoximes. Aldoximes can be easily obtained from aldehydes; a great variety of aldehydes are available. Aldoximes are known to undergo dehydration to nitriles. The dehydration of aldoximes can be achieved by a number of reagents[5] including organophosphorus compounds, i.e. phosphoric acid or phosphorus chlorides. On the other hand, nitrile to thioamide transformation has also been documented.[3a] Thiophosphoryl chloride is the sulfur analogue of phosphoryl chloride. It exhibits properties similar to phosphoryl chloride except that it also has thionating ability.[6] We reasoned that using a reagent such as thiophosphoryl chloride, which has both dehydrating as well as thionating ability, direct transformation of aldoximes to primary thioamides may be possible. A one-pot, two-step synthesis of thioamides from arylaldoximes utilizing two different sets of reagents to accomplish each step has been reported,[5f] but, a single-reagent-driven methodology for total transformation is still awaited. Single-reagent-driven, one-pot synthesis is attractive due to its chemical, economical, and environmental advantages. We envisaged that thiophosphoryl chloride would initially dehydrate aldoxime **1** into nitrile **2**, which would then undergo subsequent thiolysis with the transformed reagent to yield thioamide **3** (Scheme 1). Recently, we have demonstrated the direct preparation of thioflavones from β-diketones using thiophosphoryl chloride under solvent-free conditions.[7] To explore the possibility of single-reagent-driven preparation of thioamides from aldoximes, benzaldoxime (**1a**) was treated with thiophosphoryl chloride in an equimolar amount without solvent at 70–80 °C.



Scheme 1 A thiophosphoryl chloride interceded synthesis of benzothioamides from benzaldehyde oximes

After 30 minutes, complete conversion of aldoxime **1a** into nitrile **2a**, with traces of benzamide and benzothioamide, was observed, which indicated that this strategy has potential for the formation of thioamides from aldoximes. We expected the complete conversion of benzaldoxime (**1a**) into benzothioamide (**3a**) by using a prolonged reaction time, but this did not occur. In order to optimize the conversion, the reaction was performed using with different solvents, however, the reaction did not progress satisfactorily due to incomplete conversion of the nitrile **2a** into the thioamide **3a**, although the dehydration of the aldoxime **1a** was complete.



Scheme 2 Plausible mechanism for thiophosphoryl chloride mediated formation of thioamides from oximes

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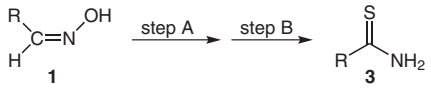
According to our proposed mechanism (Scheme 2), thiophosphoric acid **5** attack on the nitrile **2** will lead to the formation of an intermediate **6**, which upon hydrolysis by water may lead to the formation of the thioamides. Considering the proposed mechanism, we reasoned that conversion of **6** into **7** may be assisted by water. Addition of water to the reaction mixture of **1a**, to our amazement, produced a strong impact on the reaction and the formation of thioamide **3a** was favored to a significant amount. On further experimentation we found that only a limited amount of water (100–150 μL/mmol) was useful; excess water resulted in the formation of benzamide and benzoic acid as the major products. After extensive experimentation, an optimized procedure was developed: initially thiophosphoryl chloride (0.5 mmol), water (0.5 mmol), triethylamine (0.5 mmol), and benzaldoxime (**1a**, 1 mmol) were heated at 70–75 °C. After complete conversion of oxime **1a** into nitrile **2a**, which took 15–20 minutes, thiophosphoryl chloride (1.5 mmol), water (1.5 mmol), and triethylamine (2.5 mmol) were added and reaction was continued at 80–85 °C; the mixture was analyzed by GC and TLC. It was assumed that the disappearance of nitrile **2a** from the reaction mixture resulted in complete formation of intermediate **6**. Parallel formation of thioamide **3a** also occurred during this period. Next, water (100–150 μL/mmol) was added, contents were mixed thoroughly and kept overnight at room temperature for the hydrolysis of **6** to occur. Alternatively, an expedited hydrolysis can be achieved by heating the reaction mixture for a further 2–3 hours after the addition of water.

With an optimized procedure in hand, the scope of aldoximes that can be tolerated in this reaction strategy was investigated. A variety of arylaldoximes were studied. The result of formation of several thioamides **1b–l** is summarized in Table 1. Good to excellent conversion of arylaldoximes **1b–l** into thioamides **3b–l** was noticed. Dehydration of aldoximes was complete within 15–20 minutes, though the thiolysis of nitriles **2** took a comparatively longer time. All substrates containing either electron-donating or electron-withdrawing groups underwent smooth transformation to give the corresponding thioamides **3**. A sterically hindered oxime, 2,6-dichlorobenzaldoxime (**1l**) (entry 12), was also examined and it was found to be reactive under these conditions.

Substrates containing an electron-withdrawing groups **1b**,**c**,**g–i**,**k**, (Cl, NO_2, Br) and sterically hindered substrate **1l** not only required a longer time for thiolysis, but they also required a slightly higher amount of thionating agent in comparison to substrates containing electron-donating groups. This may be attributed to the difficulty in protonating nitriles containing electron-withdrawing groups. The reagent system thiophosphoryl chloride/water/triethylamine (2:2:3 mol) per mole of aldoxime **1** was used for substrates with electron-donating groups, and for substrates with electron-withdrawing groups thiophosphoryl chloride/water/triethylamine (2.5:2.5:4 mol) per mole of aldoxime **1** was used. When this protocol was examined for alkylaldoximes, the formation of alkanenitriles occurred with the same efficiency, but thionation of alkanenitriles was difficult under these reaction conditions.

Table 1 Conversion of Oximes **1** into Thioamides **3**



1 3

Entry	R	Molar ratio $PSCl_3/H_2O/Et_3N$	Temp, time A[a]	B[a]	Product	Yield[b] (%)	Ref.
1	Ph	2:2:3	70–75 °C, 0.9 h	80–85 °C, 2.5 h	**3a**	92	8
2	4-BrC_6H_4	2.5:2.5:4	85–90 °C, 0.9 h	80–85 °C, 3.5 h	**3b**	84	8
3	4-$O_2NC_6H_4$	2.5:2.5:4	95–100 °C, 1.2 h	90–95 °C, 3.5 h	**3c**	78	8
4	4-$MeOC_6H_4$	2:2:3	80–85 °C, 0.9 h	85–90 °C, 2.5 h	**3d**	86	9
5	4-MeC_6H_4	2:2:3	75–80 °C, 0.9 h	80–85 °C, 2.5 h	**3e**	88	9
6	4-pyridyl	2:2:3	90–95 °C, 1.0 h	90–95 °C, 2.5 h	**3f**	76	9
7	3-$O_2NC_6H_4$	2.5:2.5:4	95–100 °C, 1.2 h	90–95 °C, 3.5 h	**3g**	79	10
8	2,4-$Cl_2C_6H_3$	2.5:2.5:4	85–90 °C, 1.0 h	85–90 °C, 3.5 h	**3h**	81	8
9	3-ClC_6H_4	2.5:2.5:4	85–90 °C, 0.9 h	85–90 °C, 3.5 h	**3i**	83	8
10	3-$MeOC_6H_4$	2:2:3	80–85 °C, 0.8 h	80–85 °C, 2.5 h	**3j**	87	11
11	4-ClC_6H_4	2.5:2.5:4	85–90 °C, 0.9 h	80–85 °C, 3.5 h	**3k**	82	8
12	2,6-$Cl_2C_6H_3$	2.5:2.5:4	95–100 °C, 1.5 h	95–100 °C, 3.5 h	**3l**	78	12

[a] Step A = conversion of oximes **1** into intermediate **6**; step B = conversion of **6** into thioamides **3**.
[b] Yields refer to isolated pure products characterized by NMR and IR spectroscopy and mass spectrometry.

The formation of akyl thioamides was limited by the undesired formation of the corresponding acid and amide, which was produced from competing water hydrolysis reaction of the alkyl nitrile; only 40–50% conversion into thioamides was obtained.

In conclusion, a single-reagent-driven transformation of aldoximes into thioamides via nitriles under solvent-free conditions has been discovered. Thiophosphoryl chloride has been utilized as the dehydrating agent as well as thionating agent. The protocol was found to be of general applicability to arylaldoximes.

Reagents were obtained from commercial suppliers and used without further purification. Aldoximes for entries 2, 4, and 8–12 were prepared from the corresponding aldehydes by a reported procedure.[13] Solvents were purified by usual methods and stored over molecular sieve. Freshly distilled $PSCl_3$ was used. Melting points were measured by Scientific MP-DS melting point apparatus. TLC was performed using precoated aluminum sheets with silica gel $60F_{254}$. Column chromatographic purification of products was performed on silica gel (60–120 mesh). ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance II 400 MHz. Mass spectra was obtained in Agilent 5975C GC-MS. FT-IR spectra were recorded on a Perkin Elmer IBX-200 spectrophotometer, using KBr pellets.

4-Bromobenzothioamide (3b); Typical Procedure

$PSCl_3$ (102 μL, 1 mmol), H_2O (18 μL, 1 mmol), and Et_3N (139 μL, 1 mmol) was added to 4-bromobenzaldoxime (**1b**, 0.40 g, 2 mmol) and mixed thoroughly. The mixture was heated at 70–75 °C for 15 min. At this stage conversion of oxime **1b** to nitrile **2b** was almost complete. To this mixture were added $PSCl_3$ (408 μL, 4 mmol), H_2O (72 μL, 4 mmol), and Et_3N (973 μL, 7 mmol) and the mixture was heated at 85–90 °C for 40 min, H_2O (200 μL) was added and contents were heated further at 80–85 °C for 3.5 h (alternatively, after the addition of H_2O the contents were thoroughly mixed and kept overnight at r.t.). Neutralization with 10% $NaHCO_3$ soln at 0–5 °C resulted in precipitation of 4-bromothiobenzamide (**3b**) as light-yellow solid which was filtered under vacuum. The aqueous layer was further extracted with EtOAc. The combined organic layers were dried (anhyd Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was mixed with yellow solid and purified by column chromatography (silica gel, EtOAc–hexane 1:9) to give pure **3b** as greenish yellow crystals; yield: 370 mg (86%); mp 189–191 °C.

IR (KBr): 3287, 3135, 1629, 1583, 1069, 887 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.75 (br s, NH, 1 H), 7.73 (d, *J* = 6.8 Hz, 2 H), 7.53 (d, *J* = 6.8 Hz, 2 H), 7.19 (br s, 1 H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 200.98, 181.12, 137.94, 131.16, 128.08, 126.67.

MS (EI, 70 eV): *m*/*z* = 215 [M^+], 183, 181, 102, 75, 51.

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