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Facile Synthesis of Thioamides via P_2S_5-Mediated Beckmann Rearrangement of Oximes

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A facile and efficient approach to the synthesis of secondary thioamides from ketoximes via Beckmann rearrangement has been established, using phosphorus pentasulfide as a dehydrating and thiating agent. It is also efficient for the preparation of primary thiobenzamide from benzaldoxime. This approach features simple-operation, easy-control and good to excellent yields.

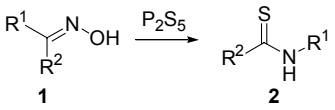
Keywords thioamides, oximes, phorphorus pentasulfide, Beckmann rearrangement, iminocarbocation

Introduction

Thioamides are widely used in biochemistry and medicine as major drugs for treatment of thyrotoxicosis and hyperthyroidism, and have been incorporated into peptides as isosteres for the amide bond as thiopeptide antibiotics.[1] Also, thioamides are synthetically versatile molecules, being key components in various transformations, especially in the preparation of many useful heterocycles.[2]

Although a variety of methods for the synthesis of thioamides have been developed to date, most of these procedures are limited to the use of amides, ketones or nitriles as precursors.[3] Only a few examples of the synthesis of thioamides from oximes or their esters via Beckmann rearrangement have been reported.[4]

Although a one-pot method has been recently reported in which $PSCl_3$[4b] is used to transform oximes to thioamides in the absence of extra activating and thionating reagents, these methods require complicated operations or prior oxime activation such as the formation of sulfonate esters. Recognition of these drawbacks prompted us to design an alternative approach to the direct conversion of oximes to thioamides. In this paper, we demonstrate a facile and highly efficient one-pot synthesis of thioamides via Beckmann rearrangement of oximes using only the commonly available reagent P_2S_5 under mild conditions (Eq. 1).



1 **2** (1)

Results and Discussion

Initially, treatment of an acetophenone oxime **1a** with P_2S_5 was chosen as a model reaction. When acetophenone oxime reacted with equimolar P_2S_5 in dry acetonitrile at ambient temperature for 7 h, the thioacetanilide **2a** was generated in 32% yield (Table 1, Entry 1). To further optimize the reaction conditions, several solvents, temperatures and oxime/P_2S_5 ratios were evaluated. As shown in Table 1, when DCM replaced MeCN, the yield was not significantly enhanced (Table 1, Entry 2), but when aromatic solvents such as xylene, toluene, and benzene were used instead, the yields increased dramatically to 75%—85% (Table 1, Entries 3, 5 and 6). Benzene as a solvent gave the best result (Table 1, Entry 6), although the longer reaction times in these solvents were required. It is noteworthy that with acetone as solvent none of the desired product was generated and the oxime could be quantitatively recovered. Elevation of the reaction temperature remarkably shortened the reaction time and slightly augmented the yield (Table 1, Entries 7—9). When refluxing in benzene, the yield was increased to 90% and the time shortened to only 0.5 h. After lowering the ratio of oxime/P_2S_5, it was found that the use of

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0.5 equivalents of P_2S_5 could afford 90% yield in the same reaction time (Table 1, Entry 9). However, when 0.33 equiv. P_2S_5 was used, a considerable amount of oxime (40%) was recovered (Table 1, Entry 10).

Table 1 Optimization of the reaction conditions[a]

Entry	Solvent[b]	Temp./℃	Time/h	Yield[c]/%
1	MeCN	30	7	32
2	CH_2Cl_2	30	72	41
3	xylene	30	72	80
4	acetone	30	7	—
5	toluene	30	＞72	75
6	benzene	30	72	85
7	benzene	50	2	88
8	benzene	80	0.5	90
9[d]	**benzene**	**80**	**0.5**	**90**
10[e,f]	benzene	80	4	50

[a] Reaction conditions: Acetophenone oxime **1a** (1 mmol), P_2S_5 (1 mmol), solvent (10 mL), air atmosphere unless otherwise stated. [b] Dried with standard methods. [c] Isolated yield based on the oxime. [d] Molar ratio **1a**/P_2S_5 1∶0.5. [e] Oxime **1a** (40%) was not converted. [f] Molar ratio **1a**/P_2S_5 1∶0.33.

Under the most favorable reaction conditions, we investigated the generality and scope of this rearrangement using various ketoximes and the results are summarized in Table 2. All the substrates tested smoothly underwent conversion to the corresponding thioamides in good to excellent yields (65%—90%), and, as expected, exclusive *anti* migration, was observed. As is customary in Beckmann rearrangements of ketoximes, electron-releasing groups on the aromatic ring facilitate the reaction giving higher yields (Table 2, Entries **2e** and **2j**), while electron-withdrawing groups retard the rearrangement resulting in relatively lower yields (Table 2, Entries **2c**, **2d**, **2f**, **2i** and **2l**). The conversion also proceeds effectively with a variety of substituents, such as methylthio, on the aromatic rings of the ketoximes. It should be noted that 1-*p*-tolylethanone oxime **2e** gave 90% yield using the established standard conditions whereas no desired product was obtained using the $PSCl_3$ method.[4b] Also, with the P_2S_5 method, 1-(3-chlorophenyl)-propan-1-one oxime **2i** gave 80% yield whereas with the $PSCl_3$ method the analogous propiophenone oxime did not produce the desired thioamide.[4b] Aliphatic ketoximes were also converted to their corresponding thioamides in good yields (Table 2, Entries **2o**—**2q**). For cyclohexanoxime **1o**, azepane-2-thione **2o** was initially obtained in only 40% yield accompanied by 30% of the ε-caprolactam. However, using freshly disilled benzene as solvent, the yield of **2o** was increased to 65%.

On the basis of the Beckmann rearrangement, a tentative mechanism is presented in Figure 1. Firstly, P_2S_5 reacts with ketoxime **1** to furnish the activated intermediate ester **A**, which genrates the reactive iminocarbocation **B** and its counteranion **C** via the Beckmann rearrangement pathway. Nucleophilic attack on **B** by **C** provides the thioamide **2**, with the elimination of phosphorus oxide-sulfide. This oxide-sulfide further reacts with another oxime to undergo this transformation. In this reaction, P_2S_5 probably works in a manner similar to the conversion of amides to thioamides.

Table 2 P_2S_5-mediated Beckamann rearrangement of ketoximes[a]

Product	R^1	R^2	Time/h	Yield[b]/%
2a	Ph	Me	0.5	90
2b	Ph	Ph	0.5	85
2c	4-BrC_6H_4	Me	3	75
2d	4-ClC_6H_4	Me	3	80
2e	4-MeC_6H_4	Me	0.5	90
2f	3-$NO_2C_6H_4$	Me	5	68
2g	naphthyl-2	Me	2.5	75
2h	naphthyl-1	Me	2	81
2i	3-ClC_6H_4	Et	2.5	80
2j	2,4-$(EtO)_2C_6H_3$	Me	2	83
2k	2-$BnOC_6H_4$	Me	2.5	75
2l	4-$CF_3C_6H_4$	Me	4	65
2m	4-BrC_6H_4	$MeSCH_2$	1	72
2n	Ph	MeS(Me)CH	1	70
2o	$(CH_2)_5$		2	65
2p	$(CH_2)_{11}$		2	80
2q	Me	Me	2	83

[a] Reaction conditions: oxime **1** (1 mmol), P_2S_5 (0.5 mmol), dry benzene (10 mL) at 80 ℃ under air atmosphere. [b] Isolated yield. The major side product was the corresponding amide.

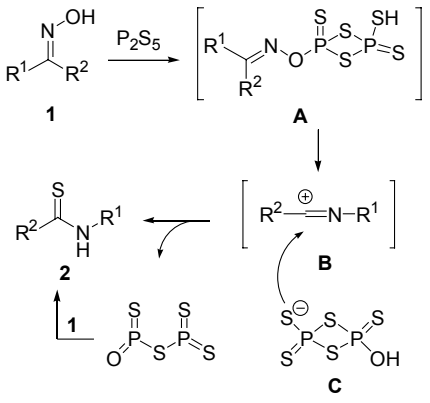
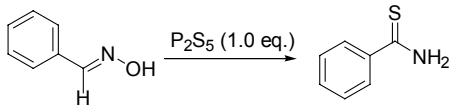


Figure 1 Plausible mechanism for P_2S_5-mediated formation of thioamides from ketoximes

In addition, treatment of benzaldoxime under the established route led to only a small amount of thiobenzamide together with benzonitrile. When the equivalent of P_2S_5 was increased to 1.0, a yield of 90% was achieved (Eq. 2). Presumably, the excess P_2S_5 converted benzonitrile to thiobenzamide.[5] Compared to the syn-

thesis using $PSCl_3$,[4d] this approach features greater generality, being easy use for transformation of aldoximes to primary thioamides simply by increasing the amount of P_2S_5.



(2)

Conclusions

In summary, a facile and efficient procedure for the synthesis of secondary thioamides via Beckmann rearrangement of the corresponding ketoximes has been developed. The reaction is mediated by the commercially available and cheap reagent P_2S_5 and occurs in one step. This approach has been successfully extended to the transformation of benzaldoximes to thiobenzamides. Further applications of this new procedure are under investigation.

Experimental

General procedure for Beckmann rearrangement of ketoximes **1** to thioamides **2**: To a solution of ketoxime (1.0 mmol) in dried benzene (10 mL) was added P_2S_5 in one portion. After stirring under reflux for the time stated in the table, the reaction mixture was allowed to cool and filtered. The solid residue was washed with freshly dried benzene. The combined organic layers were evaporated to remove benzene. Then the product was purified by column chromatography (PE/EA, 20∶1—10∶1). Typical details for the compound *N*-(4-bromophenyl)-2-(methylthio)-ethanethioamide **2m**: Yellow oily liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.36 (br, s, 1H), 7.74 (d, J=8.4 Hz, 2H), 7.54 (d, J=8.4 Hz, 2H), 3.90 (s, 2H), 2.15 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.7, 137.5, 132.3 (2C), 124.6 (2C), 120.1, 49.2, 16.0. EI-MS *m*/*z*: 277, 275 [M^+], 229, 213, 171, 155, 91, 32. Anal. calcd for $C_9H_{10}BrNOS_2$: C 39.13, H 3.65, N 5.07, S 23.22; found C 39.08, H 3.71, N 5.13, S 23.13.

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