Facile and Odorless One-Pot Process for the Synthesis of N-Substituted Thioamides via TsCl-Mediated Beckmann Rearrangement of Ketoximes

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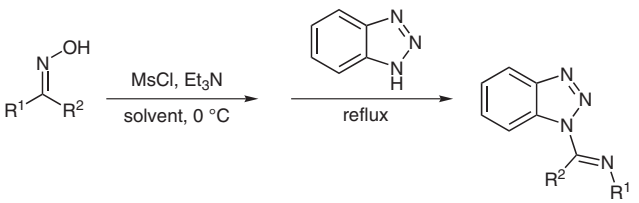
Abstract: A facile and odorless one-pot thionation process for the synthesis of N-substituted thioamides using chemically stable and inexpensive thiourea reagent via the Beckmann rearrangement of ketoximes, has been described.

Key words: Beckmann rearrangement, thioamides, tosyl chloride, ketoximes

Thioamides, serving as versatile synthetic precursors for the preparation of biologically valuable five- and six-membered S-containing heterocycles,[1,2] especially the thiazolines and thiazoles,[1a] have been extensively employed in the field of organic[1] and medicinal[2] chemistry. As a consequence, many efforts have been made to develop versatile, highly efficient and environmentally benign synthetic procedures, which can be classified into two main strategies. The first one is the thionation of corresponding amides using electrophilic reagents, such as Lawesson reagent,[3] P_4S_{10}[4] and $PSCl_3$[5] etc. The second method is the reaction of activated amides or nitriles with nucleophilic thionation reagents, such as $(TMS)_2S$[6] and $(NH_4)_2S$.[7] Recently, Pathak et. al reported a new and highly efficient synthesis of N-substituted thioamides from ketoximes via $PSCl_3$-mediated Beckmann rearrangement pathway.[8] In this procedure, $PSCl_3$ not only was used to induce the Beckmann rearrangement, but also served as a nucleophile to capture in situ formed reactive iminocarbocation intermediate. However, $PSCl_3$ is a fuming, corrosive and moisture-sensitive reagent with a pungent odor, which makes this procedure neither operational nor environmentally benign. Nevertheless, it provided us with a new idea for the construction of thioamides.

Over the past several years, we have enjoyed continued success in the field of Beckmann rearrangement of ketoximes. We found that a variety of reagents can promote the Beckmann rearrangement smoothly in catalytic amount, such as BOPCl,[9] tetraaminophthalocyanine (TAPC),[10] TsCl[11] and $AlCl_3$.[12] Recently, we developed a highly efficient MsCl-mediated one-pot procedure for the synthesis of *N*-imidoylbenzotriazoles via the Beckmann rearrangement of corresponding ketoximes.[13] In that procedure, MsCl firstly reacts with ketoximes to form oxime sulfonates, which then generate the reactive iminocarbocation intermediates via the well-known Beckmann rearrangement pathway. The nucleophilic attack to the iminocarbocation by benzotriazole (BtH) affords the *N*-imidoylbenzotriazoles (Scheme 1). In order to further extend the scope of this process, we then envisaged that the use of a stable, odorless and environment friendly thionation reagent instead of BtH would ideally provide us a straightforward and environmentally benign process for the synthesis of thioamides. As aforementioned, commonly used thio sources often suffer from the unpleasant odor, and instability in some cases. Thiourea is a chemically stable, odorless and inexpensive reagent, which could be the ideal candidate as thionation reagent. To our best knowledge, there is not a single report on the thionation using thiourea for the synthesis of thioamides to date.[14] Herein, we present our preliminary result on odorless one-pot thionation process using thiourea reagent for the synthesis of a variety of N-substituted thioamides via the Beckmann rearrangement of ketoximes.



Scheme 1 The one-pot synthesis of *N*-imidoylbenzotriazoles

Initially, acetophenone oxime (**1a**) was chosen as the substrate of model reaction and several common solvents such as THF, dioxane and MeCN were tested in the presence of Et_3N and MsCl, respectively. In view of the commercial availability and chemical stability, TsCl was also used for the optimization of reaction condition. To our delight, as expected, the reaction proceeded smoothly and generated the desired N-substituted thioamide, and the optimal result was obtained in the presence of TsCl and in MeCN to afford thioamide **2a** in 90% yield (Table 1, entry 4).

Having established the optimized reaction condition, we then examined the generality and scope of substrates by using arylalkyl ketoximes **1a**–**h**, diaryl ketoxime **1i**, dialkyl ketoximes **1j**–**m** and cycloketoximes **1n** and **1o**. As shown in Table 2, most of the arylalkyl ketoximes (**1a**–**g**)

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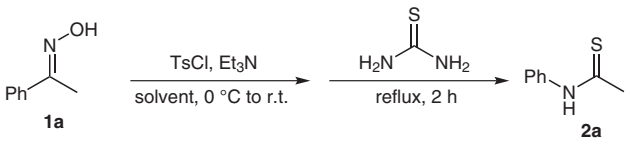
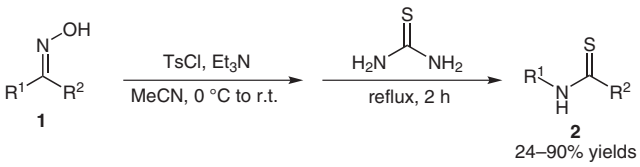
Table 1 Screening of Solvents for Model Reaction[a]



Entry	Solvent	Yield (%)[b]
1	THF	57 (60)
2	dioxane	64 (36)
3	toluene	46 (38)
4	MeCN	90 (75)
5	CH_2Cl_2	53

[a] Reaction conditions: (i) ketoxime (1.0 equiv), Et_3N (2.2 equiv), TsCl (1.1 equiv), solvent (5 mL), ice bath, then r.t. for 30 min; (ii) thiourea (2.0 equiv), reflux for 2 h.
[b] Yields in parentheses were obtained when MsCl was used instead of TsCl.

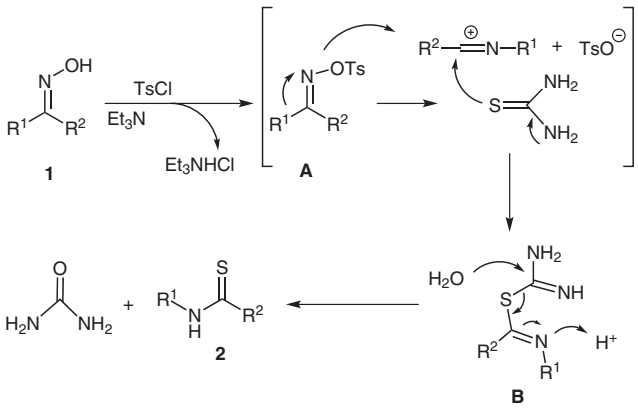
Table 2 One-Pot Synthesis of N-Substituted Thioamides



Product	R^1	R^2	Yield (%)
2a	Ph	Me	90
2b	Ph	Et	82
2c	4-MeC_6H_4	Me	88
2d	4-$MeOC_6H_4$	Me	78
2e	2-$MeOC_6H_4$	Me	87
2f	3-$MeOC_6H_4$	Me	89
2g	4-ClC_6H_4	Me	85
2h	4-$NO_2C_6H_4$	Me	38
2i	Ph	Ph	71
2j	Me	Me	24
2k	Bn	Bn	45
2l	$C(CH_3)_3$	Me	48
2m	cyclopropyl	cyclopropyl	76
2n	$(CH_2)_{11}$		35
2o	$(CH_2)_5$		69

gave the corresponding thioamides in good to excellent yields regardless the electronic effect of substituents on aromatic ring. Interestingly, 1-(4-nitrophenyl)ethanone oxime (**1h**) was not very ideal and afforded the corresponding thioamide **2h** in a relatively low yield. The benzophenone oxime (**1i**) also reacted smoothly to afford product **2i** in 71% yield. Dialkyl ketoximes **1j–l** were found to be less effective to give the corresponding thioamides **2i–l** in low to moderate yields (24–48%). Interestingly, when dicyclopropyl ketoxime was used for this reaction, the corresponding thioamide **2m** was obtained in a good yield (76%). For cycloketoximes, cyclohexanone oxime (**1o**) gave a higher yield of the corresponding product than cyclododecanone oxime (**1n**), which may be attributed to the size of the ring.

Based on the aforementioned assumption, as depicted in Scheme 2, we propose that the formation of oxime sulfonates **A** takes place in situ by reaction of the oximes **1** with sulfonyl chloride in the presence of base, followed by smooth Beckmann rearrangement of oxime sulfonate **A** to form the iminocarbocation species, which is subjected to simultaneous nucleophilic attack by thiourea to generate the intermediate **B**. The hydrolysis of **B** finally forms the N-substituted thioamides **2** accompanied by the formation of urea.



Scheme 2 Proposed reaction pathway

In conclusion, we have developed a facile, odorless and practical synthetic method[15] to produce N-substituted thioamides in 24–90% yield in a one-pot process from the corresponding ketoximes using the chemically stable, inexpensive thiourea reagent. Further studies focusing on the application of this process to the synthesis of biologically important products and synthetically useful intermediates are in progress in our laboratory.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(15) **General Procedure for the Synthesis of Thioamides**: To a solution of the ketoxime (2 mmol) and Et_3N (0.62 mL, 4.4 mmol) in anhyd MeCN (5 mL) under a nitrogen atmosphere was added TsCl (2.2 mmol) in an ice bath. After stirring at r.t. for 30 min, thiourea (4 mmol) was added and the resulting mixture was then refluxed for 2 h. After the reaction was finished (monitored by TLC), it was quenched by brine. The organic layer was extracted with CH_2Cl_2, and dried over anhyd Na_2SO_4. After evaporation of the organic layer under reduced pressure, the resulting crude product was purified by column chromatography on silica gel to give the corresponding thioamides in moderate to high yields. All products gave satisfactory analytical data and are consistent with published data.[8] The data for selected compound **2a**: mp 75–76 °C (lit.[8] 75–76 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.51 (br s, 1 H), 8.71 (br s, 1.2 H), 7.67 (d, *J* = 7.7 Hz, 2.4 H), 7.48–7.33 (m, 5.5 H), 7.29 (d, *J* = 7.4 Hz, 1 H), 7.18 (d, *J* = 7.6 Hz, 2 H), 2.75 (s, 3.6 H), 2.52 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.0, 200.7, 138.6, 137.9, 129.7, 128.9, 128.1, 127.1, 125.1, 124.3, 35.4, 30.3.