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A convenient method for the synthesis of substituted thioureas

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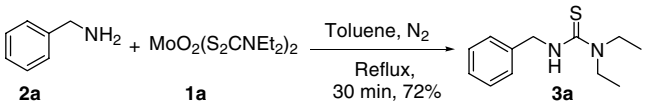
Abstract—A convenient method for the synthesis of substituted thioureas by the reaction of primary amines with molybdenum dialkyl dithiocarbamates has been developed. Primary amines on reaction with 0.5 equiv of molybdenum xanthate produce the corresponding thioureas in moderate to good yields in short times. Similar reactions with propargylamine or 2-aminoethanol produce cyclic thiaoxazolidine and oxazolidine derivatives, respectively.

Metal-oxo compounds are widely studied in organic chemistry in a number of oxo-transfer processes.[1] In particular, molybdenum(VI) oxocomplexes are the subject of significant interest due to their functional and structural similarities with several molybdo-enzymes.[2] As part of our investigation on the utility of $MoO_2(S_2CNEt_2)_2$ **(1a)**,[3] we initiated a research program to exploit the redox properties of Mo(VI) complexes in organic synthesis. Although Mo(VI) reagents are well known to transfer oxygen to a variety of substrates,[1] they are not useful in transferring oxygen to amines. However, there are many Mo(VI) reagents, which can oxidize amines in the presence of H_2O_2.[4] The Mo(IV) analogue of **1a** is known to abstract oxygen from a variety of oxides including *N*-oxides.[5] In this context, we decided to investigate the reaction of reagent **1a** with amines. In order to test the possibility of oxygen transfer from **1a** to amines, reagent **1a** was reacted with benzylamine at room temperature for a prolonged time, however, the starting amine remained intact. In subsequent experiments we discovered that the same reaction, under refluxing conditions, resulted in the disappearance of the starting material. Analysis revealed that the product was the corresponding thiourea **3a**[6,7a] (Scheme 1).



Scheme 1.

The reaction clearly took a different course than expected, that is, transfer of sulfur and nitrogen to the substrate,[7] to produce the corresponding unsymmetrical thiourea derivative.[8] Herein, we present our results on the reaction of **1a** with a variety of primary amines to produce the corresponding unsymmetrical thioureas.

Thiourea and its derivatives are biologically important compounds and are useful fungicides, herbicides,[9] and antibacterial agents.[10] They have also found use in organocatalysis.[11] There are several reports on the synthesis of thioureas, which include many hazardous and toxic procedures.[12] For example, thioureas have been synthesized by the reaction of primary and secondary amines with thiophosgene and isothiocyanates,[13] which are hazardous protocols. Therefore, safer, non-toxic, and user-friendly procedures to synthesize thioureas are still required.[14]

In continuation of our research on the oxygen transfer ability of molybdenum xanthate **1a**, we were interested in the reaction of amines with **1a**. In an initial experiment, benzylamine and **1a** in toluene were heated at reflux. The starting material disappeared after 30 min and analysis of the product revealed it to be the corresponding thiourea **3a**.[6,7a] Optimization of the reaction conditions revealed that 0.5 equiv of **1a** were sufficient to bring about the above transformation affording the corresponding thiourea **3a** in good yield (72%) in 30 min.[15–17] The above reaction appears to be general as can be seen from Table 1. α-Methylbenzylamine on treatment with **1a** produced the corresponding thiourea **3b** (68%, 30 min). Similarly, *p*-methoxybenzylamine

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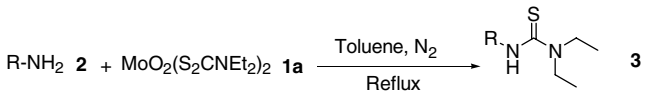
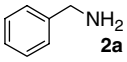
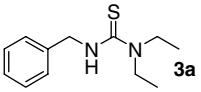
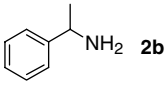
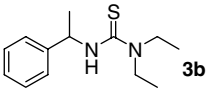
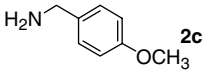
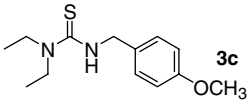
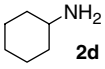
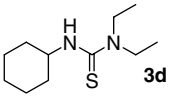
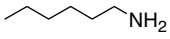
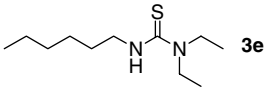
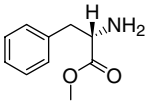
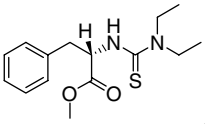
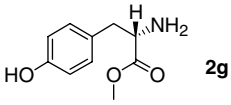
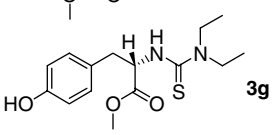
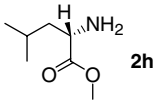
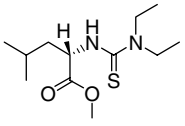
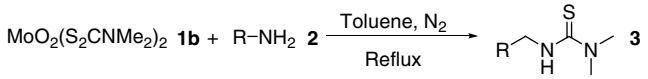
Table 1.

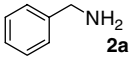
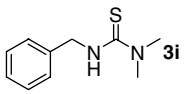
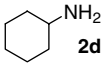
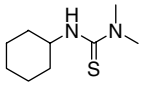
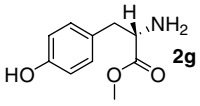
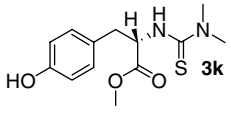


Entry	Substrate	Time	Product	Yield[a] (%)
1	 **2a**	30 min	 **3a**	72
2	 **2b**	30 min	 **3b**	68
3	 **2c**	50 min	 **3c**	70
4	 **2d**	35 min	 **3d**	66
5	 **2e**	40 min	 **3e**	85
6	 **2f**	3 h	 **3f**	51
7	 **2g**	3 h	 **3g**	52
8	 **2h**	3.5 h	 **3h**	58

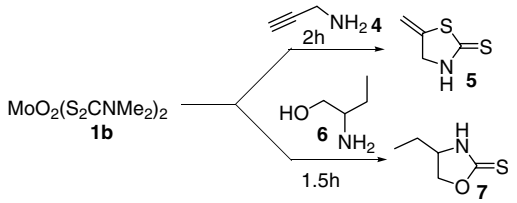
[a] Isolated yields.

Table 2.



Entry	Substrate	Time	Product	Yield[a] (%)
1	 **2a**	30 min	 **3i**	62
2	 **2d**	35 min	 **3j**	54
3	 **2g**	3 h	 **3k**	51

[a] Isolated yield.



Scheme 2.

2c produced the corresponding thiourea **3c** in good yield (70%, 50 min). Cyclohexylamine (**2d**) and *n*-hexylamine (**2e**) furnished the corresponding thioureas **3d** and **3e**[17] in 66% and 85% yields, respectively. Thiourea derivatives of amino acids are important as they can be used as organocatalysts.[11] Therefore, we subjected the methyl esters of L-phenylalanine, L-tyrosine, and L-leucine (**2f**, **2g**, and **2h**, respectively) to similar reactions with **1a**. The corresponding thiourea derivatives **3f**, **3g**, and **3h** were formed in moderate yields (51–58%). Similarly, Mo–xanthate **1b**, the methyl analogue of reagent **1a**, also produced similar results. Examples are provided in Table 2. Benzylamine, cyclohexylamine, and the methyl ester of L-phenylalanine (**2a**, **2d**, and **2g**) produced thioureas **3i**, **3j**, and **3k**,[17] respectively, in moderate yields (62%, 54%, and 51%) on reaction with **1b**. However, reaction of *p*-bromoaniline or triethylamine with reagent **1a** or **1b** failed to furnish the corresponding thioureas under similar reaction conditions.

Interestingly, when propargylamine **4** was reacted with **1b**, the cyclic thiazolidine derivative, 5-methylenethiazolidine-2-thione **5** was obtained in 48% yield.[18a] Similarly, the reaction of 2-aminobutanol **6** resulted in the formation of the oxozolidine derivative, 4-ethyloxazolidine-2-thione **7** in 52% yield[18b] (Scheme 2).

In conclusion, we have developed a mild method for the synthesis of thiourea derivatives using molybdenum xanthates **1a** and **1b**.[15] The present method also allows the synthesis of cyclic systems such as thiozolidine and oxazolidine derivatives in moderate yields.[18] Further study to determine the scope and application of this reaction with a variety of Mo–xanthates is underway in our laboratories.

Acknowledgments

We are grateful to IISc for the financial support for the above work. Our thanks are due to Prof. S. Chandrasekaran for the facilities, useful discussions and encouragement.

Supplementary data

Supplementary data (The spectral data, and ^{1}H and ^{13}C spectra of **3b**, **3c**, **3d**, **3f**, **3g**, **3h**, **3i**, **3j**, **5**, and **7**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.212.

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15. *Typical experimental procedure*: To a well-stirred solution of **2a** (50 mg, 0.466 mmol) in toluene (4 mL) was added **1a** (99 mg, 0.233 mmol) and the solution was refluxed for 30 min. The solvent was evaporated, and the crude reaction mixture was purified by column chromatography (silica gel, 1:9 EtOAc and petroleum ether) to provide product **3a** (74 mg, 72%) as a pale yellow viscous liquid.[16]
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17. *Spectral data of selected compounds*: Compound (**3a**):[16] Pale yellow viscous liquid; IR (neat, cm^{-1}): 1532, 2974, 3313; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.22 (t, $J = 7.2$ Hz, 6H), 3.67 (q, $J = 7.2$ Hz, 4H), 4.87 (d, $J = 5$ Hz, 2H), 5.56 (br s, 1H), 7.27–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.64, 45.11, 50.15, 127.51, 127.80, 128.69, 138.20, 180.28; HR-MS (*m*/*z*): Calculated for $C_{12}H_{18}N_2S$ (M+H): 223.1269, observed (M+H): 223.1261. Compound (**3e**): Pale yellow viscous liquid; IR (neat, cm^{-1}): 1531, 2958, 3321; ^1H NMR ($CDCl_3$, 400 MHz): δ0.89 (t, $J = 6.8$ Hz, 3H), 1.23 (t, $J = 7.2$ Hz, 6H), 1.25–1.40 (m, 6H), 1.55–1.65 (m, 2H), 3.60–3.70 (m, 6H), 5.30 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.66, 13.96, 22.53, 26.66, 29.34, 31.48, 44.97, 46.15, 180.19; HR-MS (*m*/*z*): Calculated for $C_{11}H_{24}N_2S$ ($M+Na^+$): 239.1558, observed ($M+Na^+$): 239.1552. Compound (**3k**): Pale yellow solid; mp: 110–114 °C, $[\alpha]_D^{25}$ +3.72 (*c* 1, $CHCl_3$), IR (KBr, cm^{-1}): 1542, 1731, 3359, 3403; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.05–3.25 (m, 8H), 3.15–3.25 (m, 7H), 3.76 (s, 3H), 5.35–5.42 (m, 1H), 5.78 (br d, 1H), 6.73 (d, $J = 8$ Hz, 2H), 6.92 (d, $J = 8$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 36.79, 52.43, 58.94, 60.53, 115.49, 127.07, 130.30, 155.21, 173.25, 180.52; HR-MS (*m*/*z*): Calculated for $C_{13}H_{18}N_2O_3S$ ($M+Na^+$): 305.0936, observed ($M+Na^+$): 305.0937.
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