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Direct Thionation and Selenation of Amides Using Elemental Sulfur and Selenium and Hydrochlorosilanes in the Presence of Amines

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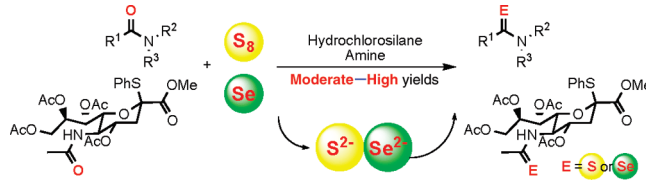
ABSTRACT



Reactions of amides with elemental sulfur in the presence of hydrochlorosilanes and amines give the corresponding thioamides in good to high yields. The process takes place via reduction of elemental sulfur by the hydrochlorosilane in the presence of a suitable amine. The methodology can be applied to the selenation of amides by using elemental selenium. Thionation and selenation of an acetyl-protected sialic acid derivative are found to take place selectively at the amide group.

The thiocarbonyl group plays an important role in organic synthesis because of its unique chemical behavior and specific reactivity profile.[1−3] One method for the synthesis of thiocarbonyl compounds[4] is through thionation reactions of carbonyl precursors by using a preformed S^{2-} generating species, such as hydrogen sulfide[5a] or its salts,[5b] silathianes,[5c] and phosphorus sulfides.[6] However, handling of these reagents is particularly cumbersome because of odor, toxicity, and stability issues, and/or the concurrent formation of inseparable byproduct.[6] In addition, pretreatment of the carbonyl group is often required.[4,5] As a consequence of these

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(4) For reviews on the synthesis of thiocarbonyl compounds, see: (a) Lebel, H. *Sci. Synth.* **2005**, *22*, 141. (b) Ishii, A.; Nakayama, J. In *Topics in Current Chemistry*; Springer: Berlin/Heidelberg, 2005; Vol. 251, pp 181−225. (c) Murai, T. In *Topics in Current Chemistry*; Springer: Berlin/Heidelberg, 2005; Vol. 251, pp 247−272. (d) Polshettiwar, V.; Kaushik, M. P. *J. Sulfur. Chem.* **2006**, *27*, 353, and references cited therein.

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(6) For reviews on thionation reactions using phosphorous sulfide derivatives and Lawesson's reagent, see: (a) Jesberger, M.; Davis, T. P.; Barner, L. *Synthesis* **2003**, 1929. (b) Ozturk, T.; Ertas, E.; Mert, O. *Chem. Rev.* **2007**, *107*, 5210. Also see: (c) Curphey, T. J. *J. Org. Chem.* **2002**, *67*, 6461. (d) Pathak, U.; Pandey, L. K.; Tank, R. *J. Org. Chem.* **2008**, *73*, 2890.

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shortcomings, a new methodology for direct thionation of carbonyl compounds, which relies on reaction of in situ generated S^{2-}, produced from easy-to-handle elemental sulfur and an appropriate reducing agent, would be especially attractive.[7] The choice of a reducing agent that can selectively reduce elemental sulfur in the presence of carbonyl compounds is essential for the design of this new methodology. Below, we describe the results of a study that has led to the development of a direct carbonyl thionation process involving in situ generation S^{2-} by reaction of elemental sulfur with hydrochlorosilanes in the presence of amines. Also, the methodology has been extended to selenations of amides using elemental selenium.[8]

Hydrosilanes are frequently used as reducing agents, but they are observed to react only sluggishly with carbonyl compounds in the absence of suitable additives.[9] Owing to this property, hydrosilanes were envisaged as likely reductants for elemental sulfur. Since the high oxophilicity of silicon in chlorosilanes could potentially facilitate elimination of oxygen from the carbonyl group, hydrochlorosilanes were identified as ideal reducing agent in an elemental sulfur based carbonyl thionation process (Figure 1).

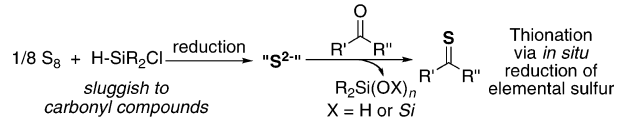
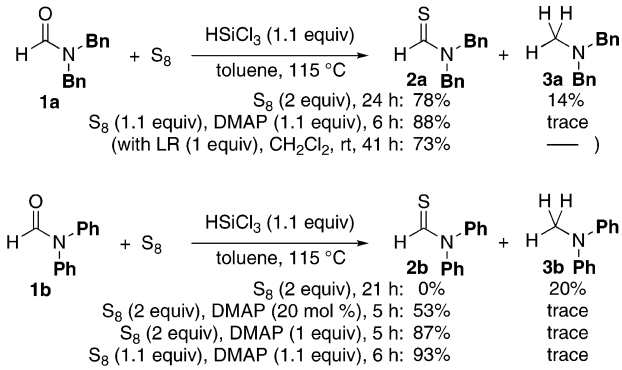


Figure 1. An approach for direct thionation of carbonyl compounds by elemental sulfur using hydrochlorosilane as a reductant.

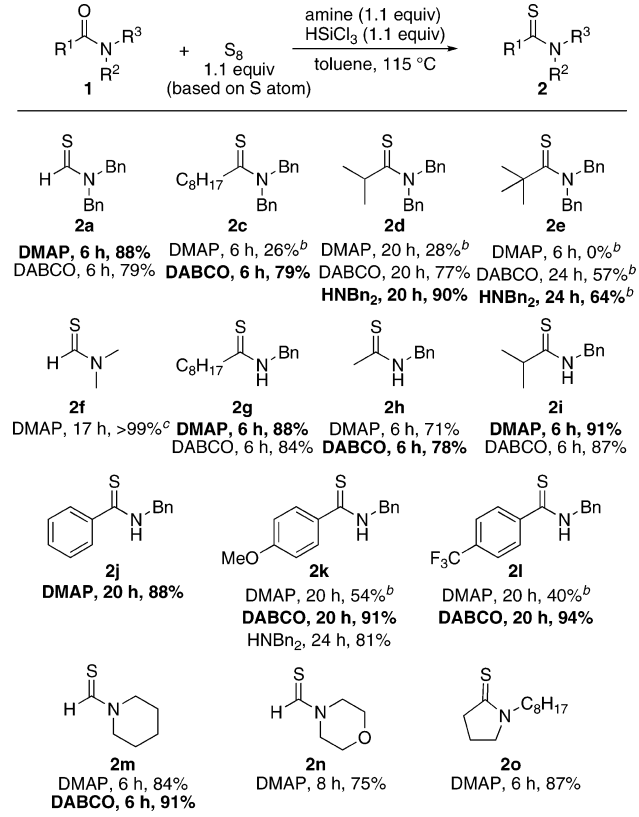
To evaluate this proposal, reaction of *N*,*N*-dibenzylformamide (**1a**) with 2 equiv of S_8 in the presence of 1.1 equiv of $HSiCl_3$ at 115 °C in toluene was carried out. Importantly, the corresponding thioformamide **2a** was generated in 78% yield along with the byproduct dibenzylmethylamine (**3a**), derived by reduction of **1a** (Scheme 1).[10] Under the $HSiCl_3$/S_8 condition *N*,*N*-diphenylformamide (**1b**) does not react to produce the thioamide product **2b**. Rather, methyldiphenylamine (**3b**) was generated as the sole product along with recovered **1b**. We hypothesized that, owing to their nucleophilicity and/or basicity, the amines formed by carbonyl reduction might play an important role in the thionation process. In fact, when DMAP (4-dimethylaminopyridine) is employed as an additive in the $HSiCl_3$/S_8 promoted thionation reaction of **1b**, thioamide **2b** is produced in a modestly high yield. In addition, the yields for production of thioamides **2a** and **2b** from the respective amides **1a** and **1b** are enhanced (88% and 93%, respectively) when a reduced amount of S_8 (1.1 equiv) is used and the reactions are run in the presence of DMAP (1.1 equiv). Thionation of **1a** with Lawesson's reagent (LR) also proceeded smoothly, but the isolation of the product **2a** by column chromatography resulted in the contamination of the byproducts. Further purification of the mixture gave **2a** in a lower isolated yield.[11]

With the optimized conditions in hand, the scope of thionation reactions of amides was explored (Scheme 2). The observations made in this effort show that amines other than DMAP (e.g., DABCO (1,4-diazabicyclo[2.2.2]octane) and dibenzylamine) serve to promote efficient thionation reactions. For example, the sterically hindered amides **1c**−**1e** do not undergo thionation reactions when DMAP is used.

Scheme 1. Optimization of Reaction Conditions



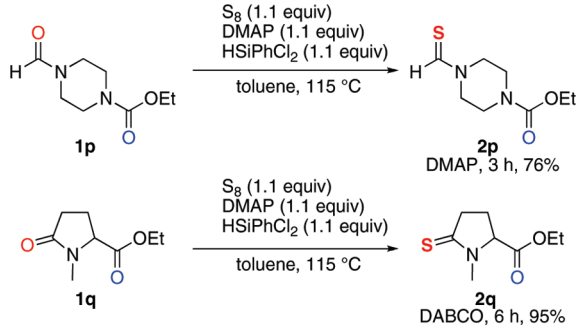
Scheme 2. Scope of Amides[a]



[a] Reaction conditions: mixtures of the amide or lactam (1 mmol), S_8, amine, and $HSiCl_3$ (1.1 equiv each) in toluene in a sealed tube under air were heated at 115 °C. [b] A major portion of the recovered material was the starting amide. [c] The yield for a 20 mmol scale reaction for a 24 h period was 80%.

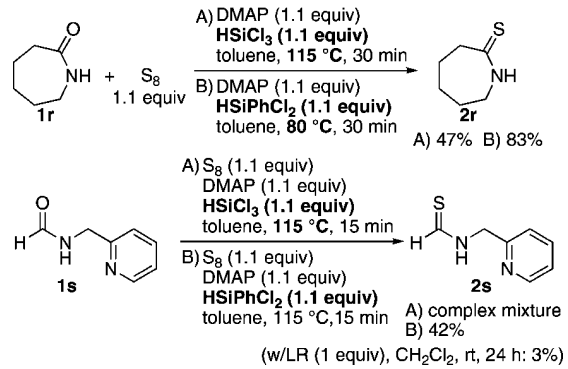
In contrast, these substances participate in efficient (79%, 90%, and 64%, respectively) thionation reactions that are promoted by DABCO or dibenzylamine. DMF (**1f**) reacts on a small scale in the presence of DMAP to yield the thioamide **2f** quantitatively and on a multigram scale without a significant loss of efficiency (80% isolated yield). Thionation reactions of secondary amides **1g**−**1l** proceed smoothly in the presence of either DMAP or DABCO to give thioamides **2f**−**2l** in high yields. The presence of electron-donating and electron-withdrawing substituents on the aromatic rings of the benzamides **1k** and **1l** does not influence the efficiency of the reaction. The piperidine and morpholine derived amides **1m** and **1n** also react to generate thionated products in good to excellent yields. In addition, the tertiary lactam **1o** is converted to the corresponding thiolactam **2o** in high efficiency under the thionation reaction conditions. Importantly, amide **1p** and lactam **1q**, which contain remote alkoxycarbonyl groups, undergo selective thionation reactions at the amide groups, yielding **2p** and **2q** in respective yields of 76% and 95% (Scheme 3). As a likely result of the

Scheme 3. Chemoselectivity of Thionation



instability of the starting amide and product thioamide, reaction of the secondary lactam **1r** under the standard

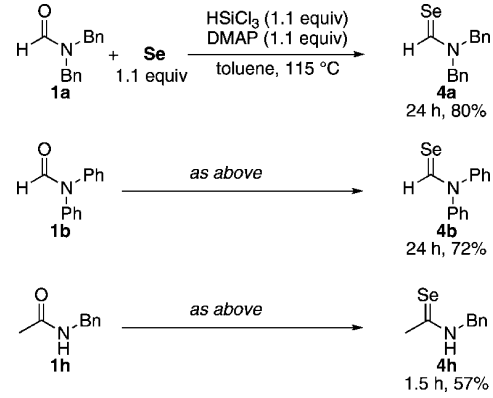
Scheme 4. Thionations with the Other Hydrochlorosilane as a Reductant



conditions gives rise to formation of a complex product mixture (Scheme 4, condition A). In contrast, the use of $HSiPhCl_2$ and a lower reaction temperature (condition B) enables efficient (83%) conversion of this substance to the thiolactam **2r**. The reaction of *N*-2-pyridylmethylformamide (**1s**) under standard conditions (condition A) also gives a complex mixture. In contrast, application of condition B to **1s** also affords the thioamide **2s** in 42% yield. The use of LR for the thionation of **1s** results in the formation of a mixture of **2s** and phosphorus-containing inseparable byproducts derived from LR.[11]

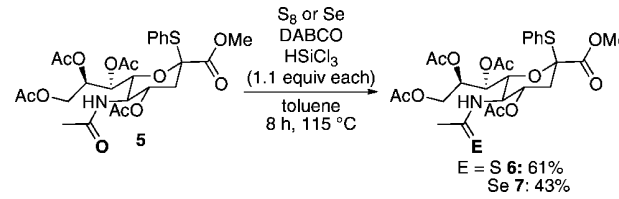
The procedure described above was applied to selenation reactions of amides **1a**, **1b**, and **1h**. Significantly, reaction of amides with elemental selenium (1.1 equiv) in the presence of $HSiCl_3$ and DMAP (1.1 equiv each) at 115 °C affords the corresponding selenoamides **4a**, **4b**, and **4h** efficiently, although the labile products partly decompose under the workup conditions (Scheme 5).

Scheme 5. Direct Selenations of Carbonyl Compounds by Elemental Selenium Using Hydrochlorosilane



To demonstrate the preparative potential of the new thionation and selenation reactions, the methodologies were applied to the structurally and functionally more complex acetyl protected sialic acid derivative **5**. Interestingly, thionation and selenation reactions of **5**, a substrate that contains a number of different carbonyl groups, take place selectively at the amide moiety to give the corresponding products **6** and **7** in moderate yields (Scheme 6). Notably, the other

Scheme 6. Thionation and Selenation of Acetyl Protected Sialic Acid Derivative



carbonyl functional groups in **5** remain intact under the reaction conditions, and most of unreacted **5** is recovered

(some decomposition of the substrate and product are observed to take place after prolonged reaction times).

In conclusion, the investigations described above have led to the development of a new methodology for direct thionation and selenation reactions of amides that employs elemental sulfur and selenium, a hydrosilane, and an amine. In the reaction pathways, elemental sulfur or selenium is reduced in situ to generate S^{2-} or Se^{2-}, which then undergo efficient thionation and selenation reactions with the amides. In addition, the results of the effort show that the reaction efficiency can be improved by simply changing the combination of readily available hydrosilane and amine used. Finally, alkoxycarbonyl groups remain intact under the reaction conditions used to transform amides to the corresponding thioamides. The observations made in this effort suggest that this methodology will have wide preparative applicability.

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Supporting Information Available: Experimental details, characterization data, and copies of ^{1}H and ^{13}C NMR for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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