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Efficient and Selective Multicomponent Oxidative Coupling of Two Different Aliphatic Primary Amines into Thioamides by Elemental Sulfur

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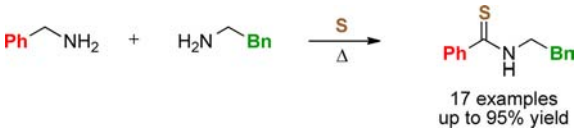
ABSTRACT



An efficient and selective multicomponent oxidative coupling of two different aliphatic primary amines into thioamides by elemental sulfur under solvent-free conditions has been developed.

Simple and effective reactions including multicomponent coupling processes using readily available reagents are seen as a key solution for the 21st century pollution problems generated by large scale chemistry. With this vision, the use of elemental sulfur in organic syntheses appears to be highly desirable to maximize atom economy and to avoid expensive complex catalysts. For this purpose, we have selected the study of the synthesis of thioamides by a coupling reaction between two amines. Molecules containing a thioamide[1] moiety play an important role in chemistry. Thioamide functions are also present in a variety of biologically active molecules.[2] They are also known as building blocks in the synthesis of heterocycles and other compounds containing both nitrogen and sulfur within their backbones.[3]

Different synthetic methods have been discovered for the synthesis of thioamides. Among these strategies, thionation of amide analogues with Lawesson's reagent is the most common,[4] but this reaction cannot been classified as an atom economical approach because of crucial limitations: only one oxygen atom is replaced by a sulfur atom, and no other new bond was created. Thus, it is worthwhile to provide a practical and environmentally benign method to synthesize thioamides. Because sulfur is nontoxic, stable under ambient conditions, easy to handle, and readily available, its use in the preparation of thioamides is highly desireable as exemplified by the Willgerodt–Kindler reaction, starting from aryl alkyl ketones, elemental sulfur, and secondary amines such as morpholine.[5]

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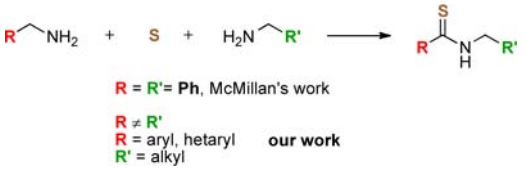
The interaction of sulfur with amines has been the subject of several studies.[6−8] McMillan observed the formation of *N*-benzylthiobenzamide when benzylamine and sulfur were heated together which is, to our knowledge, the only example of such a transformation.[7] In the same report, the reaction has also been applied for an equimolar mixture of benzylamine and morpholine and resulted in a low yield of the corresponding *N*-(thiobenzoy1) morpholine (40.6%). No information concerning the composition of the reaction mixture has been collected. To our knowledge, such a reaction with **two different aliphatic primary amines** has never been disclosed. In this paper, we wish to report a new synthetic approach to thioamide via a sulfur-mediated selective thionation−coupling reaction starting from two different amines (Scheme 1).

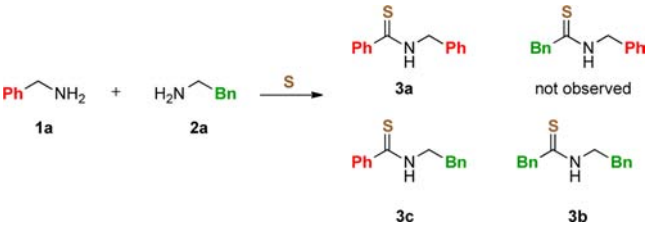
Scheme 1. Thionation−Coupling Reaction of Two Amines



The reaction of sulfur with two different aliphatic primary amines (benzylamine **1a** and 2-phenethylamine **2a**, for instance), in principle, can afford four possible thioamides (Table 1).

Such a reaction that is capable of providing a single cross-coupled thioamide selectively from two amines is highly desireable. To evaluate the potential of elemental sulfur as a thionation−coupling reagent, the homocoupling reaction conditions of McMillan were reproduced by heating benzylamine **1a** with an equimolar amount of sulfur at reflux (190 °C, 1 h) (Table 1, entry 1). Since full conversion of **1a** into *N*-benzylthiobenzamide **3a** was achieved rapidly (less than 1 h), we decided to lower the reaction temperature. At 110 °C, high conversion in **3a** (>98%) was obtained after 16 h (entry 2; compare with entry 3). The same reaction was next investigated for 2-phenethylamine **2a** and required a higher temperature (150 °C) to afford a comparable high conversion (>98%) of homocoupled thioamide (entry 4). Lowering the temperature to 130 °C resulted in incomplete conversion of **3b** (40%, entry 5). We decided to use an equimolar mixture of **1a** and **2a** for reaction at 130 °C (entry 6). In this case, the ^{1}H NMR spectrum of the crude mixture displayed the presence of both homocoupled thioamides **3a** and **3b**, only one heterocoupled thioamide **3c**, a small quantity of **2a** (~5%), and only a trace of **1a**. Interestingly, the percentage of heterocoupled thioamide **3c** is very high (92% of thioamides). Because **3c** can be yielded by the reaction of **2a** and **3a** (vide infra), an appropriate additional quantity of **2a** would help increase the conversion into **3c** and at the same time lower the amount of **3a**. To our delight, adding just 20% of **2a** to the reaction mixture substantially increased the conversion of **3a** (entry 7). However, adding more **2a** favored the formation of **3b** (entry 8).

Table 1. Reaction Conditions Screening[a]



entry[a]	**1a** (mmol)	**2a** (mmol)	temp (°C)	conversion (%)[b]	**3a:3b:3c**
1[e]	5	0	190	100[c]	100:0:0
2	5	0	110	>98[c]	100:0:0
3	5	0	100	80[c]	100:0:0
4	0	5	150	>98[d]	0:100:0
5	0	5	130	60[d]	0:100:0
6	5	5	130	>98[c]	13:3:86
7	**5**	**6**	**130**	**>98[c] (87)[f]**	**5:3:92**
8	5	7.5	130	>98[c]	4:6:90

[a] Conditions: sulfur (7.5 mmol for entries 1−5 or 15 mmol for entries 6−8, 32.1 g/mol), 16 h unless otherwise stated. [b] Based on ^{1}H NMR. [c] Based on the consumption of **1a**. [d] Based on the consumption of **2a**. [e] Reaction time 1 h. [f] 87% Isolated yield of **3c**.

In subsequent studies, we applied the optimized conditions to investigate the generality of this reaction and to demonstrate its synthetic utility (Table 2). With *N*-methylbenzylamine **1b** (entry 1), **3c** was obtained in high yield. In this reaction, no product resulting from the homocoupling of **1b** could be observed. Moreover, *N*-methylthiobenzamide was the only observable intermediate of the reaction. With *N*,*N*-dimethylbenzylamine **1c** (entry 2), because the formation of homocoupling of **1c** is not possible, the only intermediate of the reaction *N*,*N*-dimethylthiobenzamide can react exclusively with **2a** to yield **3c**. When dibenzylamine **1d** (0.5 equiv, entry 3) or tribenzylamine **1e** (0.33 equiv, entry 4) was used with **2a**, all benzyl groups of **1d**−**e** are successively transformed into the thiobenzoyl moiety of the final thioamide **3c**. Other functional benzylamines (**1f**−**g**) and 3- and 4- picolinamines (**1h**−**i**) could also be used as the **amine 1** component in this reaction without any incidents. Different substrates could be used as the **amine 2** component, including functionalized amine (**2b**), simple aliphatic amines (*n*-octylamine and *n*-hexylamine **2c**−**d**), alicyclic amine (**2e**), and secondary amine (morpholine **2f**).

To our delight, 4-picolinamine is more prone to oxidation, allowing the reaction to occur at lower temperature (entries 8−12). Interestingly, 1-phenethylamine **1j** could also be successfully employed in place of the benzylamine, leading to phenylthioacetamides **3b** and **3m** in moderate to high yields. Obviously, in these two cases, the transformation

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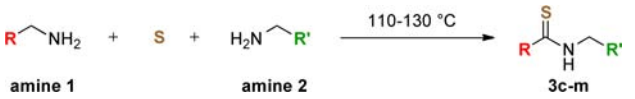
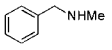
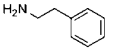
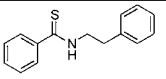
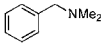
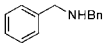
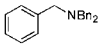
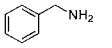
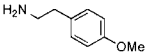
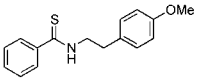
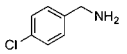
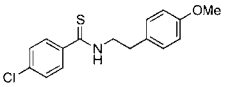
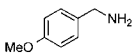
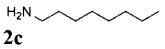
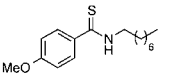
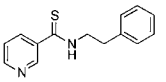
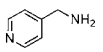
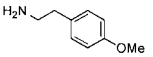
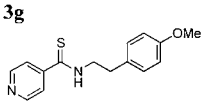
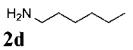
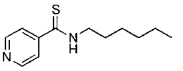
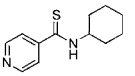
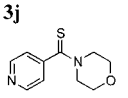
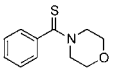
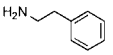
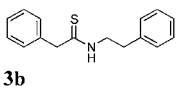
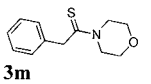
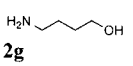
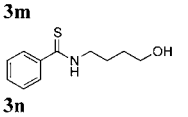
(8) For a mechanistic study of the room temperature reaction of sulfur with benzylamine, see:Sasaki, Y.; Olsen, F. P. *Can. J. Chem.* **1971**, *49*, 283.

Table 2. Conversion of Two Different Amines into *N*-Substituted Thioamides[a]



entry	amine 1	amine 2	temp (°C)	time (h)	product	yield (%)[b]
1	 **1b**	 **2a**	130	24	 **3c**	90
2	 **1c**	**2a**	130	24	**3c**	95
3	 **1d**[c]	**2a**	130	24	**3c**	87
4	 **1e**[d]	**2a**	130	24	**3c**	80
5	 **1a**	 **2b**	130	16	 **3d**	88
6	 **1f**	**2b**	130	24	 **3e**	85
7	 **1g**	 **2c**	130	24	 **3f**	88
8	 **1h**	**2a**	130	24	 **3g**	90
9	 **1i**	 **2b**	110	20	 **3h**	91
10	**1i**	 **2d**	110	20	 **3i**	80
11	**1i**	 **2e**	110	24	 **3j**	85
12	**1i**	 **2f**	110	15	 **3k**	91
13	 **1a**	**2f**	130	40	 **3l**	70
14	 **1j**	 **2a**	130	16	 **3b**	93
15	**1j**	 **2f**	120	40	 **3m**	65
16	 **1a**	 **2g**	120	60	 **3n**	62

[a] Reaction conditions: **amine 1** (5 mmol), **amine 2** (6 mmol), sulfur (15 mmol). [b] Isolated yield. [c] 2.5 mmol. [d] 1.7 mmol.

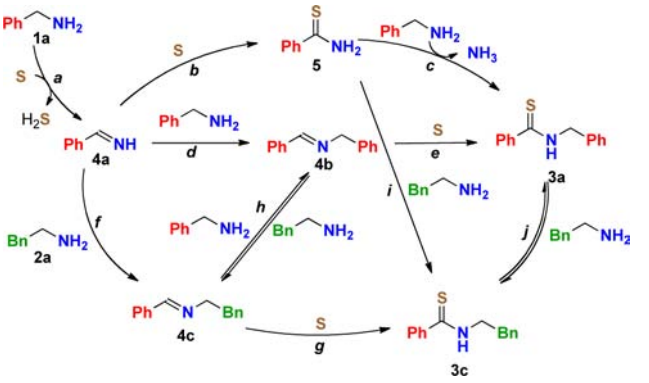
involves a Willgerodt rearrangement. Finally, the coupled product of **1a** with 4-hydroxybutylamine **2g** provides an attractive example in which the hydroxy group of **2g** remained intact during the reaction and may be useful for

further functionalization. In general, higher conversions of cross-coupled thioamide **3** were observed when the reaction mixture was heated for a longer time at appropriate temperatures which could not induce the oxidation of **amine 2** components or other side reactions.

Plausible mechanisms are described in Scheme 2. The upper part presents the mechanism when benzylamine **1a** was the only amine component.[8] The first step (step ***a***) of the reaction could be the oxidation of **1a** into benzaldimine **4a**. Imine **4a** is transformed into thiobenzamide **3a** via two possible pathways: (i) oxidation by sulfur (step ***b***) to afford thiobenzamide **5** followed by a transthioamidation (step ***c***) with benzylamine **1a**;[9] (ii) transimination[10] (step ***d***) of imine **4a** with amine **1a** to provide **4b** and subsequent oxidation (step ***e***) of **4b** by sulfur. Since the oxidation using the sulfur of imine **4a**−**b** (steps ***b*** and ***e***) is faster than that of an amine **1a** (step ***a***), the presence of imines **4a**−**b** could not be observed under our conditions. Because the transthioamidation (step ***c***) is highly favorable when ammonia is driven off on heating,[11] once generated, thiobenzamide is consumed immediately. Consequently, only **1a** and **3a** could be observed in the reaction mixture by NMR spectroscopy. The rate-determining step is therefore step ***a***. Contrary to one of the McMillan hypotheses[7] which suggested that **3a** could be obtained by condensation of two benzylamine molecules followed by oxidation, we reasoned that this condensation under gentle heating conditions is likely impossible, although reaction of dibenzylamine and sulfur can give rise to **3a**.

When 2-phenethylamine **2a** was involved in the reaction, it could react either with both imines **4a**−**b** via transimination (steps ***f*** and ***h***) or with thioamide **5** and **3a** via transthioamidation (steps ***i*** and ***j***). Due to the similar nucleophilic nature and boiling points of amines **1a** and **2a**, steps ***h*** and ***j*** might be reversible. However, the formation of **3c** in step ***j*** and **4c** in step ***h*** can be driven by continuous oxidation of the benzylamine. Since **4b** and **4c** could be oxidized further to **3a** and **3c** (steps ***e*** and ***g***), step ***j*** might be the rate-determining step. Obviously, the success of the reaction depends on the difference in reactivity of benzylamine **1a** and 2-phenethylamine **2a** in the first step of amine oxidation.

Scheme 2. Proposed Reaction Mechanism



In summary, a three-component reaction involving elemental sulfur and two different amines has been achieved for the first time and offers a straightforward and an efficient strategy for the synthesis of various thioamides. Further studies of the reaction mechanism and applications are in progress.

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Supporting Information Available. Experimental procedures, product characterization, and copies of the ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(9) In contrast to benzamide which is relatively inert to benzylamine, thiobenzamide is more labile towards a transamidation reaction. For uncatalyzed transthioamidation, see: (a) Schlatter, M. J. *J. Am. Chem. Soc.* **1942**, *64*, 2722. For selected examples of catalyzed transamidation, see: (b) Zhang, M.; Imm, S.; Bahn, Neubert, S. L.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3905. (c) Nguyen, T. B.; Sorres, J.; Tran, M. Q.; Ermolenko, L.; Al-Mourabit, A. *Org. Lett.* **2012**, *14*, 3202. (d) Hoerter, J. M.; Otte, K. M.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 5177. (e) Kissounko, D. A.; Guzei, L. A.; Gellman, S. H.; Stahl, S. S. *Organometallics* **2005**, *24*, 5208. (f) Eldred, S. E.; Stone, D. A.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2003**, *125*, 3422. (g) Stephenson, N. A.; Zhu, J.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, *131*, 10003. (h) Hoerter, J. M.; Otte, K. M.; Gellman, S. H.; Cui, Q.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 647. (i) Kissounko, D. A.; Hoerter, J. M.; Guzei, L. A.; Cui, Q.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 1776. (j) Allen, C. L.; Atkinson, B. N.; Williams, J. M. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 1383.

(10) Belowich, M. E.; Stoddart, J. F. *Chem. Soc. Rev.* **2012**, *41*, 2003.

(11) Wallach reported that the reaction in a sealed tube (without ammonia removal) at 180° C of benzylamine with sulfur gave thiobenzamide:Wallach, O. *Ann.* **1890**, *259*, 300. On the other hand, step ***c*** was not favored if *N*-methyl- was used due to steric hindrance or was not possible if *N*,*N*-dimethylbenzylamine was used.