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Three-Component Reaction between Alkynes, Elemental Sulfur, and Aliphatic Amines: A General, Straightforward, and Atom Economical Approach to Thioamides

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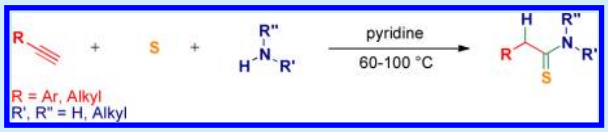
Supporting Information

ABSTRACT: A general, straightforward, and atom-economical three-component synthesis of thioamides from alkynes, elemental sulfur, and aliphatic amines has been developed.



Thioamide moieties[1] are among the most widely used functional groups in the synthesis of sulfur-containing molecules,[2] and other compounds[3] including heterocycles[4] and natural products.[5] Moreover, the thioamide group, an isosteric replacement of the amide group,[6] is present in a variety of bioactive molecules although the presence of a thioamide group is very rare in natural products.[7] Replacement of the oxygen atom by a sulfur one in the carboxamide moieties in peptides and other amide compounds has been used to modify the stability,[8] biological,[9] physical,[10] and catalytic[11] activities of the target molecules or to act as an efficient tool for monitoring structural changes in proteins.[12]

Although a wide range of preparative methods of thioamides have been developed, there is an ongoing search for new methods which should (1) be operationally simple, (2) be based on an atom-, step-, and redox-economical transformations, (3) use readily available and inexpensive starting materials, and (4) tolerate a wide range of functional groups that are generally incompatible with Lawesson's reagent and other known reaction conditions. As a consequence of our recent efforts on the development of new reactions taking advantage of the unique and interesting physicochemical properties of elemental sulfur,[13] we were eager to search for a general three-component approach to thioamides starting from amines, elemental sulfur, and alkynes (Scheme 1). Indeed, such an approach has been described at 145 °C and higher temperatures by simple heating[14] or under microwave irradiation[15] for phenylacetylene and stable secondary amines (morpholine,[14a] dimethylamine[16]) or ammonia[14a,b] and for unsubstituted acetylene and unfunctionalized simple amines to provide thioacetamides or dithiooxalodiamides[17] under un-

Scheme 1. Atom-, Step-, and Redox-Economical Approach to Thioamide

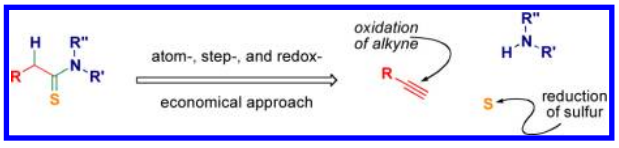
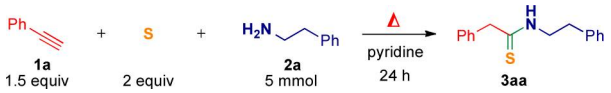


Table 1. Survey of Reaction between Phenylacetylene, Elemental Sulfur, and 2-Phenethylamine[a]



entry	catalyst	V pyridine (mL)	temp (°C)	conversion (%)[c]
1	–	0	100	>95
2	–	0	80	>95
3	–	0	60	>95
4	–	0	50	85
5	–	0.5	60	>95
6	CuCl	0.5	60	93
7	$NiCl_2$	0.5	60	90
8	$CoCl_2$	0.5	60	72
9	$MnCl_2$	0.5	60	81
10	Ag_2O[b]	0.5	60	>95
11	Ag_2O[b]	0.5	50	85

[a]Reaction conditions: 2-phenethylamine (5 mmol), sulfur (10 mmol, 320 mg), phenylacetylene (7.5 mmol), catalyst (5 mol % unless otherwise noted). [b]2.5 mol %. [c]Determined by ^{1}H NMR spectroscopy based on **2a**; >95% means no trace of **2a** was observed.

catalyzed conditions. On the other hand, lithium alkynides (generated *in situ* from the parent alkynes and *n*-BuLi) are reported to react with sulfur in refluxed diethylamine to provide the corresponding *N*,*N*-diethyl thioamides.[18] Such experimental procedures are obviously of limited scope.

At the beginning of our study, we examined the reaction between phenylacetylene, 2-phenethylamine, and elemental sulfur (Table 1).[19] To our surprise, we found, however, that this reaction always works to more or less the same extent even at temperatures as low as 60 °C in high conversion (entries 1,2 vs entry 3). The presence of pyridine even in a small quantity (0.1 mL for 1 mmol amine) results in a more homogeneous reaction mixture and cleaner conversion. The addition of simple metallic salts (CuCl, $NiCl_2$, $CoCl_2$, $MnCl_2$, Ag_2O) which

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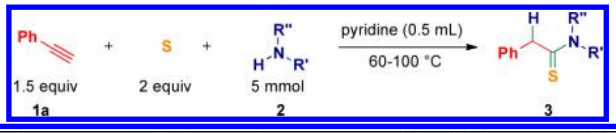
Table 2. Reaction of Phenylacetylene with Sulfur and Amines[a]

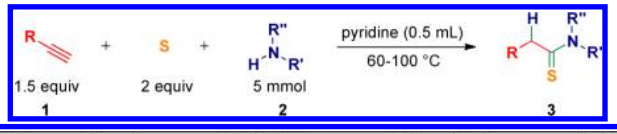


entry	amine 2	temp (°C)	thioamide 3	yield (%)
1	n = 2, **2a**	60	n = 2, **3aa**	75
2	n = 3, **2b**	60	n = 3, **3ab**	82
3	n = 4, **2c**	60	n = 4, **3ac**	86
4	**2d**	60	**3ad**	70
5	**2e**	60	**3ae**	85
6	**2f**	60	**3af**	82
7	**2g**	60	**3ag**	70
8	**2h**	60	**3ah**	73
9	**2i**	60	**3ai**	61
10	**2j**	80	**3aj**	84
11	**2k**	80	**3ak**	82
12	**2l**	60	**3al**	72
13	**2m**	60	**3am**	73
14	**2n**	60	**3an**	73
15	**2o**	60	**3ao**	81
16	**2p**	60	**3ap**	86
17	**2q**	60	**3aq**	76
18	**2r**	80	**3ar**	85
19		100		0
20		100		0

[a]Reaction conditions: amine (5 mmol), sulfur (10 mmol, 320 mg), phenylacetylene (7.5 mmol).

were known to be catalytically active in other reactions involving alkynes were shown to be detrimental (entries 6–9) or ineffective (entry 10 vs 5, entry 11 vs 4) in accelerating this transformation.

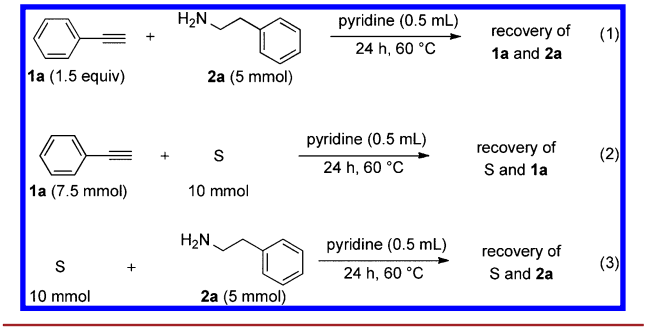
Table 3. Reaction of Alkynes with Sulfur and Amines[a]



entry	alkyne 1	amine 2	temp (°C)	thioamide 3	yield (%)
1	**1b**	**2b**	60	**3bb**	72
2	**1c**	**2b**	60	**3cb**	56
3	**1d**	**2b**	60	**3db**	75
4	**1e**	n = 2, **2a**	100	n = 2, **3ea**	71
5	**1e**	n = 4, **2c**	100	n = 4, **3ec**	67
6	**1e**	**2s**	80	**3es**	76
7	**1e**	**2t**	100	**3et**	69
8	**1f**	**2b**	100	**3fb**	72
9	**1g**	**2b**	100	**3gb**	71
10	**1g'**	**2b**	100	**3gb**	51
11	**1h**	**2c**	100	**3hc'**	72

[a]Reaction conditions: amine (5 mmol), sulfur (10 mmol, 320 mg), alkyne (7.5 mmol).

Scheme 2. Investigation of the Reaction Pathway



The optimized reaction conditions (Table 1, entry 5) were next applied to a wide range of amines (Table 2).

Different primary (entries 1–15) and secondary (entries 16–18) aliphatic amines were proven to be competent substrates and provided the corresponding thioamides in moderate to high yields. Functional groups such as aromatic halogens

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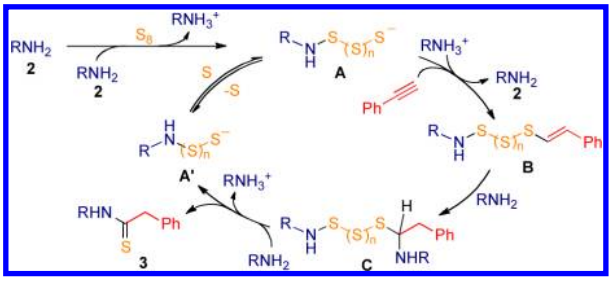
Scheme 3. Proposed Mechanism



(entries 4–5), methoxy (6–7), hydroxy (entries 12–13), tertiary amine (entry 14), and aniline (entries 8 and 15) were shown to be highly compatible with the present reaction conditions. Due to the lower reaction temperature of the present conditions compared to that of our previous work (60 °C vs 110 °C),[13a] the reaction of benzylamines **2g,h** with phenylacetylene **1a** afforded the desired *N*-benzyl thiobenzamides **3af**, **3ag** in high yields. Finally, an aliphatic alcohol such as *n*-butanol (entry 19) and aniline (entry 20) were totally inactive under these conditions.

The scope of alkyne was shown in Table 3. While phenylacetylene derivatives (entries 1–3) displayed a comparably high reactivity, reactions with aliphatic alkynes (entries 4–9) required higher temperatures (80–100 °C) than with phenylacetylene. Finally, the reactions with 3-phenylpropyne (entry 9) and 1-phenylpropyne (entry 10) provided the same terminal thioamide **3gb** as a result of the migration of the triple bond in **1g′**. This observation revealed that the reaction shared some characters with the Willgerodt rearrangement.[20] Finally, by using silylated acetylene **1h** instead of gaseous acetylene, this protocol could furnish thioacetamide **3hc′** as a result of a desilylative hydrolysis of the corresponding silylated thioamide **3hc** initially obtained during column chromatography purification on silica gel.

We next explored the reaction mechanism of the formation of thioamide **3aa** from **1a**, **2a**, and elemental S. To this end, the starting materials were heated at 60 °C for 24 h in pyridine (Scheme 2, eqs 1–3). In all cases, all starting materials were recovered unchanged. No trace of products issued from hydroamination[21] (eq 1) or thiolation[22] (eq 2) was observed. It should be noted that when 2-phenethylamine **2a** and sulfur were mixed together in pyridine (eq 3), an intensely brown solution was yielded but sulfur was crystallized out when the solution was diluted with chloroform. This intense coloration has been attributed to polysulfides resulted from the scission of S–S bonds by stepwise nucleophilic attack on S_8 rings by the aliphatic amines.[23]

Based on these elements, we tentatively proposed a mechanism which probably begins with the nucleophilic attack of amine **2** on S_8 to generate polysulfide **A** (Scheme 3). Highly nucleophilic due to the α effect of the polysulfur chain, **A** subsequently adds to the triple bond of alkyne **1a** to yield vinyl polysulfide **B**. Polarized by the presence of a sulfur substituent, the double bond of **B** is further attacked by amine **2** to provide thioaminal **C**. Finally, elimination of polysulfide **A′** from **C** leads to thioamide **3**.

In conclusion, we have reported a convenient synthesis of thioamides from a three-component reaction between alkynes, elemental sulfur, and alkylamines with a high tolerance to various functional groups. Operationally simple, the reaction with full respect to the atom-, step-, and redox-economical criteria provides a straightforward and uncatalyzed access to a wide range of thioamides. Further study and extension of the present result are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

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.

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Notes

The authors declare no competing financial interest.

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