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Thioamides via thiatriazolines

Robert V. Kolakowski, Ning Shangguan and Lawrence J. Williams*

Contribution from the Department of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey, Piscataway, NJ 08854, USA

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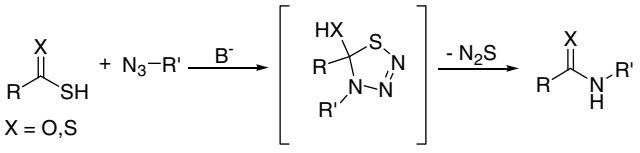
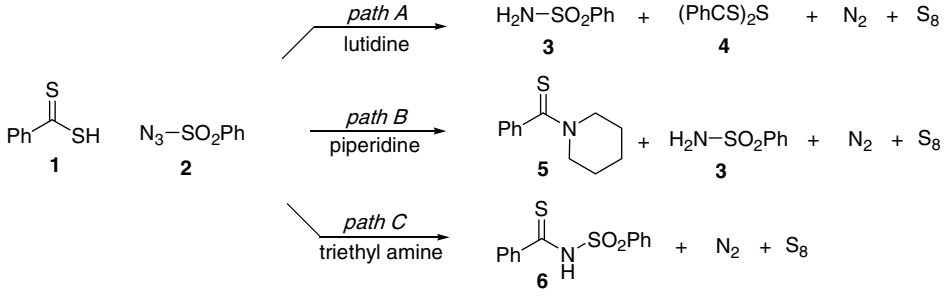
Abstract—A method for thioamide formation from dithioacids and azides is described and a mechanistic framework is presented.

Thioamides serve as isosteric replacements for amides and as versatile synthetic precursors to thiazolines and thiazoles.[1] Most approaches to the construction of thioamides involve formation of the parent amide followed by thionation.[2] Recently, we showed that thioacids and azides form amides in a base-promoted reaction:[3,4] the azide and thioacid appear to couple directly to form a thiatriazoline and then fragment to form amide, N_2, and S_8 products (Eq. 1, X = O).[5] Here we report a new route to thioamides (X = S) from dithioacids and azides and introduce data suggestive of the mechanistic pathway.



(1)

Electron deficient azides couple with thioacids rapidly and quantitatively.[6] Consequently, we studied the reaction between dithiobenzoic acid (**1**) and benzene sulfonazide (**2**). As shown in Scheme 1, the reaction outcome is remarkably dependent on the nature of the base promoter. We focus here on the effects of lutidine, piperidine, and triethylamine. In the presence of lutidine (path A), **1** converted **2** rapidly and completely to benzenesulfonamide (**3**), nitrogen, and sulfur. Dithiobenzoic anhydride (**4**) also formed. Thus, while being the base of choice for the thioacid/azide amidation, lutidine is ineffective for the thioamide coupling. Piperidinium salts of dithioacids are easy to handle and are stable at room temperature. The piperidine salt of **1** also proved stable in solution;[7] however, subsequent addition of **2** led to rapid formation of piperidine-derived thioamide (**5**), as well as **3**, nitrogen, and sulfur (path B). Table 1 summarizes a series of experiments that more completely probe this outcome. Piperidinium dithiobenzoate (1.3 equiv)



Scheme 1.

Keywords: Thioamides; Thioacids; Azides; Amidation; Thiatriazolines.
* Corresponding author. E-mail: ljw@rutchem.rutgers.edu

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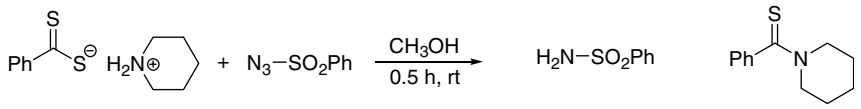
Table 1.



Equiv		% Yield (equiv)	
1.3	0.0	0	10
1.3	0.25	96 (0.24)	35
1.3	0.50	94 (0.47)	54
1.3	0.75	84 (0.63)	63
1.3	1.0	62 (0.62)	62

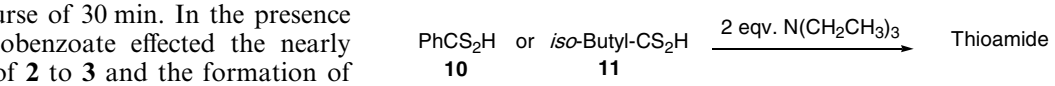
formed small quantities of **5** (10%) in methanol at room temperature over the course of 30 min. In the presence of **2**, piperidinium dithiobenzoate effected the nearly quantitative conversion of **2** to **3** and the formation of significantly more **5** than expected under these conditions. As the amount of sulfonazide was increased, the amount of **5** and **3** isolated from the reaction mixture increased as well, while the relative ratio of **5**:**3** remained 1:1. These experiments establish that the conversion of piperidinium dithiobenzoate to **5** is stoichiometric in sulfonyl azide (**2**) and produces an equivalent amount of **3**. In contrast to the weakly basic lutidine and the highly nucleophilic piperidine, triethylamine promoted the smooth coupling of **1** with **2** to give *N*-benzenesulfonyl thioamide (**6**) in excellent yield (path C).

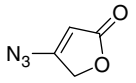
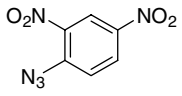
Having determined that triethylamine displays the desired properties for the coupling, we moved to develop a dithioacid/azide thioamidation method. We generated the dithioacid from the corresponding Grignard reagent and carbon disulfide.[8] Exposure of the dithioacid to the azide in the presence of triethylamine gave the desired thioamide. Examples of thioamidation are shown in Table 2.[9] The most convenient method was to generate the dithioacid under standard conditions, to carry out an aqueous acid workup, which removes magnesium salts, and then to treat the dithioacid with triethylamine and then azide. By using a slight excess of dithioacid (1.3 equiv crude), triethylamine (2 equiv), and azide (1.0 equiv) in a suitable solvent at 0 °C for 1–4 h, the desired thioamide could be obtained in good overall yield.

As with our thioacid/azide amidation, electron deficient azides react rapidly and efficiently with dithioacids, while electron rich azides require heating for prolonged periods in order to achieve good conversions. Thionation of amides *N*-substituted with electron withdrawing groups, such as with sulfonyl, often require heating at 150 °C with phosphorous pentasulfide or exposure to Lawesson's reagent in refluxing toluene for 24 h.[10] The method reported here is mild, chemoselective, compatible with hydroxylic solvents, and complementary to other thioamide syntheses.

The mechanistic framework in Scheme 2 readily rationalizes the reaction outcomes in Scheme 1. In the presence of base, the thiolate adds to the terminal nitrogen of the azide forming a linear anionic intermediate in

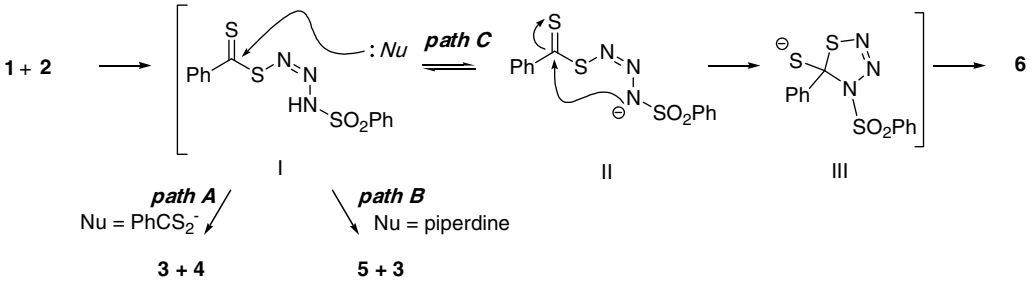
Table 2.



Azide	Dithioacid	Conditions	Yield (%)
2	**10**	—[a]	83
 **12**	**10**	—[a]	85
 **13**	**10**	—[a]	75
N_3–Bn **14**	**10**	—[b]	56
2	**11**	—[a]	93
12	**11**	—[a]	67
13	**11**	—[a]	75
14	**11**	—[b]	36
2	**10**	—[c]	86

[a] Conditions: CH_3OH, 0 °C to rt, 4 h.
[b] Conditions: $CHCl_3$, reflux, 36 h.
[c] Conditions: H_2O/acetone 3:1, 0 °C to rt, 30 min.

equilibrium with the neutral species (**I**/**II**). Intermediate **I** would be expected to exhibit active ester character. The weaker base, lutidine, should favor the protonated form to a much greater degree than piperidine or triethylamine. Nucleophilic attack of a second molecule of dithioacid at the thiocarbonyl of **I** should result in fragmentation to **3**, **4**, nitrogen, and sulfur as shown (path A).[11] This pathway would be less relevant in the presence of stronger bases; however, the active ester could undergo nucleophilic acyl substitution by the highly nucleophilic piperidine (path B). Addition of piperidine to **I** followed by collapse of the tetrahedral intermediate would give the observed products.[12] In this way, benzenesulfonazide appears to serve as a stoichiometric activator of a dithioacid, and piperidine appears sufficiently nucleophilic to intercept the linear intermediate (**I**/**II**). As shown in path C, triethylamine enforces formation of the anion (**I**→**II**) but does not otherwise interfere and thus enables **II** to cyclize to thiatriazoline **III**. The thiatriazoline then undergoes fragmentation, either stepwise or in a concerted [3+2] mechanism,[13] to give the thioamide (**6**).



Scheme 2.

Additional control experiments support this mechanistic framework. Benzenesulfonamide (**3**) does not react under these conditions with dithiobenzoic acid (**1**) or dithiobenzoic anhydride (**4**), even in the presence of triethylamine, thus demonstrating that the dithioacid/azide amidation does not proceed through an amine intermediate. Examination of the reaction profile by ESI-MS revealed the presence of a species that corresponds to a 1:1 adduct of dithioacid:azide. ESI-MS/MS of this species indicates loss of fragments corresponding to phenyl (77), benzenesulfonyl (141), sulfhydryl (33), and nitrous sulfide (60), consistent with its formulation as thiatriazoline **III**.[4]

The thioacid/azide amidation may prove to be broadly applicable for the synthesis of complex amides.[14] The reactivity principles deduced from the amidation provided the conceptual basis for this new route to thioamides. We have shown that dithioacids couple efficiently with electron deficient azides to give thioamide products under very mild conditions. The dithioacid/azide thioamidation does not proceed through an amine intermediate, but rather through a thiatriazoline. The attributes of the thioacid/azide amidation, namely the high degree of chemoselectivity, solvent compatibility, high coupling efficiency of electron deficient azides, and the non-toxic byproducts nitrogen and sulfur, appear to be retained for thioamide synthesis as well.

Acknowledgements

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9. *Procedure:* To a 15 mL round bottom flask charged with 5 mL of MeOH cooled to 0 °C, was added dithiobenzoic acid (202 mg, 1.3 mmol) and triethylamine (202 mg, 2.0 mmol). The resultant reddish/dark brown solution was treated with **12** (125 mg, 1 mmol) in one portion. Evolution of nitrogen was noted upon addition of azide and precipitation of sulfur was noted during the course of the reaction. The solution was allowed to warm to room temperature, and after 4 h the solution was concentrated in vacuo. Flash column chromatography (3:7 EtOAc/hexanes) provided 187 mg (85%) of the thioamide as viscous yellow oil. IR (neat) ν_{max} 3110, 1717, 1235; δ_H (400 MHz,

$CDCl_3$) 3.94 (s, 2H), 7.17 (s, 1H), 7.41 (m, 3H), 7.89 (2H), 11.2 (br s, 1H); δ_c (100 MHz, $CDCl_3$) 37.1, 116.9, 127.1, 129.5, 130.8, 133.4, 149.5, 169.1, 174.8; *m/z* (ESI-MS) calcd for $C_{11}H_9NNaO_2S$ $[M+Na]^+$ 242.0, found: 242.1.

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11. Dithiobenzoic anhydride (**4**), which forms upon exposure of dithiobenzoic acid to air and light, is observed as an impurity in the reagent. The levels of **4**, as monitored by GCMS, rapidly increased significantly above background levels during the reaction. In principle, it would be possible for lutidine to add to **I**. Fragmentation of the tetrahedral intermediate could give the *N*-acyllutidinium ion, nitrogen, sulfur, and **3**. Attack on the *N*-acyllutidinium intermediate by **1** would lead to the observed products. However, this type of side reaction is not observed in the parent thioacid/azide amidation where, given the higher reactivity of a carbonyl over a thiocarbonyl, such a pathway would be more facile than in the present context. Moreover, the intermediacy of an *N*-acyllutidinium species is unlikely: addition of lutidine to the thiocarbonyl of **I** would be slow, yet the velocity of the reaction presented here is high.
12. The alternative mechanism, wherein dithiobenzoic anhydride is formed as in path A and then reacts with piperidine to give the observed acylation product (**5**) and benzenesulfonamide (**3**), can be ruled out, as **3** is not generated in significant quantities in the presence of triethylamine (see path C), and **3** is not acylated by dithiobenzoic anhydride.
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