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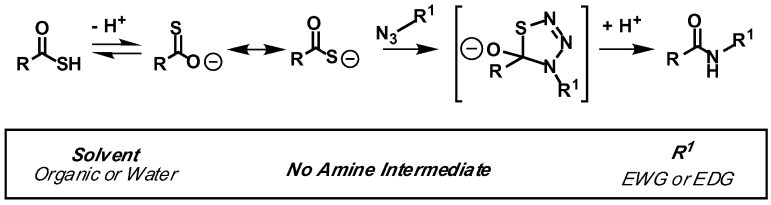

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The Reaction of Thio Acids with Azides: A New Mechanism and New Synthetic Applications

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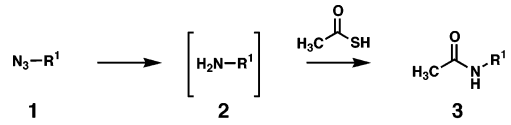
Conventional methods for the chemical synthesis of amides utilize active esters and amines as precursors and are extraordinarily efficient at producing simple peptide products. Nevertheless, many classes of amides, including those found in many natural products, bioconjugates, and pharmaceutical candidates, pose significant challenges to these methodologies. Here we present an amide synthesis strategy based on a fundamental mechanistic revision of the reaction of thio acids and organic azides. Moreover, we report the application of this methodology to the selective preparation of several classes of complex amides in nonpolar and polar solvents, including water.

Thioacetic acid, applied as solvent or cosolvent, acts on organic azides to provide the corresponding acetamide product (eq 1).[1−3] Evidence has been presented in support of a reaction mechanism wherein the azide is reduced in situ to give the corresponding amine (**2**) followed by unusually rapid acetylation of the amine intermediate.[1] Hence, it was suggested that thioacetic acid-induced formation of amides from azides involves a very rapid, but otherwise conventional, nucleophilic acyl substitution reaction.



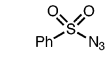
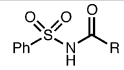
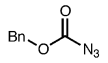
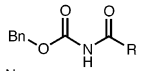
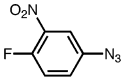
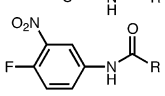
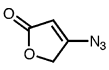
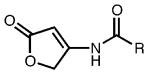
1 2 3 (1)

Is a free amine an obligatory intermediate? We found that treatment of benzylamine in dichloromethane (0.5 M) with trifluoroacetic acid (1.0 equiv) followed by a slight excess (1.3 equiv) of thioacetic acid gave virtually no amide product (<4%) after 15 h at room temperature. Benzyl azide under these conditions, however, gave *N*-benzyl acetamide in 42% yield. Benzenesulfonyl azide reacted in minutes upon exposure to thio acids to form *N*-acyl sulfonamides in excellent yields (>95%), whereas benzenesulfonamide failed to react even after several days. *Taken together, these experiments suggest that thio acids react with organic azides to give amide products without prior reduction to the amine.*

As summarized in Tables 1−4, simple and complex amide products can be formed with this methodology, and the use of thio acid as solvent or cosolvent can be avoided. Reaction solvents include methanol, chloroform, and water, although serviceable yields were obtained using other common solvents as well. Importantly, 2,6-lutidine was found to significantly accelerate the reaction and was superior to other bases, including pyridine and 2,6-di-*tert*-butyl pyridine. The data indicate that yields depend primarily upon the electronic and steric properties of the azide and secondarily upon the thio acid.

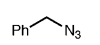
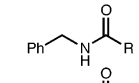
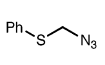
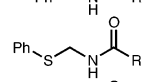
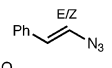
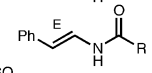
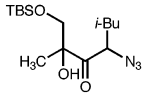
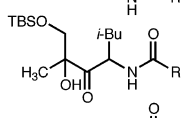
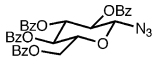
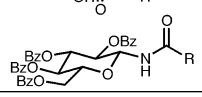
Our studies with benzene sulfonyl azide prompted us to examine other organic azides bearing electron-withdrawing functionality (Table 1). Thus, *N*-acyl carbamates (entry 2), *N*-aryl amides (entry 3), and, remarkably, enamides (entry 4) were efficiently prepared under very mild conditions.

Table 1. Thio Acid/Azide Coupling in Polar Organic Solvent[a]

Entry	Azide	°C/time/solvent	Amide	Yield
1		a) 25/15 min/MeOH b) 25/15 min/MeOH		a) 98% b) 96%
2		a) 25/2 h/MeOH b) 25/2 h/MeOH		a) 99% b) 96%
3		a) 25/15 h/MeOH b) 25/15 h/MeOH		a) 95% b) 94%
4		a) 0/2 h/MeOH b) 0/2 h/MeOH		a) 98% b) 95%

[a] Conditions: 0.94−0.024 M azide; 1:1.3:1.3 azide:2,6-lutidine:thio acid. (a) Thiobenzoic acid, R = C_6H_5. (b) Thioacetic acid, R = CH_3.

Table 2. Thio Acid/Azide Coupling in Nonpolar Organic Solvent[a]

Entry	Azide	°C/time/solvent	Amide	Yield
1		a) 60/15 h/$CHCl_3$ b) 60/15 h/$CHCl_3$		a) 78% b) 86%
2		a) 60/15 h/$CHCl_3$ b) 60/15 h/$CHCl_3$		a) 77% b) 85%
3		a) 60/10 h/$CHCl_3$ b) 60/18 h/$CHCl_3$		a) 66% b) 79%
4		a) 25/30 h/$CHCl_3$ b) 60/24 h/$CHCl_3$		a) 94% b) 88%
5		a) 60/36 h/$CHCl_3$ b) 60/36 h/$CHCl_3$		a) 64% b) 97%

[a] Conditions: 1.0−0.18 M azide; 1:1.3−2.6:1.3−2.6 azide:2,6-lutidine: thio acid. (a) Thiobenzoic acid, R = C_6H_5. (b) Thioacetic acid, R = CH_3. For entry 5a, yield based on recovered starting material: 95%.

Similarly, electron-rich azides smoothly coupled with thio acids (Table 2); however, heating and base additives were found to be necessary for more challenging alkyl substrates (entries 2−5). Interestingly, *E*/*Z* mixtures of β-azido styrene provided exclusively the (*E*)-enamide products (entry 3). In contrast, when exposed to thio acid, the unprotected hydroxy azide (entry 4) was selectively converted to the hydroxy amides without measurable side reaction or epimerization of the azide.

The direct conversion of glycosyl azides to the *N*-acyl products was also examined. It should be noted that glycosylamines are configurationally unstable under many acylation reaction conditions,[4] whereas glycosyl azides are configurationally stable. In the event, conversions took place in good yield (entry 5, Table 2), and the reactions proceeded with complete stereochemical fidelity.

We further attempted the synthesis of amides in water (Table 3). β-Glucosyl azide was cleanly converted to the β-*N*-amidoglycoside without isomerization[4b,c] (entry 1), 3′-azido-3′-deoxythymi-

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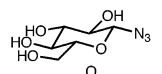
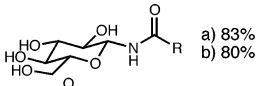
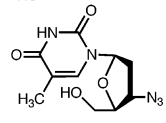
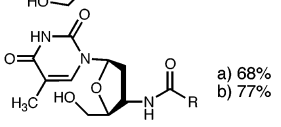
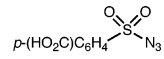
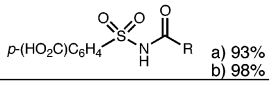
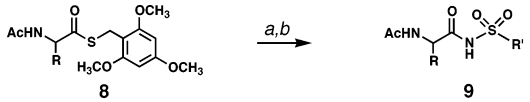
Table 3. Thio Acid/Azide Coupling in Water[a]

Entry	Azide	°C/time/solvent	Amide	Yield
1		a) 60/36 h/H_2O b) 60/36 h/H_2O		a) 83% b) 80%
2		a) 60/36 h/H_2O b) 60/36 h/H_2O		a) 68% b) 77%
3		a) 25/1 h/H_2O b) 25/1 h/H_2O		a) 93% b) 98%

[a] Conditions: 0.25−0.040 M azide; 1:1.3−5 azide:thio acid; entry 1, $NaHCO_3$(aq); entry 2, PBS buffer pH 7.4; entry 3, 1.8 equiv of 2,6-lutidine. (a) Thiobenzoic acid, R = C_6H_5. (b) Thioacetic acid, R = CH_3.

Table 4. Preparation of α-Aminoacyl Sulfonamide Derivatives[a]



8 **9**

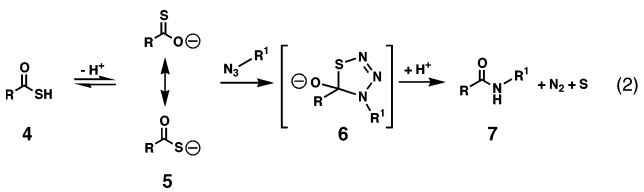
entry	8	R	azide	9	yield (two steps)
1	**a**	*i*-Bu	N_3-Bs	**9a**, *N*-Ac-Leu-NH-Bs	91%
2	**b**	(*R*)-*sec*-Bu	N_3-Ts	**9b**, *N*-Ac-alle-NH-Ts	87%
3	**c**	(*S*)-*sec*-Bu	N_3-Ts	**9c**, *N*-Ac-lle-NH-Ts	72%
4	**d**	(*R*)-*sec*-Bu	N_3-dansyl	**9d**, *N*-Ac-alle-NH-dansyl	73%
5	**e**	*i*-Bu	N_3-dansyl	**9e**, *N*-Ac-Leu-NH-dansyl	73%

[a] Conditions: (a) TFA/DCM (40−80% v/v), $HSiEt_3$; (b) CH_3OH, 0.16−0.17 M thio acid; 2−5 equiv of azide, 3−6 equiv of 2,6-lutidine, room temperature.

dine was converted to the corresponding amides (entry 2), and *N*-acyl sulfonamides (entry 3) were smoothly fashioned without complication in aqueous solution.

The entries in Table 4 illustrate four further advances. *N*-Acetyl α-amino acyl sulfonamides were prepared from thioesters **8a**−**c**.[5] Liberation of the thio acid, followed by treatment with sulfonyl azide, gave **9a**−**e**. Hence, sophisticated thio acids participate predictably in this reaction as well. No epimerization of the thio acid partner occurred as determined by careful comparison of the diastereomeric products from entries 2 and 3.[5] Entries 1−3 also demonstrate a new route to highly useful "safety catch" linkers,[6] while entries 4 and 5 represent C-terminal fluorescently labeled peptide derivatives.

Equation 2 presents a new mechanistic framework for this reaction. Formation of a thiatriazoline intermediate (**6**), rather than reduction of the azide to amine, accounts for our observations.[7] This intermediate could form via either a 2+3 cycloaddition or a stepwise diazo transfer-like mechanism. Decomposition of **6**, stepwise or by a retro-[2+3] reaction, would ultimately lead to amide, nitrogen, and sulfur.[8]



4 **5** **6** **7** (2)

Thio acid/azide coupling has several advantages over conventional amidation reactions. Amine analogues of azides in Tables 1 and 4 would resist mild acylation conditions due to significantly reduced nucleophilic properties, whereas amine analogues of Table 2, entries 2−5, would be expected to undergo facile side reactions. In addition, many problems in amide synthesis are exacerbated in methanol and water, where amine nucleophilicity is reduced, and active esters are rendered susceptible to solvolysis (see Tables 1, 3, and 4). *Thus, with this methodology, both simple and complex amides difficult to access using conventional methods have been prepared without the use of protecting groups and in aqueous solution.*

These findings complement impressive advances in protein synthesis,[9] engineering,[10] as well as unconventional amide synthesis approaches recently reported.[4c,11,12] Considering the ease of preparation of azides and thio acids in solution and on solid support,[13] this method could prove highly useful in the construction of natural and designed peptides and amide-containing natural products. Further synthetic, mechanistic, and computational studies will be reported in due course.

Acknowledgment. Financial support by Merck & Co. and Rutgers, The State University of New Jersey is gratefully acknowledged. The authors would like to thank Prof. Spencer Knapp for critical reading of the manuscript, and Kavita Joshi and James Huber for preliminary studies.

Supporting Information Available: Synthetic methods and characterization data, including the preparation of **9a**−**e** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) See Supporting Information for details of preparation and characterization.
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