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Thio Acid/Azide Amidation: An Improved Route to *N*-Acyl Sulfonamides

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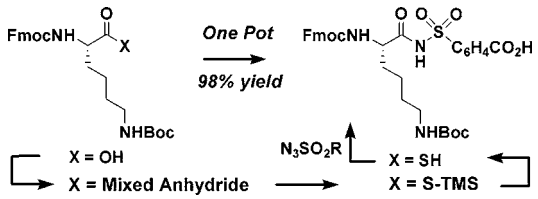
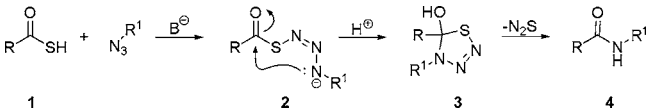
ABSTRACT



A one-pot procedure for the conversion of carboxylic acids to *N*-acyl sulfonamides, via thio acid/azide amidation, is presented. The method is compatible with acid- and base-sensitive amino acid protection. *N*-Acyl sulfonamide synthesis on solid support, peptide thio acid/sulfonazide coupling, and *N*-alkyl amide synthesis via selective cleavage of sulfonyl from an *N*-alkyl-*N*-acyl sulfonamide are also reported.

Sulfonyl azides react very rapidly with thio acids (Scheme 1) to give *N*-acyl sulfonamides,[1] a product class useful in

Scheme 1



medicinal chemistry,[2] solid support linking strategies,[3] and for conjugation and ligation applications[1,4] among others. Here we report our studies on an improved route to *N*-acyl sulfonamides and related findings.

We have used trimethoxybenzyl (TMOB[5]) thio esters as thio acid precursors;[1] however, this approach is limited, as illustrated in Scheme 2. TMOB−thio esters are readily prepared[6] from the corresponding carboxylic acid and

(1) (a) Method: Shangguan, N.; Katukojvala, S.; Greenberg, R.; Williams, L. J. *J. Am. Chem. Soc.* **2003**, *125*, 7754. (b) Mechanism: Kolakowski, R. V.; Shangguan, N.; Wang, Z.; Sauers, R. R.; Williams, L. J. Submitted.

(2) (a) Abbate, F.; Supuran, C. T.; Scozzafava, A.; Orioli, P.; Stubbs M. T.; Klebe, G. A.; Jones, B. R. *J. Med. Chem.* **2002**, *45*, 3583. (b) Uehling, D. E.; Donaldson, K. H.; Deaton, D. N.; Hyman, C. E.; Sugg, E. E.; Barrett, D. G.; Hughes, R. G.; Reitter, B.; Adkison, K. K.; Lancaster, M. E.; Lee, F.; Hart, R.; Paulik, M. A.; Sherman, B. W.; True, T.; Cowan, C. *J. Med. Chem.* **2002**, *45*, 567. (c) Mader, M.; Shih, C.; Considine, E.; De Dios, A.; Grossman, S.; Hipskind, P.; Lin, H.; Lobb, K.; Lopez, B.; Lopez, J.; et al. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 617. (d) Johansson, A.; Poliakov, A.; Åkerblom, E.; Wiklund, K.; Lindeberg, G.; Winiwarter, S.; Danielson, U.; Samuelsson, B.; Hallberg, A. *Bioorg. Med. Chem.* **2003**, *11*, 2551.

(3) (a) Kenner, G. W. *Chem. Commun.* **1971**, 636. (b) Backes, B. J.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 2322. (c) Shin, Y.; Winans, K. A.; Backes, B. J.; Kent, S. B. H.; Ellman, J. A.; Bertozzi, C. R. *J. Am. Chem. Soc.* **1999**, *121*, 11684. (d) Ingenito, R.; Dreznjak, D.; Guffler, S.; Wenschuh, H. *Org. Lett.* **2002**, *4*, 1187. (e) Mclean, D.; Hale, R.; Chen, M. *Org. Lett.* **2001**, *3*, 2977.

(4) For ligation reactions, see: (a) Kemp, D. S. *Biopolymers* **1981**, *20*, 1793. (b) Tam, J. P.; Yu, Q.; Miao, Z. *Biopolymers* **1999**, *51*, 311. (c) Coltart, D. M. *Tetrahedron* **2000**, *56*, 3449. (d) Prescher, J. A.; Bertozzi, C. R. *Nat. Chem. Biol.* **2005**, *1*, 13. (e) Saxon, E.; Bertozzi, C. R. *Science* **2000**, *287*, 2007. (f) Kochendoerfer, G. G.; Kent, S. B. H. *Curr. Opin. Chem. Biol.* **1999**, *3*, 665. (g) Köhn, M.; Wacker, R.; Peters, C.; Schröder, H.; Soulère, L.; Breinbauer, R.; Niemeyer, C. M.; Waldmann, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5830. For a potential thio acid/sulfonazide amidation strategy for ligation, see: (h) Merkx, R.; Brouwer, A. J.; Rijkers, D. T. S.; Liskamp, R. M. J. *Org. Lett.* **2005**, *7*, 1125.

(5) Acronyms: Boc = *tert*-butoxycarbonyl, DCC = dicyclohexyl carbodiimide, DIC = diisopropyl carbodiimide, DIEA = ethyl diisopropylamine, DMAP = 4-dimethylamino pyridine, DMF = *N*,*N*-dimethylformamide, DMSO = methyl sulfoxide, Fmoc = 9-fluorenylmethoxycarbonyl, IBCF = isobutyl chloroformate, SES-N_3 = trimethylsilylethyl sulfonazide, TBAF = tetrabutylammonium fluoride, TLC = thin-layer chromatography, TMOB = 2,4,6-trimethoxybenzyl.

(6) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.

10.1021/ol052671d CCC: $33.50
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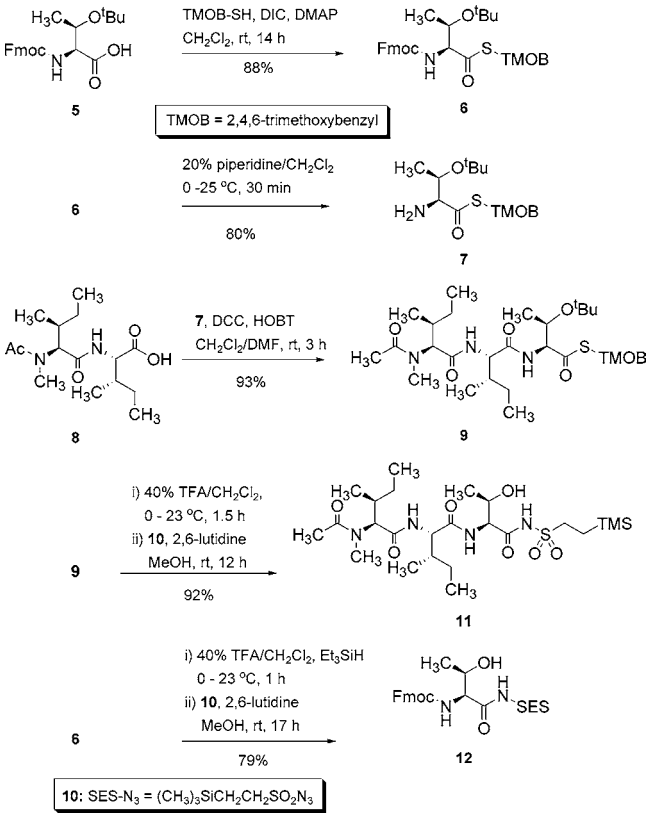
Scheme 2



TMOB−thiol.[7] Conversion of protected threonine **5** to TMOB−thio ester **6** and removal of the Fmoc protection gave amine **7**, and DCC-mediated coupling of **7** with dipeptide **8**[8] gave peptide thio ester **9** in excellent yield.[9] TFA cleavage of both the TMOB and the *tert*-butyl groups gave the crude peptide thio acid,[10] which upon treatment with trimethylsilylethyl sulfonazide (**10**)[11] gave the peptide conjugate **11** in 92% yield. Similar treatment of **6** gave the corresponding amide product **12**. These experiments demonstrate the ease with which thio acid/azide amidation can be adapted to ligation/conjugation reactions. The major limitations being that TMOB removal is slow, prolonged exposure to TFA is required for good conversion, and preparation of **11** by way of **6**, while high yielding, is an uneconomical route to simple amino acid-derived *N*-acyl sulfonamides. Furthermore, this approach is not compatible with acid-sensitive functional groups.

Scheme 3

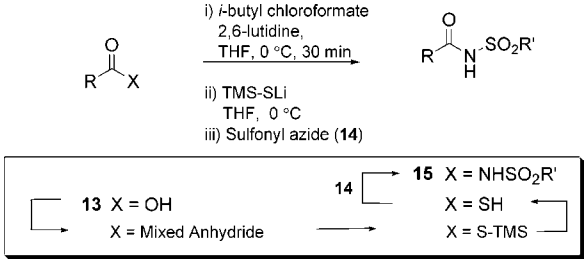
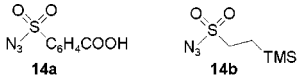
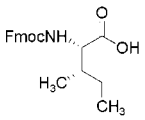
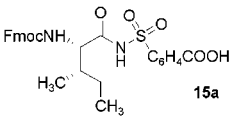
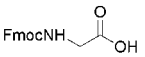
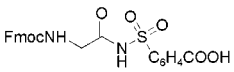
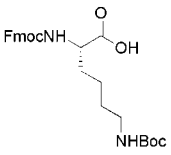
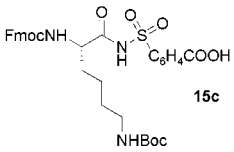
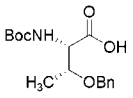
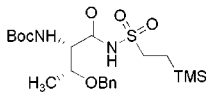
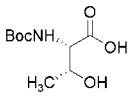
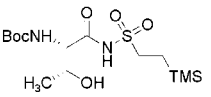


Table 1.



entry	acid	azide	product	yield
1		14a	 15a	86%
2		14a	 15b	83%
3		14a	 15c	98%
4		14b	 15d	96%
5		14b	 15e	94%

Our goal, therefore, was to develop an *N*-acyl sulfonamide synthesis procedure compatible with acid- and base-sensitive functionality. Scheme 3 summarizes the general approach, and Table 1 provides several examples of the method. Protected amino acids (**13**, Scheme 3) were transformed to amino thio acids by exposure to isobutyl chloroformate,[12] and then trimethylsilyl thiolate, followed by dilution with methanol and then removal of volatiles under reduced pressure. The *N*-acyl sulfonamide products (**15**) were formed by dilution of the thio acid in mildly basic methanol, addition of sulfonyl azide (**14**),[13] stirring at room temperature, followed by removal of solvent, and then silica gel chromatographic purification. Anhydrous trimethylsilyl thiolate was prepared from bis(trimethylsilyl) sulfide[14] upon treatment with methyllithium.[15]

(7) Vetter, S. *Synth. Commun*. **1998**, *28*, 3219.
(8) Katukojvala, S.; Barlett, K. N.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc*. **2004**, *126*, 15348.
(9) No epimerization for this coupling was evident. For a closely related coupling, see ref 8.
(10) In dilute acid, the *tert*-butyl group is cleaved rapidly (<2 h), whereas the TMOB group is cleaved slowly (>2 h).
(11) SES-N_3 is readily prepared from $(SES)_2O$. See: Weinreb, S. M.; Chase, C. E.; Wipf, P.; Venkatraman, S. *Organic Syntheses*; Wiley & Sons: New York; Collect. Vol. 10, p 707.
(12) Dudash, J.; Jiang, J.; Mayer, S. C.; Joullie, M. M. *Synth. Commun.* **1993**, *23*, 349.
(13) Sulfonyl azides are readily prepared in excellent yields from sulfonyl chlorides or anhydrides and sodium azide. See: (a) Regitz, M.; Hocker, J.; Liedhgener, A. *Organic Syntheses*; Wiley & Sons: New York, 1973; Collect. Vol. 5, p 179. (b) Hazen, G. G.; Bollinger, F. W.; Roberts, F. E.; Russ, W. K.; Seman, J. J.; Staskiewicz, S. *Organic Syntheses*; Wiley & Sons: New York; Collect. Vol. 9, p 400.

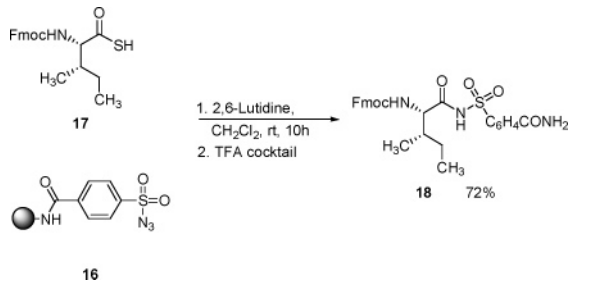
Presumably, the trimethylsilyl thioester generated from addition of the thiolate to the mixed anhydride rearranges to the trimethylsilyl thionoester under the reaction conditions. Upon methanolysis, the thio acid is liberated. Subsequent exposure to the azide leads to the amide according to the mechanism outlined in Scheme 1.

This approach has many favorable qualities, including reactant stoichiometry (near 1:1 for all reagents), volatility of most reagents and reaction byproducts, reliably high yields, and that the choice of solvent in the coupling reaction can be determined by the solubility properties of the reactants since the thio acid/azide amidation is effective in a range of organic and aqueous solvents.[1,16] Moreover, *N*-acyl sulfonamides often display significant water solubility. Avoidance of aqueous workup and the lack of significant byproducts and excess reagents, commonly used for other sulfonamide couplings, also adds to the attractiveness of the method. In generating the thio acid, the less convenient use of hydrogen sulfide, sodium sulfide,[15c−f] or the less atom economical use of thiols, such TMOB-thiol[7] and related hydrogen sulfide equivalents,[15g,h] is avoided by using bis(trimethylsilyl) sulfide. The generation of trimethylsilyl thiolate from bis(trimethylsilyl) sulfide with methyllithium conveniently leads to excellent overall yields of amide.[15a] Solutions of tetrabutylammonium fluoride in THF dried over activated molecular sieves performed as well as methyllithium and gave yields that were superior to those obtained with wet tetrabutylammonium fluoride;[15b] however, methyllithium reactions are easier to monitor and are not contaminated by nonvolatile tetrabutylammonium salts. In addition to the favorable qualities mentioned above, this method is highly complementary to other *N*-acyl sulfonamide syntheses. Direct amidation of sulfonamides with active esters usually requires strong base and/or highly active esters and excess reagents.[3,17] The conditions presented here are mildly basic and compatible with a range of functionality, including acid- and base-sensitive protecting groups as well as certain unprotected functionality.

For the entries in Table 1, the same procedure was followed, modified only by the reaction time allowed for the consumption of mixed anhydride by thiolate, a parameter readily monitored by TLC. Coupling partners include base-sensitive substrates (entries 1−3), acid-sensitive substrates (entries 3−5), protected alcohol (entry 4), free alcohol (entry 5), and free carboxylic acid (**14a**, entries 1−3). Methyllithium and dried tetrabutylammonium fluoride were used for the trimethylsilyl thiolate formation step of entry 5, and the overall yields were equally effective within experimental error.

The ability to employ unprotected coupling partners, such as 4-carboxy bezenesulfonazide (**14a**), enables direct subsequent functionalization without having to implement a protecting group strategy. For example, Fmoc-Ile-OH, was converted to **15a** (Table 1) and taken directly and immobilized on the amine-functionalized Wang amide resin. The same overall sequence, leading to an identically functionalized resin, was achieved by formation of the *N*-acyl sulfonamide on solid support (Scheme 4). Thus, Wang amide

Scheme 4



resin was coupled with commercial **14a**[18] and then exposed to the crude Fmoc-Ile-SH (**17**) prepared according to our method. The consumption of resin-bound azide was readily monitored,[19] and the only modification to the amidation protocol was the use of excess **17** (2 equiv based on the parent carboxylic acid) and methylene chloride instead of methanol.[20] Proof that we had indeed succeeded in effecting thio acid/azide amidation on solid support was secured by comparison of the spectral characteristics of the purified cleavage products from the two resins, which were shown to be identical. The overall isolated yield of the **18** was 72% based on the loading capacity of the resin.

In Table 1, entries 4 and 5 employed trimethylsilylethyl sulfonazide (SES-N_3). We wondered if *N*-acyl sulfonamides derived from the Weinreb SES group would offer the opportunity of mild sulfonamide N−S bond cleavage (Scheme 5).[21] Removal of the SES protecting group from an amine usually requires high temperature and excess fluoride reagent.[22] These conditions are readily attributable to the poor leaving group ability of the anionic amine. An *N*-acyl sulfonamide represents a substrate with comparatively su-

(14) **Caution:** Bis(trimethylsilyl) sulfide hydrolyzes to hydrogen sulfide, which is highly toxic. Although we have noted no problems with compounds described in this report, azides may be explosive.

(15) For other methods to generate thio acids, see: (a) Kraus, G. A.; Andersh, B. *Tetrahedron Lett.* **1991**, *32*, 2189. (b) Schwabacher, A. W.; Maynard, T. L. *Tetrahedron Lett.* **1993**, *34*, 1269 and references therein. (c) Yamashiro, D.; Blake, J. *Int. J. Peptide Protein Res.* **1981**, *18*, 383 and references therein. (d) Pansare, S. V.; Vederas, J. C. *J. Org. Chem.* **1989**, *54*, 2311. (e) Hoeg-Jensen, T.; Holm, A.; Sorensen, H. *Synthesis* **1996**, 383. (f) Lee, A. H. F.; Chan, A. S. C.; Li, T. *Tetrahedron* **2003**, *59*, 833. (g) Goldstein, A. S. Gleb, M. H. *Tetrahedron Lett.* **2000**, *41*, 2797. (h) Gartner, H.; Villain, M.; Botti, P.; Canne, L. *Tetrahedron Lett.* **2004**, *45*, 2239.

(16) DMSO is an exception. We believe this is due to oxidation of the thio acid. Selenocarboxylates appear to behave similarly. See: Wu, X.; Hu, L.; *Tetrahedron Lett.* **2005**, *46*, 8401.

(17) Wieland, T.; Hennig, H. J. *Chem. Ber.* **1960**, *93*, 1236. For alternatives applicable to solid support synthesis, see refs 2, 3d, and 3e.

(18) Carboxybenzene sulfonazide was attached to amine functionalized Wang amide resin. The reaction was monitored until completion as determined by the Kaiser test: Kaiser, E.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *34*, 595. See Supporting Information.

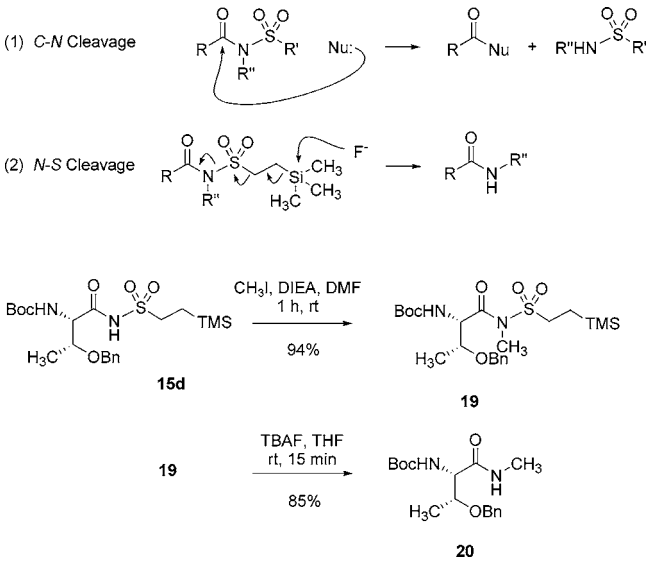
(19) Punna, S.; Finn, M. G. *Synlett* **2004**, 99.

(20) The thio acid/azide amidation is compatible with a wide range of solvents (see also, ref 16).

(21) For other examples of mild *N*-acyl sulfonamide cleavage, see: (a) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353. (b) Fukuyama, T.; Cheung, M.; Jow, C.; Hidai, Y.; Kan, T. *Tetrahedron Lett.* **1997**, *38*, 5931. (c) Ahmed, N.; Tsang, W. Y.; Page, M. I. *Org. Lett.* **2004**, *6*, 595 and references therein.

(22) Weinreb, S. M.; Demko, D. M.; Lessen, T. A., Demers, J. P. *Tetrahedron Lett.* **1986**, *27*, 2099.

Scheme 5



perior leaving group ability. However, even weakly basic reagents would generate the stable, anionic acyl sulfonamide and would convert the acyl appendage to a very poor leaving group.[23] Moreover, *N*-alkyl-*N*-acyl sulfonamides usually react with nucleophiles at the acyl center, effect cleavage of the C−N bond, and give the substituted acyl product along with the corresponding sulfonamide.[3]

In contrast to these established trends, we anticipated that *N*-alkyl-*N*-acyl SES amides would react with fluoride to give the *N*-alkyl amide with concomitant disintegration of the SES moiety.[22] Hence, the N−S bond would rupture by an eliminative process initiated by fluoride at silicon, and the normal mode of reactivity for *N*-alkyl-*N*-acyl sulfonamides would be avoided (compare 1 with 2, Scheme 5). This sequence of transformations, carboxylic acid → sulfonamide → amide, would constitute a mild, chemoselective route to *N*-alkyl amides that avoids amine intermediates. To demonstrate the concept, we subjected **15d** to methyl iodide in the presence of ethyl diisopropylamine, which gave the crude *N*-methyl *N*-isoleucyl SES amide **19** as expected. Upon brief, room temperature treatment with TBAF, **19** was smoothly converted to methyl amide **20** in excellent yield (85%). Thus, the Weinreb SES group participated in the thio acid/azide reaction to form an *N*-acyl sulfonamide, promoted smooth *N*-alkylation, and was rapidly cleaved in this context under mild conditions.

This approach to effect mild N−S bond cleavage of *N*-alkyl-*N*-acyl sulfonamides complements other methods and avoids the high temperatures and/or strong reducing agents required sometimes required.[24] Demonstrated compatibility with the Fmoc protecting group is especially attractive and suggests good functional group compatibility.

This report offers a mild, chemoselective alternative to the preparation of *N*-acyl sulfonamides from active esters and sulfonamides that is compatible with acid- and base-sensitive protecting groups and, in certain cases, unprotected functionality. Generation of the thio acid from the parent carboxylic acid followed by addition of sulfonyl azide gives the desired product in excellent yield. The feasibility of *N*-acyl sulfonamide synthesis with peptide segments and solid support has also been demonstrated. Similarly, SES-N_3 has been shown to give *N*-acyl sulfonamides. Following *N*-alkylation, the SES group is readily cleaved upon brief, room temperature fluoride treatment. The generality of these findings, including applications in target-oriented synthesis, studies in chemical biology, and related amidations, will be reported in due course.

Acknowledgment. Financial support by Merck & Co., Johnson & Johnson Innovative Research Award, the Petroleum Research Fund, administered by the ACS, and Rutgers, The State University of New Jersey is gratefully acknowledged.

Supporting Information Available: Complete list of authors for ref 2c. Experimental procedures and spectral data for new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL052671D

(23) The pK_a of acyl sulfonamides is ∼2.5. See ref 3a.

(24) (a) Knowles, H. S.; Parsons, A. F.; Pettiefer, R. M.; Rickling, S. *Tetrahedron* **2000**, *56*, 979 and references therein. (b) Luo, J.; Huang, W. *Molecular Diversity* **2003**, *6*, 33.