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N,*O*-Bis(trifluoroacetyl)hydroxylamine as a Useful Electrophilic Nitrogen Source: Catalytic Synthesis of *N*-(Trifluoroacetyl)sulfilimines

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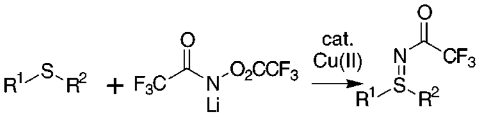
ABSTRACT



In the presence of catalytic quantites of Cu(OTf)$_2$ the novel hydroxamic acid anhydride salt functions competently in the trifluoroacetamidation of sulfides to afford *N*-(trifluoroacetyl)sulfilimines. The salient features of this salt include its ease of synthesis from the inexpensive, commercially available starting materials trifluoroacetic anhydride and hydroxylamine hydrochloride.

The development of reagents and methods that effect oxidative functionalization of simple raw materials constitutes an active area of research in chemistry.[1] To date, among the most versatile of such processes are oxidations that generate epoxides, or diols.[2] In this regard, the vast selection of chalcogen (peracids, dioxirane, oxone), pnictide (oxaziridines), and transition metal based oxygen-atom transfer reagents has led to the development of a myriad of methods that provide access to powerful building blocks for synthesis.[3] In contrast, the paucity of electrophilic-nitrogen equivalents limits the selection of methods available to effect nitrogen-atom transfer, despite the enormous potential of such methodology.[4] Although recently there have been notable advances in this area,[4−6] there continues to be a need for new readily available, easily prepared reagents that serve as sources of electrophilic nitrogen. We have been interested in the discovery and study of reaction methods and reagents for nitrogen-atom transfer.[7] Herein, we wish to report the discovery of the hydroxamic acid anhydride salt **1** that in the presence of catalytic Cu(II) functions competently in the

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(1) (a) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidation of Organic Compounds*; Academic: New York, 1981. (b) Jacobsen, E. N. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Willkinson, G., Eds.; Pergamon: Oxford, U.K., 1995; Vol. 12, p 1097. (c) Murahashi, S.-I.; Naota, T. In ref 1b, p 1177.

(2) (a) Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; p 159. (b) Johnson, R. A.; Sharpless, K. B. In ref 2a, p 103. (c) For a review of the Sharpless dihydroxylation reaction, see: Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (d) The continuous discovery and development of novel oxygen atom transfer process (epoxidation) is an intensively active area of investigation; see: Yudin, A. K.; Sharpless, K. B. *J. Am. Chem. Soc.* **1997**, *119*, 11536 and references therein.

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(6) (a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742. (b) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328. (c) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326. (d) For a mechanistic discussion of the aziridination reaction, see: Li, Z.; Quan, R. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5889.

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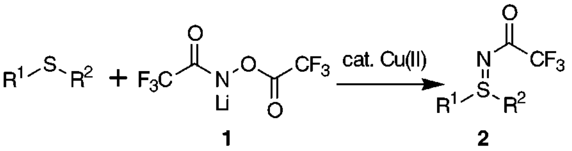
trifluroacetamidation of sulfides to afford *N*-(trifluoroacetyl)-sulfilimines:

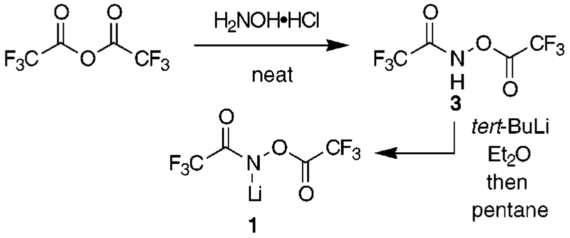


The salient features of this novel salt **1** include its ease of synthesis from the inexpensive, commercially available starting materials trifluoroacetic anhydride and hydroxylamine hydrochloride.

Only a handful of reagents are available that directly aminate organic molecules to furnish the corresponding nitrogenous compound. Among the more popular sources of active electrophilic nitrogen reagents are azides,[8] *N*-haloamides,[4,9] and the related *N*-arylsulfonyliminoiodobenzenes.[6,10] Acyl and carbamoyl azides have been utilized in alkene aziridination, although the process is of limited preparative use. Of particular importance, Sharpless has recently documented the use of *N*-haloamides and carbamates as versatile and practical amination reagents in the catalytic aziridination of olefins and enantioselective, catalytic amido hydroxylation.[4,5] The use of hydroxamic acid derivatives as electrophilic nitrogen equivalents with metal catalysts, however, lacks precedence, despite the fact that they would enjoy some unique features as potential electrophilic aminating reagents.[11−15] In this regard, *N*-hydroxyamides and their derivatives are trivially prepared and as a class these enjoy greater shelf life than their *N*-haloamide counterparts. Moreover, the successful development of such compounds as electrophilic aminating reagents would afford trifluoroacetamides, which may be easily converted to the corresponding free amine under neutral ($NaBH_4$) or mildly alkaline ($K_2CO_3/H_2O/MeOH$, 25 °C) conditions.[16]

N,*O*-Bis(trifluoroacetyl)hydroxylamine (**3**) is conveniently prepared in large quantity (0.8 mol) as a crystalline solid by treatment of neat trifluoroacetic anhydride with hydroxylamine hydrochloride (Scheme 1).[17] Although this hydroxamic acid anhydride (**3**) proved sluggish in the reaction with sulfides under a variety of conditions, we observed that the corresponding lithium salt **1** serves as an electrophilic nitrogen equivalent in the presence of transition-metal catalysts. This salt was generated upon treatment of **3** with *t*-BuLi in Et_2O at −78 °C with warming to 23 °C. This previously unknown salt can be isolated as an analytically pure white solid[18] following trituration with pentane. It is worth noting that in our hands **1** can be stored for extended periods of time at ambient temperature without decomposition. As part of a comprehensive study, we outline below the use of this electrophilic nitrogen source for the preparation of *N*-(trifluoroacetyl)sulfilimines from sulfides. The preparation of sulfilimines has been accomplished by treatment of sulfides with the traditional known sources of electrophilic nitrogen, namely, *N*-halosulfonamides, the related *N*-arylsulfonyliminoiodobenzenes, and acyl or carbamoyl azides.[8,19] This class of sulfur compounds enjoys rich synthetic chemistry[20] and, for example, can be utilized to prepare aziridines[21] and oxazolinones.[22] Moreover, optically active sulfilimines can be stereospecifically converted to the corresponding optically active sulfoxides.[23,24]

Scheme 1. Reagent Synthesis



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[8] Bach, T.; Körber, C. *Tetrahedron Lett.* **1998**, *39*, 5015.

[9] Reddy, K. L.; Dress, K. R.; Sharpless, K. B. *Tetrahedron Lett.* **1998**, *39*, 3667.

[10] (a) Yamada, Y.; Yamamoto, T.; Okawara, M. *Chem. Lett.* **1975**, 361. (b) Breslow has utilized this reagent in the tosylamidation of cyclohexane with Mn(III) or Fe(III) porphyrins; see: Breslow, R.; Gellman, S. H. *J. Chem. Soc., Chem. Commun.* **1982**, 1400. More recently this reagent has been utilized in Cu-catalyzed olefin aziridination reactions.[6]

[11] For the asymmetric synthesis of α-amino acid derivatives via an electrophilic amination of chiral amide cuprates, see: Zheng, N.; Armstrong, J. D.; McWilliams, J. C.; Volante, R. P. *Tetrahedron Lett.* **1997**, *38*, 2817.

[12] Tamura has described the use of the highly reactive *N*-[((trifluoromethyl)sulfonyl)oxy]carbamate in the thermal reaction of sulfides to give sulfilimines. The preferred mode for reagent preparation prescribes the use of the thallium salt of ethyl *N*-hydroxycarbamate; see: Tamura, Y.; Ikeda, H.; Mukai, C.; Morita, I.; Ikeda, M. *J. Org. Chem.* **1981**, *46*, 1732.

[13] For the amination using an N-BOC-benzoylhydroxylamine, see: Cardillo, G.; Gentilucci, L.; Bastardas, I. R.; Tolomelli, A. *Tetrahedron* **1998**, *54*, 8217.

[14] The activated ethyl [((4-nitrophenyl)sulfonyl)oxy]carbamate (NsONHCO$_2$Et) has been utilized in Michael addition reactions to activated unsaturated acceptors to give enolates that subsequently undergo ring closure to the corresponding aziridine; see: Fioravanti, S.; Pellacani, L.; Stabile, S.; Tardella, P. A. *Tetrahedron* **1998**, *54*, 6169.

[15] Genêt has utilized *tert*-butyl *N*-(tosyloxy)carbamate as an aminating reagent with organolithiums (*n*-BuLi, MeLi), organocopper (PhCu), and ester enolates (Li^+ and Zn^{2+}); see: Genêt, J. P.; Mallart, S.; Greck, C.; Piveteau, E. *Tetrahedron Lett.* **1991**, *32*, 2359. In addition, Genêt has utilized lithium allyl [(arylsulfonyl)oxy]carbamates as aminating reagents; see: Greck, C.; Bischoff, L.; Ferreira, F.; Genêt, J. P. *J. Org. Chem.* **1995**, *60*, 7010.

[16] Greene, T. W.; Wutts, P. G. M. *Protecting Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991; p 353.

[17] For the preparation of the parent hydroxamic acid, see: Pomeroy, J. H.; Craig, C. A. *J. Am. Chem. Soc.* **1959**, *81*, 6340.

[18] ^{19}F NMR (CD_2Cl_2, 296 K): δ −70.3, −75.2 ppm. IR (KBr): 1786, 1655 cm^{-1}. Anal. Calcd for $C_4NO_3LiF_6$: C, 20.80; N, 6.06. Found: C, 20.67; N, 6.02.

[19] For recent developments in the synthesis of sulfilimines, see: (a) Takada, H.; Nishibayashi, Y.; Ohe, K.; Uemura, S. *Chem. Commun.* **1996**, 931. (b) Takada, H.; Nishibayashi, Y.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1997**, *62*, 6512. (c) Bach, T.; Korber, C. *Tetrahedron Lett.* **1998**, *39*, 5015.

[20] For a recent review on sulfilimine chemistry, see: Davis, F. A.; Zhou, P.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13.

[21] Yoshimure, T.; Akasaka, T.; Furukawa, N.; Oae, S. *Heterocycles* **1977**, *7*, 287.

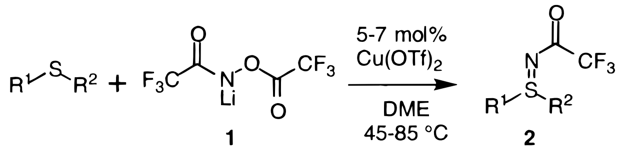
[22] Abou-Gharbia, M.; Ketcha, D. M.; Zacharias, D. E.; Swern, D. *J. Org. Chem.* **1985**, *50*, 2224.

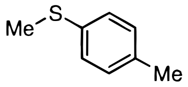
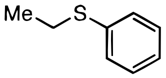
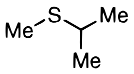
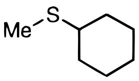
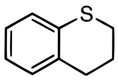
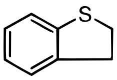
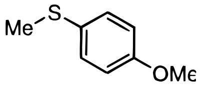
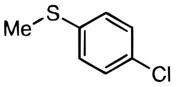
[23] Day, J.; Cram, D. J. *J. Am. Chem. Soc.* **1965**, *87*, 4398.

[24] For catalytic methods for the preparation of sulfoxides from sulfides, see: (a) Brunel, J. M.; Diter, P.; Duetsch. M.; Kagan, H. B. *J. Org. Chem.* **1995**, *60*, 8086. (b) Brunel, J.-M.; Kagan, H. B. *Bull. Soc. Chem. Fr.* **1996**, *113*, 1109. (c) Brunel, J. M.; Kagan, H. B. *Synlett* **1996**, 404. Also see: Palucki, M.; Hanson, P.; Jacobsen, E. N. *Tetrahedron Lett.* **1992**, *33*, 7111. For a related process, see: Cogan, D. A.; Liu, G. C.; Kim, K. J.; Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011.

Treatment of sulfides with **1** and 1−7 mol % $Cu(OTf)_2$ in dimethoxyethane (DME) at 45−85 °C cleanly furnishes *N*-(trifluoroacetyl)sulfilimines in up to 95% yield (Table 1).[25]

Table 1. Catalytic Amidation of Sulfides with 1[a]



Entry	Sulfide	% Cu(II)	Yield
1		7%	78%
2		1%	65%
3		5%	77%
4		7%	76%
5		7%	80%
6		7%	68%
7		7%	65%
8		5%	95%
9		7%	72%

[a] Reaction conditions: sulfide, 5−7 mol % $Cu(OTf)_2$, **4** (2 equiv), dimethoxyethane (0.10 M) for 6−15 h at 45−85 °C. Upon completion, the reaction mixture is concentrated in vacuo and purified by chromatography on silica gel. [b] All of the sulfides utilized are either commercially available or have been prepared according to known procedures.

As shown in Table 1, the processes are applicable to a range of sulfides including cyclic as well as acyclic dialkyl and alkyl/aryl sulfides. Electron-rich aryl sulfides afford adducts at a faster rate than their electron-deficient counterparts. Several observations that we have made in the course of our preliminary investigations deserve noting. Following a study of the reaction in a number of solvents (MeCN, THF, Et_2O, CH_2Cl_2), DME proved to be optimal. In the other solvents either **1** was only sparingly soluble or, soon after the initiation of the reaction, precipitates were observed with concomitant detrimental effects on the reaction rate. Although the structure of the active aminating reagent in solution is presently unknown, we speculate that the adduct of Cu(II) with **1** may correspond to the observed precipitate that subsequently removes the catalyst from solution in solvents other than DME.[26] The amination reaction of sulfides by **3** or **1** is not catalyzed by Brønsted acid. Thus, when sulfide, **3** or **1**, and *p*-toluenesulfonic acid were stirred at 60 °C for 15 h, no sulfilimine adduct was isolated. However, although we have observed that other metal salts such as $Mg(OTf)_2$ and $Sn(OTf)_2$ function as catalysts, the best yields and rates were obtained with either Cu(I) or Cu(II) triflates; the use $Cu(OTf)_2$ offers advantages, since it is readily handled on the benchtop.

We have demonstrated the ability of the novel salt of hydroxamic acid anhydride **1** to serve as a source of electrophilic nitrogen. In the presence of this reagent and 1−7 mol % $Cu(OTf)_2$ a range of sulfides were converted to the corresponding N-trifluoroacetylated sulfilimines in good yields. The salient features of **1** as an aminating reagent include its facile, convenient synthesis from inexpensive, readily available starting materials and, importantly, the ease with which it can be handled and stored. Ready access to this novel reagent allows further potential applications in inorganic coordination chemistry for the preparation of novel transition metal nitrides and imines. Moreover, in addition to the process reported herein, **1** may also find use in other processes for catalytic nitrogen-transfer reactions in organic synthesis. Such investigations are ongoing and will be reported as results become available.

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Supporting Information Available: Full characterization data and proton spectra for **1** and the sulfilimine products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) The amidation reaction may be conducted with only 1% $Cu(OTf)_2$ (Table 1, entry 1), albeit with longer reaction times. We have found that 5−7 mol % catalyst affords the products in an expeditious manner (6−10 h).

(26) It is interesting to note that of the solvents examined DME is unique in its ability to potentially form chelates; thus, it will be interesting to examine chiral bidentate ligands for the corresponding asymmetric amidation of sulfides.