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Thiolysis and Hydrolysis of Imino and Iminium Triflates: Synthesis of Secondary and Tertiary Thioamides and ^{18}O-Labeled Amides.

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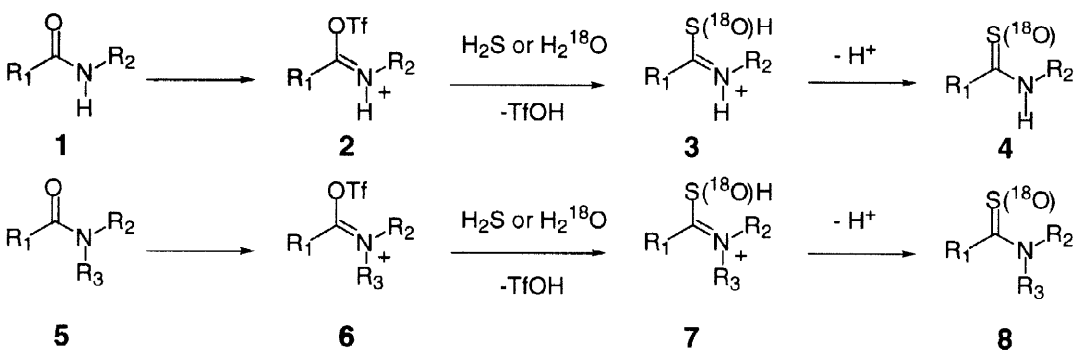
Abstract: Secondary and tertiary amides were treated with trifluoromethanesulfonic (triflic) anhydride in the presence of pyridine at low temperatures to generate imino and iminium triflates. Subsequent treatment with hydrogen sulfide immediately gave rise to the corresponding thioamide in good to excellent yields at low temperature. Alternatively, treatment with stoichiometric amounts of ^{18}O-labeled water produced the ^{18}O-labeled amide.

Imino **2** and iminium **6** triflates are useful synthetic intermediates since they can be readily generated from secondary or tertiary amides with trifluoromethanesulfonic (triflic) anhydride at low temperatures. They were first used as precursors of ketiminium cations which could be used as electrophilic substrates in cycloadditions.[1] Their electrophilic nature has also been demonstrated with cyanide[2] and azide ions.[3] Recently, we have shown that these intermediates can be generated in the presence of pyridine and treated with triols to give rise to orthoesters in a mildly acidic pyridine/pyridinium hydrotriflate medium.[4] In this communication, we would like to report that the same electrophilic intermediates can be treated at low temperatures with stoichiometric amounts of H_2S (CAUTION: toxic gas) or $H_2{}^{18}O$ to selectively substitute the oxygen atom of the amide with a sulfur or oxygen-18 atom (Scheme 1). In essence, we have developed a new method for the synthesis of secondary and tertiary thioamides and ^{18}O-labeled amides.

Scheme 1



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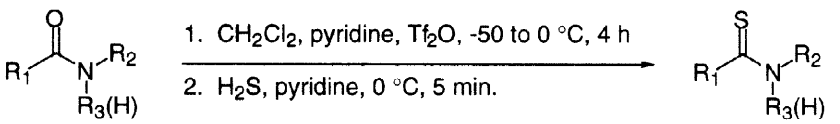
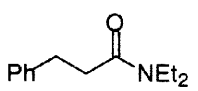
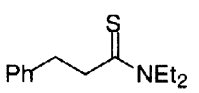
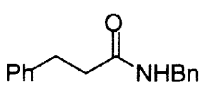
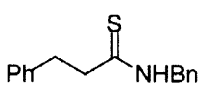
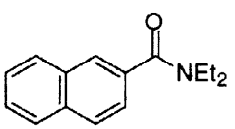
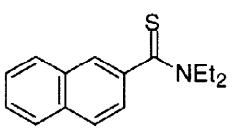
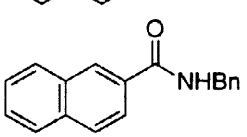
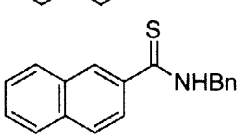
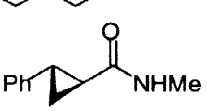
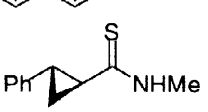
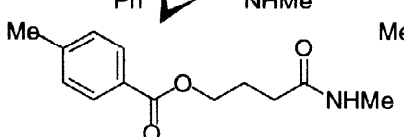
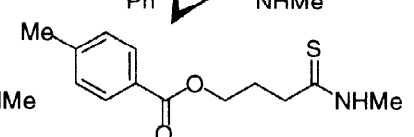
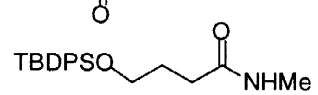
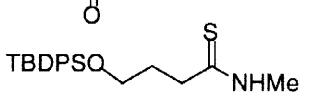
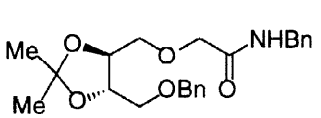
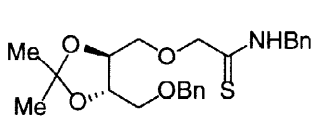
Thioamides. Traditionally, thioamides have been made by extensively heating the amide with P_2S_5.[5] Other methods include the **Willgerodt-Kindler reaction**[6] and tin-assisted sulfuration.[7] More recently, Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,2,3,4-dithiaphosphetane-2,4-disulfide) has become the reagent of choice for the synthesis of thioamides.[8] However, secondary and tertiary amides must be heated in toluene or benzene with Lawesson's reagent to affect this transformation which is problematic for substrates bearing thermally labile functionality.[9] Wipf has recently reported the sulfhydrolysis of oxazolines to generate 2-hydroxyethyl-thioamides by using a saturated basic H_2S solution.[10] However, for secondary and tertiary amides which have acyclic or exocyclic C-N bonds, the intermediate alkyl imidate or alkyl iminium ether undergoes irreversible sulfhydrolyses of the C-N bond to yield the thionoester.[11] Our approach takes advantage of the leaving group ability of the triflate anion such that sulfhydrolysis of the C-N bond does not occur.[12] Another advantage is that imino and iminium triflates are strong electrophiles which react instantaneously with stoichiometric amounts of H_2S at low temperatures to immediately produce the thioamide.

Table 1. Conversion of amides into thioamides

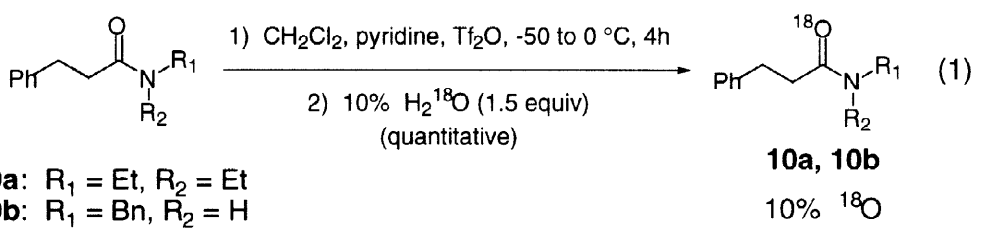


Entry	Starting Material	Product	Isolated Yield
1			92 %
2			94 %
3			96 %
4			95%
5			91 %
6			82 %
7			86 %
8			70 %

Results with various secondary and tertiary amides are summarized in Table 1. The typical reaction conditions consists of adding pyridine (3.5 equiv) to a CH_2Cl_2 solution of the secondary or tertiary amide (~0.1 M). The solution is cooled to -50 °C under argon and triflic anhydride (1.3 equiv) is then added slowly.[13] The solution is then stirred at 0 °C for at least 4 hours to complete the formation of the imino or iminium triflate. A minimal amount of H_2S is then bubbled slowly into the reaction until the reaction is judged complete by thin layer chromatography. Pyridine (3.5 equiv) is again added to neutralize the reaction. Alternatively, an anhydrous solution of NaSH in acetonitrile or acetone could be used in place of gaseous H_2S.[11] The meta-stable geminal bis-thiol has been observed in instances where excess H_2S has been added. In this case, the septum is removed and the solution is stirred in the fume hood until the thioamide is regenerated. Workup is achieved by filtration through silica get followed by flash chromatography to give the desired thioamide in good to excellent yields.

The method works well with secondary and tertiary amides of both aliphatic as well as aromatic acids (entries 1-4). *N*-Methyl-3-phenylcyclopropane carboxamide (Entry 5) was readily converted to its thioamide; the reaction on the *N,N*-dimethyl analog yielded only decomposition products, which could be attributed to the phenylcyclopropyl iminium triflate having a propensity to undergo carbocationic cyclopropane ring opening. Entries 6-8 demonstrate that functional groups such as esters, silyl ethers, acetonides, and benzyl ethers are stable to these conditions.

^{18}O-Labeled Amides: Typically, labeling amides requires dissolving the parent acid in $H_2{}^{18}O$ to equilibrate the oxygens. The $H_2{}^{18}O$ solvent is then recovered while the acid is isolated and then coupled to the amine residue to form the ^{18}O-labeled amide.[14] Since the reactivity of H_2O is very similar to that of H_2S, we envisioned that by replacing H_2S with $H_2{}^{18}O$, we could transform the amide to the ^{18}O-labeled amide (eq 1).



(1)

9a: R_1 = Et, R_2 = Et
9b: R_1 = Bn, R_2 = H

10a, 10b
10% ^{18}O

As expected, treatment of iminium and imino triflates with stoichiometric amounts of ^{18}O-enriched water produced the ^{18}O-labeled amide. Using mass spectrometry, the isotopic purity of the amide was determined to be the same as that of the $H_2{}^{18}O$ used in the reaction. Thus, only a slight excess of the expensive and commercially available $H_2{}^{18}O$ is required. Furthermore, this method requires only one pot to isotopically label the amide instead of a multistep equilibration and derivatization sequence.

In conclusion, imino or iminium triflates react efficiently with H_2S and $H_2{}^{18}O$ to give thioamides and ^{18}O-labeled amides, respectively. Both secondary and tertiary amides undergo this reaction and various functional groups can tolerate the reaction conditions. This method provides a low temperature alternative to Lawesson's reagent for thioamide synthesis. Finally, because this method uses only stoichiometric amounts of isotopic water, this one pot synthesis of ^{18}O-labeled amides is more efficient than traditional methods.

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13. Addition of triflic anhydride must be slow since an exotherm can cause triflic anhydride to react with pyridine to form trifyl pyridinium triflate which is not reactive enough to *O*-sulfonylate the amide. The addition of triflic acid can be done in the absence of pyridine to avoid the formation of triflyl pyridinium triflate, but no pyridine would then be present to neutralize any adventitious acid.
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