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Generation of N-Acyl Iminium Ions from Ionization-Rearrangement Reactions of N-Triflyloxy Amides

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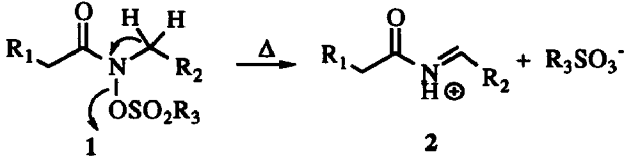
Summary: N-Triflyloxy amides undergo ionization in refluxing isopropanol to give N-acyliminium ions which can be trapped by addition of allyltrimethylsilane to the reaction mixture. Alternatively they can be converted to N-(isopropoxy)alkyl amides and then back to N-acyliminium ions under a variety of conditions.

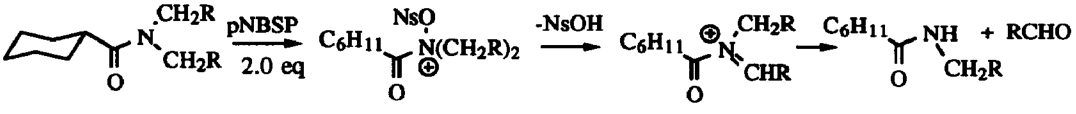
Studies of the chemistry of N-sulfonyloxyamines has demonstrated that the N-O bond in these substances is weak and highly prone to ionization.[1] As a result N-sulfonyloxyamines readily undergo concerted ionization-rearrangement reactions in the absence of bases under very mild conditions.[2] If N-sulfonoxylamides **1** were to undergo similar chemistry (Eqn. 1), then a new approach to the synthesis of N-acyliminium ions **2** could be developed which is simple and highly convergent. The versatility of N-acyliminium ions for the synthesis of a wide variety of nitrogenous materials[3] underscores the continuing need to find new methods for their preparation.



1 **2**

(1)

Initial indication that this route to N-acyliminium ions was feasible came from the reactions of N,N-dimethylamides with p-nitrobenzenesulfonyl peroxide (pNBSP). When amides **3a** and **3b** were treated with pNBSP in ethyl acetate saturated with water, N-dealkylation occurred to produce secondary amides **4a** and **4b**.[4] It was assumed that initial formation of N-nosyloxyamide **6** followed by loss of p-nitrobenzenesulfonic acid gave the iminium ion **5**. Hydrolysis of **5** gave dealkylated amide **4** and formaldehyde (Eqn. 2). This reaction scenario was supported by dimedone trapping of the formaldehyde produced upon hydrolysis of **5a**.[5]



(2)

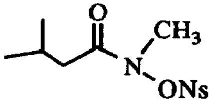
3a R=H
3b R=CH_3

6

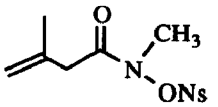
5

4a 82%
4b 43%

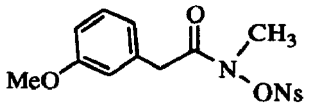
This oxidative approach was unfortunately limited to saturated compounds and could not be generalized. The results did suggest, however, that N-sulfonyloxyamides prepared by other, non-oxidative, routes could potentially be useful N-acyliminium ion precursors. N-Nosyloxy amides **1a-c** were prepared from the corresponding hydroxamic acid with p-nitrobenzenesulfonyl chloride.[6] While these and other N-sulfonyloxy amides were found to undergo fascinating and very useful base-promoted chemistry,[6b, 7, 8] heating in refluxing xylene (140°C) for five days resulted in slow loss of starting material, but failed to give recognizable products from ionization-rearrangement processes.



1a

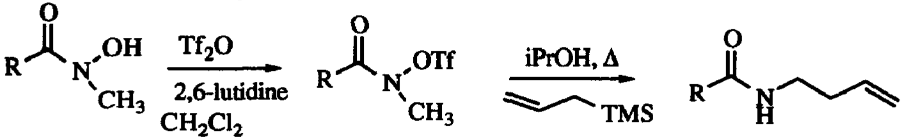


1b



1c

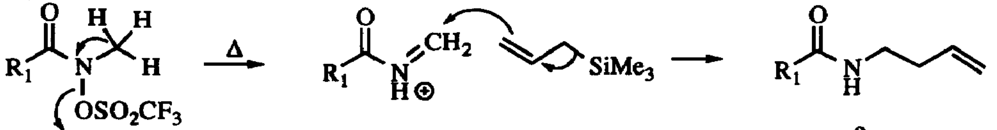
Not unexpectedly it was found that ionic decomposition of N-sulfonyloxy amides was greatly influenced by the solvent polarity and the leaving ability of the N-sulfonyloxy group. Consequently a series of N-triflyloxy amides **8a-f** were prepared by the reaction of triflic anhydride with the corresponding hydroxamic acids[9] at -78°C. The crude N-triflyloxy amides[10] were dissolved in isopropanol and allyltrimethylsilane (10 eq) and the mixture was refluxed for 15-20 hrs. Aqueous workup gave N-(4-butenyl)amides **9a-f** in good yields (Eqn. 3).[11]



(3)

8a $R=CH_3$	**9a**, 60%
8b $R=(CH_3)_2CHCH_2$	**9b**, 61%
8c $R= CH_2=CHCH_2$	**9c**, 68%
8d R= 1-cyclohexenyl-CH_2	**9d**, 56%
8e $R=C_6H_5$	**9e**, 80%
8f $R=C_6H_5CH(CH_3)$	**9f**, 65%

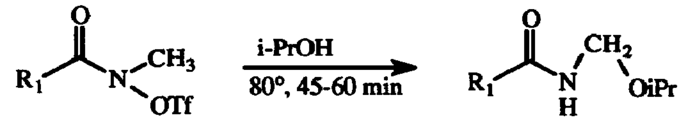
These results show that the ionization of N-triflyloxy amides in isopropanol occurs under fairly mild reaction conditions. The N-acyliminium ion **2** produced by ionization-rearrangement is trapped by allyltrimethylsilane present in the reaction mixture to give the N-butenylamide product **9** (Eqn.4).



(4)

8 **2** **9**

It was further discovered that when N-triflyloxy amides **8** were heated to reflux in isopropanol for 45-60 min, N-(isopropoxymethyl) amides **10** were obtained in good to excellent yields (Eqn. 5).[11] N-(Isopropoxymethyl) amides **10** are stable materials which were obtained analytically pure by chromatography or recrystallization . Capture of iminium ion **2** by isopropanol is the probable origin of **10**. It is likely that iminium ion trapping by allyltrimethylsilane shown in Eqn. 3 is mediated by the initial formation of N-(isopropoxymethyl) amides **10** from **8**. N-(Alkoxyalkyl)amides such as **10** are themselves excellent N-acyliminium ion precursors[3] and could serve as the proximate source of iminium ions trapped by allyltrimethylsilane.

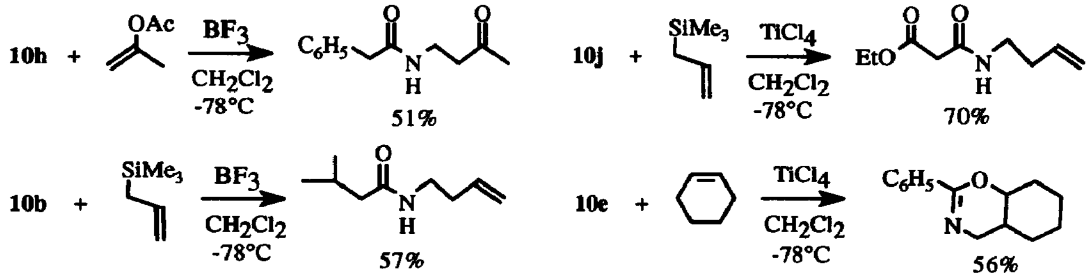


(5)

8b, $R_1 = (CH_3)_2CHCH_2$	**10b**, 78%
8c, $R_1 = CH_2{=}CHCH_2$	**10c**, 74%
8e, $R_1 = C_6H_5$	**10e**, 85%
8h, $R_1 = C_6H_5CH_2$	**10h**, 90%
8i, $R_1 = 3\text{-}CH_3OC_6H_4CH_2$	**10i**, 86%
8j, $R_1 = EtO_2CCH_2$	**10j**, 62%
8k, $R_1 = Cl\text{-}CH_2$	**10k**, 73%
8l, $R_1 =$ 2-furyl	**10l**, 92%

N-(Isopropoxymethyl) amides **10** can also be converted to N-acyliminium ions by Lewis acid catalysis and trapped with a variety of π-bonded carbon nucleophiles. In fact, conversion of N-triflyloxy amides to N-(isopropoxymethyl) amides **10** followed by iminium ion trapping reactions is a more versatile strategy than *in situ* trapping because a wider variety of reaction conditions and catalysts can be used to generate the iminium ion. Chart 1 demonstrates several structures that have been produced from N-(isopropoxymethyl) amides **10** in standard iminium ion trapping reactions.[3]

Chart 1



The formation of N-(isopropoxymethyl) amides **10** and then N-acyliminium ions from N-triflyloxy amides has several noteworthy features. It is, to our knowledge, the first general method for accessing N-acyliminium ions from N-oxidized precursors.[12] Second the method is highly convergent. Third, and most importantly, the method is tolerant of a wide variety of functional groups. Preliminary results also show that groups other than methyl can be attached to the nitrogen atom.[13]

The work described here provides an important adjunct to current methods for the formation of N-(alkoxyalkyl) amides and then N-acyliminium ions. The electrochemical oxidation of amides[3c] is very useful, but only functional groups less oxidizable than the amide can be present in the substrates. Only scattered reports of aryl, olefinic, ester, or ketone groups can be found.[3] Katritzky recently reported that the condensation of aldehydes, amides and benzotriazole followed by treatment with alkoxides gives N-(alkoxyalkyl)amides.[14] While this approach could be an important addition to the methodology, only alkyl and aryl groups have been utilized thus far. The range of functionality compatible with the present route is striking (Eqn. 5), and well beyond the limitations known for electrochemical oxidation or reported for the benzotriazole route.

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10. Triflate **8e** is a light yellow solid which was recrystallized to analytical purity. The remaining triflates **8a-d, f-h** were isolated as light yellow oils of >90% purity by nmr analysis and had spectra consistent with the N-triflyloxy structure. They were unstable at room temperature and began to darken upon removal of solvent. They were used immediately after isolation with excellent results.

11. Products were characterized completely spectroscopically. The yields reported are average yields of analytically or spectroscopically pure products from duplicate runs.

12. Fowler has used FVP to convert N-acetoxy amides to N-acylimines which undergo intramolecular Diels-Alder reactions. However, this method is not amenable to the general production of N-acyliminium ions. See Huang, N. Z.; Miller, M. J.; Fowler, F. W., *Heterocycles*, **1988**, *27*, 1821 and references therein.

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