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DIMETHYL SULFIDE DITRIFLATE: A NEW REAGENT FOR THE CONVERSION OF AMINO HETEROCYCLES TO IMINOSULFURANES

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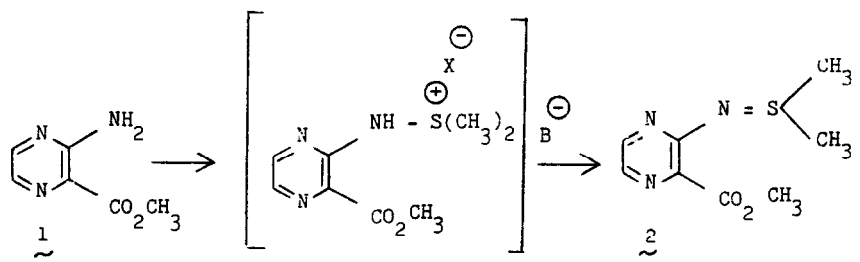
ABSTRACT: A general method for the preparation of iminosulfuranes is described. Treatment of amino heterocycles with dimethyl sulfide ditriflate under mild conditions affords, after base treatment, the corresponding iminosulfuranes in high yield.

Iminosulfuranes have proven to be important intermediates in the synthesis of a variety of heterocycles by virtue of their ability to participate in alkylation, acylation, oxidation, reduction and sigmatropic reactions.[1] As part of a program directed at the synthesis of novel nitro heterocycles, we required the iminosulfurane derivatives of various amino heterocycles. Gilchrist, et al.,[1,2] and more recently Taylor, et al.[3] have reported that iminosulfurane derivatives of unsubstituted or methyl substituted aminopyridines, aminopyrimidines and aminopyrazines could be prepared by treatment of the appropriate heterocycle with dimethylsulfide/N-chlorosuccinimide complex. Several other procedures have also been developed for this transformation,[4,5] including those involving the activation of dimethyl sulfoxide with Lewis acids,[6] dicyclohexyl carbodiimide,[7] and trifluoroacetic anhydride.[8]

Despite the literature precedent for this transformation, we found that conversion of methyl 3-aminopyrazinoate (1)[11] to its corresponding iminosulfurane 2 utilizing known methodology was problematic. For example, treatment of 1 with dimethyl sulfide/N-chlorosuccinimide,[1-3] or with tert-butyl hypochlorite/dimethyl sulfide[5] resulted only in recovery of starting materials. Treatment of 1 with a 1.5 molar

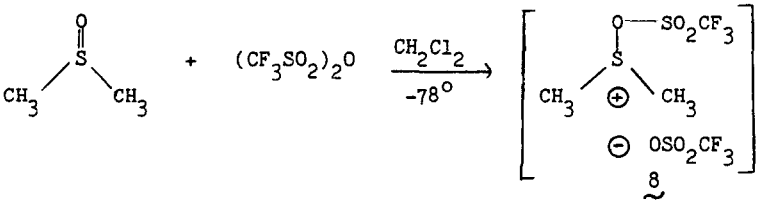


1 2

excess of dimethyl sulfoxide/trifluoroacetic anhydride[8] gave a complex product mixture, containing starting material and desired sulfilimine (ca. 50% yield). Further increases in the molar amount of this oxidant

and/or longer reaction times to effect complete conversion gave dramatically reduced yields of products. We also encountered, in addition to 1, several other amino heterocycles 3-7 (Table I) possessing either electron-withdrawing groups or extended conjugation which behaved in similar fashion toward these oxidants.

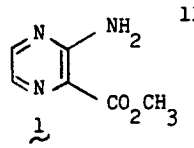
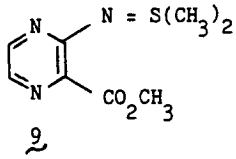
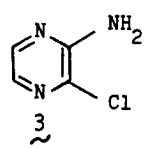
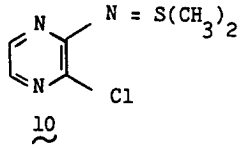
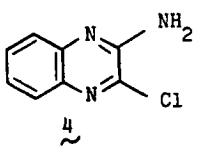
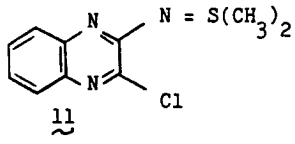
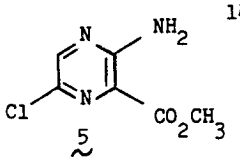
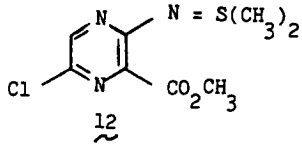
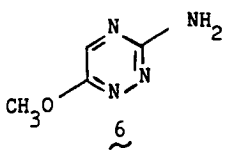
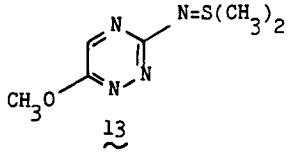
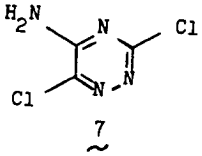
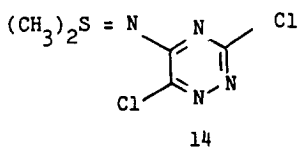
The poor reactivity of these molecules (1, 3-7) toward the reagents mentioned is apparently due to the diminished nucleophilicity of the amino group. We anticipated that successful conversion of these amino heterocycles to their iminosulfuranes would require a more reactive sulfonium species, i.e. one possessing a better leaving group, than so far employed. We have found that treatment of 1 with a 1.2 molar excess of dimethyl sulfide ditriflate (8), prepared from dimethyl sulfoxide and trifluoromethane-sulfonic anhydride,[9] resulted in a clean reaction affording the iminosulfurane 2 in 85% isolated yield, uncontaminated by starting material. In a similar manner, the iminosulfuranes of each of the compounds 3-7 were readily prepared in high yield.



In view of the modest yields[9] of carbonyl compounds produced when alcohols are treated with dimethyl sulfide ditriflate (8), the success of this reagent for oxidation of the amine function is noteworthy. The formation of methylthiomethyl derivatives, which plagued the alcohol oxidations, was not seen in the present case. The reaction of amino heterocycles with the sulfur atom of 8 is apparently a more favorable process than the corresponding reaction of alcohols, possibly due to the "soft"[10] nature of both nitrogen and sulfur.

Considering the high yields and mild reaction conditions, the present technique would appear to constitute the method of choice for the conversion of amino heterocycles, particularly those whose amino functions are of low nucleophilicity, to their corresponding iminosulfuranes. A typical procedure is as follows: To a mechanically stirred solution of 0.46 g (0.0059 mol) of dimethyl sulfoxide in 10 ml of methylene chloride cooled to -78° under nitrogen was added dropwise 1.13 g (0.004 mol) of trifluoromethane-sulfonic anhydride at such a rate that the temperature was maintained at -78°. To this suspension was added dropwise a solution of 0.5 g (0.0033 mol) of 1 at -70°. The resulting orange suspension was stirred at -78° for 2 hours and then at -55° for 1 hour. The reaction was quenched with 20 ml of 5% aqueous sodium hydroxide added at such a rate that the temperature was maintained at less than -10°. Another 30 ml of methylene chloride was added and after five minutes stirring, the phases were separated. The aqueous phase was extracted with 30 ml of methylene chloride, the organic phases were combined and washed with three 10-ml portions of water. The methylene chloride solution was dried (Na_2SO_4) and the solvent was removed on the rotary evaporator to afford 0.60 g (85%) of the desired sulfilimine as a stable yellow oil.

Table I. Preparation of Sulfilimines with Dimethyl Sulfide Ditriflate (8)

Substrate	Product [17]	Yield (%)
 11 1	 9	85
 12 3	 10	79
 13 4	 11	88
 14 5	 12	91
 15 6	 13	84
 16 7	 14	93

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(17) 60MHz ^{1}H NMR data: 9 [$(CD_3)_2SO$], δ 2.80 (6H, s), 3.74 (3H, s), 7.48 (1H, d), 7.91 (1H, d); 10 ($CDCl_3$), δ 2.86 (6H, s), 7.55 (1H, d), 7.87 (1H, d); 11 [$(CD_3)_2SO$], δ 2.87 (6H, s), 7.45 (4H, m); 12 ($CDCl_3$), δ 2.77 (6H, s), 3.88 (3H, s), 7.86 (1H, s); 13 ($CDCl_3$) δ 2.80 (6H, s), 3.87 (3H, s), 7.84 (1H, s); 14 [$(CD_3)_2SO$], δ 2.90 (6H, s).

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