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Reductive Cleavage of N-O Bonds in Hydroxylamine and Hydroxamic Acid Derivatives Using SmI₂/THF

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Abstract: The title reaction affords a general method for the reductive cleavage of N-O bonds, and is successful in some cases where established methods fail.

Many very useful synthetic methods for the synthesis of nitrogen containing compounds proceed via intermediates possessing N-O bonds which must ultimately be cleaved to provide the more commonly encountered oxidation states of nitrogen. Examples include [4+2] cycloadditions of acylnitroso compounds,¹ ene reactions of acylnitroso compounds,² free radical additions to oxime ethers,³ [3+2] cycloadditions utilizing nitrile oxides and nitrones,⁴ [3+2] cycloaddition reactions of O-silyl nitronates,⁵ [4+2] cycloadditions of nitroalkenes,⁶ etc. The most common procedures for such reductive cleavage reactions employ hydrogenolysis,⁷ reduction with Mg(Hg)/TiCl₄,⁸ reduction by Al(Hg) or Na(Hg),⁹ and reduction using TiCl₃.¹⁰ Recently, however, we encountered a case for which the more common procedures proved inadequate, which led us to consider the use of SmI₂¹¹ in such reductions. Although isolated examples of the reductive cleavage of N-O bonds by SmI₂ have been previously recorded,^{12,13} the general utility of the reagent for this transformation has not been established.

Specifically, we needed to effect reduction of the hydroxamic acid derivative 1 to afford the secondary trifluoroacetamide 2 (see Eq. 1). Our previously developed protocols using Al(Hg) or $Na(Hg)^9$ gave none of the desired product in this case.¹⁴ Similarly ineffective were hydrogenolysis protocols previously used successfully in N-O bond cleavages.

However, the use of SmI₂/THF proved very efficient, affording 2 in 91% isolated yield.³ A survey of other substrates indicates that this reaction protocol is indeed quite general, particularly with TFA derivatives, which do not give good results using our previous method.⁹ Compatibility with the TFA group is of course quite desirable, since this group can itself be removed under reasonably mild alkaline conditions (e.g. $K_2CO_3/MeOH$).



(1)

The results obtained with such substrates are tabulated in Table I. To preclude isolation difficulties with low molecular weight primary amines, some of the yields given are overall yields for acetamides or trifluoroacetamides prepared by quenching the SmI₂ reductions with Ac₂O or TFAA. The reaction protocol employed in all cases was as follows: To a stirring solution of substrate (0.40 mmol) in dry THF (2 mL), maintained under nitrogen at the desired temperature, was added a freshly prepared solution of SmI₂ (9.8 mL of 0.088 M in THF, prepared¹⁵ from I₂ and Sm metal in refluxing THF) dropwise. After TLC analysis indicated complete reaction, the reaction mixture was diluted with 30 ml (3 volumes) of CH₂Cl₂, then quenched with 20 ml (2 volumes) of 10% aqueous sodium thiosulfate solution.¹⁶ Alternatively, after TLC monitoring indicated complete reaction, acetic anhydride or TFAA (1.8 mmol, 4.5 eq) was added and the resulting mixture was stirred for 15 min before dilution with CH₂Cl₂ and addition of sodium thiosulfate solution as described above. Normal extractive workup, drying over MgSO₄, filtration, and concentration afforded the crude products, which were isolated by chromatography over silica gel.

As can be seen by the results given in entries 1-6, the reduction is successful even with simple hydroxylamines when carried out at rt or -23 °C. One substrate (entries 4-6) which could be cleaved at these temperatures gave no reaction at -78 °C. In general, however, N-acyl derivatives (*i.e.* hydroxamic acid derivatives) were reduced under milder conditions than the hydroxylamines. Entries 7-12 show the need for oxygen substitution to effect these reductions. Thus, the hydroxamic acid in entries 7-8 is recovered essentially unchanged after reaction at rt for 50 min; the O-acetyl, O-benzyl, and O-methyl derivatives in entries 9-12 are all cleaved within 15 min at rt. The O-benzyl trifluoroacetamide of entries 10 and 11, which gave good results in the SmI₂ reduction, was also used as a substrate for attempted reduction with both Al(Hg) and Na(Hg). In neither case was the desired product obtained; in both instances the only observed product resulted from base induced cleavage of the trifluoracetamide group. With aluminum amalgam (0 °C - rt, 10 h) starting material (64%) was recovered along with 32% of the cleavage product; with sodium amalgam (0 °C, 90 min) an 82% isolated yield of the cleavage product was obtained.

Examination of the results given in Table I shows that this procedure is applicable to N, O dialkylhydroxylamines as well as various N-acyl (acetyl, trifluoroacetyl, benzoyl, benzyloxycarbonyl) derivatives. The bicyclic substrates (entries 15 and 16) conform to the general trend that higher yields are generally obtained with N-acyl substrates than with N-alkyl ones; however, in this particular case at least part of the diminished yield can be attributed to isolation difficulties with the highly polar product. The very mild nature of this reaction leads to compatibility with trifluoroacetamides, and may thus provide a useful complement to a variety of existing synthetic methodology.^{1-6,17}

Entry	Substrate	Time	Temperature	Product	Yield
		(min)	(°C)		(%) ^a
1		300	rt		69
2	Ph N- OBn I H	15	rt		906
3		15	rt		91¢
4	•	15	rt	Γ _Q	65 ^c
5		15 240	-23 -78	Ph N CF3	51¢
Ŭ	н	240		н	0c
7 8	Ph N CH ₃ OH	50 240	rt 65		trace 45
9		15	rt		95
10 11		15 15	rt -78		80 82
12		15	rt		70
13	OF OBn CH3	240	rt	CT N CH3	93
14		15	rt		95
15	A N Ph	90	-78	но(Ph)= о но(N	93 ^d
16	A.o. Ph	15	rt		55d

Table 1. Yields for Reductive Cleavage of N-O Bonds Promoted by SmI2

^aValues represent isolated yields. ^bReaction was quenched with acetic anhydride. ^cReaction was quenched with TFAA. ^dStarting material racemic, only one enantiomer is shown.

References and Notes

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- 16. Use of saturated (ca. 20%) aqueous sodium thiosulfate solution leads to the formation of an emulsion which makes workup much more difficult.
- For an example in which a C-O bond is cleaved using SmI₂ in the presence of an N-O bond, see: Schkeryantz, J. M.; Danishefsky, S. J. J. Am. Chem. Soc. 1995, 117, 4722.

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