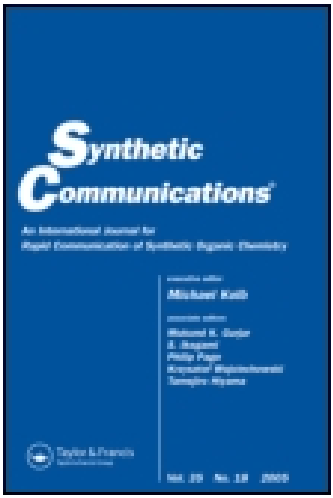

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Reduction of Aryl Trifluoromethyl Oximes

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REDUCTION OF ARYL TRIFLUOROMETHYL OXIMES

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Summary: Borane-tetrahydrofuran complex reduces trifluoromethyl oximes to trifluoromethyl hydroxylamines in good yields.

Due to the beneficial medicinal effects that fluorine can impart to biologically active molecules there is intense interest in the synthesis of organofluorine compounds.[1] Recently, enzyme inhibitors prepared from hydroxylamine intermediates have been reported.[2] Unfortunately, there are no known methods to access N-(2,2,2-trifluoro-1-arylethyl) hydroxylamines. We report herein the synthesis of N-(2,2,2-trifluoro-1-arylethyl)hydroxylamines by borane-tetrahydrofuran reduction of their oxime precursers.

In the literature there are reported only a few examples of N-(2,2,2-trifluoro-1-alkylethyl)hydroxylamines.[3] These compounds are generally prepared by hydrogenation of the corresponding nitroalkanes. In our investigations, hydrogenation of the aryl oximes under similar conditions gave low yields of product. For oximes lacking the trifluoromethyl group, there exist various methods for reduction of the oxime to the corresponding hydroxylamine. We found that under usual conditions, borane-pyridine,[4] borane-dimethylsulfide,[5] sodium cyanoborohydride,[6] and sodium borohydride[7] were ineffective or inefficient in achieving this transformation, probably due to the inductive effects of the highly

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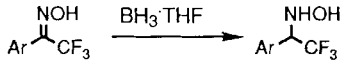
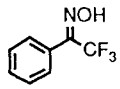
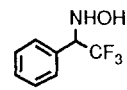
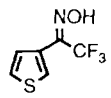
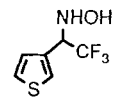
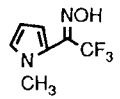
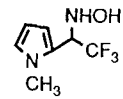
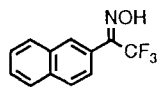
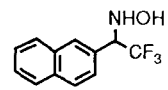
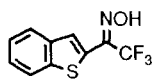
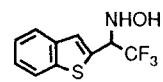
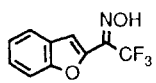
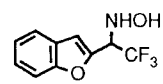
Table I. Reduction of Aryl Trifluoromethyl Oximes.



Entry	Oxime	Hydroxylamine[a]	mp°C	Yield(%)[b]
1			89-90	72
2			94-95	68
3			125-126	64
4			120-121	69
5			117-118	66
6			111-112	62

[a] All spectral and analytical data were consistent with the assigned structures.
[b] Yield of isolated pure material.

electronegative trifluoromethyl group on the oximino functionality. Borane-tetrahydrofuran complex, however, reduced the oximes to the hydroxylamines in good yields following an acidic hydrolysis. The oximes utilized were obtained in high yields as mixtures of the syn and anti isomers by standard techniques, i.e. by heating the corresponding ketones to reflux in 50% aqueous methanol solution with two equivalents of hydroxylamine hydrochloride and four equivalents of sodium acetate for several hours.

The typical experimental procedure used for the examples in Table I is described as follows: Borane-tetrahydrofuran complex (16 ml of 1M solution in tetrahydrofuran, 16 mmol) was added dropwise to the oxime (10 mmol) in tetrahydrofuran (50 ml) at 0°C under nitrogen. The reaction mixture was allowed to warm to 23°C and stirred at that temperature for 12 h. The tetrahydrofuran was removed, 20% aqueous hydrochloric acid (12 ml) was added slowly to the ice cooled flask, and the solution was heated to reflux for 1 h. The reaction mixture was cooled and made basic with 10% aqueous sodium hydroxide. The solution was extracted with ethyl acetate and the organic extracts washed with brine and dried ($MgSO_4$). The solvent was removed and the residue chromatographed or crystallized to afford the hydroxylamine.

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