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A CONVENIENT SYNTHESIS OF NITRONES BY N-ALKYLATION OF O-TRIMETHYLSILYLOXIMES

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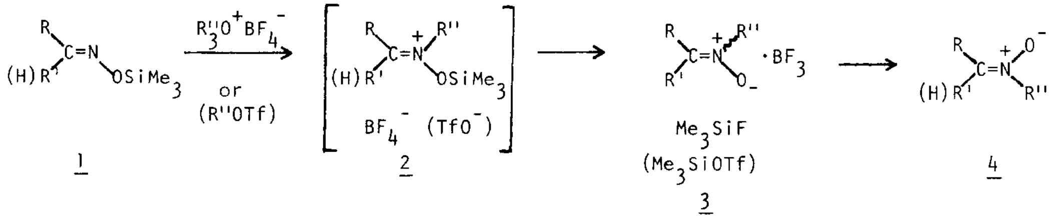
Abstract: Aldoxime and ketoxime-O-trimethylsilyl ethers can be alkylated with trialkyloxonium tetrafluoroborates and alkyl triflates at or below room temperature to produce nitrones in good yields.

Nitrones are versatile synthetic intermediates, especially for 1,3-dipolar cycloaddition reactions.[2] Condensation of carbonyl compounds with N-substituted hydroxylamines and oxidation of N,N-disubstituted hydroxylamines are the most common methods for their synthesis.[3] However, the yields can be quite variable and the conditions employed are sometimes incompatible with the presence of other functional groups. There is a continuing need to develop mild and versatile procedures for the synthesis of nitrones. One such method is outlined below.



O-Trimethylsilyloximes are well known derivatives and are readily obtained by heating the oximes with hexamethyldisilazane in an inert atmosphere.[4] Treatment of the compounds 1 with 1.1 equivalents of trimethyloxonium tetrafluoroborate in dichloromethane at room temperature under argon for several hours proceeds by N-alkylation (via the salts 2) and *in situ* desilylation to give initially the BF_3-ate complexes 3 of the nitrones. Many of these complexes are stable, crystalline solids, and they can be isolated, recrystallized and stored. Liberation of the nitrones 4 is carried out by solution of the complexes 3 in acetonitrile, adding one equivalent of potassium fluoride, followed by filtering, evaporating the solvent(s) and crystallizing or distilling the product. Alternatively, one equivalent of tetrabutylammonium fluoride may be added after Meerwein's reagent, and then standard workup to give the nitrones 4 directly. Triethyloxonium tetrafluoroborate, methyl triflate and allyl triflate are also effective alkylating agents. Presumably other triflates will also be suitable.[5] An excess of the alkylating agent is to be avoided as the product nitrones can be O-alkylated.

These procedures obviate the problem associated with alkylation of oximates, namely competing O- and N-alkylation except for (Z)-aldehyde oximates.[6]

In the case of aldoximes, the usually pure (E)-O-trimethylsilyloximes were employed. Alkylation should occur cis to the substituent and the (E) isomer of the nitrone should result initially. Indeed, alkylation and rapid ice-cold workup followed by examination with ^{1}H NMR allows the detection of both (E) and (Z) isomers in several cases. Purification invaribly results in the isolation of the more stable (Z)-aldonitrones.

Representative examples are shown in the Table. The last two entries demonstrate that the nitrones need not be isolated and can be heated in toluene after fluoride treatment to give the intramolecular cycloadducts. The methods are especially valuable because aqueous workup can be avoided if desirable.

(Z)-C-Phenyl-N-methylnitrone; Typical Procedure for Method A. To a solution of 1.94 g (10 mmol) of (E)-O-trimethylsilylbenzaldoxime (5) in 30 mL of dichloromethane, under argon, was added rapidly 1.48 g (11 mmol) of Meerwein's reagent. After stirring for 7 h at room temperature, the solvent was removed by rotary evaporation to give 2.5 g (95%) of the boron trifluoride complex, mp 143-145°C after recrystallization from a mixture of ethyl acetate and hexane. To a solution of 100 mg of the complex in 10 mL of acetonitrile was added 29 mg (1 equiv.) of potassium fluoride and the mixture was stirred for 1 h. Evaporation of the solvent followed by addition of 10 mL of cold water and extraction with dichloromethane (3 x 10 mL), drying and concentration gave 65 mg (98%) of the nitrone, mp 83-84°C after recrystallization (lit.[7] mp 84°C). To avoid aqueous treatment, the crude nitrone obtained after evaporation of acetonitrile is taken up in dichloromethane; the solution is dried, filtered and concentrated to give essentially pure nitrone.

Typical Procedure for Method B. To a solution of 1.94 g (10 mmol) of 5 in 15 mL of dichloromethane, under argon, was added 1.24 mL (11 mmol) of methyl trifluoromethanesulfonate. The mixture was allowed to stir for 9 h at room temperature and then was shaken with cold, aqueous sodium bicarbonate. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 10 mL). The combined organic layer was dried and concentrated to give 1.24 g (92%) of (Z)-C-phenyl-N-methylnitrone, mp 83-84 °C. Again aqueous conditions can be eliminated by thorough rotary evaporation of the crude followed by recrystallization or distillation of a liquid nitrone.

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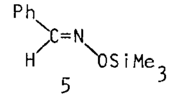
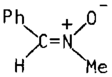
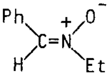
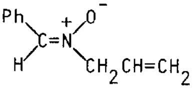
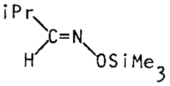
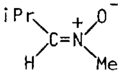
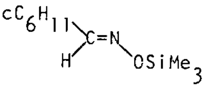
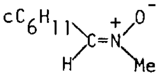
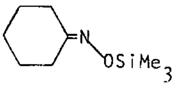
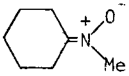
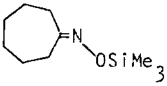
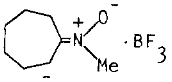
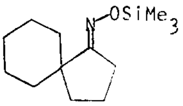
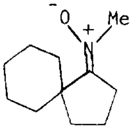
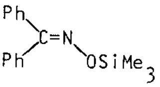
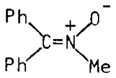
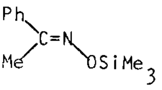
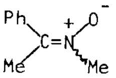
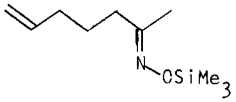
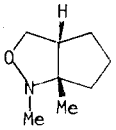
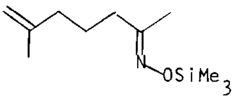
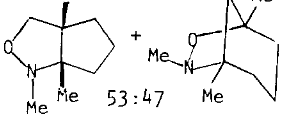
TABLE

O-Trimethylsilyloxime	Product[a]	Yield(%)[b,c] Method A	B	References & Remarks
		A	B	
 5		93	92	Refs 6,7 initial (E):(Z)=65:35[d]
5		80	--	Ref 6 (E),(Z) isomers seen[d]
5		--	71	this work
		87	89	this work initial (E):(Z)=5:1[d]
		82	77	this work initial (E):(Z)=4:1[d]
		78	--	Ref 8 BF_3-complex, mp 83-86°C
		65^e	--	this work mp 65°C
		79	--	this work mp 112°C
		65	--	Ref 8
		91^g	--	Ref 8 bp 52-53°C (0.002 mm)
		78^f	--	Ref 9
	 53:47	74^f	--	Ref 10

Footnotes to the Table

[a] Products were identified by comparison of spectral data and melting points (when available) with literature values. All new compound gave satisfactory spectral data, C,H,N analytical data and/or high resolution mass spectrometry analysis.

[b] Numbers represent yields of isolated products.

[c] Method A: trialkyloxonium tetrafluoroborates; Method B: alkyl trifluoromethanesulfonates (see text).

[d] Approximate (Z):(E) ratios determined by ^{1}H NMR in separate experiments.

[e] Attempted liberation of the free nitrone from the complex gave excessive decomposition.

[f] Isolated as the isoxazolidine by heating in toluene after fluoride treatment.

[g] *A mixture of (E) and (Z) isomers; Ref. 8 reports mp 115°C for (probably) (Z)-nitrone.*

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