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Nucleophilic Perfluoroalkylation of Nitrones

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Abstract

New methods for perfluoroalkylation of carbon-nitrogen double bonds have been developed. Addition of (trifluoromethyl)trimethylsilane ($TMSCF_3$) to α,N-diarylnitrones produced a series of α-(trifluoromethyl)-N-hydroxyl amines protected as their O-trimethylsilyl derivatives. An alternate procedure using pentafluoroethyllithium (F_5C_2Li) and chlorotrimethylsilane (TMSCl) afforded O-trimethylsilyl-α-(pentafluoroethyl)-N-hydroxyl amines.

Keywords: *Hydroxylamines; Nitrones; Perfluoroalkyl Compounds; Silicon and Compounds.*

Introduction. A perfluoroalkyl group can impart characteristic chemical and physical properties when appended to an organic molecule.[1] Numerous methods for the introduction of the trifluoromethyl group have been developed,[2] and the generation of synthetic equivalents for the trifluoromethyl anion has constituted a goal of synthetic fluorine chemists. Trifluoromethide transfer from $TMSCF_3$ (**2**) to a suitable electrophile using

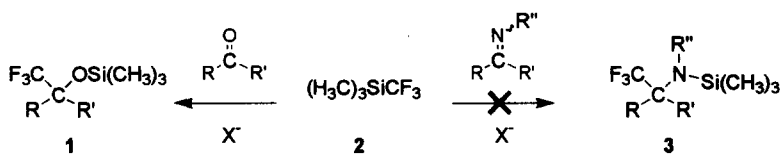

Figure 1. Trifluoromethylation of carbonyl compounds but not imines using $TMSCF_3$.

nucleophilic initiators offers a versatile route to a variety of trifluoromethylated organic compounds,[3] but this method has not proven successful for the preparation of α-(trifluoromethyl)amines from the corresponding imines (Figure 1).[4] The lability and inherent weakness of the nitrogen-silicon bond have been invoked to rationalize the inability of **1** to react with imines.

The addition of **2** to nitrones offered a possible route to α-trifluoromethylamine derivatives. Addition of organometallic nucleophiles to the 1,3-dipole moiety of nitrones has previously been used to prepare substituted hydroxyl amines.[5] Upon addition of a trifluoromethide group to the electrophilic carbon of the nitrone, the resulting intermediate should have a negatively charged oxygen capable of propagating the catalytic cycle (Figure 2). The present study demonstrates the transfer of a trifluoromethyl group to the electrophilic carbon of a nitrone with ultimate formation of the silylated hydroxyl amine. A brief survey of initiators, solvents, and

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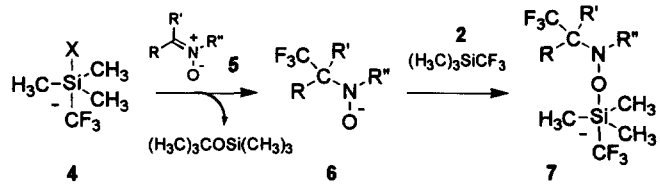
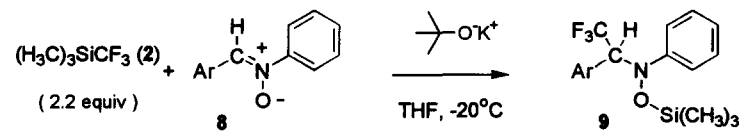


Figure 2. Proposed intermediates in the catalytic cycle for trifluoromethylation of nitrones using $TMSCF_3$.

potential substrates was conducted. A route to pentafluoroethylated hydroxylamine derivatives via a two step procedure using F_5C_2Li[6] and TMSCl was developed for use with nitrones that were unreactive with $TMSCF_3$.

Results. The nitrones were prepared by condensation of an aldehyde with an hydroxylamine (or its hydrochloride salt),[7] or by oxidation of a secondary amine using sodium tungstate catalyst with hydrogen peroxide.[8] The $TMSCF_3$ was prepared by a modified version of the published procedure[9] using iodotrifluoromethane instead of bromotrifluoromethane.[10] Addition of **2** to nitrones with aromatic substituents at both carbon and nitrogen proceeded smoothly at temperatures as low as -78°C, but the limited solubility of the nitrones necessitated the use of higher temperatures. The reactions were initiated by the addition of



entry	Ar (**8** and **9**)	% isolated yield of **9**
a	H_3CO-C$_6$H$_4$-	62
b	C$_6$H$_5$-	89
c	Cl-C$_6$H$_4$-	67
d	O_2N-C$_6$H$_4$-	54
e	1-naphthyl	83
f	2-furyl	69

Table 1. Alkoxide initiated condensation of **1** with *C*-aryl-*N*-phenyl nitrones.

potassium *t*-butoxide slurry in THF at regular intervals. The results for trifluoromethylation of nitrones bearing different aryl substituents at carbon are summarized in Table 1. The silyl ethers of the trifluoromethylated hydroxylamines were isolated by flash chromatography (silica gel/ hexanes - product R_f ~ 0.3-0.4). The adducts were quite stable and withstood analysis by GC and GC-MS, but decomposition occurred upon exposure to UV light (λ = 254 nm). The ^{1}H NMR spectra ($CDCl_3$) of the products exhibited quartets at ~4.4 ppm from ^{1}H-^{19}F coupling. Characteristic $^1J_{CF}$ (~ 285 Hz) and $^2J_{CF}$ (~28 Hz) coupling were observed in the ^{1}H-decoupled ^{13}C NMR spectra of the adducts.

In certain cases, notably with furan derivative **9f**, excess alkoxide caused decomposition of the product by the pathway shown in Figure 3. This addition-elimination pathway predominated at higher temperatures as well

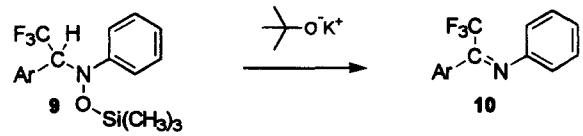
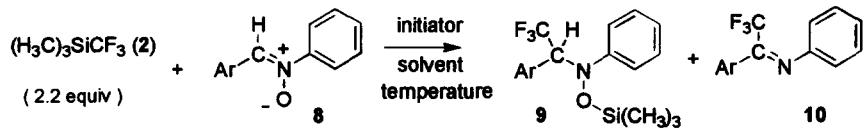


Figure 3. Formation of α-CF_3 imines by an elimination pathway.

as when other initiator/solvent combinations such as potassium fluoride/acetonitrile (MeCN) or tetrabutylammonium fluoride (TBAF)/THF were employed. The present study focused on optimization of conditions for formation of adduct **9**. A two-step sequence to trifluoromethylated imines (**10**) from the corresponding aryl aldehydes should prove valuable, however. A brief survey of the influence of initiator, solvent, and temperature revealed that the reactions could be directed to favor formation of either the protected hydroxylamine or the imine (Table 2).

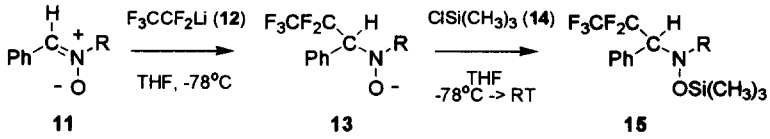


entry	Ar (**8**, **9**, and **10**)	conditions	% isolated yield **9**	% isolated yield **10**
b-i		TBAF (20 mol%), THF, RT	<5	35
b-ii	"	TBAF (20 mol%), THF, -20°C	37	10
b-iii	"	*t*-BuOK THF, RT	53	14
f-i		*t*-BuOK, THF, RT	<5	63
f-ii	"	*t*-BuOK, THF, -78°C	54	<5

Table 2. Product distribution as a function of *C*-substituent, initiator, solvent, and temperature.

The reactions of nitrones with $TMSCF_3$ worked well when aryl substituents were appended to the carbon or nitrogen of the dipole. Poor yields were obtained, however, with other common nitrones. In particular, nitrones with *N*-alkyl substituents produced modest yields (<<10%) of the $TMSCF_3$ adducts. An alternate perfluoroalkylation method was used to circumvent this problem. Nucleophilic addition of pentafluoroethyllithium (**12**)[6] to nitrones and subsequent trapping of the deprotonated hydroxylamine (**13**) by TMSCl (Table 3) afforded *O*-trimethylsilyl-α-(pentafluoroethyl)hydroxylamines (**15**). The physical properties of the perfluoroethyl compounds paralleled their trifluoromethyl counterparts. Table 3 lists the results of the reactions of selected nitrones with the pentafluoroethylating reagent. As with the trifluoromethyl compounds, distinctive ^1H-^{19}F and ^{13}C-^{19}F coupling were observed in the ^1H and ^{13}C NMR spectra, respectively, of the products listed in Table 3.

The methods presented here constitute practical additions of perfluoralkylating reagents to the carbon-nitrogen double bonds of nitrones. Only one case of trifluoromethylation of a carbon-nitrogen double bond (fluoride-induced addition of **2** to an azirine) has been reported.[4] The nitrone-$TMSCF_3$ reactions represent examples of a new reactivity manifold, and the resulting structures are novel and highly functionalized. The addition protocol should facilitate the preparation of new trifluoromethylated amines and their derivatives. The perfluoroethyl derivatives prepared by the two-step sequence complement the formal $TMSCF_3$ adducts. The steric properties of the CF_3 and the C_2F_5 groups differ substantially, but the electronic effects and influence on



entry	R (**11** and **15**)	% isolated yield of **15**
a		73
b		46
c		59
d		62

Table 3. α-(Pentafluoroethyl)hydroxylamine derivatives from the addition of F_5C_2Li to nitrones.

chemical reactivity are similar.[11] The adducts **9** and **15** can be transformed into amines, hydroxylamines, and imines, all of which are common building blocks for organic synthesis. Details of these transformations and studies on the chemical behavior of the α-perfluoroalkylamine derivatives will be reported in due course.

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References

1. For several perspectives, see: (a) Hudlicky, M.; Pavlath, A. E.; Eds. *Chemistry of Organic Fluorine Compounds II: A Critical Review*; ACS Press: Washington, 1995 (b) Becker, A., Ed. *Inventory of Industrial Fluorobiochemicals*; Eyrolles, Paris, 1996. (c) Banks, R. E.; Smart, B. E.; Tatlow, J. C., Eds. *Organofluorine Chemistry - Principals and Commercial Applications*; Plenum Press: New York, 1994. (d) Filler, R.; Kobayashi, Y.; Yagupolski, L. M. *Organofluorine in Medicinal Chemistry and Biochemical Applications*; Elsevier: Amsterdam, 1993.
2. For a discussion of specific organometallic reagents, see Ref 1(a) p 674-708. For other methods, see: (b) Hartkopf, U.; DeMeijere, A. *Angew. Chem., Int. Ed. Engl.* **1982**, *94*, 444. (c) Matsui, K.; Tobita, E.; Ando, Kondo, K. *Chem. Lett.* **1981**, 1719. (d) Carr, G. E.; Chambers, R. D.; Holmes, T. F.; Parker, D. G. *J. Chem. Soc., Perkin Trans. I* **1988**, 921. (e) Cantacuzene, D.; Wakselman, C.; Dorme, R. J. *J. Chem. Soc., Perkin Trans. I* **1977**, 1365. (f) Kitazume, T.; Ishikawa, N. *J. Am. Chem. Soc.* **1985**, *107*, 5186. (g) Umemoto, T. *Chem. Rev.* **1996**, *96*, 1757. (h) Farnham, W. B. *Chem. Rev.* **1996**, *96*, 1633.
3. Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757.
4. Felix, C. P.; Khatimi, N.; Laurent, A. *Tetrahedron Lett.* **1994**, *35*, 3303.
5. For a review, see: (a) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. For other recent examples, see: (a) Dondoni, A.; Merchan, F. L.; Merino, P.; Tejero, T. *Synth. Commun.* **1994**, *24*, 2551. (b) Schwartz, M. A.; Hu, X. *Tetrahedron Lett.* **1992**, *33*, 1689. (c) Murahashi, , S.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S. *J. Org. Chem.* **1990**, *55*, 1736.
6. Gassman, P. G.; O'Reilly, N. J. *J. Org. Chem.* **1987**, *52*, 2481.
7. Bruning, I.; Grashey, R.; Hauck, H.; Huisgen, R.; Seidl, H. *Org. Synth., Coll. Vol. V* **1973**, 1124.
8. Murahashi, S.-I.; Shiota, T.; Imada, Y. *Org. Synth.* **1991**, *70*, 265. Also, see Ref. 5c.
9. For a general procedure, see: Ramaiah, P.; Krishnamurti, R.; Prakash, G. K. S. *Org. Synth.* **1993**, *72*, 232.
10. The F_3Cl was obtained in bulk from Ajay North America; Powder Springs, GA.
11. Nelson, D. W.; O'Reilly, N. J.; Speier, J.; Gassman, P. G. *J. Org. Chem.* **1994**, *59*, 8157.