

## Nucleophilic Perfluoroalkylation of Nitrones

Derek W. Nelson,\* Regina A. Easley,<sup>a</sup> and Benjamin N. V. Pinteá

Department of Chemistry, Loyola University of Chicago, 6525 North Sheridan Road, Chicago, IL 60626

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### Abstract

New methods for perfluoroalkylation of carbon-nitrogen double bonds have been developed. Addition of (trifluoromethyl)trimethylsilane (TMSCF<sub>3</sub>) to  $\alpha$ ,N-diarylnitrones produced a series of  $\alpha$ -(trifluoromethyl)-N-hydroxyl amines protected as their O-trimethylsilyl derivatives. An alternate procedure using pentafluoroethyl lithium (F<sub>5</sub>C<sub>2</sub>Li) and chlorotrimethylsilane (TMSCl) afforded O-trimethylsilyl- $\alpha$ -(pentafluoroethyl)-N-hydroxyl amines. © 1998 Elsevier Science Ltd. All rights reserved.

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**Introduction.** A perfluoroalkyl group can impart characteristic chemical and physical properties when appended to an organic molecule.<sup>1</sup> Numerous methods for the introduction of the trifluoromethyl group have been developed,<sup>2</sup> and the generation of synthetic equivalents for the trifluoromethyl anion has constituted a goal of synthetic fluorine chemists. Trifluoromethyl transfer from TMSCF<sub>3</sub> (**2**) to a suitable electrophile using

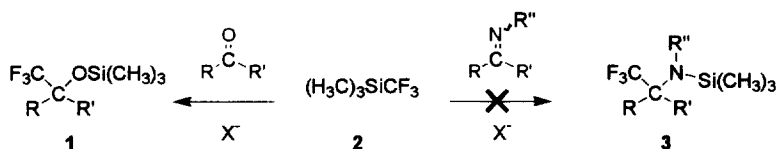


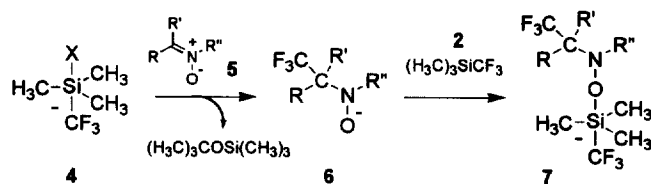
Figure 1. Trifluoromethylation of carbonyl compounds but not imines using TMSCF<sub>3</sub>.

nucleophilic initiators offers a versatile route to a variety of trifluoromethylated organic compounds,<sup>3</sup> but this method has not proven successful for the preparation of  $\alpha$ -(trifluoromethyl)amines from the corresponding imines (Figure 1).<sup>4</sup> 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  $\alpha$ -trifluoromethylamine derivatives. Addition of organometallic nucleophiles to the 1,3-dipole moiety of nitrones has previously been used to prepare substituted hydroxyl amines.<sup>5</sup> Upon addition of a trifluoromethyl 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

\*Corresponding author. Contact information: phone - (773)508-3125; fax - (773)508-3086; email - dnelson@luc.edu

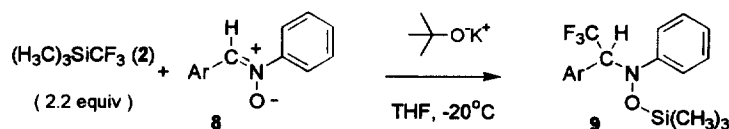
<sup>a</sup> Participant in the NSF-REU Program at Loyola University of Chicago, June-August 1998.



**Figure 2.** Proposed intermediates in the catalytic cycle for trifluoromethylation of nitrones using  $\text{TMSCF}_3$ .

potential substrates was conducted. A route to pentafluoroethylated hydroxylamine derivatives via a two step procedure using  $\text{F}_5\text{C}_2\text{Li}^6$  and  $\text{TMSCl}$  was developed for use with nitrones that were unreactive with  $\text{TMSCF}_3$ .

**Results.** The nitrones were prepared by condensation of an aldehyde with an hydroxylamine (or its hydrochloride salt),<sup>7</sup> or by oxidation of a secondary amine using sodium tungstate catalyst with hydrogen peroxide.<sup>8</sup> The  $\text{TMSCF}_3$  was prepared by a modified version of the published procedure<sup>9</sup> using iodotrifluoromethane instead of bromotrifluoromethane.<sup>10</sup> Addition of **2** to nitrones with aromatic substituents at both carbon and nitrogen proceeded smoothly at temperatures as low as  $-78^\circ\text{C}$ , but the limited solubility of the nitrones necessitated the use of higher temperatures. The reactions were initiated by the addition of



entry	Ar ( <b>8</b> and <b>9</b> )	% isolated yield of <b>9</b>
a		62
b		89
c		67
d		54
e		83
f		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  $R_f \sim 0.3$ - $0.4$ ). The adducts were quite stable and withstood analysis by GC and GC-MS, but decomposition occurred upon exposure to UV light ( $\lambda = 254 \text{ nm}$ ). The  $^1\text{H}$  NMR spectra ( $\text{CDCl}_3$ ) of the products exhibited quartets at  $\sim 4.4 \text{ ppm}$  from  $^1\text{H}$ - $^{19}\text{F}$  coupling. Characteristic  $^1J_{\text{CF}}$  ( $\sim 285 \text{ Hz}$ ) and  $^2J_{\text{CF}}$  ( $\sim 28 \text{ Hz}$ ) coupling were observed in the  $^1\text{H}$ -decoupled  $^{13}\text{C}$  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

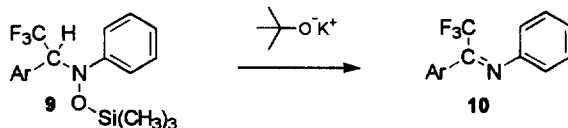


Figure 3. Formation of  $\alpha$ -CF<sub>3</sub> imines by an elimination pathway.

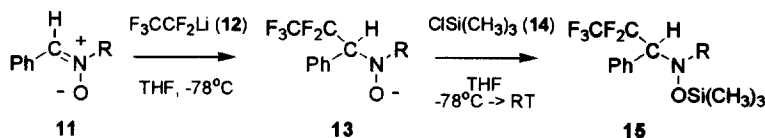
as when other initiator/solvent combinations such as potassium fluoride/acetonitrile (MeCN) or tetrabutylammonium fluoride (TBAF)/THF were employed. The present study focused on optimization of conditions for formation of adduct **9**. A two-step sequence to trifluoromethylated imines (**10**) from the 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 ( <b>8</b> , <b>9</b> , and <b>10</b> )	conditions	% isolated yield	
			<b>9</b>	<b>10</b>
<i>b-i</i>		TBAF (20 mol%), THF, RT	<5	35
<i>b-ii</i>	"	TBAF (20 mol%), THF, -20°C	37	10
<i>b-iii</i>	"	<i>t</i> -BuOK, THF, RT	53	14
<i>f-i</i>		<i>t</i> -BuOK, THF, RT	<5	63
<i>f-ii</i>	"	<i>t</i> -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<sub>3</sub> 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<sub>3</sub> adducts. An alternate perfluoroalkylation method was used to circumvent this problem. Nucleophilic addition of pentafluoroethylolithium (**12**)<sup>6</sup> to nitrones and subsequent trapping of the deprotonated hydroxylamine (**13**) by TMSCl (Table 3) afforded *O*-trimethylsilyl- $\alpha$ -(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 <sup>1</sup>H-<sup>19</sup>F and <sup>13</sup>C-<sup>19</sup>F coupling were observed in the <sup>1</sup>H and <sup>13</sup>C NMR spectra, respectively, of the products listed in Table 3.

The methods presented here constitute practical additions of perfluoroalkylating 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.<sup>4</sup> The nitron-TMSCF<sub>3</sub> 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<sub>3</sub> adducts. The steric properties of the CF<sub>3</sub> and the C<sub>2</sub>F<sub>5</sub> 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	-CH <sub>3</sub>	62

**Table 3.**  $\alpha$ -(Pentafluoroethyl)hydroxylamine derivatives from the addition of F<sub>3</sub>C<sub>2</sub>Li to nitrones.

chemical reactivity are similar.<sup>11</sup> 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  $\alpha$ -perfluoroalkylamine derivatives will be reported in due course.

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