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Nucleophilic Trifluoromethylation Using Trifluoromethyl Iodide. A New and Simple Alternative for the Trifluoromethylation of Aldehydes and Ketones

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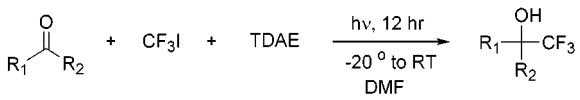
ABSTRACT



A novel method for nucleophilic trifluoromethylation of aldehydes and ketones, based on photoinduced reduction of trifluoromethyl iodide by tetrakis(dimethylamino)ethylene (TDAE), is presented.

Compounds containing the trifluoromethyl group are of great interest in the pharmaceutical and agrochemical industry. Among the numerous methods for incorporation of the trifluoromethyl group into organic compounds,[1] one of the most useful involves the use of reagents that effectively generate the unstable CF_3^- anion as an in situ species for the purpose of nucleophilic trifluoromethylation of electrophilic substrates such as aldehydes and ketones. Because of the limited number of such reagents and because of specific limitations that pertain to each, there remains considerable interest in the development of new trifluoromethyl anion reagents that might offer an experimental or cost advantage. We wish to report, at this time, a novel use of the currently relatively inexpensive compound, trifluoromethyl iodide, as a ready source of a new trifluoromethyl anionic reagent that adds to aldehydes and ketones to provide addition products in very good to excellent yield.

Currently, there are two major, preferred trifluoromethyl anion methodologies that receive most of the attention from synthetic chemists around the world. Because of its diversity of applicability, deriving from extensive recent work by the groups of Prakash,[2] Shreeve,[3] and others,[2,3] (trifluoromethyl)-trimethylsilane (Me_3SiCF_3) is generally considered to be the most effective reagent of this type, but recent advances from Langlois' group on the use of trifluoroacetaldehyde hemiaminals and their derivatives as trifluoromethylating reagents in reactions with nonenolizable aldehydes and ketones have also sparked considerable interest.[4,5]

Trifluoromethyl iodide has previously been used for the purpose of nucleophilic trifluoromethylation of carbonyl compounds, via its derived organozinc reagent. However, the required use of ultrasound for these reactions, developed by Kitazume and Ishikawa, seems to have limited their use by synthetic chemists.[6,7]

Beginning in 1998, we demonstrated in a series of papers that tetrakis(dimethylamino)ethylene (TDAE) could be used

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(1) McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555−6666.
(2) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757−786.
(3) Singh, R. P.; Shreeve, J. M. *Tetrahedron* **2000**, *56*, 7613−7632.
(4) Large, S.; Roques, N.; Langlois, B. R. *J. Org. Chem.* **2000**, *65*, 8848−8856.
(5) Billard, T.; Langlois, B. R.; Blond, G. *Eur. J. Org. Chem.* **2001**, 1467−1471.

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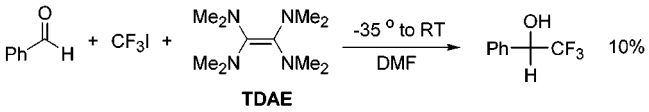
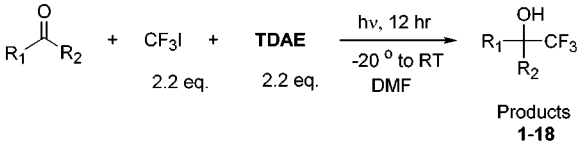
as an effective reductant to generate synthetically competent nucleophilic heterocyclic difluoromethyl anions from chloro- and bromodifluoromethyl precursors.[8,9] It was a natural extension to determine whether a combination of TDAE and trifluoromethyl iodide could be used to generate synthetically competent trifluoromethyl anions. Pawelke earlier demonstrated that the combination of CF_3I and TDAE could be used to prepare CF_3TMS from TMSCl.[10]

Initial results were, however, quite discouraging, because when TDAE was added to a solution of benzaldehyde and trifluoromethyl iodide in dry DMF at −35 °C and the solution allowed to warm with stirring to room temperature, although the reagents were totally consumed, the desired trifluoromethyl addition product was obtained in only poor yield. (Petrov has very recently reported a similar result in a paper that appeared as our own work was nearing completion.)[11]



In contrast to the results obtained when the reaction is carried out thermally, when the same reaction is carried out at −20 °C, *under irradiation by a sun lamp*,[12] its outcome was remarkably improved, with a yield of 80% being obtained. Subsequent reactions carried out in this manner with a large number of aldehydes and ketones exhibited similar success, as indicated in Table 1 below. A representative procedure is given in a footnote.[13]



The yields derived under photochemical conditions were generally far superior to those that could be obtained in the absence of light, and for most substrates examined the yields of alcohols were comparable to those obtained in analogous CF_3TMS reactions.

The mechanism of the reaction appears to proceed via an initially formed charge-transfer complex (red color) between CF_3I and TDAE, followed by stepwise, photoinduced single-electron transfers of two electrons from TDAE to CF_3I to form a complex between CF_3^- anion and $TDAE^{+2}$ dication, which presumably is the active trifluoromethylating agent.[8] Although DMF is presently the preferred solvent, the reaction

Table 1. Photopromoted Nucleophilic Trifluoromethylation of Aldehydes and Ketones Using CF_3I/TDAE Reagent[a]

products	R_1	R_2	NMR yield	isolated yield
1[14]	Ph	H	80	78
2[15]	*p*-Cl-Ph	H	89	81
3[16]	*p*-CN-Ph	H	89	82
4[16]	*p*-F-Ph	H	95	90
5[15]	*o*-Br-Ph	H	91	86
6[17]	1-naphthyl	H	quant	93
7[b]	4-Me_2N-1-naphthyl	H	91	86
8[15]	3-thienyl	H	74	68
9[16]	2-furanyl	H	82	78
10[b]	4-pyridyl	H		73
11[4]	PhCH=CH	H		78
12[b]	2-OMe-PhCH=CH	H	83	79
13[4]	Ph	Ph	68	
14[4]	PhCH=CH	Ph	65	53
15[18]	*i*-C_3H_7	H	52	48
16[14]	*c*-C_6H_{11}	H	68	53
17[16]	*n*-C_3H_7	H	15	
18[14]	Ph	CH_3	18	
19[4]	fluorenyl	73	65	19[4]
20[14]	$(CH_2)_5$	quant	76	20[14]

[a] All products except **7**, **10**, and **12** have been previously reported, with appropriate references being given. [b] The mp's and ^1H, ^{13}C, and ^{19}F NMR spectra of the new products are given in ref 19.

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(7) For related work using CF_3Br, see: Francese, C.; Tordeux, M.; Wakselman, C. *J. Chem. Soc., Chem. Commun.* **1987**, 642−643.

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(12) A temperature of −20 °C was chosen for the photoinduced process in order to minimize the extent of thermal decomposition of the charge-transfer complex, which occurs at room temperature.

(13) **Synthesis of 1-Phenyl-2,2,2-trifluoroethanol.** Into a three-necked flask equipped with a dry ice reflux condenser and a nitrogen inlet were added, at −35 °C, 15 mL of anhydrous DMF, benzaldehyde (1 mL, 9.8 mmol), and CF_3I (1.8 mL, 21.6 mmol). The solution was stirred and maintained at this temperature for 15 min, and then to it was added TDAE (5 mL, 21.5 mmol) at −20 °C. A red color developed with formation of a white precipitate. The solution was vigorously stirred at −20 °C for 10 min and then was irradiated by a sun lamp for 8 h, during which time the mixture warmed to room temperature. The resulting orange-red solution was then filtered, and the solid washed with ether. The DMF solution was then hydrolyzed with water, and the resulting aqueous mixture was extracted with ether (3 times). The combined ether solutions were washed with brine (5 times) and dried over $MgSO_4$. The solvent was removed, and the crude product was purified by silica gel chromatography (CH_2Cl_2/hexane = 8:2) to give 1-phenyl-2,2,2-trifluoroethanol in a yield of 78%.

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(19) **Compound 7:** light orange solid, mp 85−86 °C; ^1H NMR δ 8.26 (m, 1H), 7.85 (m, 1H), 7.66 (d, J = 7.9 Hz, 1H), 7.50 (m, 2H), 7.00 (d, J = 7.9 Hz, 1H), 5.66 (q, J = 6.6 Hz, 1H), 3.60 (br s, 1H), 2.88 (s, 6H); ^{19}F NMR δ −77.07 (d, J = 6.7 Hz); ^{13}C NMR δ 152.0, 132.3, 128.5, 126.7, 126.5, 125.9, 125.0, 124.8 (q, J = 269 Hz), 124.4, 113.1, 69.5 (q, J = 33 Hz), 45.0 ppm. **Compound 10:** white solid, mp 76−77 °C; ^1H NMR δ 8.5 (br s, 2H), 7.52 (d, J = 5.4 Hz, 2H), 5.08 ppm (q, J = 6.5 Hz, 1H); ^{19}F NMR δ −78.2 ppm (d, J = 6.5 Hz); ^{13}C NMR δ 148.9, 145.3, 124.0 (q, J = 270 Hz), 122.9, 70.8 (q, J = 32 Hz). **Compound 12:** cream solid, mp 63.5−64.5 °C; ^1H NMR δ 7.45 (dd, J = 7.6, J = 1.7 Hz, 1H), 7.30 (m, 1H), 7.17 (d, J = 16 Hz, 1H), 6.86 (m, 2H), 6.26 (dd, J = 16.1, J = 6.5 Hz, 1H), 4.64 (m, 1H), 3.85 (s, 3 H), 2.40 (d, J = 5.5 Hz, 1H); ^{19}F NMR δ −79.41 (d, J = 6.5 Hz); ^{13}C NMR δ 157.1, 131.7, 129.9, 127.4, 127.0, 124.2 (q, J = 275 Hz), 121.2, 121.2, 120.7, 110.9, 72.1 (q J = 32 Hz).

also gives good results when other solvents are used. For example, in the reaction with aldehyde **6**, a 53% yield was obtained in dimethoxyethane (DME), and a 72% yield when DME/HMPA (1:1) was used. Therefore, there is no *need* to invoke the intermediacy of Langois' CF_3^- adduct with DMF in these reactions. Additional mechanistic studies are in progress.

The success of the reaction with aliphatic aldehydes and ketones appears to be dependent on the kinetic acidity of their carbonyl α-H's, with poor results being obtained generally for aldehydes having a RCH_2CHO structure and for methyl ketones.

In conclusion, this new procedure for nucleophilic trifluoromethylation of aldehydes and ketones, because of the high yields generally obtained, should provide a relatively inexpensive synthetic alternative to the currently popular CF_3TMS method.

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