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New Stable Reagents for the Nucleophilic Trifluoromethylation. 1. Trifluoromethylation of Carbonyl Compounds with *N*-Formylmorpholine Derivatives

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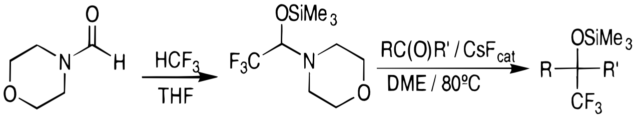
ABSTRACT



A new stable equivalent of the trifluoromethyl anion has been synthesized from fluoroform. It reacts with nonenolizable carbonyl compounds such as the Ruppert's reagent.

The number of new organofluorine compounds appearing every year[1] is steadily growing because of the unique properties of these products.[2] Among them, trifluoromethyl-substituted molecules are of huge interest for different applications.[3]

At present, many reliable methods are available to introduce a CF_3 moiety into organic substrates[4] but the nucleophilic strategy is one of the most popular.

Nevertheless, the very unstable $^{-}CF_3$ anion must be stabilized, for example, by dispersing the negative charge into remote orbitals in order to avoid its dissociation into fluoride anion and difluorocarbene (Scheme 1).

Scheme 1. Dissociation of $^{-}CF_3$ Anion

$$^{\ominus}CF_3 \rightleftharpoons F^{\ominus} + :CF_2$$

Presently, the commercial Ruppert's reagent (CF_3SiMe_3) is the best tool that fulfills this requirement. Under fluoride activation, it behaves as a $^{-}CF_3$ equivalent, even at lower temperature.[5] However, its synthesis is rather tricky and starts from CF_3Br which is now banned for environmental reasons. These reasons prompt us to investigate new reagents for the nucleophilic trifluoromethylation.

It has been previously shown that the deprotonation of fluoroform by a strong base in DMF leads to a $^{-}CF_3$ anion which is stabilized by trapping with DMF. The resulting adduct is rather stable when formed in situ and can act as a $^{-}CF_3$ reservoir (Scheme 2).[6,7]

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(1) Schofield, H. *J. Fluorine Chem.* **1999**, *100*, 7−11.

(2) Groβ, U.; Rüdiger, S$_T$. In *Organo-Fluorine Compounds*; Baasner, B., Hagemann, H., Tatlow, J. C., Eds; Houben-Weyl: Methods of Organic Chemistry; Thieme: Stuttgart, 1999; Vol. E10a, 18−26.

(3) (a) Filler, R.; Kobayashi, Y.; Yagulpolskii, Y. L. *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Elsevier: Amsterdam, 1993. (b) Banks, R. E.; Smart, B. E.; Tatlow, J. C. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum Press: New York, 1994. (c) Hudlicky, M.; Pavlath, A. E. *Chemistry of Organic Fluorine Compounds II. A critical Review*; ACS Monograph 187; American Chemical Society: Washington, DC, 1995.

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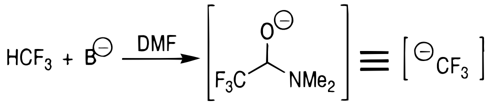
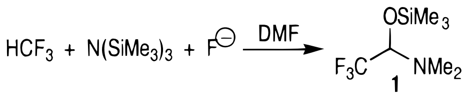
Scheme 2. Reaction of $^{-}CF_3$ with DMF



More recently, when using $N(TMS)_3/F^-$ as base for the deprotonation of fluoroform in DMF, we were able to detect the silyl ether of the former adduct (Scheme 3).[7]

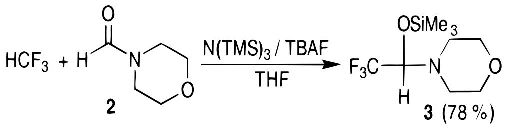
Scheme 3. Formation of Silylated Tetrahedral Intermediate



Thus, we decided to focus our attention to this new silylated compound. Unfortunately, it could not be isolated in a pure form and decomposed rather rapidly. Then we tried to carry out the same reaction with heavier *N*,*N*-dialkylformamides, used as substrates in THF.

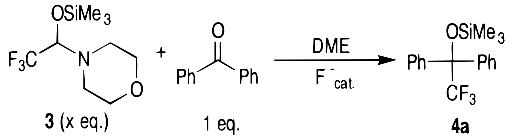
N-Formylpiperidine, -pyrrolidine, and -dibutylamine offered disappointing results either on the yield or stability point of view. Nevertheless, *N*-formylmorpholine delivered, in a high yield, the desired adduct **3** which can be easily purified by chromatogaphy over silica gel (Scheme 4).

Scheme 4. Reaction of Fluoroform with *N*-Formylmorpholine



To study the reactivity of **3**, we first examined its reaction with benzophenone in DME (1,2-dimethoxyethane) under fluoride activation (Table 1).

Table 1. Reaction of **3** with Benzophenone

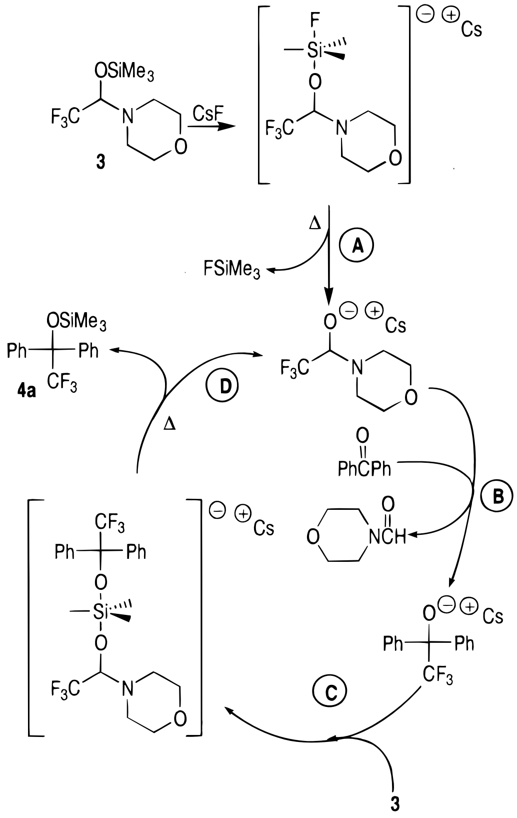


entry	x	F⁻	*T* (°C)	*t* (h)	**4a**[a] (%)
1	1	CsF	rt	48	0
2	1	TBAF [b]	rt	48	0
3	1	TBAT [c]	rt	48	0
4	1	CsF	60	20	58
5	1	CsF	80	5	57
6	1	CsF	80	5	79
7	2	CsF	40	25	50
8	2	CsF	50	24	71
9	2	CsF	60	5	70
10	2	CsF	80	5	78
11	2	CsF	80	5	81

[a] Determined by ^{19}F NMR with internal standard ($PhOCF_3$). [b] Tetrabutylammonium fluoride. [c] Tetrabutylammonium triphenyldifluorosilicate.

When comparing entries 5 and 6 in Table 1, it appears that the results were not reproducible when using only 1

Scheme 5. Proposed Mechanism for the Reaction of **3** with Carbonylated Compounds



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(4) McClinton, M. A.; McClinton D. A. *Tetrahedron* **1992**, *48*, 6555−6666.

(5) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757−786.

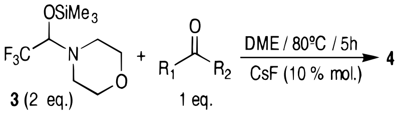
(6) (a) Russel, J.; Roques, N. *Tetrahedron* **1998**, *54*, 13771−13782. (b) Folleas, B.; Mareck, I.; Normant, J. F.; Saint-Jalmes, L. *Tetrahedron Lett.* **1998**, *39*, 2973−2976. (c) Folleas, B.; Mareck, I.; Normant, J. F.; Saint-Jalmes, L. *Tetrahedron* **2000**, *56*, 275−283.

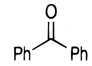
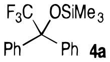
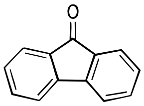
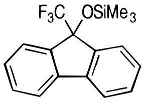
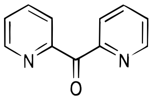
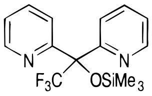
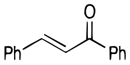
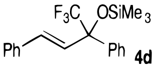
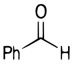
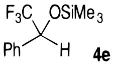
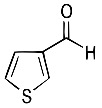
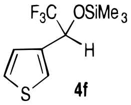
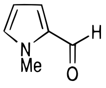
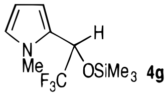
(7) Large, S.; Roques, N.; Langlois, B. R. *J. Org. Chem.* In press.

(8) (a) Wiedemann, J.; Heiner, T.; Mleston, G.; Prakash, G. K. S.; Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 820−821. (b) Maggiarosa, N.; Tyrra, W.; Naumann, D.; Kirij, N. V.; Yagupolskii, Y. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2252−2253.

(9) **Typical Procedure.** To a solution of **3** (2 mmol) and the electrophile (1 mmol) in DME (1 mL) was added a catalytic amount (≈10% mol) of CsF (dried at 250 °C and stored at 110 °C). The mixture was heated at 80 °C for 5 h. Then, the crude mixture was directly purified by chromatography over silica gel.

Table 2. Reaction of **3** with Various Electrophiles



Substrate	**4** (%)[a]	
	 **4a**	75 (81)
	 **4b**	90 (100)
	 **4c**	78 (91)
	 **4d**	70 (80)[b]
	 **4e**	95 (99)
	 **4f**	80 (95)
	 **4g**	92 (98)

[a] Isolated yield. In parentheses: crude yield determined by ^{19}F NMR with internal standard (PhOCF$_3$). [b] Heating during 9 h instead of 5 h.

equiv of **3**, whereas 2 equiv delivered a constant yield (entries 10−11). The reaction temperature was then optimized under these conditions (entries 7−10): a satisfying kinetics was reached at 80 °C. Thus, optimal results were obtained in DME with 2 equiv of **3** and a catalytic amount of CsF (10%), at 80 °C for 5 h. In such a way, **3** behaves as the Ruppert's reagent.

By analogy with the mechanism postulated for this latter reagent,[8] we can propose the following one concerning **3** (Scheme 5).

In this mechanism, steps A and D involve the cleavage of strong O−Si bonds and could justify that heating is needed, in contrast with the case of the Ruppert's reagent where a weaker C−Si bond has to be cleaved. However, such a mechanism is not yet able to explain why 2 equiv of **3** is preferable. It must be refined in light of further experiments.

This trifluoromethylation technique has been extended to others substrates.[9] As shown in Table 2, nonenolizable ketones and aldehydes provide excellent isolated yields (70−95%), even in the heterocylic series. Trifluoromethylation of enolizable carbonyl compounds follows a different route resulting in a α-(trifluoromethyl)methylenation which will be reported in a next paper.

In conclusion, we have shown that it is possible to synthesize from fluoroform, the simplest trifluoromethyl-containing compound which is environmentally benign, a new nucleophilic trifluoromethylating agent which acts as the Ruppert's reagent and is stable enough to be stored and sold. Further studies on the reactivity of this compound and some analogues are in progress in our laboratory.

Supporting Information Available: Experimental procedure and characterization data for compounds **3** and **4a**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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