Pergamon

Tetrahedron Letters 39 (1998) 2973–2976

TETRAHEDRON
LETTERS

Fluoroform: an efficient precursor for the trifluoromethylation of aldehydes

Benoît Folléas[#], Ilan Marek[#]*[1], Jean-F. Normant[#]*, Laurent Saint. Jalmes[$]

[#]Laboratoire de Chimie des Organoéléments, associé au CNRS
Tour 44-45, 2ème étage, boîte 183.
75252 PARIS CEDEX 05 - France
[$]Centre de Recherche, d'industrialisation et de Technologie
Rhone-Poulenc Industrialisation
85 Av. des Frères Perret. B.P. 62
69192 Saint-Fons Cedex- France

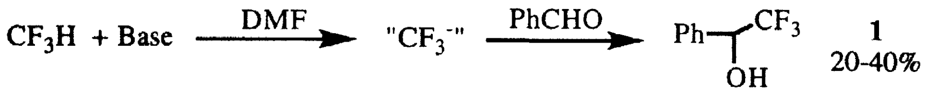
Received 3 February 1998; accepted 18 February 1998

Abstract: Fluoroform is shown to be an efficient trifluoromethylating agent when deprotonated using standard reagents in DMF. The important role of DMF in that reaction was demonstrated.

Organic compounds containing fluorine possess special chemical properties[2] and hence often exhibit an interesting physiological profile[3]. Among these, molecules bearing a trifluoromethyl group are of great interest. This has stimulated intensive research and many reliable methods are now available to introduce the CF_3 moiety into organic substrates[4]. Presently, the usual sources for the preparation of CF_3^- equivalents are CF_3I[5], CF_3Br[5], CF_2Br_2[6] or CF_3SiMe_3[7]. However, except in the last case, these reagents are expensive and bannished for ecological reasons. Moreover, as described in the litterature, the synthesis of these anions are difficult and their stabilities are greatly dependent on the choice of the associated counter-ion. For example, while CF_3Cu is able to trifluoromethylate aromatic halides at 90°C in DMF[3], CF_3MgI[8] and CF_3Li[9] decompose at very low temperatures, probably *via* an α-elimination process. From these considerations, the development of new strategies for the incorporation of CF_3 groups in organic molecules with the preservation of the ecological environment became an absolute necessity and we were thus interested by using fluoroform (this gas is a side-product of the industrial multi-step synthesis of Teflon®) as a source of the trifluoromethyl group. In this regards, we were recently intrigued by the results obtained by Shono *et al.*[10] who reported that a trifluoromethyl anion equivalent could be efficiently formed by deprotonation of trifluoromethane with a potassium or sodium base (or even better with an electrogenerated base) as described in Scheme 1.

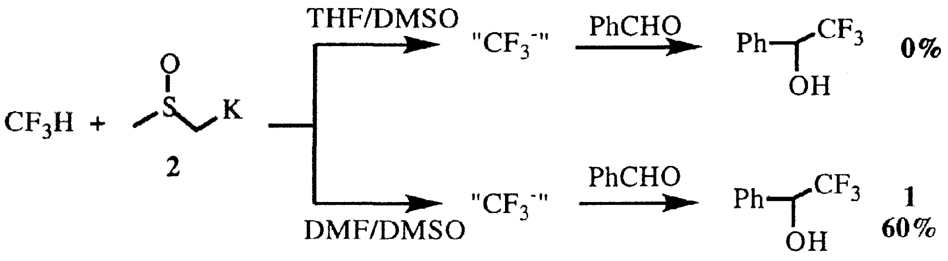
*Fax: 33 01 44 27 75 67.e-mail : normant@moka.ccr.jussieu.fr

0040-4039/98/$19.00 © 1998 Published by Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(98)00391-8



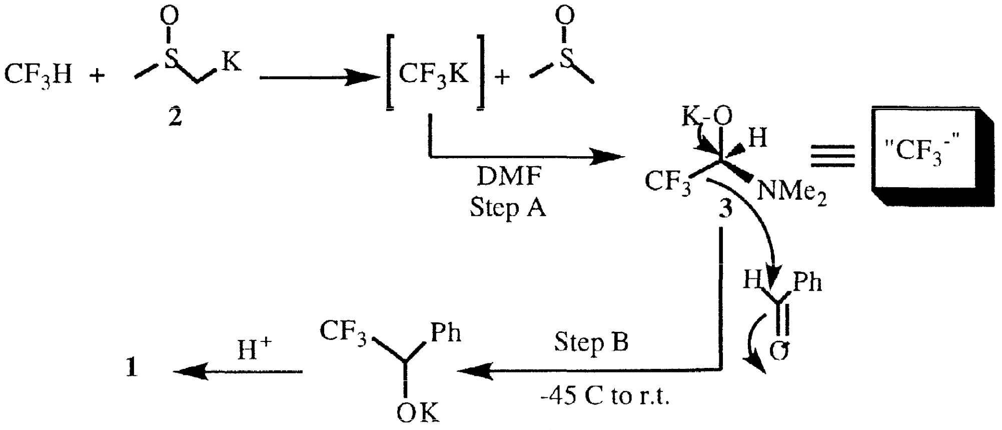
Scheme 1

However, it was difficult to imagine that a trifluoromethylpotassium (or sodium) complex could be the reactive trifluoromethylating agent in this reaction since the previous reports have demonstrated the low thermal stability of lithium and magnesium trifluoromethylated organometallics[8,9]. So, we decide to investigate in details this reaction and we would like to report in this letter our preliminary result on the extraordinary ambiphilic aspect of the solvent DMF. Indeed, as expected deprotonation of CF_3H with various bases (*tert*BuOK, KH, NaH, *n*BuLi, LDA...) in THF as solvent led to failure but more interestingly reaction of potassium dimsylate **2** at low temperature in DMF followed by the addition of benzaldehyde, results in the corresponding trifluoromethylated carbinol **1** being formed in moderate yield[11] (Scheme 2).



Scheme 2

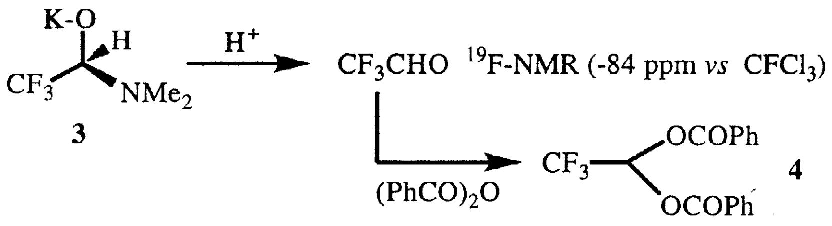
This result can be explained by the following mechanism: deprotonation of fluoroform by potassium dimsylate **2** furnishes the trifluoromethyl anion which is *in situ* trapped by the DMF to form the *gem*-aminoalcoholate **3** (step A). This intermediate is a *masked* and *stable* form of the trifluoromethyl anion therefore avoiding the degradation of the carbenoid CF_3K. After addition of an aldehyde (step B), the trifluoromethyl moiety is transferred from **3** to the aldehyde to form the corresponding trifluoromethyl carbinol **1**.



Scheme 3

Then the DMF solvent play the role of an *in situ* electrophile to give the trifluoromethylated alcoholate **3** and then this latter react as a nucleophile with a stronger electrophile (i.e. aldehyde) to give the corresponding carbinol.

In order to assess this mechanistic hypothesis, the intermediate **3** have been hydrolyzed at -25C, without adding any electrophiles. As expected, fluoral was identified by ^{19}F-NMR (-84 ppm *vs* CFCl$_3$). Moreover, treatment of this latter (or its hydrate form) with benzoic anhydride (Bouveault reaction[12]), we obtained the corresponding diacylate: obtained 1,1,1-trifluoro-2,2-di(phenylcarbonyloxy)ethane **4** as described in Scheme 4



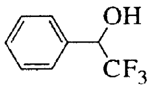
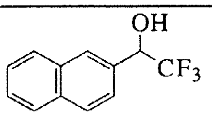
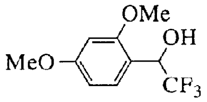
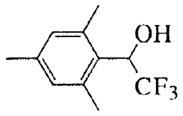
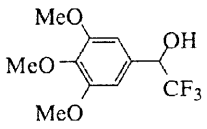
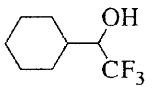
Scheme 4

Moreover, this *gem*-aminoalcoholate has already been observed by Périchon *et al* [5a]during electroreduction experiments of bromotrifluoromethane in DMF to form trifluoromethylzinc bromide and also by Lang *et al*[13] during the formation of fluoral by reduction of iodotrifluoromethane by zinc metal in DMF.

On the other hand, trifluoromethylation of benzaldehyde was attempted using the dimethylacetal of DMF as solvent; here, the carbonyl of DMF is masked. In this instance addition of fluoroform at low temperature resulted in a violent exothermic reaction and the reaction mixture immediately become black. This exothermic color change is often caracteristic of carbenoid degradation. Moreover, at the end of the reaction, no trace of the expected trifluoromethylated carbinol could be detected.

Various trifluoromethylated carbinols can be obtained by this simple reaction in moderate yield as described in the following table and according to the general Scheme 3.

Table: trifluoromethylated alcohols obtained from the corresponding aldehydes according to the procedure described in note 11.

Entry	Product	Yield[a]	Entry	Product	Yield[a]
1		60%	4		50%
2		45%	5		20%
3		20%	6		45%

[a] : isolated yields.

In conclusion, we have proved that it is possible to deprotonate fluoroform at low temperature using standard reagents and to trifluoromethylate aldehydes with the trifluoromethyl anion so obtained. The key-step of this reaction seems to be the nucleophilic addition of the trifluoromethyl anion onto the carbonyl moiety of DMF to form **3**, a masked and stable form of the trifluoromethyl anion. Experiments are underway to improve the reaction and confirm the proposed mechanism.

Acknowledgement : We thank RHONE-POULENC for financial support.

References and notes

1. Department of Chemistry, Technion Institute of Technology, Technion City 32 000 Haifa, Israel
2. (a) Hudlicky, M. *Chemistry of Organic Fluorine Compounds*; 2nd ed.; Ellis Horwood: New York, 1992. (b) Banks, R. E. *Organofluorine Chemicals and Their Industrial Applications*; Ellis Horwood: Chichester, 1979. (c) Banks, R. E. *Preparation, Properties and Industrial Applications of Organofluorine Compounds*; Ellis Horwood: Chichester, **1982**. (d) Olah, G. A.; Chambers, R. D.; Prakash, G. K. *Synthetic Fluorine Chemistry*; Wiley-Interscience: New York, **1992**.
3. (a) Newbold, G. T. in reference 2b; chapter 8, 169-187. (b) Filler, R.; Kobayashi, Y. *Biomedical Aspects of Fluorine Chemistry*; Elsevier Biomedical Press: Amsterdam, **1982**. (c) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123-3197. Rzepa, H. S. *Chem. Com.* **1997**, 645-652.
4. For reviews, see: (a) Burton, D. J.; Yang, Z. Y. *Tetrahedron* **1992**, *48*, 189-275. (b) McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555-6666.
5. (a) Sibille, S.; Mcharek, S.; Perichon, J. *Tetrahedron* **1989**, *45*, 1423-1428. (b) Sibille, S.; Perichon, J. *Synth. Commun.* **1989**, *19*, 2449-2452. (c) O'Reilly, N.J.; Maruta, M.; Ishikawa, N. *Chem. Lett.* **1984**. 517-520. (d) Kitazume, T.; Ishikawa, N. *J. Am. Chem. Soc.* **1985**, *107*, 5186-5191
6. (a) Burton, J.D.; Wiemers, D.M. *J. Am. Chem. Soc.* **1985**, *107*, 5014-5015. (b) Wiemers, D.M.; Burton, J.D. *J. Am. Chem. Soc.* **1986**, *108*, 832-834
7. (a) Ruppert, I.; Schlich, K; Volbach, N. *Tetrahedron Lett.* **1984**, *25*, 2195-2198. (b) For a review,see: Prakash,G.K.S.;Yudin, A.K. *Chem.Rev.* **1997**, *97*, 757-786.
8. (a) Emeleus, H. J.; Haszeldine, R. N. *J. Chem. Soc.* **1949**, 2953-2955. (b) Haszeldine, R. N. *J. Chem. Soc.* **1954**, 1273-1279. (c) McBee, E. T.; Battershell, R. D.; Braendlin, H.P. *J. Org. Chem.* **1963**, *28*, 1131-1132.
9. (a) Emeleus, H. J.; Haszeldine, R. N. *J. Chem. Soc.* **1949**, 2948-2952. (b) Pierce, O. R.; McBee, E. T.; Judd, G. F. *J. Am. Chem. Soc.* **1954**, *76*, 474-478.
10. Shono, T.; Ishifune, M.; Okada, T.; Kashimura, S. *J. Org. Chem.* **1991**, *56*, 2-4.
11. Typical procedure : *preparation of potassium dimsylate* : a two-necked flask equipped with a magnetic stirrer and a nitrogen inlet was charged with potassium hydride (20 mmol) and pentane (15 ml). After stirring and decantation the pentane was discarded, DMSO (10 ml) was then added at room temperature and stirring was continued for 45 min. *Trifluoromethylation of aldehydes* : The solution of dimsylate prepared as above was added to a solution of fluoroform (20 mmol) in DMF (20 ml) at -45°C (internal temperature) in a four-necked flask equipped with a mechanical stirrer. After 30 min at -45°C, a solution of aldehyde (10 mmol) in DMF (5 ml) was added to the reaction mixture and the temperature was allowed to reach r.t.. After hydrolysis with hydrochloric acid 1N (10 ml), extraction with ether (2 x 30ml) and drying over $MgSO_4$, the crude product was purified by column chromatography on silica gel.
12. Olah, G.; Prakash, G. K. S.; Arvanaghi, M. *Synthesis* **1978**, 228-230.
13. Lang, R. W. *Helv. Chim. Acta* **1988**, *71*, 369-373.