The Trifluoromethylacetophenone-*N,N*-dimethyltrimethylsilylamine Adduct – A New Shelf Stable Reagent for Nucleophilic Trifluoromethylation.

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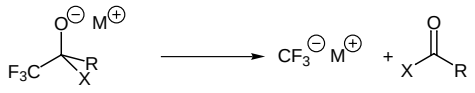
Received 5 February 2002

Abstract: The simple thermal addition product of *N,N*-dimethyltrimethylsilylamine with trifluoromethylacetophenone provides a shelf-stable reagent for nucleophilic trifluoromethylation of the carbonyl group.

Key words: nucleophilic trifluoromethylation, trifluoromethyl carbinols, aldehydes, ketones

The enhanced lipophilicity, relatively small size, and powerful electron withdrawing character of the trifluoromethyl group have all combined to produce a unique set of properties which have proven to be especially valuable over a wide range of targets within the pharmaceutical and agrochemical industries, as well as materials science.[1] From a preparative standpoint, whilst a variety of more classical methods are available for the incorporation of this moiety,[2] the anionic trifluoromethylation strategy has emerged in recent years as one of the most powerful, with Ruppert's reagent, trifluoromethyltrimethylsilane[3] proving to be the reagent of choice in terms of efficiency, mild reaction conditions and versatility.[4] Unfortunately however, whilst the metalloid nature of the carbon silicon bond provides the ideal compromise between nucleophilic reactivity and stability relative to the undesirable generation of difluorocarbene, the preparation of the reagent requires the use of either bromo- or iodotrifluoromethane which have now been banned for ecological reasons. In view of the above situation, it was therefore of interest to investigate the possibility of preparing new reagents for anionic trifluoromethylation.

Our own study began with the observation that there is considerable literature precedent[5–7] for expulsion of the trifluoromethyl anion from tetrahedral oxyanionic intermediates **1** of the type shown in Scheme 1.



1

R = alkyl, aryl
X = OR', NR'$_2$

Scheme 1

Within this context and during the course of our own work, the most exciting and important manifestation of this phenomenon has been made by Normant and coworkers,[6] who reported that the use of dimethylformamide as solvent was mandatory for successful trifluoromethylation of non enolisable carbonyl compounds using deprotonation of fluoroform by dimsyl potassium. This observation was in agreement with earlier work by Shono[5] and led to the supposition, later confirmed by both Normant[6] and Roques,[7] that the tetrahedral intermediate **1** (R = H, X = NMe_2, M = K) could function as a latent source of the trifluoromethyl anion. Most recently, and in a conceptually similar vein to our own work (vide infra), an elegant study by Langlois[8] has shown that deprotonation of fluoroform using fluoride anion and tris(trimethylsilyl)amine in the presence of *N*-formylmorpholine leads to in situ silylation of the tetrahedral intermediate **1** (R = H, X = morpholino, M = Cs) with formation of a new shelf stable equivalent of the Ruppert reagent. It is curious to note that the selection of the morpholino group is crucial in the above sequence and that *N*-formylpiperidine, -pyrolidine, -dibutylamine, and even dimethylformamide itself were reported to give disappointing results.

In the first instance, our own efforts also focused on silylation of an oxyanionic tetrahedral intermediate, but generated through reaction of phenyllithium with *N,N*-diethyltrifluoromethylacetamide. Unfortunately, in spite of extensive experimentation, only intractable reaction mixtures, characteristic of difluorocarbene formation and subsequent degradation, were formed.

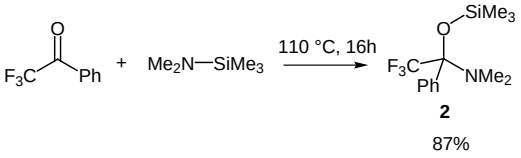
Careful scrutiny of the literature then directed our attention towards an intriguing paper by Abel and Crow,[9] who demonstrated that the reaction of a series of perhalogenated propanone derivatives (including hexafluoroacetone) with *N,N*-dimethyltrimethylsilylamine led to the formation of isolable tetrahedral compounds of the desired structure.

Given the ready availability of trifluoromethyl ketones,[10] we therefore elected to examine the analogous reaction of trifluoromethyl acetophenone. Gratifyingly, as shown in Scheme 2, this provided a very simple and experimentally convenient method for preparation of the novel shelf-stable reagent **2** in excellent yield.[11]

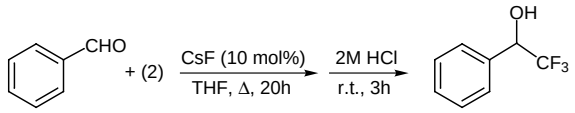
The results[12] for a series of reactions with aldehydes and ketones using two equivalents of reagent **2** and caesium fluoride (10 mol%) as the preferred initiator (Scheme 3) are shown in the Table, and confirm that the isolated

Synlett 2002, No. 4, 29 03 2002. Article Identifier:
1437-2096,E;2002,0,04,0646,0648,ftx,en;D02202ST.pdf.

ISSN 0936-5214



Scheme 2

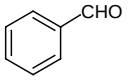
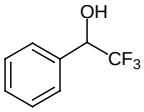
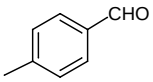
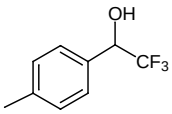
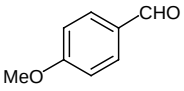
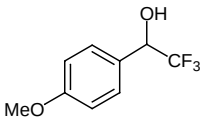
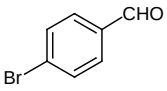
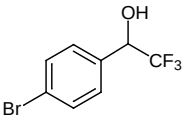
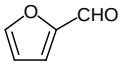
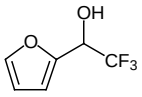
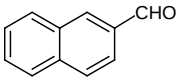
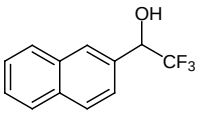
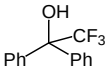
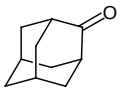
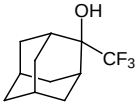
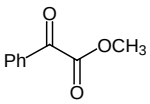
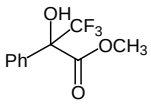


Scheme 3

yields of trifluoromethyl carbinols are comparable to those obtained by other nucleophilic trifluoromethylation methods.

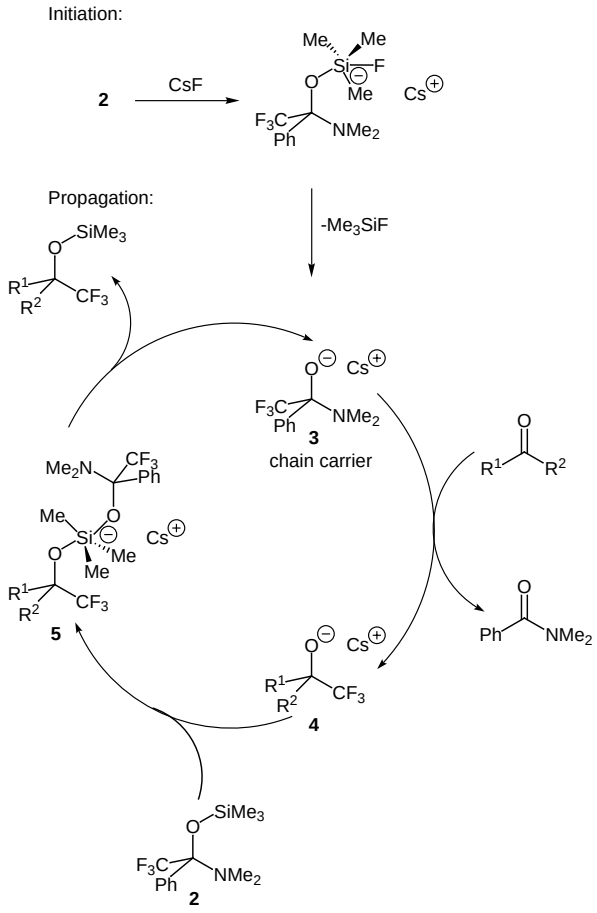
From a mechanistic standpoint, as shown in Scheme 4, it is reasonable to consider that a parallel may be drawn with the postulated behaviour of the Ruppert reagent.[13] Thus, initiation by fluoride anion leads to the formation of the 'ate' complex which can function, either in its own right, or after elimination of trimethylsilyl fluoride, to give **3** as the latent source of the trifluoromethyl anion for delivery to the carbonyl group, with concomitant expulsion of *N*,*N*-dimethylbenzamide. The caesium alkoxide **4** of the product can then react with reagent **2** to form a second 'ate'

Table Reaction of **2** (2 equiv) with Aldehydes and Ketones and Caesium Fluoride (10 mol%) as the Preferred Initiator

Entry	Substrate	Product	Yield[a] (%)	^{19}F NMR
1			89 (2)	–79.2
2			69 (16)	–78.8
3			71 (29)	–79.1
4			82 (6)	–78.9
5			73 (26)	–78.4
6			75	–78.4
7			92[b]	–72.9
8			87 (13)	–76.1
9[c]			41 (16)	–76.9

[a] Isolated Yields. The numbers in parentheses indicate the yield of the recovered substrate. All products gave satisfactory ^{1}H and ^{19}F NMR data.
[b] Product was isolated as the TMS ether after acidic work up.
[c] Substrate heated to 110 °C in NMR.

complex **5**, whose breakdown leads to the formation of the product trimethylsilyl ether, and liberation of the tetrahedral oxyanionic intermediate **3** once again as the chain carrier. Clearly from a thermodynamic standpoint, since cleavage of a silicon oxygen bond in **5** is required to propagate the chain, the overall sequence is more energetically demanding than in the case of the Ruppert reagent, although to some extent, this is offset overall by formation of the amide carbonyl group.



Scheme 4

In summary, the thermal addition of *N*,*N*-dimethyltrimethylsilylamine to trifluoromethylacetophenone provides a very simple, experimentally convenient, and environmentally friendly preparation of a shelf stable reagent for anionic trifluoromethylation of non enolisable aldehydes and ketones.

Acknowledgement

We are grateful to Zeneca Plc. for the provision of financial support from their Strategic Research Fund (SRF 281, 1997–1999) for this work, and also, following on from the merger to create Astra–Zeneca and the demerger to create Syngenta, for the permission to publish this study. We especially wish to thank Dr S. Lee (Astra–Zeneca, Macclesfield) and Dr R. Salmon (Syngenta, Bracknell) for their enthusiasm and stimulating discussions during the project.

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(11) Synthesis of **2**: *N*,*N*-Dimethylaminotrimethylsilane (5 mL, 0.031 mol) and trifluoroacetophenone (4.34 mL, 0.031 mol) were added to a round bottom flask equipped with a reflux condenser. The neat mixture was heated in an oil bath at 110 °C for 16 h under a nitrogen atmosphere. The product was distilled between 117–118 °C/18 mmHg to give a clear oil (7.93 g, 87% yield). Calculated for $C_{13}H_{20}F_3NOSi$: C, 53.59; H, 6.92; N, 4.81. Found: C, 53.45; H, 7.07; N, 4.80; IR(neat)/cm^{-1}: 2958, 2846, 2799, 1255, 1163, 1050. δ_H (300 MHz) 0.20 [9 H, s, Si-$(CH_3)_3$], 2.29 [6 H, d, J = 1, N-$(CH_3)_2$], 7.35 (3 H, m), 7.58 (2 H, m). δ_F (282 MHz) –71.3. δ_C (75 MHz) 1.7 [Si-$(CH_3)_3$], 39.9 [N-$(CH_3)_2$], 93.1 (q, J = 28.5, C-CF_3), 124.2 (q, J = 292, CF_3), 127.5, 127.8, 128.5, 139.2.

(12) Representative procedure: Dry, distilled THF (5 mL) was added to a round bottom flask equipped with a reflux condenser, containing pre-dried caesium fluoride (15 mg, 0.098 mmol). Benzaldehyde (100 mL, 0.98 mmol)was then added, followed by **2** (466 mL, 1.97 mmol), and the mixture was heated to reflux for 20 h. Hydrochloric acid (2 M, 1 mL) was then added and stirring was continued for 3 h. The mixture was diluted with diethyl ether, washed with water (3 × 5 mL), sat. brine (5 mL), dried with $MgSO_4$, and the solvent removed in vacuo. The crude product was purified by flash chromatography on silica gel using diethyl ether–hexane (1:9) to give the product as a yellow oil (139 mg, 89%) whose properties were identical with those reported in the literature.

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