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New stable reagents for the nucleophilic trifluoromethylation. Part 2: Trifluoromethylation with silylated hemiaminals of trifluoroacetaldehyde

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Abstract

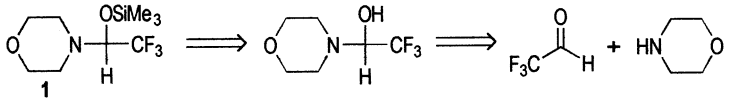
New reagents for the nucleophilic trifluoromethylation have been easily synthesized from fluoral hemiketal. They provide silylated trifluoromethylcarbinol from non-enolizable carbonyl compounds.

Keywords: trifluoromethylation; fluoral; hemiaminal; trifluoromethylcarbinol.

Because of the specific properties of the CF_3 moiety, its introduction in organic compounds represents, at present, a classical modification used in the screening of new bio-active compounds.[1] Among the panel of available methods for introducing this group, the nucleophilic strategy is one of the most popular.

In our quest for new nucleophilic trifluoromethylating reagents, we have recently shown that 2,2,2-trifluoro-1-morpholinoethyl trimethylsilyl ether (**1**) constitutes a stable new reagent[2] which trifluoromethylates non-enolizable carbonyl compounds to provide the corresponding silylated trifluoromethylcarbinols, in the same way as Ruppert's reagent.[3]

Nevertheless, this reagent was obtained from gaseous fluoroform which is not very easy to handle.



Scheme 1. Retrosynthesis of **1**

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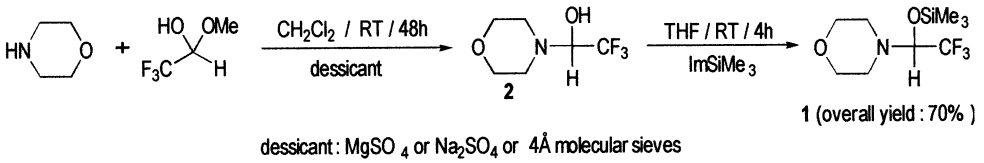
When looking at compound **1** from a retrosynthetical point of view, it can also be considered as a silylated hemiaminal arising from trifluoroacetaldehyde (fluoral) (Scheme 1).

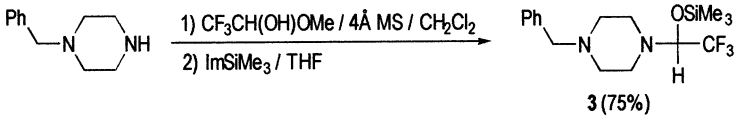
Fluoral itself is a very electrophilic gaseous compound which is conveniently available in its methyl hemiketal form that we planned to use for the synthesis of **1**. Usually, this hemiketal generates free fluoral by distillation of over P_2O_5 but some authors described its direct reaction in the presence of dessicants.[4]

Indeed, the reaction of methyl hemiketal of fluoral with morpholine led to hemiaminal (**2**) which was silylated with *N*-trimethylsilyl imidazole, under neutral conditions, to yield **1** (Scheme 2).



Scheme 2. Synthesis of **1** from methyl hemiketal of fluoral

By the same procedure, another silylated hemiaminal (**3**)[5,6] was synthesized from *N*-benzyl piperazine (Scheme 3). Like **1**, **3** is a stable compound which can be easily purified and stored for a long time.



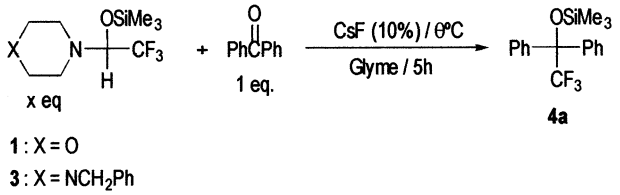
Scheme 3. Synthesis of **3** from methyl hemiketal of fluoral

Although **1** behaves as an efficient trifluoromethylating reagent, the necessity to use two equivalents of it (versus substrate) constitutes a disadvantage. In this respect, the reactivities of compounds **3** and **1** were compared with benzophenone (Table 1).

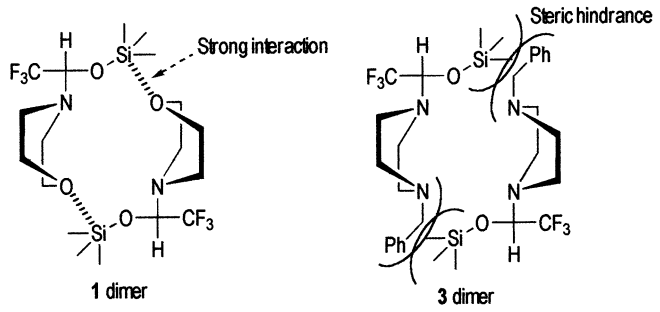
It appears from Table 1 that, at 80°C, which was the optimal temperature previously determined for reacting **1**, similar results were obtained with one equivalent of **3** and two equivalents of **1** (entries 1 and 2). Moreover, in contrast to **1**, the reactivity of **3** was not affected when lowering the temperature to 60°C (entry 3). Thus **3** exhibits a better reactivity than **1**.

The exact reason for this difference is not yet completely understood. Nevertheless, it can be suggested that **1** could form a dimer because of the strong interaction between oxygen and silicium, whereas this phenomenon should be less important with **3**, first because of the weaker interaction between nitrogen and silicium and, furthermore, because of the steric hindrance introduced by the benzyl group (Scheme 4). This hypothesis justifies the use of 2 equivalents of **1**. A better understanding of this mechanism is under study in our laboratory.

Table 1
Comparative study of the reactivities of **1** and **3**



Entry	θ (°C)	**4a** (%)	
		From **1** ($\times$equiv.)	From **3** ($\times$equiv.)
1	80	57 (1)	86 (1)
2	80	80 (2)	
3	60	70 (2)	85 (1)
4	50	55 (2)	57 (1)
5	40	19 (2)	28 (1)



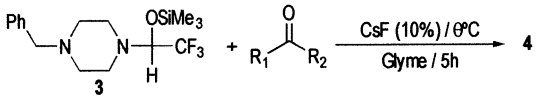
Scheme 4. Dimeric forms of **1** and **3**

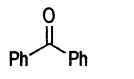
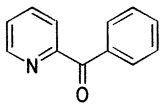
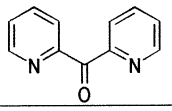
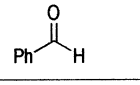
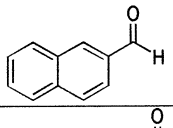
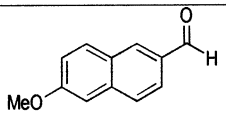
Reagent **3** has also been opposed to other carbonyl compounds (Table 2).

As shown in Table 2, non-enolizable ketones and aldehydes provided α-trifluoromethylated carbinols in good isolated yields. It can be noticed that for the less reactive substrates, the yield can be improved by increasing the temperature from 60 to 80°C (entries 2 and 5). Concerning the trifluoromethylation of enolizable carbonyl compounds, the reaction follows a different route which leads to β-(trifluoromethyl)-β-(piperazino)carbonyl compounds. This process will be reported in a future paper.

In conclusion, we have shown that **1** and **3** constitute powerful trifluoromethylating reagents towards non-enolizable ketones and aldehydes. They are easy to handle and readily prepared from the liquid and commercially available methyl hemiketal of fluoral.

Table 2
Reaction of **3** with carbonyl compounds



Entry	Substrate	θ°C	4[a] (%)
1		60 80	80 (85) (86)
2		60 80	(64) 77 (83)
3		60 80	70 (78) (79)
4		60	90 (95)
5		60 80	(84) 84 (95)
6		60 80	70 (78) 77 (80)

[a] Isolated yields. In parentheses : yields determined by ^{19}F NMR with internal standard ($PhOCF_3$)

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5. Typical procedure for the preparation of **3**: To a solution of *N*-benzylpiperazine (14.77 g, 84 mmol) in CH_2Cl_2 (80 mL; dried over 4 Å molecular sieves), were added 4 Å molecular sieves, followed by methyl hemiketal of fluoral (12 g, 92 mmol). The reaction mixture was stirred at room temperature for 48 h then filtered and evaporated in vacuo. The residue was dissolved in CH_2Cl_2 and the hemiaminal of fluoral was precipitated by pentane to yield 17.56 g of a white solid. *N*-Trimethylsilyl imidazole (9.38 mL, 64 mmol) was added at 0°C to a solution of this white solid in THF (30 mL, freshly distilled over sodium/benzophenone). After 20 min at 0°C, stirring was continued for 5 h at room temperature. Then, the reaction mixture was treated with pentane and 6% aqueous $NaHCO_3$. The organic layer was washed twice with 6% aqueous $NaHCO_3$ and dried over Na_2SO_4. After evaporation in vacuo, **3** was obtained as a yellow oil (20.81 g, 71%).
6. Spectral data of **3**: ^1H *NMR*: δ 7.24–7.42 (massif, 5H); 4.47 (q, 1H, $J=5.7$ Hz); 3.55–3.54 (2s, 2H); 2.85 (dt, 2H, $J=10.8$ Hz, $J=4.9$ Hz); 2.78 (dt, 2H, $J=10.9$ Hz, $J=4.8$ Hz); 2.49 (t, 4H, $J=4.6$ Hz); 0.22 (S, 9H). ^{13}C *NMR*: δ 138.40; 129.64; 128.67; 127.53; 123.93 (q, $J=286.8$ Hz); 85.69 (q, $J=32.4$ Hz); 63.49; 53.64; 47.82; 0.36. ^{19}F *NMR*: δ −76.85 (d, $J=5.7$ Hz). ^{29}Si *NMR*: δ 21.14. *Mass spectra*: m/z 346 ($M^{+\bullet}$); 277; 175; 91; 73; 42; 28. *Anal. calcd for* $C_{16}H_{25}F_3N_2OSi$: C (55.47%) H (7.27%) N (8.09%). *Found*: C (55.56%) H (7.53%) N (8.33%).