Reactivity of Stable Trifluoroacetaldehyde Hemiaminals. 1. An Unexpected Reaction with Enolizable Carbonyl Compounds

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In the presence of enolizable carbonyl compounds, hemiaminals of fluoral and related polyfluoroaldehydes behave as equivalents of fluoroalkyl iminium compounds and provide *β*-polyfluoroalkyl *β*-dialkylamino ketones, which are easily transformed, under acidic conditions, into *β*-polyfluoroalkylenones.

Introduction

The unique behavior of fluorinated compounds makes them suitable for various applications.[1] In particular, the lipophilicity attached to the trifluoromethyl moiety makes trifluoromethylated molecules of great interest, especially for biological purposes. However, their preparation by direct introduction of a nucleophilic CF_3 moiety on organic substrates, which is the most promising general route, is still suffering from a limited number of efficient reagents, able to stabilize the very unstable $^-CF_3$ anion.[2]

Our investigations for designing new nucleophilic trifluoromethylating reagents, recently led us to describe a family of suitable reagents, namely the hemiaminals of fluoral,[3] which effectively transform nonenolizable carbonyl compounds into trifluoromethyl carbinols.[3a−c] In the present paper, we describe their reaction toward enolizable substrates, which follows a completely different pathway.

Results and Discussion

During our studies of the behavior of fluoral hemiaminals **1**−**3** as nucleophilic trifluoromethylating reagents (Scheme 1), we were driven to put them in reaction with acetophenone. Surprisingly, when the procedures previously used to trifluoromethylate benzophenone were applied to this substrate, the expected trifluoromethyl carbinol was never obtained.

For example, when **1** (2 equiv) was reacted with potassium *tert*-butoxide (2 equiv) and acetophenone (1 equiv), self-aldolization of the latter compound extensively occurred (Table 1, entry 1). However, when **2** or **3** (2 equiv) was opposed to acetophenone (1 equiv) in the presence of a catalytic amount of fluoride, 3-trifluoromethyl-3-dialkylaminopropiophenone **4** was produced (Table 1, entries 5−9). Moreover, the same product was

Scheme 1. Hemiaminals of Fluoral

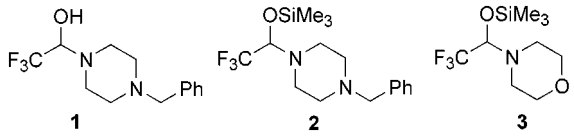
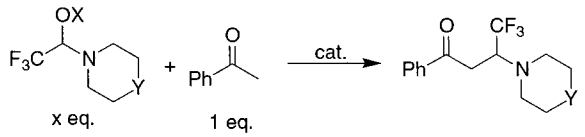


Table 1. Reaction of 1−3 with Acetophenone



1 : X=H, Y=NCH_2Ph
2 : X=$SiMe_3$, Y=NCH_2Ph
3 : X=$SiMe_3$, Y=O

4a : Y=NCH_2Ph
4b : Y=O

entry	**1**, **2** or **3** (equiv)	conditions	**4a** or **b**[a] (%)	recovd **1**, **2**, or **3**[b] (%)
1	**1** (2)	THF/rt *t*-BuOK (2 equiv)/24 h	0	0
2	**1** (2)	THF/rt *t*-BuOK (0.1 equiv)	24 h: **4a** (14) 4 days: **4a** (48)	
3	**1** (2)	THF/80 °C *t*-BuOK (0.1 equiv)	7 h: **4a** (68) 24 h: **4a** (76)	45 40
4	**1** (1)	THF/80 °C/24 h *t*-BuOK (0.1 equiv)	**4a** (30)	20
5	**2** (1)	DME[c]/80 °C/5 h cat. CsF	**4a** (50)	30
6	**2** (2)	DME[c]/80 °C/5 h cat. CsF	**4a** (90)	47
7	**2** (2)	DME[c]/rt cat. CsF	5 h: **4a** (7) 24 h: **4a** (23)	
8	**3** (1)	DME[c]/80 °C/5 h cat. CsF	**4b** (50)	30
9	**3** (2)	DME[c]/80 °C/5 h cat. CsF	**4b** (80)	40

[a] Crude yields vs acetophenone determined by ^{19}F NMR with internal standard ($PhOCF_3$). [b] Yield vs **1**, **2**, or **3** determined by ^{19}F NMR with internal standard ($PhOCF_3$). [c] DME: 1,2-dimethoxyethane.

(1) (a) Gross, 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, pp 18−26. (b) Filler, R.; Kobayashi, Y.; Yagulpolskii, Y. L. *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Elsevier: Amsterdam, 1993. (c) Banks, R. E.; Smart, B. E.; Tatlow, J. C. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum Press: New York, 1994. (d) Hudlicky, M.; Pavlath, A. E. *Chemistry of Organic Fluorine Compounds II. A critical Review*; ACS Monograph 187; American Chemical Society: Washington, DC, 1995.

(2) (a) McClinton M. A.; McClinton D. A. *Tetrahedron* **1992**, *48*, 6555−6666. (b) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757−786.

(3) (a) Billard, T.; Bruns, S.; Langlois, B. R. *Org. Lett.* **2000**, *2*, 2101−2103. (b) Billard, T.; Langlois, B. R.; Blond, G. *Tetrahedron Lett.* **2000**, *41*, 8777−8780. (c) Billard, T.; Langlois, B. R.; Blond, G. *Eur. J. Org. Chem.* **2001**, 1467−1471. (d) Blond, G.; Billard, T.; Langlois, B. R. *Tetrahedron Lett.* **2001**, *42*, 2473−2475.

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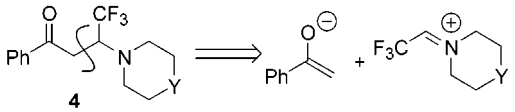
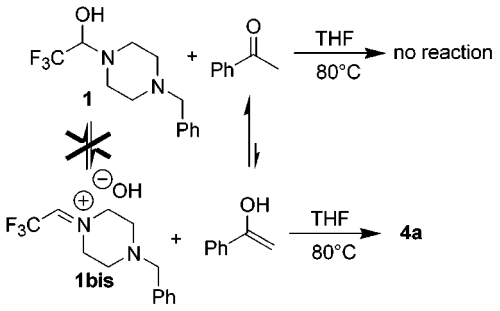
Scheme 2. Retrosynthesis of 4



Scheme 3. Hypothesis on the Formation of 1bis



obtained from acetophenone, **1** (2 equiv), and a catalytic amount of potassium *tert*-butoxide (0.1 equiv) (Table 1, entries 2−4).

When only 1 equivalent of reagents **1**, **2**, or **3** was used, the yield of **4** did not exceed 50% and approximately 30−40% of **1**, **2**, or **3** was recovered (Table 1, entries 4, 5, and 8). With 2 equiv of these reagents, the yield of **4** increased up to 80% and, again, around 1 equiv of **1**, **2**, or **3** was recovered (Table 1, entries 3, 6, and 9).

Therefore, the optimal yield of **4** was obtained at 80 °C with 2 equiv of **1**, **2**, or **3** and catalytic amounts of CsF or *t*-BuOK (ca. 10%).

The surprising nature of product **4** and the fact that 2 equiv of **1**, **2**, or **3** was needed to get good results, whereas only 1 equiv seemed to react, prompted us to investigate the mechanism of this reaction. As these three reagents led to almost the same result under similar conditions, we focused our attention on **1**.

Because of the structure of **4**, it could be anticipated that this compound resulted, at least formally, from the reaction between a trifluoromethyl iminium deriving from **1** and the enolate of acetophenone (Scheme 2). In such a hypothesis, the role of catalytic *t*-BuOK in the formation of these intermediates must be elucidated.

To ascertain that the catalytic base was necessary and that **1** was not already in equilibrium with the iminium hydroxide **1bis**, the same reaction was carried out without base. As expected, no reaction took place (Scheme 3). Nevertheless, the absence of detectable product may only reflect the low concentration of enolate under these conditions. To determine if **1bis** was really formed, even in low quantities, two complementary experiments were carried out: one in the presence of methanol and another in the presence of ^{18}O-enriched water. In both cases, no transformation of **1** was observed at all, and no methoxy- or ^{18}O-containing product was formed. This allows us to assert that **1** is not in equilibrium with the iminium hydroxide **1bis**.

Since *t*-BuOK was proved to be essential in the formation of **4a**, we determined which reactant (acetophenone or **1**) was deprotonated first. For this purpose, the reaction was carried out in two steps, the first one being the deprotonation of one of the two reactants (acetophenone or **1**) with 0.1 equiv of *t*-BuOK before adding the second partner. In both cases, the same yield of **4a** was obtained. This result demonstrated that both **1** and acetophenone were in equilibrium with their conjugated bases which, consequently, must be considered as intermediates in the formation of **4a** (Scheme 4).

As 2 equiv of **1** was required to get a good yield of **4a** though 1 equiv of **1** was recovered, it can be assumed that the real active species are a hydrogen-bonded dimeric form of **1** and/or a 1:1 complex between **1** and its conjugated base. This latter hypothesis is in accordance with our previous work,[3c] which demonstrated that, in THF, the potassium salt of **1** is a dimer in which the K^+ cation of one molecule is complexed by the nitrogen atoms of the second one. These elements are taken into account

Scheme 4. Mechanism of the Reaction

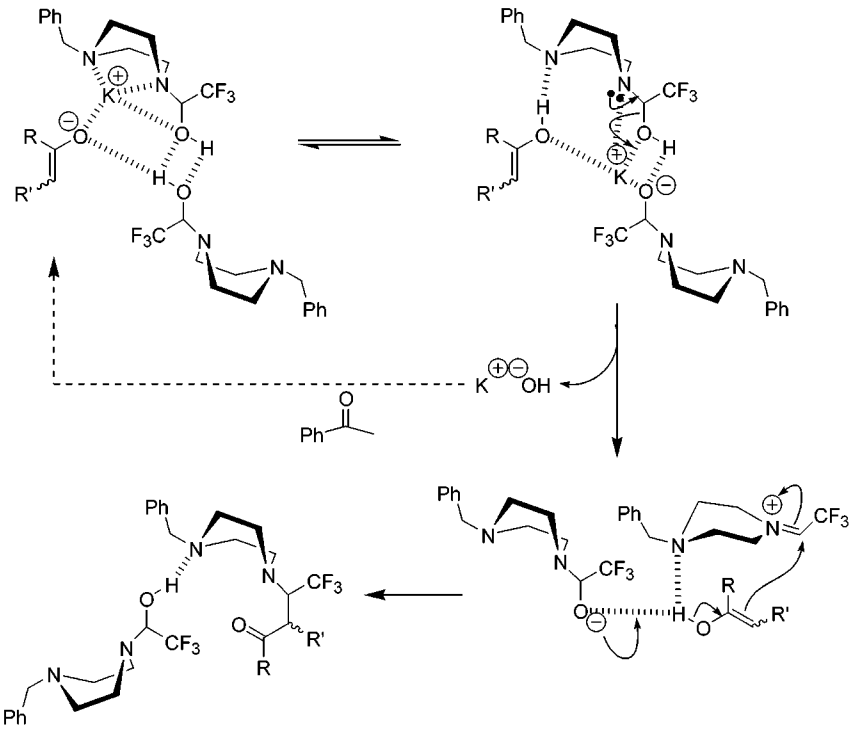
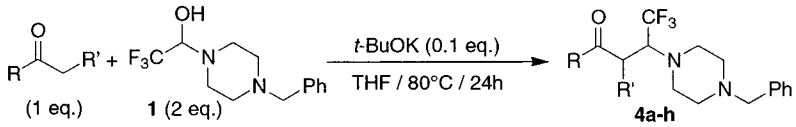
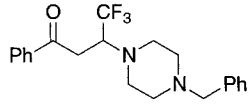
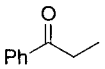
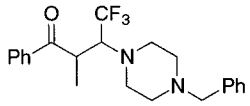
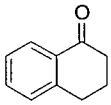
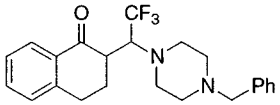
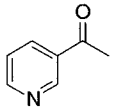
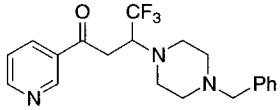
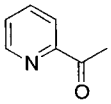
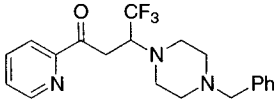
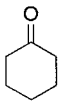
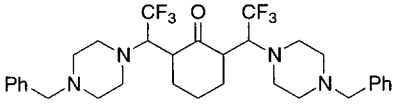
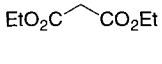
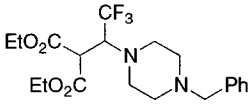


Table 2. Synthesis of β-Trifluoromethyl, β-(*N*′-Benzyl)piperazino Carbonyl Compounds



Entry		4 (%)[a]	
1			**4a** 59 (79)
2			**4c** 31 (41) 2 diast.
3			**4d** 39 (40) 2 diast.
4			**4**[e] 80 (82)
5			**4f** 75 (80)
6			**4g**[b] 30 (56) 5 diast.
7			**4h** 75 (80)

[a] Isolated yield. In parentheses: crude yield determined by ^{19}F NMR with internal standard ($PhOCF_3$). [b] With 4 equiv of **1**.

in the mechanism we propose to explain the formation of an iminium salt from **1** (Scheme 4).

This mechanism implies that potassium hydroxide is formed and regenerates the conjugated base of acetophenone or that of **1**, justifying the fact that *t*-BuOK must be used in a catalytic amount. This hypothesis was confirmed by replacing *t*-BuOK by KOH (50% in water): under these conditions, the same result was obtained.

A similar mechanism can be postulated from **2** or **3**. In this case, CsF acts as a base to enolize acetophenone[4] or generate the conjugate base of **1** (from **2**) or that of its morpholino analogue (from **3**), whereas the trimethylsilanolate anion plays the role of the hydroxide anion in the catalytic cycle.

On a synthetic point of view, this reaction allows the easy preparation of β-trifluoromethyl-β-dialkylaminoacetophenone in one step from the parent carbonylated substrate. It has been extended not only to other alkyl aryl ketones, but also to alkyl heteroaryl ketones and alicyclic ketones or malonic esters (Table 2).

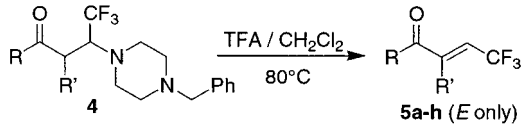
The synthesis of some of these compounds have been already described in the literature from hemiaminals[5] or aminals[6] of fluoral and silyl enol ethers but not from ketones. The reaction of a trifluoromethylated iminium with an enolizable ketone has been reported one time only, but the resulting compound has not been isolated.[7] We, too, mentioned the formation of 3-trifluoromethyl-3-dimethylaminopropiophenone from fluoroform and 2-benzoyl-1-dimethylaminoethylene.[8] Neverteless, in all these works, the access to reagents and/or substrates is not always easy. In contrast, stable reagents **1**−**3** are readily available, even on a large scale,[3] and are able to react directly, in an effective way, with carbonyl compounds.

Apart from their potential biological activity, the main interest of compounds **4** lies in their sensitivity to acids and their ability to eliminate, under such conditions, morpholine or *N*-benzylpiperazine to deliver *trans*-β-trifluoromethyl enones **5** (Table 3).

Thus, (*E*)-β-trifluoromethyl enones can be prepared in an efficient two-step procedure by a formal (trifluoromethyl)methylidenation of ketones. These electron-withdrawing substituted enones constitute very valuable synthetic intermediates. Moreover, compound **5g** could

(4) Clark, J. H. *Chem. Rev.* **1980**, *80*, 429−452.
(5) Takaya, J. H.; Kagoshima, H.; Akiyama, T. *Org. Lett.* **2000**, *2*, 1577−1579.
(6) (a) Dolbier, W. R., Jr.; Xu, Y. *Tetrahedron Lett.* **1998**, *39*, 9151−9154. (b) Dolbier, W. R., Jr.; Xu, Y. *J. Org. Chem.* **2000**, *65*, 2134−2137. (c) Fuchigami, T.; Nakagawa, Y.; Nonaka, T. *J. Org. Chem.* **1987**, *52*, 5489−5491.
(7) Ates, C.; Janousek, Z.; Viehe, H. G. *Tetrahedron Lett.* **1993**, *34*, 5711−5714.
(8) Large, S.; Roques, N.; Langlois, B. R. *J. Org. Chem.* **2000**, *65*, 8848−8856.

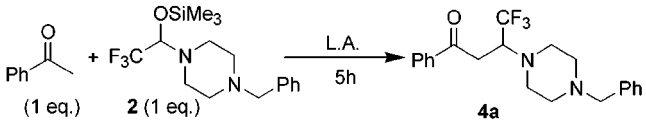
Table 3. Synthesis of β-Trifluoromethyl Enones



Entry	4	5 (%)[a]
1	**4a**	**5a** 70 (80)
2	**4c**	**5c** 80 (85)
3	**4d**	**5d** 81 (86)
4	**4e**	**5e** 37 (42)
5	**4g**	**5g** 75 (80)
6	**4h**	**5h** 75 (80)

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

Table 4. Use of Lewis Acid to Generate Iminium



entry	Lewis acid (equiv)	conditions	4a[a] (%)
1	$BF_3{\cdot}Et_2O$ (1)	THF/rt	30
2	$BF_3{\cdot}Et_2O$ (2)	THF/rt	58
3	$BF_3{\cdot}Et_2O$ (3)	THF/rt	59
4	$BF_3{\cdot}Et_2O$ (0.1)	THF/rt	0
5	$BF_3{\cdot}Et_2O$ (1.2)	THF/rt	58
6	$ClTi(O\text{-}i\text{-}Pr)_3$ (1.2)	THF/rt	0
7	$Ti(O\text{-}i\text{-}Pr)_4$ (1.2)	THF/rt	0
8	$BF_3{\cdot}Et_2O$ (1)	CH_2Cl_2/50 °C	51
9	$BF_3{\cdot}Et_2O$ (1.2)	CH_2Cl_2/50 °C	70
10	$BF_3{\cdot}Et_2O$ (2)	CH_2Cl_2/50 °C	66

[a] Determined by ^{19}F NMR with internal standard ($PhOCF_3$).

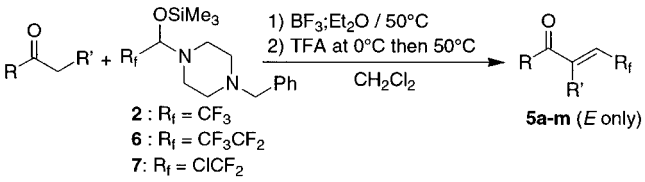
be an interesting analogue of the choleretic drug Cyclovalone (2,6-bis-(3-methoxy-4-hydroxybenzylidene)cyclohexanone).[9]

Coming back to compounds **4**, it was important to confirm that iminium species were involved as intermediates in their synthesis. For this purpose, we decided to generate iminium salts from **2** and Lewis acids and to react them with enolizable ketones (Table 4).

As expected, **4a** was produced in this way from acetophenone, **2**, and BF_3 etherate (Table 4). It must be noticed that Ti(IV) derivatives were not able to catalyze this condensation (Table 4, entries 6 and 7). Best results, similar to those resulting from fluoride activation of **2**, were obtained with 1.2 equiv of boron trifluoride (Table 4, entries 5 and 9). Probably 1 equiv was necessary to generate the iminium intermediate and 0.2 equiv to catalyze the enolization of acetophenone.

This reaction confirms the possibility to generate a trifluoromethylated iminium from **1**−**3** and, therefore, reinforce the mechanism proposed in Scheme 4. It also offers a second route to compounds **4**. Moreover, as this new synthesis of **4** is carried out under acidic conditions, like the transformation of **4** to **5**, these two steps were combined in a one-pot preparation of **5** from simple carbonyl compounds.

Table 5. (Perhalogenoalkyl)Methylidenation of Carbonyl Compounds



Entry	5 (%)[a]
1	**5a** 73 (75)
2	**5d** 80 (76)
3	**5g**[b] 31 (42)
4	**5i** 45 (51)
5	**5j** 72 (75)
6	**5k** 75 (70)
7	**5l** 70 (76)
8	**5m** 65 (73)

[a] Isolated yields vs ketones. In parentheses: crude yield determined by ^{19}F NMR with internal standard ($PhOCF_3$). [b] With 2 equiv of **2**.

As silylated hemiaminals of pentafluoropropionaldehyde and chlorodifluoroacetaldehyde can be prepared in the same way as **2** from the hydrates of the corresponding aldehydes, this methodology has been successfully extended to the one-pot (perhalogenoalkyl)methylidenation of carbonyl compounds, even elaborated ones such as cholestenone (Table 5).

In conclusion, this study shows that the stable and readily available hemiaminals of fluoral can, under specific conditions, generate iminium species that react with enolizable carbonyl compounds to deliver β-trifluoromethyl β-dialkylamino carbonyl compounds in an efficient way. In a second step, which can be carried out in the same pot, trifluoromethylenones can be prepared

(9) Rumpel, W. Austrian Patent No. 180258, 1954.

from them under acidic conditions. This reaction can be extended to hemiaminals of other perhalofluoroaldehydes. The synthetic potential of perhalofluoro iminiums species is under study in our laboratory.

Experimental Section

General Remarks. Solvents were distilled prior to use. Other reagents were used as received. Flash chromatography was performed on silica gel 60M (0.04−0.063 mm). Reagents **1**−**3** were prepared according to our previous work.[3a−c] Pentafluoroethyl (**6**) and chlorodifluoro analogues (**7**) were prepared with the same techniques.

Typical Procedure for the Synthesis of 4 under Catalysis with *t*-BuOK. A 1 M solution of *t*-BuOK in THF (1 mL) was added, at room temperature, to a solution of **1** (2 mmol) and enolizable carbonyl substrate (1 mmol) in THF (1 mL). Then, the reaction mixture was heated to 80 °C for 24 h. After cooling, the crude mixture was evaporated and purified by flash chromatography. Because of their rather limited stability, compounds **4** were rapidly engaged in the elimination step after NMR control.

Typical Procedure for the Synthesis of 4 under Catalysis with BF_3·Et_2O. BF_3·Et_2O (1.2 mmol) was added, at room temperature, to a solution of **2**, **6**, or **7** (1 mmol) and enolizable carbonyl substrate (1 mmol) in CH_2Cl_2 (1 mL). Then, the mixture was heated to 50 °C for 5 h. After cooling and evaporation, the crude mixture was deposited at the top of a column filled with silica gel and eluted.

Typical Procedure for the Synthesis of 5 from 4. Trifluoroacetic acid (0.5 mL) was added, at 0 °C, to a solution of **4** (1 mmol) in CH_2Cl_2 (1 mL). The mixture was heated in a closed vessel at 80 °C for 5 h. After cooling, it was washed twice with a 6% aqueous solution of $NaHCO_3$, dried over Na_2SO_4, and evaporated in vacuo at room temperature. Then, the crude residue was purified by flash chromatography.

Typical Procedure for the One-Pot Synthesis of 5 from 2, 6, or 7. BF_3·Et_2O (1.2 mmol) was added, at room temperature, to a solution of **2**, **6**, or **7** (1 mmol) and enolizable carbonyl substrate (1 mmol) in CH_2Cl_2 (1 mL). Then, the mixture was heated to 50 °C for 5 h. After the mixture was cooled to 0 °C, trifluoroacetic acid (0.5 mL) was added and the mixture was heated again to 50 °C for 5 h. After cooling and evaporation, the crude mixture was deposited at the top of a column filled with silica gel and eluted.

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Supporting Information Available: Characterization data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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