Trifluoromethylation of Nonenolizable Carbonyl Compounds with a Stable Piperazino Hemiaminal of Trifluoroacetaldehyde[‡]

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A new stable hemiaminal of fluoral (**1**) can easily be obtained from the methyl hemiketal of fluoral and *N*-benzylpiperazine. This white crystalline compound can be used under basic conditions as an efficient nucleophilic trifluoromethylating reagent towards nonenolizable carbonyl compounds.

Introduction

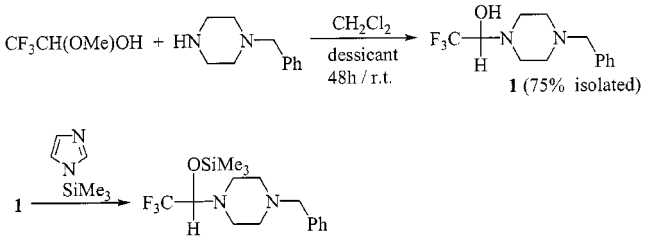
Because of the intrinsic properties of fluorine, fluorinated organic compounds present unique properties and often exhibit unusual reactivities.[1] Among them, trifluoromethyl-substituted molecules are of great interest for different applications.[2–4] Nevertheless, the efficient introduction of the CF_3 moiety to organic substrates always constitutes an important challenge for chemists.

At present, many reliable methods are available[5] but the nucleophilic strategy, which is the most promising one, still suffers from a limited number of efficient reagents able to overcome the great instability of the CF_3^- anion, which is known to decompose rapidly into fluoride ion and difluorocarbene.

Presently, the most popular commercial reagent is Ruppert's reagent (CF_3SiMe_3).[6] However, this compound is prepared from bromotrifluoromethane (CF_3Br), the industrial production of which is now restricted.[7] This drawback prompted us to investigate new reagents useful for the nucleophilic trifluoromethylation and easily accessible from simple, cheap and readily available starting materials.

Results and Discussion

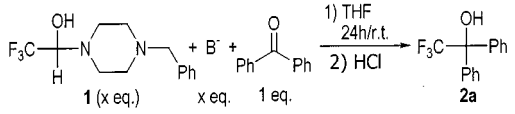
Trifluoroacetaldehyde (fluoral), in its hemiketal form, fulfils these latter conditions and we recently showed that it reacts very easily with *N*-benzyl piperazine to provide, after silylation, the corresponding *O*-silylated hemiaminal.[8] This new stable compound is able to trifluoromethylate nonenolizable carbonyl compounds by fluoride activation. However, as shown in Scheme 1, its synthesis needs the intermediate preparation of the free hemiaminal **1**, which can easily be purified by precipitation from its dichloromethane solution with pentane.



Scheme 1. Synthesis of the hemiaminal of fluoral **1**

This led us to study the trifluoromethylating ability of **1** under basic conditions. First, we determined which basic system was most suitable for the trifluoromethylation of benzophenone with **1**. (Table 1)

Table 1. Determination of the best basic system for trifluoromethylation of **1**



Entry	**1** (equiv.)	Base	Trifluoromethyl carbinol **2a** (%)[a]
1	1	*t*BuOK	50
2	2	*t*BuOK	90
3	2	*t*BuONa	0
4	2	*t*BuOLi	0
5	2	KH	95
6	2	NaH	0
7	2	$KN(SiMe_3)_2$	90
8	2	BuLi	0
9	2	PhMgCl	0
10	2	DBU[b]	0
11	2	Imidazole	0
12	2	DABCO[c]	0

[a] Determined by ^{19}F NMR spectroscopy with internal standard ($PhOCF_3$). – [b] DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene. – [c] DABCO: 1,4-Diazabicyclo[2.2.2]octane.

It appears from Table 1 that two equivalents of **1** and base are necessary to obtain good yields (entries 1 and 2). Furthermore, the nature of the base counter-cation plays a

[‡] New Stable Reagents for Nucleophilic Trifluoromethylation, 3. – Part 2: Ref.[8]

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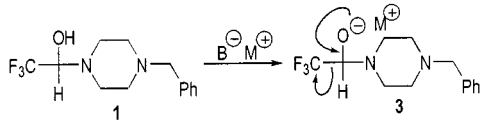
crucial role. Indeed, if we assume, according to our previous work,[8] that the trifluoromethylating species is the hemiaminolate **3** (Scheme 2), the better the ion pair is separated, the better the generation of CF_3^-: reagents **3** forming tight ionic pairs [Li salts (entries 4 and 8) or Na salts (entries 3 and 6)] or too covalent O−M bonds [Mg salts (entry 9)] do not lead to the expected product **2a**. Negative results were also obtained with amines (entries 10−12), which are probably not basic enough to deprotonate **1**.



Scheme 2. Generation of a CF_3^- equivalent from **1**

To verify the influence of the pair separation we carried out the same reaction in solvents exhibiting higher polarities and basicities than THF, or in the presence of chelating agents. (Table 2)

Table 2. Effect of solvation on the trifluoromethylation of **1**

Entry	Base	Solvent	**2a** (%)[a]
1	NaH	DMF	90
2	*t*BuONa	DMF	90
3	*t*BuOK	DMF	91
4	*t*BuOLi	DMF	0
5	BuLi	THF + TMEDA (2 equiv.)[b]	0

[a] Determined by ^{19}F NMR spectroscopy with internal standard ($PhOCF_3$). − [b] TMEDA: *N*,*N*′-tetramethylethylenediamine.

Table 2 shows that solvents with high donor-numbers like DMF (DMF: $DN^N = 0.8$ vs. THF: $DN^N = 0.52$),[9] which is able to chelate cations more efficiently than THF, lead to the same results with sodium and potassium salts (entries 1−3). This underlines the importance of ion-pair separation on the trifluoromethylation efficiency. Nevertheless, the ion-bonding of lithium salts is so strong that even DMF or TMEDA are not chelating enough to allow trifluoromethylation (entries 4, 5).

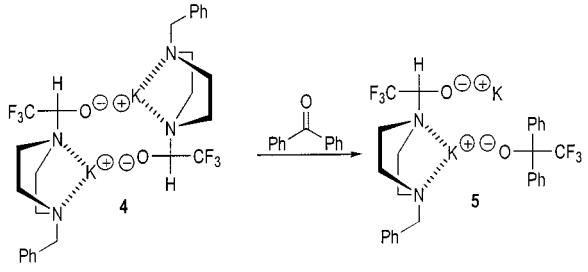
As chelating phenomena could also shed some light on the necessity of using two equivalents of **1** and base to reach good trifluoromethylation yields, we had a deeper insight into solvent effects on the stoichiometry of the reaction (Table 3).

Table 3. Solvent effect on the reactivity of **3** with benzophenone

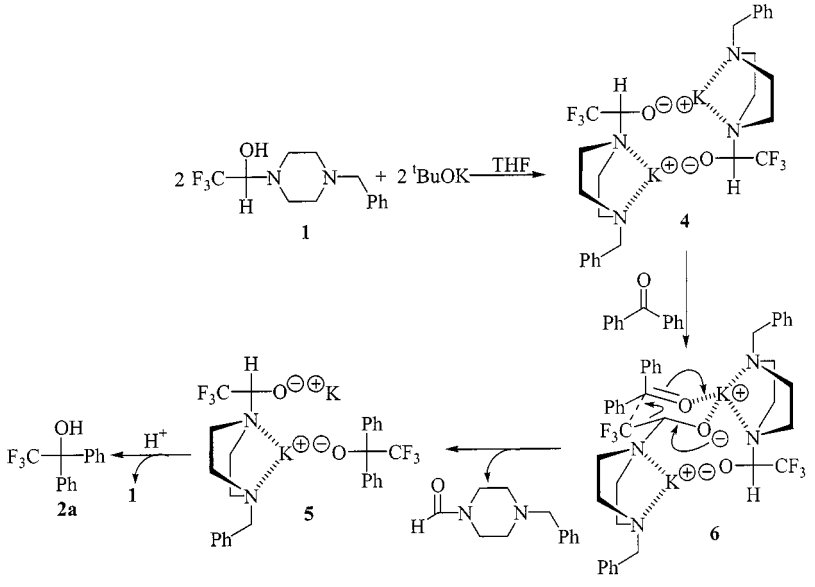
Entry	**3** (equiv.)	Solvent	**2a** (%)[a]
1	2	THF	90
2	1	THF/DMF (1:1: v/v)	91
3	1	THF + DMF (1 equiv.)	68
4	1	DMF	93
5	1	THF + 18-c-6 (1 equiv.)[b]	85
6	1	DME[c]/THF (1:1: v/v)	68

[a] Determined by ^{19}F NMR spectroscopy with internal standard ($PhOCF_3$). − [b] 18-c-6: 18-crown-6. − [c] DME: 1,2-Dimethoxyethane.

It appears from Table 3 that the use of DMF as solvent or co-solvent leads to the same yield as in pure THF but with only one equivalent of **1** and *t*BuOK instead of two



Scheme 3. Self-activation of **3** through a dimeric form



Scheme 4. Mechanism of the trifluoromethylation reaction of **1**

(entries 2, 4). A similar result can be obtained by adding 18-crown-6 to THF as a specific chelating agent for potassium cations (entry 5). The use of only one equivalent of DMF (entry 3), or of a co-solvent like DME, with a DN between those of THF and DMF, (entry 6) also increased the yield but to a lesser extent.

These observations led us to propose that, in THF, **3** (M = K) exists in a dimeric form (**4**) which allows the self-activation of ion pairs. After reaction with benzophenone, **4** is transformed into complex **5** in which one equivalent of **3** is replaced by the conjugate base of **2a** (Scheme 3). Obviously, the potassium hemiaminolate moiety included in **5** is no longer activated by chelation and remains inactive towards benzophenone. This could explain the necessity of two equivalents of **1** for getting good trifluoromethylation yields.

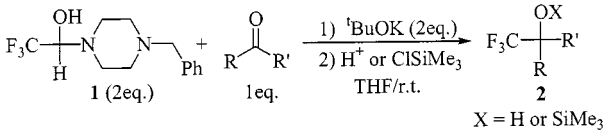
On the contrary, when the reaction was carried out in the presence of DMF, DME or 18-crown-6, **4** cannot exist because of the external chelation of the potassium cation with such species. Consequently, the following refined mechanism can be proposed for the trifluoromethylation of benzophenone with **1** in THF. (Scheme 4)

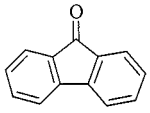
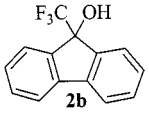
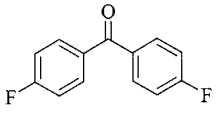
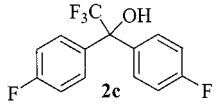
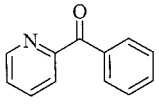
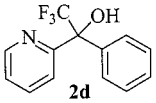
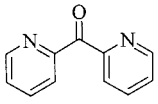
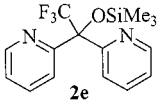
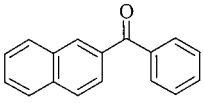
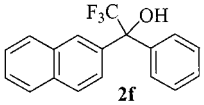
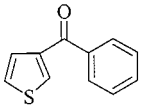
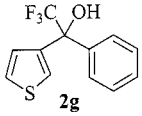
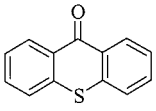
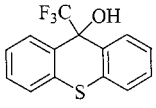
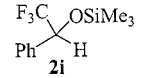
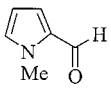
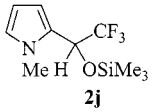
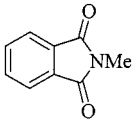
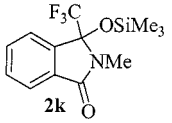
In this mechanism, it can be assumed that the transfer of the CF_3 moiety from **4** to the ketone occurs in a concerted way through a six-membered transition state **6**, in order to account for the fact that no free CF_3^- was formed, as indicated by the absence of fluoride ions in the crude mixture (^{19}F NMR spectroscopy). After acidic hydrolysis, **5** gives the trifluoromethyl carbinol **2a** and, theoretically, one equivalent of **1**; this compound, however, is too acid sensitive and could not be recovered.

After model studies with benzophenone, this trifluoromethylation reaction has been extended to other nonenolizable carbonyl compounds. (Table 4)

As shown in Table 4, good yields were usually obtained from various non enolizable ketones or aldehydes (entries 1−6, 9) even in heterocyclic series (entries 7, 8, 10). Phthalimide could also be trifluoromethylated without opening the cyclic imide moiety (entry 11). After reaction, both free alcohols or silylated ethers could be obtained, depending on the treatment of the crude mixture either with acid or chlorotrimethylsilane.

Table 4. Trifluoromethylation of nonenolizable carbonyl compounds with **1**



	Carbonyl compounds	2 (%) [a]
1		 **2a** 80 (90)
2		 **2b** 64 (63)
3		 **2c** 75 (90)
4		 **2d** 80 (85)
5		 **2e** 60 (70)
6		 **2f** 80 (94)
7		 **2g** 47 (50)
8		 **2h** 71 (76)
9		 **2i** 65 (72)
10		 **2j** 96 (100)
11		 **2k** 76 (79)

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

Conclusion

In conclusion, we have shown that it is possible to obtain, in one step from the industrially available methyl hemiketal of trifluoroacetaldehyde, a new stable crystalline compound, which acts as an efficient nucleophilic trifluoromethylating agent towards nonenolizable carbonyl compounds under mild conditions. It can also react with enolizable carbonyl substrates but in a completely different way. In this case, the reaction occurs at the α-carbon center and will be described in future papers.

Experimental Section

General Remarks: Solvents were distilled prior to use. Aldehydes were also distilled or recrystallized prior to use. Other reagents were used as received. ^1H, ^{13}C and ^{19}F NMR spectra were recorded in $CDCl_3$ at 300, 75 and 188 MHz, respectively. Chemical shifts are

given in ppm relative to TMS (^1H, ^{13}C) or $CFCl_3$ (^{19}F) as internal references. Coupling constants are given in Hz. Mass spectrometry was performed at 70 eV. Flash chromatography was performed on silica gel 60M (0.04−0.063 mm). Melting points (uncorrected) were determined in capillary tubes on a Büchi apparatus. Elemental analyses were carried out by the "Centre de Microanalyse" of the CNRS at Solaize.

Synthesis of 1-(4-Benzylpiperazino)-2,2,2-trifluoroethanol (1): Molecular sieves (4 Å) and the methyl hemiketal of fluoral (12 g, 92 mmol) were added to a solution of *N*-benzylpiperazine (14.77 g, 84 mmol) in CH_2Cl_2 (80 mL; dried over 4 Å molecular sieves). The reaction mixture was stirred at room temperature for 48 h then filtered and the solvents evaporated in vacuo at room temperature. The residue was dissolved in CH_2Cl_2. Compound **1** was precipitated from this solution by addition of pentane to yield 17.56 g of a white solid (76%). M.p. 101−102 °C. − ^1H NMR: δ = 7.28−7.38 (m, 5 H), 4.68 (broad s, 1 H), 4.49 (q, *J* = 5.9, 1 H), 3.56 (s, 2 H), 2.87 (t, *J* = 4.85, 4 H), 2.50 (broad t, *J* = 4.85, 4 H). − ^{13}C NMR: δ = 137.4, 129.9, 128.7, 127.7, 124.0 (q, *J* = 287.4), 84.5 (q, *J* = 32.0), 63.3, 53.3, 47.2. − ^{19}F NMR: δ = −76.1 (d, *J* = 5.8). − MS: *m/z* = 274 [$M^{+\cdot}$], 257, 176, 134, 91. − $C_{13}H_{17}F_3N_2O$ (274.28): C 56.93, H 6.25, N 10.21; found C 57.13, H 6.22, N 10.23.

General Procedure for the Trifluoromethylation of 1: In a two-necked flask **1** (0.548 g, 2 mmol), the carbonyl substrate (1 mmol) and dry THF (1 mL) were successively introduced, under nitrogen. After solubilization, *t*BuOK (2 mL of a 1 M solution in THF, 2 mmol) was added. The reaction mixture was stirred at room temperature for 24 h. After reaction, $ClSiMe_3$ (0.5 mL) or aqueous 1 M HCl (1 mL) was dropped into the reaction mixture, which was then extracted twice with brine and ether. The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo at room temperature. The crude residue was purified by flash chromatography. Eluents are indicated for each compound.

2,2,2-Trifluoro-1,1-diphenylethanol (2a): Petroleum ether/acetone (19:1). Oil (202 mg, 80%).^1H NMR: δ = 7.46−7.50 (m, 4 H), 7.31−7.34 (m, 6 H), 3.09 (s, 1 H). − ^{13}C NMR: δ = 139.5, 128.7, 127.5 (q, *J* = 1.6), 125.5 (q, *J* = 286.0), 79.6 (q, *J* = 28.7). − ^{19}F NMR: δ = −74.70. − MS: *m/z* = 252 [$M^{+\cdot}$], 189, 105, 77, 51, 39. − $C_{14}H_{11}F_3O$ (252.23): C 66.67, H 4.39; found C 66.68, H 4.55.

9-(Trifluoromethyl)-9*H*-fluoren-9-ol (2b): Petroleum ether/acetone (20:1). Beige solid (160 mg, 64%). M.p. 91 °C. − ^1H NMR: δ = 7.67 (m, 4 H), 7.48 (m, 2 H), 7.36 (m, 2 H), 2.99 (broad s, 1 H). − ^{13}C NMR: δ = 141.4, 141.3, 131.2, 128.8, 125.6 (q, *J* = 1.7), 125.5 (q, *J* = 284.1), 120.8, 81.8 (q, *J* = 30.8). − ^{19}F NMR: δ = −79.1. − MS: *m/z* = 250 [$M^{+\cdot}$], 181, 152, 76. − $C_{14}H_9F_3O$ (250.22): C 67.20, H 3.63; found C 66.94, H 3.70.

2,2,2-Trifluoro-1,1-bis(4-fluorophenyl)ethanol (2c): Petroleum ether/diethyl ether (19:1) Oil (216 mg, 75%). − ^1H NMR: δ = 7.49 (broad dd, *J* = 5.2, *J* = 8.3, 4 H), 7.07 (t, *J* = 8.3, 4 H), 3.13 (s, 1 H). − ^{13}C NMR: δ = 163.2 (d, *J* = 248.3), 135.4 (d, *J* = 3.5), 129.8 (dq, *J* = 8.1, *J* = 1.7), 125.5 (q, *J* = 286.4), 115.7 (d, *J* = 21.8), 79.2 (q, *J* = 28.9). − ^{19}F NMR: δ = −75.01 (s, 3F), −113.04 (m, 2F). − MS: *m/z* = 288 [$M^{+\cdot}$], 219, 123, 95, 75, 69. − $C_{14}H_9F_5O$ (288.21): C 58.34, H 3.15; found C 57.98, H 3.36.

2,2,2-Trifluoro-1-phenyl-1-(2-pyridyl)ethanol (2d): Petroleum ether/diethyl ether (9:1) Beige solid (202 mg, 80%). M.p. 60−61 °C. − ^1H NMR: δ = 8.61−8.63 (m, 1 H), 7.70−7.78 (m, 3 H), 7.50−7.55 (m, 1 H), 7.32−7.47 (m, 4 H), 7.06 (broad s, 1 H).^{13}C NMR: δ = 155.3, 147.6, 138.7, 137.9, 129.0, 128.9, 127.4 (q, *J* = 2.1), 125.5 (q, *J* = 286.4), 124.4, 123.3 (q, *J* = 1.9), 78.1 (q, *J* = 28.9). − ^{19}F NMR: δ = −75.19. − MS: *m/z* = 253 [$M^{+\cdot}$], 184, 176, 106, 78, 77, 69, 51. − $C_{13}H_{10}F_3NO$: C 61.66, H 3.98, N 5.53; found C 62.01, H 4.35, N 5.36.

2,2,2-Trifluoro-1,1-di(2-pyridyl)ethyl Trimethylsilyl Ether (2e): Petroleum ether/acetone (4:1). Oil (196 mg, 60%). − ^1H NMR: δ = 8.54−8.57 (m, 2 H), 7.70−7.81 (m, 4 H), 7.21−7.26 (m, 2 H), 0.06 (s, 9 H). − ^{13}C NMR: δ = 158.9, 148.7, 136.9, 125.0 (q, *J* = 287.7), 123.6, 123.2 (q, *J* = 1.7), 83.6 (q, *J* = 27.6), 2.3. − ^{19}F NMR: δ = −73.55. − MS: *m/z* = 326 [$M^{+\cdot}$], 311, 257, 242, 215, 187, 168, 150, 121, 106, 78, 73, 51. − $C_{15}H_{17}F_3N_2OSi$ (326.39): C 55.20, H 5.25, Si 8.60; found C 55.29, H 5.64, Si 8.25.

2,2,2-Trifluoro-1-(2-naphthyl)-1-phenylethanol (2f): Petroleum ether/diethyl ether (30:1). Oil (242 mg, 80%). − ^1H NMR: δ = 8.21 (s, 1 H), 7.84−7.96 (m, 3 H), 7.56−7.65 (m, 5 H), 7.41−7.54 (m, 3 H), 3.25 (s, 1 H). − ^{13}C NMR: δ = 139.7, 137.0, 133.5, 133.1, 129.2, 129.1, 128.8, 128.6, 128.0 (q, *J* = 1.7), 128.0, 127.4, 127.0, 127.0 (q, *J* = 1.5), 125.9 (q, *J* = 286.6), 125.6 (q, *J* = 1.5), 80.1 (q, *J* = 28.5). − ^{19}F NMR: δ = −74.38. − $C_{18}H_{13}F_3O$ (302.29): C 71.52, H 4.33; found C 71.28, H 4.66.

2,2,2-Trifluoro-1-phenyl-1-(2-thienyl)ethanol (2g): Petroleum ether/acetone (9:1). Oil (121 mg, 47%). − ^1H NMR: δ = 7.64−7.70 (m, 2 H), 7.38−7.44 (m, 4 H), 7.25−7.27 (m, 1 H), 7.04−7.07 (m, 1 H), 3.32 (s, 1 H). − ^{13}C NMR: δ = 143.6, 138.2, 129.5, 128.6, 127.6 (q, *J* = 2.1), 127.4 (q, *J* = 1.5), 127.3, 127.2, 125.2 (q, *J* = 286.4), 78.2 (q, *J* = 29.9). − ^{19}F NMR: δ = −76.70. − MS: *m/z* = 258 [$M^{+\cdot}$], 189, 111, 105, 77, 69, 51, 39. − $C_{12}H_9F_3OS$ (258.26): C 55.81, H 3.51, S 12.42; found C 55.56, H 3.68, S 12.10.

9-(Trifluoromethyl)-9*H*-thioxanthen-9-ol (2h): Petroleum ether/acetone (19:1). Beige solid (200 mg, 71%). M.p. 121 °C. − ^1H NMR: δ = 7.96−7.99 (m, 2 H), 7.28−7.39 (m, 6 H), 3.06 (s, 1 H). − ^{13}C NMR: δ = 132.2, 130.3, 129.7, 128.9, 126.7, 126.3, 125.2 (q, *J* = 288.1), 74.3 (q, *J* = 30.7). − ^{19}F NMR: δ = −81.11. − MS: *m/z* = 282 [$M^{+\cdot}$], 213, 184, 152, 77, 69. − $C_{13}H_{17}F_3N_2O$ (274.28): C 59.57, H 3.21, S 11.36; found C 59.81, H 3.29, S 11.45.

2,2,2-Trifluoro-1-phenylethyl Trimethylsilyl Ether (2i): Petroleum ether. Oil (161 mg, 65%). − ^1H NMR: δ = 7.53−7.57 (m, 2 H), 7.42−7.47 (m, 3 H), 5.01 (q, *J* = 6.6, 1 H), 0.21 (s, 9 H). − ^{13}C NMR: δ = 135.9 (q, *J* = 1.2), 129.5, 128.7, 128.0 (q, *J* = 1.2), 124.7 (q, *J* = 282.2), 73.7 (q, *J* = 31.8), 0.1. − ^{19}F NMR: δ = −78.90 (d, *J* = 7.7). − MS: *m/z* = 248 [$M^{+\cdot}$], 179, 137, 109, 77, 73.

2,2,2-Trifluoro-1-(1-methyl-1*H*-pyrrol-2-yl)ethyl Trimethylsilyl Ether (2j): Petroleum ether. Oil (241 mg, 96%). − ^1H NMR: δ = 6.66 (dd, *J* = 2.6, *J* = 2, 1 H), 6.27 (dd, *J* = 3.7, *J* = 1.8, 1 H), 6.13 (dd, *J* = 2.7, *J* = 3.7, 1 H), 5.08 (q, *J* = 7.1, 1 H), 3.73 (s, 3 H), 0.16 (s, 9 H). − ^{13}C NMR: δ = 125.5, 125.2, 124.6 (q, *J* = 282.0), 111.5 (q, *J* = 1.2), 107.6, 68.8 (q, *J* = 33.9), 35.2 (q, *J* = 2.3), −0.1. − ^{19}F NMR: δ = −77.66 (d, *J* = 7.3). − MS: *m/z* = 251 [$M^{+\cdot}$], 182, 162, 140, 73. − $C_{10}H_{16}F_3NOSi$ (251.32 : C 47.79, H 6.42, N 5.57; found C 47.94, H 6.41, N 5.30.

2-Methyl-3-(trifluoromethyl)-3-[(trimethylsilyl)oxy]-1-isoindolinone (2k): Pure after extraction. Brown solid (230 mg, 76%). M.p. 80−83 °C. − ^1H NMR: δ = 7.85 (m, 1 H), 7.60−7.65 (m, 3 H), 3.08 (s, 3 H), −0.07 (s, 9 H). − ^{13}C NMR: δ = 167.4, 140.1, 133.4, 132.3, 131.3, 127.3 (q, *J* = 1.5), 123.7, 122.9 (q, *J* = 287.0), 88.5 (q, *J* = 39.0), 25.2, 0.8. − ^{19}F NMR: δ = −80.76. − MS: *m/z* = 234, 214, 164, 151, 73.

[1] U. Groß, S. Rüdiger, in *Organo-Fluorine Compounds* (Eds.: B. Baasner, H. Hagemann, J. C. Tatlow), Houben-Weyl: Methods

of Organic Chemistry, Thieme, Stuttgart, **1999**, Vol. E10a, 18−26.
[2] R. Filler, Y. Kobayashi, Y. L. Yagulpolskii, *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*, Elsevier, Amsterdam, **1993**.
[3] R. E. Banks, B. E. Smart, J. C. Tatlow, *Organofluorine Chemistry: Principles and Commercial Applications*, Plenum Press, New York, **1994**.
[4] M. Hudlicky, A. E. Pavlath, *Chemistry of Organic Fluorine Compounds II. A critical Review*, ACS Monograph 187, American Chemical Society, Washington DC, **1995**.
[5] M. A. McClinton, D. A. McClinton, *Tetrahedron* **1992**, *48*, 6555−6666.
[6] G. K. S. Prakash, A. K. Yudin, *Chem. Rev.* **1997**, *97*, 757−786.
[7] As for ref.[4] pp. 1092−1100.
[8] T. Billard, B. R. Langlois, G. Blond, *Tetrahedron Lett.* **2000**, *41*, 8777−8780.
[9] C. Reichardt, *Solvents and Solvents Effects in Organic Chemistry*, VCH, New York, **1999**, 20−21.

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