Trifluoroacetic Acid Derivatives as Nucleophilic Trifluoromethylating Reagents

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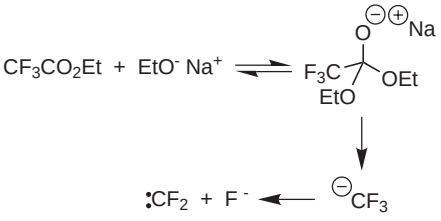
Abstract: Secondary trifluoroacetamides and alkyl trifluoroacetates can be used as nucleophilic trifluoromethylating reagents towards non-enolizable ketones by action of potassium *tert*-butoxide.

Key words: trifluoromethylation, trifluoroacetamide, fluorinated compounds, trifluoromethylcarbinols, tetrahedral intermediate

The unique properties of the trifluoromethyl group make it an especially valuable substituent for organic substrates over a wide range of targets for pharmaceutical and agrochemical chemistry.[1]

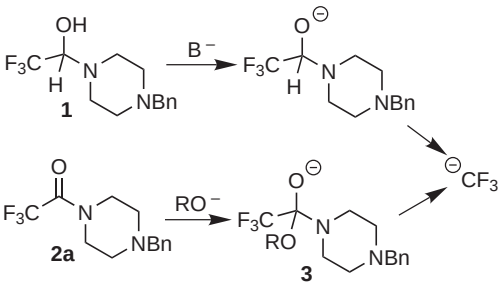
At present, many reliable methods are available to introduce a CF_3 moiety into organic substrates[2] but the anionic trifluoromethylation strategy has emerged in recent years as one of the most powerful.[3]

In our quest for new nucleophilic trifluoromethylating reagents, we have previously reported that hemiaminals of trifluoroacetaldehyde are efficient trifluoromethylating agents for non-enolizable carbonyl compounds,[4] disulfides and diselenides.[5] Nevertheless, as fluoral is usually produced by reduction of trifluoroacetic acid, it should be economically more judicious, on an industrial point of view, to design new reagents directly from CF_3CO_2H. The decarbethoxylation of perfluoroacid esters was described a long time ago.[6] In this paper, the author postulated the formation of a trifluoromethyl anion, which collapses immediately, upon treatment of ethyl trifluoroacetate with an alcoholic solution of sodium ethoxide (Scheme 1).



Scheme 1

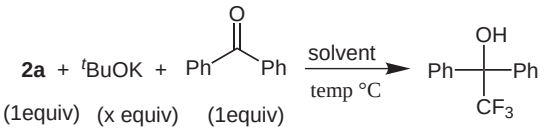
In view of this result, we decided to apply the same strategy to *N*-trifluoroacetyl, *N*-benzyl piperazine **2a** in order to generate a tetrahedral intermediate (**3**) similar to hemiaminal **1** (Scheme 2).



Scheme 2

On a practical point of view, we carried out this reaction with a commercially available 1 M solution of *t*-BuOK in THF to avoid protic solvents. The trifluoromethylating ability of **3** has been examined with benzophenone as model substrate (Table 1).

Table 1 Trifluoromethylation of Benzophenone with **2a**



4a
(after hydrolysis)

Entry	x	Solvent	t	Temp (°C)	**4a** (%)[a]
1	1	THF	7 d	r.t.	50
2	1	THF	24 h	60	20
3	1	THF/DMF (1/1 v/v)	24 h	r.t.	100
4	0.1	THF/DMF (1/1 v/v)	24 h	r.t.	0

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

It appears from these results that the solvent polarity seems to be crucial to achieve good yields with satisfactory rates (entries 1, 3). Thermal activation is harmful for the reaction (entry 2), certainly because of a too rapid decomposition of the tetrahedral intermediate. All these results are similar to those resulting from trifluoromethylation using hemiaminal **1**.[4c] It can also be noticed that the

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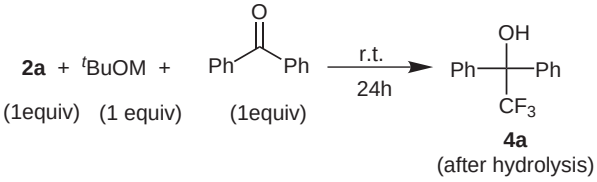
trifluoromethyl alcoholate arising from this reaction is not nucleophilic enough to add on **2a**, precluding a catalytic use of *t*-BuOK (entry 4).

Concerning the influence of the solvent polarity, we postulated, as in our previous study,[4c] that the crucial parameter governing the $^{-}CF_3$ liberation is the ion pair separation in the tetrahedral intermediate arising from the addition of *t*-$BuO^{-}M^{+}$ to **2a**. To confirm such a hypothesis the reaction was performed under various conditions (Table 2).

Table 2 Effect of Ion Pair Separation on Trifluoromethylation



Entry	*t*-BuOM	Conditions	**4a** (%)[a]
1	*t*-BuOK	DMF/THF (1/1 v/v)	100
2	*t*-BuOLi	DMF/THF (1/1 v/v)	0
3	*t*-BuOK	THF/18-C-6[b] (1 equiv)	70

[a] Crude yield determined by ^{19}F NMR with internal standard ($PhOCF_3$).
[b] 18-C-6: 18 crown 6.

Similar results were obtained in THF with 18-C-6, a specific potassium chelate, as in THF/DMF (entries 1, 3). It confirms the importance of the ion pair separation. This is in agreement with the lack of transfer observed with a tighter ionic pair such as O-Li (entry 2). Then the optimal conditions are the use of an equivolume mixture of DMF/THF.

To extend the scope of this process, trifluoromethylation of benzophenone was performed with other trifluoroacetamides **2** under the same conditions (Table 3).

Table 3 Trifluoromethylation of Benzophenone with other Trifluoroacetamides

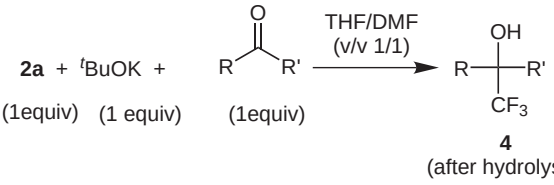
Entry	Trifluoroacetamide Issued from	**4a** (%)[a]	**2** Recovered (%)*
1	*N*-Benzylpiperazine	100	0
2	Morpholine	90	7
3	Piperidine	92	7
4	Dimethylamine	53	0
5	Dibutylamine	77	7
6	Benzylmethylamine	50	1
7	Diisopropylamine	60	30

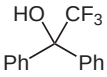
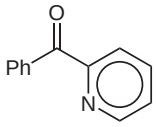
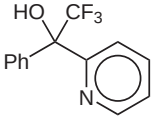
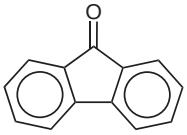
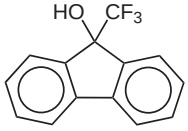
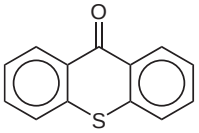
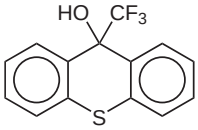
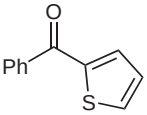
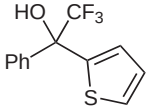
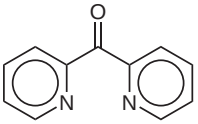
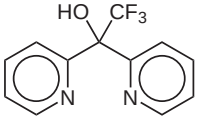
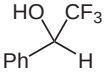
[a] Crude yield determined by ^{19}F NMR with internal standard ($PhOCF_3$).

Generally, all trifluoroacetamides gave rise to trifluoromethylation but cyclic amine derivatives provided better yields (entries 1–3). In the case of linear amines, it can be supposed that less hindrance in the tetrahedral intermediate did not favor the ejection of CF_3 (entries 4–6). Concerning hindered acyclic amides, their reactivity towards *t*-BuOK was probably too low (entry 7). Thus *N*-benzylpiperazine, morpholine and piperidine derivatives constituted a good compromise.

Since **2a** seemed to be a good reagent for nucleophilic trifluoromethylation of benzophenone, this technique has been extended to other carbonylated substrates (Table 4).[7]

Table 4 Reaction of **2a** with Various Electrophiles

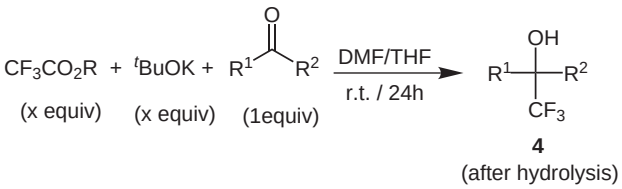


RC(O)R′	**4** (%)[a]
	 **4a**: 95 (100)
	 **4b**: 95 (100)
	 **4c**: 95 (100)
	 **4d**: 60 (60)
	 **4e**: 10 (13)
	 **4f**: 20 (26)
	 (0)

[a] Isolated yield. In parentheses: crude yield determined by 19F NMR with internal standard (PhOCF3).

To extend this technique, the same reaction was performed with trifluoroacetic esters instead of trifluoroacetamides (Table 5).

Table 5 Trifluoromethylation with Trifluoroacetates



Entry	R	x	$R^1C(O)R^2$	**4** (%)[a]
1	Me	1	Benzophenone	**4a**: (42)
2	Me	2	Benzophenone	**4a**: 70 (77)
3	Menthyl	2	Benzophenone	**4a**: (61)
6	Me	2	2-Benzoylpyridine	**4b**: 25 (27)
4	Me	2	Fluorenone	**4c**: 20 (22)
5	Me	2	Thioxanthen-9-one	**4d**: 20 (25)
7	Me	2	Benzaldehyde	(0)

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

It can be noticed that, provided that 2 equivalents of ester were used, trifluoromethylation also occurred (entries 1–3) with trifluoroacetates. Nevertheless, these trifluoroacetic acid derivatives are more restricted in their utility (entries 4–7).

To conclude, we have shown that trifluoroacetates and trifluoroacetamides can be used as nucleophilic trifluoromethylating reagents. In particular, trifluoroacetamides are very interesting candidates but their lack of reactivity towards aldehydes can constitute an important drawback. Similar processes with more reactive compounds towards *t*-BuOK will be described in the next paper.[8]

Acknowledgement

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(7) **Typical Procedure:** To a solution of **2a** (1 mmol) and the electrophile (1 mmol) in DMF (1 mL) was added a 1 M solution of *t*-BuOK in THF (1 mL). After 24 h, the crude mixture was hydrolyzed by HCl 1 M (1 mL) overnight and extracted with diethyl ether. The organic phase was dried on Na_2SO_4 and the the solvent removed in vacuo. The crude products were purified by chromatography over silica gel. **Spectral Data:** Compound **4b**: ^1H NMR (300 MHz, $CDCl_3$): δ = 8.61–8.63 (massif, 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 (br s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.3, 147.6, 138.7, 137.9, 129.0, 128.9, 127.4 (q, *J* = 2.1 Hz), 125.5 (q, *J* = 286.4 Hz), 124.4, 123.3 (q, *J* = 1.9 Hz), 78.1 (q, $^2J_{C\text{-}F}$ = 28.9 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –75.19. MS: *m/z* = 253 (M^+), 184, 176, 106, 78, 77, 69, 51. Compound **4f**: ^1H NMR (300 MHz, $CDCl_3$): δ = 8.61 (d, 2 H, *J* = 4.7 Hz), 8.13 (d, 2 H, *J* = 8.1 Hz), 7.75 (td, 2 H, *J* = 7.8 Hz, *J* = 7.7 Hz), 7.42 (s, 1 H), 7.30 (dd, *J* = 7.5 Hz, *J* = 4.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.4, 148.0, 137.5, 124.9 (q, *J* = 286.4 Hz), 124.2, 123.6 (q, *J* = 1.7 Hz), 77.5 (q, *J* = 28.3 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –76.47. MS: *m/z* = 254 (M^+), 237, 185, 176, 106, 78, 52.

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