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Tetrahedron Letters 44 (2003) 1055–1057

TETRAHEDRON LETTERS

Trifluoroacetophenone as nucleophilic trifluoromethylating reagent

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Received 26 November 2002; revised 28 November 2002; accepted 28 November 2002

Abstract—Trifluoroacetophenone can be used as nucleophilic trifluoromethylating reagent towards non-enolizable ketones by action of potassium *tert*-butoxide.

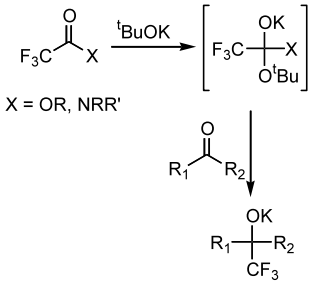
Because of the particular properties of fluorine, the introduction of such an element on organic substrates induces dramatic consequences on their physical, chemical and biological properties.[1] Among fluorinated compounds, trifluoromethylated ones present unique biological activities.[2] For this reason, a variety of methods have been developed for their preparation.[3] In recent years, the anionic trifluoromethylation strategy has emerged as one of the most powerful.[4]

In our quest for new nucleophilic trifluoromethylating reagents, we previously reported that hemiaminals of trifluoroacetaldehyde are efficient trifluoromethylating agents for non-enolizable carbonyl compounds.[5] More recently, we also demonstrated that trifluoroacetic derivatives (amides and esters) can also constitute powerful trifluoromethylating reagents towards non-enolizable compounds by action of potassium *tert*-butoxide (Scheme 1).[6]

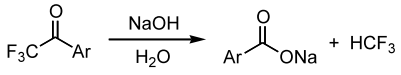
In relation with this concept, we now focus our interest on an older well-known reaction: the haloform reaction from trifluoromethylketones (Scheme 2).[7] Indeed, in this reaction, carboxylic acids are obtained by releasing a CF_3 anion but, to our knowledge, nobody tried to trap it with an electrophile.

In order to use this reaction to achieve nucleophilic trifluoromethylation, we decided to react potassium *tert*-butoxide (solution 1 M in THF), which gave satisfactory results with trifluoroacetamides,[6] with trifluoroacetophenone in the presence of benzophenone (Table 1).

We can notice, in the case of trifluoroacetamides, that the use of DMF seems to be essential to reach good yields. In contrast, the reaction time was shorter (20 min instead of 24 h). Nevertheless, 2 equiv. of trifluoroacetophenone and *tert*-butoxide were necessary to achieve quantitative yields. This could be explained by the high instability of the tetrahedral intermediate arising from the addition of ^{t}BuOK on **1** which then released the CF_3 anion too fast. Thus the latter partly collapsed before adding to benzophenone. This hypothesis is in accordance with the shortened reaction timed.



Scheme 1. Trifluoromethylation with trifluoroacetic acid derivatives.



Scheme 2. Haloform reaction with trifluoromethylketones.

Keywords: trifluoroacetophenone; nucleophilic trifluoromethylation; fluorinated compounds; trifluoromethylcarbinol.

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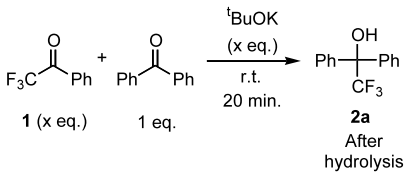
0040-4039/03/$ - see front matter
PII: S0040-4039(02)02718-1

Table 1. Trifluoromethylation of benzophenone with trifluoroacetophenone.

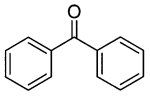
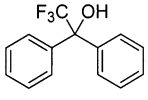
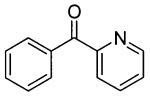
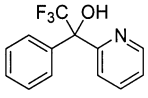
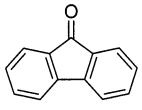
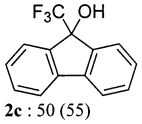
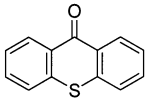
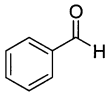
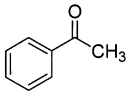


Entry	Solvent	*x* (equiv.)	**2a**[a] (%)
1	THF	1	25
2	THF/DMF (v/v: 1/1)	1	55
3	THF/DMF (v/v: 2/1)	2	100

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

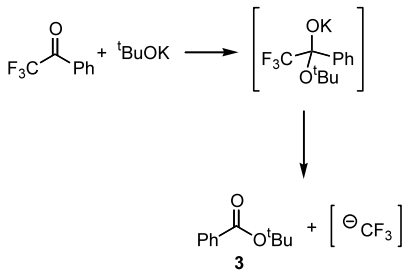
These optimal conditions were then applied to other carbonyl derivatives compounds (Table 2).†

Table 2. Trifluoromethylation with trifluoroacetophenone

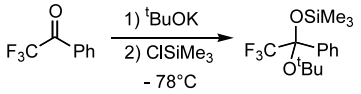
Entry	Carbonylated Compound	**2**[a] (%)
1		 **2a** : 98 (100)
2		 **2b** : 99 (100)
3		 **2c** : 50 (55)
4		 **2d** : 90 (100)
5		0
6		0

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

† *Typical procedure*: To a solution of **1** (2 mmol) and the electrophile (1 mmol) in DMF (1 mL) was added a 1 M solution of ^{t}BuOK in THF (2 mL). After 20 min, the crude mixture was hydrolyzed by 1 M HCl (1 mL) overnight and extracted with diethyl ether. The organic phase was dried on Na_2SO_4 and the solvent evaporated in vacuo. The crude products were purified by chromatography over silica gel.



Scheme 3. Postulated mechanism.



Scheme 4. Characterization of tetrahedral intermediate.

As in the case of trifluoroacetamides,[6] this reaction led to good results with non-enolizable ketones (entries 1–4). However, with enolizable ones and aldehydes, no trifluoromethylation was observed (entries 5 and 6). This was replaced by more favorable side reactions: aldolisation and Cannizaro, respectively.

From a mechanistic point of view, it can be reasonably postulated that a tetrahedral intermediate was formed and should consitute the real trifluoromethylating agent (Scheme 3).

This postulate was confirmed by the recovery of *tert*-butyl benzoate (**3**) at the end of the reaction. It has been also confirmed by the characterization, at low temperature, of the silylated derivative of the tetrahedral intermediate, obtained by quenching the reacting media with $ClSiMe_3$, at −78°C (Scheme 4).

In conclusion, we have shown that the fluoroform reaction is an efficient process for the nucleophilic trifluoromethylation of non-enolizable ketones.

Acknowledgements

We thank the CNRS and the French Ministry of Research for financial support.

References

1. Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3–11.
2. (a) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley & Sons: New York, 1991; (b) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I.; McCarthy, J. R.; Welch, J. T., Eds.; ACS Symposium Series 639, American Chemical Society: Washington, DC, 1996; (c) *Fluorine-Containing Amino Acids. Synthesis and Properties*; Kukhar, V. P.; Soloshonok, V. A., Eds.; John Wiley & Sons: Chichester, 1995; (d) Hiyama, T. *Organofluorine Compounds: Chemistry and Properties*;

Springer: Berlin, 2000; Chapter 5, pp. 137–182; (e) Becker, A. *Inventory of Industrial Fluoro-Biochemicals*; Eyrolles: Paris, 1996.

3. McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555–6666.
4. (a) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev*. **1997**, *97*, 757–786; (b) Singh, R. P.; Shreeve, J. M. *Tetrahedron* **2000**, *56*, 7613–7632; (c) Prakash, G. K. S.; Mandal, M. *J. Fluorine Chem*. **2001**, *112*, 123–131; (d) Folleas, B.; Mareck, I.; Normant, J. F.; Saint-Jalmes, L. *Tetrahedron Lett*. **1998**, *39*, 2973–2976; (e) Folleas, B.; Mareck, I.; Normant, J. F.; Saint-Jalmes, L. *Tetrahedron* **2000**, *56*, 275–283; (f) Large, S.; Roques, N.; Langlois, B. R. *J. Org. Chem*. **2000**, *65*, 8848–8856; (g) Motherwell, W. B.; Storey, L. J. *Synlett* **2002**, 646–648.
5. (a) Billard, T.; Bruns, S.; Langlois, B. R. *Org. Lett*. **2000**, *2*, 2101–2103; (d) 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.
6. Jablonski, L.; Joubert, J.; Billard, T.; Langlois, B. R. *Synlett* **2003**, in press.
7. (a) Simons, J. H.; Ramler, E. O. *J. Am. Chem. Soc*. **1943**, *65*, 389–390; (b) Guthrie, J. P.; Cossar, J. *Can. J. Chem*. **1990**, *68*, 1640–1642; (c) Delgado, A.; Clardy, J. *Tetrahedron Lett*. **1992**, *33*, 2789–2790.