Trifluoromethylation

Trifluoroacetamides from Amino Alcohols as Nucleophilic Trifluoromethylating Reagents**

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In memory of Odile Miani

Fluorinated compounds exhibit unique properties,[1] which are of huge interest in a wide range of applications.[2] Consequently, the number of new organofluorine products that appear each year is growing steadily.[3] Trifluoromethyl-substituted compounds constitute a particular class with specific properties, such as the high lipophilicity provided by this group. Thus, such molecules find pharmaceutical applications,[2] as illustrated by two drugs recently introduced for

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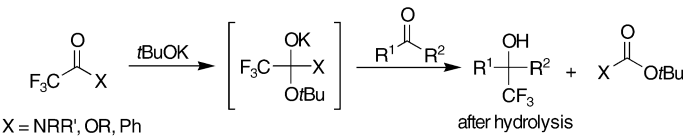
the treatment of human diseases, efavirenz[4] (anti-HIV) and celecoxib[5] (antiarthritic).

In the last two decades, many reliable methods have been reported for the introduction of a CF_3 group into organic compounds,[6] and in recent years, anionic trifluoromethylation has emerged as one of the most powerful strategies. However, these anionic methods suffer from the limited availability of efficient reagents that are able to overcome the high instability of the CF_3 anion, which is known to decompose rapidly and almost irreversibly into a fluoride anion and difluorocarbene.

The most popular reagent for these anionic methods is currently (trifluoromethyl)trimethylsilane (CF_3SiMe_3, Ruppert–Prakash reagent), which is both very powerful for synthetic applications and commercially available.[7] However, its preparation from CF_3Br, the industrial production of which is now restricted for ecological reasons,[8] constitutes a drawback for large-scale applications.

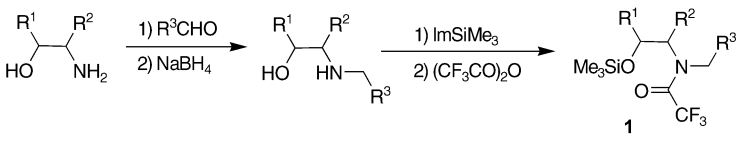
In our quest for new trifluoromethylating reagents, we have recently shown that some hemiaminals of trifluoroacetaldehyde are useful tools for the nucleophilic trifluoromethylation of non-enolizable carbonyl compounds.[9] More recently, we demonstrated that trifluoroacetamides,[10a] trifluoromethanesulfinamides,[10b] and α,α,α-trifluoroacetophenone[10c] also behave as efficient trifluoromethylating reagents under the action of potassium *tert*-butoxide (Scheme 1).



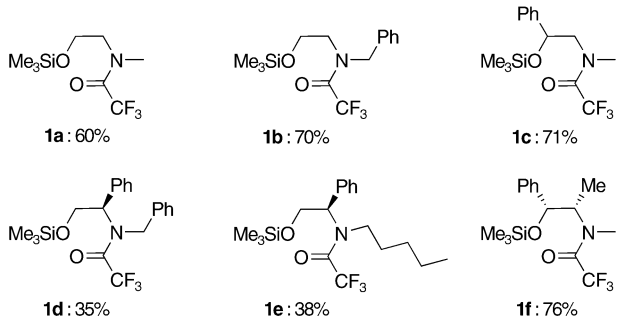
Scheme 1. Trifluoromethylation with trifluoroacetic acid derivatives.

Although trifluoroacetic acid derivatives are economically and ecologically friendly trifluoromethylating agents, the presence of a strong base in these reactions precludes the use of enolizable substrates. To circumvent this drawback, we envisaged a strategy in which slow delivery of the alcoholate would favor nucleophilic attack over deprotonation by this species. This led us to study the reactivity of trifluoroacetamides derived from *O*-silylated *vic*-amino alcohols. These compounds were easily prepared from commercially available amino alcohols (Scheme 2).

A variety of reagents were synthesized by this procedure, as shown in Scheme 3 (overall yields are given for the purified compounds). To access their potential as trifluoromethylating reagents, **1a–f** were desilylated with CsF in 1,2-dimethoxyethane (DME), according to the method used in our previous



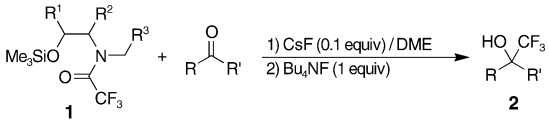
Scheme 2. Synthesis of *N*-trifluoroacetyl *O*-trimethylsilyl *vic*-amino alcohols. $ImSiMe_3$ = *N*-(trimethylsilyl)imidazole.



Scheme 3. *N*-trifluoroacetyl *O*-trimethylsilyl *vic*-amino alcohols.

studies.[9a–b] As models for different types of carbonyl electrophiles, we chose benzophenone (for non-enolizable substrates), benzaldehyde (for aldehyde substrates), and acetophenone (for enolizable substrates). The results are summarized in Table 1.

Table 1: Trifluoromethylation of benzophenone, benzaldehyde, and acetophenone with trifluoroacetamides **1**.

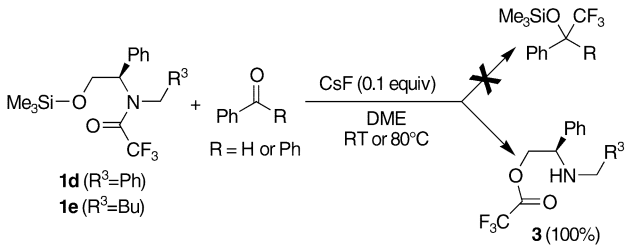


Entry	**1**	*T* [°C]	Yield [%] (*t* [h]) R = R′ = Ph (**2a**)	R = Ph, R′ = H (**2b**)	R = Ph, R′ = CH_3 (**2c**)
1	**a**	[a]	no transfer[b]		
2	**a**	50	59 (24)	no transfer[c]	21 (108)
3	**a**	80	60 (5)	43 (24)	41 (24)
4	**b**	50	50 (30)		
5	**b**	80	50 (24)	52 (24)	28 (24)
6	**c**	50	44 (24)		
7	**c**	80	54 (24)	56 (24)	26 (24)
8	**f**	50	71 (6)	85 (6)	
9	**f**	80	74 (2)		
10	**f**	[a]	76 (24)	89 (24)	58 (120)

[a] Room temperature. [b] 3 days. [c] 24 h.

Table 1 shows that the substitution at the nitrogen atom did not greatly influence the ability of these new reagents to transfer their CF_3 group (entries 1–5). In contrast, the influence of substituents R^1 and R^2 was more important. Indeed, when no substituent was present ($R^1 = R^2 = H$), or when only one substituent was present, and in the α position relative to the oxygen atom, trifluoromethylation occurred under heating at 80 °C (Table 1, entries 3, 5, and 7). However, when a substituent was present in the α position relative to the nitrogen atom (and $R^1 = H$), no CF_3 transfer was observed, and instead migration of the trifluoroacetyl group from the nitrogen atom to the oxygen atom occurred (Scheme 4). On the other hand, when both adjacent carbon centers were substituted, as in the case of **1f**, trifluoromethylation proceeded even at room temperature (Table 1, entries 8–10).

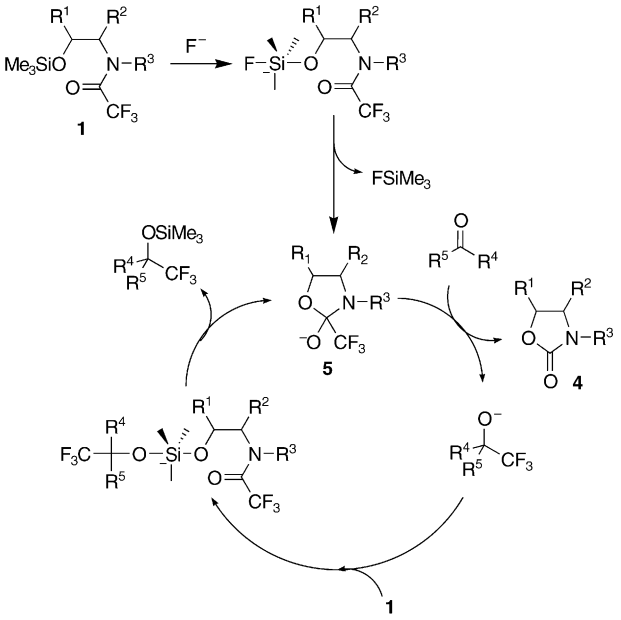
Thus, this new family of reagents allowed the trifluoromethylation of both non-enolizable and enolizable carbonyl



Scheme 4. Trifluoroacetyl migration with **1d** and **1e**.

compounds. Compound **1f**, derived from cheap and commercially available ephedrine, was the best candidate, as it promoted the formation of the desired products in good yields even at room temperature. Furthermore, **1f** is a stable white solid that can be stored for long periods of time, whereas **1a–c** have a shelf life of less than 48 h. The long reaction time of **1f** with acetophenone led us to use soluble tetrabutylammonium triphenyldifluorosilicate (TBAT)[11] in THF instead of CsF in DME as the desilylating agent. With this reagent a 60% yield of **2c** was observed after 6 h, in contrast to the 5 days required with CsF/DME (Table 1, entry 10).

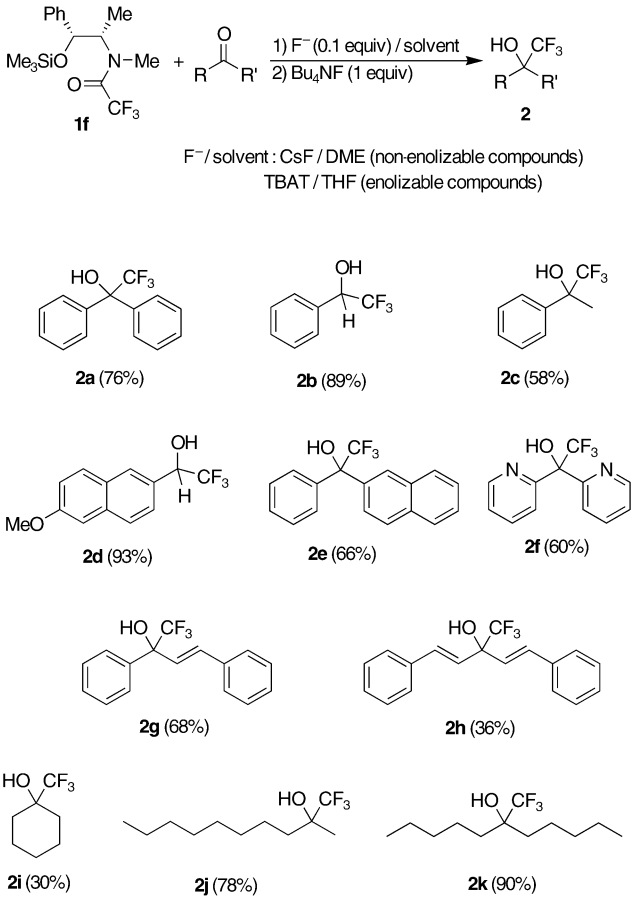
The mechanism shown in Scheme 5 could be proposed, by analogy with previous work.[7a,9a] This proposal was supported by the isolation and characterization of oxazolidinones **4** from



Scheme 5. Mechanism of the trifluoromethylation with **1**.

the reaction. Nevertheless, studies to better understand the role of the various substituents are in progress in our laboratory.

From these preliminary results with simple substrates, compound **1f** appeared to be the most powerful trifluoromethylating reagent of those studied. Consequently, its reactivity toward diverse carbonyl compounds was examined (Scheme 6).



Scheme 6. Reactivity of **1f**.

Thus, a wide range of non-enolizable and enolizable carbonyl compounds (aldehydes, ketones, α,β-unsaturated ketones) were trifluoromethylated with **1f** in satisfactory yields. Although **1f** is a chiral reagent, it did not induce any chirality in the trifluoromethylation of prochiral carbonyl substrates. No enantiomeric excess was observed for any of the products.

In conclusion, we have demonstrated that trifluoroacetamides derived from *O*-silylated *vic*-amino alcohols constitute a new class of nucleophilic trifluoromethylating reagents. The trifluoroacetamide derived from ephedrine is especially promising, as it trifluoromethylates both enolizable and non-enolizable carbonyl compounds in satisfying yields under mild conditions. To our knowledge, this is the first reagent that is likely to provide competition for the Ruppert–Prakash reagent. Our new challenge is to design similar reagents for enantioselective trifluoromethylation. These studies are in progress in our laboratory.

Experimental Section

Typical procedure: **1f**: A flame-dried three-necked vessel was successively charged with ephedrine (6.6 g, 40 mmol) and dichloromethane (40 mL) under nitrogen. The resulting mixture was cooled to 0 °C, then *N*-(trimethylsilyl)imidazole (6 mL, 41 mmol) was added. The reaction mixture was stirred at 0 °C for 40 min, then warmed to

room temperature and stirred for a further 2 h. After this period, diisopropylethylamine (7.2 mL, 41.4 mmol) was added and the mixture was cooled again to 0 °C. A solution of trifluoroacetic anhydride (5.6 mL, 40 mmol) in CH_2Cl_2 (16 mL) was then added dropwise over 1.5 h, after which the mixture was stirred at 0 °C for 10 min, then at room temperature for 4 h. The reaction mixture was then washed with 6% aqueous $NaHCO_3$ and the organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by chromatography over silica gel.

Typical trifluoromethylation procedure: A solution of tetrabutylammonium triphenyldifluorosilicate (TBAT; 54 mg, 0.1 equiv) in THF (0.5 mL) was added dropwise over 15 min to a stirred solution of **1f** (1 mmol) and the electrophile (1 mmol) in THF (1 mL). After 6 h, the crude product was desilylated by treatment with TBAF (1M in THF, 1 mL) for 1 h, then the mixture was extracted with pentane and brine. The organic phase was dried over Na_2SO_4 and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography over silica gel.

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[1] a) "Organo-Fluorine Compounds": U. Groß, S. Rüdiger, *Methods Org. Chem. (Houben-Weyl) 4th ed. 1952–*, Vol. E10a, pp. 18–26; b) B. E. Smart, *J. Fluorine Chem.* **2001**, *109*, 3–11.

[2] a) R. Filler, Y. Kobayashi, L. M. Yagulpolskii, *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*, Elsevier, Amsterdam, **1993**; b) R. E. Banks, B. E. Smart, J. C. Tatlow, *Organofluorine Chemistry: Principles and Commercial Applications*, Plenum, New York, **1994**; c) J. T. Welch, S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry*, Wiley, New York, **1991**; d) *Fluorine-containing Amino Acids. Synthesis and Properties* (Eds.: V. P. Kukhar, V. A. Soloshonok), Wiley, Chichester, **1995**; e) T. Hiyama, *Organofluorine Compounds: Chemistry and Properties*, Springer, Berlin, **2000**, chap. 5, pp. 137–182; f) A. Becker, *Inventory of Industrial Fluoro-Biochemicals*, Eyrolles, Paris, **1996**.

[3] H. Schofield, *J. Fluorine Chem.* **1999**, *100*, 7–11.

[4] a) J. Ren, J. Milton, K. L. Weaver, S. A. Short, D. I. Stuart, D. K. Stammers, *Structure* **2000**, *8*, 1089–1094; b) O. S. Pedersen, E. B. Pedersen, *Synthesis* **2000**, 479–495.

[5] a) L. M. Jackson, C. J. Hawkey, *Drugs* **2000**, *59*, 1207–1216; b) M. L. P. Price, W. J. Jorgensen, *J. Am. Chem. Soc.* **2000**, *122*, 9455–9466.

[6] M. A. McClinton, D. A. McClinton, *Tetrahedron* **1992**, *48*, 6555–6666.

[7] a) G. K. S. Prakash, A. K. Yudin, *Chem. Rev.* **1997**, *97*, 757–786; b) R. P. Singh, J. M. Shreeve, *Tetrahedron* **2000**, *56*, 7613–7632; c) G. K. S. Prakash, M. Mandal, *J. Fluorine Chem.* **2001**, *112*, 123–131; d) T. Billard, B. R. Langlois, *Tetrahedron Lett.* **1996**, *37*, 6865–6868; e) T. Billard, S. Large, B. R. Langlois, *Tetrahedron Lett.* **1997**, *38*, 65–68.

[8] a) M. Hudlicky, A. E. Pavlath, *Chemistry of Organic Fluorine Compounds II. A Critical Review*, ACS Monograph 187, American Chemical Society, Washington, DC, **1995**, pp. 1092–1100; b) B. D. Key, R. D. Howell, C. S. Criddle, *Environ. Sci. Technol.* **1997**, *31*, 2445–2454.

[9] a) T. Billard, S. Bruns, B. R. Langlois, *Org. Lett.* **2000**, *2*, 2101–2103; b) T. Billard, B. R. Langlois, G. Blond, *Tetrahedron Lett.* **2000**, *41*, 8777–8780; c) T. Billard, B. R. Langlois, G. Blond, *Eur. J. Org. Chem.* **2001**, 1467–1471; d) B. R. Langlois, T. Billard, *Synthesis* **2003**, 185–194.

[10] a) L. Jablonski, J. Joubert, T. Billard, B. R. Langlois, *Synlett* **2003**, *2*, 230–232; b) D. Inschauspe, J.-B. Sortais, T. Billard, B. R. Langlois, *Synlett* **2003**, *2*, 233–235; c) L. Jablonski, T. Billard, B. R. Langlois, *Tetrahedron Lett.* **2003**, *44*, 1055–1057.

[11] C. J. Handy, Y.-F. Lam, P. DeShong, *J. Org. Chem.* **2000**, *65*, 3542–3543.

