A novel and convenient synthesis of (Z)-3,3,3-trifluoropropenyl alkyl ethers and CF_3-substituted propyl acetals as versatile CF_3-containing building blocks

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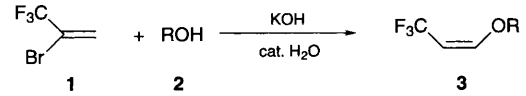
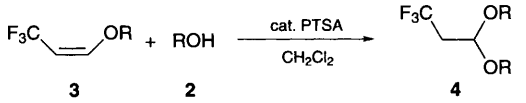
A novel and convenient preparation of (Z)-3,3,3-trifluoropropyl alkyl ethers and their further transformation into CF_3-substituted propyl acetals is described.

Methods for the synthesis of fluorine-containing compounds have received attention in recent years, as such compounds often exhibit biological activity.[1] Generally, replacement of hydrogen by fluorine increases lipid solubility, thus enhancing the rate of absorption and transport of active compounds *in vivo*.[2] In particular, the CF_3 group is particularly lipophilic, and the selective introduction of the CF_3 moiety into organic compounds has become one of the major targets in orano-fluorine chemistry.[3] A building block approach, which possessing high selectivity, mild reaction conditions and good yields, would be of particular significance. Many CF_3-containing building blocks[4] for introducing the CF_3 group into organic compounds have been reported. On the other hand, enol ethers are valuable intermediates in organic synthesis by virtue of their rich chemistry,[5] and CF_3-containing enol ethers should be potentially versatile CF_3-containing building blocks. Although (Z)-3,3,3-trifluoropropenyl methyl and ethyl ethers were prepared 40 years ago,[6] their preparation using 3,3,3-trifluoropropyne as a starting material has hampered its synthetic application. A more convenient synthetic method is highly desirable. Herein, we describe a novel and convenient synthesis of (Z)-3,3,3-trifluoropropenyl alkyl ethers in excellent yields (Scheme 1) and their transformation into CF_3-substituted acetals (Scheme 2).



1 2 3

Scheme 1



3 2 4

Scheme 2

A typical procedure for the preparation of (Z)-3,3,3-trifluoropropenyl ethers is as follows. Potassium hydroxide (17.0 g, 250 mmol) was dissolved in water (4 cm^3) and alcohol **2** (R = Me, Et, Pr, Pr^i, allyl) (40 cm^3), then 2-bromo-3,3,3-trifluoropropene **1** (17.0 g, 100 mmol) was added dropwise with stirring, using dry ice–acetone as the coolant for the condenser. The reaction was exothermic and completed in 1–1.5 h. Excess alcohol was washed off with water. The crude product was dried over Na_2SO_4 and distilled, to give only the *cis*-isomer (**3a–e**)‡ in yields of 86–96% (Table 1). However, when R = Bu and Bu^i, the reaction must be carried out in the presence of 18-crown-6 at 60 °C for 3–3 h. ^{19}F NMR revealed that the enol ether products were formed quantitatively. Because the excess alcohol could not be removed by washing with water, the enol ethers were transformed into acetals during distillation.

CF_3-containing enol ethers are highly reactive towards alcohols. Several CF_3-substituted acetals, another kind of CF_3-containing building block,[7] were readily obtained in high yields through treatment of the enol ethers with alcohol, catalysed by

Table 1 Preparation of (Z)-3,3,3-trifluoropropenyl alkyl ethers

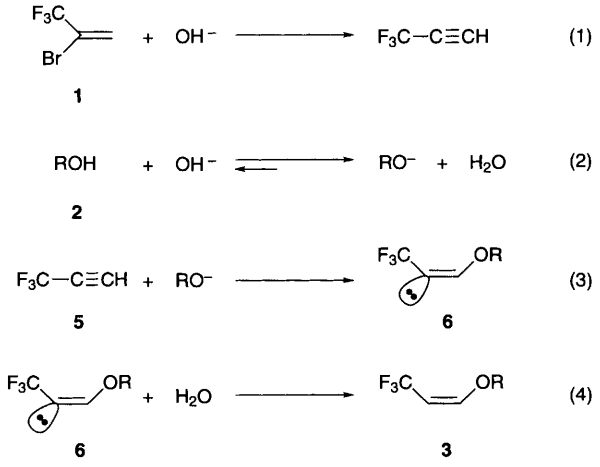
ROH **2**	Time/h	Product **3**[a]	Yield (%)[c]
MeOH **2a**	1	**3a**	96
EtOH **2b**	1	**3b**	95
PrOH **2c**	1	**3c**	93
Pr^{i}OH **2d**	1.5	**3d**	92
H_2C=$CHCH_2OH$	1.5	**3e**	86
BuOH **2f**	2.5	**3f**[b]	[d]
Bu^{i}OH **2g**	3	**3g**[b]	[d]

[a] **3a–e** were isolated and fully characterized by IR, ^1H and ^{19}F-NMR spectroscopy, MS, microanalysis or HRMS. [b] Determined by ^{19}F NMR spectroscopy and further transformed into the acetal during distillation. [c] Isolated yield. [d] 100% conversion.

Table 2 Preparation of 3,3,3-trifluoropropyl acetals[a]

Enol ether **3** R	Product **4**[b]	Yield (%)[c]
Me **3a**	**a**	96
Et **3b**	**b**	97
Bu **3f**	**f**	90
Bu^i **3g**	**g**	92

[a] Reaction was carried out by mixing the enol ether **3** (30 mmol) with alcohol **2** (60 mmol) and PTSA (3 mmol) in CH_2Cl_2. This mixture was stirred at 40 °C for 2 h. [b] The products were characterized by IR, ^1H and ^{19}F NMR spectroscopy, MS, microanalysis or HRMS. [c] Isolated yield.



Scheme 3

toluene-*p*-sulfonic acid, (PTSA) in CH_2Cl_2 at 40 °C (Scheme 2, Table 2).

Compared with the reported methods, the present procedure possesses two advantages. Firstly, 2-bromo-3,3,3-trifluoropropene may be directly used as starting material instead of 3,3,3-trifluoropropyne, which is usually prepared from 2-bromo-3,3,3-trifluoropropene in three steps.[8] Secondly, the reaction can be carried out more conveniently because 2-bromo-3,3,3-trifluoropropene is a liquid (bp 34 °C) while 3,3,3-trifluoropropyne is a gas (bp −46 °C).

Based on the fact that alkoxides react with alkynes to give the corresponding enol ethers,[9] the following mechanism is proposed (Scheme 3).

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Footnotes

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‡ *Selected data* for **3a**: δ_H ($CDCl_3$) 3.8 (3 H, s), 4.58–4.76 (1 H, m) and 6.3 (1 H, d, *J* 7.0 Hz); δ_F ($CDCl_3$, CF_3CO_2H) −20 (s, CF_3). For **3b**: δ_H 1.32 (3 H, t, *J* 7.0 Hz), 4.0 (2 H, q, *J* 7.0 Hz), 4.56–4.74 (1 H, m) and 6.32 (1 H, d, *J* 7.0 Hz); δ_F −20 (s, CF_3). For **3c**: δ_H 0.9 (3 H, t, *J* 7.0 Hz), 1.25–2.0 (2 H, m), 3.8 (2 H, t, *J* 7.0 Hz), 4.15–4.78 (1 H, m) and 6.2 (1 H, d, *J* 7.0 Hz); δ_F −20 (s, CF_3). For **3d**: δ_H 1.25 (6 H, d, *J* 7.0 Hz), 3.7–4.2 (1 H, m), 4.3–4.7 (1 H, m), 6.3 (1 H, d, *J* 7.0 Hz); δ_F −20 (s, CF_3). For **3e**: δ_H 4.41 (2 H, d, *J* 5.0 Hz), 4.58–4.75 (1 H, m), 5.24–5.42 (2 H, m), 5.8–6.0 (1H, m) and 6.35 (1 H, d, *J* 7.5 Hz); δ_F −20 (s, CF_3).

References

1 J. T. Welch, *Tetrahedron*, 1987, **43**, 3123; R. Filler and Y. Kobayashi, *Biomedicinal Aspect of Fluorine Chemistry*, Kodansha, Tokyo, 1983.

2 J. F. Liebman, A. Greenberg and W. R. Dolbier, Jr., *Fluorine-Containing Molecules, Structure, Reactivity, Synthesis and Application*, VCH, New York, 1988.

3 R. W. Lang, *Helv. Chim. Acta*, 1986, **69**, 881; M. Fujita, T. Hiyama and K. Kondo, *Tetrahedron Lett.*, 1986, **27**, 2139; M. Fujita and T. Hiyama, *Tetrahedron Lett.*, 1986, **27**, 3655; M. A. McClinton and D. A. McClinton, *Tetrahedron*, 1992, **48**, 6555.

4 M. L. Boys, E. W. Collington, H. Finch, S. Swanson and J. F. Whitehead, *Tetrahedron Lett.*, 1988, **29**, 3365; G. Shi and Y. Xu, *J. Chem. Soc., Chem. Commun.*, 1987, 607; R. Krishnamurti, D. R. Bellew and G. K. S. Prakash, *J. Org. Chem.*, 1991, **56**, 984; B. Jiang and Y. Xu, *J. Org. Chem.*, 1991, **56**, 7336; B. Jiang and Y. Xu, *Tetrahedron Lett.*, 1992, **33**, 511; I. Ojima, *Chem. Rev.*, 1988, **88**, 1011; C. Hu, F. Hong and Y. Xu, *J. Fluorine Chem.*, 1993, **63**, 1; T. Taguchi, A. Hosode, G. Tomizawa, A. Kawara, T. Masuo, Y. Suda, M. Nakajima and Y. Kobayashi, *Chem. Pharm. Bull.*, 1987, **35**, 909; D. J. Burton and Z. Yang, *Tetrahedron*, 1992, **48**, 189; C. Hu, F. Hong and Y. Xu, *J. Fluorine Chem.*, 1993, **64**, 1; F. Hong, X. Tang and C. Hu, *J. Chem. Soc., Chem. Commun.*, 1994, 289; K. Mizutani, T. Yamazaki and T. Kitazume, *J. Chem. Soc., Chem. Commun.*, 1995, 51.

5 P. Fisher, in *The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and Their Sulphur Analogues*, Supplement E, pt 2, Wiley, 1980, pp. 761–782; C. M. Anderson and A. Hallberg, *J. Org. Chem.*, 1989, **54**, 1502; H. Henniges, H. C. Militzer and A. Meijere, *Synlett.*, 1992, 735; Y. Bessiere, Y. Bessard, T. Kotani and M. Schlosser, *Tetrahedron*, 1991, **47** 4355; I. P. Smoliakova, R. Caple and J. W. Brenny, *Synlett*, 1995, 275.

6 A. L. Henne and M. Nager, *J. Am. Chem. Soc.*, 1952, **74**, 650; R. N. Haszeldine, *J. Chem. Soc.*, 1952, 3490; E. K. Raunio and T. G. Frey, *J. Org. Chem.*, 1972, **36**, 345.

7 M. E. Gihani and H. Heaney, *Synlett*, 1993, 583; T. Mukaiyama and M. Hayashi, *Chem. Lett.*, 1974, **15**; A. Ghribi, A. Alexakis and J. F. Normant, *Tetrahedron Lett.*, 1984, **25**, 3075.

8 A. L. Henne and M. Nager, *J. Am. Chem. Soc.*, 1951, **73**, 1042.

9 V. I. Laba, A. A. Kron and E. N. Prilezhaeva, *Izv. Akad. Nauk SSSR, Ser, Khim.*, 1976, 1546.

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