Available online at www.sciencedirect.com

Tetrahedron Letters 45 (2004) 7775–7777

Tetrahedron Letters

Stereospecific synthesis of trifluoromethyl-substituted polyfunctionalized cyclopropanes

Yi Wang, Xiaoming Zhao, Youhua Li and Long Lu*

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, PR China

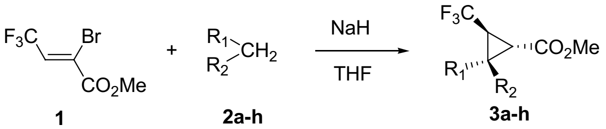
Received 28 May 2004; revised 19 July 2004; accepted 6 August 2004

Abstract—Treatment of methyl (*Z*)-2-bromo-4,4,4-trifluoro-2-butenoate **1** with active methylene compounds **2** in the presence of NaH as base affords a stereospecific synthetic route to trifluoromethyl substituted cyclopropanes in good yields.

The cyclopropyl group is a vital structural unit in many synthetic and naturally occurring compounds, exhibiting a wide spectrum of biologic properties, ranging from enzyme inhibition to herbicidal, antibiotic, antitumor, and antiviral activities.[1,2] In particular, cyclopropanes containing trifluoromethyl (–CF_3) group are attractive to organic chemists because the introduction of fluorine atoms may bring in different physiochemical properties and bioactivities of organic compounds.[3] Though the synthetic methods of cyclopropanes have long been well documented,[4] so far, a few approaches toward the stereoselective synthesis of CF_3-substituted cyclopropyl derivatives have been reported.[5] However, these methods have some drawbacks, such as difficulty of obtaining the starting materials, low yields of the products, and low stereoselectivities. Indeed, the development of an efficient and practical method for the synthesis of CF_3-containing cyclopropanes in a stereoselective manner is still highly desirable. Herein, we report a stereoselective synthesis of CF_3-containing cyclopropanes under mild reaction conditions in good yields.

A novel building block with a CF_3 group, methyl (*Z*)-2-bromo-4,4,4-trifluoro-2-butenoate **1**, was synthesized in our group.[6] The sodium salt of $PhSO_2CH_2CN$ (using NaH as base) was treated with **1** in THF at −30 °C for 30 min, and then at room temperature for 2 h to afford the cyclopropyl derivative (**3a**) in 83% yield. The behavior of a series of active methylene compounds was examined and all of them reacted with **1** to afford the corresponding CF_3-containing cyclopropanes as the sole product in good to excellent yields under these reaction conditions (Scheme 1).[7] The results were summarized in Table 1.

The stereochemistry of compounds **3a**–**h** was established by the ^{19}F and ^{1}H NMR spectra. The ^{19}F NMR spectra



Scheme 1.

Table 1. Reactions of methyl (*Z*)-2-bromo-4,4,4-trifluoro-2-butenoate **1** with active methylenes **2** ($R_1CH_2R_2$)

Entry	$R_1CH_2R_2$	Product	Yield (%)[a]
1	$R_1 = PhSO_2$, $R_2 = CN$	**3a**	83
2	$R_1 = R_2 = COMe$	**3b**	80
3	$R_1 = R_2 = CO_2Et$	**3c**	85
4	$R_1 = R_2 = CO_2Me$	**3d**	87
5	$R_1 = CO_2Et$, $R_2 = CN$,	**3e**	75
6	$R_1 = R_2 = CN$	**3f**	68
7	$R_1 = Ph$, $R_2 = COMe$	**3g**	64
8	$R_1 = Ph$, $R_2 = CO_2Et$	**3h**	78

[a] Yields are based on methyl (*Z*)-2-bromo-4,4,4-trifluoro-2-butenoate **1**.

Keywords: Active methylene compounds; Trifluoromethyl; Cyclopropane.

* Corresponding author. Tel.: +86 21 64163300; fax: +86 21 64165203; e-mail: lulong@mail.sioc.ac.cn

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.08.064

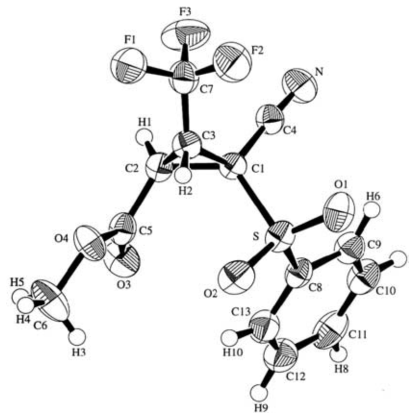


Figure 1. The ORTEP view of **3a**.

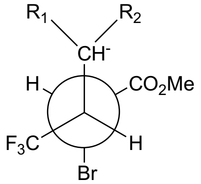
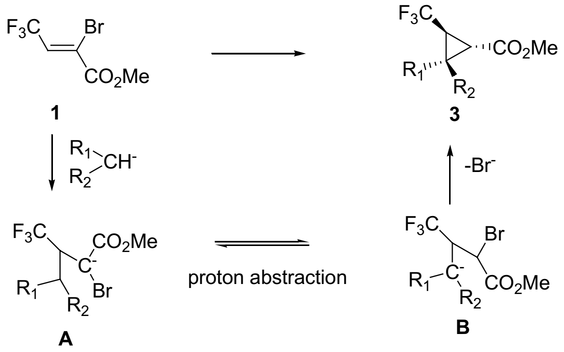


Figure 2. Newman projection formula of **B**.

of **3a** shows a peak at −13.1 ppm (d, $J = 5.6$ Hz, CF_3COOH as internal standard), indicating one sole trifluoromethylated compound was obtained. In addition, the ^1H NMR spectra of compound **3a** shows a new set of signals: doublets at 3.14 ppm ($J = 8.2$ Hz, 1H) were assigned to the cyclopropyl proton in α-position to CO_2Me group and the multiplets at 3.41 (1H) ppm were assigned to the other cyclopropyl proton. For **3b–h**, the ^{19}F and ^1H NMR spectra of compounds **3b–h** manifest themselves in a similar manner. In all of compounds **3a–h**, the coupling constant of the two vicinal cyclopropyl protons is in the range of 7.1–8.4 Hz, which is a distinctive clue for deducing a *trans* relationship between the vicinal hydrogen atoms.[8] Moreover, the analysis of NOESY for compound **3b** shows there is no NOE effect for the two vicinal protons. Based on these results, we deduce that the vicinal protons on the **3a–h** are *trans*.

Furthermore, the stereochemistry of compound **3a** was confirmed by a single crystal X-ray crystallographic study (Fig. 1).[9] It is unambiguous to observe the *trans* relationship between CF_3 and both CO_2Me and $PhSO_2$.

Using building block **1**, a series of stereospecific products **3a–h** were obtained. We assumed that the Michael addition reaction of carbanion to **1** was involved to yield **A**, which could institute a proton transfer from C_1 to C_3 to form **B**. From the Newman projection formula of **B**, a conformational analysis of **B** reveals that in an *anti* conformation, CF_3 and CO_2Me will be *trans*, and the large groups, R_2 and R_1, will be far apart from CF_3 (Fig. 2). Thus, the cyclopropanation occurred stereospecificaly via an intramolecular anionic attack to release a Br^- (Scheme 2).



Scheme 2. Proposed reaction pathway.

In summary, highly functionalized cyclopropanes containing the trifluoromethyl group were stereospecificaly synthesized under mild conditions in good yield. These versatile cyclopropane building blocks may have potential applications in the synthesis of trifluoromethylated natural products.

Acknowledgements

We thank the National Natural Science Foundation of China (Grant Number 29825104 and 20121202) and the Chinese Academy of Sciences for financial support.

References and notes

1. (a) Boger, D. L.; Hughes, T. V.; Hedrick, M. P. *J. Org. Chem.* **2001**, *66*, 2207–2216; (b) Baba, Y.; Saha, G.; Nakao, S.; Iwata, C.; Tanaka, T.; Ibuka, T.; Ohishi, H.; Takemoto, Y. *J. Org. Chem.* **2001**, *66*, 81–88; (c) Gerwick, W. H.; Proteau, P. J.; Nagle, D. G.; Hamel, E.; Blokhin, A.; Slate, D. L. *J. Org. Chem.* **1994**, *59*, 1243–1245; (d) Graham, D. W.; Ashton, W. T.; Barash, L.; Brown, J. E.; Brown, R. D.; Canning, L. F.; Chen, A.; Springer, J. P.; Rogers, E. F. *J. Med. Chem.* **1987**, *30*, 1074–1090; (e) Kojima, S.; Hiroike, K.; Ohkata, K. *Tetrahedron Lett.* **2004**, *45*, 3565–3568; (f) Yoshida, S.; Rosen, T. C.; Meyer, O. G. J.; Sloan, M. J.; Ye, S.; Haufe, G.; Kirk, K. L. *Bioorg. Med. Chem.* **2004**, *12*, 2645–2652.
2. For reviews, see: (a) Reissig, H. U. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: New York, NY, 1987; pp 375–443; (b) Faust, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2251–2253; (c) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589–8627; (d) Wessjohann, L. A.; Brandt, W.; Thiemann, T. *Chem. Rev.* **2003**, *103*, 1625–1647.
3. (a) *Fluorine in Bioorganic Chemistry*; Welch, J. T., Eswarakrishnan, S., Eds.; John Wiley & Sons: New York, NY, 1991; (b) *Organofluorine Compounds in Medicinal and Biomedical Applications*; Filler, R., Kobayashi, Y., Yagupolskii, L. M., Eds.; Elsevier: Amsterdam, 1993; (c) Kirk, K. L.; Filler, R. In *Biomedical Frontier of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; American Chemical Society: Washington DC, 1996, pp 1–24; (d) Banks, R. E. *J. Fluorine Chem.* **1998**, *87*, 1–17; (e) *Organofluorine Compounds: Chemistry and Application*; Hiyama, T., Ed.; Springer: New York, 2000.
4. (a) Tsuji, T.; Nishida, S. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: New York, 1987, pp 307–373; (b) Salaun, J. *Chem. Rev.* **1989**, *89*, 1247–1270; (c) Salaun, J. *Top. Curr. Chem.* **2000**, *207*, 1–227;

(d) Ohkita, M.; Nishida, S.; Tsuji, T. *Chemistry of Cyclopropyl Group* **1995**, *2*, 261–318.

5. (a) Fuchikami, T.; Shibata, Y.; Suzuki, Y. *Tetrahedron Lett.* **1986**, *27*, 3173–3176; (b) Shinohara, N.; Haga, J.; Yamazaki, T.; Nakamura, S. *J. Org. Chem.* **1995**, *60*, 4363–4374; (c) Moss, R. A.; Guo, W. J.; Denney, D. Z.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1981**, *103*, 6164–6169; (d) Katagiri, T.; Irie, M.; Uneyema, K. *J. Org. Lett.* **2000**, *2*, 2423–2425; (e) Katagiri, S.; Yamaji, S.; Handa, M.; Irie, M.; Uneyama, K. *Chem. Commun.* **2001**, 2054–2055; (f) Jiang, B.; Zhang, F. J.; Xiong, W. N. *Chem. Commun.* **2003**, 536–537.
6. Lu, L.; Wang, Y. unpublished results.
7. Typical experimental procedure: To a stirred solution of **2a** (181 mg, 1 mmol) in THF (2 mL) NaH (40 mg, 60% in mineral oil, 1 mmol) was added at room temperature under argon. The resulting mixture was stirred for 10 min at the same temperature. Then the mixture was cooled to −30 °C, methyl (*Z*)-2-bromo-4,4,4-trifluoro-2-butenoate was added, and the mixture was stirred for 30 min. Then the mixture was allowed to warm to room temperature and stirred for further 2 h, quenched with aqueous saturated NH_4Cl, and finally extracted with ether (30 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by flash column chromatography on silica gel (ethyl acetate/hexane = 1:10) to afford **3a** (276 mg) in 83% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, $J = 7.6$ Hz, 2H), 7.83 (t, $J = 7.4$ Hz, 1H), 7.69 (t, $J = 7.7$ Hz, 2H), 3.89 (s, 3H), 3.41–3.44 (m, 1H), 3.14 (d, $J = 8.2$ Hz, 1H); ^{19}F NMR ($CDCl_3$, ppm): δ −13.1; elemental analysis calculated for $C_{13}H_{10}F_3NO_4S$: C, 46.85; H, 3.02; F, 17.10; found: C, 47.01; H, 3.09; F, 16.97.
8. Pretsch, E.; Bűhlmann, P.; Affolter, C. *Structure Determination of Organic Compounds Tables of Spectral Data*; Zurich, Switzerland, 2000.
9. Crystallographic data (CCDC 242613) can be obtained free of charge via from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; email: deposit@ccdc.cam.ac.uk. Data for **3a**: $C_{13}H_{10}NSO_4F_3$, $M = 333.28$, monoclinic, space group $P2_1/n$, $a = 3.173(2)$, $b = 7.3773(9)$, $c = 15.252(3)$ Å, $\beta = 107.59(1)°$, $V = 1412.9(3)$ Å^3, $Z = 4$, μ (Mo-Kα) = 2.81 cm^{-1}, 3149 unique reflection measured ($R_{\text{int}} = 0.035$), 2027 reflections with $I > 1.50\sigma I$), $R = 0.050$, $R_W = 0.053$.