Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters 47 (2006) 4737–4739
Tetrahedron Letters

Highly efficient synthesis of 4-trifluoromethylfuran derivatives via a sequential deprotection-annulation reaction

Jiming Zhang, Xiaoming Zhao, Youhua Li and Long Lu*

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

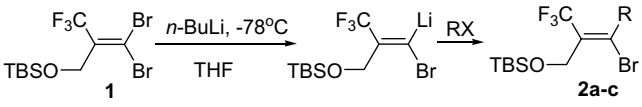
Received 15 March 2006; revised 20 April 2006; accepted 21 April 2006
Available online 19 May 2006

Abstract—(*E*)-O-protected-2-trifluoromethyl-1-bromo-1-substituted allylic alcohol reacted with terminal alkynes under Sonogashira reaction condition to give the corresponding (*E*)-2-en-4-ynoic alcohol derivatives, which was further converted to the corresponding 4-trifluoromethylfuran derivatives via a sequential deprotection-annulation reaction in moderate to excellent yields.

Polysubstituted furans play an important role in organic chemistry because of their presence as a structural unit in many biologically active and naturally occurring compounds.[1] There has been considerable interest in organofluorine compounds as pharmaceutical and agrochemical agents as well.[2] The introduction of fluorine atoms may alter the physiochemical and biological properties of organic compounds.[3,4] Although many fluorinated furans have been reported,[5,6] it is still desirable to develop an efficient method for the synthesis of trifluoromethylated furans. Recently, a stereoselective lithium–bromine exchange reaction of O-protected-2-trifluoromethyl-1,1-dibromoallylic alcohols has been developed in our laboratory.[7] Based on this work, we would like to report a synthetic approach towards the polysubstituted 4-trifluoromethylfurans through a sequential deprotection-annulation reaction.

O-Protected-2-trifluoromethyl-1,1-dibromoallylic alcohol **1** stereoselectively underwent a lithium–bromine exchange reaction in THF, followed by quenching with methanol, methyl iodide or benzyl bromide, to give the corresponding (*E*)-O-protected-2-trifluoromethyl-1-bromo-1-substituted allylic alcohol (**2a**, **2b** and **2c**) in 58–79% yields (Table 1). The structures of **2a**–**c** were established by their ^{1}H, ^{19}F and ^{13}C NMR spectra.[7]

Table 1. Preparation of (*E*)-O-protected-2-trifluoromethyl-1-bromo-1-substituted allylic alcohol **2a**–**c**



	RX	**2** (Yield, %)[a]
a	MeOH	70
b	MeI	79
c	BnBr	58

[a] Isolated yield after chromatography.

Compounds **2a**–**c** reacted with a series of terminal alkynes under Sonogashira reaction condition to give the corresponding coupling products **3** in 47–97% yields (Table 2). The TBS group was removed with TBAF at 0 °C, followed by cyclization and aromatization, to give the corresponding 2,3-disubstituted-4-trifluoromethylfurans **6** in 42–94% yields (Table 2). However, in the case of R being *n*-pentyl, no furan derivative was obtained (entries 6 and 12) (Scheme 1).

The structure of 2,3-disubstituted-4-trifluoromethylfurans was characterized with ^{1}H, ^{13}C and ^{19}F NMR spectra.[8,9] For example, the ^{1}H NMR and ^{1}H ^{13}C COSY spectra of compound **6aa** showed two singlets at 6.17 (1H) and 7.65 (1H) ppm which were assigned to 3-H and 5-H of the furan ring. Two signals at 103.8 and 141.0 (q, $J = 6.0$ Hz) ppm in ^{13}C NMR were assigned to 3-C and 5-C of the furan ring, which was also in

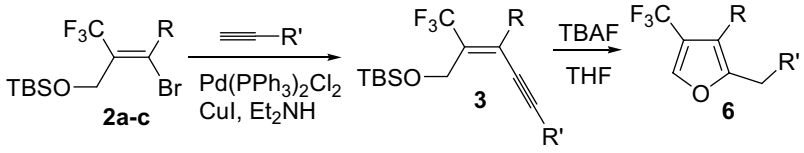
Keywords: Trifluoromethyl; Lithium-bromide exchange reaction; Furan.
* Corresponding author. E-mail: lulong@mail.sioc.ac.cn

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.04.110

Table 2. Palladium-catalyzed reaction of **2** with terminal alkynes, followed by the treatment with TBAF

Entry	2	R	R′	3 (Yield, %)[a]	6 (Yield, %)[a]
1	**2a**	H	Ph	**3aa**, 90	**6aa**, 87
2	**2a**	H	4-MeO–Ph	**3ab**, 93	**6ab**, 94
3	**2a**	H	4-MeOOC–Ph	**3ac**, 80	**6ac**, 83
4	**2a**	H	4-Me–Ph	**3ad**, 87	**6ad**, 82
5	**2a**	H	CH_2OBn	**3ae**, 91	**6ae**, 46
6	**2a**	H	*n*-Pentyl	**3af**, 97	—
7	**2b**	Me	Ph	**3ba**, 96	**6ba**, 86
8	**2b**	Me	4-MeO–Ph	**3bb**, 95	**6bb**, 86
9	**2b**	Me	4-MeOOC–Ph	**3bc**, 87	**6bc**, 50
10	**2b**	Me	4-Me–Ph	**3bd**, 96	**6bd**, 85
11	**2b**	Me	CH_2OBn	**3be**, 85	**6be**, 42
12	**2b**	Me	*n*-Pentyl	**3bf**, 89	—
13	**2c**	Bn	Ph	**3ca**, 59	**6ca**, 73
14	**2c**	Bn	4-MeO–Ph	**3cb**, 47	**6cb**, 76
15	**2c**	Bn	4-MeOOC–Ph	**3cc**, 55	**6cc**, 67

[a] Isolated yield.



Scheme 1.

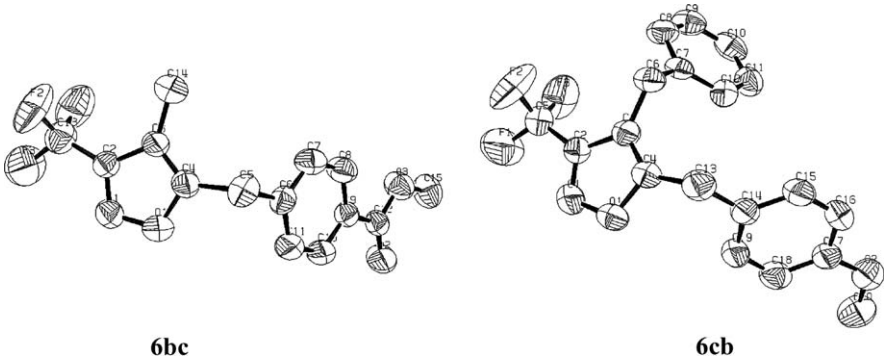
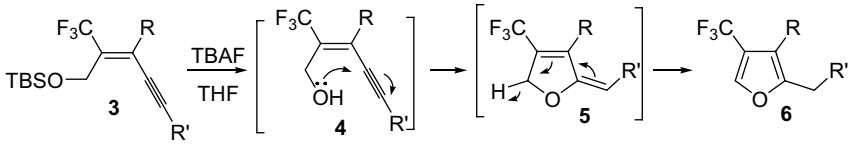


Figure 1. The ORTEP view of **6bc** and **6cb** with all H atoms omitted for clarity.

agreement with the literature.[10] The single crystal X-ray diffraction study of **6bc** and **6cb** further proved the stereochemistry of the furans (Fig. 1).[11]

A possible mechanism for the formation of 2,3-disubstituted-4-trifluoromethylfurans was proposed in Scheme 2,[12] which involved the deprotection of TBS group of **3** with TBAF, followed by a ring-forming through intramolecular nucleophilic attack to alkyne in 5-*Exo-Dig* mode. Consequently, intermediate **5** was aromatized to the final products **6** in situ. The formation of dihydrofuran **5** (R = H, R′ = CH_2OBn, Scheme 2) was monitored by ^1H NMR, in which there was a singlet at 6.57 ppm characteristic for the double bond on the five member ring, a singlet at 5.08 ppm for the CH_2 group of the ring, and a triplet at 4.88 ppm ($J = 6.9$ Hz) for another proton on the exocyclic double bond. Unfortunately, it was difficult to isolate the pure dihydrofurans



Scheme 2.

5, which were labile to cyclization during the course of the workup.[13]

In summary, we have developed an efficient method for the preparation of CF_3-containing polysubstituted furans, which is potentially useful for further conversion to the trifluoromethylated analogues of natural and biologically active compounds.

Acknowledgements

We thank the National Natural Science Foundation of China (Grant Number 29825104 and 29632003) for the financial support.

References and notes

1. (a) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795–819; (b) Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955–2020.
2. (a) Liu, Y. S.; Purrington, S. T.; Huang, W. Y. *J. Org. Chem.* **1998**, *63*, 5623–5626; (b) McAtee, J. J.; Schinazi, R. F.; Liotta, D. C. *J. Org. Chem.* **1998**, *63*, 2161–2167; (c) Jiang, J.; DeVita, R. J.; Doss, G. A.; Goulet, M. T.; Wyvratt, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 593–594; (d) Dieter, G.; Elilitz, H.; Pulst, M.; Riedel, D.; Wecks, M. *J. Fluorine Chem.* **1999**, *94*, 91–103; (e) Rivkin, A.; Biswas, K.; Chou, T. C.; Danishefsky, S. J. *Org. Lett.* **2002**, *4*, 4081–4084.
3. (a) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123–3197; (b) Resnati, G. *Tetrahedron* **1996**, *52*, 1–165.
4. (a) Fried, J.; Sabo, E. F. *J. Am. Chem. Soc.* **1954**, *26*, 1455–1456; (b) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley & Sons: New York, 1991.
5. (a) Forrest, A. K.; Ohanlon, P. J. *Tetrahedron Lett.* **1995**, *36*, 2117–2118; (b) Sham, H. L.; Betebenner, D. A. *J. Chem. Soc., Chem. Commun.* **1991**, 1134–1135.
6. (a) Kawada, K.; Kitagawa, O.; Mandal, B. K.; Filler, R.; Beery, J. W. *J. Fluorine Chem.* **1997**, *81*, 123–128; (b) Burger, K.; Helmreich, B. *J. Chem. Soc., Chem. Commun.* **1992**, 348–349; (c) Bambury, R. E.; Yaktin, H. K.; Wyckoff, K. K. *J. Heterocycl. Chem.* **1968**, *5*, 95; (d) Qing, F.; Gao, W.; Ying, J. *J. Org. Chem.* **2000**, *65*, 2003–2006.
7. Li, Y.; Lu, L.; Zhao, X. *Org. Lett.* **2004**, *6*, 4467–4470.
8. Typical experimental procedure for **6aa**–**cc**: To a stirred solution of **3ba** (284 mg, 0.8 mmol) in THF (4 mL), 1.6 mL of TBAF (1 M solution in THF, containing ca. 5% water) was added dropwise at 0 °C under an argon atmosphere. The reaction was completed (TLC) in 20 min and then 5 mL of water was added. The reaction mixture was extracted with Et_2O (3×10 mL), washed with water (2×10 mL) and then brine (20 mL), successively. The organic phases were dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by chromatography on silica gel (PE) to afford **6ba** (165 mg) in 86% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.30–7.14 (m, 5H), 3.89 (s, 2H), 2.05 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −59.7; ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.1, 140.7 (q, $J = 7.2$ Hz), 137.7, 128.7, 128.4, 126.7, 123.1 (q, $J = 265.6$ Hz), 118.9 (q, $J = 34.3$ Hz), 112.9, 32.1, 7.9; IR (film) 3033, 1576, 1345, 1169, 1130, 1030, 725 cm^{-1}; MS (EI) m/z 240 (M^+, 100), 239 (31), 225 (69), 177 (20), 163 (22), 143 (17); HRMS calcd for $C_{13}H_{11}F_3O$: 240.0759, found: 240.0751.
9. ^{19}F NMR spectra were recorded on a Bruker AM300 spectrometer using $CFCl_3$ as the external standard, and with downfield shifts being designed as negative.
10. Hill, A. S.; McAdam, D. P.; Edward, S. L.; Skerritt, J. H. *J. Agric. Food Chem.* **1993**, *41*, 2011–2018.
11. Crystallographic data of **6bc** (CCDC 257591) and **6cb** (CCDC 257621) can be obtained free of charge from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB 1EZ, UK; email: deposit@ccdc.cam.ac.uk.
12. Kou, H.; Rumi, J.; Mitsuyoshi, K.; Akito, Y.; Takao, S. *Tetrahedron* **2001**, *57*, 9697–9710.
13. (a) Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1995**, *60*, 5966–5968; (b) Marshall, J. A.; DuBay, W. J. *J. Org. Chem.* **1993**, *58*, 3435–3443.