[Chem. Pharm. Bull. 33(9)3670—3674(1985)]

Studies on Organic Fluorine Compounds. XLV.[1] Synthesis and Regioselective Substitution Reaction of 3-Trifluoromethylfuran

KOSUKE KAWADA, OSAMU KITAGAWA, and YOSHIRO KOBAYASHI*

Tokyo College of Pharmacy, 1432–1 Horinouchi, Hachioji, Tokyo 192–03, Japan

(Received January 9, 1985)

3-Trifluoromethylfuran (**1**) was efficiently synthesized by the reaction of 4-methyloxazole with 3,3,3-trifluoropropyne. Lithiation of **1** with *n*-butyllithium followed by reaction with an electrophile gave the corresponding 2-substituted 3-trifluoromethylfuran (**4**). Starting from 2-triethylsilyl-3-trifluoromethylfuran (**4a**), 2-substituted 4-trifluoromethylfurans (**6**) were synthesized.

Keywords——3-trifluoromethylfuran; 4-methyloxazole; 3,3,3-trifluoropropyne; 2-triethylsilyl-3-trifluoromethylfuran

Introduction

It is well known that furan derivatives are versatile intermediates in synthetic organic chemistry and a number of applications to syntheses of natural products have been reported.[2–4] In the course of our studies on the development of synthetic methods for trifluoromethylated compounds utilizing trifluoromethylated heterocyclic compounds as intermediates,[5] we investigated the synthesis and reactions of 3-trifluoromethylfuran (**1**). Compound **1** is expected to be a useful intermediate for the synthesis of a variety of trifluoromethylated bioactive compounds such as cyclopentenone derivatives or sugar derivatives. In this paper we wish to report an efficient synthesis of **1** and the regioselective introduction of a substituent at the 2 or 5 position of **1**.

Results and Discussion

Compound **1** was reported to be synthesized by partial trifluoromethylation of furan-3,4-dicarboxylic acid with sulfur tetrafluoride, followed by decarboxylation.[6] The use of toxic gaseous sulfur tetrafluoride and the low yield of **1** in this method are disadvantages. To overcome these problems, an attempt was made to utilize 4-methyloxazole (**2**), and it was found that **1** can be efficiently prepared from **2** and 3,3,3-trifluoropropyne (**3**) through the Diels–Alder reaction followed by the retrograde Diels–Alder reaction in a one-pot procedure.[7] Thus, a mixture of **2** and **3** in toluene was heated at 180—190 °C for 13 h to give **1** in 67% yield (Chart 1).

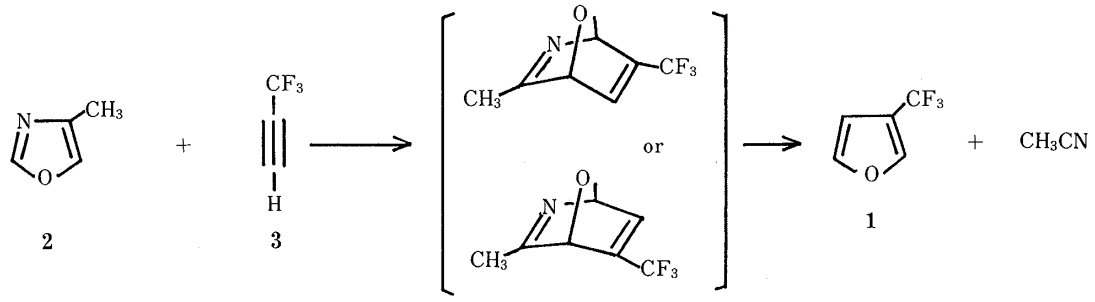
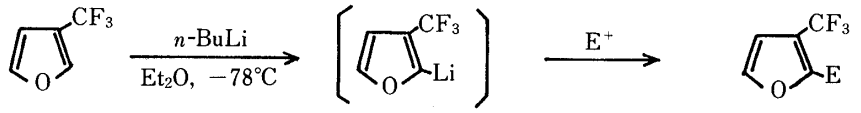


Chart 1

It is expected that deprotonation would occur at the 2-position of **1** on treatment of **1** with a base because of the inductive effect of the trifluoromethyl group at the 3-position. Indeed, reaction of **1** with *n*-butyllithium in ether at −78 °C for 1 h followed by reaction with triethylsilyl chloride afforded the product (**4a**) silylated at the 2-position in 58% yield. In a similar manner, reaction of the 2-lithio derivative with aldehydes gave the carbinols (**4b—d**) in good yields (Table).

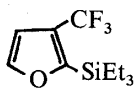
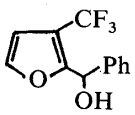
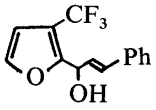
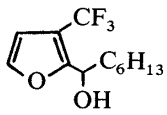
Although lithiation of furan produces 2-lithiofuran at low temperature, at relatively high temperature disproportionation takes place to form an equilibrium mixture of 2-lithiofuran, 2,5-dilithiofuran and furan. Consequently, further reaction with electrophiles gave rise to a mixture of 2-substituted and 2,5-disubstituted compounds.[8] Furthermore, in the case of 3-alkylfuran, lack of regiospecificity in the lithiation step was observed.[8] In contrast, no regioisomer of **4** nor any 2,5-disubstituted compound could be identified in the reactions of **1** mentioned above.



1 **4**

Chart 2

TABLE. Reaction of 2-Lithio-3-CF_3furan with Electrophiles

Electrophile	Product		Yield (%)
Et_3SiCl		**4a**	58
PhCHO		**4b**	81
PhCH=CHCHO		**4c**	78
n-$C_6H_{13}CHO$		**4d**	72

To introduce a substituent at the 5-position of **1**, lithiation was carried out on the 2-triethylsilyl derivative (**4a**). Thus, treatment of **4a** with *n*-butyllithium in tetrahydrofuran (THF) at −15 °C for 1 h (these reaction conditions are crucial for deprotonation at the 5-position of **4a**) followed by the reaction with an aldehyde afforded the carbinol (**5**), which was smoothly desilylated by treatment with tetrabutylammonium fluoride (TBAF) to give the desired product (**6**) with the substituent at the 5-position of **1** (Chart 3).

It was reported that acid treatment of (2-furyl)carbinol gave the corresponding cyclopentenone derivative through a pentadienyl cation.[9] Cyclopentenone derivatives can be used as intermediates for the construction of biologically important cyclopentanoids. Such compounds bearing a trifluoromethyl group are of interest. It was found that the benzaldehyde adduct (**4b**) reacted in the presence of sulfuric acid in a mixture of methanol and water at room temperature to give the cyclopentenone derivative (**7**) in 40% yield (Chart 4). Similar

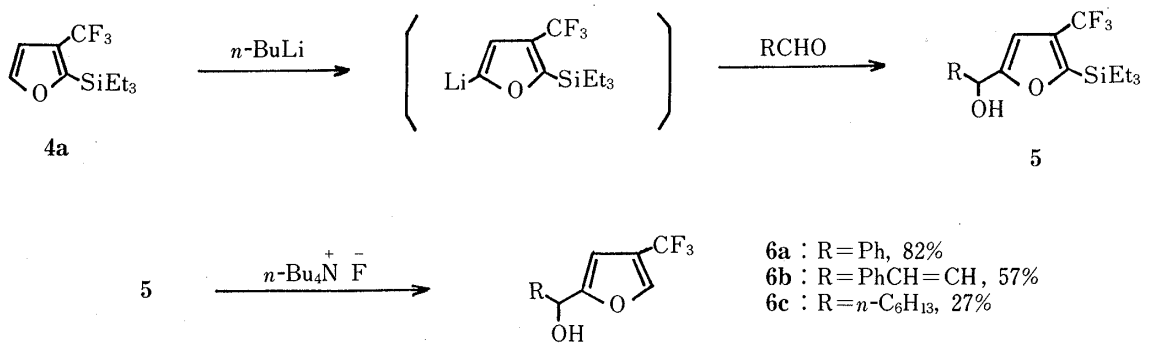


Chart 3

reaction with the acetate of **4b** gave **7** in 80% yield. However, similar reaction with **4c** gave the rearranged product (**16**) and that with **4d** gave the dehydrated product (**17**).

Neither **16** nor **17** could be transformed to the cyclopentenone derivatives under more drastic reaction conditions, such as refluxing in a mixture of water and methanol; such conditions resulted in their decomposition. Thus, the formation of the carbonium ion (**9**) and its relative stability seemed to be key factors in relation to the subsequent rearrangement *via* the pentadienyl cation (**12b**). From mechanistic considerations (Chart 4), the cyclopentenone derivative (**13b**) may be formed initially, and the following conversion of **13b** to the final product (**7**) may involve the cationic intermediate **15b**, but it is not clear whether the cyclopentadienone (**14b**) is an intermediate in this reaction. The formation of 2,4-diphenyl-5-trifluoromethylcyclopentenone (**8**) by the treatment of **7** with sulfuric acid in benzene is consistent with the involvement of the cationic intermediate (**15b**) or the cyclopentadienone (**14b**).

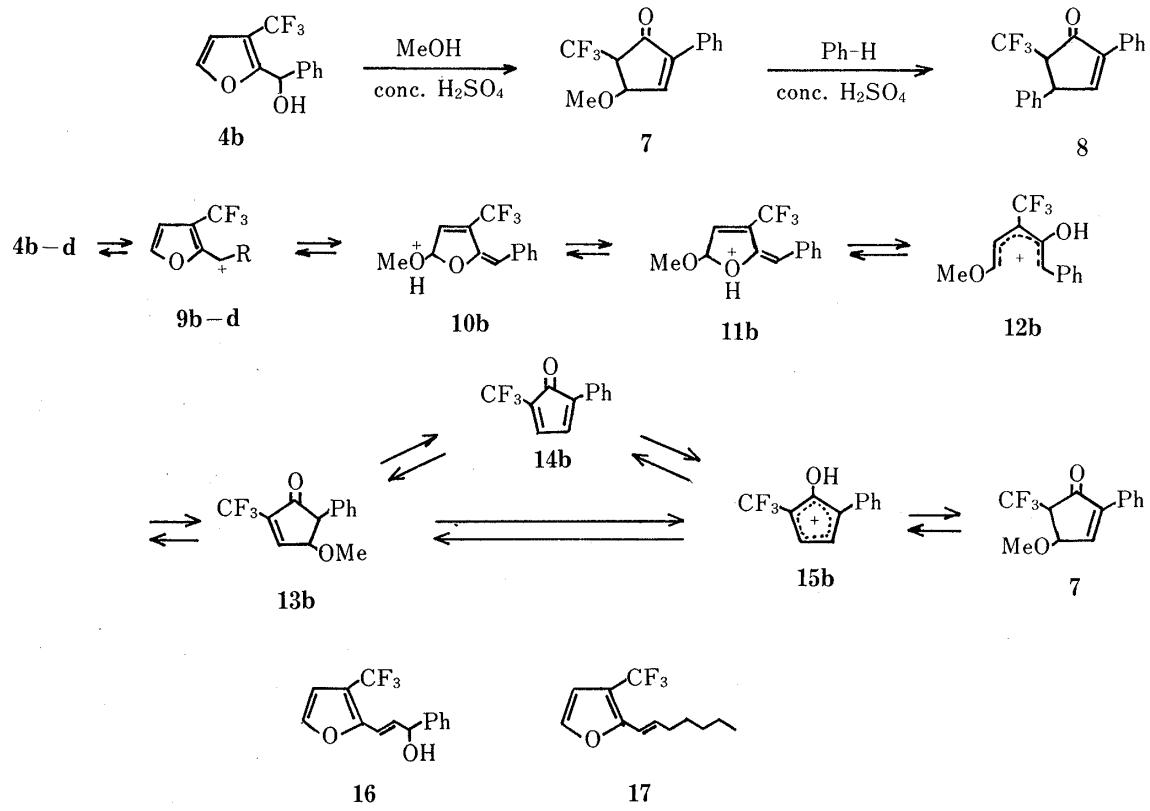


Chart 4

In conclusion, **1** is lithiated at the 2-position exclusively on treatment with *n*-butyllithium, and subsequent reaction with an electrophile gives the corresponding **1** having a substituent at the 2-position. Starting from 2-triethylsilyl-3-trifluoromethylfuran (**4a**), lithiation at the 5-position followed by reaction with an aldehyde and TBAF gives the corresponding 4-trifluoromethylfuran having a substituent at the 2-position. Furthermore, (3-trifluoromethyl-2-furyl)phenylcarbinol (**4b**) gives the trifluomethylated cyclopentenone (**7**) on acid treatment.

Experimental

Melting points were taken on a hot-stage microscope (Yanagimoto) and are uncorrected. Infrared (IR) spectra were recorded with a JASCO IRA-1 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Varian EM 390L spectrometer. Chemical shifts are reported in parts per million (ppm) on the δ scale relative to tetramethylsilane as an internal standard. Fluorine nuclear magnetic resonance (^{19}F-NMR) spectra were recorded on a Varian EM 360L spectrometer. Chemical shifts are reported in parts per million relative to benzotrifluoride as an external standard, and a plus sign indicates high field. Mass spectra (MS) were recorded on a Hitachi RMU-7L instrument.

3-Trifluomethylfuran (1)——In a 50 ml stainless steel vessel, a mixture of **2** (10 g, 120 mmol) and **3** [5 ml (d=1.25)] in toluene (10 ml) was shaken at 180—190 °C for 13 h. The reaction mixture was distilled under atmospheric pressure using a 15 cm vigrue column to give **1** (6.1 g, 67%). From the gas-liquid chromatography (GLC) analysis, **1** contained a small amount of acetonitrile (about 6%). **1**: bp 62—64 °C (lit. 56.5 °C).[6] IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1610, 1350, 1190, 1150, 1080, 1020, 940, 880. ^{1}H-NMR ($CDCl_3$) δ: 6.63 (br s, 1H), 7.53 (m, 1H), 7.82 (m, 1H). MS *m/z*: 136 (M^+), 118, 107, 88.

2-Triethylsilyl-3-trifluoromethylfuran (4a)——Under an argon atmosphere, a mixture of **1** (1.0 g, 7.35 mmol) and *n*-butyllithium (8 mmol) in ether was stirred for 2 h at −78 °C (dry ice–acetone bath), then triethylsilyl chloride (1.2 g, 8 mmol) was added and the reaction mixture was stirred for 2 h. After extractive work-up (ether for extraction), the extracts were dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was distilled in a Kugelrohr apparatus to give **4a** (1.06 g, 58%). **4a**: bp 108—109 °C/40 mmHg. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2960, 2880, 1495, 1320, 1190, 1140, 965. ^{1}H-NMR ($CDCl_3$) δ: 0.40—1.30 [15H, m, $Si(CH_2CH_3)_3$], 6.51 (1H, d, J=2 Hz), 7.58 (1H, m). ^{19}F-NMR ($CDCl_3$) −8.2 (br s). MS *m/z*: 250 (M^+), 221, 165, 137, 113. High-resolution MS Calcd for $C_{11}H_{17}F_3OSi$: 250.0999. Found: 250.0997.

(3-Trifluoromethyl-2-furyl)phenylcarbinol (4b)——Under an argon atmosphere, a mixture of **1** (200 mg, 1.47 mmol) and *n*-butyllithium (1.6 mmol) in ether was stirred for 1 h at −78 °C (dry ice–acetone bath), then benzaldehyde (160 mg, 1.5 mmol) was added and the reaction mixture was stirred for 1 h. The mixture was quenched by addition of 1 N HCl and then extracted with ether. The ether extracts were washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The residue was chromatographed on silica gel to give **4b** (290 mg, 81%) as colorless crystals. **4b**: mp 75—76 °C. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3340, 1180, 1130. ^{1}H-NMR ($CDCl_3$) δ: 2.60 (1H, d, J=5 Hz, –OH), 6.11 (1H, d, J=5 Hz, methyne), 6.58 (1H, d, J=2 Hz), 7.33 (6H, br s). ^{19}F-NMR ($CDCl_3$) −8.17 (s). High-resolution MS Calcd for $C_{12}H_9F_3O_2$: 242.0576. Found: 242.0565.

In a similar manner, **4c** and **4d** were synthesized by using cinnamaldehyde and *n*-heptanal.

4c: IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3340, 1630, 1185, 1140, 970. ^{1}H-NMR ($CDCl_3$) δ: 2.32 (1H, br s, –OH), 5.63 (1H, d, J=6 Hz), 6.46 (1H, dd, J=6 and 15 Hz), 6.60 (1H, d, J=2 Hz), 6.75 (1H, d, J=15 Hz), 7.27—7.60 (6H, m). ^{19}F-NMR ($CDCl_3$) −7.07 (s). MS *m/z*: 268 (M^+), 251, 250, 249, 219, 190, 163, 105. High-resolution MS Calcd for $C_{14}H_{11}F_3O_2$: 268.0710. Found: 268.0690.

4d: bp 125 °C/15 mmHg (bulb-to-bulb distillation). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3610, 3360, 2940, 1625, 1185, 1135, 990. ^{1}H-NMR (CCl_3) δ: 0.88 (3H, m), 1.30 (8H, br s), 1.72—2.13 (2H, m), 2.30 (1H, br s, –OH), 4.93 (1H, t, J=7 Hz), 6.57 (1H, d, J=2 Hz), 7.45 (1H, d, J=2 Hz). ^{19}F-NMR ($CDCl_3$) −7.07 (s). MS *m/z*: 250 (M^+), 165, 145. High-resolution MS Calcd for $C_{12}H_{17}F_3O_2$: 250,1179. Found: 250.1178.

(4-Trifluoromethyl-2-furyl)phenylcarbinol (6a)——Under an argon atmosphere, a mixture of **4a** (120 mg, 0.48 mmol) and *n*-butyllithium (0.52 mmol) in THF was stirred for 1.5 h at −15——10 °C (ice–NaCl bath), then benzaldehyde (1.1 mmol) was added and the reaction mixture was stirred for 1 h at −10 °C. After being quenched by addition of 1 N HCl, the reaction mixture was extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, then concentrated *in vacuo*. The residue was treated with TBAF (3 eq mol) in THF for 0.5 h at room temperature. The solvent was evaporated off *in vacuo*, and the residue was chromatographed on silica gel to give the carbinol (**6a**) (110 mg, 82%) as a colorless oil. **6a**: IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600, 3340, 1620, 1190, 1170, 1150, 945. ^{1}H-NMR ($CDCl_3$) δ: 2.74 (1H, br s, –OH), 5.78 (1H, s), 6.30 (1H, s), 7.43 (5H, s), 7.72 (1H, q, J=2 Hz). ^{19}F-NMR ($CDCl_3$) −4.8 (d, J=2 Hz). MS *m/z*: 242 (M^+), 225, 163, 105. High-resolution MS Calcd for $C_{12}H_8F_3O$ (M^+ −OH): 225.0525. Found: 225.0516.

In a similar manner, **6b** was synthesized in 57% yield by using cinnamaldehyde.

6b: IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600, 3360, 1185, 1145. ^{1}H-NMR ($CDCl_3$) δ: 2.55 (1H, br s, –OH), 5.43 (1H, d, J=6 Hz), 6.35

(1H, dd, $J=6$ and 16 Hz), 6.45 (1H, d, $J=1$ Hz), 6.74 (1H, d, $J=16$ Hz), 7.37 (5H, m), 7.70 (1H, dq, $J=1$ and 1.5 Hz). ^{19}F-NMR ($CDCl_3$) −4.9 (br s). MS *m/z*: 269, 268 (M^+), 164, 105. High-resolution MS Calcd for $C_{14}H_{11}F_3O_2$: 268.0709. Found: 268.0693.

2-Phenyl-4-methoxy-5-trifluoromethylcyclopentenone (7)——A solution of **4b** (240 mg, 1 mmol) in a mixture of methanol and water in the presence of conc. sulfuric acid (3 drops) was refluxed for 2 h. The reaction mixture was diluted with water and then extracted with ether. The ether extracts were washed with brine, dried over $MgSO_4$, then concentrated *in vacuo*. The residue was chromatographed on silica gel to give the cyclopentenone (**7**) (101 mg, 40%). **7**: bp 140—148 °C/4 mmHg (bulb-to-bulb distillation). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1725, 1175, 1120. ^{1}H-NMR ($CDCl_3$) δ: 3.13 (1H, dq, $J=2.5$ and 10 Hz), 3.44 (3H, s), 4.55 (1H, t, $J=2.5$ Hz), 7.07—7.40 (3H, m), 7.40—7.70 (3H, m). ^{19}F-NMR ($CDCl_3$) +2.0 (d, $J=10$ Hz). MS *m/z*: 256 (M^+), 225, 197, 117. High-resolution MS Calcd for $C_{13}H_{11}F_3O_2$: 256.0710. Found: 256.0696.

2,4-Diphenyl-5-trifluoromethylcyclopentenone (8)——A mixture of **4b** (75.6 mg) and sulfuric acid (100 mg) in benzene (3 ml) was stirred for 2 h at room temperature. The reaction mixture was diluted by the addition of water and extracted with ether. The ether extract was dried over $MgSO_4$ and then concentrated *in vacuo*. The residue was subjected to preparative thin-layer chromatography (TLC) (*n*-hexane–ethyl acetate 20 : 1) to give 87 mg (97.5%) of **8** as colorless crystals. **8**: mp 95—97 °C (from *n*-hexane). IR ν_{max}^{KBr} cm^{-1}: 3330, 1710, 1250, 1200, 1155, 1090. ^{1}H-NMR ($CDCl_3$) δ: 3.30 (1H, dq, $J=3$ and 10 Hz), 4.38 (1H, t, $J=3$ Hz), 7.23—8.07 (11H, m). ^{19}F-NMR ($CDCl_3$) +2.8 (d, $J=10$ Hz). MS *m/z*: 302 (M^+). High-resolution MS Calcd for $C_{18}H_{13}F_3O$: 302.0917. Found: 302.0911.

References

1) Part XLIV: Y. Kobayashi, T. Yoshida, M. Nakajima, A. Ando, Y. Hanzawa, and I. Kumadaki, *Chem. Pharm. Bull.*, **33**, 3608 (1985).
2) A. I. Meyers, "General Heterocyclic Chemistry Series," Vol. 3, ed. by E. C. Taylor and A. Weissberger, John Wiley and Sons, Inc., New York, 1973, p. 1.
3) Y. Hayakawa, M. Sakai, and R. Noyori, *Chem. Lett.*, **1973**, 3.
4) G. Schmid, T. Fukuyama, K. Akasaka, and Y. Kishi, *J. Am. Chem. Soc.*, **101**, 259 (1979).
5) K. Kawada, O. Kitagawa, T. Taguchi, Y. Hanzawa, and Y. Kobayashi, *Chem. Pharm. Bull.*, in press.
6) V. V. Lyalin, R. V. Grigorash, L. A. Alekseeva, and L. M. Yagnopol'skii, *Zh. Organ. Khim.*, **11**, 1086 (1975).
7) H. König, F. Graf, and V. Weberndörfer, *Justus Liebigs Ann. Chem.*, **1981**, 668.
8) D. J. Chadwick and C. Willbe, *J. Chem. Soc., Perkin Trans. 1*, **1977**, 887.
9) G. Piancatelli, A. Scettri, G. David, and M. D'Auria, *Tetrahedron*, **34**, 2775 (1978).