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Studies on Organic Fluorine Compounds. XLVI.[1] Synthesis of 4-Trifluoromethyl-2(5*H*)-furanone and 4-Trifluoromethyl-*N*-substituted Dihydropyrrol-2-ones

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4-Trifluoromethyl-2(5*H*)-furanone (**2**) and 4-trifluoromethyl-*N*-substituted dihydropyrrol-2-ones (**4**) were effectively prepared from ethyl (*Z*)-4-bromo-3-trifluoromethyl-2-butenoate (**1**). The dihydropyrrol-2-ones (**4**) were found to consist of the Δ^3- and/or Δ^4-form, and the electronic nature of the substituent on nitrogen affected the isomer ratio.

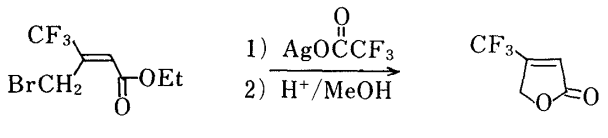
Keywords——4-trifluoromethyl-2(5*H*)-furanone; 4-trifluoromethyl-1,5-dihydropyrrol-2-one; 4-trifluoromethyl-1,3-dihydropyrrol-2-one; ethyl 4-bromo-3-trifluoromethyl-2-butenoate

Heterocyclic compounds such as furan or pyrrole derivatives are useful intermediates in synthetic chemistry due to their potential reactivities.[2] In recent years, a number of fluorine-modified bioactive compounds have attracted attention, and the trifluoromethyl group is now recognized as an important substituent in the field of medicinal chemistry, because of its characteristic properties.[3] In this paper we wish to report a convenient synthesis of 4-trifluoromethyl-2(5*H*)-furanone (**2**) and 4-trifluoromethyl-*N*-substituted dihydropyrrol-2-ones (**4**), which may be useful precursors for the preparation of trifluoromethylated bioactive compounds.[4] Other bioactive pyrrol-2-one derivatives include aphicides, fungicides and miticides, so the activities of such compounds containing a trifluoromethyl group are of interest.[5]

4-Trifluoromethyl-2(5*H*)-furanone (2)

For the synthesis of **2** and **4**, ethyl (*Z*)-4-bromo-3-trifluoromethyl-2-butenoate (**1**), which is easily prepared by the reaction of ethyl diethylphosphonoacetate with trifluoroacetone followed by bromination (NBS), may be an excellent starting material owing to the *Z*-stereochemistry of its double bond and the high reactivity of the allylic bromide.[6–8]

Reaction of **1** with silver trifluoroacetate in acetonitrile for 4 h at room temperature followed by acid treatment (conc. HCl) in methanol gave the butenolide (**2**) in 90% yield (Chart 1). Instead of CF_3COOAg, siliver acetate can be used, but more severe reaction conditions are required: refluxing in acetonitrile for 20 h for the first step and refluxing in methanol for 16 h for the second step, to give **1** in 88% yield. Compound **1** also reacted with carboxylate (CH_3COOK or C_6H_5COONa) in dimethylformamide (DMF) as a solvent to give the acetate (90%) or the benzoate (quantitative yield) without allylic rearrangement.



1 2

Chart 1

Reaction of 1 with Primary Amines (3)

N-Arylamines (**3a**—**c**) reacted with **1** in the presence of *sym*-collidine in DMF to give the dihydropyrrol-2-ones (**4**) in moderate yield. Similar reaction with primary *N*-alkylamines (**3d** and **3e**) gave a mixture of the dihydropyrrol-2-one (**4**) and the α-substituted ester (**5**). These results are summarized in Table I. From the nuclear magnetic resonance (NMR) spectra ($CDCl_3$), the *N*-aryldihydropyrrol-2-ones (**4a**—**c**) thus obtained consist of the Δ^4- and Δ^3-isomers, while the *N*-alkyldihydropyrrolones (**4d** and **4e**) have the Δ^4-form exclusively. Thus, with 4-trifluoromethyldihydropyrrolones (**4**) an electron-donating group on the nitrogen may favor the Δ^4-pyrrolone structure, because of the electron-withdrawing character of the trifluoromethyl group at the 4-position.[9]

Complete separation of the Δ^4- and Δ^3-isomers of the *N*-aryl derivatives (**4a**—**c**) could not be achieved by silica gel chromatography, presumably due to a relatively rapid equilibrium between the isomers catalyzed by silica gel. The acid or base-catalyzed equili-

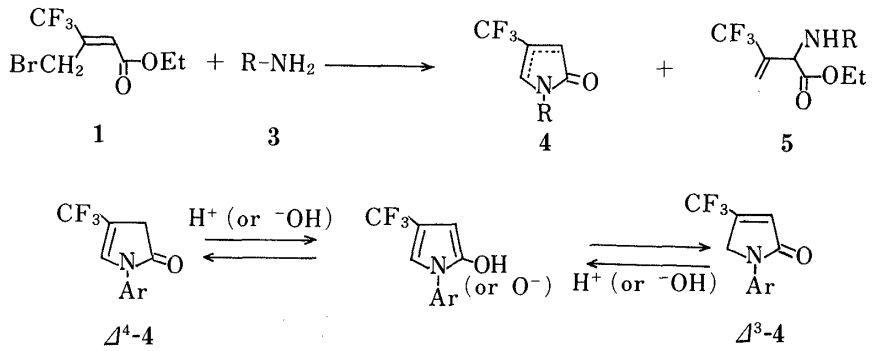


Chart 2

TABLE I. Reaction of **1** with Primary Amines (**3**)

3	R	**4** (%)	(Δ^3/Δ^4)	**5** (%)
a	*p*-$MeOC_6H_4$	59	(1/10)	—
b	C_6H_5	49	(1/5)	—
c	*p*-ClC_6H_4	57	(1/3.4)	—
d	*n*-C_4H_9	23	Δ^4-Only	27
e	*c*-C_6H_{11}	23	Δ^4-Only	23

TABLE II. ^{1}H-NMR and ^{19}F-NMR Data for the 4-Trifluoromethyl-*N*-substituted Dihydropyrrol-2-ones (**4**) in $CDCl_3$

	R		^{1}H-NMR δ	^{19}F-NMR ppm
a	*p*-$MeOC_6H_4$	Δ^4-**4a**	3.43 (H-3), 3.83 (OCH_3), 6.93 (H-5), 6.96—7.43 (aromatic-H)	0
		Δ^3-**4a**	3.83 (OCH_3), 4.58 (H-5), 6.70 (H-3), 6.96—7.43 (aromatic-H)	+2.2
b	C_6H_5	Δ^4-**4b**	3.43 (H-3), 7.33 (H-5), 7.45 (aromatic-H)	0
		Δ^3-**4b**	4.57 (H-5), 6.69 (H-3), 7.45 (aromatic-H)	+2.5
c	*p*-ClC_6H_4	Δ^4-**4c**	3.40 (H-3), 7.33 (H-5), 7.40 (aromatic-H)	+0.3
		Δ^3-**4c**	4.57 (H-5), 6.67 (H-3), 7.40 (aromatic-H)	+2.4
d	*n*-C_4H_9	Δ^4-**4d**	0.97—1.77 (7H, alkyl), 3.21 (H-3), 3.45 (NCH_2-Pr), 6.88 (H-5)	−0.4
e	cyclo-C_6H_{11}	Δ^4-**4e**	1.10—2.00 (10H, $-(CH_2)_5-$), 3.26 (H-3), 3.97 (methyne), 7.57 (H-5)	−0.5

bration of **4c** was qualitatively examined by fluorine-19 nuclear magnetic resonance (^{19}F-NMR) analysis of the Δ^3-isomer or Δ^4-isomer-enriched fraction obrained by rapid chromatographic separation (SiO_2 column) of **4c**. A mixture of Δ^3- and Δ^4-**4c** (ratio 1 : 13) in tetrahydrofuran (THF) was found to reach equilibrium within 40 min in the presence of 1 N HCl to give Δ^3- and Δ^4-**4c** in the ratio of 1 : 3.7, and within 10 min in the presence of 1 N NaOH in the ratio of 1 : 3.9. Similarly, a mixture of Δ^3- and Δ^4-**4c** (ratio 1 : 2) in THF changed its ratio to 1 : 3.6 after 20 min in the presence of 1 N HCl and to 1 : 3.4 after 10 min in the presence of 1 N NaOH.

In conclusion, **1** is an efficient starting material for the preparation of 4-trifluoromethyl-2(5*H*)-furanone (**2**) and 4-trifluoromethyldihydropyrrol-2-ones (**4**). The electronic nature of the substituent on the nitrogen affected the structure of **4**.

Experimental

Melting points were taken on a hot-stage microscope (Yanagimoto) and are uncorrected. Infrared (IR) spectra were recorded on 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. ^{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.

4-Trifluoromethyl-2(5*H*)-furanone (2)——A mixture of ethyl 4-bromo-3-trifluoromethyl-2-butenoate (**1**, 25 g, 95 mmol) and silver trifluoroacetate (23 g, 104 mmol) in acetonitrile (80 ml) was stirred for 6 h at room temperature. The precipitates were filtered off through Celite and the filtrate was diluted with water. This solution was extracted with ether and the extracts were dried over $MgSO_4$. After removal of the solvent *in vacuo*, the residue was treated with conc. HCl (0.5 ml) in methanol (150 ml) for 16 h at room temperature. The reaction mixture was diluted with water (200 ml) and extracted with ether (200 ml × 2), and the extract was dried over $MgSO_4$. After removal of the solvent *in vacuo*, the residue was distilled under a vacuum to give **2** (13.1 g, 90%). **2**: Colorless oil; bp 108—113 °C (140 mmHg). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1800, 1760, 1450, 1380, 1345, 1250—1100. ^{1}H-NMR ($CDCl_3$) δ: 5.09 (2H, m, methylene), 6.70 (1H, m, olefinic-H). ^{19}F-NMR ($CDCl_3$) ppm: +0.96 (s). MS *m/z*: 152 (M^+), 133.

Reaction of 1 with Aniline——A mixture of aniline (232 mg, 2.50 mmol) and *sym*-collidine (308 mg, 2.55 mmol) in DMF (8 ml) was added to a solution of **1** (650 mg, 2.49 mmol) in DMF (9 ml) at 0 °C. After being stirred for 6 h at room temperature, the reaction mixture was poured into water and extracted with ether. The extract was dried over $MgSO_4$, then concentrated *in vacuo*. The residue was chromatographed on silica gel (*n*-hexane–dichloromethane 3 : 1) to give **4b** (270 mg, 49%) as colorless crystals. **4b**: mp 137—138 °C (*n*-hexane–dichloromethane). IR ν_{max}^{KBr} cm^{-1}: 3100, 3070, 1725, 1700, 1660. MS *m/z*: 227 (M^+), 198. *Anal.* Calcd for $C_{11}H_8F_3NO$: C, 58.16; H, 3.55; F, 25.09; N, 6.15. Found: C, 57.98; H, 3.44; F, 25.10; N, 6.30.

Similarly, reaction of **1** with *p*-anisidine (**3a**) and *p*-chloroaniline (**3c**) gave the dihydropyrrol-2-ones (**4a** and **4c**), respectively. **4a**: mp 122—125 °C (*n*-hexane–CH_2Cl_2). IR ν_{max}^{KBr} cm^{-1}: 1735. MS *m/z*: 257 (M^+), 229. *Anal.* Calcd for $C_{12}H_{10}F_3NO_2$: C, 56.04; H, 3.92; F, 22.16; N, 5.45. Found: C, 56.11; H, 3.89; F, 21.94; N, 5.47. **4c**: IR ν_{max}^{KBr} cm^{-1}: 1705. MS *m/z*: 263 [M^+ (^{37}Cl)], 261 [M^+ (^{35}Cl)], 198. High-resolution MS Calcd for $C_{11}H_7ClF_3NO$: 261.0169. Found: 261.0177.

Reaction of 1 with *n*-Butylamine (3d)——A mixture of **1** (522 mg, 2 mmol), *n*-butylamine (2 mmol) and *sym*-collidine (2 mmol) in DMF (6 ml) was stirred for 30 min at 0 °C. After extractive work-up (ether for extraction), the extract was chromatographed on a silica gel column; elution with a mixture of *n*-hexane and dichloromethane (3 : 1) gave **5d** (135 mg, 27%) and **4d** (96 mg, 23%) successively. **5d**: bp 95—100 °C (4.5 mmHg) (Kugelrohr). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735, 1175. ^{1}H-NMR ($CDCl_3$) δ: 0.78—1.00 (3H, m), 1.28 (3H, t, J=7.2 Hz), 1.10—1.62 (9H, m), 2.57 (2H, t, J=6.6 Hz, >NCH_2Pr), 4.01 (1H, br s, >NCHCO), 5.79 (1H, m, vinylic), 5.98 (1H, m, vinylic). ^{19}F-NMR ($CDCl_3$) ppm: +3.5 (m). MS *m/z*: 253 (M^+), 210, 180. High-resolution MS Calcd for $C_{11}H_{18}F_3NO_2$: 253.1290. Found: 253.1263. **4d**: bp 75—80 °C (4 mmHg) (Kugelrohr). IR ν_{max}^{KBr} cm^{-1}: 1725, 1650. MS *m/z*: 207 (M^+), 164. High-resolution MS Calcd for $C_9H_{12}F_3NO$: 207.0868. Found: 207.0839.

Reaction of 1 with Cyclohexylamine (3e)——A mixture of **1** (2 mmol), cyclohexylamine (2 mmol) and triethylamine (2 mmol) in DMF was stirred for 1 h at 0 °C. Extractive work-up (ether for extraction), followed by silica gel column chromatography (*n*-hexane–dichloromethane 3 : 1) gave **5e** (120 mg, 23%) and **4e** (108 mg, 23%) successively. **5e**: bp 90 °C (5 mmHg) (Kugelrohr). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740, 1175. ^{1}H-NMR ($CDCl_3$) δ: 1.02—1.83 (10H, m), 1.28 (3H, t, J=6.9 Hz), 1.65 (1H, br s, NH), 2.38 (1H, m), 4.06 (1H, s, >NCHCO), 4.20 (2H, q, J=6.9 Hz), 5.72 (1H, m, vinylic), 5.87 (1H, m, vinylic). ^{19}F-NMR ($CDCl_3$) ppm: +3.3 (m). MS *m/z*: 279 (M^+), 206. High-resolution MS Calcd for $C_{13}H_{20}F_3NO$: 279.1441. Found: 279.1425. **4e**: mp 93—112 °C (pet. ether). IR ν_{max}^{KBr} cm^{-1}: 1700. MS *m/z*:

233 (M^+), 152. High-resolution MS Calcd for $C_{11}H_{14}F_3NO$: 233.1024. Found: 233.1038.

References and Notes

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