Pergamon

Tetrahedron 56 (2000) 6219–6222

TETRAHEDRON

# Reaction of 5-(Trifluoromethyl)-2(5*H*)-furanone under Basic Conditions: Stereo-Controlled Michael Dimerization

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Received 18 May 2000; accepted 23 June 2000

**Abstract**—Treatment of 5-trifluoromethyl-2(5*H*)-furanone under basic conditions gave a stereoisomeric mixture of two out of four possible stereoisomers of bis(trifluoromethyl)dihydro-2,4-bisfuranonyl depending on the reaction conditions. Butenolide anion generated with LDA is kinetically stable and reaction with 2-cyclohexenone stereoselectively gave a Michael adduct. © 2000 Elsevier Science Ltd. All rights reserved.

## Introduction

Recently, we found that *N*-substituted 5-(difluoromethylene)-2-pyrrolinones derived from the corresponding trifluoromethylated precursors via dehydrofluorination could be actually generated and that the difluoroolefins were highly reactive with the enolate anion of the pyrrolinone and immediately gave a dimer by an addition–elimination mechanism even at −78°C.[1] This unexpected reactivity of trifluoromethylpyrrolinones prompted us to investigate the chemistry of the *O*-analog of trifluoromethylpyrrolinone, namely 5-trifluoromethyl-2(5*H*)-furanone (**1**). Unfortunately, however, similar dehydrofluorination of **1** did not occur because of the stability of the enolate anion of **1** and the reactivity of **1** as a Michael acceptor. In 1993, Yoshida et al. reported reaction of butenolide **1** with $K_2CO_3$ in acetonitrile to give dimeric substances.[2] They mentioned that products were Michael reaction products of **1** reacted at C-5 position although the described products were only two of the four possible stereoisomers. We attempted dehydrofluorination of **1** under various reaction conditions and, while our attempts to obtain difluoromethylene-protoanemonin completely failed, we found that the stereochemistry of the dimeric products changes considerably depending on the reaction conditions. Here, we report the stereochemistry of the dimeric products and the stereochemical alternation observed for the variation of reaction conditions used.

## Results and Discussion

Butenolide **1**[3–5] was treated with $Li_2CO_3$ in aqueous THF at room temperature and gave **2a** in 71% isolated yield as the sole product unlike the reaction with $K_2CO_3$ reported by Yoshida et al.[2] Reaction of **1** with amine base, DBU (Table 1; entry 2) gave also predominantly **2a**. However, *t*-BuOK gave **2b** as the major product (29% yield) accompanied by **2a** (14%) although in this case some unidentified by-products were also obtained (entry 3). The product ratios are dependent on the pH of the reaction media. The reaction in 5 v/v% aqueous 10 M NaOH/THF gave predominantly **2b** but the total yield of the products was low because of the hydrolytic decomposition of lactone **1** and/or dimers **2ab** (entry 4). The result of the reaction in 5 v/v% 1 M NaOH/THF was comparable to the case using DBU (entry 5). Slower reaction in 33 v/v% 0.1 M and 33 v/v% 0.01 M NaOH/THF afforded mostly **2a** (entries 7 and 8). These product ratios suggest that **2a** is the kinetic product which is given in the presence of relatively weak base such as a tertiary amine or $Li_2CO_3$. Under the stronger base (*t*-BuOK) conditions, equilibration back to the starting **1** occurs and the slightly more stable isomer **2b** is the major product.[†] Accordingly, when similar reaction conditions (*t*-BuOK in THF at 0°C) were applied to **2a**, the product mixture was essentially identical to that obtained in the reaction of **1** with *t*-BuOK.

Isomeric components **2a** and **2b** could be separated by $SiO_2$ chromatography and the stereochemistry of these dimers was partly determined by analysis of the $^1$H NMR coupling

*Keywords*: fluorine and compounds; lactones; Michael reactions; stereochemistry.

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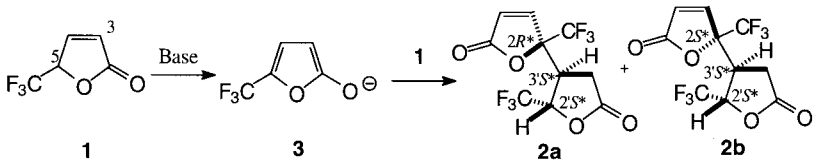
[†] According to the X-ray structure of **2b** and the $^1$H NMR spectra of **2ab**, unfavorable steric interaction between the trifluoromethyl group and γ-butyorolactone ring appears to exist in **2a**.


PII: S0040-4020(00)00581-0

**Table 1.** Product ratios of Michael dimerization of trifluoromethyl-2(5*H*)-furanone (**1**)




| Entry | Base | Conditions | Yields[a] **2a** (%), **2b** (%) | Conversion (%) |
|---|---|---|---|---|
| 1 | $Li_2CO_3$ (1.0 equiv.) | RT/1 v/v% $H_2O$–THF/3 h | 88, 2 (71, –)[b] | 95 |
| 2 | DBU (1.0 equiv.) | 0°C/1 v/v% $H_2O$–$Et_2O$/1 h | 65, 16 | 88 |
| 3 | *t*-BuOK (1.0 equiv.) | 0°C/$Et_2O$/1 h | 23, 41 (14, 29)[b] | 96 |
| 4 | 10 M NaOH (3.0 equiv.) | RT/5 v/v% THF/15 min | 1.9, 2.6 | 100 |
| 5 | 1 M NaOH (0.3 equiv.) | RT/5 v/v% THF/30 min | 67, 12 | 97 |
| 6 | 0.7 M NaOH (0.2 equiv.) | RT/5 v/v% THF/1 h | 82, 11 | 94 |
| 7 | 0.1 M NaOH (0.3 equiv.) | RT/33 v/v% THF/5 d | 71.7 | 81 |
| 8 | 0.01 M NaOH (0.03 equiv.) | RT/33 v/v% THF/41 d | 62.3 | 70 |

[a] GLC yields.
[b] Figures in parentheses are isolated yields.

constants, $J_{H4'-H5'}$. Relatively small coupling constants (**2a**: 3.9 Hz and **2b**: 2.1 Hz) suggested that both the products **2ab** seem to have the *trans*-C4′–C5′ stereochemistry. This stereoselectivity can be attributed to the steric effect of trifluoromethyl group in the Michael acceptor. Finally, X-ray single crystal analysis of the minor product **2b** determined the stereochemistry (Fig. 1). Thus, the stereochemistry of the epimeric counterpart **2a** was assigned as shown in Table 1. With regard to the anionic dimerization of α-angelica lactone, a parent methyl derivative of **1**, no rigorous discussion on the stereochemistry seems to be presented.[6] The reported stereochemistry of the Michael addition of butenolide anions is still ambiguous. There are reports of *endo*-selectivity,[7–9] *exo*-selectivity,[10] and low selectivity,[11,12] and there is no mention of which are the kinetic or thermodynamic products. Fukuyama et al.[9] suggested the Diels–Alder mechanism for the *endo*-selective Michael addition of 5-ethylthio-2-trimethylsiloxyfuran using Lewis acid. In the reaction of anion **3**, Diels–Alder mechanism through an *endo*-transition state seems to be unlikely because the transient tricyclic anion intermediate (hemiacetal anion)[13] would be more unstable than unusually stable **3**. However, secondary orbital interaction[‡,14] between C3's of **3** and **1** as in the Diels–Alder mechanism can also operate to control the stereochemistry of dimer **2a** (*endo*-product) in Michael reaction. Furanone **1** is relatively acidic due to the $CF_3$ group and so that anion **3** can be generated even with weaker bases. This mild basic condition for dimerization unveiled the susceptible kinetic stereoselectivity of **1** to **2a**.

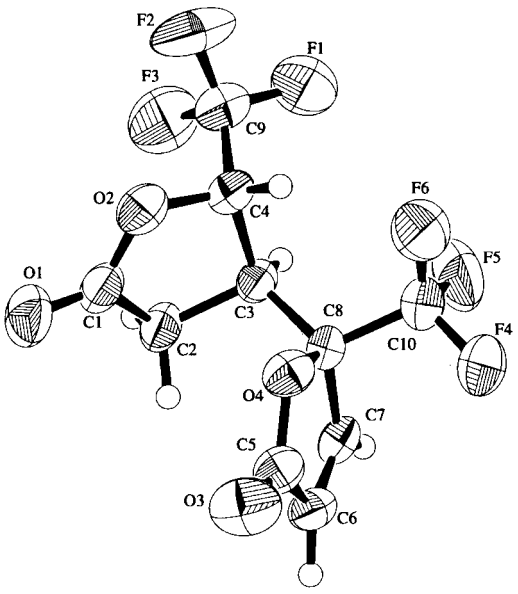



**Figure 1.** Molecular structure of compound **2b**.

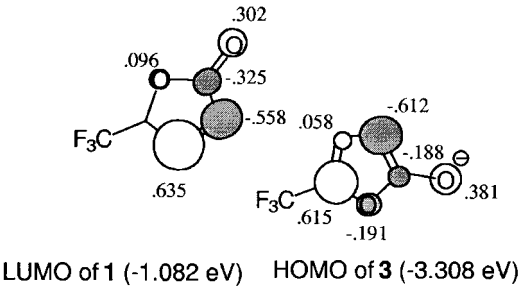


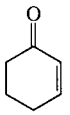
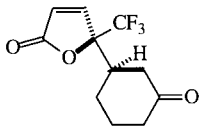
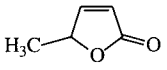
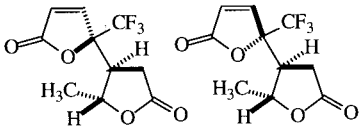
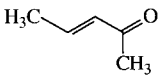
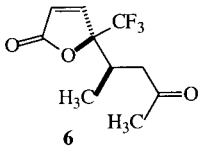

**Figure 2.** The molecular orbital coefficients of the HOMO of **3** and the LUMO of **1** calculated by PM3/MNDO method.

When LDA (1.1 equiv.) was used as a kinetic base at −78°C and the mixture was stirred at room temperature for 5 min, 90% of furanone **1** was recovered after addition of the ethereal solution of HCl. This suggests enolate **3** is highly stable and elimination of fluoride from **3** is unexpectedly slow. This is the reason why the reaction of furanone **1** did not afford the dehydrofluorination product, difluoroprotoanemonin, under relatively strong-base conditions.

The above described unusual relative stability of enolate **3** supports its applicability as a Michael donor. Yoshida also

‡ PM3/MNDO calculation (performed by HyperChem 4.5®) as shown below suggests a favorable secondary orbital interaction in the pseudo-*endo*-transition state at C3 region in the MO interaction of the HOMO of enolate **3** and the LUMO of the furanone **1** (Fig. 2).

**Table 2.** Michael reaction of lactone **1** lithiated with LDA

| entry | Michael acceptors | Products | Yields (%) |
|---|---|---|---|
| 1 |  |  **4** | 49 |
| 2 |  |  **5a** **5b** | 50 (86 : 14)[a] |
| 3 |  |  **6** | 43 |

[a] Isomeric ratio was determined by the $^1$H NMR spectrum.

reported facile 1,4-addition of furanone **1** to some reactive Michael acceptors under mild conditions using $K_2CO_3$ as a base.[2] However, **1** is also a good Michael acceptor and we have found that competitive reaction with a poor Michael acceptor gives only a mixture of dimers **2ab**. For example, reaction of 2-cyclohexenone with furanone **1** in the presence of a catalytic amount of $Li_2CO_3$ gave only a mixture of dimers **2ab**. Alternatively, enolate **3** was formed by lithiation of furanone **1** with 1.1 equiv. of LDA[13] at −78°C and was reacted with 2-cyclohexenone at that temperature and then gradually warmed up to room temperature. In this way, 1,4-adduct **4** was stereoselectively obtained in 49% yield (Table 2, entry 1). Similarly, β-angelica lactone and (*E*)-3-penten-2-one gave corresponding Michael products **5ab** and **6**, stereoselectively (entries 2 and 3). While the stereochemistry of these products is uncertain at present because these products were not solid at room temperature, similar consideration of secondary orbital interactions in the transition state for the kinetic products suggests that these are all *endo*-products.

## Experimental

$^1$H NMR spectra were recorded in $CDCl_3$ at 200 or 300 MHz with TMS as an internal standard. $^{19}$F NMR spectra were recorded in $CDCl_3$ at 282 MHz. Chemical shifts of $^{19}$F NMR spectra were reported in ppm ($\delta$) relative to $CFCl_3$ using $CF_3COOEt$ as an internal standard ($\delta$ −75.75).

**(2*R**,2′*S**,3′*S**)-2,2′-Bis(trifluoromethyl)-3′,4′-dihydro-2,3′-bifuran-5′(2*H*,2′*H*)-dione (2a).** Trifluoromethylfuranone **1** (77 mg, 0.50 mmol) was dissolved in THF (5 mL) and $H_2O$ (50 μL). To the stirring mixture, $Li_2CO_3$ (37 mg, 0.50 mmol) was added in one portion at 0°C. The resulting mixture was stirred at the temperature for 1 h and then diluted with $H_2O$ (10 mL). The mixture was extracted with ether and the combined extract was dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was recrystallized from EtOH to give dimer **2a** as colorless needles: 55 mg (71%); mp 94–95°C, $^1$H NMR (200 MHz) $\delta$ 7.375 (1H, dq, *J*=5.8, 0.8 Hz), 6.618 (1H, d, *J*=5.8 Hz), 4.488 (1H, qd, *J*=6.1, 3.9 Hz), 3.413 (1H, ddd, *J*=9.8, 5.6, 3.9 Hz), 2.994 (1H, dd, *J*=19.0, 9.8 Hz), 2.827 (1H, dd, *J*=19.0, 5.6 Hz); $^{19}$F NMR $\delta$ −75.19 (3F, s), −78.99 (3F, d, *J*=6.1 Hz); MS *m/z* (%) 304 (3.7, $M^+$), 235 (13), 152 (8.5), 151 (100), 83 (13), 69 (39), 55 (39). HRMS Found: $M^+$; 304.0173. Required for $C_{10}H_6O_4F_6$; 304.0170.

**(2*R**,2′*R**,3′*R**)-2,2′-Bis(trifluoromethyl)-3′,4′-dihydro-2,3′-bifuran-5,5′(2*H*,2′*H*)-dione (2b).** Trifluoromethylfuranone **1** (152 mg, 1.0 mmol) was dissolved in anhydrous $Et_2O$ (10 mL). To the stirring mixture, KO$^t$Bu (112 mg, 1.0 mmol) was added in one portion at 0°C. The resulting mixture was stirred at the temperature for 40 min. After filtration of the reddish–brown mixture, the solvent was removed under reduced pressure. The residue was chromatographed on a silica gel column (4:1 hexane–EtOAc). Dimer **2a**: 21 mg (14%). Dimer **2b**: 44 mg (29%); mp 165–166°C; $^1$H NMR (200 MHz) $\delta$ 7.356 (1H, d, *J*=5.8 Hz), 6.635 (1H, d, *J*=5.8 Hz), 4.763 (1H, qd, *J*=6.2, 2.1 Hz), 3.435 (1H, ddd, *J*=10.8, 2.8, 2.1 Hz), 2.973 (1H, dd, *J*=18.8, 10.8 Hz), 2.494 (1H, dd, *J*=18.8, 2.8 Hz); $^{19}$F NMR $\delta$ −75.02 (3F, s), −79.43 (3F, d, *J*=6.2 Hz); MS *m/z* (%) 304 (0.6, $M^+$), 235 (21), 152 (11), 151 (100), 83 (14), 69 (46), 55 (33). HRMS Found: $M^+$; 304.0172. Required for $C_{10}H_6O_4F_6$; 304.0170.

X-Ray crystallographic data of **2b**: triclinic cell; dimensions, *a*=7.790(1) Å, *b*=13.005(2) Å, *c*=6.291(2) Å, $\alpha$=99.41(2)°, $\beta$=101.94(2)°, $\gamma$=104.69(1)°; V=587.3(2) Å$^3$; *Z*=2, Space group, $P\bar{1}$(#2); $D_{calcd}$=1.720 g/cm$^3$; *R*=0.045.

### GLC yields determination of dimers 2ab

Trifluoromethylfuranone **1** (52 mg, 0.33 mmol) was dissolved

in the solvent given in Table 1 (2–5 mL). To the stirring mixture, the base or the solution containing base given in Table 1 was added in one portion. After stirring for a period of reaction time shown in Table 1, a THF solution of internal standard (benzophenone) was added, and the resulting mixture was immediately analyzed by GLC (silicone OV-17: a 2-m packed column).

**3-[5-(Trifluoromethyl)-2(5*H*)-furanon-5-yl]cyclohexanone (4).** To a $Et_2O$ solution of LDA (0.6 mmol; 10 mL), $Et_2O$ solution (2 mL) of furanone 1 (77 mg, 0.5 mmol) was added at −78°C in 1 min. The mixture was stirred for 5 min, and then $Et_2O$ solution (1 mL) of 2-cyclohexenone (100 mg, 1.0 mmol) was added at that temperature. The mixture was stirred at −78°C for more 2 h and warmed up to room temperature. To the mixture, a saturated hydrogen chloride $Et_2O$ solution (2 mL) and $Et_2O$ (30 mL) were added. After filtration of the precipitates, the solvent was removed under reduced pressure. The residue was chromatographed on a $SiO_2$ column (hexane–EtOAc, 2:1) to give lactone **4** as pale yellow oil: 61 mg (49%); $^1$H NMR (300 MHz) $\delta$ 7.414 (1H, d, $J$=5.7 Hz), 6.422 (1H, d, $J$=5.7 Hz), 2.70–2.55 (2H, m), 2.440 (1H, br d, $J$=14.1 Hz), 2.33–2.11 (3H, m), 1.967 (1H, br d, $J$=13.2 Hz), 1.668 (1H, qdd, $J$=12.8, 4.5, 3.3 Hz), 1.484 (1H, qd, $J$=12.6, 3.0 Hz); $^{19}$F NMR $\delta$ −73.71 (s). Anal. Calcd for $C_{11}H_{11}F_3O_3$: C; 53.23, H; 4.47. Found: C; 53.01, H; 4.18.

**2′-Methyl-2-(trifluoromethyl)-3′,4′-dihydro-2,3′-bifuran-2,2′(5*H*,5′*H*)-dione (5).** To a THF solution of LDA (1.1 mmol; 10 mL), THF solution (1 mL) of furanone **1** (152 mg, 1.0 mmol) was added at −78°C in 5 min. The mixture was stirred for 5 min, and then THF solution (1 mL) of β-angelica lactone (98 mg, 1.0 mmol) was added at that temperature. The mixture was stirred at −78°C for more 2 h and warmed up to room temperature. To the mixture, a saturated hydrogen chloride $Et_2O$ solution (2 mL) and $Et_2O$ (30 mL) were added. After filtration of the precipitates, the solvent was removed under reduced pressure. The residue was chromatographed on a $SiO_2$ column (hexane–EtOAc, 2:1) to give a mixture of stereoisomers **5ab** as pale yellow oil: 124 mg (50%); $^1$H NMR (500 MHz) **5a**: $\delta$ 7.326 (0.86H, d, $J$=5.5 Hz), 6.441 (0.86H, d, $J$=5.5 Hz), 4.219 (0.86H, dq, $J$=6.5, 6.0 Hz), 2.860 (0.86H, td, $J$=8.5, 6.5 Hz), 2.783 (0.86H, ddq, $J$=18.0, 8.5, 2.0 Hz), 2.717 (0.86H, ddq, $J$=18.0, 8.5, 1.0 Hz), 1.375 (2.58H, d, $J$=6.0 Hz); **5b**: $\delta$ 7.356 (0.14H, d, $J$=6.0 Hz), 6.483 (0.14H, d, $J$=6.0 Hz), 4.363 (0.14H, dq, $J$=6.0, 6.0 Hz), 2.944 (0.14H, ddd, $J$=10.0, 8.0, 6.0 Hz), 2.759 (0.14H, dd, $J$=17.0, 11.0 Hz), 2.448 (0.14H, ddq, $J$=17.0, 8.5, 0.5 Hz), 1.424 (0.42H, d, $J$=6.0 Hz); $^{19}$F NMR $\delta$ −74.28 (s). Anal. Calcd for $C_{10}H_9F_3O_4$: C; 48.01, H; 3.63. Found: C; 47.97, H; 3.79.

**5-(1-Methyl-3-oxobutyl)-5-(trifluoromethyl)furan-2(5*H*)-one (6).** To a THF solution of LDA (1.1 mmol; 10 mL), THF solution (1 mL) of furanone **1** (152 mg, 1.0 mmol) was added at −78°C in 5 min. The mixture was stirred for 5 min, and then THF solution (1 mL) of (*E*)-3-penten-2-one (70% pure; 360 mg, 3.0 mmol) was added at that temperature. The mixture was stirred at −78°C for more 2 h and warmed up to room temperature. To the mixture, a saturated hydrogen chloride $Et_2O$ solution (2 mL) and $Et_2O$ (30 mL) were added. After filtration of the precipitates, the solvent was removed under reduced pressure. The residue was distilled with Kugel–Rohr distillatory apparatus (200°C/3 mmHg) to give ketone as colorless oil: 102 mg (43%); $^1$H NMR (300 MHz) $\delta$ 7.386 (1H, d, $J$=6.0 Hz), 6.388 (1H, d, $J$=6.0 Hz), 3.035 (1H, dqd, $J$=9.3, 6.9, 3.3 Hz), 2.683 (1H, dd, $J$=18.3, 3.3 Hz), 2.262 (1H, dd, $J$=18.3, 9.3 Hz), 2.155 (3H, s), 1.025 (3H, d, $J$=6.9 Hz); $^{19}$F NMR $\delta$ −75.99 (s). Anal. Calcd for $C_{10}H_{11}F_3O_3$: C; 50.85, H; 4.69. Found: C; 50.52, H; 4.40.

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