Ultrasound-Promoted Synthesis of Fluorinated β-Keto-γ-butyrolactones

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A number of β-keto-γ-butyrolactones and tetronic acids bearing a fluorine atom or a trifluoromethyl group were prepared by the ultrasound-promoted, Reformatsky-type reaction of O-trimethylsilylated cyanohydrins and ethyl α-fluoro(or α-trifluoromethyl)bromoacetate.

A variety of natural products with an unsaturated γ-butyrolactone ring as a common structural feature have been studied for the last two decades[1,2]. However, studies on the fluorinated γ-butyrolactone derivatives remain unexplored from a practical point of view.

In fact, we found that it was not easy to prepare the fluorinated γ-butyrolactones with the usual Reformatsky-type reaction of ethyl α-fluoro(or α-trifluoromethyl) bromoacetate (2), probably due to the low stability or low reactivity of fluoroalkylmetallic reagents[3-6].

Recently, we have reported that ultrasound[7,8] has been utilized in fluorine chemistry to accelerate a number of synthetically useful reactions[9-11], such as "Grignard-type" and "Reformatsky-type" reactions. As part of our continuing study to prepare new useful fluorinated materials by ultrasound-promoted reactions, we now wish to report a practical method for the synthesis of fluorinated γ-butyrolactones, which are expected to have significant biological activity[12,13].
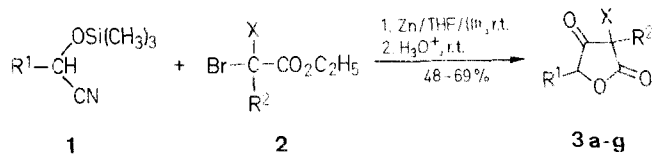

3	R^1	R^2	X	3	R^1	R^2	X
a	CH$_3$	H	F	e	4-CH$_3$OC$_6$H$_4$	H	F
b	CH$_3$	CH$_3$	F	f	CH$_3$	H	CF$_3$
c	C$_6$H$_5$	H	F	g	C$_6$H$_5$	H	CF$_3$
d	C$_6$H$_5$	CH$_3$	F				

A Reformatsky-type reaction between O-trimethylsilylated cyanohydrins (1)[2] and ethyl α-fluorobromoacetate (2; X = F, R^2 = H) proceeded at room temperature with the assistance of ultrasonic irradiation. Without ultrasonic promotion, the reaction did not proceed at all. Using commercially available, unactivated zinc powder in tetrahydrofuran (dried over 4A molecular sieves) the corresponding β-keto-γ-butyrolactones (3) were obtained after acid hydrolysis of reaction intermediates. In addition to ethyl α-fluorobromoacetate[11], ethyl α-trifluoromethylbromoacetate[14] was used, and the corresponding β-keto-γ-butyrolactones with the trifluoromethyl group were obtained.

The structures of the fluorinated β-keto-γ-butyrolactones obtained were confirmed by their ^{19}F- and ^{1}H-NMR and mass spectra. In the cases where R^2 = H, the ^{19}F-NMR

spectra in DMSO-d_6 solution revealed only one signal at ca. − 5(CF$_3$) and/or ca. + 110(CF) ppm from external trifluoroacetic acid, while in the ^{1}H-NMR spectra one broad signal due to the OH proton appeared at ca. 11 ppm, in addition to the other signals due to alkyl or aryl protons. Furthermore, no absorption band due to a carbonyl group except for the lactone group was observed in the spectra of these γ-butyrolactones. These results suggest that the tetronic acid type structure is preferred to the β-keto-γ-butyrolactone type one. This may be ascribed to the hydrogen bond formation between the oxygen atom and the fluorine atom, which stabilizes the enol form rather than the keto form.
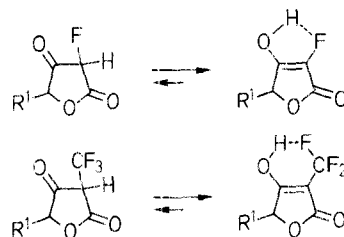
On the other hand, the β-keto-γ-butyrolactone structure is reasonable for compounds 3 where R^2 ≠ H.

α-Phenyl-γ-fluorotetronic acid (3c):

Into a 100 ml 3-necked flask equipped with a dry-ice condenser, are placed commercially available zinc powder (3.92 g, 0.06 g-atom), the O-trimethylsilylated cyanohydrin of benzaldehyde (5.1 g, 25 mmol) and tetrahydrofuran (30 ml). Ethyl α-fluorobromoacetate (3.70 g, 20 mmol) in tetrahydrofuran (5 ml) is added to the mixture and irradiated in the water bath of an ultrasonic laboratory cleaner (32 KHz; 35 W). After 2 h of irradiation, the reaction mixture is poured onto a mixture of ice (300 g) and conc. sulfuric acid (20 ml), and then allowed to stand at room temperature overnight. The organic layer is extracted with several portions of ethyl acetate, and dried over anhydrous magnesium sulfate. After removing the solvent, the crude product is recrystallized from ethanol to afford 3c; yield: 2.40 g (62%); m.p. 102–105°C.

C$_{10}$H$_7$FO$_3$ calc. C 61.86 H 3.63
(194.2) found 61.92 3.76

HRMS (20 eV): m/e = 194.174 (calc. for C$_{10}$H$_7$FO$_3$: 194.161).
IR (KBr): ν = 3400–3100, 1725, 1630, 1220, 1160, 1100, 1040 cm^{-1}
^{1}H-NMR (DMSO-d_6): δ = 5.86 (s, 1 H); 7.10–7.30 (m, 5 H$_{arom}$) 10.6 ppm (br s, 1 H).
^{19}F-NMR (DMSO-d_6/external CF$_3$CO$_2$H): δ = + 106 ppm (s).

Table. Fluorinated β-Keto-γ-butyrolactones or Tetronic Acids Prepared

Product 3	Yield[a] [%]	b.p. [°C]/torr (m.p., °C)	Molecular Formula[b]	^{1}H-NMR (DMSO-d_6) δ [ppm]	^{19}F-NMR (DMSO-d_6/CF$_3$CO$_2$H) δ [ppm]
a	51	80–82/25	C$_5$H$_5$FO$_3$ (132.1)	1.28 (d, 3H, J = 5.7 Hz); 5.74 (q, 1H, J = 5.7 Hz); 10.8 (br s, 1H)	+ 108 (s)
b	65	81–85/15	C$_6$H$_7$FO$_3$ (146.1)	1.26 (d, 3H, J = 6.0 Hz); 1.30 (d, 3H, J = 5.6 Hz); 5.69 (q, 1H, J = 6.0 Hz)	+ 112 (q, J_{F-CH_3} = 5.6 Hz)
c	62	(102–105)	C$_{10}$H$_7$FO$_3$ (194.2)	5.86 (s, 1H); 7.10–7.30 (m, 5H$_{arom}$); 10.6 (br s, 1H)	+ 106 (s)
d	69	(121–123)	C$_{11}$H$_9$FO$_3$ (208.2)	1.31 (d, 3H, J = 5.6 Hz); 5.82 (s, 1H); 7.10–7.30 (m, 5H$_{arom}$)	+ 113 (q, J_{F-CH_3} = 5.6 Hz)
e	56	(113–115)	C$_{11}$H$_9$FO$_4$ (224.2)	2.10 (s, 3H); 5.78 (s, 1H); 7.05–7.30 (m, 4H$_{arom}$); 10.7 (br s, 1H)	+ 109 (s)
f	48	84–86/14	C$_6$H$_5$F$_3$O$_3$ (182.1)	1.27 (d, 3H, J = 6.0 Hz); 5.76 (q, 1H, J = 6.0 Hz); 10.7 (br s, 1H)	− 6.5 (s)
g	53	(118–121)	C$_{11}$H$_7$F$_3$O$_3$ (244.2)	5.84 (s, 1H); 7.10–7.30 (m, 5H$_{arom}$); 10.7 (br s, 1H)	− 6.0 (s)

[a] Yield of isolated product.
[b] Satisfactory microanalyses obtained: C ± 0.25, H ± 0.25.

α-Phenyl-γ-trifluoromethyltetronic acid (3g):

Ethyl α-trifluoromethylbromoacetate (2.4 g, 10 mmol), the O-trimethylsilylated cyanohydrin of benzaldehyde (2.6 g, 13 mmol) and zinc powder (1.9 g, 0.03 g-atom) in tetrahydrofuran (30 ml) are reacted as above to give 3 g; yield: 1.30 g (53%); m.p. 118—121 °C (ethanol).

$C_{11}H_7F_3O_3$　　calc.　C 54.11　　H 2.89
(244.2)　　　　found　　54.33　　　2.68

HRMS (20 eV): m/e = 244.174 (calc. for $C_{11}H_7F_3O_3$: 244.168).

IR (KBr): ν = 3350–3000, 1720, 1640, 1230, 1165, 1105, 1030 cm^{-1}.

^{1}H-NMR (DMSO-d_6): δ = 5.84 (s, 1 H); 7.10–7.30 (m, 5 H$_{arom}$); 10.7 ppm (br s, 1 H).

^{19}F-NMR (DMSO-d_6)/external CF$_3$CO$_2$H): δ = − 6.0 ppm (s).

Other Reformatsky-type reactions were carried out in the same manner and the results are listed in the Table.

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