Organic Chemistry

Reaction of fluoroalkyl-containing 1,3-dicarbonyl compounds with benzylideneacetone

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The reaction of fluoroalkyl-containing 1,3-dicarbonyl compounds with benzylideneacetone with the use of pyridine or triethylamine as a catalyst gave new 3-fluoroalkyl-4-ethoxycarbonyl(acyl)-5-phenylcyclohexan-3-ol-1-ones in yields of 16—33%.

Key words: fluoroalkyl-containing 1,3-dicarbonyl compounds, benzylideneacetone, Michael condensation; cyclization; cyclohexan-3-ol-1-ones.

It is known that base-catalyzed addition to activated olefins (Michael reaction) is typical of 1,3-dicarbonyl compounds.[1] This reaction has been well studied for nonfluorinated 1,3-ketoesters and 1,3-diketones.[2,3] Data on the possible involvement of fluorinated 1,3-dicarbonyl compounds in Michael condensation are available only for the reactions of α- and γ-mono-, α,γ- and γ,γ-di-, and γ,γ,γ-trifluoroacetoacetic esters with methyl vinyl ketone, chalcone, and acrylonitrile.[4] These reactions yield predominantly monoaddition products along with diadducts and cyclohexenones (in the reactions of γ-monofluoro-β-ketoesters with chalcone, with the cyclization proceeding *via* the participation of the acyl group of ketoester).

In this work, we demonstrated that the reactions of fluorine-containing β-ketoesters (**1a,b**) and 1,3-diketones (**1c,d**) with benzylideneacetone in the presence of bases (Et_3N, C_5H_5N, or EtONa) involve monoaddition followed by cyclization at the carbonyl group that is bonded to the fluoroalkyl substituent to yield 3-fluoroalkyl-4-ethoxycarbonyl(acyl)-5-phenylcyclohexan-3-ol-1-ones **2a—d** (Scheme 1).

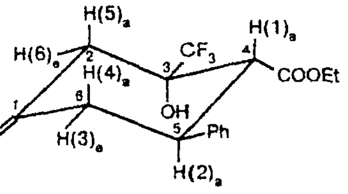
Et_3N is the most preferable catalyst for this reaction, whereas EtONa is of little use because of very low yields (3—5%) of the products obtained in the presence of the latter catalyst.

Note the stability of cyclohexanolones obtained. These compounds do not undergo dehydration upon heating in air or *in vacuo* or upon boiling in toluene with azeotropic distillation of water.

In the ^1H and ^{19}F NMR spectra of product **2a** in $CDCl_3$, sets of signals of two isomers (apparently epimers with respect to the C(4) atom, Table 1) were observed in a ratio of 4 : 1.

To simplify identification of the ^1H NMR spectrum, we used pyridine-d_5, which exhibits anisotropic properties.[5] Besides, the use of this solvent (as a base) leads to conversion of the mixture to one epimer. Therefore, the ^{19}F NMR spectrum in pyridine-d_5 showed only one signal of the CF_3 group, whereas in the ^1H NMR spectrum, a set of signals of the ethyl fragment was observed (see Table 1).

Based on the ^1H NMR spectral data, it can be assumed that in pyridine-d_5 cyclohexanolone **2a** has a chair conformation with the equatorial orientations of the phenyl, ethoxycarbonyl, and, apparently, trifluoromethyl substituents.



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Scheme 1

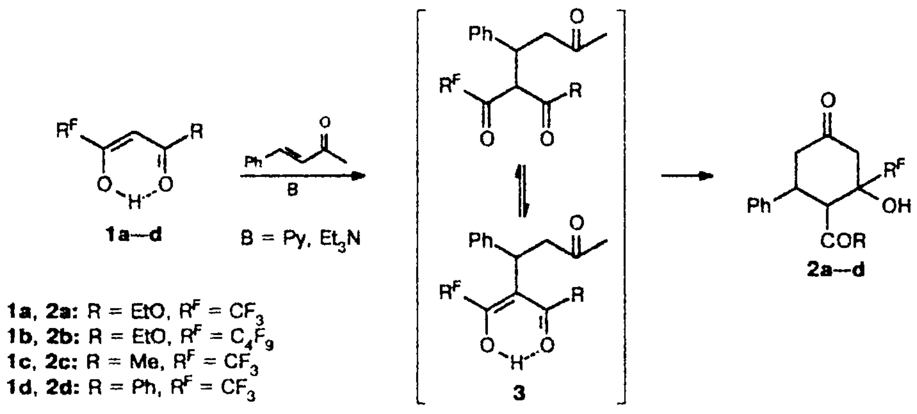

Table 1. Principal characteristics of compounds **2a—d**

Compo-und	Yield (%) [M.p./°C]	Found / Calculated (%) C	H	F	Molecular formula	IR, ν/cm^{-1}	NMR (pyridine-d_5)[a] δ ^{1}H (J/Hz, Δν/Hz)	δ ^{19}F
2a[b]	30 (*A*) 33 (*B*) [181—182]	58.00 58.18	5.53 5.19	17.44 17.26	$C_{16}H_{17}F_3O_4$	1710 (C=O); 1725 (COOEt); 3300 (OH)	0.80 (t, 3 H, Me, ^3J = 7.2); 2.92 (m, 2 H, C(6)H_aH_e, AB system, Δν = 23.0, $^2J_{ae}$ = −15.0, $^3J_{H_aH_aC(5)}$ = 12.0, $^3J_{H_eH_aC(5)}$ = 5.0, $^4J_{H_eH_eC(2)}$ = 1.1); 3.19 (m, 2 H, 2 CH_aH_e, AB system, Δν = 13.0, $^2J_{ae}$ = −14.0, $^4J_{H_eH_eC(6)}$ = 1.1); 3.80 (q, 2 H, CH_2O); 3.94 (d, 1 H, H_aC(4), $^3J_{H_aH_aC(5)}$ = 13.0); 4.16 (dt, 1 H, C(5)H_a, $^3J_{H_aH_aC(6)}$ = $^3J_{H_aH_aC(4)}$ = 12.0, $^3J_{H_aH_eC(6)}$ = 5.0); 4.80 (br.s, 1 H, OH); 7.20 (m, 5 H, Ph)	80.2 (s, CF_3)
2b[b]	16 (*A*) 21 (*B*) [164—165]	47.18 47.26	3.29 3.37	34.09 33.64	$C_{19}H_{17}F_9O_4$	1710 (C=O); 1725 (COOEt); 3330 (OH)	0.7 (t, 3 H, Me, J = 7.1); 3.8 (q, 2 H, CH_2O, J = 7.1); 2.6—3.5 (m, 6 H, CH, CH_2); 5.2 (br.s, 1 H, OH); 7.3 (m, 5 H, Ph)	81.2 (m, 3 F, CF_3); 117.04—125.4 (m, 6 F, $(CF_2)_3$)
2c	22 [171—172]	60.00 60.00	5.11 5.04	18.98 18.98	$C_{15}H_{15}F_3O_3$	1710 (C=O); 3310 (OH)	2.1 (s, 3 H, Me); 2.4—3.3 (m, 4 H, CH_2); 3.8—4.2 (m, 2 H, CH); 5.1 (br.s, OH); 7.2—7.7 (m, 5 H, Ph)	79.4 (s, CF_3)
2d	25 [197—198]	66.10 66.29	4.75 4.73	15.75 15.73	$C_{20}H_{17}F_3O_3$	1710 (C=O); 1670 (PhC=O); 3300 (OH)	2.6—3.5 (m, 4 H, CH_2); 3.9—4.4 (m, 2 H, CH); 5.2 (br.s, OH); 7.1—7.9 (m, 10 H, Ph)	78.8 (s, CF_3)

[a] Compound **2a**: ^{1}H NMR ($CDCl_3$), δ: 0.80, 0.92 (both t, 3 H, Me, ^3J = 7.2 Hz); 2.52—3.64 (m, 6 H, cyclohexanone); 3.81, 3.89 (both q, 2 H, CH_2O, ^3J = 7.2 Hz); 4.80, 4.91 (both br.s, 2 H, OH); 7.27—7.37 (m, 5 H, Ph). ^{19}F NMR ($CDCl_3$), δ: 82.5, 82.6 (both s, CF_3).

[b] The yields of compounds obtained according to procedures *A* and *B* are given.

Experimental

The IR spectra were recorded on a Specord 75 IR spectrophotometer in the range of 400—4000 cm^{-1} (as Nujol mulls). The ^{1}H NMR spectra were measured on a Tesla BS-567 A spectrometer (100 MHz) relative to $SiMe_4$. The ^{19}F NMR spectra were recorded on a Tesla BS-587 spectrometer (75 Hz) relative to $CFCl_3$.

4-Ethoxycarbonyl-3-trifluoromethyl-5-phenylcyclohexan-3-ol-1-one (2a). *A.* A mixture of ketoester **1a** (1.85 g, 1 mmol), benzylideneacetone (1.46 g, 1 mmol), and pyridine (6 mL) was heated at 80 °C for 4 h, cooled, poured into water (50 mL), and acidified with hydrochloric acid to pH 5. The product was extracted with chloroform (2×25 mL), precipitated with hexane, and recrystallized from *n*-butyl alcohol. Product **2a** was obtained in a yield of 0.99 g (see Table 1).

B. A mixture of ketoester **1a** (5.55 g, 3 mmol), Et_3N (2.2 mL, 3 mmol), and benzylideneacetone (4.38 g, 3 mmol) was heated at 70 °C for 2.5 h and then cooled. Crystals precipitated were filtered off, washed with hexane, and recrystallized from *n*-butyl alcohol. Product **2a** was obtained in a yield of 3.27 g (see Table 1).

4-Ethoxycarbonyl-3-nonafluorobutyl-5-phenylcyclohexan-3-ol-1-one (2b). Product **2b** was prepared according to procedure *A* from ketoester **1b** (3.34 g, 1 mmol), benzylideneacetone (1.46 g, 1 mmol), and pyridine (6 mL) in a yield of 0.81 g (see Table 1).

Product **2b** was prepared according to procedure *B* from ketoester **1b** (10.02 g, 3 mmol), Et_3N (2.2 mL, 3 mmol), and benzylideneacetone (4.38 g, 3 mmol) in a yield of 3.2 g (see Table 1).

4-Acetyl-3-trifluoromethyl-5-phenylcyclohexan-3-ol-1-one (2c). Et_3N (2.2 mL, 3 mmol) was carefully added to diketone **1c** (4.42 g, 3 mmol). Then benzylideneacetone (4.38 g, 3 mmol) was added. The reaction mixture was heated at 70 °C for 5 h and kept at 20 °C for 10 h. The precipitate was filtered off, washed with hexane, and recrystallized from *n*-butyl alcohol. Product **2c** was obtained in a yield of 1.95 g (see Table 1).

4-Benzoyl-3-trifluoromethyl-5-phenylcyclohexan-3-ol-1-one (2d). Product **2d** was obtained analogously to **2c** from diketone **1d** (6.48 g, 3 mmol), Et_3N (2.2 mL), and benzylideneacetone (4.38 g, 3 mmol) in a yield of 2.3 g (see Table 1).

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