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Dedicated to Full Member of the Russian Academy of Sciences N.S. Zefirov on His 70th Anniversary

Synthesis of β-Fluoroalkyl-β,β-dimethoxy Ketones and β-Fluoroalkyl-β-methoxy-α,β-enones

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Abstract—α-Bromo-β-fluoroalkyl-α,β-enones react with sodium methoxide in methanol to give the corresponding β-fluoroalkyl-β,β-dimethoxy ketones which eliminate methanol molecule to produce a mixture of *E*/*Z*-isomeric β-fluoroalkyl-β-methoxyvinyl ketones, the *Z* isomer prevailing.

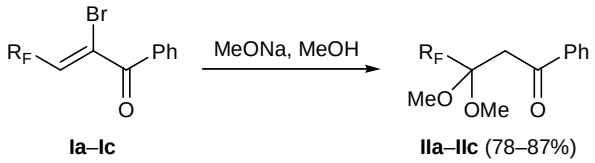
Introduction of fluorine-containing groups into molecules of organic compounds is known to strongly affect their chemical and physical properties, thus making them sometimes unique and important for practical application. Therefore, development of new methods for the synthesis of fluorine-containing compounds is stimulated [1]. An extensively explored strategy in the synthesis of organofluorine compounds, specifically of heterocycles possessing fluoroalkyl substituents, is based on the use of fluorine-containing building blocks. In the recent review [2], such synthons as β-alkoxy-α,β-enones having fluoroalkyl groups were shown to be promising; however, the available data refer to enones in which the fluoroalkyl and alkoxy groups are arranged in the β-position with respect to each other. Chemical properties of regioisomeric enones with geminal arrangement of these groups were not reported; presumably, such compounds are difficult to obtain.

Among known synthetic approaches to β-fluoroalkyl-β-alkoxy enones, the two main methods are based on the Wittig reaction of stabilized phosphorus ylides with fluorinated carboxylic acid esters [3] and reaction of polyfluoroalkylacetones with alkali metal alkoxides [4]. However, the first of these is characterized by poor yields of the target products, while the second is limited due to low accessibility of fluorine-containing reagents.

In the present communication we report on a new approach to the synthesis of β-fluoroalkyl-β,β-dimethoxy ketones via methoxylation of accessible α-bromo-β-polyfluoroalkyl-α,β-enones [5] with sodium methoxide and to β-fluoroalkyl-β-methoxyvinyl ketones which are formed by elimination of methanol from the methoxylation products. The following published data led us to presume that methoxylation of α-bromo-β-polyfluoroalkyl-α,β-enones is possible: (1) reaction of α-bromo-β-polyfluoroalkyl α,β-enones with hydrazine hydrate gives fluoroalkyl-substituted pyrazoles [6] rather than aziridinyl ketones (the latter are formed in the reactions with amines [6, 7]) and (2) treatment of α,β-dibromochalcone with sodium diethylene glycolate yields β-oxo ketone acetal [8].

We have found that fluorinated α-bromo-α,β-enones **Ia**–**Ic** react with 2 equiv of sodium methoxide in methanol to give fluorine-containing β-oxo ketone acetals **IIa**–**IIc** in good yields (Scheme 1). The reaction mixtures obtained from compounds **Ib** and **Ic** also contained small amounts of alkoxy enones **IIIb** and **IIIc** which cannot be removed by vacuum distillation, or the latter were formed via partial demethoxylation of acetals **IIb** and **IIc**. The structure of compounds **IIa**–

Scheme 1.



Ia–**Ic** **IIa**–**IIc** (78–87%)

R_F = CF_3 (**a**), C_3F_7 (**b**), C_4F_9 (**c**).

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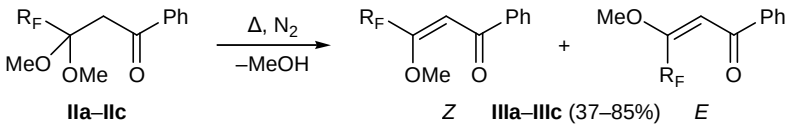
Scheme 2.



IIa–IIc *Z* **IIIa–IIIc** (37–85%) *E*

IIc was confirmed by the presence in their ^{1}H NMR spectra of six- and two-proton multiplets in the regions δ 3.45–3.48 and 3.41–3.50 ppm (quartet for **Ia** and triplets for **IIb** and **IIc**), which were assigned to the two methoxy groups and one methylene group, respectively. The structure of compound **IIa** was additionally confirmed by the ^{19}F and ^{13}C NMR spectra.

Acetals **IIa**–**IIc** fairly readily lose methanol molecule. Compounds **IIIb** and **IIIc** were obtained in high yield (76–85%) by simple distillation of dimethoxy ketones **IIb** and **IIc** under atmospheric pressure (Scheme 2). However, distillation of acetal **IIa** was accompanied by strong tarring, and the maximal yield of enone **IIIa** was only 37%.

Alkoxy enones **IIIa**–**IIIc** exist as mixtures of *Z* and *E* isomers, the former prevailing. The ^{1}H NMR signals were assigned to particular isomers by comparing chemical shifts of the olefinic protons with the corresponding values for fluoroalkyl- and aryl-substituted 1,3-diketones (δ 6.48–6.63 ppm) [9] which were postulated to have *Z* configuration. Signals from the olefinic protons in *Z*-alkoxy enones **IIIa**–**IIIc** appeared in the ^{1}H NMR spectra at δ 6.45–6.49 ppm, while protons of the methoxy group gave signals in the region δ 3.87–3.89 ppm. The corresponding signals of the *E* isomers were located in a stronger field, at δ 5.98–6.01 and 3.83–3.84 ppm, respectively. The downfield position of these signals in the spectra of the *Z* isomers may be explained by deshielding effects of the fluoroalkyl (olefinic protons) and benzoyl groups (methoxy protons). In the ^{19}F NMR spectra of compounds **IIa** and **IIb**, signals from the fluoroalkyl group of the *E* isomers (the characteristic signal of compound **IIb** is that belonging to the CF_2 group linked to the β-carbon atom) are displaced appreciably downfield relative to the corresponding signals of the *Z* isomers: $\Delta\delta_{ZE}$ = 4.51 (**IIa**) and 4.14 ppm (**IIb**). This difference may be caused by strong deshielding effect of the benzoyl group in the *E* isomers.

Thus methoxylation of α-bromo-β-polyfluoroalkyl-α,β-enones by the action of sodium methoxide provides an efficient procedure for the synthesis of β-fluoroalkyl-β,β-dimethoxy ketones which are readily converted into difficultly accessible β-fluoroalkyl-β-methoxy-α,β-enones.

EXPERIMENTAL

The NMR spectra were recorded on a Bruker DRX-400 spectrometer at 400.13 (^{1}H), 100.61 (^{13}C), and 376.47 MHz (^{19}F) using $CDCl_3$ as solvent and tetramethylsilane (^{1}H, ^{13}C) or C_6F_6 (^{19}F) as internal reference. The IR spectra were measured on a Perkin–Elmer Spectrum I instrument from samples prepared as thin films. Initial α-bromo-β-polyfluoroalkyl-α,β-enones **Ia**–**Ic** were synthesized by the procedure described in [5].

β-Fluoroalkyl-β,β-dimethoxy ketones IIa–IIc (*general procedure*). A solution of sodium methoxide [prepared from 0.12 g (5.2 mmol) of metallic sodium and 3 ml of anhydrous methanol] was added dropwise to a solution of 2.5 mmol of α-bromoenone **Ia**–**Ic** in 3 ml of anhydrous methanol. The mixture was stirred for 2 days, 50 μl of acetic acid was added, and the mixture was stirred for 5 min, poured into 50 ml of water, and treated with diethyl ether (5×10 ml). The extracts were dried over Na_2SO_4, the solvent was distilled off, and the residue was purified by recrystallization or chromatography on Al_2O_3 using hexane as eluent.

4,4,4-Trifluoro-3,3-dimethoxy-1-phenylbutan-1-one (IIa). Yield 83%. Colorless crystals, mp 45–46°C (from hexane). IR spectrum, ν, cm^{-1}: 3062, 2956, 2847, 1685. ^{1}H NMR spectrum, δ, ppm: 3.41 q (2H, CH_2, $^4J_{HF}$ = 0.9 Hz), 3.46 q (6H, OCH_3, $^5J_{HF}$ = 1.0 Hz), 7.43–7.97 m (5H, C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 39.30 s (CH_2); 50.73 s (OCH_3); 98.65 q (CF_3**C**, $^2J_{CF}$ = 30.3 Hz); 122.66 q (CF_3, $^1J_{CF}$ = 291.7 Hz); 128.45 s, 128.58 s, 133.13 s, 137.59 s (C_6H_5); 194.29 s (C=O). ^{19}F NMR spectrum: δ_F 84.84 ppm, m (3F, CF_3). Found, %: C 54.90; H 5.05; F 21.54. $C_{12}H_{13}F_3O_3$. Calculated, %: C 54.96; H 5.00; F 21.73.

4,4,5,5,6,6,6-Heptafluoro-3,3-dimethoxy-1-phenylhexan-1-one (IIb). Yield 78%. Colorless viscous liquid. ^{1}H NMR spectrum, δ, ppm: 3.48 t (6H, OCH_3, $^5J_{HF}$ = 1.2 Hz), 3.50 t (2H, CH_2, $^4J_{HF}$ = 1.1 Hz), 7.45–7.97 m (5H, C_6H_5). ^{19}F NMR spectrum, δ_F, ppm: 37.45–37.52 m (2F, CF_2), 43.47–43.63 m (2F, CF_2), 80.99 t (3F, CF_3, $^4J_{FF}$ = 10.4 Hz).

7,7,7,4,4,5,5,6,6-Nonafluoro-3,3-dimethoxy-1-phenylheptan-1-one (IIc). Yield 87%. Colorless viscous liquid. ^{1}H NMR spectrum, δ, ppm: 3.48 t (6H,

OCH_3, $^5J_{HF}$ = 1.1 Hz), 3.51 t (2H, CH_2, $^4J_{HF}$ = 1.0 Hz), 7.45–7.97 m (5H, C_6H_5).

β-Fluoroalkyl-β-methoxyvinyl ketones IIIa–IIIc (*general procedure*). Compound **IIa**–**IIc**, 1 mmol, was heated for 5–10 min at the boiling point in a stream of nitrogen, and the resulting material was distilled first under atmospheric pressure and then in a vacuum.

4,4,4-Trifluoro-3-methoxy-1-phenyl-2-buten-1-one (IIIa). Yield 37%. Light yellow viscous liquid, bp 110–125°C (6 mm). *Z*/*E*-Isomer ratio 62:38. ^{1}H NMR spectrum, δ, ppm: *Z* isomer: 3.88 s (3H, OCH_3), 6.49 s (1H, =CH), 7.46–7.97 m (5H, C_6H_5); *E* isomer: 3.84 d (3H, OCH_3, $^5J_{HH}$ = 0.4 Hz), 6.01 m (1H, =CH), 7.46–7.97 m (5H, C_6H_5). NMR spectrum ^{19}F: *Z* isomer: δ_F 89.88 ppm, s (3F, CF_3); *E* isomer: δ_F 94.39 ppm, d (3F, CF_3, $^4J_{HF}$ = 0.9 Hz). Found, %: C 57.18; H 4.11; F 24.53. $C_{11}H_9F_3O_2$. Calculated, %: C 57.40; H 3.94; F 24.76.

4,4,5,5,6,6,6-Heptafluoro-3-methoxy-1-phenyl-2-hexen-1-one (IIIb). Yield 76%. Transparent viscous liquid, bp 124–142°C (10 mm). *Z*/*E*-Isomer ratio 86:14. IR spectrum, ν, cm^{-1}: 3063, 2951, 1677, 1627, 1598, 1582. ^{1}H NMR spectrum, δ, ppm: *Z* isomer: 3.87 s (3H, OCH_3), 6.48 s (1H, =CH), 7.48–7.95 m (5H, C_6H_5); *E* isomer: 3.83 s (3H, OCH_3), 6.03 s (1H, =CH), 7.48–7.95 m (5H, C_6H_5). ^{19}F NMR spectrum, δ_F, ppm: *Z* isomer: 35.24–35.25 m (2F, CF_2), 44.63 q.m (2F, CF_2, $^4J_{FF}$ = 8.9 Hz), 81.00 t.m (3F, CF_3, $^4J_{FF}$ = 8.9 Hz); *E* isomer: 36.25–36.29 m (2F, CF_2), 48.77 q.m (2F, CF_2, $^4J_{FF}$ = 9.1 Hz), 80.97 t.m (3F, CF_3, $^4J_{FF}$ = 9.1 Hz). Found, %: C 47.38; H 2.89; F 40.11. $C_{13}H_9F_7O_2$. Calculated, %: C 47.29; H 2.75; F 40.27.

4,4,5,5,6,6,7,7,7-Nonafluoro-3-methoxy-1-phenyl-2-hepten-1-one (IIIc). Yield 85%. Light yellow viscous liquid, bp 126–137°C (6 mm). *Z*/*E*-Isomer ratio 89:11. IR spectrum, ν, cm^{-1}: 3067, 2950, 1675, 1629, 1599, 1582. ^{1}H NMR spectrum, δ, ppm: *Z* izomer: 3.87 s (3H, OCH_3), 6.48 s (1H, =CH), 7.48–7.95 m (5H, C_6H_5); *E* izomer: 3.83 s (3H, OCH_3), 6.03 s (1H, =CH), 7.48–7.95 m (5H, C_6H_5). Found, %: C 44.25; H 2.31; F 44.90. $C_{14}H_9F_9O_2$. Calculated, %: C 44.23; H 2.39; F 44.97.

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