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SHORT COMMUNICATIONS

Reaction of Ethyl 3-(1-Adamantyl)-3-oxopropanoate with Fluorobenzoyl Chlorides

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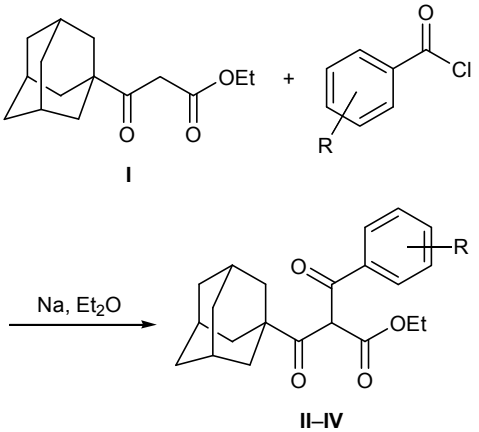
Introduction of fluorine atoms into organic molecules essentially modifies their biological activity, in many cases enhancing their efficiency as medical agents and chemical means for plant protection [1–4]. On the other hand, a number of effective drugs for various destinations contain an adamantane fragment as pharmacophoric base [5]. In this connection, development of a general procedure for the synthesis of acyclic and heterocyclic compounds containing fluorine atoms and adamantane fragment in a single molecule as novel biologically active substances is an important problem.

We previously reported [6] on the acylation of ethyl 3-(1-adamantyl)-3-oxopropanoate (**I**), ethyl acetoacetate, and ethyl cyanoacetate with adamantanecarbonyl chloride and adamantylacetyl chloride. As a result, we isolated only the corresponding C-acylation products. With a view to obtain compounds containing both fluorine atoms and an adamantane fragment, we examined acylation of ester **I** with 4-fluoro-, 2,3,4,5-tetrafluoro-, and 2-chloro-4-fluorobenzoyl chlorides (Scheme 1). In the IR spectra of compounds **II**–**IV** thus obtained we observed absorption bands assignable to stretching vibrations of ester carbonyl group at 1732–1744 cm^{-1} and two ketone carbonyl groups (two bands in the region 1647–1705 cm^{-1}). Compounds **II**–**IV** displayed in the ^1H NMR spectra a signal from one CH proton at δ 5.73–6.42 ppm. These findings indicated that we isolated only the corresponding C-acylation products, ethyl 3-(1-adamantyl)-2-(fluorobenzoyl)-3-oxopropanoates **II**–**IV**.

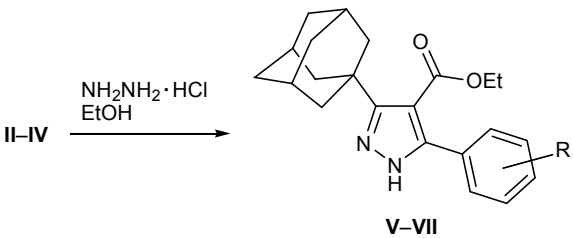
Compounds **II**–**IV** attract specific interest due to the presence in their molecules of three electrophilic centers, two ketone carbonyl groups and one ester moiety. Therefore, it was reasonable to examine their reactions with nucleophiles, in particular with hydrazine and its derivatives. It is known that such reactions could involve both ketone and ester carbonyl groups, depending on the conditions [7]. By reactions of diketo esters **II**–**IV** with hydrazine hydrate in alcohol we obtained mixtures of 3-adamantylpyrazol-5-one [8] and the corresponding fluorobenzoic acid hydrazides.

Scheme 1.



II, R = 4-F; **III**, R = 2,3,4,5-F_4; **IV**, R = 2-Cl-4-F.

Scheme 2.



V, R = 4-F; **VI**, R = 2,3,4,5-F_4; **VII**, R = 2-Cl-4-F.

However, compounds **II**–**IV** reacted with hydrazine hydrochloride in ethanol (under "milder" conditions) to give pyrazoles **V**–**VII** (Scheme 2). In this case, the reaction involved only ketone carbonyl groups in the substrate, whereas the ester group remained intact.

Ethyl 3-(1-adamantyl)-2-(4-fluorobenzoyl)-3-oxopropanoate (II). A mixture of 2.00 g (8 mmol) of ester **I** [9] and 0.18 g (8 mmol) of metallic sodium in 30 ml of anhydrous diethyl ether was stirred for 24 h at room temperature, 1.27 g (8 mmol) of 4-fluorobenzoyl chloride was added over a period of 2 h, and the mixture was heated for 2 h under reflux, cooled, poured into water, and acidified with 2% sulfuric acid. The organic phase was separated and dried over sodium sulfate, the solvent was distilled off, and the residue was recrystallized from petroleum ether (bp 40–60°C). Yield 1.87 g (63%), colorless crystals, mp 126–128°C. IR spectrum, ν, cm^{-1}: 2908, 2854 (C−H_{Ad}), 1744 (C=O, ester), 1705, 1682 (C=O, ketone), 1597 (C–C_{arom}), 852, 821 (δC–H_{arom}). ^{1}H NMR spectrum, δ, ppm: 1.09 t (3H, CH_3), 1.49–1.92 m (15H, Ad), 4.04 q (2H, OCH_2), 6.42 s (1H, CH), 7.34 d (2H, H_{arom}), 7.98 d (2H, H_{arom}). Found, %: C 70.85; H 6.54. $C_{22}H_{25}FO_4$. Calculated, %: C 70.97; H 6.72.

Compounds **III** and **IV** were synthesized in a similar way.

Ethyl 3-(1-adamantyl)-3-oxo-2-(2,3,4,5-tetrafluorobenzoyl)propanoate (III) was synthesized from 2.00 g (8 mmol) of ester **I** and 1.70 g (8 mmol) of 2,3,4,5-tetrafluorobenzoyl chloride. Yield 2.66 g (78%), colorless crystals, mp 266–268°C. IR spectrum, ν, cm^{-1}: 2908, 2854 (C−H_{Ad}), 1740 (C=O, ester), 1686, 1647 (C=O, ketone), 1593 (C–C_{arom}), 806, 787, 763 (δC–H_{arom}). ^{1}H NMR spectrum, δ, ppm: 0.90 t (3H, CH_3), 1.26–2.18 m (15H, Ad), 4.22 q (2H, OCH_2), 5.73 s (1H, CH), 7.35 q (1H, H_{arom}). Found, %: C 61.99; H 5.36. $C_{22}H_{22}F_4O_4$. Calculated, %: C 61.97; H 5.16.

Ethyl 3-(1-adamantyl)-2-(2-chloro-4-fluorobenzoyl)-3-oxopropanoate (IV) was synthesized from 2.00 g (8 mmol) of ester **I** and 1.54 g (8 mmol) of 2-chloro-4-fluorobenzoyl chloride. Yield 1.66 g (51%), colorless crystals, mp 179–180°C. IR spectrum, ν, cm^{-1}: 2908, 2854 (C−H_{Ad}), 1732 (C=O, ester), 1697 (C=O, ketone), 1596 (C–C_{arom}), 914, 872 (δC–H_{arom}). ^{1}H NMR spectrum, δ, ppm: 1.19 t (3H, CH_3), 1.63–1.96 m (15H, Ad), 4.13 q (2H, OCH_2), 5.79 s (1H, CH), 7.27 m (2H, H_{arom}), 7.70 m (1H, H_{arom}). Found, %: C 65.27; H 6.05. $C_{22}H_{24}O_4ClF$. Calculated, %: C 65.02; H 5.91.

Ethyl 3-(1-adamantyl)-5-(4-fluorophenyl)-1*H*-pyrazole-4-carboxylate (V). Hydrazine hydrochloride, 0.04 g (0.39 mmol), was added to a solution of 0.12 g (0.32 mmol) of compound **II** in 5 ml of ethanol, the mixture was stirred for 16 h at room temperature and heated for 3 h at 80°C, and the precipitate was filtered off and recrystallized from ethanol. Yield 0.09 g (80%), colorless crystals, mp 176–178°C. IR spectrum, ν, cm^{-1}: 3240 (N−H), 2908, 2851 (C−H_{Ad}), 1713 (C=O), 1608 (C–C_{arom}), 840, 813 (δC–H_{arom}). ^{1}H NMR spectrum, δ, ppm: 1.00 t (3H, CH_3), 1.71–2.12 m (15H, Ad), 3.99 q (2H, OCH_2), 7.14 d (2H, H_{arom}), 8.22 d (2H, H_{arom}), 10.05 br.s (1H, NH). Found, %: C 71.89; H 6.92; N 7.56. $C_{22}H_{25}FN_2O_2$. Calculated, %: C 71.74; H 6.79; N 7.61.

Compounds **VI** and **VII** were synthesized in a similar way.

Ethyl 3-(1-adamantyl)-5-(2,3,4,5-tetrafluorophenyl)-1*H*-pyrazole-4-carboxylate (VI) was synthesized from 0.12 g (0.28 mmol) of compound **III** and 0.04 g (0.39 mmol) of hydrazine hydrochloride. Yield 0.08 g (71%), colorless crystals, mp 301°C. IR spectrum, ν, cm^{-1}: 3234 (N−H), 2908, 2851 (C−H_{Ad}), 1710 (C=O), 1604 (C–C_{arom}), 837 (δC–H_{arom}). ^{1}H NMR spectrum, δ, ppm: 1.17 t (3H, CH_3), 1.79–2.23 m (15H, Ad), 4.15 q (2H, OCH_2), 8.10 q (1H, H_{arom}), 9.88 br.s (1H, NH). Found, %: C 62.64; H 5.34; N 6.98. $C_{22}H_{22}F_4N_2O_2$. Calculated, %: C 62.56; H 5.21; N 6.64.

Ethyl 3-(1-adamantyl-5-(2-chloro-4-fluorophenyl)-1*H*-pyrazole-4-carboxylate (VII) was synthesized from 0.12 g (0.30 mmol) of compound **IV** and 0.04 g (0.39 mmol) of hydrazine hydrochloride. Yield 0.075 g (63%), colorless crystals, mp 210–211°C. IR spectrum, ν, cm^{-1}: 3230 (N−H), 2908, 2851 (C−H_{Ad}), 1710 (C=O), 1604 (C–C_{arom}), 842, 810 (δC–H_{arom}). ^{1}H NMR spectrum, δ, ppm: 1.05 t (3H, CH_3), 1.85–2.10 m (15H, Ad), 4.07 q (2H, OCH_2), 7.87 m and 8.22 m (3H, H_{arom}), 10.10 br.s (1H, NH). Found, %: C 65.78; H 5.23; N 6.94. $C_{22}H_{24}ClFN_2O_2$. Calculated, %: C 65.51; H 5.46; N 6.95.

The IR spectra were measured in KBr on a Shimadzu FTIR-8400S spectrometer. The ^{1}H NMR spectra were recorded on a Bruker AM 300 instrument at 300 MHz using DMSO-d_6 as solvent and tetramethylsilane as internal reference. The elemental compositions were determined on a Thermo Finnigan Flash 1112 NCH analyzer. The purity of the products was checked by TLC (Silufol) and GLC.

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