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Adamantyl-Containing Fluorinated 1,3-Diketones

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Abstract—A convenient one-step procedure has been developed for the synthesis of fluorine-containing 2-(adamant-1-yl)-1,3-diketones by reaction of fluorinated 1,3-diketones with 1,3-dehydroadamantane. The products can be used as starting compounds for the preparation of new fluorinated adamantyl-containing heterocyclic compounds.

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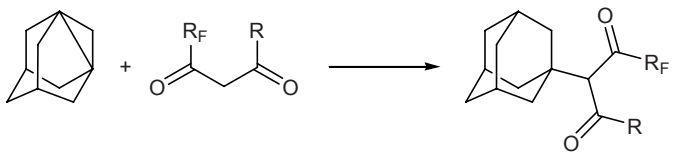
Introduction of fluorine atoms into molecules of organic compounds essentially changes their biological activity and in many cases enhances their efficiency as medical agents and agrochemicals [1–3]. The effect is fairly strong in the case of such modification of heterocyclic compounds [4]. On the other hand, molecules of many effective drugs possessing various pharmacological activities contain an adamantane moiety as key pharmacophoric fragment [5].

Development of a general method for the synthesis of acyclic and heterocyclic compounds containing both fluorine atoms and an adamantane fragment attracts strong interest from the viewpoint of design of new biologically active substances. The goal of the present work was to synthesize adamantyl-containing fluorinated β-diketones in which the adamantanyl substituent is attached to the carbon atom located between the carbonyl groups. Fluorinated 1,3-diketones per se exhibit biological activity [6]; on the other hand, they are multipurpose synthons for the preparation of various fluorinated heterocyclic compounds which are also extensively studied as drugs and pesticides [4].

Introduction of an adamantyl fragment into fluorinated β-diketone molecules via commonly used C-alkylation at the activated methylene group is feasible only in rare cases [6], while their C-adamantylation has not been reported. We have found that C-adamantylation of fluorinated β-diketones at the methylene carbon atom can be successfully accomplished with the use of tetracyclo[$3.3.1.1^{3,7}.0^{1,3}$]decane (**I**, 1,3-dehydroadamantane) as alkylating agent. We previously synthesized the corresponding adamantyl-containing β-dicarbonyl compounds by reaction of compound **I** with keto esters and cyclic β-diketones [7, 8].

In fact, 1,3-dehydroadamantane (**I**) smoothly and quickly (in 1.5–2 h) reacted with various fluorine-containing 1,3-diketones of the general formula $R_FC(O)CH_2C(O)R$ (**IIa**–**IIj**) in boiling diethyl ether

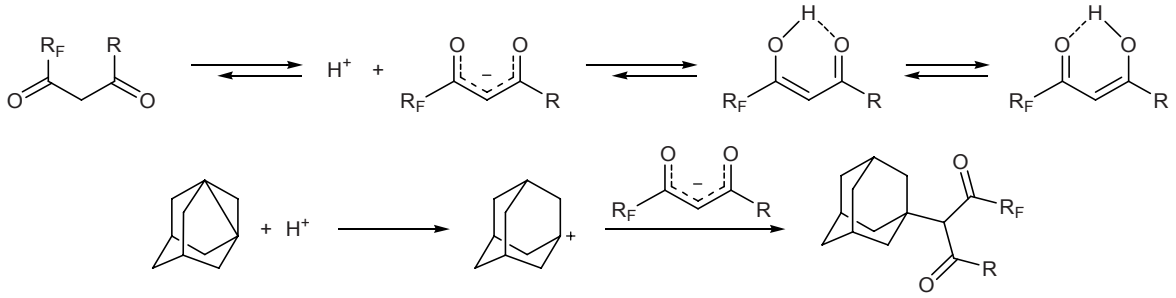
Scheme 1.



I **IIa–IIj** **IIIa–IIIj**

R_F = CF_3, R = CF_3 (**a**), Ph (**b**), 4-ClC_6H_4 (**c**), 3,4-$(MeO)_2C_6H_3$ (**d**), 1,3-benzodioxol-5-yl (**e**), 2-furyl (**f**), 2-thienyl (**g**), 4-(1*H*-pyrrol-1-yl)phenyl (**h**), *t*-Bu (**i**); R_F = CHF_2, R = Ph (**j**).

Scheme 2.



under dry oxygen-free nitrogen (Scheme 1). The corresponding fluorine-containing 2-(1-adamantanyl)-1,3-diketones **IIIa**–**IIIj** were formed in 83–98% yield. The reaction is accompanied by appreciable heat evolution, and no any catalyst is necessary. The optimal molar ratio **I**:**II** was 1:(1.5–2); in the reactions with lesser amounts of 1,3-diketones **II** the conversion of **I** was incomplete. Lowering the temperature from 35 to 20°C almost does not affect the yield of the target products.

The structure of compounds **IIIa**–**IIIj** was proved by the IR, ^{1}H NMR, and mass spectra. Their IR spectra contained absorption bands in the region 1748–1780 cm^{-1} due to stretching vibrations of the carbonyl group in the diketone tautomer. The fact that the adamantane fragment in molecules **III** is linked to the carbon rather than oxygen atom follows from the ^{1}H NMR spectra: the chemical shift of the CH proton indicates sp^3 hybridization of the corresponding carbon atom (the same carbon atom in *O*-adamantyl derivative should have sp^2 hybridization). According to the spectral data, compounds **IIIa**–**IIIj** exist in the diketone form, in contrast to initial fluorine-containing 1,3-diketones which exist mainly as enol tautomer [6]. Additional supports to the diketone structure of the synthesized compounds were obtained by X-ray analysis of a single crystal of compound **IIIi** (the X-ray diffraction data will be reported elsewhere) and by comparison of the ^{1}H NMR spectrum of **IIIi** with the spectra of the other products.

Presumably, C-adamantylation of fluorine-containing β-diketones follows Scheme 2. High nucleophilicity of compound **I** [9] favors initial proton transfer from 1,3-diketone **II** to 1,3-dehydroadamantane, and recombination of the cation–anion couple thus formed gives the corresponding fluorine-containing 2-(1-adamantyl)-1,3-diketone. Reactions of stable organic cations with anions are commonly regarded as a thermodynamically controlled process leading to bonding of electrophile (organic cation) at the most basic and nucleophilic center of ambident anion; such center in anions derived from 1,3-dicarbonyl compounds is located on the carbon atom between the carbonyl groups [10, 11].

Thus we were the first to synthesize fluorinated 1,3-diketones having an adamantyl group at the methylene carbon atom by reaction of 1,3-dehydroadamantane with fluorinated 1,3-diketones $R_FC(O)CH_2C(O)R$.

EXPERIMENTAL

The IR spectra of compounds **IIIb**, **IIIc**, and **IIIj** were recorded in KBr on a UR-20 instrument. The ^{1}H NMR spectra were measured on Bruker DAX-500 (500.13 MHz; **IIIa**–**IIIh**; DMSO-d_6) and Bruker AC-200 spectrometers (200.13 MHz; **IIIi**; $CDCl_3$). The mass spectra (electron impact, 70 eV) were obtained on Kratos MS-30 (**IIIc**–**IIIj**) and Finnigan MAT INCOS-50 instruments (**IIIb**). Initial fluorinated 1,3-diketones **IIa**–**IIj** were synthesized according to the procedures reported in [12].

Fluorine-containing 2-(1-adamantyl)-1,3-diketones (*general procedure***).** A solution of freshly sublimed compound **I** in anhydrous diethyl ether was added dropwise to 1.5–2 equiv of 1,3-diketone **IIa**–**IIj** under dry deoxygenated nitrogen. The mixture was heated to the boiling point and was kept boiling under reflux for 1.5–2 h. When the reaction was complete, the solvent and excess initial 1,3-diketone were distilled off, and the residue was purified by distillation under reduced pressure (**IIIa**, **IIIi**) or recrystallization from isopropyl alcohol (**IIIb**–**IIId**).

3-(1-Adamantyl)-1,1,1,5,5,5-hexafluoropentane-2,4-dione (IIIa) was obtained from 10 g (48 mmol) of 1,1,1,5,5,5-hexafluoropentane-2,4-dione and 4 g (30 mmol) of compound **I**. Yield 8.5 g (83%), colorless viscous liquid, bp 129–131°C (10 mm), n_D^{20} = 1.4382. ^{1}H NMR spectrum, δ, ppm: 1.55–1.7 m (12H, CH_2, Ad), 1.98 s (3H, CH, Ad), 4.9 s (1H, CH). Mass spec-

trum, *m*/*z* (I_{rel}, %): 342 (2.3) $[M]^+$, 245 (4.6) $[CF_3C(O)CHAd]^+$, 135 (100) $[Ad]^+$, 97 (7) $[C(O)CF_3]^+$, 69 (48) $[CF_3]^+$.

2-(1-Adamantyl)-4,4,4-trifluoro-1-phenylbutane-1,3-dione (IIIb) was obtained from 10 g (46 mmol) of 4,4,4-trifluoro-1-phenylbutane-1,3-dione and 4 g (30 mmol) of compound **I**. Yield 9.7 g (93%), colorless crystals, mp 95–96°C. IR spectrum, ν, cm^{-1}: 2912, 2884 (C–H); 1764 (C=O). ^1H NMR spectrum, δ, ppm: 1.59–1.62 q (6H, CH_2, Ad), 1.7–1.73 q (6H, CH_2, Ad), 1.92 s (3H, CH, Ad), 5.45 s (1H, CH), 7.6 t (2H, H_{arom}), 7.75 t (1H, H_{arom}), 8.15 d (2H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 350 (10) $[M]^+$, 253 (4.6) $[PhC(O)CHAd]^+$, 245 (5) $[CF_3C(O)CHAd]^+$, 135 (20) $[Ad]^+$, 105 (100) $[PhCO]^+$, 77 (50) $[Ph]^+$, 69 (2.5) $[CF_3]^+$.

2-(1-Adamantyl)-1-(4-chlorophenyl)-4,4,4-trifluorobutane-1,3-dione (IIIc) was obtained from 12 g (48 mmol) of 1-(4-chlorophenyl)-4,4,4-trifluorobutane-1,3-dione and 4 g (30 mmol) of compound **I**. Yield 10 g (87%), colorless crystals, mp 129–130°C. IR spectrum, ν, cm^{-1}: 2900, 2848 (C–H); 1768, 1668 (C=O). ^1H NMR spectrum, δ, ppm: 1.6–1.62 q (6H, CH_2, Ad), 1.7–1.72 q (6H, CH_2, Ad), 1.9 s (3H, CH, Ad), 5.45 s (1H, CH), 7.65 d (2H, H_{arom}), 8.2 d (2H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 384 (10) $[M]^+$, 287 (21) $[ClC_6H_4C(O)CHAd]^+$, 245 (11) $[CF_3C(O)CHAd]^+$, 135 (76) $[Ad]^+$, 139 (100) $[C(O)ClC_6H_4]^+$, 111 (49) $[ClC_6H_4]^+$, 69 (6) $[CF_3]^+$.

2-(1-Adamantyl)-1-(3,4-dimethoxyphenyl)-4,4,4-trifluorobutane-1,3-dione (IIId) was obtained from 6.2 g (22 mmol) of 1-(3,4-dimethoxyphenyl)-4,4,4-trifluorobutane-1,3-dione and 2 g (15 mmol) of compound **I**. Yield 5.7 g (93%), colorless crystals, mp 146–147°C. ^1H NMR spectrum, δ, ppm: 1.62–1.78 m (12H, CH_2, Ad), 1.93 s (3H, CH, Ad), 3.85 s and 3.92 s (3H each, OCH_3), 5.3 s (1H, CH), 7.1 d (2H, H_{arom}), 7.5 s (1H, H_{arom}), 7.85 d (1H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 410 (46) $[M]^+$, 313 (12) $[(CH_3O)_2C_6H_4C(O)CHAd]^+$, 165 (100) $[(CH_3O)_2C_6H_4CO]^+$, 135 (43) $[Ad]^+$, 137 (24) $[(CH_3O)_2C_6H_4]^+$, 69 (3) $[CF_3]^+$.

2-(1-Adamantyl)-1-(1,3-benzodioxol-5-yl)-4,4,4-trifluorobutane-1,3-dione (IIIe) was obtained from 6 g (23 mmol) of 1-(1,3-benzodioxol-5-yl)-4,4,4-trifluorobutane-1,3-dione and 2 g (15 mmol) of compound **I**. Yield 5.2 g (88%), colorless crystals, mp 121–122°C. ^1H NMR spectrum, δ, ppm: 1.63–1.7 m (12H, CH_2, Ad), 1.85 s (3H, CH, Ad), 5.3 s (1H, CH), 6.2 s (2H, CH_2), 7.1 d (1H, H_{arom}), 7.65 s (1H, H_{arom}), 7.87 d (1H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 394 (23) $[M]^+$, 297 (9) $[C_7H_5O_2C(O)CHAd]^+$, 149 (100) $[C(O)C_7H_5O_2]^+$, 135 (49) $[Ad]^+$, 121 (47) $[C_7H_5O_2]^+$, 69 (6) $[CF_3]^+$.

2-(1-Adamantyl)-4,4,4-trifluoro-1-(2-furyl)-butane-1,3-dione (IIIf) was synthesized from 5 g (24 mmol) of 4,4,4-trifluoro-1-(2-furyl)butane-1,3-dione and 2 g (15 mmol) of compound **I**. Yield 4.9 g (97%), colorless crystals, mp 56–57°C. ^1H NMR spectrum, δ, ppm: 1.63–1.72 m (12H, CH_2, Ad), 1.95 s (3H, CH, Ad), 4.95 s (1H, CH), 6.75 s (1H, CH_2), 7.75 s (1H, CH), 8.05 s (1H, CH). Mass spectrum, *m*/*z* (I_{rel}, %): 340 (42) $[M]^+$, 243 (82) $[C_4H_3OC(O)CHAd]^+$, 95 (100) $[C_4H_3OC(O)]^+$, 135 (78) $[Ad]^+$, 69 (22) $[CF_3]^+$, 67 (60) $[C_4H_3O]^+$.

2-(1-Adamantyl)-4,4,4-trifluoro-1-(2-thienyl)-butane-1,3-dione (IIIg) was obtained from 6 g (27 mmol) of 4,4,4-trifluoro-1-(2-thienyl)butane-1,3-dione and 2 g (15 mmol) of compound **I**. Yield 4.8 g (90%), colorless crystals, mp 112–113°C. ^1H NMR spectrum, δ, ppm: 1.64–1.75 m (12H, CH_2, Ad), 1.96 s (3H, CH, Ad), 5.15 s (1H, CH), 7.25 t (1H, CH_2), 8.1 d (1H, CH), 8.3 d (1H, CH). Mass spectrum, *m*/*z* (I_{rel}, %): 356 (30) $[M]^+$, 259 (76) $[C_4H_3SC(O)CHAd]^+$, 110 (100) $[C(O)C_4H_3S]^+$, 135 (71) $[Ad]^+$, 83 (30) $[C_4H_3S]^+$, 69 (16) $[CF_3]^+$.

2-(1-Adamantyl)-4,4,4-trifluoro-1-[4-(1*H*-pyrrol-1-yl)phenyl]butane-1,3-dione (IIIh) was obtained from 6 g (21 mmol) of 4,4,4-trifluoro-1-[4-(1*H*-pyrrol-1-yl)phenyl]butane-1,3-dione and 2 g (15 mmol) of compound **I**. Yield 5.9 g (95%), colorless crystals, mp 126–127°C. ^1H NMR spectrum, δ, ppm: 1.62–1.7 m (12H, CH_2, Ad), 1.96 s (3H, CH, Ad), 5.42 s (1H, CH), 6.35 s (2H, CH), 7.55 s (2H, CH), 7.8 d (2H, H_{arom}), 8.25 d (2H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 415 (41) $[M]^+$, 318 (6) $[C_4H_4NC_6H_4C(O)CHAd]^+$, 170 (100) $[C(O)C_4H_4NC_6H_4]^+$, 135 (44) $[Ad]^+$, 142 (53) $[C_4H_4NC_6H_4]^+$, 69 (6) $[CF_3]^+$.

3-(1-Adamantyl)-1,1,1-trifluoro-5,5-dimethylhexane-2,4-dione (IIIi) was obtained from 10 g (51 mmol) of 1,1,1-trifluoro-5,5-dimethylhexane-2,4-dione and 4 g (30 mmol) of compound **I**. Yield 8.5 g (86%), colorless liquid, n_D^{20} = 1.4790, bp 165–167°C (7 mm). ^1H NMR spectrum, δ, ppm: 1.1 s (9H, CH_3), 1.54–1.65 m (6H, CH_2, Ad), 1.75–1.8 m (6H, CH_2, Ad), 1.94 s (3H, CH, Ad), 4.82 s (1H, CH). Mass spectrum, *m*/*z* (I_{rel}, %): 330 (2) $[M]^+$, 233 (1.8) $[t\text{-BuC(O)CHAd}]^+$, 86 (20) [HC(O)Bu-*t*], 135 (25) $[Ad]^+$, 69 (3) $[CF_3]^+$, 57 (100) $[t\text{-Bu}]^+$.

2-(1-Adamantyl)-4,4-difluoro-1-phenylbutane-1,3-dione (IIIj) was obtained from 10 g (50 mmol) of 4,4-difluoro-1-phenylbutane-1,3-dione and 4 g (30 mmol) of compound **I**. Yield 9.7 g (98%), colorless crystals, mp 64–65°C. IR spectrum, ν, cm^{-1}: 2892, 2848 (C–H); 1748, 1668 (C=O). ^1H NMR spectrum, δ, ppm: 1.54–1.86 m (12H, CH_2, Ad), 1.96 s (3H, CH, Ad), 4.96 s (1H, CH), 5.66 t (1H, CHF_2), 7.27 s (1H, H_{arom}), 7.47–7.66 m (2H, H_{arom}), 7.99–8.03 m (2H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 332 (24) $[M]^+$, 253 (21) $[PhC(O)CHAd]^+$, 105 (100) $[PhCO]^+$, 135 (76) $[Ad]^+$, 77 (17) $[Ph]^+$, 51 (6) $[CF_3]^+$.

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