ISSN 1070-4280, Russian Journal of Organic Chemistry, 2010, Vol. 46, No. 8, pp. 1178–1180. © Pleiades Publishing, Ltd., 2010.
Original Russian Text © G.M. Butov, V.M. Mokhov, G.Yu. Parshin, S.A. Shevelev, I.L. Dalinger, I.A. Vatsadze, T.K. Shkineva, 2010, published in Zhurnal Organicheskoi Khimii, 2010, Vol. 46, No. 8, pp. 1177–1179.

Synthesis of 4-(1-Adamantyl)-3-polyfluoromethyl-1*H*-pyrazoles

G. M. Butov[a], V. M. Mokhov[b], G. Yu. Parshin[a], S. A. Shevelev[c], I. L. Dalinger[c], I. A. Vatsadze[c], and T. K. Shkineva[c]

[a] *Volzhsk Polytechnic Institute (a Division of Volgograd State Technical University), ul. Engel'sa 42a, g. Volzhskii, Volgogradskaya oblast, 404121 Russia*
e-mail: butov@volpi.ru

[b] *Volgograd State Technical University, Volgograd, Russia*

[c] *Zelinskii Institute of Organic Chemistry, Russian Academy of Sciences, Leninskii pr. 47, Moscow, 119991 Russia*

Received July 10, 2009

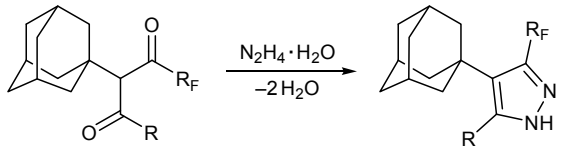
Abstract—4-(1-Adamantyl)-3-polyfluoromethylpyrazoles were synthesized for the first time in high yields by condensation of fluorinated 2-(1-adamantyl)-1,3-diketones with hydrazine hydrate.

DOI: 10.1134/S1070428010080117

Fluorinated 1,3-diketones and heterocyclic compounds based thereon are known to exhibit a stronger biological activity as compared to their nonfluorinated analogs. Polyfluorinated pyrazole possess anti-inflammatory and analgesic activity; they are used for the treatment of hyperglycemia and are heat-resistant heat-transfer agents and surfactants [1]. Introduction of an adamantane fragment into organic molecules changes their properties and often enhances or modifies their biological activity [2]. The chemistry of hetaryl-substituted adamantanes was reviewed in [3, 4]. Some adamantyl-substituted pyrazoles were synthesized from adamantyl-containing 1,3-diketones [4–7]. However, there are no published data on fluorinated adamantyl-containing pyrazoles and methods for their preparation.

We previously synthesized a series of adamantyl-containing fluorinated 1,3-diketones **Ia**–**Ie** with high yields under mild conditions [8, 9]. Structural specificity of such 1,3-diketones is the presence of a strong electron-donor adamantyl group at the α-carbon atom and an electron-withdrawing trifluoromethyl group at one carbonyl carbon atom. Therefore, these compounds may be regarded as novel synthons for various heterocyclic compounds. It seemed important to examine chemical properties of adamantyl-containing fluorinated 1,3-diketones with a view to obtain heterocyclic compounds based thereon.

Scheme 1.



Ia–Ih **IIa–IIh**

R_F = CF_3, R = Ph (**a**), 4-ClC_6H_4 (**b**), 3,4-$(MeO)_2C_6H_3$ (**c**), 1,3-benzodioxol-5-yl (**d**), 2-furyl (**e**), 2-thienyl (**f**), 4-(1*H*-pyrrol-1-yl)phenyl (**g**); R_F = CF_2H, R = Ph (**h**).

Our results showed that, unlike 1,3-diketones having no adamantyl fragment [1], compounds **Ia**–**Ie** do not form chelates with copper(II) salts and, unlike nonfluorinated analogs [4, 6], they do not react with phenylhydrazine under standard conditions. By reactions of 1,3-diketones **Ia**–**Ih** with hydrazine hydrate we synthesized hitherto unknown 4-(1-adamantyl)-5-aryl-(hetaryl)-3-tri(or di)fluoromethyl-1*H*-pyrazoles **Ia**–**Ih** (Scheme 1). The reactions were carried out in boiling ethanol using equimolar amounts of the reactants (or slight excess of hydrazine hydrate), the reaction time was 2–4 h, and target products **IIa**–**IIh** were isolated in 80–90% yield. The condensation was accompanied by appreciable heat evolution. Pyrazoles **IIa**–**IIh** are colorless high-melting crystalline substances. Their structure was confirmed by mass and ^{1}H NMR spectra.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker DAX-500 spectrometer operating at 500.13 MHz using $CDCl_3$ (**IIa**–**IIf**, **IIh**) or DMSO-d_6 (**IIg**) as solvent. The mass spectra (electron impact, 70 eV) were obtained

on a Kratos MS-30 instrument. Initial fluorinated 2-(1-adamantyl)-1,3-diketones **Ia**–**Ih** were synthesized according to the procedures described in [3].

4-(1-Adamantyl)-5-aryl(hetaryl)-3-tri(di)fluoromethyl-1*H*-pyrazoles IIa–IIh (*general procedure***).** 1,3-Diketone **Ia**–**Ih**, was dissolved in ethanol, 1.2–1.5 equiv of hydrazine hydrate was added, and the mixture was heated to the boiling point and kept for 6 h under reflux. When the reaction was complete, the mixture was cooled to room temperature, and the precipitate was filtered off, dried, and recrystallized from isopropyl alcohol.

4-(1-Adamantyl)-5-phenyl-3-trifluoromethyl-1*H*-pyrazole (IIa) was synthesized from 2 g (57 mmol) of 2-(1-adamantyl)-4,4,4-trifluoro-1-phenylbutane-1,3-dione and 0.33 ml (68 mmol) of hydrazine hydrate. Yield 1.7 g (86%), colorless crystals, mp 215–216°C. ^{1}H NMR spectrum, δ, ppm: 1.61 s (12H, CH_2, Ad), 1.9 s (3H, CH, Ad), 7.32–7.5 m (5H, Ph), 9.93 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 346 (100) $[M]^+$, 135 (18) $[Ad]^+$, 69 (27) $[CF_3]^+$. Found, %: C 69.54; H 6.31; N 7.89. $C_{20}H_{21}F_3N_2$. Calculated, %: C 69.35; H 6.11; N 8.08. *M* 346.39

4-(1-Adamantyl)-5-(4-chlorophenyl)-3-trifluoromethyl-1*H*-pyrazole (IIb) was synthesized from 2 g (52 mmol) of 2-(1-adamantyl)-1-(4-chlorophenyl)-4,4,4-trifluorobutane-1,3-dione and 0.33 ml (68 mmol) of hydrazine hydrate. Yield 1.7 g (87%), colorless crystals, mp 223–224°C. ^{1}H NMR spectrum, δ, ppm: 1.63 s (12H, CH_2, Ad), 1.91 s (3H, CH, Ad), 7.31 d (2H, H_{arom}), 7.43 d (2H, H_{arom}), 12.5 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 380 (100) $[M]^+$, 135 (17) $[Ad]^+$, 69 (22) $[CF_3]^+$. Found, %: C 63.13; H 5.40; N 7.27. $C_{20}H_{20}ClF_3N_2$. Calculated, %: C 63.08; H 5.29; N 7.36. *M* 380.83.

4-(1-Adamantyl)-5-(3,4-dimethoxyphenyl)-3-trifluoromethyl-1*H*-pyrazole (IIIc) was synthesized from 2 g (48 mmol) of 2-(1-adamantyl)-1-(3,4-dimethoxyphenyl-4,4,4-trifluorobutane-1,3-dione and 0.28 ml (57 mmol) of hydrazine hydrate. Yield 1.6 g (80%), colorless crystals, mp 218–219°C. ^{1}H NMR spectrum, δ, ppm: 1.62 s (12H, CH_2, Ad), 1.91 s (3H, CH, Ad), 3.89 s (3H, OMe), 3.95 s (3H, OMe), 6.81–6.95 m (3H, H_{arom}), 11.2 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 406 (100) $[M]^+$, 135 (19) $[Ad]^+$, 69 (59) $[CF_3]^+$. Found, %: C 65.07; H 6.33; N 6.81. $C_{22}H_{25}F_3N_2O_2$. Calculated, %: C 65.01; H 6.20; N 6.89. *M* 406.44.

4-(1-Adamantyl)-5-(1,3-benzodioxol-5-yl)-3-trifluoromethyl-1*H*-pyrazole (IIId) was synthesized from 2 g (50 mmol) of 2-(1-adamantyl)-1-(1,3-benzodioxol-5-yl)-4,4,4-trifluorobutane--1,3-dione and 0.33 ml (68 mmol) of hydrazine hydrate. Yield 1.8 g (90%), colorless crystals, mp 207–209°C. ^{1}H NMR spectrum, δ, ppm: 1.6 s (12H, CH_2, Ad), 1.91 s (3H, CH, Ad), 6.06 s (2H, CH_2), 6.75 s (3H, H_{arom}), 9.91 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 390 (100) $[M]^+$, 135 (19) $[Ad]^+$, 69 (23) $[CF_3]^+$. Found, %: C 64.65; H 5.51; N 7.15. $C_{21}H_{21}F_3N_2O_2$. Calculated, %: C 64.61; H 5.42; N 7.18. *M* 390.40.

4-(1-Adamantyl)-5-(2-furyl)-3-trifluoromethyl-1*H*-pyrazole (IIIe) was synthesized from 2 g (58 mmol) of 2-(1-adamantyl)-4,4,4-trifluoro-1-(2-furyl)butane-1,3-dione and 0.35 ml (72 mmol) of hydrazine hydrate. Yield 1.67 g (85%), colorless crystals, mp 139–141°C. ^{1}H NMR spectrum, δ, ppm: 1.68 s (12H, CH_2, Ad), 1.98 s (3H, CH, Ad), 6.48–6.6 m (2H, CH), 7.69 s (1H, CH), 10.18 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 336 (100) $[M]^+$, 135 (19) $[Ad]^+$, 69 (46) $[CF_3]^+$. Found, %: C 64.52; H 5.74; N 8.29. $C_{18}H_{19}F_3N_2O$. Calculated, %: C 64.28; H 5.69; N 8.33. *M* 336.35.

4-(1-Adamantyl)-5-(2-thienyl)-3-trifluoromethyl-1*H*-pyrazole (IIIf) was synthesized from 2 g (56 mmol) of 2-(1-adamantyl)-4,4,4-trifluoro-1-(2-thienyl)butane-1,3-dione and 0.35 ml (72 mmol) of hydrazine hydrate. Yield 1.64 g (84%), colorless crystals, mp 192–193°C. ^{1}H NMR spectrum, δ, ppm: 1.66 s (12H, CH_2, Ad), 1.96 s (3H, CH, Ad), 7.09–7.18 m (2H, CH), 7.51 s (1H, CH), 10.1 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 352 (100) $[M]^+$, 135 (19) $[Ad]^+$, 69 (42) $[CF_3]^+$. Found, %: C 61.50; H 5.51; N 7.91; S 9.26. $C_{18}H_{19}F_3N_2S$. Calculated, %: C 61.35; H 5.43; N 7.95; S 9.10. *M* 352.42.

4-(1-Adamantyl)-5-[4-(1*H*-pyrrol-1-yl)phenyl]-3-trifluoromethyl-1*H*-pyrazole (IIIg) was synthesized from 2 g (48 mmol) of 2-(1-adamantyl)-4,4,4-trifluoro-1-[4-(1*H*-pyrrol-1-yl)phenyl]butane-1,3-dione and 0.28 ml (57 mmol) of hydrazine hydrate. Yield 1.75 g (88%), colorless crystals, mp 247–248°C. ^{1}H NMR spectrum, δ, ppm: 1.62 s (12H, CH_2, Ad), 1.91 s (3H, CH, Ad), 6.30 d (2H, CH), 7.31 s (2H, CH), 7.45 d (2H, C_6H_4), 7.61 d (2H, C_6H_4), 13.18 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 411 (100) $[M]^+$, 135 (20) $[Ad]^+$, 69 (34) $[CF_3]^+$. Found, %: C 70.29; H 5.95; N 10.25. $C_{24}H_{24}F_3N_3$. Calculated, %: C 70.06; H 5.88; N 10.21. *M* 411.46.

4-(1-Adamantyl)-3-difluoromethyl-5-phenyl-1*H*-pyrazole (IIIh) was synthesized from 2 g (60 mmol) of 2-(1-adamantyl)-4,4-difluoro-1-phenylbutane-1,3-dione and 0.35 ml (72 mmol) of hydrazine hydrate.

Yield 1.6 g (81%), colorless crystals, mp 184–185°C. ^{1}H NMR spectrum, δ, ppm: 1.62 s (12H, CH_2, Ad), 1.91 s (3H, CH, Ad), 6.94 t (1H, CF_2H), 7.31–7.98 m (5H, Ph), 9.1 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 328 (100) $[M]^+$, 135 (18) $[Ad]^+$, 69 (25) $[CF_3]^+$. Found, %: C 73.26; H 6.82; N 8.57. $C_{20}H_{22}F_2N_2$. Calculated, %: C 73.15; H 6.75; N 8.53. *M* 328.40.

REFERENCES

1. Pashkevich, K.I., Saloutin, V.I., and Postovskii, I.Ya., *Usp. Khim*., 1981, vol. 50, p. 325.
2. Morozov, I.S., Petrov, V.I., and Sergeeva, S.A., *Farmakologiya adamantanov* (Pharmacology of Adamantanes), Volgograd: Volgograd. Med. Akad., 2001.
3. Shvekhgeimer, G.A. and Litvinov, V.P., *Russ. J. Org. Chem*., 1999, vol. 35, p. 165.
4. Shvekhgeimer, G.A., *Usp. Khim*., 1996, vol. 65, p. 606.
5. Makarova, N.V., Moiseev, I.K., and Zemtsova, M.N., *Russ. J. Org. Chem*., 2001, vol. 37, p. 269
6. Gonzalez, A., Marquet, J., and Moreno, M., *Tetrahedron*, 1986, vol. 42, p. 4253.
7. Klimochkin, Yu.I., Tili, T.S., and Moiseev, I.K., *Zh. Org. Khim*., 1988, vol. 24, p. 1780.
8. Butov, G.M., Mokhov, V.M., Parshin, G.Yu., Kunaev, R.U., Shevelev, S.A., Dalinger, I.L., and Vatsadze, I.A., *Russ. J. Org. Chem*., 2008, vol. 44, p. 1157.
9. No, B.I., Butov, G.M., Mokhov, V.M., and Parshin, G.Yu., Russian Patent no. 2187493, 2002; *Byull. Izobret*., 2002, no. 23.