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SHORT COMMUNICATIONS

New Method of Preparation of 1-Adamantylthioacetic Acids Dialkylamides from 4-(1-Adamantyl)-1,2,3-thiadiazole

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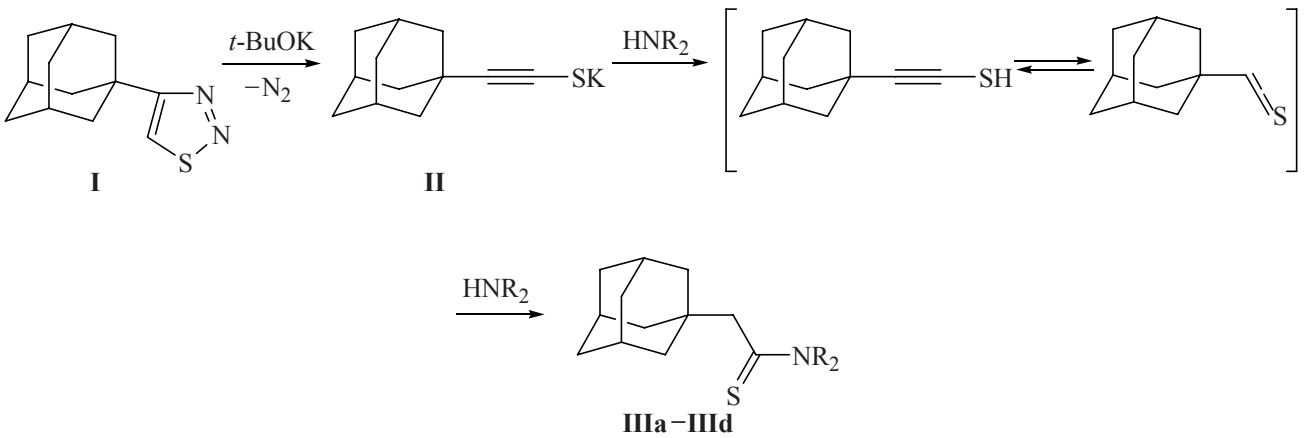
Three specimens of adamantylthioacetic acids amides are known, and all of them have been obtained by different methods: 1-Adamantylthioacetamide has been prepared by treating 1-amantylacetonitrile with hydrogen sulfide [1], piperidylamide of 1-adamantylthioacetic acid, by treating piperidylamide of 1-adamantylacetic acid with Lawesson's reagent [2], morpholinamide of 1-adamantylthioacetic acid, by reaction of acetylthiomorpholine with 1-iodoadamantane [3]. Amides of adamantylthioacetic acids exhibit high antiviral activity [1, 4].

We developed a new method of preparation of 1-adamantylthioacetic acids dialkylamides from the easily accessible 4-(1-adamantyl)-1,2,3-thiadiazole. The initial 4-(1-adamantyl)-1,2,3-thiadiazole we recently synthesized from 1-adamantyl methyl ketone via the formation of the corresponding ethoxycarbonylhydrazone followed by treatment with thionyl chloride [5].

4-(1-Adamantyl)-1,2,3-thiadiazole (**I**) under the action of a strong base like potassium *tert*-butylate in anhydrous tetrahydrofuran readily decomposed with nitrogen elimination giving potassium 2-(1-adamantyl)-ethynethiolate (**II**) [5]. Further treatment of the reaction mixture with excess secondary amine led to the formation of the corresponding dialkylamides of 1-adamantylthioacetic acids **IIIa–IIId**. A presumed intermediate compound in this process was adamantylthioketene (see scheme).

The structure of dialkylthioamides **IIIa–IIId** was proved by ^{1}H and ^{13}C NMR and mass spectra and by

Scheme.



NR_2 = $(CH_2CH_2)_2NPh$ (**a**), $(CH_2CH_2)_2O$ (**b**), $(CH_2Ph)_2$ (**c**), $(CH_2)_5$ (**d**).

coincidence of the physical constants with those published for known compounds.

1-Adamantylthioacetic acid *N*-phenylpiperazinamide (IIIa). To a solution of 1.5 g (6.8 mmol) of thiadiazole **I** in 25 ml of anhydrous THF was added 0.83 g (7.4 mmol) of potassium *tert*-butylate under an argon atmosphere at room temperature. The reaction mixture was stirred for 5 min till the end of gas evolution. After precipitation of potassium thiolate **II** to the reaction mixture was added a solution of 11.03 g (68 mmol) of N-phenylpiperazine in 15 ml of anhydrous THF. The reaction mixture was stirred for 5 h, then poured into 150 ml of water and extracted with chloroform (3 × 15 ml). The extracts were combined, dried with anhydrous sodium sulfate, boiled with activated carbon, filtered, and evaporated. On recrystallization from ethanol we obtained 1.5 g (62%) of chromatographically pure thioamide **IIIa** (here and hereinafter eluents chloroform–hexane, 1:1; ethyl acetate–hexane, 1:10). Colorless crystals, mp 152–153°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.62 m (6CH_2, Ad), 1.94 m (3CH, Ad), 2.10 s (CH_2CS), 3.10 m ($CSNCH_2CH_2$), 3.62 m ($CSNCH_2$), 6.77 t (H^4 Ph), 6.89 d (H^2, H^6 Ph), 7.18 t (H^3, H^5 Ph). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 28.53 (CH Ad), 34.34 (C^1 Ad), 36.40 + 42.96 (CH_2 Ad), 48.26 + 49.46 (CH_2NPh), 49.18 + 50.42 (CH_2NCS), 55.94 (CH_2CS), 115.95 (C^2, C^6 Ph), 120.21 (C^4 Ph), 128.99 (C^3, C^5 Ph), 149.94 (C^1 Ph), 200.08 (CS). Mass spectrum, *m*/*z* (I_{rel}, %): 354 (18) [*M*]$^+$, 321 (7) [*M* – H – S]$^+$, 235 (11), 219 (37) [*M* – Ad]$^+$, 132 (100), 120 (25), 104 (27), 91 (21), 77 (28), 56 (11), 41 (13). Found, %: C 74.41, 74.69; H 8.45, 8.76. $C_{22}H_{30}N_2S$. Calculated, %: C 74.53; H 8.53. *M* 354.55.

Compounds **IIIb–IIId** were similarly obtained.

1-Adamantylthioacetic acid morpholinamide (IIIb) was obtained from 1 g (4.5 mmol) of thiadiazole **I**, 0.55 g (4.7 mmol) of potassium *tert*-butylate, and 3.9 g (45 mmol) of morpholine. On recrystallization from ethanol we obtained 0.7 g (48%) of chromatographically pure thioamide **IIIb**. Colorless fine needle crystals, mp 147–148°C (148–149°C [3]). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.64 m (6CH_2, Ad), 1.94 m (3CH, Ad), 2.76 s (CH_2CS), 3.61 m + 3.66 m ($CSNCH_2CH_2$), 3.82 m + 4.26 m ($CSNCH_2$). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 28.03 (CH Ad), 34.23 (C^1 Ad), 36.29 + 42.32 (CH_2 Ad), 49.58 + 51.27 (CH_2N), 54.70 (CH_2CS), 65.94 (CH_2O), 198.82 (CS). Mass spectrum, *m*/*z* (I_{rel}, %): 279 (43) [*M*]$^+$, 278 (42) [*M* – H]$^+$, 246 (12) [*M* – H – S]$^+$, 192 (9) [*M* – H – $N(CH_2CH_2)_2O$]$^+$, 144 (92) [*M* – Ad]$^+$, 135 (70) [Ad]$^+$, 110 (31), 86 (77), 67 (31), 55 (44), 41 (100). Found, %: C 68.42, 68.73; H 8.89, 9.15. $C_{16}H_{25}NOS$. Calculated, %: C 68.77; H 9.02. *M* 279.44.

1-Adamantylthioacetic acid *N,N*-dibenzylamide (IIIc) was obtained from 1 g (4.5 mmol) of thiadiazole **I**, 0.55 g (4.7 mmol) of potassium *tert*-butylate, and 8.87 g (45 mmol) of dibenzylamine. On recrystallization from ethanol we obtained 1.7 g (70%) of chromatographically pure thioamide **IIIc**. Colorless crystals, mp 151–152°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.71 m (6CH_2, Ad), 1.93 m (3CH, Ad), 2.83 s (CH_2CS), 4.82 s + 5.23 s ($CSNCH_2$), 7.17 d + 7.31 m (Ph). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 28.43 (CH Ad), 34.95 (C^1 Ad), 36.43 + 42.61 (CH_2 Ad), 54.79 + 55.25 (CH_2N), 55.87 (CH_2CS), 126.64 (C^4 Ph), 127.61 + 127.82 + 127.98 (C^2, C^6 Ph), 128.58 + 129.03 (C^3, C^5 Ph), 135.86 + 136.41 (C^1 Ph), 202.15 (CS). Found, %: C 79.89, 80.05; H 7.87, 8.11. $C_{26}H_{31}NS$. Calculated, %: C 80.16; H 8.02. *M* 389.6.

1-Adamantylthioacetic acid piperidylamide (IIId) was obtained from 1 g (4.5 mmol) of thiadiazole **I**, 0.55 g (4.7 mmol) of potassium *tert*-butylate, and 8.62 g (101 mmol) of piperidine. On recrystallization from ethanol we obtained 0.7 g (49%) of chromatographically pure thioamide **IIId.** Colorless crystals, mp 91–93°C (91–93°C [2]). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.67 m (6CH_2, Ad), 1.97 m (3CH, Ad), 2.76 s (CH_2CS), 3.78 m + 4.32 m ($CSNCH_2CH_2$). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 23.53 + 25.05 + 26.43 ($NCH_2CH_2CH_2$), 28.23 (CH Ad), 34.14 (C^1 Ad), 36.32 + 42.38 (CH_2 Ad), 50.66 + 51.76 (CH_2N), 55.12 (CH_2CS), 197.20 (CS). Mass spectrum, *m*/*z* (I_{rel}, %): 277 (30) [*M*]$^+$, 276 (31) [*M* – H]$^+$, 244 (12) [*M* – H – S]$^+$, 192 (3) [*M* – H – $N(CH_2CH_2)_2CH_2$]$^+$, 142 (83) [*M* – Ad]$^+$, 135 (21) [Ad]$^+$, 110 (20), 84 (53), 67 (35), 55 (37), 41 (100). Found, %: C 73.23, 73.49; H 9.76, 9.93. $C_{17}H_{27}NS$. Calculated, %: C 73.59; H 9.81. *M* 277.47.

Melting points were measured on a Boëtius heating block. ^{1}H and ^{13}C NMR spectra were registered on a spectrometer Bruker AMX-400 (400 and 100 MHz) using as internal references the signals of residual protons (^{1}H) and carbon nuclei (^{13}C) of deuterated solvents. Mass spectra were taken on a Kratos MS 890 instrument with a direct sample admission into the ion source, ionizing electrons energy 70 eV, ionization chamber temperature 200°C. The reaction progress was monitored by TLC on Silufol UV-254 plates, spots visualized under UV irradiation or in iodine vapor. All solvents used in the study were purified and dried by standard procedures.

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REFERENCES

1. Aigami, K., Inamoto, Y., Takaishi, N., Nattori, K., Takatsuki, A., and Tamura, G., *J. Med. Chem.,* 1975, vol. 18, p. 713.
2. Klimko, Yu.E., Isaev, S.D., and Yurchenko, A.G., *Zh. Org. Khim.,* 1995, vol. 31, p. 191.
3. Murguia, M.C. and Rossi, R.A. *Tetrahedron Lett.,* 1997, vol. 38, p. 1355.
4. Aigami, K. and Inamoto, Y., US Patent 396228, 1976; *Chem. Abstr.,* 1977, vol. 86, 43297v.
5. Petrov, M.L., Shchipalkin, A.A., and Kuznetsov, V.A., *Zh. Org. Khim.,* 2007, vol. 43, p. 631.