ISSN 1070-4280, Russian Journal of Organic Chemistry, 2007, Vol. 43, No. 12, pp. 1870–1873. © Pleiades Publishing, Ltd., 2007.
Original Russian Text © D.A. Androsov, M.L. Petrov, A.A. Shchipalkin, 2007, published in Zhurnal Organicheskoi Khimii, 2007, Vol. 43, No. 12, pp. 1863–1865.

SHORT COMMUNICATIONS

New Method for the Preparation of *N*,*N*-Dimethyl-(thioacetamides) from 4-Substituted 1,2,3-Thiadiazoles

D. A. Androsov, M. L. Petrov, and A. A. Shchipalkin

St. Petersburg State Institute of Technology, Moskovskii pr. 26, St. Petersburg, 190013 Russia
e-mail: mlpetrov@lti-gti.ru

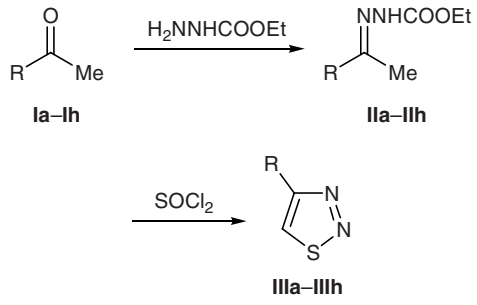
Received May 18, 2007

DOI: 10.1134/S1070428007120226

N,*N*-Dialkylethanethioamides are obtained via decomposition of 4-substituted 1,2,3-thiadiazoles by the action of strong bases in the presence of secondary amines [1]. This procedure seems to be applicable for the preparation of the corresponding *N*,*N*-dimethylamides. We propose to use dimethylformamide instead of dimethylamine (which is inconvenient to handle with due to its low boiling point, 7.4°C) in the synthesis of *N*,*N*-dimethylethanethioamides from 4-substituted 1,2,3-thiadiazoles.

Initial 4-substituted 1,2,3-thiadiazoles are readily accessible according to Hurd and Mori [2]. Following this procedure we synthesized 4-*tert*-butyl-1,2,3-thiadiazole (**IIIa**) from pinacolone (**Ia**) [3], 4-(1-adamantyl-1,2,3-thiadiazole) (**IIIb**) from 1-adamantyl methyl ketone (**Ib**) [4], 4-phenyl-1,2,3-thiadiazole (**IIIc**) from acetophenone (**Ic**) [2], 4-(4-chlorophenyl)-1,2,3-thiadiazole (**IIId**) from 4-chloroacetophenone (**Id**) [5], 4-(4-bromophenyl)-1,2,3-thiadiazole (**IIIe**) from 4-bromoacetophenone (**Ie**) [6], (4-methylphenyl)-1,2,3-thiadiazole (**IIIg**) from 4-methylacetophenone (**Ig**) [7], and (4-methoxyphenyl)-1,2,3-thiadiazole (**IIIh**) from 4-methoxyacetophenone (**Ih**) [5]. Likewise, 2-fluoroacetophenone (**If**) was converted into ethoxycarbonylhydrazone **IIf**, and the latter was treated with thionyl chloride to obtain previously unknown 4-(2-fluorophenyl)-1,2,3-thiadiazole (**IIIf**) (Scheme 1).

Scheme 1.

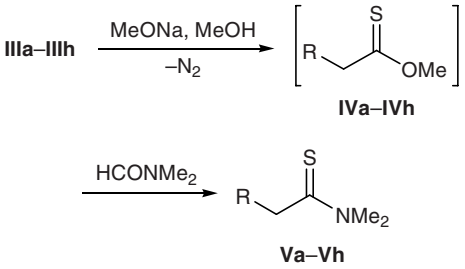


Ia–Ih IIa–IIh IIIa–IIIh

R = *t*-Bu (**a**), 1-Ad (**b**), Ph (**c**), 4-ClC_6H_4 (**d**), 4-BrC_6H_4 (**e**), 2-FC_6H_4 (**f**), 4-MeC_6H_4 (**g**), 4-$MeOC_6H_4$ (**h**).

1,2,3-Thiadiazoles **IIIa**–**IIIh** readily undergo decomposition with liberation of nitrogen by the action of such a strong base as sodium methoxide. The subsequent treatment of the reaction mixture with excess DMF gives the corresponding *N*,*N*-dimethylethanethioamides **Va**–**Vh** (Scheme 2). Using 4-(2-fluorophenyl)-1,2,3-thiadiazole (**IIIf**) as an example we showed that the reaction involves intermediate formation of methyl (2-fluorophenyl)ethanethioate (**IVf**). The structure of compounds **Va**–**Vh** was proved by ^1H and ^{13}C NMR spectroscopy and mass spectrometry, as well as by comparison with published data.

Scheme 2.



For R, see legend to Scheme 1.

Ethyl 2-[1-(2-fluorophenyl)ethylidene]hydrazine-1-carboxylate (IIf). A mixture of 1 g (7.25 mmol) of 2-fluoroacetophenone (**If**), 0.8 g (7.69 mmol) of ethyl hydrazinecarboxylate, 7 ml of propan-2-ol, and one

drop of glacial acetic acid was heated for 20 min under reflux. The mixture was then kept for 8 h, and the precipitate was filtered off and dried. The product was chromatographically pure and was used in further syntheses without additional purification. Yield 1.3 g (83%), fine colorless prisms, mp 111°C (from propan-2-ol), R_f 0.17 (chloroform). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.24 t (CH_3CH_2), 2.19 d (CH_3C=N, J_{HF} = 2.5 Hz), 4.16 q (OCH_2), 7.19–7.26 m (3-H, 4-H), 7.41–7.43 m (5-H), 7.50 d.t (6-H, J_{HF} = 7.7 Hz), 10.19 s (NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.92 (CH_3CH_2), 17.64/17.70 (CH_3C=N), 60.95 (CH_2), 116.18/116.47 (C^3), 124.68/124.72 (C^5), 127.77/127.94 (C^1), 130.08/130.12 (C^6), 130.93/131.05 (C^4), 147.24 (C=N), 154.51 (C=O), 158.53/161.81 (C^2). Mass spectrum, *m*/*z* (I_{rel}, %): 224 (74) $[M]^+$, 151 $[M - CO_2Et]^+$, 136 (100) $[M - NHCO_2Et]^+$, 121 (55), 110 (67), 90 (24), 83 (38), 75 (58), 57 (29). Found, %: C 58.72, 58.89; H 5.52, 5.79. $C_{11}H_{13}FN_2O_2$. Calculated, %: C 58.92; H 5.84. *M* 224.23.

4-(2-Fluorophenyl)-1,2,3-thiadiazole (IIIf). A flask equipped with a magnetic stirrer, reflux condenser, and a gas-outlet tube (connected to a system for absorption of liberated hydrogen chloride) was charged with 1.23 g (5.49 mmol) of hydrazone **IIf**, 15 ml of freshly distilled thionyl chloride was added on cooling to 0°C, and the mixture was stirred for 0.5 h at 50°C. When vigorous gas evolution ceased, the mixture was stirred for 1.5 h at 70°C and cooled to 20–25°C, and excess thionyl chloride was distilled off under reduced pressure. The residue was washed with water and dried. Yield 0.846 g (86%), light yellow prisms, mp 32–33°C, R_f 0.78 (chloroform). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.21–7.45 m (3-H, 4-H, 5-H), 8.48 d.t (6-H, J_{HF} = 7.4 Hz), 8.92 d (5′-H, J_{HF} = 1.1 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 116.08/116.47 (C^3), 118.86/118.97 (C^1), 124.90/124.94 ($C^{5'}$), 130.23/130.27 (C^5), 130.76/130.88 (C^6), 133.51/133.70 (C^4), 156.29/156.34 ($C^{4'}$), 158.03/161.36 (C^2). Mass spectrum, *m*/*z* (I_{rel}, %): 180 (18) $[M]^+$, 132 (19) $[M - CS]^+$, 120 (22) $[M - N_2 - S]^+$, 108 (43) $[o\text{-}C_6H_4CHF]^+$, 107 (51) $[o\text{-}C_6H_4CF]^+$, 93 (16), 75 (15), 69 (22). Found, %: C 53.17, 53.49; H 2.98, 3.11. $C_8H_5FN_2S$. Calculated, %: C 53.32; H 2.80. *M* 180.20.

Methyl 2-(2-fluorophenyl)ethanethioate (IVf). Thiadiazole **IIIf**, 0.35 g (1.94 mmol), was added to a solution of sodium methoxide prepared from 20 ml of anhydrous methanol and 0.134 g (5.8 mmol) of metallic sodium. The mixture was heated for 4 h, cooled, poured into 30 ml of water, and extracted with chloroform (5×10 ml). The extract was dried over sodium sulfate, the solvent was distilled off, and the residue was purified by column chromatography on silica gel L (40–100 μm) using carbon tetrachloride as eluent. A light yellow fraction was collected. Yield 0.25 g (70%), oily substance with a sharp odor, R_f 0.51 (chloroform). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.29 s (OCH_3), 4.65 s (CH_2), 6.78–7.31 m (C_6H_4). Mass spectrum, *m*/*z* (I_{rel}, %): 184 (26) $[M]^+$, 152 (7) $[M - S]^+$, 139 (15) $[M - CHS]^+$, 109 (93) $[FC_6H_4CH_2]^+$, 83 (27), 75 (100) $[CSOCH_3]^+$, 47 (15). Found, %: C 58.86, 58.92; H 5.05, 5.17. C_9H_9FOS. Calculated, %: C 58.68; H 4.92. *M* 184.23.

***N*,*N*,3,3-Tetramethylbutanethioamide (Va).** Thiadiazole **IIIa**, 1 g (7 mmol), was added to a solution of sodium methoxide prepared from 5 ml of anhydrous methanol and 0.207 g (9 mmol) of metallic sodium. The mixture was heated for 1 h under reflux, 5 ml of anhydrous dimethylformamide was added, methanol was distilled off, 50 ml of water was added to the residue, and the mixture was extracted with ethyl acetate (3×10 ml). The extract was dried over anhydrous sodium sulfate, the drying agent was filtered off, the filtrate was treated with silica gel on heating under reflux, the solvent was distilled off under reduced pressure, and the precipitate was recrystallized from 10 ml of cyclohexane. Yield 0.45 g (40%), colorless crystals, mp 38–39°C (from cyclohexane); published data [8]: mp 38.5–40°C. The product was chromatographically pure in the systems chloroform–hexane (1:1) and ethyl acetate–hexane (1:10). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.03 m (CH_3), 2.86 s (CH_2), 3.28 s and 3.44 s (NCH_3). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 29.97 (CH_3), 32.51 [$C(CH_3)_3$], 42.86 and 44.39 (NCH_3), 201.81 (C=S). Found, %: C 60.46, 60.57; H 10.61, 10.88. $C_8H_{17}NS$. Calculated, %: C 60.32; H 10.76.

2-(1-Adamantyl)-*N*,*N*-dimethylethanethioamide (Vb) was synthesized in a similar way from 0.4 g (1.8 mmol) of thiadiazole **IIIb** using 0.12 g (5.4 mmol) of sodium, 10 ml of anhydrous methanol, and 10 ml of anhydrous DMF. After removal of methanol, the mixture was diluted with 30 ml of water, and the precipitate was filtered off, dried, and recrystallized from 15 ml of methanol. Yield 0.2 g (47%), colorless needles, mp 155–157°C (from methanol), R_f 0.5 (chloroform). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.66 m (CH_2, Ad), 1.95 m (CH, Ad), 2.72 s (CH_2CS), 3.33 s and 3.39 s (NCH_3). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 28.24 (CH, Ad), 34.33 (C^1, Ad), 36.36 (CH_2, Ad), 42.38 (CH_2, Ad), 43.05 and 44.04 (NCH_3), 55.31

(CH_2), 199.15 (C=S). Mass spectrum, *m*/*z* (I_{rel}, %): 237 (43) $[M]^+$, 236 (78) $[M - H]^+$, 204 (19) $[M - H - S]^+$, 135 (48) $[Ad]^+$, 102 (17) $[M - Ad]^+$, 88 (73) $[S{=}CN(CH_3)_2]^+$, 79 (68), 70 (63), 55 (61), 41 (100). Found, %: C 70.55, 69.76; H 9.84, 9.97. $C_{14}H_{23}NS$. Calculated, %: C 70.83; H 9.76. *M* 237.40.

***N*,*N*-Dimethyl-2-phenylethanethioamide (Vc)** was synthesized in a similar way from 1 g (6.2 mmol) of thiadiazole **IIIc** using 0.285 g (12.4 mmol) of sodium, 30 ml of anhydrous methanol, and 10 ml of anhydrous DMF. After removal of methanol, the mixture was poured into 100 ml of water, and the precipitate was filtered off, washed with water (5×20 ml), and dried. Yield 0.85 g (77%), orange crystals, mp 81°C (from benzene or petroleum ether); published data [9]: mp 79–80°C; R_f 0.58 (chloroform). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.19 s and 3.49 s (NCH_3), 4.31 (CH_2), 7.32 m (C_6H_5). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 42.27 and 44.80 (NCH_3), 50.92 (CH_2), 126.93 (C^4), 128.06 (C^2, C^6), 128.79 (C^3, C^5), 135.65 (C^1), 200.60 (C=S). Found, %: C 70.23, 70.31; H 7.44, 7.63. $C_{10}H_{13}NS$. Calculated, %: C 66.99; H 7.31.

2-(4-Chlorophenyl)-*N*,*N*-dimethylethanethioamide (Vd) was synthesized in a similar way from 1 g (5.1 mmol) of thiadiazole **IIId** using 0.24 g (10.2 mmol) of sodium. Yield 0.85 g (78%), orange–brown crystals, mp 74°C (from methanol); published data [10]: mp 73–74°C; R_f 0.4 (chloroform). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.17 s and 3.46 s (NCH_3), 4.22 (CH_2), 7.25 m (C_6H_4). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 42.24 and 44.82 (NCH_3), 49.58 (CH_2), 128.87 (C^3, C^5), 129.55 (C^2, C^6), 132.76 (C^4), 134.20 (C^1), 200.00 (C=S). Mass spectrum, *m*/*z* (I_{rel}, %): 213 (60) $[M]^+$, 180 (25) $[M - SH]^+$, 165 (30) $[M - SH - CH_3]^+$, 134 (24) $[M - Cl - S{=}CN(CH_3)_2]^+$, 125 (54) $[ClC_6H_4CH_2]^+$, 88 (100) $[S{=}CN(CH_3)_2]^+$, 73 (51), 70 (66). Found, %: C 55.93, 56.07; H 5.42, 5.64. $C_{10}H_{12}ClNS$. Calculated, %: C 56.20; H 5.66. *M* 213.72.

2-(4-Bromophenyl)-*N*,*N*-dimethylethanethioamide (Ve) was synthesized in a similar way from 1 g (4.15 mmol) of thiadiazole **IIIe** using 0.19 g (8.3 mmol) of sodium. Yield 0.85 g (78%), light orange needles, mp 69–70°C (from methanol), R_f 0.38 (chloroform). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.16 s and 3.44 s (NCH_3), 4.19 (CH_2), 7.18 d (2-H, 6-H), 7.40 d (3-H, 5-H). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 42.27 and 44.82 (NCH_3), 50.01 (CH_2), 120.82 (C^4), 129.94 (C^3, C^5), 131.81 (C^2, C^6), 134.74 (C^1), 199.85 (C=S). Mass spectrum, *m*/*z* (I_{rel}, %): 259 (48) $[M]^+$, 226 (14) $[M - SH]^+$, 171 (25) $[BrC_6H_4CH_2]^+$, 134 (31) $[M - Br - S{=}CN(CH_3)_2]^+$, 88 (100) $[S{=}CN(CH_3)_2]^+$, 73 (39), 70 (66). Found, %: C 46.78, 46.81; H 4.33, 4.61. $C_{10}H_{12}BrNS$. Calculated, %: C 46.52; H 4.68. *M* 358.18.

2-(2-Fluorophenyl)-*N*,*N*-dimethylethanethioamide (Vf) was synthesized in a similar way from 0.32 g (1.78 mmol) of thiadiazole **IIIf** using 0.114 g (4.95 mmol) of sodium and 20 ml of anhydrous methanol. The mixture was heated for 2 h under reflux, 5 ml of anhydrous DMF was added, methanol was distilled off, and the mixture was heated for 2 h under reflux, poured into 50 ml of water, and extracted with chloroform (3×10 ml). The extract was dried over sodium sulfate, the solvent was distilled off, and the residue was purified by column chromatography on silica gel L (40–100 μm) using carbon tetrachloride and chloroform as eluent. A light yellow fraction was collected. Yield 0.25 g (86%), light yellow rhombic plates, mp 32–34°C, R_f 0.43 (chloroform). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.19 s and 3.46 s (NCH_3), 4.21 (CH_2), 6.68–7.42 m (C_6H_4). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 42.01 and 42.67 (NCH_3), 44.77 (CH_2), 115.09/115.28 (C^3), 123.02/123.14 (C^1), 124.42 (C^5), 128.70/128.76 (C^4), 129.80/129.83 (C^6), 159.07/161.03 (C^2), 199.76 (C=S). Found, %: C 60.57, 60.82; H 6.31, 6.43. $C_{10}H_{12}FNS$. Calculated, %: C 60.88; H 6.13.

***N*,*N*-Dimethyl-2-(4-methylphenyl)ethanethioamide (Vg)** was synthesized in a similar way from 1 g (5.7 mmol) of thiadiazole **IIIg** using 0.23 g (10.1 mmol) of sodium. Yield 0.8 g (73%), light brown needles, mp 72°C (from methanol); published data [11]: mp 72°C; R_f 0.32 (chloroform). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.30 s (CH_3), 3.18 s and 3.46 s (NCH_3), 4.24 (CH_2), 7.10 d (2-H, 6-H), 7.20 d (3-H, 5-H). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 21.03 (CH_3), 42.24 and 44.80 (NCH_3), 50.52 (CH_2), 127.98 (C^3, C^5), 129.43 (C^2, C^6), 132.57 (C^4), 136.50 (C^1), 200.90 (C=S). Found, %: C 68.45, 68.63; H 7.51, 7.81. $C_{11}H_{15}NS$. Calculated, %: C 68.35; H 7.82.

2-(4-Methoxyphenyl)-*N*,*N*-dimethylethanethioamide (Vh) was synthesized in a similar way from 1 g (5.2 mmol) of thiadiazole **IIIh** using 0.24 g (10.4 mmol) of sodium. Yield 0.85 g (78%), yellow needles, mp 79°C (from methanol); published data [10, 11]: mp 75–76°C; R_f 0.27 (chloroform). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.18 s and 3.46 s (NCH_3), 3.76 s (CH_3O), 4.21 (CH_2), 6.85 d (2-H, 6-H),

7.23 d (3-H, 5-H). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 41.92 and 44.58 (NCH_3), 49.80 (CH_2), 55.04 (CH_3O), 113.92 (C^3, C^5), 127.44 (C^1), 128.93 (C^2, C^6), 158.28 (C^4), 200.91 (C=S). Mass spectrum, *m*/*z* (I_{rel}, %): 209 (61) $[M]^+$, 164 (38) $[M - NH(CH_3)_2]^+$, 121 (90) $[M - S{=}CN(CH_3)_2]^+$, 88 (100) $[S{=}CN(CH_3)_2]^+$, 78 (59), 70 (65), 51 (35). Found, %: C 62.87, 63.05; H 7.43, 7.56. $C_{11}H_{15}NOS$. Calculated, %: C 63.12; H 7.22. *M* 209.31.

The melting points were determined on a Boetius melting point apparatus. The ^1H and ^{13}C NMR spectra were measured on Bruker Avance (300 and 75 MHz, respectively) and Bruker AMX-400 instruments (400 and 100 MHz) relative to the residual proton (^1H) and carbon signals (^{13}C) of deuterated solvents. The mass spectra (electron impact, 70 eV) were obtained on a Kratos MS 890 mass spectrometer with direct sample admission into the ion source (ion source temperature 200°C). The progress of reactions was monitored by TLC on Silufol UV-254 plates; spots were visualized under UV light or by treatment with iodine vapor. All solvents used in this work were purified and dehydrated according to standard procedures.

REFERENCES

1. Malek-Yazdi, F. and Yalpani, M., *Synthesis*, 1977, p. 328.
2. Hurd, C.D. and Mori, R.I., *J. Am. Chem. Soc*., 1955, vol. 77, p. 5359.
3. Seybold, G. and Heibl, C., *Chem. Ber*., 1977, vol. 110, p. 1225.
4. Petrov, M.L., Shchipalkin, A.A., and Kuznetsov, V.A., *Russ. J. Org. Chem*., 2007, vol. 43, p. 630.
5. Raap, R. and Micetich, R.G., *Can. J. Chem*., 1968, vol. 46, p. 1057.
6. Petrova, L.L., Trufanova, L.V., Petrov, M.L., Abramov, M.A., Zmitrovich, N.I., and Terent'eva, N.A., *Khim. Farm. Zh*., 1994, vol. 28, no. 1, p. 19.
7. Zmitrovich, N.I., Petrov, M.L., and Petrov, A.A., *Zh. Org. Khim*., 1991, vol. 27, p. 1394.
8. Schuijl, P.J.W. and Brandsma, L., *Recl. Trav. Chim. Pays–Bas*, 1968, vol. 87, p. 38.
9. Bobylev, V.A., Petrov, M.L., and Petrov, A.A., *Zh. Org. Khim*., 1982, vol. 18, p. 274.
10. Ogura, K., Ito, Y., and Tsuchihashi, G., *Synthesis*, 1980, p. 736.
11. Schroth, W. and Andersch, J., *Synthesis*, 1989, p. 202.