Russian Journal of Organic Chemistry, Vol. 38, No. 2, 2002, pp. 297–299. Translated from Zhurnal Organicheskoi Khimii, Vol. 38, No. 2, 2002, pp. 318–320.

SHORT COMMUNICATIONS

Reaction of Thiosemicarbazones from Heterocyclic Series with Acetic Anhydride

V. N. Elokhina, R. V. Karnaukhova, A. S. Nakhmanovich, L. I. Larina, and V. A. Lopyrev

Faworsky Irkutsk Institute of Chemistry, Siberian Division, Russian Academy of Sciences, Irkutsk, 664033 Russia

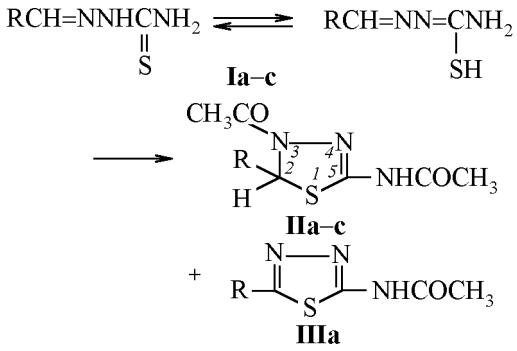
Received December 8, 2000

Several procedures are known for the synthesis of 1,3,4-thiadiazolines and 1,3,4-thiadiazoles from thiosemicarbazones and thiobenzhydrazide.

2,4-Substituted 5,5-pentamethylene-4,5-dihydro-1,3,4-thiadiazole was prepared by treating cyclohexanone thiosemicarbazone with acetic anhydride at heating or with acetyl chloride in pyridine [1, 2]. 1,4-Diphenylthiosemicarbazide on long standing with formaldehyde in dioxane afforded 4-phenyl-2-phenylamino-1,3,4-thiadiazolidine [3].

Substituted 4-carbamoyl-2-ureido-4,5-dihydro-1,3,4-thiadiazoles were obtained by cyclization of thiosemicarbazones of benzaldehyde, 2-furaldehyde, acetone, cyclopentanone, and cyclohexanone with isocyanates at heating (100°C) [4]. Thiobenzoylhydrazones at prolonged heating in chloroform cyclized into 2,5-substituted 1,3,5-thiadiazoles [5]. By treating at heating (100°C) with acetic anhydride thiosemicarbazones of benzaldehyde, formaldehyde, acetone, and acetophenone were prepared 4-acetyl-2-acetylamino-Δ^2-1,3,4-thiadiazolines and 5-amino-3-acetyl-Δ^2-2,3-dihydro-1,3,4-thiadiazolines [6]. Substituted 2,3-dihydro-1,3,4-thiadiazoles were obtained by reaction of N-phenylthiobenzoylhydrazide with aliphatic, aromatic, and heterocyclic aldehydes and ketones in the presence of trimethylsilyl chloride in benzene [7].

With the aim to prepare compounds promising as biologically active substances we carried out in this study acetylation with acetic anhydride of thiosemicarbazones prepared from 4-pyridinecarboxaldehyde, 2-thiophenecarboxaldehyde, 2-furaldehyde, and isatin. The reaction involved cyclization by addition of the mercapto group across the C=NH bond and simultaneous acetylation of the NH groups in the ring and NH_2 groups in the side chain resulting in 4-acetyl-2-acetylamino-5-heteryl-1,3,4-thiadiazolines **IIa–c**.



R = 4-pyridyl (**a**), 2-thienyl (**b**), 2-furyl (**c**).

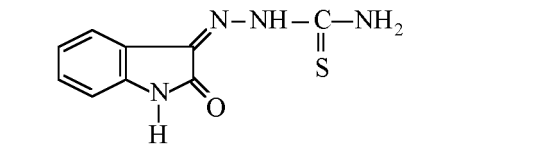
The reaction between 4-pyridinecarboxaldehyde thiosemicarbazone with acetic anhydride at 100°C within 2 h afforded a mixture of 3-acetyl-5-acetylamino-2-(4-pyridyl)-2,3-dihydro-1,3,4-thiadiazole (**IIa**) (yield 37%) and 5-acetylamino-2-(4-pyridyl)-1,3,4-thiadiazole (**IIIa**) (yield 25%). The reaction performed at 120°C for 5 h furnished only compound **IIIa** in 63% yield.

The reactions with acetic anhydride of thiosemicarbazones of the 2-thiophenecarboxaldehyde and the 2-furaldehyde were carried out at 75–80°C for 3–4 h. As the only products were obtained 3-acetyl-5-acetylamino-2-thienyl(2-furyl)-2,3-dihydro-1,3,4-thiadiazoles (**IIb, c**) in 98 and 75% yield respectively. Here unlike the acetylation of the 4-pyridinecarboxaldehyde thiosemicarbazone we failed to isolate 1,3,4-thiazoles **IIIb, c**.

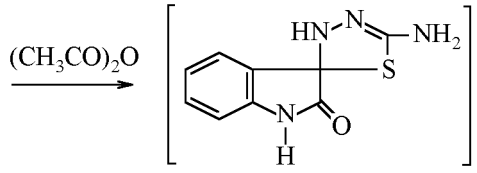
At heating to 115–120°C for 4 h with acetic anhydride isatin-3-thiosemicarbazone (**IV**) underwent cyclization into intermediate **V** that on acetylation of the NH and NH_2 groups afforded tetrahydro-1,3,4-thiadiazole-2-spiro-3'-indol-2'-one (**VI**) in 74% yield.

In the IR spectra of compounds **IIa–c, IIIa, VI** are present absorption bands from stretching vibrations

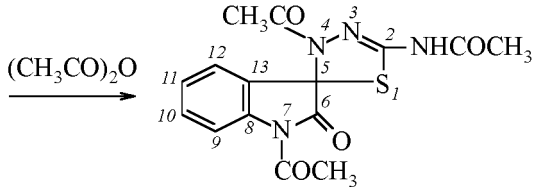
1070-4280/01/3802-297$27.00 © 2002 MAIK "Nauka/Interperiodica"



IV



V



VI

of bonds C–S, at 690–695, C=N at 1580–1590, C=O at 1630–1649, 1690–1710, and NH at 3150–3210 cm^{-1}.

Acetyl-5-acetylamino-2-(4-pyridyl)-2,3-dihydro-1,3,4-thiadiazole (IIa). A mixture of 3.2 g (0.02 mol) of 4-pyridinecarboxaldehyde thiosemicarbazone and 20 ml of acetic anhydride was stirred for 2 h at heating to 100°C, then the mixture was cooled to 0°C, the separated precipitate was filtered off and dissolved in 30 ml of ethanol. The insoluble part of the precipitate was filtered off, the ethanol solution was partly evaporated, cooled to 0°C, the separated precipitate was filtered off and dried in a vacuum. We obtained 1.1 g (38%) of compound **IIa**, mp 224–226°C. ^{1}H NMR spectrum, δ, ppm: 2.04 s (3H, CH_3), 2.44 s (3H, CH_3), 6.84 s (1H, CHS), 7.26–8.56 m (4H, pyridyl), 11.81 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 21.67 and 22.43 ($2CH_3$), 64.56 (C^5), 119.87 ($C^{2,6}$, pyridyl), 145.80 (C^1, pyridyl), 149.45 (C^2), 150.06 ($C^{3,5}$, pyridyl), 167.66 and 169.52 (2C=O). Found, %: C 49.26; H 4.43; N 21.16; S 12.10. $C_{11}H_{12}N_4O_2S$. Calculated, %: C 50.00; H 4.55; N 21.21; S 12.12.

3-Acetyl-5-acetylamino-2-(2-thienyl)-2,3-dihydro-1,3,4-thiadiazole (IIb). A mixture of 1 g (5 mmol) of 2-thiophenecarboxaldehyde thiosemicarbazone and 15 ml of acetic anhydride was stirred for 4 h at heating to 75–80°C, then cooled, the separated precipitate was filtered off and dried in a vacuum. Yield 1.32 g (98%), mp 215–216°C (from methanol). ^{1}H NMR spectrum, δ, ppm: 2.06 s (3H, CH_3), 2.16 s (3H, CH_3), 6.94–7.47 m (3H, thienyl), 7.11 s (1H, CHS), 11.76 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 21.71 and 22.48 ($2CH_3$), 61.46 (C^5), 121.23, 126.11, 126.74 ($C^{3,4,5}$, thienyl), 144.54 (C^2, thienyl), 146.12 (C^2), 167.22 and 169.43 (2C=O). Found, %: C 44.38; H 3.98; N 15.48; S 23.50. $C_{10}H_{11}N_3O_2S_2$. Calculated, %: C 44.61; H 4.08; N 15.61; S 23.79.

3-Acetyl-5-acetylamino-2-(2-furyl)-2,3-dihydro-1,3,4-thiadiazole (IIc). A mixture of 1.43 g (8 mmol) of 2-furaldehyde thiosemicarbazone and 15 ml of acetic anhydride was stirred for 3 h at heating to 80°C, then cooled, the separated precipitate was filtered off and dried in a vacuum. Yield 1.5 g (75%), mp 185–186°C (from methanol). ^{1}H NMR spectrum, δ, ppm: 2.00 s (3H, CH_3), 2.21 s (3H, CH_3), 6.31–7.59 m (3H, furyl), 6.90 s (1H, CHS), 11.73 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 21.86 and 22.56 ($2CH_3$), 59.38 (C^5), 107.19 (C^4, furyl), 110.69 (C^3, furyl), 143.17 (C^5, furyl), 145.87 (C^2, furyl), 151.60 (C^2), 167.42 (C=O), 169.55 (C=O). Found, %: C 47.12; H 4.12; N 16.47; S 12.55. $C_{10}H_{11}N_3O_3S$. Calculated, %: C 47.43; H 4.34; N 16.60; S 12.65.

5-Acetylamino-2-(4-pyridyl)-2,3-dihydro-1,3,4-thiadiazole (IIIa). (a) The precipitate insoluble in ethanol during isolation of compound **IIa** was recrystallized from DMSO and dried in a vacuum. Yield 0.55 g (25%), mp 337–338°C. (b) In reaction of 4-pyridinecarboxaldehyde thiosemicarbazone (**Ia**) with acetic anhydride carried out at 120°C for 5 h from the reaction mixture was separated only compound **IIIa** in 63% yield. ^{1}H NMR spectrum, δ, ppm: 2.34 s (3H, CH_3), 7.89–8.72 m (4H, pyridyl), 11.85 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 22.32 (CH_3), 120.69 ($C^{2,6}$, pyridyl), 137.14 (C^1, pyridyl), 150.61 ($C^{3,5}$, pyridyl), 159.48, 159.53 ($C^{2,5}$), 168.81 (C=O). Found, %: C 49.00; H 3.55; N 25.25; S 14.12. $C_9H_8N_4OS$. Calculated, %: C 49.09; H 3.63; N 25.45; S 14.55.

1′,3-Diacetyl-5-acetylamino-2,2′,3,3′-tetrahydro-1,3,4-thiadiazol-2-spiro-3′-indol-2′-one (VI). A mixture of 4.4 g of isatin-3-thiosemicarbazone (**IV**) and 30 ml of acetic anhydride was stirred for 4 h at heating to 115–120°C, then it was cooled to 20°C and poured into ice water. The separated precipitate was filtered off and washed with acetone on the filter. Yield of compound **VI** 5.14 g (74%), mp 238–241°C. ^{1}H NMR spectrum, δ, ppm: 2.10 s (3H, $C\underline{H}_3CONH$), 2.15 s (3H, $C\underline{H}_3CON^4$), 2.56 s (3H, CH_3CON^7), 7.27–8.08 m (4H, H arom), 12.01 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 21.86 ($\underline{C}H_3CONH$),

22.33 ($\underline{C}H_3CON^4$), 26.05 ($\underline{C}H_3CON^7$), 75.13 (C^5), 11572 (C^9), 123.96 (C^{10}), 125.88 (C^{11}), 127.75 (C^{13}), 130.37 (C^{12}), 139.11 (C^8), 143.91 (C^2), 167.22 (C^6), 170.20, 170.37 (CONH, CON^4), 172.95 (CON^7). Found, %: C 51.81; H 4.14; N 15.92; S 8.88. $C_{15}H_{14}N_4O_4S$. Calculated, %: C 52.02; H 4.04; N 16.18; S 9.24.

The ^1H and ^{13}C NMR spectra were registered on Bruker DPX-400 instrument at operating frequencies 400.13 and 100.61 MHz respectively from solutions in DMSO-d_6.

REFERENCES

1. Andreae, S., Schmitz, E., *Z. Chem.*, 1983, vol. 23, pp. 450–451.
2. Andreae, S., Schmitz, E., and Seeboth, H., *J. Pr. Chem.*, 1986, vol. 328, no. 2, pp. 205–214.
3. Evans, G.W. and Milligan, B., *Austral. J. Chem.*, 1967, vol. 20, no. 8, pp. 1783–1785.
4. Graubaum, H., Nadolski, K., and Andreae, S., *Z. Chem.*, 1986, vol. 26, pp. 99–100.
5. Yakimovich, S.I., Zelenin, K.N., Nikolaev, V.N., Koshmina, N.V., Alekseev, V.V., and Khrustalev, V.A., *Zh. Org. Khim.*, 1983, vol. 19, no. 9, pp. 1875–1881.
6. Kubota, S., Ueda, Y., Fujikane, K., Toyooka, K., and Shibuya, M., *J. Org. Chem.*, 1980, vol. 45, no. 8, pp. 1473–1477.
7. Matsubara, Y., Kitano, K., Yamamoto, T., and Maeshima, T., *Chem. Pharm. Bull.*, 1998, vol. 46, no. 2, pp. 329–331.