One-pot synthesis of 2-amino-5-aryl-5*H*-thiazolo[4,3-*b*]-1,3,4-thiadiazoles

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Equimolar mixtures of aromatic aldehydes with thioglycolic acid and thiosemicarbazide in H_2SO_4 transform into 2-amino-5-aryl-5*H*-thiazolo[4,3-*b*]-1,3,4-thiadiazoles.

Key words: aromatic aldehydes, thioglycolic acid, thiosemicarbazide, 2-aryl-(4-oxothiazolidin-3-yl)thiourea, cyclodehydration, 2-amino-5-aryl-5*H*-thiazolo[4,3-*b*]-1,3,4-thiadiazoles.

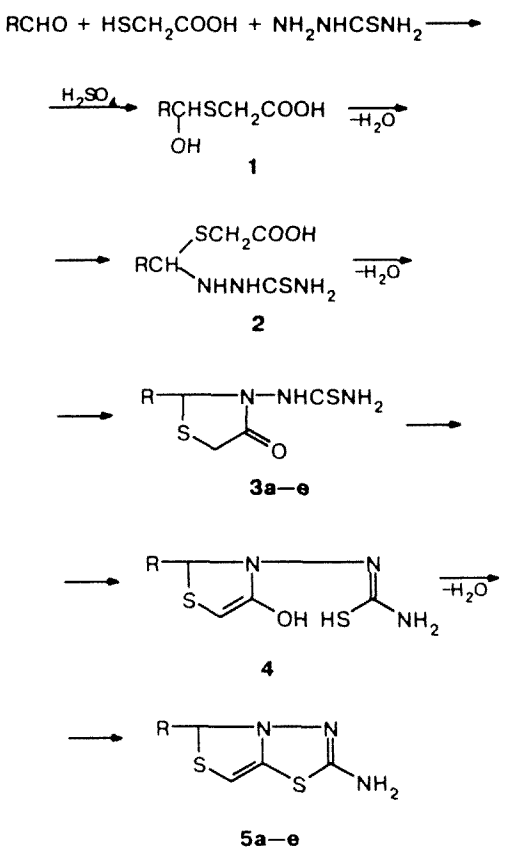
Recently, *N*-substituted-2-amino-5-aryl-5*H*-thiazolo[4,3-*b*]-1,3,4-thiadiazoles, active against pathogenic fungi of agricultural crops, have become substances, among other 1,3,4-thiadiazoles, that have drawn the attention of researchers.[1—3] The only known method giving rise to that heterocyclic system is based on cyclodehydration of (4-oxothiazolidine-3-yl)thioureas (in concentrated H_2SO_4 medium), which in turn are formed upon cyclodehydration of the products of addition of thioglycolic acid to the azomethine fragment of arylthiosemicarbazones.[1] Thus, the synthesis of the finished products from aromatic aldehydes, thiosemicarbazide, and thioglycolic acid involves three steps.

We have developed a procedure for one-pot synthesis of 2-amino-5-aryl-5*H*-thiazolo[4,3-*b*]-1,3,4-thiadiazoles (**5a—e**) (Scheme 1) from equimolar quantities of an aromatic aldehyde, thioglycolic acid, and thiosemicarbazide. The interaction between equimolar quantities of aromatic aldehydes and thioglycolic acid proceeds with heat liberation and probably results in semithioacetals of thioglycolic acid (**1**), which further react with thiosemicarbazide to give functionalized *N,S*-acetals (**2**). Thioureas **3** are obtained as a result of cyclodehydration of the latter in concentrated H_2SO_4 medium; they transform into compounds **5a—e** through intermediates **4**. We also obtained compound **5a** using a known procedure[1] for cyclization of 2-phenyl-(4-oxothiazolidine-3-yl)thiourea, synthesized by interaction between benzaldehyde, thioglycolic acid, and thiourea in a boiling benzene solution.

The structure of compounds **5a—e** was confirmed by IR and ^{1}H NMR spectroscopy.

The IR spectra of these compounds have no absorption band in the region of 1680—1630 cm^{-1}, characteristic of the stretching vibrations of the carbonyl group of the amide fragment in compounds of type **3**, which confirms the hydrothiazolo[4,3-*b*]-1,3,4-thiadiazole structure. There are two absorption bands in the region 3470—3400 cm^{-1} and 3250—3220 cm^{-1} that might be interpreted as asymmetric and symmetric stretching vibrations of the amino group. Four peaks, due to the CH-stretching vibrations of the aromatic ring, were recorded in the interval 3180—2820 cm^{-1}. An intense

Scheme 1



R = Ph (**a**), 4-$O_2NC_6H_4$ (**b**), 4-FC_6H_4 (**c**), 2-OH-5-BrC_6H_3 (**d**), 4-$Me_2NC_6H_4$ (**e**)

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absorption band is observed in the spectra at 1960 cm^{-1}, which can be assigned to the C—C normal vibrations of the aromatic ring. A group of the absorption bands in the 1600—500 cm^{-1} region is likely to be associated with the 5-phenyl-5*H*-thiazolo[4,3-*b*]-1,3,4-thiadiazole system.

The methine proton signals and those of the proton in the 5H-position of the thiazole ring are detected in the ^1H NMR spectra at 7.96—8.3 ppm. The resonance lines of the phenyl ring protons are observed at 7.08—8.27 ppm.

Experimental

IR spectra of the substances in KBr tablets were recorded on a UR-20 spectrometer; ^1H NMR spectra were registered on a "Tesla 587 C" (100 MHz) instrument in DMSO-d_6 (inner standard HMDS). The melting point was determined on a Boetius microheated stage.

General procedure of synthesis of compounds 5a—e. An aromatic aldehyde (0.02 mole) and thioglycolic acid (0.02 mole) were mixed, and after 10—15 min. 0.022 mole of thiosemicarbazide was added; then 10 mL of concentrated H_2SO_4 was added in portions upon cooling. The mixture was homogenized and left for 18—24 h at ~20 °C. The reaction mass was treated with 30—50 g ice, the precipitated solid was decanted, water was added, and the obtained suspension was neutralized with 40 % NaOH until a weak alkaline reaction. Compounds **5a—e** were recrystallized from aqueous dioxane solution.

2-Amino-5-phenyl-5*H*-thiazolo[4,3-*b*]-1,3,4-thiadiazole (5a), yield 87.3%, m.p. 158—160 °C, yellowish crystals. Found (%): N, 17.63. $C_{10}H_9N_3S_2$. Calculated (%): N, 17.86.

IR spectrum (ν/cm^{-1}): 3440; 3260; 3160; 2990; 2860; 1605; 1550; 1475; 1380; 1300; 1230; 1110; 1060; 950; 875; 825; 770; 695; 630; 548; 512.

^1H NMR spectrum (δ, ppm): 11.14 (s, CH); 7.98 (s, CH); 7.68 (m, Ph); 7.30 (m, Ph).

2-Amino-5-(4-nitrophenyl)-5*H*-thiazolo[4,3-*b*]-1,3,4-thiadiazole (5b), yield 90%, m.p. 245—247 °C, yellowish crystals. Found (%): N, 19.80. $C_{10}H_8N_4O_2S_2$. Calculated (%): N, 20.00.

IR spectrum (ν/cm^{-1}): 3410; 3260; 3180; 2990; 2850; 1610; 1540; 1480; 1365; 1300; 1235; 1110; 1080; 940; 850; 825; 740; 710; 680; 635; 550; 525.

^1H NMR spectrum (δ, ppm): 11.19 (s, CH); 7.98 (s, CH); 8.27 (d, C_6H_4); 7.67 (d, C_6H_4).

2-Amino-5-(4-fluorophenyl)-5*H*-thiazolo[4,3-*b*]-1,3,4-thiadiazole (5c), yield 77%, m.p. 188—190 °C, pale yellow crystals. Found (%): N, 16.80. $C_{10}H_8FN_3S_2$. Calculated (%): N, 16.52.

IR spectrum (ν/cm^{-1}): 3400; 3250; 3170; 3030; 2820; 1610; 1545; 1470; 1375; 1300; 1235; 1105; 1090; 955; 935; 880; 840; 635; 570; 520.

^1H NMR spectrum (δ, ppm): 11.14 (s, CH); 7.96 (s, CH); 7.74 (d, C_6H_4); 7.08 (d, C_6H_4).

2-Amino-5-(5-bromo-2-oxyphenyl)-5*H*-thiazolo[4,3-*b*]-1,3,4-thiadiazole (5d), yield 85%, m.p. 247—250 °C, yellow-orange crystals. Found (%): N, 12.53. $C_{10}H_8BrN_3OS_2$. Calculated (%): N, 12.72.

IR spectrum (ν/cm^{-1}): 3470; 3260; 3160; 3060; 3050; 1615; 1560; 1485; 1360; 1300; 1270 (C—O); 1185 (C—O); 1130; 1090; 950; 920; 880; 830; 780; 700; 630; 560; 540.

^1H NMR spectrum (δ, ppm): 11.22 (s, CH); 8.3 (s, CH); 8.06 (d, C_6H_3); 7.28 (m, C_6H_3), 6.76 (d, C_6H_3).

2-Amino-5-(4-dimethylaminophenyl)-5*H*-thiazolo[4,3-*b*]-1,3,4-thiadiazole (5e), yield 83%, m.p. 210—212 °C, yellowish crystals. Found (%): N, 18.04. $C_{12}H_{14}N_4S_2$. Calculated (%): N, 18.28.

IR spectrum (ν/cm^{-1}): 3430; 3270; 3170; 3115; 2940; 2830; 1610; 1560; 1365; 1300; 1230; 1190; 1065; 975; 925; 885; 820; 685; 535.

^1H NMR spectrum (δ, ppm): 11.09 (s, CH); 7.86 (s, CH); 7.50 (d, C_6H_4); 6.70 (d, C_6H_4); 2.49 (s, Me).

2-Phenyl-(4-oxothiazolidine-3-yl)thiourea (3a). a. A mixture of 0.1 mole of benzaldehyde, 0.1 mole thioglycolic acid, and 0.1 mole thiosemicarbazide was boiled in 150 mL of benzene using the Dean and Stark distillation head until complete water separation. After elimination of the solvent the residue was recrystallized from ethanol; **3a** was obtained in 81.5% yield, m.p. 146—148 °C, white crystals.

b. Compound **3a** was obtained using procedure[1] from benzaldehyde thiosemicarbazone, yield 86%, m.p. 148—150 °C (*i*-PrOH).

Synthesis of 5a from 3a. Compound **5a** was obtained from 0.02 mole 2-phenyl-4-oxothiazolidine-3-yl-thiourea and 10 mL concentrated H_2SO_4, yield 90%, m.p. 159—161 °C.

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