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Synthesis and transformations of 1-[2-(toluene-4-sulfonamido)ethyl]thiourea

Abstract: Readily available 2-(toluene-4-sulfonylamino) ethylamine is a convenient starting material for a two-step synthesis of 1-[2-(toluene-4-sulfonamido)ethyl]thiourea (**2**). Heterocyclization of the thiourea moiety in **2** furnished a thiazole derivative **3** which was further functionalized into substituted thiazoles **4–6**. A series of 2-(thiazol-5-yl)-[1,3,4]oxadiazoles **8**, **10** and 2-(thiazol-5-yl)-[1,3,4] thiadiazoles **9**, **11** were obtained.

Keywords: heterocyclization; 1,3,4-oxadiazoles; 1,3,4-thiadiazoles; thiazole; 1-[2-(toluene-4-sulfonamido)ethyl] thiourea.

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Introduction

Thiazole, 1,3,4-thiadiazole and 1,3,4-oxadiazole are interesting and important heterocyclic systems, derivatives of which possess a large diversity of biological activity (http://www.alanwood.net/pesticides/class_pesticides.html, [1]). In particular, we have established that thiazolyl-substituted 1,3,4-thiadiazoles and 1,3,4-oxadiazoles are fungicidal and growth-stimulant agents [1].

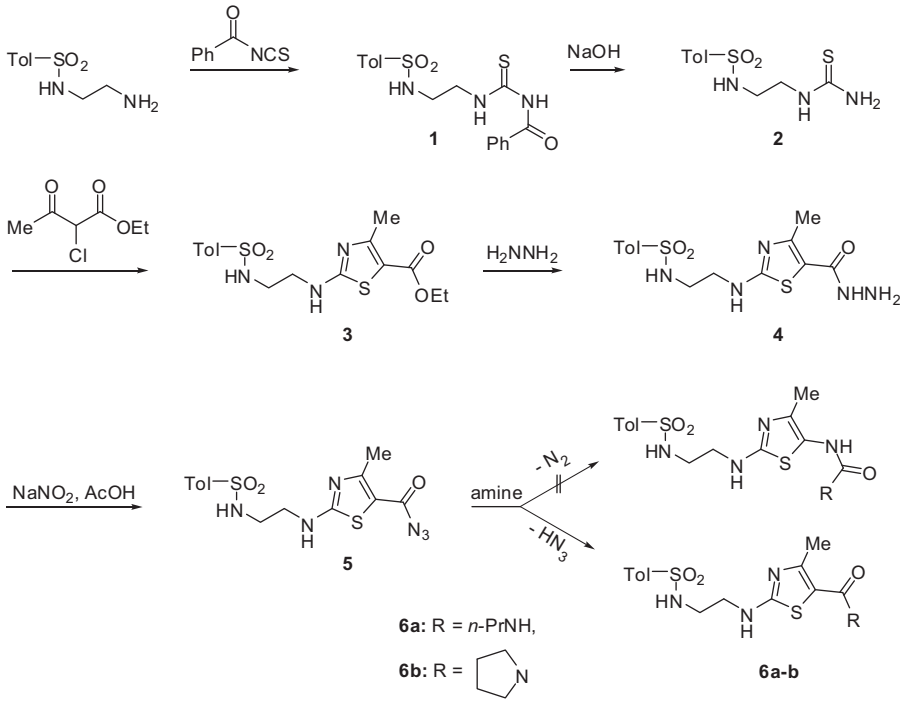
The aim of this investigation was to develop facile and efficient methods for the synthesis of derivatives mentioned above, containing pharmacophore 2-(toluene-4-sulfonylamino)-ethylamino moiety. It can be predicted that the desired products may show interesting physiological activity.

Results and discussion

Synthesis

1-(Toluene-4-sulfonamidoethyl)-3-benzoylthiourea (**1**) was synthesized by the reaction of 2-(toluene-4-sulfonylamino)ethylamine with benzoyl isothiocyanate (Scheme 1). Debenzoylation of **1** furnished 1-(toluene-4-sulfonamidoethyl)thiourea (**2**), heterocyclization of which with ethyl 2-chloro-3-oxobutyrate afforded ethyl 4-methyl-2-[2-(toluene-4-sulfonylamino)ethylamino]thiazole-5-carboxylate (**3**). Treatment of ester **3** with hydrazine hydrate yielded 4-methyl-2-[2-(toluene-4-sulfonylamino) ethylamino]thiazole-5-carboxylic acid hydrazide (**4**), which was subsequently transformed into azide **5**. The reactions of azide **5** with propylamine and pyrrolidine did not proceed with the expected elimination of nitrogen and formation of 3-ureido derivatives. Instead, the respective product **6** was obtained. The isolation of **6** is fully consistent with ^{1}H NMR and mass spectra. In particular, the mass spectra of **6a** (R = C_3H_7NH) and **6b** (R = pyrrolidino) show the respective molecular ion peaks at m/z 396 and m/z 408, as calculated for these structures.

4-Methyl-2-[2-(toluene-4-sulfonylamino)ethylamino]thiazole-5-carboxylic acid hydrazide (**4**) was also used as an initial compound for the syntheses of noncondensed bicyclic systems, including thiazole ring in combination with [1,3,4]oxadiazole and [1,3,4] thiadiazole heterocycles (Scheme 2). First, the reaction of hydrazide **4** with carbon disulfide and potassium hydroxide in ethanol furnished the potassium salt of 2-{2-[2-(toluene-4-sulfonylamino)ethylamino]-4-methylthiazole-5-carbonyl}hydrazinecarbodithioic acid (**7**). Then, alkaline and acidic hydrolysis of 7 furnished 2-{[2-(toluene-4-sulfonylamino)ethylamino]-4-methylthiazol-5-yl}-5-thioxo-4,5-dihydro[1,3,4]oxadiazole (**8**) and 2-{[2-(toluene-4-sulfonylamino)ethylamino]-4-methylthiazol-5-yl}-5-thioxo-4,5-dihydro[1,3,4]thiadiazole (**9**), respectively.

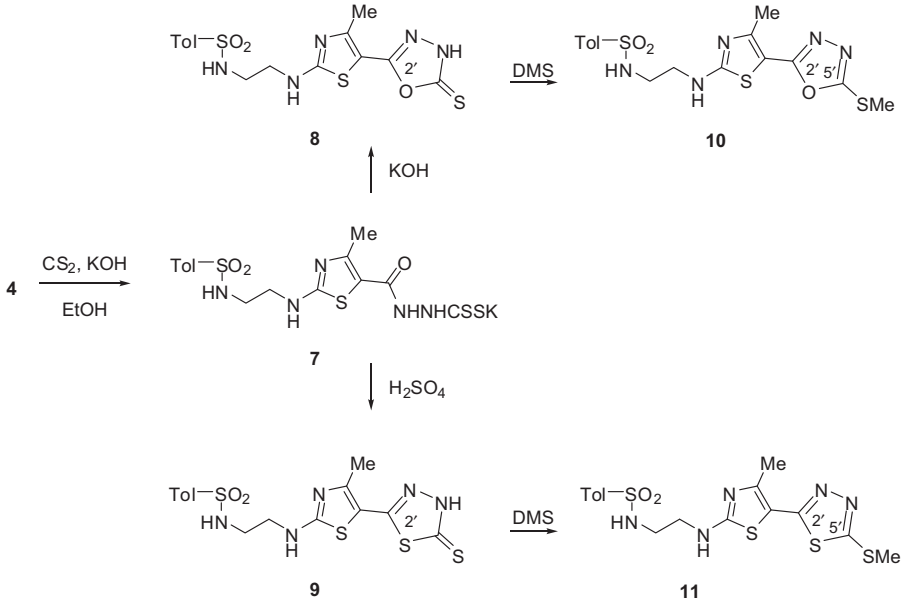


Scheme 1

The suggested thione forms of **8** and **9** are consistent with their ^{13}C NMR spectra that show signals at 176 ppm for the C=S function. The reaction of compounds **8** and **9** with dimethyl sulfate yielded their respective S-methylated derivatives **10** and **11**. In ^{13}C NMR spectra of these compounds instead of the C=S bond signals, new signals due to C=N bond of 1,3,4-oxadiazole or 1,3,4-thiadiazole system appear.

Biological activity

In preliminary biological tests the growth regulatory properties of synthesized compounds were investigated for their aqueous emulsions (25 mg/L and 50 mg/L) on the germination, growth and survivability of seeds and seedlings of dicotyledonous bean (*Phaseolus vulgaris* L.). The activities of these compounds were compared with that of heteroauxin.



Scheme 2

Practically all investigated substances **1–11** have shown strongly pronounced growth stimulant properties and their calculated activities were in the interval of 75–98%.

Experimental section

General

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian Mercury-300 spectrometer, in a mixture of DMSO-d_6 and CCl_4 (1:3) or in pure DMSO-d_6. The reaction progress and purity of products were checked by using TLC on Silufol UV-254 plates with acetone/hexane (2:1) as an eluent. Melting points are uncorrected. 2-(Toluene-4-sulfonylamino)ethylamine was obtained as described previously [2].

3-Benzoyl-1-(toluene-4-sulfonamidoethyl)thiourea (1) The mixture of 2-(toluene-4-sulfonylamino)-ethylamine (10.7 g, 0.05 mol) and benzoyl isothiocyanate (8.15 g, 0.05 mol) in 50 mL of toluene in the presence of catalytic amounts of pyridine was heated under reflux for 4 h. The precipitate of product **1** was filtered and washed with hexane: yield 17.7 g (94%) of white crystals; mp 148–150°C; ^{1}H NMR: δ 2.36 (s, 3H), 3.08 (m, 2H), 3.75 (m, 2H), 7.23–8.00 (m, 10H), 10.88 (brs, 1H), 10.96 (t, 1H, J = 5.5 Hz). Anal. Calcd for $C_{17}H_{19}N_3O_3S_2$: C, 54.09; H, 5.07; N, 11.13; S, 16.99. Found: C, 54.15; H, 4.95; N, 10.82; S, 16.73.

1-(Toluene-4-sulfonamidoethyl)thiourea (2) A suspension of compound **1** (3.8 g, 0.01 mol) in 12 mL of 10% NaOH solution was heated under reflux with continuous stirring for 3 h. After cooling, 10 mL of water was added and the solution was acidified with acetic acid. In 1 h the compound **2** was separated: yield 1.86 g (68%) of white crystals; mp116–118°C; ^{1}H NMR: δ 2.42 (s, 3H), 2.88 (m, 2H), 3.38 (m, 2H), 6.80 (brs, 2H), 7.23–7.82 (m, 5H), 8.17 (t, 1H, J = 5.5 Hz). Anal. Calcd for $C_{10}H_{15}N_3O_2S_2$: C, 43.93; H, 5.53; N, 15.37; S, 23.46. Found: C, 43.76; H, 5.41; N, 15.09; S, 23.21.

4-Methyl-2-[2-(toluene-4-sulfonylamino)ethylamino]thiazole-5-carboxylic acid ethyl ester (3) A suspension of compound **2** (2.75 g, 0.01 mol), ethyl 2-chloro-3-oxobutyrate (1.65 g, 0.01 mol) and 94% K_2CO_3 (0.75 g, 0.005 mol) in 20 mL of absolute ethanol was heated under reflux with continuous stirring for 5 h. After concentration on a rotary evaporator, the solid residue of **3** was treated with 20 mL of water, filtered and washed with 50% ethanol: yield 2.83 g (74%) of white crystals; mp 152–154°C; ^{1}H NMR: δ 1.30 (t, 3H, J = 7.0 Hz), 2.40 (s, 3H), 2.42 (s, 3H), 2.92 (m, 2H), 3.35 (m, 2H), 4.18 (t, 2H, J = 7.0 Hz), 7.22–7.70 (m, 4H) 7.43 (t, 1H, J = 5.5 Hz), 7.95 (t, 1H, J = 5.5 Hz). Anal. Calcd for $C_{16}H_{21}N_3O_4S_2$: C, 50.11; H, 5.52; N, 10.96; S, 16.72. Found: C, 49.97; H, 5.40; N, 10.68; S, 16.49.

4-Methyl-2-[2-(toluene-4-sulfonylamino)ethylamino]thiazole-5-carboxylic acid hydrazide (4) A suspension of compound **3** (3.83 g, 0.01 mol) in 20 mL of hydrazine hydrate (53%) was stirred at 20–25°C for 48 h. The precipitate of **4** was filtered, washed with water and dried: yield 2.9 g (79%) of white crystals; mp 206–208°C; ^{1}H NMR: δ 2.38 (s, 3H), 2.42 (s, 3H), 2.95 (m, 2H), 3.32 (m, 2H), 4.08 (brs, 2H), 7.22–7.72 (m, 4H), 7.45 (t, 1H, J = 5.5 Hz), 7.70 (brs, 1H), 8.50 (brt, 1H). Anal. Calcd for $C_{14}H_{19}N_5O_3S_2$: C, 45.51; H, 5.18; N, 18.96; S, 17.36. Found: C, 45.38; H, 5.06; N, 18.67; S, 17.08.

4-Methyl-2-[2-(toluene-4-sulfonylamino)ethylamino]thiazole-5-carboxylic acid azide (5) To a suspension of compound **4** (3.7 g 0.01 mol) in 30 mL of water, 1.75 g (0.025 mol) of $NaNO_2$ was added. Then the mixture was cooled to 0°C and treated portion-wise with 1.5 mL (0.025 mol) of acetic acid. After stirring at 20–25°C for 3 h, the resultant precipitate of **5** was filtered, washed with 30 mL of water and dried: yield 3.42 g (90%) of white crystals; mp 135–136°C; ^{1}H NMR: δ 2.42 (s, 3H), 2.45 (s, 3H), 2.95 (m, 2H), 3.36 (m, 2H), 7.24–7.70 (m, 4H) 7.50 (t, 1H, J = 5.5 Hz), 8.43 (brt, 1H). Anal. Calcd for $C_{14}H_{16}N_6O_3S_2$: C, 44.20; H, 4.24; N, 22.09; S, 16.86. Found: C, 44.03; H, 4.12; N, 21.80; S, 16.59.

General procedure for 6a,b

A suspension of compound **5** (1.14 g, 0.003 mol) and 0.0033 mol of *n*-propylamine or pyrrolidine in 20 mL of anhydrous benzene in the presence of a catalytic amount of pyridine was heated under reflux for 2 h. Concentration under reduced pressure was followed by crystallization of the residue from aqueous ethanol (50%).

***N*-Propyl-2-[2-(toluene-4-sulfonylamino)ethylamino]-4-methylthiazole-5-carboxamide (6a)** Yield 1.1 g (89%) of white crystals; mp 210–212°C; ^{1}H NMR: δ 0.90 (t, 3H, J = 7 Hz), 1.53 (m, 2H), 2.38 (s, 3H), 2.42 (s, 3H), 2.95 (m, 2H), 3.12 (q, 2H, J = 7 Hz), 3.30 (m, 2H), 7.00 (t, 1H, J = 5 Hz), 7.25–7.70 (m, 4H) 7.46 (brt, 1H, J = 5 Hz), 7.60 (t, 1H); MS: m/z 396 (M+). Anal. Calcd for $C_{17}H_{24}N_4O_3S_2$: C, 51.49; H, 6.10; N, 14.13; S, 16.17. Found: C, 51.32; H, 6.00; N, 13.88; S, 15.80.

2-[2-(Toluene-4-sulfonylamino)ethylamino]-4-methyl-5-(pyrrolidinocarbonyl)thiazole (6b) Yield 1.1 g (87%) of white crystals; mp 150–152°C; ^{1}H NMR: δ 1.90 (m, 4H), 2.22 (s, 3H), 2.42 (s, 3H), 2.95 (m, 2H), 3.30 (m, 2H), 3.48 (m, 4H), 7.25–7.70 (m, 4H) 7.46 (brt, 1H), 7.55 (t, 1H, J = 5 Hz); MS: m/z 408 (M+). Anal. Calcd for $C_{18}H_{24}N_4O_3S_2$: C, 52.92; H, 5.92; N, 13.71; S, 15.70. Found: C, 52.80; H, 5.82; N, 13.47; S, 15.49.

Potassium salt of 2-{2-[2-(toluene-4-sulfonylamino)ethylamino]-4-methylthiazole-5-carbonyl}hydrazinocarbodithioic acid (7) A suspension of compound **4** (3.7 g, 0.01 mol) and KOH (0.84 g, 0.015 mol) in 20 mL of absolute ethanol was cooled to 0°C and treated dropwise with 0.9 mL (0.015 mol) of carbon disulfide. The mixture was briefly stirred at 20–25°C and then allowed to stand for 24 h. The precipitate of **7** was filtered and washed with 10 mL of cool ethanol: yield 3.96 g (82%) of white crystals; mp 136–138°C; ^{1}H NMR: δ 2.40 (s, 3H), 2.42 (s, 3H), 2.95 (m, 2H), 3.31 (m, 2H), 7.22–7.72 (m, 4H), 7.15 (brs, 1H), 7.40 (t, 1H, J = 5.5 Hz), 7.65 (brs, 1H), 8.32 (brt, 1H). Anal. Calcd for $C_{15}H_{18}N_5O_3S_4$: C, 37.25; H, 3.75; N, 14.48; S, 26.52. Found: C, 37.06; H, 3.58; N, 14.20; S, 26.29.

2-{[2-(Toluene-4-sulfonylamino)ethylamino]-4-methylthiazol-5-yl}-5-thioxo-4,5-dihydro-[1,3,4]oxadiazole (8) A mixture of compound 7 (2.42 g, 0.005 mol) and KOH (0.42 g, 0.0075 mol) in 20 mL of water was heated under reflux for 2 h. After cooling the solution was acidified with dilute solution of hydrochloric acid to pH 4–5, allowed to stand for 1 h, and the resultant precipitate of 8 was filtered and crystallized from 50% aqueous ethanol: yield 1.8 g (87%) of white crystals; mp 253–255°C (dec); ^{1}H NMR: δ 2.40 (s, 3H), 2.42

(s, 3H), 2.95 (m, 2H), 3.37 (m, 2H), 7.22–7.70 (m, 4H), 7.50 (t, 1H, J = 5.5 Hz), 8.20 (brt, 1H), 14.05 (brs, 1H); ^{13}C NMR: δ 17.0, 20.9, 41.3, 43.7, 99.2, 126.4, 128.9, 137.5, 141.7, 154.2, 156.6, 168.6, 175.9. Anal. Calcd for $C_{15}H_{17}N_5O_3S_3$: C, 43.78; H, 4.16; N, 17.02; S, 23.38. Found: C, 43.62; H, 4.10; N, 16.77; S, 23.11.

2-{[2-(Toluene-4-sulfonylamino)ethylamino]-4-methylthiazol-5-yl}-5-thioxo-4,5-dihydro-[1,3,4]thiadiazole (9) To 3 mL of concentrated sulfuric acid, 2.42 g (0.005 mol) of compound **7** was added portion-wise and the mixture was briefly stirred at 20–25°C and then allowed to stand overnight. The transparent solution was transferred into a beaker with 50 mL of cold water and neutralized by cooling with 25% solution of ammonium hydroxide. The precipitate of **9** was filtered, washed with water, dried and crystallized from aqueous (50%) ethanol: yield 1.75 g (82%) of white crystals; mp 134–136°C (dec); ^{1}H NMR: δ 2.40 (s, 3H), 2.48 (s, 3H), 2.96 (m, 2H), 3.40 (m, 2H), 7.23–7.72 (m, 4H) 7.50 (brt, 1H), 8.20 (brt, 1H), 14.00 (brs, 1H). Anal. Calcd for $C_{15}H_{17}N_5O_2S_4$: C, 42.13; H, 4.01; N, 16.38; S, 30.00. Found: C, 41.95; H, 4.09; N, 16.11; S, 29.77.

General procedure for 10, 11

A solution of KOH (0.01 mol) in 10 mL of water was treated at 0°C with 0.01 mol of compound **8** (or **9**) with continuous stirring, and then portion-wise with 1.1 mL (0.011 mol) of dimethyl sulfate. The mixture was briefly stirred at 20°C and then allowed to stand overnight. The precipitate of **10** (or **11**) was filtered, washed with water and dried.

2-{[2-(Toluene-4-sulfonylamino)ethylamino]-4-methylthiazol-5-yl}-5-methylsulfanyl-[1,3,4]oxadiazole (10) Yield 2.72 g (64%) of yellow crystals; mp 176–178°C; ^{1}H NMR: δ 2.40 (s, 3H), 2.43 (s, 3H), 2.75 (s, 3H), 2.95 (m, 2H), 3.38 (m, 2H), 7.25–7.73 (m, 4H), 7.47 (t, 1H, J = 5.3 Hz), 8.05 (t, 1H, J = 5.3 Hz); ^{13}C NMR: δ 14.1, 16.8, 20.8, 41.3, 43.6, 99.7, 126.4, 128.8, 137.5, 141.6, 153.2, 160.7, 161.2, 168.6. Anal. Calcd for $C_{16}H_{19}N_5O_3S_3$: C, 45.16; H, 4.50; N, 16.46; S, 22.60. Found: C, 45.03; H, 4.41; N, 16.20; S, 22.29.

2-{[2-(Toluene-4-sulfonylamino)ethylamino]-4-methylthiazol-5-yl}-5-methylsulfanyl-[1,3,4]thiadiazole (11) Yield 3.13 g (71%) of yellow crystals; mp 180–182°C; ^{1}H NMR: δ 2.38 (s, 3H), 2.42 (s, 3H), 2.78 (s, 3H), 2.97 (m, 2H), 3.38 (m, 2H), 7.25–7.72 (m, 4H), 7.46 (t, 1H, J = 5.3 Hz), 8.05 (brt, 1H). Anal. Calcd for $C_{16}H_{19}N_5O_2S_4$: C, 43.52; H, 4.34; N, 15.86; S, 29.04. Found: C, 43.39; H, 4.27; N, 15.55; S, 28.76.

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