Synthesis of sulfonate derivatives of 4-heteryl-isoxazoles*

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Synthesis procedure of 3,5-dimethyl-4-heteryl-isoxazoles by reaction between heterocyclic aldehydes and nitroethane in the presence of base was developed. Sulfochlorination of the resulting compounds was studied.

Key words: isoxazole, cyclocondensation, sulfochlorination, electrophilic substitution.

Synthesis of 4-heteryl substituted 3,5-dimethyl-isoxasoles and their functionalization by electrophilic substitution reactions have not been investigated according to the literature. One pot synthesis of 3,5-dimethyl-4-aryl-isoxazoles from corresponding aromatic aldehydes and nitroethane by refluxing in a water-ethanolic solution of alkali is known.[1] The need of complex chromatographic purification of target compounds from a great number of by-products is a major drawback of the procedure. The synthesis of 3,5-dimethyl-4-aryl-isoxazoles[2] from aromatic aldehydes and nitroethane in the presence of aluminum oxide at 140 °C under microwave irradiation has also been reported. Higher yields of the products are achieved in this work, but a more complicated procedure of the synthesis is required. Absence of microwave irradiation under the same conditions leads to very low yields (less than 3%)[3] of the products formed on the solid support. The use of other bases for cyclocondensation — sodium carbonate and *N*-butylamine,[4] triethylamine,[5] or pyrrolidine[6] — also led to low yield and low purity of target products. Sulfofunctionalization of 3,5-dimethyl-4-aryl-isoxazoles proceeds *via* sulfochlorination reactions,[7,8] while investigations for heterocyclic derivatives have not been done.

We have developed two-stage scheme of 3,5-dimethyl-4-heteryl-isoxazole synthesis from corresponding heterocyclic aldehydes **1** (Scheme 1). At the first stage, their reaction with nitroethane in the presence of butylamine acting as a base results in the formation of nitro adducts **2**. Subsequent cyclocondensation with the second molecule of nitroethane has been carried out in an alkaline water-ethanolic solution at ambient temperature during 21 days. The temperature increase led to significant rise of the number of by-products and to resinification of reaction mixture. As a result, 3,5-dimethyl-4-heteryl-isoxazoles **3** were obtained.

On the base of 3,5-dimethyl-4-heteryl-isoxazoles **3** obtained, corresponding sulfonyl chlorides **4** were synthesized by their reaction with chlorosulfuric acid. Sulfochlorination was carried out with the excess of chlorosulfuric acid in the presence of thionyl chloride at 60 °C. Structure and purity of synthesized compounds were proved by the combination of elemental analysis, mass spectrometry and NMR spectroscopy methods. Electrophilic attack at sulfochlorination of compounds **3a**,**b** proceeds at position 5 of the thiophene or furan ring, and it is confirmed by the existence of two doublet signals with coupling constants of 3.7 Hz in ^{1}H NMR spectra of compounds **4a**,**b**.

As ^{1}H NMR spectra of compounds **4c**—**g** are difficult to interpret, two-dimensional homonuclear NOESY ^{1}H NMR spectraof their sulfonamide derivatives **5a**—**e** were recorded in order to reliably confirm the structures. Compounds **5a**—**e** were synthesized by heating corresponding sulfonyl chloride **4c**—**g** with pyrrolidine in acetonitrile in the presence of pyridine. Couplings of nearly located protons based on the interpretation of ^{1}H NMR NOESY spectra of compounds **5a**,**b**, are presented below.

Coupling between methylene protons of the pyrrolidine fragment and protons of methyl groups at position 5 of furan (or thiophene) is observed for compounds **5a** and **5b**, coupling of proton of furan (or thiophene) with the protons of methyl group at position 3 of the isoxazole ring and with methylene protons of pyrrolidine fragment is also observed. This type of coupling confirms the presence of aromatic proton at position 3 and sulfonyl group at position 4 of heterocycle. Simultaneous coupling of one of the furan or thiophene protons with methyl protons of the isoxazole ring and with methylene protons of the pyrrolidine fragment is observed for compounds **5c** and **5d**, respectively. This type of proton coupling proves the presence of sulfonyl group at position 5 of the heterocycle. Simultaneous coupling of thiophene proton with the methyl protons at position 3 of thiophene and with methyl-

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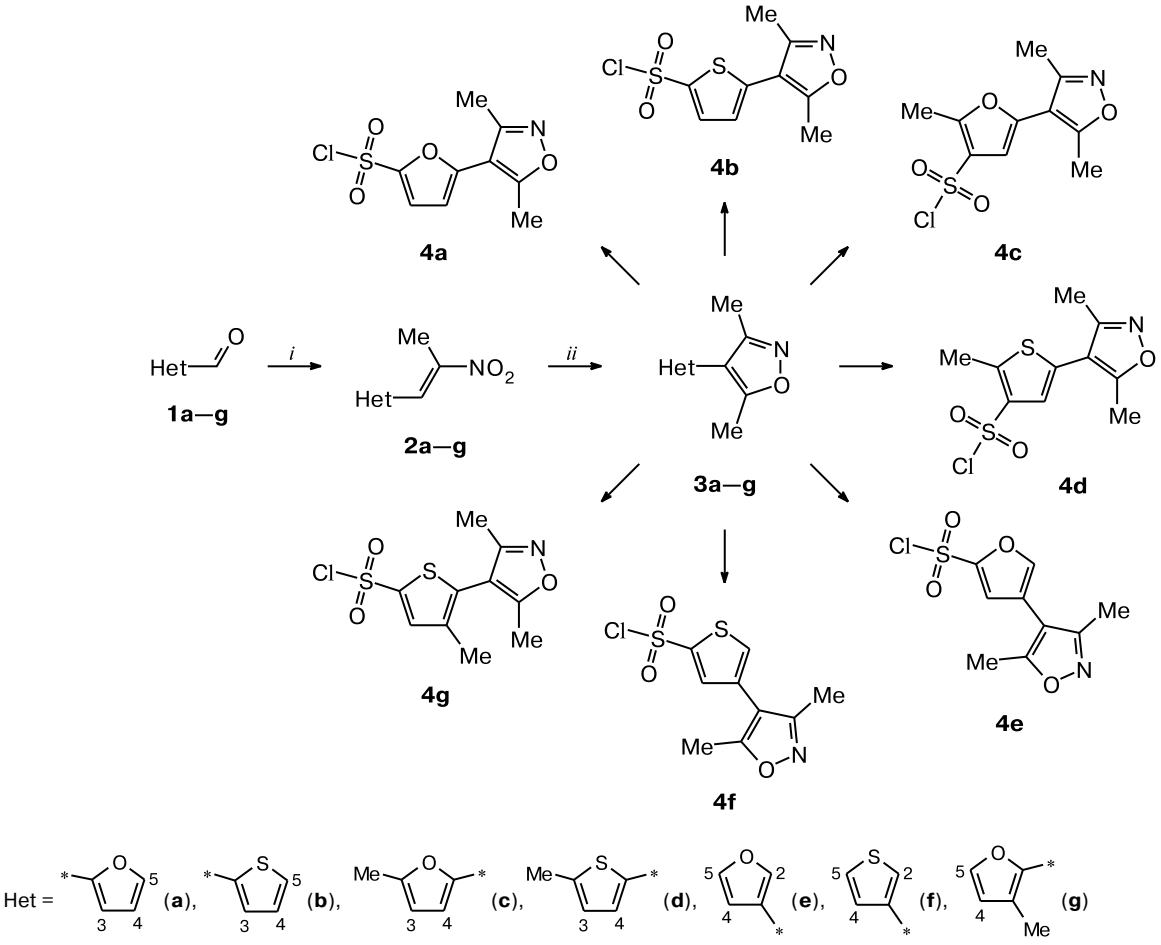
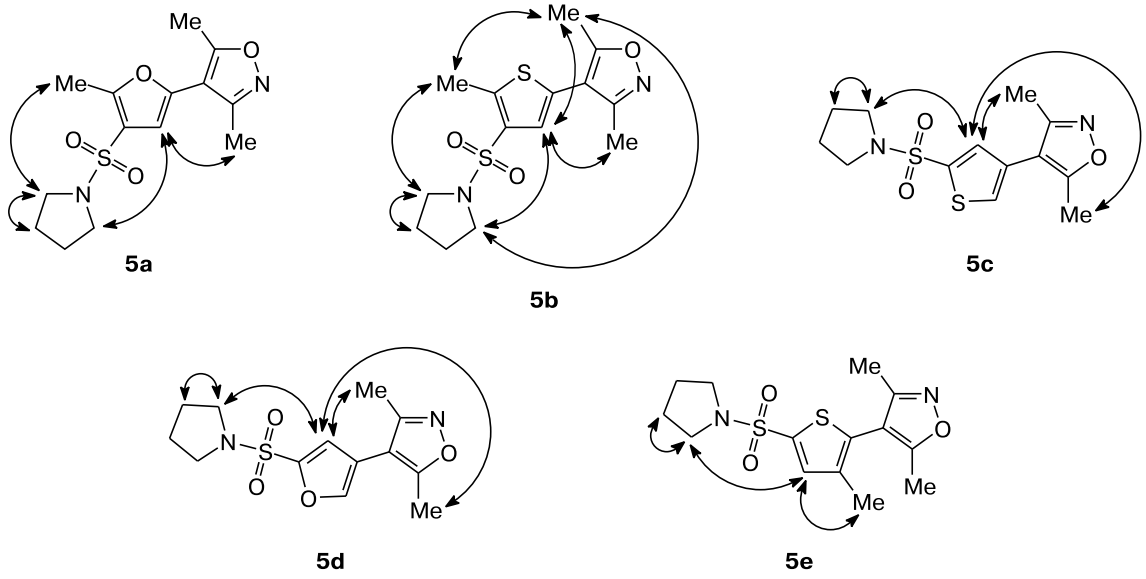
Scheme 1



i. $EtNO_2$, $BuNH_2$, MeOH, 8 h, Δ; *ii*. $EtNO_2$, NaOH, EtOH, 21 days.



ene protons of pyrrolidine fragment is observed for sulfonamide **5e**, which confirms the existence of sulfonyl group at position 5.

Experimental

GC-MS analysis was carried out on an Applied Biosystems instrument (Shimadzu 10-AV LC, Gilson-215 automatic sampling, API 150EX mass-spectrometer, UV (215 and 254 nm) and ELS detectors, Luna-C18 column, Phenomenex, 5 cm×2 mm).

^{1}H NMR spectra of the samples in DMSO-d_6 and $CDCl_3$ solutions were recorded on a Bruker MSL-300 spectrometer. Two-dimensional homonuclear NOESY ^{1}H NMR spectra of the samples in DMSO-d_6 solutions were recorded on a Varian XL-400 instrument.

Elemental analyses were performed by the Laboratory of organic microanalysis of N. D. Zelinsky Institute of Organic Chemistry of Russian Academy of Sciences. Melting points were obtained by using a Buchi Melting Point M-560 instrument.

Synthesis of compounds 2 (general procedure). A mixture of appropriate aldehyde **1** (0.10 mol), nitroethane (0.10 mol), and butylamine (1 mL) in 20 mL of methanol was refluxed for 8 h. After that the mixture was cooled to −18 °C. Large crystals of precipitate were filtered off, washed with 30 mL of methanol, and dried at room temperature.

2-(2-Nitroprop-1-enyl)furan (2a), 76% yield, brown crystals, m.p. 99.5—100 °C (methanol). Found (%): C, 54.85; H, 4.61; N, 9.19. $C_7H_7NO_3$. Calculated (%): C, 54.91; H, 4.61; N, 9.15. ^{1}H NMR (DMSO-d_6, δ, *J*/Hz)**: 2.51 (s, 3 H, Me); 6.77 (dd, 1 H, C(4)H_{fur}, J_1 = 1.5, J_2 = 3.3); 7.21 (d, 1 H, C(3)H_{fur}, J = 3.3); 7.93 (s, 1 H, C<u>H</u>CMe); 8.05 (d, 1 H, C(5)H_{fur}, J = 1.5).

2-(2-Nitroprop-1-enyl)thiophene (2b), 78% yield, yellow crystals, m.p. 59—60 °C (methanol). Found (%): C, 49.65; H, 4.17; N, 8.32; S, 18.99. $C_7H_7NO_2S$. Calculated (%): C, 49.69; H, 4.17; N, 8.28; S, 18.95. ^{1}H NMR (DMSO-d_6, δ, *J*/Hz)**: 2.48 (s, 3 H, Me); 7.3 (dd, 1 H, C(4)H_{thioph}, J_1 = 3.7, J_2 = 4.8); 7.77 (d, 1 H, C(3)H_{thioph}, J = 3.7); 8.03 (d, 1 H, C(5)H_{thioph}, J = 4.8); 8.40 (s, 1 H, C<u>H</u>CMe).

2-Methyl-5-(2-nitroprop-1-enyl)furan (2c), 82% yield, orange crystals, m.p. 77—78 °C (methanol). Found (%): C, 59.55; H, 6.13; N, 7.77. $C_8H_9NO_3$. Calculated (%): C, 59.66; H, 6.12; N, 7.73. ^{1}H NMR (DMSO-d_6, δ, *J*/Hz): 2.39 (s, 3 H, Me); 2.49 (s, 3 H, Me); 6.42 (d, 1 H, CH_{fur}, J = 2.9); 7.13 (d, 1 H, CH_{fur}, J = 2.9); 7.86 (s, 1 H, C<u>H</u>CMe).

2-Methyl-5-(2-nitroprop-1-enyl)thiophene (2d), 76% yield, yellow crystals, m.p. 98—100 °C (methanol). Found (%): C, 52.35; H, 4.96; N, 7.68; S, 17.53. $C_8H_9NO_2S$. Calculated (%): C, 52.44; H, 4.95; N, 7.64; S, 17.50. ^{1}H NMR (DMSO-d_6, δ, *J*/Hz): 2.43 (s, 3 H, Me); 2.54 (s, 3 H, Me); 7.02 (d, 1 H, CH_{thioph}, J = 3.3); 7.60 (d, 1 H, CH_{thioph}, J = 3.3); 8.31 (s, 1 H, C<u>H</u>CMe).

3-(2-Nitroprop-1-enyl)furan (2e), 78% yield, brown crystals, m.p. 56—57 °C (methanol). Found (%): C, 54.85; H, 4.61; N, 9.19. $C_7H_7NO_3$. Calculated (%): C, 54.91; H, 4.61; N, 9.15. ^{1}H NMR (DMSO-d_6, δ, *J*/Hz): 2.40 (s, 3 H, Me); 7.21 (d, 1 H, C(5)H_{fur}, J = 5.1); 7.58 (dd, 1 H, C(4)H_{fur}, J_1 = 2.8, J_2 = 5.1); 8.22 (d, 1 H, C(2)H_{fur}, J = 2.8); 8.25 (s, 1 H, C<u>H</u>CMe).

3-(2-Nitroprop-1-enyl)thiophene (2f), 80% yield, light-brown crystals, m.p. 68—70 °C (methanol). Found (%): C, 49.65; H, 4.17; N, 8.32; S, 18.99. $C_7H_7NO_2S$. Calculated (%): C, 49.69; H, 4.17; N, 8.28; S, 18.95. ^{1}H NMR (DMSO-d_6, δ, *J*/Hz): 2.44 (s, 3 H, Me); 7.47 (d, 1 H, C(5)H_{thioph}, J = 5.1); 7.74 (dd, 1 H, C(4)H_{thioph}, J_1 = 2.9, J_2 = 5.1); 8.12 (m, 2 H, C(2)H_{thioph}, C<u>H</u>CMe).

3-Methyl-2-(2-nitroprop-1-enyl)thiophene (2g), 80% yield, light-brown crystals, m.p. 75.5—77 °C (methanol). Found (%): C, 52.35; H, 4.96; N, 7.68; S, 17.53. $C_8H_9NO_2S$. Calculated (%): C, 52.44; H, 4.95; N, 7.64; S, 17.50. ^{1}H NMR (DMSO-d_6, δ, *J*/Hz): 2.39 (s, 3 H, Me); 2.48 (s, 3 H, Me); 7.17, 7.96 (both d, to 1 H, CH_{thioph}, J = 5.1); 8.29 (s, 1 H, C<u>H</u>CMe).

Synthesis of 4-heteryl-isoxazoles 3 (general procedure). Compound **2** (0.1 mol) was added to a mixture of nitroethane (0.1 mol) and sodium hydroxide (0.25 mol) in 80 mL of water-ethanol solution (30 : 70) while stirring without heating for 21 days. The reaction mixture was extracted with 100 mL of ethyl acetate—petroleum ether mixture (50 : 50). The extract was dried by sodium sulfate, flash-chromatographed on silica, and the solvent was evaporated. Residual dark oil is crystallized on friction.

3,5-Dimethyl-4-(furan-2-yl)isoxazole (3a), 84% yield, brown crystals, m.p. 44—45 °C (ethyl acetate). Found (%): C, 66.15; H, 5.57; N, 8.63. $C_9H_9NO_2$. Calculated (%): C, 66.25; H, 5.56; N, 8.58. ^{1}H NMR (DMSO-d_6, δ, *J*/Hz): 2.33 (s, 3 H, Me); 2.54 (s, 3 H, Me); 6.61 (m, 2 H, 2 CH_{fur}); 7.77 (m, 1 H, CH_{fur}). MS (EI, 150 eV), *m*/*z* (I_{rel} (%)): 163 $[M]^+$ (28), 107 (15), 94 (10), 66 (41), 65 (8), 51 (26), 50 (11), 43 (100).

3,5-Dimethyl-4-(thiophen-2-yl)isoxazole (3b), 74% yield, brown crystals, m.p. 54—55 °C (ethyl acetate). Found (%): C, 60.25; H, 5.07; N, 7.85; S, 17.92. C_9H_9NOS. Calculated (%): C, 60.31; H, 5.06; N, 7.81; S, 17.89. ^{1}H NMR (DMSO-d_6, δ, *J*/Hz): 2.30 (s, 3 H, Me); 2.48 (s, 3 H, Me); 7.19 (m, 2 H, 2 CH_{fur}); 7.64 (d, 1 H, CH_{thioph}, J = 4.6). MS (EI, 150 eV), *m*/*z* (I_{rel} (%)): 179 $[M]^+$ (56), 136 (9), 122 (9), 111 (7), 110 (69), 109 (16), 96 (44), 95 (22), 69 (29), 66(14).

3,5-Dimethyl-4-(5-methylfuran-2-yl)isoxazole (3c), 79% yield, dark liquid, b.p. 198—200 °C. Found (%): C, 67.65; H, 6.26; N, 7.94. $C_{10}H_{11}NO_2$. Calculated (%): C, 67.78; H, 6.26; N, 7.90. ^{1}H NMR (DMSO-d_6, δ, *J*/Hz): 2.31 (s, 6 H, 2 Me); 2.52 (s, 3 H, Me); 6.20 (d, 1 H, C(4)H_{fur}, J = 3.3); 6.47 (d, 1 H, C(3)H_{fur}, J = 3.3). MS (EI, 150 eV), *m*/*z* (I_{rel} (%)): 177 $[M]^+$ (6), 125 (8), 108 (10), 107 (8), 93 (9), 79 (7), 65 (9), 53 (15), 51 (14), 43 (100).

3,5-Dimethyl-4-(5-methylthiophen-2-yl)isoxazole (3d), 74% yield, brown crystals, m.p. 61—62 °C (ethyl acetate). Found (%): C, 62.05; H, 5.74; N, 7.28; S, 16.62. $C_{10}H_{11}NOS$. Calculated (%): C, 62.15; H, 5.74; N, 7.25; S, 16.59. ^{1}H NMR (DMSO-d_6, δ, *J*/Hz): 2.27 (s, 3 H, Me); 2.46 (s, 3 H, CH_3); 2.50 (s, 3 H, C(2)H_{thioph}); 6.86 (d, 1 H, CH_{thioph}, J = 2.6); 6.98 (d, 1 H, CH_{thioph}, J = 2.6). MS (EI, 150 eV), *m*/*z* (I_{rel} (%)): 193 $[M]^+$ (39), 167 (8), 150 (6), 149 (32), 123 (16), 110 (13), 109 (11), 69 (24), 57 (34).

3,5-Dimethyl-4-(furan-3-yl)isoxazole (3e), 82% yield, brown crystals, m.p. 95—97 °C (ethyl acetate). Found (%): C, 66.15; H, 5.57; N, 8.63. $C_9H_9NO_2$. Calculated (%): C, 66.25; H, 5.56; N, 8.58. ^{1}H NMR (DMSO-d_6, δ, *J*/Hz): 2.26 (s, 3 H, Me); 2.43 (s, 3 H, Me); 6.74 (d, 1 H, CH_{fur}); 6.79 (s, 1 H, CH_{fur}); 7.91 (d, 1 H, CH_{fur}). MS (EI, 150 eV), *m*/*z* (I_{rel} (%)): 163 $[M]^+$ (28), 107 (5), 94 (10), 79 (8), 66 (41), 51 (26), 50 (11), 43 (100).

3,5-Dimethyl-4-(thiophen-3-yl)isoxazole (3f), 81% yield, brown crystals, m.p. 70—72 °C (ethyl acetate). Found (%):

* H_{fur} are furan atoms.

** H_{thioph} are thiophene atoms.

C, 60.25; H, 5.07; N, 7.85; S, 17.92. C_9H_9NOS. Calculated (%): C, 60.31; H, 5.06; N, 7.81; S, 17.89. ^{1}H NMR (DMSO-d_6, δ, *J*/Hz): 2.26 (s, 3 H, Me); 2.43 (s, 3 H, Me); 7.27 (d, 1 H, CH_{thioph}, $J = 4.4$); 7.61 (s, 1 H, CH_{thioph}); 7.69 (d, 1 H, CH_{thioph}, $J = 4.4$). MS (EI, 150 eV), *m*/*z* (I_{rel} (%)): 179 $[M]^+$ (16), 110 (13), 109 (5), 95 (7), 77 (100), 68 (10), 51 (84), 39 (29).

3,5-Dimethyl-4-(3-methylthiophen-2-yl)isoxazole (3g), 80% yield, brown crystals, m.p. 90—92 °C (ethyl acetate). Found (%): C, 62.05; H, 5.74; N, 7.28; S, 16.62. $C_{10}H_{11}NOS$. Calculated (%): C, 62.15; H, 5.74; N, 7.25; S, 16.59. ^{1}H NMR (DMSO-d_6, δ, *J*/Hz): 2.04 (s, 3 H, CH_3); 2.10 (s, 3 H, CH_3); 2.29 (s, 3 H, CH_3); 7.04 (d, 1 H, CH_{thioph}, $J = 5.3$); 7.58 (d, 1 H, CH_{thioph}, $J = 5.3$). MS (EI, 150 eV), *m*/*z* (I_{rel} (%)): 193 $[M]^+$ (14), 149 (11), 124 (17), 123 (7), 110 (12), 109 (9), 69 (12), 57 (21).

Synthesis of sulfonyl chlorides 4 (general procedure). Appropriate 4-heteryl-isoxazole **3** (0.01 mol) was added portionwise to a cooled (by ice bath) mixture of chlorosulfuric acid (0.10 mol) and thionyl chloride (0.01 mol) with intensive stirring. The mixture was kept cooled till the complete dissolution of precipitate, then it was heated at 60 °C during 1 h. The reaction mixture was poured into a mixture of ice and chloroform (50 mL). The organic layer was separated, washed with 50 mL of 5% sodium bicarbonate solution, and dried by sodium sulfate. The solution was flash-chromatographed on silica, the solvent was evaporated. Petroleum ether (50 mL) was added to the residue, and the crystals of sulfonyl chloride **4** were filtered.

5-(3,5-Dimethylisoxazol-4-yl)furan-2-sulfonyl chloride (4a), 78% yield, brown crystals, m.p. 61—63 °C (petroleum ether). Found (%): C, 41.19; H, 3.08; N, 5.38; S, 12.28. $C_9H_8ClNO_4S$. Calculated (%): C, 41.31; H, 3.08; N, 5.35; S, 12.25. ^{1}H NMR ($CDCl_3$, δ, *J*/Hz): 2.44 (s, 3 H, CH_3); 2.64 (s, 3 H, CH_3); 6.53 (d, 1 H, CH_{fur}, $J = 3.7$); 7.36 (d, 1 H, CH_{fur}, $J = 3.7$). MS (EI, 150 eV), *m*/*z* (I_{rel} (%)): 261 $[M]^+$ (16), 178 (9), 136 (15), 134 (27), 121 (62), 90 (22), 79 (40), 76 (18), 65 (15).

5-(3,5-Dimethylisoxazol-4-yl)thiophene-2-sulfonyl chloride (4b), 82% yield, brown crystals, m.p. 82—84 °C (petroleum ether). Found (%): C, 38.85; H, 2.91; N, 5.07; S, 23.13. $C_9H_8ClNO_3S_2$. Calculated (%): C, 38.31; H, 5.06; N, 7.81; S, 17.89. ^{1}H NMR ($CDCl_3$, δ, *J*/Hz): 2.39 (s, 3 H, CH_3); 2.56 (s, 3 H, CH_3); 7.04 (d, 1 H, CH_{thioph}, $J = 3.7$); 7.87 (d, 1 H, CH_{thioph}, $J = 3.7$). MS (EI, 150 eV), *m*/*z* (I_{rel} (%)): 277 $[M]^+$ (7), 194 (5), 152 (8), 137 (23), 120 (17), 109 (11), 95 (12), 93 (12), 69 (13).

5-(3,5-Dimethylisoxazol-4-yl)-2-methylfuran-3-sulfonyl chloride (4c), 80% yield, white crystals, m.p. 115—117 °C (petroleum ether). Found (%): C, 43.55; H, 3.66; N, 5.11; S, 11.65. $C_{10}H_{10}ClNO_4S$. Calculated (%): C, 43.56; H, 3.66; N, 5.08; S, 11.63. ^{1}H NMR ($CDCl_3$, δ, *J*/Hz): 2.39 (s, 3 H, CH_3); 2.56 (s, 3 H, CH_3); 2.69 (s, 3 H, CH_3); 6.63 (s, 1 H, CH_{fur}). MS (EI, 150 eV), *m*/*z* (I_{rel} (%)): 275 $[M]^+$ (32), 240 (16), 192 (11), 148 (13), 124 (20), 123 (15), 106 (15), 90 (29), 43 (100).

5-(3,5-Dimethylisoxazol-4-yl)-2-methylthiophene-3-sulfonyl chloride (4d), 76% yield, dark-brown crystals, m.p. 78—80 °C (petroleum ether). Found (%): C, 41.15; H, 3.46; N, 4.82; S, 22.02. $C_{10}H_{10}ClNO_3S_2$. Calculated (%): C, 41.17; H, 3.45; N, 4.80; S, 21.98. ^{1}H NMR ($CDCl_3$, δ, *J*/Hz): 2.26 (s, 3 H, CH_3); 2.42 (s, 3 H, CH_3); 2.75 (s, 3 H, CH_3); 7.18 (s, 1 H, CH_{thioph}). MS (EI, 150 eV), *m*/*z* (I_{rel} (%)): 291 $[M]^+$ (6), 256 (3), 148 (6), 123 (7), 69 (9), 63 (7), 59 (14), 43 (100).

4-(3,5-Dimethylisoxazol-4-yl)furan-2-sulfonyl chloride (4e), 76% yield, brown crystals, m.p. 62—65 °C (petroleum ether). Found (%): C, 41.19; H, 3.08; N, 5.38; S, 12.28. $C_9H_8ClNO_4S$. Calculated (%): C, 41.31; H, 3.08; N, 5.35; S, 12.25. ^{1}H NMR ($CDCl_3$, δ, *J*/Hz): 2.22 (s, 3 H, CH_3); 2.42 (s, 3 H, CH_3); 7.04 (s, 1 H, CH_{fur}); 7.35 (s, 1 H, CH_{fur}). MS (EI, 150 eV), *m*/*z* (I_{rel} (%)): 261 $[M]^+$ (12), 162 (7), 157 (6), 43 (100).

4-(3,5-Dimethylisoxazol-4-yl)thiophene-2-sulfonyl chloride (4f), 80% yield, brown crystals, m.p. 103—105 °C (petroleum ether). Found (%): C, 38.85; H, 2.91; N, 5.07; S, 23.13. $C_9H_8ClNO_3S_2$. Calculated (%): C, 38.31; H, 5.06; N, 7.81; S, 17.89. ^{1}H NMR ($CDCl_3$, δ, *J*/Hz): 2.24 (s, 3 H, CH_3); 2.41 (s, 3 H, CH_3); 7.19 (s, 1 H, CH_{thioph}); 7.47 (s, 1 H, CH_{thioph}). MS (EI, 150 eV), *m*/*z* (I_{rel} (%)): 277 $[M]^+$ (4), 178 (5), 173 (5), 48 (8), 45 (12), 43 (100), 30 (6).

5-(3,5-Dimethylisoxazol-4-yl)-4-methylthiophene-2-sulfonyl chloride (4g), 82% yield, brown crystals, m.p. 102—104 °C (petroleum ether). Found (%): C, 41.15; H, 3.46; N, 4.82; S, 22.02. $C_{10}H_{10}ClNO_3S_2$. Calculated (%): C, 41.17; H, 3.45; N, 4.80; S, 21.98. ^{1}H NMR ($CDCl_3$, δ, *J*/Hz): 2.03 (s, 3 H, CH_3); 2.10 (s, 3 H, CH_3); 2.26 (s, 3 H, CH_3); 7.64 (s, 1 H, CH_{thioph}). MS (EI, 150 eV), *m*/*z* (I_{rel} (%)): 291 $[M]^+$ (16), 256 (7), 166 (10), 152 (5), 151 (53), 134 (22), 123 (20), 109 (22), 93 (17), 69 (20).

Synthesis of sulfonamides 5a—e (general procedure). Pyrrolidine (0.001 mol) was added to a mixture of sulfonyl chloride **4** (0.001 mol) and pyridine (0.002 mol) in acetonitrile (5 mL). The reaction mixture was stirred at 60 °C for 0.5 h. Water (5 mL) was added to the mixture, the resulting precipitate was filtered off and recrystallized from isopropyl alcohol.

3,5-Dimethyl-4-[5-methyl-4-(pyrrolidin-1-sulfonyl)furan-2-yl]isoxazole (5a), 71% yield, white crystals, m.p. 145—147 °C (isopropyl alcohol). Found (%): C, 54.09; H, 5.85; N, 9.07; S, 10.35. $C_{14}H_{18}N_2O_4S$. Calculated (%): C, 54.18; H, 5.85; N, 9.03; S, 10.33. ^{1}H NMR (DMSO-d_6, δ, *J*/Hz)*: 1.74 (m, 4 H, 2 CH_{2pyr}); 2.34 (s, 3 H, Me); 2.50 (s, 3 H, Me); 2.57 (s, 3 H, Me); 3.20 (m, 4 H, 2 CH_2N_{pyr}); 6.82 (d, 1 H, $C(3)H_{fur}$). MS (EI, 150 eV), *m*/*z* (I_{rel} (%)): 310 $[M]^+$ (10), 177 (9), 176 (10), 175 (9), 148 (9), 124 (24), 106 (9), 70 (100), 42 (50).

3,5-Dimethyl-4-[5-methyl-4-(pyrrolidine-1-sulfonyl)thiophen-2-yl]isoxazole (5b), 77% yield, light-brown crystals, m.p. 115—117 °C (isopropyl alcohol). Found (%): C, 51.48; H, 5.56; N, 8.62; S, 19.68. $C_{14}H_{18}N_2O_3S_2$. Calculated (%): C, 51.51; H, 5.56; N, 8.58; S, 19.64. ^{1}H NMR (DMSO-d_6, δ, *J*/Hz): 1.75 (m, 4 H, 2 CH_{2pyr}); 2.29 (s, 3 H, Me); 2.48 (s, 3 H, Me); 2.70 (s, 3 H, Me); 3.22 (m, 4 H, 2 CH_2N_{pyr}); 7.25 (s, 1 H, $C(3)H_{thioph}$). MS (EI, 150 eV), *m*/*z* (I_{rel} (%)): 326 $[M]^+$ (53), 191 (18), 148 (9), 70 (40), 69 (11), 65 (6), 59 (16), 43 (100).

3,5-Dimethyl-4-[5-(pyrrolidine-1-sulfonyl)thiophen-3-yl]-isoxazole (5c), 79% yield, light-brown crystals, m.p. 90—92 °C (isopropyl alcohol). Found (%): C, 49.88; H, 5.17; N, 9.01; S, 20.57. $C_{13}H_{16}N_2O_3S_2$. Calculated (%): C, 49.98; H, 5.16; N, 8.97; S, 20.52. ^{1}H NMR (DMSO-d_6, δ, *J*/Hz): 1.70 (m, 4 H, 2 CH_{2pyr}); 2.28 (s, 3 H, Me); 2.45 (s, 3 H, Me); 3.23 (m, 4 H, 2 CH_2N_{pyr}); 7.82 (d, 1 H, $C(4)H_{thioph}$, $J = 1.1$); 8.06 (d, 1 H, $C(2)H_{thioph}$, $J = 1.1$). MS (EI, 150 eV), *m*/*z* (I_{rel} (%)): 312 $[M]^+$ (14), 179 (14), 178 (12), 137 (10), 110 (11), 109 (11), 95 (11), 70 (15), 69 (10), 43 (96).

3,5-Dimethyl-4-[5-(pyrrolidine-1-sulfonyl)furan-3-yl]isoxazole (5d), 73% yield, white crystals, m.p. 104—106 °C (isopropyl alcohol). Found (%): C, 52.63; H, 5.45; N, 9.50; S, 10.84.

* H_{pyr} are pyrrolidine atoms.

$C_{13}H_{16}N_2O_4S$. Calculated (%): C, 52.69; H, 5.44; N, 9.45; S, 10.82. ^{1}H NMR (DMSO-d_6, δ, *J*/Hz): 1.62 (m, 4 H, 2 CH_{2pyr}); 2.30 (s, 3 H, Me); 2.51 (s, 3 H, Me); 3.22 (m, 4 H, 2 CH_2N_{pyr}); 7.68 (s, 1 H, C(4)H_{fur}); 8.20 (s, 1 H, C(2)H_{fur}). MS (EI, 150 eV), *m*/*z* (I_{rel} (%)): 296 $[M]^+$ (17), 163 (15), 121 (12), 95 (7), 69 (12), 43 (100).

3,5-Dimethyl-4-[3-methyl-5-(pyrrolidine-1-sulfonyl)thiophen-2-yl]isoxazole (5e), 73% yield, light-brown crystals, m.p. 116—118 °C (isopropyl alcohol). Found (%): C, 51.48; H, 5.56; N, 8.62; S, 19.68. $C_{14}H_{18}N_2O_3S_2$. Calculated (%): C, 51.51; H, 5.56; N, 8.58; S, 19.64. ^{1}H NMR (DMSO-d_6, δ, *J*/Hz): 1.72 (m, 4 H, 2 CH_{2pyr}); 2.08 (s, 3 H, Me); 2.13 (s, 3 H, Me); 2.33 (s, 3 H, Me); 3.21 (m, 4 H, 2 CH_2N_{pyr}); 7.63 (s, 1 H, C(4)H_{thioph}). MS (EI, 150 eV), *m*/*z* (I_{rel} (%)): 326 $[M]^+$ (21), 193 (29), 166 (7), 151 (43), 134 (11), 124 (17), 109 (16), 70 (22), 69 (11).

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