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SHORT COMMUNICATIONS

Cyclization of 2-Amino-4-methyl-3-[2-aryl(hetaryl)-2-oxoethyl]-thiazolium Bromides in Aqueous Medium. A Simple Synthesis of Substituted Imidazo[2,1-*b*]thiazoles

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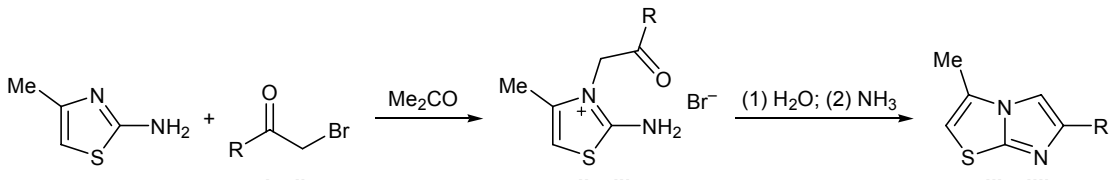
Relatively large number of natural and biologically active compounds contain an imidazo[2,1-*b*]thiazole fragment [1–3]. Among a broad spectrum of biological activity intrinsic to imidazo[2,1-*b*]thiazole derivatives, immunosuppressive [4], inotropic [5, 6], and antiallergic activity [7] should be noted. However, no general methods for the synthesis of this heterocyclic system have been reported. The most widely used procedure is based on the reaction of α-halo ketones with substituted 2-aminothiazoles. There are some versions of this procedure, e.g., preliminary heating of a mixture of reactants to obtain *N*-alkylthiazole and its subsequent cyclization in an organic solvent (ethanol, butan-1-ol, toluene) or in the presence of aqueous HCl [8, 9] or one-pot synthesis in an appropriate organic solvent [8, 10–13]. As a rule, these procedures are not free from some disadvantages, the main of which are low yield (20–60%) and difficult isolation of the target product (chromatographic separation is often required).

We made an attempt to synthesize imidazo[2,1-*b*]-thiazoles containing various aryl (hetaryl) substituents in the 6-position via cyclization of the corresponding 2-amino-4-methyl-3-[2-aryl(hetaryl)-2-oxoethyl]thiazolium bromides **IIa**–**IIh** in water as solvent. The use of a cheap and nontoxic solvent in the key step of the synthesis conforms to one of the basic "green" chemistry principles [14].

Initial salts **IIa**–**IIh** were prepared by alkylation of 2-amino-4-methylthiazole with α-bromo ketones **Ia**–**Ih** in acetone. The yield of **IIa**–**IIh** was 88–96% almost independently of the substituent in the benzene ring of **Ia**–**Ig**. Although this step was carried out in an organic solvent, it also fits one "green" chemistry principle [14] taking into account high atom efficiency (100%) of the alkylation of the endocyclic nitrogen atom in 2-aminothiazole.

Compounds **IIa**–**IIh** were subjected to cyclization by heating in boiling water for 4 h. Compounds **IIIa**–**IIIh** were thus formed as hydrobromides, and the free bases were isolated in 88–94% yield by treatment of the reaction mixtures with an ammonia solution.

Compounds **IIb**–**IIg**, **IIIb**–**IIId**, **IIIf**, and **IIIh** were not reported previously. Imidazo[2,1-*b*]thiazoles **IIIa**–**IIIh** characteristically showed in the ^{1}H NMR spectra singlets from protons in the imidazo[2,1-*b*]thiazole fragment at δ 8.12–8.56 (5-H) and 6.87–6.96 ppm (2-H), as well as signals belonging to protons in the



Ia–Ih **IIa–IIh** **IIIa–IIIh**

R = Ph (**a**), 4-MeC_6H_4 (**b**), 4-$EtOC_6H_4$ (**c**), 4-$MeSC_6H_4$ (**d**), 4-ClC_6H_4 (**e**), 4-BrC_6H_4 (**f**), 3-$O_2NC_6H_4$ (**g**), 2-thienyl (**h**).

3-methyl and 6-aryl(hetaryl) substituents. The IR spectra contained absorption bands due to bending vibrations of the heterocyclic fragment in the region 1601–1067 cm^{-1}.

Thus, we have proposed a simple "green" procedure for the two-step synthesis of 6-arylimidazo-[2,1-*b*]thiazoles in high yields.

2-Amino-4-methyl-3-[2-aryl(hetaryl)-2-oxoethyl]thiazolium bromides IIa–IIh (*general procedure*). A mixture of 30 mmol of 4-methylthiazol-2-amine and 30 mmol of α-bromo ketone **Ia–Ih** in 40 mL of anhydrous acetone was stirred for 12 h at room temperature. The precipitate was filtered off, washed with diethyl ether (2×15 mL), and dried in air.

2-Amino-4-methyl-3-(2-oxo-2-phenylethyl)-thiazolium bromide (IIa). Yield 92%, mp 210–211°C (decomp.); published data [15]: mp 216°C. IR spectrum, ν, cm^{-1}: 3110, 3014, 1687 (C=O), 1627, 1556, 1404, 1231, 998, 765. ^{1}H NMR spectrum, δ, ppm: 2.14 s (3H, CH_3), 5.82 s (2H, CH_2CO), 6.79 s (1H, 5-H), 7.51 t (1H, 4′-H, *J* = 7.9 Hz), 7.65 t (2H, 3′-H, 5′-H, *J* = 7.9 Hz), 8.08 d (2H, 2′-H, 6′-H, *J* = 7.9 Hz), 9.57 br.s (2H, NH_2). Found, %: C 45.96; H 4.21; N 8.99. $C_{12}H_{13}BrN_2OS$. Calculated, %: C 46.02; H 4.18; N 8.94.

2-Amino-4-methyl-3-[2-(4-methylphenyl)-2-oxoethyl]thiazolium bromide (IIb). Yield 96%, mp 254–256°C (decomp.). IR spectrum, ν, cm^{-1}: 3109, 3013, 1687 (C=O), 1628, 1559, 1408, 1232, 818, 557. ^{1}H NMR spectrum, δ, ppm: 2.11 s (3H, CH_3), 2.43 s (3H, CH_3), 5.76 s (2H, CH_2CO), 6.78 s (1H, 5-H), 7.45 d (2H, 3′-H, 5′-H, *J* = 8.6 Hz), 7.97 d (2H, 2′-H, 6′-H, *J* = 7.9 Hz), 9.53 br.s (2H, NH_2). Found, %: C 47.66; H 4.65; N 8.62. $C_{13}H_{15}BrN_2OS$. Calculated, %: C 47.71; H 4.60; N 8.56.

2-Amino-3-[2-(4-ethoxyphenyl)-2-oxoethyl]-4-methylthiazolium bromide (IIc). Yield 95%, mp 211–212°C (decomp.). IR spectrum, ν, cm^{-1}: 3119, 3017, 1681 (C=O), 1630, 1600, 1560, 1408, 1233, 1178, 1040, 919, 840. ^{1}H NMR spectrum, δ, ppm: 1.37 t (3H, $OCH_2C\mathbf{H}_3$, *J* = 7.0 Hz), 2.11 s (3H, CH_3), 4.18 q (2H, OCH_2, *J* = 7.3 Hz), 5.75 s (2H, CH_2CO), 6.79 s (1H, 5-H), 7.15 d (2H, 3′-H, 5′-H, *J* = 8.5 Hz), 8.03 d (2H, 2′-H, 6′-H, *J* = 9.2 Hz), 9.54 br.s (2H, NH_2). Found, %: C 47.01; H 4.83; N 7.87. $C_{14}H_{17}BrN_2O_2S$. Calculated, %: C 47.07; H 4.80; N 7.84.

2-Amino-4-methyl-3-[2-(4-methylsulfanylphenyl)-2-oxoethyl]thiazolium bromide (IId). Yield 91%, mp 204–206°C (decomp.). IR spectrum, ν, cm^{-1}: 3115, 3014, 1683 (C=O), 1631, 1585, 1556, 1405, 1236, 1092, 995, 815. ^{1}H NMR spectrum, δ, ppm: 2.11 s (3H, CH_3), 2.53 s (3H, SCH_3), 5.77 s (2H, CH_2CO), 6.78 s (1H, 5-H), 7.48 d (2H, 3′-H, 5′-H, *J* = 8.5 Hz), 7.98 d (2H, 2′-H, 6′-H, *J* = 8.5 Hz), 9.55 br.s (2H, NH_2). Found, %: C 43.48; H 4.25; N 7.76. $C_{13}H_{15}BrN_2OS_2$. Calculated, %: C 43.46; H 4.21; N 7.80.

2-Amino-3-[2-(4-chlorophenyl)-2-oxoethyl]-4-methylthiazolium bromide (IIe). Yield 89%, mp 264–265°C (decomp.). IR spectrum, ν, cm^{-1}: 3140, 3017, 1693 (C=O), 1628, 1557, 1406, 1227, 995, 826. ^{1}H NMR spectrum, δ, ppm: 2.13 s (3H, CH_3), 5.78 s (2H, CH_2CO), 6.79 s (1H, 5-H), 7.87 d (2H, 3′-H, 5′-H, *J* = 8.5 Hz), 8.08 d (2H, 2′-H, 6′-H, *J* = 8.5 Hz), 9.53 br.s (2H, NH_2). Found, %: C 41.43; H 3.51; N 8.11. $C_{12}H_{12}BrClN_2OS$. Calculated, %: C 41.46; H 3.48; N 8.06.

2-Amino-3-[2-(4-bromophenyl)-2-oxoethyl]-4-methylthiazolium bromide (IIf). Yield 88%, mp 258–260°C (decomp.). IR spectrum, ν, cm^{-1}: 3140, 3110, 3016, 1694 (C=O), 1628, 1557, 1408, 1227, 995, 826. ^{1}H NMR spectrum, δ, ppm: 2.12 s (3H, CH_3), 5.77 s (2H, CH_2CO), 6.78 s (1H, 5-H), 7.88 d (2H, 3′-H, 5′-H, *J* = 8.6 Hz), 7.99 d (2H, 2′-H, 6′-H, *J* = 8.5 Hz), 9.53 br.s (2H, NH_2). Found, %: C 36.74; H 3.12; N 7.21. $C_{12}H_{12}Br_2N_2OS$. Calculated, %: C 36.76; H 3.08; N 7.14.

2-Amino-4-methyl-3-[2-(3-nitrophenyl)-2-oxoethyl]thiazolium bromide (IIg). Yield 89%, mp 254–255°C (decomp.). IR spectrum, ν, cm^{-1}: 3116, 3025, 1706 (C=O), 1627, 1556, 1527, 1353, 1223, 1085, 819, 735. ^{1}H NMR spectrum, δ, ppm: 2.09 s (3H, CH_3), 5.92 s (2H, CH_2CO), 6.80 s (1H, 5-H), 7.75 t (1H, 5′-H, *J* = 7.9 Hz), 8.14–8.16 m (1H, 4′-H), 8.29 d (1H, 6′-H, *J* = 7.9 Hz), 8.66–8.68 m (1H, 2′-H), 9.59 br.s (2H, NH_2). Found, %: C 40.20; H 3.41; N 11.78. $C_{12}H_{12}BrN_3O_3S$. Calculated, %: C 40.24; H 3.38; N 11.73.

2-Amino-4-methyl-3-[2-oxo-2-(thiophen-2-yl)-ethyl]thiazolium bromide (IIh). Yield 91%, mp 232–234°C (decomp.). IR spectrum, ν, cm^{-1}: 3116, 3025, 1706 (C=O), 1627, 1556, 1527, 1353, 1223, 1085, 819, 735. ^{1}H NMR spectrum, δ, ppm: 2.14 s (3H, CH_3), 5.73 s (2H, CH_2CO), 6.77 s (1H, 5-H), 7.40 t (1H, 5′-H, *J* = 4.2 Hz), 7.89 d (1H, 4′-H, *J* = 4.9 Hz), 8.21–8.19 m (1H, 3′-H), 9.57 br.s (2H, NH_2). Found, %: C 37.58; H 3.51; N 8.81. $C_{10}H_{11}BrN_2OS_2$. Calculated, %: C 37.63; H 3.47; N 8.77.

3-Alkyl-6-aryl(hetaryl)imidazo[2,1-*b*]thiazoles IIIa–IIIh (*general procedure*). A mixture of 10 mmol

of bromide **IIa–IIh** and 100 mL of water was heated for 4 h under reflux, 15 mL of 25% aqueous ammonia was added to the hot solution, and the mixture was cooled. An oily material separated and crystallized. The product was filtered off and recrystallized from DMF–water (9:1).

3-Methyl-6-phenylimidazo[2,1-*b*]thiazole (IIIa). Yield 91%, mp 112–113°C (from PhMe–EtOH, 4:1); published data [16]: mp 113°C; R_f 0.71. IR spectrum, ν, cm^{-1}: 3068, 1601, 1531, 1470, 1439, 1185, 708, 592. ^1H NMR spectrum, δ, ppm: 2.43 s (3H, CH_3), 6.89 s (1H, 2-H), 7.26 t (1H, 4′-H, J = 7.3 Hz), 7.40 t (2H, 3′-H, 5′-H, J = 7.6 Hz), 7.86 d (2H, 2′-H, 6′-H, J = 8.6 Hz), 8.26 s (1H, 5-H). Found, %: C 67.27; H 4.68; N 13.12. $C_{12}H_{10}N_2S$. Calculated, %: C 67.22; H 4.71; N 13.07.

3-Methyl-6-(4-methylphenyl)imidazo[2,1-*b*]thiazole (IIIb). Yield 92%, mp 121–122°C (from PhMe–EtOH, 4:1), R_f 0.70. IR spectrum, ν, cm^{-1}: 3057, 1547, 1471, 1408, 1188, 817, 725, 692. ^1H NMR spectrum, δ, ppm: 2.13 s (3H, CH_3), 2.42 s (3H, CH_3), 6.87 s (1H, 2-H), 7.20 d (2H, 3′-H, 5′-H, J = 8.5 Hz), 7.74 d (2H, 2′-H, 6′-H, J = 7.9 Hz), 8.19 s (1H, 5-H). Found, %: C 68.33; H 5.27; N 12.33. $C_{13}H_{12}N_2S$. Calculated, %: C 68.39; H 5.30; N 12.27.

6-(4-Ethoxyphenyl)-3-methylimidazo[2,1-*b*]thiazole (IIIc). Yield 87%, mp 101–102°C (from PhMe–EtOH, 4:1), R_f 0.67. IR spectrum, ν, cm^{-1}: 3117, 2973, 1544, 1464, 1263, 1241, 1172, 1044, 920, 830, 685. ^1H NMR spectrum, δ, ppm: 1.35 t (3H, $OCH_2C\mathbf{H}_3$, J = 7.0 Hz), 2.47 s (3H, CH_3), 4.10 q (2H, OCH_2, J = 6.7 Hz), 6.88 s (1H, 2-H), 7.08 d (2H, 3′-H, 5′-H, J = 8.5 Hz), 7.76 d (2H, 2′-H, 6′-H, J = 8.5 Hz), 8.52 s (1H, 5-H). Found, %: C 65.05; H 5.42; N 10.96. $C_{14}H_{14}N_2OS$. Calculated, %: C 65.09; H 5.46; N 10.84.

3-Methyl-6-[4-(methylsulfanyl)phenyl]imidazo-[2,1-*b*]thiazole (IIId). Yield 94%, mp 132–133°C (from PhMe–EtOH, 4:1), R_f 0.69. IR spectrum, ν, cm^{-1}: 3102, 1535, 1465, 1405, 1184, 1095, 820, 731, 687. ^1H NMR spectrum, δ, ppm: 2.42 s (3H, CH_3), 2.50 s (3H, SCH_3), 6.88 s (1H, 2-H), 7.29 d (2H, 3′-H, 5′-H, J = 8.5 Hz), 7.80 d (2H, 2′-H, 6′-H, J = 8.6 Hz), 8.23 s (1H, 5-H). Found, %: C 60.01; H 4.69; N 10.81. $C_{13}H_{12}N_2S_2$. Calculated, %: C 59.97; H 4.65; N 10.76.

6-(4-Chlorophenyl)-3-methylimidazo[2,1-*b*]thiazole (IIIe). Yield 89%, mp 122–123°C (from PhMe–EtOH, 4:1); published data [17]: mp 124–126°C; R_f 0.64. IR spectrum, ν, cm^{-1}: 3105, 1534, 1466, 1402, 1178, 1087, 833, 724, 683. ^1H NMR spectrum, δ, ppm: 2.43 s (3H, CH_3), 6.91 s (1H, 2-H), 7.46 d (2H, 3′-H, 5′-H, J = 8.6 Hz), 7.87 d (2H, 2′-H, 6′-H, J = 8.6 Hz), 8.31 s (1H, 5-H). Found, %: C 57.93; H 3.68; N 11.31. $C_{12}H_9ClN_2S$. Calculated, %: C 57.95; H 3.65; N 11.26.

6-(4-Bromophenyl)-3-methylimidazo[2,1-*b*]thiazole (IIIf). Yield 91%, mp 131–132°C (from PhMe–EtOH, 4:1), R_f 0.72. IR spectrum, ν, cm^{-1}: 3076, 1533, 1464, 1176, 1067, 1003, 832, 722, 682. ^1H NMR spectrum, δ, ppm: 2.43 s (3H, CH_3), 6.91 s (1H, 2-H), 7.59 d (2H, 3′-H, 5′-H, J = 8.5 Hz), 7.81 d (2H, 2′-H, 6′-H, J = 8.6 Hz), 8.32 s (1H, 5-H). Found, %: C 49.09; H 3.12; N 9.60. $C_{12}H_9BrN_2S$. Calculated, %: C 49.16; H 3.09; N 9.55.

3-Methyl-6-(3-nitrophenyl)imidazo[2,1-*b*]thiazole (IIIg). Yield 88%, mp 121–122°C (from PhMe–EtOH, 4:1), R_f 0.70. IR spectrum, ν, cm^{-1}: 3104, 1544, 1514, 1477, 1348, 1197, 873, 729, 691. ^1H NMR spectrum, δ, ppm: 2.45 s (3H, CH_3), 6.96 s (1H, 2-H), 7.70 t (1H, 5′-H, J = 7.9 Hz), 8.10 d.d (1H, 4′-H, J = 7.6, 2.1 Hz), 8.29 d (1H, 6′-H, J = 7.9 Hz), 8.56 s (1H, 5-H), 8.66 t (1H, 2′-H, J = 1.8 Hz). Found, %: C 55.52; H 3.47; N 16.27. $C_{12}H_9N_3O_2S$. Calculated, %: C 55.59; H 3.51; N 16.21.

3-Methyl-6-(thiophen-2-yl)imidazo[2,1-*b*]thiazole (IIIh). Yield 90%, mp 136–137°C (from PhMe–EtOH, 4:1); published data [18]: mp 138–139°C; R_f 0.68. IR spectrum, ν, cm^{-1}: 3069, 1564, 1467, 1277, 1205, 1172, 850, 705, 557. ^1H NMR spectrum, δ, ppm: 2.41 s (3H, CH_3), 6.89 s (1H, 2-H), 7.07–7.09 m (1H, 5′-H), 7.38 d (1H, 4′-H, J = 3.7 Hz), 7.42 d (1H, 3′-H, J = 4.9 Hz), 8.12 s (1H, 5-H). Found, %: C 54.53; H 3.64; N 12.79. $C_{10}H_8N_2S_2$. Calculated, %: C 54.49; H 3.69; N 12.72.

The ^1H NMR spectra were recorded at 33°C on a Bruker DRX 500 spectrometer (500 MHz) from solutions in DMSO-d_6 using tetramethylsilane as internal reference. The IR spectra were recorded in KBr on an FSM-1201 spectrometer. The elemental compositions were determined on a Vario El Cube elemental analyzer. The melting points were measured on a Boetius hot stage and are uncorrected. The progress of reactions was monitored by TLC on Silufol UV-254 plates using toluene–ethanol (4:1) as eluent; spots were visualized by treatment with iodine vapor.

Initial α-bromo ketones **Ia–Ih** were prepared by bromination of the corresponding acetophenones in alcohol according to a standard procedure. 4-Methylthiazol-2-amine was synthesized as described in [19].

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