Russian Journal of Organic Chemistry, Vol. 39, No. 10, 2003, pp. 1467–1470. Translated from Zhurnal Organicheskoi Khimii, Vol. 39, No. 10, 2003, pp. 1536–1539.

Dedicated to Full Member of the Russian Academy of Sciences B.A. Trofimov on the 65th Anniversary of His Birth

Synthesis of 1,3-Dialkylimidazolium and 1,3-Dialkylbenzimidazolium Salts

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Received June 23, 2003

Abstract—A number of *N*-alkylimidazoles and *N*-alkylbenzimidazoles were synthesized by reactions of imidazole and benzimidazole with alkyl halides. The reaction rate increases by a factor of 2 to 3 under conditions of microwave activation. Subsequent treatment of the resulting *N*-alkylazoles with alkyl halides afforded the corresponding 1,3-dialkylimidazolium and 1,3-dialkylbenzimidazolium halides.

Several methods for the synthesis of *N*-alkylazoles and *N*-alkylbenzazoles are known [1–4]. *N*-Allenylazoles were obtained from the corresponding azoles and 2-propynyl chloride or 1,2,3-trichloropropane in one preparative step [2]. Monosubstituted imidazoles were synthesized under conditions of phase-transfer catalysis in a solid–liquid system [3]. Monoalkylated imidazoles exhibit surfactant properties and are precursors of 1,3-dialkylimidazolium salts which are used as hygroscopic ionic liquids with low melting points (from –30°C to ambient) [1, 4, 5]. In addition, dialkylazolium salts are used in the synthesis of stable heterocyclic carbenes [6, 7].

Microwave activation of organic reactions attracts increasing interest of chemists working in the field of organic synthesis [8, 9]. Studies on the N-alkylation of imidazoles, pyrroles, indoles, and carbazoles with butyl bromide and decyl chloride in the presence of K_2CO_3/KOH and a catalytic amount of tetrabutylammonium bromide under microwave irradiation have been reported [10–12]. Imidazole and its 4-substituted derivatives are known to relatively readily react with various alkylating agents to give N^1-substituted imidazoles in high yields [13]. On the other hand, the yields of alkylation products from benzimidazole are sometimes poor.

We performed alkylation of unsubstituted imidazole according to the procedure reported in [2]. The reaction readily occurred at the nitrogen atom. As alkylating agents we used *i*-PrBr, *i*-BuBr, *i*-BuI, and BzlCl. The corresponding *N*-alkylimidazoles were thus obtained in good yields (60–80%). For comparison, the alkylation of imidazole was carried out under conditions of microwave activation. The reaction of imidazole with isobutyl bromide in DMSO gave 33% of 1-isobutylimidazole in 1 h. When this reaction was carried out in DMF, 26% of the product was formed in 7 min. The yield increased to 56% on prolonging the reaction to 60 min.

An analogous pattern was observed in the alkylation with benzyl bromide: the yield of the product was 15% in 7 min and 68% in 60 min.

Benzimidazole was alkylated both by the procedure described in [2] and under microwave irradiation. By the classical reaction of benzimidazole with isobutyl bromide 1-isobutylbenzimidazole (**V**) was isolated in 29% yield. The microwave-activated reaction was carried out in different solvents: acetonitrile, methyl alcohol, DMSO, and DMF. The best results were obtained in DMF in the presence of KOH. Here, as in the microwave-activated reaction with imidazole, the yield of the product increased from 39 to 67% on prolonging the reaction from 15 to 60 min. No appreciable increase in the product yield was attained by variation of the solvent (in particular, using acetonitrile, methanol, or DMSO), reaction time, and radiation power, as well as by replacement of KOH by *t*-BuOK. We also made an attempt to modify the

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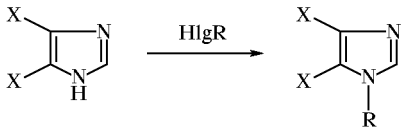
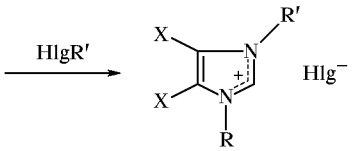
synthetic procedure: alkyl halide was added dropwise to a mixture of benzimidazole and alkali in appropriate solvent. In the reaction with isobutyl bromide, the yield of 1-isobutylbenzimidazole was 47%, and the yield of 1-isopropylbenzimidazole in the reaction with isopropyl bromide was 54%.



I–VI



VII–XV

I, **IV**, R = *i*-Pr; **II**, **V**, R = *i*-Bu; **III**, **VI**, R = CH_2Ph; **I**–**VI**, Hlg = I, Br, Cl; X = H; **VII**, **XI**, R = R′ = *i*-Pr, Hlg = Br; **VIII**, **XIII**, R = R′ = *i*-Bu, Hlg = Br; **IX**, **XIV**, R = R′ = *i*-Bu, Hlg = I; **X**, **XV**, R = R′ = $PhCH_2$, Hlg = Cl; **XII**, R = Me, R′ = *i*-Bu, Hlg = Br; **I**–**III**, **VII**–**X**, X = H; **IV**–**VI**, **XI**–**XV**, XX = CH=CH−CH=CH.

According to Jones and Young [14], treatment of imidazole with 2 equiv of acrylic acid in methanol or water directly afforded zwitterionic imidazolium-1,3-diacetate. We failed to obtain the corresponding 1,3-dialkyldiazolium salts by treatment of imidazole or benzimidazole with 2 equiv of alkylating agent. The reaction gave a mixture of monoalkylated azole, dialkylazolium salt, and potassium halide, which was difficult to separate. Therefore, 1,3-dialkylazolium salts were obtained in two steps. Initially, *N*-alkylazoles were synthesized and isolated and were then treated with 3 equiv of alkyl halide. As a result, the *N*,*N*′-dialkyl derivatives were formed in good yields.

The IR spectra of the products contain absorption bands due to stretching vibrations of the endocyclic C=C and C=N bonds (1468–1547 cm^{-1}), CH and CH_2 groups (ν C−H 2873–2934 cm^{-1}), and CH_3 groups (ν C−H 2962–2977 cm^{-1}).

EXPERIMENTAL

The IR spectra were recorded on a Bruker IFS-25 spectrometer in KBr. The ^1H and ^{13}C NMR spectra were obtained on a Bruker DPX-400 instrument at 400.13 and 100.61 MHz, respectively, from solutions in DMSO-d_6.

***N*-Alkylazoles (*general procedure*).** *a*. Potassium hydroxide, 0.84 g (0.015 mol), was added to a solution of 0.01 mol of imidazole or benzimidazole in 20 ml of DMSO, the mixture was stirred for 30 min at 18–20°C, and 0.01 mol of the corresponding alkyl halide was added dropwise under vigorous stirring and cooling with a water bath. After 2 h, the mixture was diluted with 200 ml of water and extracted with chloroform (6 × 25 ml), the combined extracts were washed with water and dried over $MgSO_4$, the solvent was distilled off, and the residue was either distilled under reduced pressure or recrystallized from hexane.

b. The reaction was carried out in a one-neck round-bottom flask equipped with a reflux condenser, which was placed in an LG Electronics MS-192A household microwave oven. The flask was charged with 0.01 mol of imidazole or benzimidazole, 0.84 g (0.015 mol) of potassium hydroxide, 20 ml of DMF, and 0.01 mol of alkyl halide, and the mixture was irradiated for 60 min at a power of 90 W. The mixture was then cooled and treated as described in *a*.

1-Isopropylimidazole (I). Method *a*. Yield 80%. Colorless viscous liquid, bp 68–72°C (3 mm); published data [15]: 62°C (2 mm).

1-Isobutylimidazole (II). Yield 60% (*a*), 56% (*b*). Colorless viscous liquid, bp 78°C (3 mm); published data [15]: bp 92°C (2 mm).

1-Benzylimidazole (III). Yield 77% (*a*), 68% (*b*). Colorless crystals, mp 69–70°C (from hexane); published data [15]: mp 70–71.5°C.

1-Isopropylbenzimidazole (IV). Yield 79% (*a*). Colorless viscous liquid, bp 135–140°C (1 mm). ^1H NMR spectrum, δ, ppm: 8.39 (2-H), 7.85 (4-H), 7.26 (5-H), 7.28 (6-H), 7.55 (7-H), 4.6 (CH), 1.47 (CH_3). ^{13}C NMR spectrum, δ_C, ppm: 144.06 (C^2), 141.4(C^9), 133.3 (C^8), 122.15 (C^6), 121.48 (C^5), 119.76 (C^4), 110.66 (C^7), 47.2 (CH), 22.1 (CH_3). Found, %: C 75.03; H 7.62; N 17.44. $C_{10}H_{12}N_2$. Calculated, %: C 74.97; H 7.55; N 17.48.

1-Isobutylbenzimidazole (V). Yield 29% (*a*), 67% (*b*). Colorless viscous liquid, bp 155–165°C (1 mm), which crystallized at room temperature to give colorless crystals with mp 49–50°C. ^1H NMR spectrum, δ, ppm: 8.19 (2-H), 7.64 (4-H), 7.18 (5-H), 7.23 (6-H), 7.58 (7-H), 4.05 (2-H), 2.14 (CH), 1.47 (CH_3). ^{13}C NMR spectrum, δ_C, ppm: 144.31 (C^2), 143.33 (C^9), 134.07 (C^8), 122.12 (C^6), 121.26 (C^5), 119.35 (C^4), 110.5 (C^7), 51.2 (CH_2), 29.1 (CH), 20.2 (CH_3). Found, %: C 75.73; H 8.06; N 16.21. $C_{11}H_{14}N_2$. Calculated, %: C 75.82; H 8.10; N 16.08.

1-Benzylbenzimidazole (VI). Yield 85% (*a*). Colorless crystals, mp 106–108°C; published data [16]: mp 116–118°C.

1,3-Dialkylimidazolium and 1,3-dialkylbenzimidazolium halides (*general procedure*). Alkyl halide, 0.3 mol, was added dropwise under vigorous stirring to a mixture of 0.1 mol of 1-alkylazole or 1-alkylbenzimidazole in 20 ml of appropriate solvent which was dried by standard procedure [17]. The mixture was stirred for 8–36 h at a temperature indicated below, the solvent was distilled off, the residue was ground with anhydrous THF, and the precipitate was filtered off and dried under reduced pressure.

1,3-Diisopropylimidazolium bromide (VII). Reaction time 12 h (toluene). Yield 60%. Colorless powder, mp 136–138°C. ^{1}H NMR spectrum, δ, ppm: 9.35 t (2-H, ^4J = 1.7 Hz), 7.94 d (4-H, ^4J = 1.6 Hz), 7.94 d (5-H, ^4J = 1.6 Hz), 4.63 (CH), 1.49 (CH_3). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 133.65 (C^2), 120.71 (C^4), 120.71 (C^5), 52.3 (CH), 22.4 (CH_3). Found, %: C 46.55; H 7.18; Br 34.25; N 12.02. $C_9H_{17}BrN_2$. Calculated, %: C 46.36; H 7.35; Br 34.27; N 12.01.

1,3-Diisobutylimidazolium bromide (VIII). Reaction time 18 h (2-propanol). Yield 65%. Colorless powder, mp 84–86°C. ^{1}H NMR spectrum, δ, ppm: 9.27 s (2-H), 7.82 d (4-H, J = 1.6 Hz), 7.82 d (5-H, J = 1.6 Hz), 4.04 (CH_2), 2.12 (CH), 0.85 (CH_3). ^{13}C NMR spectrum, δ_C, ppm: 136.47 (C^2), 122.96 (C^4), 122.96 (C^5), 55.63 (CH_2), 28.81 (CH), 19.16 (CH_3). Found, %: C 51.02; H 8.10; Br 29.83; N 11.05. $C_{11}H_{21}BrN_2$. Calculated, %: C 50.58; H 8.10; Br 30.59; N 10.72.

1,3-Diisobutylimidazolium iodide (IX). Reaction time 8 h (acetonitrile). Yield 66%. Colorless powder, mp 118–120°C. ^{1}H NMR spectrum, δ, ppm: 9.27 s (2-H), 7.82 d (4-H, J = 1.6 Hz), 7.82 d (5-H, J = 1.6 Hz), 4.04 (CH_2), 2.12 (CH), 0.85 (CH_3). ^{13}C NMR spectrum, δ_C, ppm: 136.47 (C^2), 122.96 (C^4), 122.96 (C^5), 55.63 (CH_2), 28.81 (CH), 19.16 (CH_3). Found, %: C 43.02; H 7.10; I 40.98; N 8.90. $C_{11}H_{21}IN_2$. Calculated, %: C 42.87; H 6.87; I 41.18; N 9.09.

1,3-Dibenzylimidazolium chloride (X). Reaction time 11 h (toluene). Yield 85%. Colorless hygroscopic powder which quickly liquified on exposure to air. ^{1}H NMR spectrum, δ, ppm: 9.78 s (2-H), 7.9 m (4-H), 7.9 m (5-H), 5.49 (NCH_2) 7.43 m (Ph). ^{13}C NMR spectrum, δ_C, ppm: 136.52 (C^2); 128.72 (C^4); 128.72 (C^5); 122.83, 128.94, 128.53, 135.06 (Ph); 51.84 (CH_2). Found, %: C 71.14; H 6.20; Cl 12.65; N 10.01. $C_{17}H_{17}ClN_2$. Calculated, %: C 71.69; H 6.02; Cl 12.45; N 9.84.

1,3-Diisopropylbenzimidazolium bromide (XI). Reaction time 26 h (toluene). Yield 31%. Colorless powder, mp 124–126°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.91 (2-H), 8.15 (4-H), 7.7 (5-H), 7.7 (6-H), 8.15 (7-H), 5.1 (CH), 1.7 (CH_3). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 139.07 (C^2), 130.5(C^8), 130.5 (C^9), 126.4 (C^5), 126.4 (C^6), 114.02 (C^4), 114.02 (C^7), 53.1 (CH), 28.2 (CH_2), 19.3 (CH_3). Found, %: C 55.09; H 6.65; Br 28.55; N 9.71. $C_{13}H_{19}BrN_2$. Calculated, %: C 55.13; H 6.76; Br 28.21; N 9.89.

1-Isobutyl-3-methylbenzimidazolium bromide (XII). Reaction time 17 h (toluene). Yield 46%. Colorless powder, mp 185–186°C. ^{1}H NMR spectrum, δ, ppm: 9.88 (2-H), 8.13 (4-H), 7.68 (5-H), 7.7 (6-H), 8.03 (7-H), 4.37 (CH_2), 4.06 (NCH_3), 2.26 (CH), 0.98 (CH_3). ^{13}C NMR spectrum, δ_C, ppm: 144.04 (C^2), 132.96 (C^9), 132.47 (C^8), 127.67 (C^6), 127.61 (C^5), 114.89 (C^4), 114.81 (C^7), 54.25 (CH), 34.5 (NCH_3), 29.57 (CH_2), 20.58 (CH_3). Found, %: C 53.56; H 6.76; Br 29.35; N 10.33. $C_{12}H_{17}BrN_2$. Calculated, %: C 53.54; H 6.36; Br 29.68; N 10.41.

1,3-Diisobutylbenzimidazolium bromide (XIII). Reaction time 18 h (acetonitrile). Yield 29%. Colorless powder, mp 176–179°C. ^{1}H NMR spectrum, δ, ppm: 9.9 (2-H), 8.13 (4-H), 7.69 (5-H), 7.69 (6-H), 8.13 (7-H), 4.36 (CH_2), 2.24 (CH), 0.99 (CH_3). ^{13}C NMR spectrum, δ_C, ppm: 142.5 (C^2), 131.3 (C^8), 131.3 (C^9), 126.5 (C^5), 126.5 (C^6), 113.9 (C^4), 113.9 (C^7), 53.1 (CH), 28.2 (CH_2), 19.3 (CH_3). Found, %: C 57.87; H 7.64; Br 25.64; N 8.85. $C_{15}H_{23}BrN_2$. Calculated, %: C 57.88; H 7.45; Br 25.67; N 9.00.

1,3-Diisobutylbenzimidazolium iodide (XIV). Reaction time 36 h (acetonitrile). Yield 70%. Colorless powder, mp 158–160°C. ^{1}H NMR spectrum, δ, ppm: 9.9 (2-H), 8.13 (4-H), 7.69 (5-H), 7.69 (6-H), 8.13 (7-H), 4.36 (CH_2), 2.24 (CH), 0.99 (CH_3). ^{13}C NMR spectrum, δ_C, ppm: 142.5 (C^2), 131.3 (C^8), 131.3 (C^9), 126.5 (C^5), 126.5 (C^6), 113.9 (C^4), 113.9 (C^7), 53.1 (CH), 28.2 (CH_2), 19.3 (CH_3). Found, %: C 50.50; H 6.20; I 35.28; N 8.02. $C_{23}H_{15}IN_2$. Calculated, %: C 50.29; H 6.47; I 35.42; N 7.82.

1,3-Dibenzylbenzimidazolium chloride (XV). Reaction time 13 h (toluene). Yield 87%. Colorless powder, mp 210–212°C. ^{1}H NMR spectrum, δ, ppm: 10.4 (2-H), 7.98 (4-H), 7.62 (5-H), 7.62 (6-H), 7.98 (7-H), 5.83 (CH_2), 7.55 (*o*-H), 7.4 (*p*-H, *m*-H). ^{13}C NMR spectrum, δ_C, ppm: 142.96 (C^2), 131.12 (C^8), 131.12 (C^9), 126.84 (C^5), 126.84 (C^6), 114.12 (C^4), 114.12 (C^7), 134.1 (C^i), 129.1 (C^o), 128.8 (C^p), 128.4 (C^m), 50.06 (CH_2). Found, %: C 75.29; H 5.80; Cl 10.48; N 8.42. $C_{21}H_{19}ClN_2$. Calculated, %: C 75.32; H 5.72; Cl 10.58; N 8.37.

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