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REACTION OF CHLORO-SUBSTITUTED *N*-CYANO-BENZIMIDAZOLES WITH HYDRAZINES. A ROUTE TO 1*H*-[1,2,4]TRIAZOLO[4,3-*a*]BENZIMIDAZOLE AND [1,2,4]TRIAZINO[4,5-*a*]BENZIMIDAZOLE

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Bicyclic compounds containing bridgehead nitrogen atoms in their structure are of both theoretical and practical interest [1]. We have previously proposed [2] a synthesis of 1*H*-imidazo[5,1-*c*][1,2,4]triazole by the intramolecular cyclization of 4,5-dichloro-1*H*-imidazol-1-ylcarboxamidrazone (prepared from the corresponding *N*-cyanoimidazole and hydrazine). In this work, we have now studied transformations of the corresponding benzimidazole derivatives in similar reactions. Treatment of the 2-chlorobenzimidazole (**1a**) with cyanogen bromide in the presence of Et_3N at low temperature gave the *N*-cyano derivative **2a** in 80% yield. Due to the highly active chlorine atom, the cyanation of compound **1b** was achieved by refluxing with BrCN in EtOAc, and the product **2b** was obtained in 58% yield. Compound **2a** was introduced in the reaction with hydrazine hydrate or phenylhydrazine in EtOH solution at 0-5°C in the presence of Et_3N and gave compounds **3a**,**b** in 78 and 69% yield, respectively. The reaction of compound **2b** with phenylhydrazine was carried out in MeCN medium at 0ºC. Thanks to the high mobility of the chlorine atom, its intramolecular cyclization occurred without the need for Et_3N, and led to a six-membered heterocycle. After treatment of the reaction mixture with $NaHCO_3$, the product **4** was isolated as free base in 73% yield. The structures of all of the compounds were determined using ^1H and ^{13}C NMR spectroscopy. In the case of compounds **3a**,**b** and **4**, the structure was additionally confirmed using COSY and ^{13}C HSQC 2D NMR experiments.

Hence, we have proposed a novel method for the synthesis of 1*H*-[1,2,4]triazolo[4,3-*a*]benzimidazole derivatives [3] and for the novel [1,2,4]triazino[4,5-*a*]benzimidazole heterocyclic system.

IR spectra were recorded on an FSM-1201 instrument for KBr pellets. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-400 instrument (400 and 100 MHz, respectively). The COSY and ^{13}C HSQC experiments were carried out on a Bruker Avance III spectrometer (600 MHz for ^1H and 150 MHz for ^{13}C). In all cases the solvent was DMSO-d_6 and the internal standard was TMS. Elemental analysis was performed on a vario EL cube analyzer. Melting points were determined on a Boetius hot stage apparatus and were not corrected.

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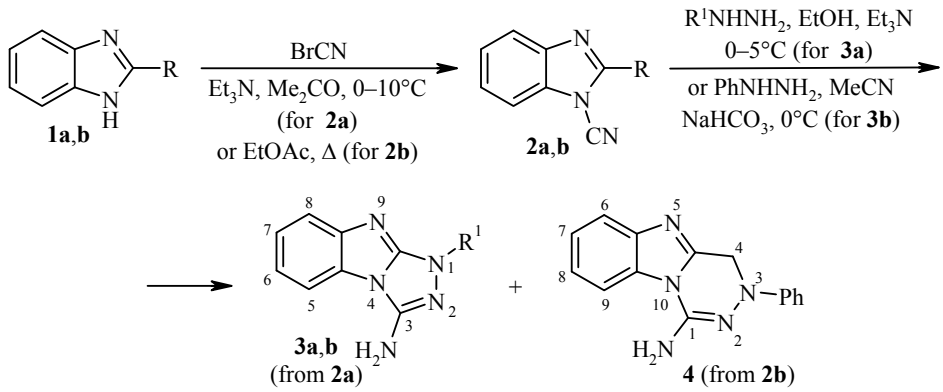

2-Chloro-1-cyanobenzimidazole (2a). Et_3N (2.9 ml, 2.12 g, 21 mmol) was added to a solution of azole **1a** (3.05 g, 20 mmol) in absolute acetone (40 ml) cooled to 0°C, and the reaction mixture was maintained below 10°C while a solution of cyanogen bromide (2.12 g, 20 mmol) in acetone (10 ml) was added. After 20 min, the mixture was filtered, and the filtrate was evaporated. The dry residue after evaporation was then recrystallized from hexane. Yield 2.84 g (80%). White crystalline powder. Mp 129-130°C (decomp.). IR spectrum, ν, cm^{-1}: 2257, 1612, 1512, 1459, 1354, 1246, 1200, 756, 744. ^1H NMR spectrum, δ, ppm: 7.56-7.54 (2H, m, H-6,7); 7.51-7.49 (2H, m, H-4,5). ^{13}C NMR spectrum, δ, ppm: 102.1 (CN); 109.8 (C-7); 119.8 (C-4); 123.3 (C-5); 123.5 (C-6); 133.6 (C-7a); 140.2 (C-3a); 145.3 (C-2). Found, %: C 54.02; H 2.21; N 23.59. $C_8H_4ClN_3$. Calculated, % C 54.11; H 2.27; N 23.66.

2-(Chloromethyl)-1-cyanobenzimidazole (2b). A solution of cyanogen bromide (2.12 g, 20 mmol) in EtOAc (10 ml) was added dropwise with vigorous stirring to a refluxing solution of azole **1b** (6.66 g, 40 mmol) in EtOAc (40 ml). The reaction mixture was refluxed for a further 30 min and cooled. The precipitated crystals of 2-(chloromethyl)benzimidazole hydrobromide were filtered off and the filtrate was evaporated on a rotary evaporator. The dry residue after evaporation was recrystallized from a mixture of hexane and EtOAc (9:1). Yield 2.23 g (58%). White crystalline powder. Mp 122-124°C. IR spectrum, ν, cm^{-1}: 2335, 1621, 1539, 1422, 1244, 1141, 806. ^1H NMR spectrum, δ, ppm: 4.63 (2H, s, CH_2Cl); 7.32-7.04 (2H, m, H-5,6); 7.95-7.81 (2H, m, H-4,7). ^{13}C NMR spectrum, δ, ppm: 41.2 (CH_2Cl); 99.7 (CN); 112.8 (C-7); 120.5 (C-4); 123.3 (C-6); 124.0 (C-5); 133.7 (C-7a); 139.4 (C-3a); 151.9 (C-2). Found, %: C 56.33; H 3.12; N 21.89. $C_9H_6ClN_3$. Calculated, %: C 56.41; H 3.16; N 21.93.

1*H*-[1,2,4]Triazolo[4,3-*a*]benzimidazol-3-amine (3a). A mixture of Et_3N (0.84 ml, 0.607 g, 6.0 mmol) and hydrazine hydrate (0.28 ml, 0.285 g, 5.7 mmol) in EtOH (5 ml) was added with stirring to a solution of compound **2a** (0.854 g, 5.6 mmol) in EtOH (10 ml) cooled to 0-5°C. The reaction mixture was heated to room temperature and stirred for 1 h. The solution was evaporated on a rotary evaporator. The residue was dissolved in acetone (5 ml), and $Et_3N{\cdot}HCl$ was filtered off. The acetone solution was again evaporated and the dry residue was recrystallized from EtOH. Yield 0.756 g (78%). White crystalline powder. Mp 203-205°C. IR spectrum, ν, cm^{-1}: 3214-3125, 1659, 1557, 1471, 1278, 1242, 1005, 814. ^1H NMR spectrum, δ, ppm: 11.40 (1H, br. s, NH); 7.82-7.78 (2H, m, H-5,8); 7.32-7.27 (2H, m, H-6,7); 7.06 (2H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 110.7 (C-5); 120.9 (C-6); 121.3 (C-8); 122.7 (C-7); 128.1 (C-4a); 139.1 (C-8a); 147.5 (C-9a); 152.0 (C-3). Found, %: C 55.51; H 4.01; N 40.48. $C_8H_7N_5$. Calculated, %: C 55.49; H 4.07; N 40.44.

1-Phenyl-1*H*-[1,2,4]triazolo[4,3-*a*]benzimidazol-3-amine (3b) was obtained similarly using phenylhydrazine instead of hydrazine hydrate. Yield 0.963 g (69%). White crystalline powder. Mp 191-192°C. IR spectrum, ν, cm^{-1}: 3306-3126, 1632, 1474, 1443, 1339, 1292, 1027. ^1H NMR spectrum, δ, ppm: 7.94-7.87 (1H, m, H-8); 7.51-7.34 (3H, m, H-5, H Ph); 7.31-7.05 (5H, m, H-6,7, H Ph); 6.41 (1H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 110.6 (C-5); 119.9 (C Ph); 120.8 (C-6); 121.1 (C-8); 122.6 (C-7); 129.0 (C-4a); 129.1 (C Ph); 130.3 (C Ph); 136.1 (C Ph); 139.3 (C-8a); 151.6 (C-9a); 153.9 (C-3). Found, %: C 67.49; H 4.43; N 28.16. $C_{14}H_{11}N_5$. Calculated, %: C 67.46; H 4.45; N 28.09.

3-Phenyl-3,4-dihydro[1,2,4]triazino[4,5-*a*]benzimidazol-1-amine (4). A solution of phenylhydrazine (1.18 ml, 1.30 g, 12.0 mmol) in MeCN (5 ml) was added dropwise to a solution of compound **2b** (2.01 g, 10.5 mmol) in MeCN (10 ml) cooled to 0°C, and the temperature was maintained at no higher than 0°C. After addition of all of the phenylhydrazine, the reaction mixture was heated to room temperature, stirred for 1 h, and dry $NaHCO_3$ (1.00 g) was added. The mixture was stirred for a further 20 min, then filtered, and the filtrate evaporated. The dry residue was crystallized from 2-PrOH. Yield 2.01 g (73%). Cream-colored crystalline powder. Mp 192-194°C. IR spectrum, ν, cm^{-1}: 3320-3178, 1632, 1522, 1458, 1420, 1373, 1279. ^{1}H NMR spectrum, δ, ppm: 7.95 (1H, d, H-6); 7.73 (1H, d, H-9); 7.48-7.26 (4H, m, H-7,8, H Ph); 7.23-6.90 (3H, m, H Ph); 6.18 (2H, br. s, NH_2); 4.78 (2H, s, 4-CH_2). ^{13}C NMR spectrum, δ, ppm: 47.0 (C-4); 112.1 (C Ph); 115.2 (C-9); 118.9 (C-6); 120.0 (C Ph); 121.5 (C-8); 123.9 (C-7); 129.6 (C Ph); 136.5 (C-9a); 138.2 (C-4a); 145.1 (C Ph); 147.2 (C-5a); 152.9 (C-1). Found, %: C 68.36; H 5.07; N 26.65. $C_{15}H_{13}N_5$. Calculated, %: C 68.43; H 4.98; N 26.60.

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