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Synthesis of Some Benzimidazolyl- and Ethylbenzimidazolylamine Derivatives

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Benzimidazolylamine **3(a-e)** and methylbenzimidazolylamine **3(f-j)** derivatives were synthesized under reflux condition by a simple nucleophilic reaction of an appropriate aromatic or aliphatic amine with 2-chloromethylbenzimidazole and 2-(chloromethyl)-5-methyl-1*H*-3-benzimidazole, respectively. The yields of products following recrystallization from ethanol were of the order of 50-80 %. ^{1}H NMR and IR spectra together with elemental analysis data were used to identification of these compounds.

Key Words: *o*-Phenylenediamine, Benzimidazole, Amine.

INTRODUCTION

Amines are one of the most common features of naturally occurring biologically active compounds and are widely used as a base in chemical process in order to prepare fine chemicals, pharmaceuticals and agrochemicals[1]. Amines have showed an important role in chemotherapeutic approach to a variety of diseases[2-4] due to having unique biological properties. However derivatives of amines such as benzimidazolylamines and methylbenzimidazolylamines which may have more biological activity due to having a benzimidazole ring were not studied well. The most general and simple method for the synthesis of secondary amines is direct nucleophilic addition of primary amines to an alkyl or aryl halide. This method can be used for the synthesis of substituted amines containing a biologically active ring like benzimidazole[5-10].

Owing to the versatility of amines and benzimidazoles and as a continuation of previous studies[11-13] we have extended the reaction of 2-chloro-methylbenzimidazole and 2-(chloromethyl)-5-methyl-1*H*-3-benzimidazole with different amines in order to preparation of some new benzimidazolyl- and methylbenzimidazolylamines.

EXPERIMENTAL

2-Chloro-methylbenzimidazole and 2-(chloromethyl)-5-methyl-1*H*-3-benzimidazole were prepared by reaction of chloroacetic acid with 1,2-phenylenediamine and 4-methyl-1,2-phenylenediamine following a procedure in our earlier report[14]. ^{1}H NMR spectra were recorded on a Bruker (300 MHz) spectrometer. TMS was

used as an internal standard. The IR spectra were recorded on Galaxy FT-IR 500 spectrometer. Microanalyses were performed by the Elemental Analyzer (Elemental, Vario EL III) at the Arak University. The Microanalyses results were agreed favourably with the calculated values. Reaction courses and product mixtures were monitored by thin layer chromatography.

General procedure: A solution of 2-chloromethylbenzimidazole or 2-(chloromethyl)-5-methyl-1*H*-3-benzimidazole (5 mmol) and corresponding amine (5 mmol) in ethanol (10 mL) was refluxed for 3 h. The reaction mixture was then cooled in an ice bath and the precipitate filtered to give crude products **3(a-j)**, which then recrystallized from ethyl acetate or ethanol.

N-(1*H*-1,3-Benzimidazol-2-ylmethyl)-N-propylamine (3a): Yield 75 %, m.p. = 124-125 ºC. IR (KBr, ν_{max}, cm^{-1}): 3400-3100, 1433, 1271, 767. ^{1}H NMR (DMSO-d_6): δ = 0.76-1.65 (m, 7H, propyl), 2.77 (bs, 1H, NH), 3.98 (s, 2H, CH_2), 7.13-7.56 (m, 4H, Ar-H) 12.30 (bs, 1H, NH). Anal. calcd. for $C_{11}H_{15}N_3$: C, 69.81; H, 7.99; N, 22.20 %. Found: C, 69.51; H, 8.14; N, 22.34 %.

N-(1*H*-1,3-Benzimidazol-2-ylmethyl)-N-butylamine (3b): Yield 70 %, m.p. = 94-95 ºC. IR (KBr, ν_{max}, cm^{-1}): 3014, 1454, 1271, 767. ^{1}H NMR (DMSO-d_6): δ = 0.75-1.54 (m, 9H, butyl), 2.73 (bs, 1H, NH), 4.19 (s, 2H, CH_2), 7.14-7.69 (m, 4H, Ar–H) 12.40 (bs, 1H, NH). Anal. calcd. for $C_{12}H_{17}N_3$: C, 70.90; H, 8.43; N, 20.67 %. Found: C, 70.80; H, 8.30; N, 20.88 %.

N-(1*H*-1,3-Benzimidazol-2-ylmethyl)-N-(4-methylphenyl)amine (3c): Yield 55 %, m.p. = 78-79 ºC. IR (KBr, ν_{max}, cm^{-1}): 3319, 3011, 2912, 1521, 1458, 1269, 806, 742. ^{1}H NMR (DMSO-d_6): δ = 2.20 (s, 3H, CH_3), 2.57 (bs, 1H, NH), 4.05 (s, 2H, CH_2), 6.35-7.34 (m, 8H, Ar-H) 12.25 (bs, 1H, NH). Anal. calcd. for $C_{15}H_{15}N_3$: C, 75.92; H, 6.37; N, 17.71 %. Found: C, 76.31; H, 6.10; N, 17.57 %.

N-(1*H*-1,3-Benzimidazol-2-ylmethyl)-N-mesitylamine (3d): Yield 60 %, m.p. = 194-195 ºC. IR (KBr, ν_{max}, cm^{-1}): 3308, 3011, 2980, 1624, 1485, 1201, 842, 740. ^{1}H NMR (DMSO-d_6): δ = 2.13 (s, 3H, CH_3), 2.27 (s, 6H, 2 × CH_3), 2.73 (bs, 1H, NH), 4.62 (s, 2H, CH_2), 6.54-7.64 (m, 6H, Ar-H). Anal. calcd. for $C_{17}H_{19}N_3$: C, 76.95; H, 7.22; N, 15.84 %. Found: C, 77.33; H, 7.09; N, 15.55 %.

N-(1*H*-1,3-Benzimidazol-2-ylmethyl)-N-benzylamine (3e): Yield 50 %, m.p. = 102-103 ºC. IR (KBr, ν_{max}, cm^{-1}): 3057, 2661, 1620, 1433, 1273, 842, 742. ^{1}H NMR (DMSO-d_6): δ = 2.75 (bs, 1H, NH), 3.73 (s, 2H, CH_2), 4.65 (s, 2H, CH_2), 7.14-8.50 (m, 9H, Ar–H), 12.7 (bs, 1H, NH). Anal. calcd. for $C_{15}H_{15}N_3$: C, 75.92; H, 6.37; N, 17.71 %. Found: C, 75.88; H, 6.51; N, 17.60 %.

N-[(5-Methyl-1*H*-1,3-benzimidazol-2-yl)methyl]-N-propylamine (3f): Yield 73 %, m.p. = 111-112 ºC. IR (KBr, ν_{max}, cm^{-1}): 3192, 2962, 1448, 804. ^{1}H NMR (DMSO-d_6): δ = 0.76-1.67 (m, 7H, propyl), 2.40 (s, 3H, CH_3), 2.75 (bs, 1H, NH), 3.95 (s, 2H, CH_2), 7.00-7.44 (m, 3H, Ar-H) 12.40 (bs, 1H, NH). Anal. calcd. for $C_{12}H_{17}N_3$: C, 70.90; H, 8.43; N, 20.67 %. Found: C, 70.69; H, 8.24; N, 21.01 %.

N-Butyl-N-[(5-methyl-1*H*-1,3-benzimidazol-2-yl)methyl]amine (3g): Yield 80 %, m.p. = 93-94. C. IR (KBr, ν_{max}, cm^{-1}): 3138, 2957, 1448, 1278, 804. ^{1}H NMR

(DMSO-d_6): δ = 0.74-1.50 (m, 9H, butyl), 2.39 (s, 3H, CH_3), 2.75 (bs, 1H, NH), 3.90 (s, 2H, CH_2), 6.93-7.42 (m, 3H, Ar–H), 12.42 (bs, 1H, NH). Anal. calcd. for $C_{13}H_{19}N_3$: C, 71.85; H, 8.81; N, 19.34 %. Found: C, 72.23; H, 8.59; N, 19.15 %.

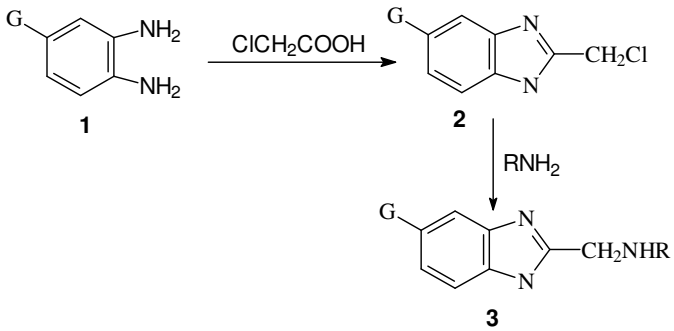
N-[(5-Methyl-1*H*-1,3-benzimidazol-2-yl)methyl]-N-(4-methylphenyl)amine (3h): Yield 50 %, m.p. = 71-72 ºC. IR (KBr, ν_{max}, cm^{-1}): 3310, 3014, 2843, 1518, 1448, 806. ^{1}H NMR (DMSO-d_6): δ = 2.13 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.66 (bs, 1H, NH), 4.30 (s, 2H, CH_2), 6.58-7.57 (m, 7H, Ar–H) 12.20 (bs, 1H, NH). Anal. calcd. for $C_{16}H_{17}N_3$: C, 76.46; H, 6.82; N, 16.72 %. Found: C, 76.25; H, 6.83; N, 16.88 %.

N-Mesityl -N-[(5-methyl-1*H*-1,3-benzimidazol-2-yl)methyl]amine (3i): Yield 54 %, m.p. = 176-177 ºC. IR (KBr, ν_{max}, cm^{-1}): 3315, 3011, 28600, 1622, 1446, 1219, 846. ^{1}H NMR (DMSO-d_6): δ = 2.14 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 2.22 (s, 6H, 2 × CH_3), 2.77 (bs, 1H, NH), 4.48 (s, 2H, CH_2), 6.75-7.67 (m, 5H, Ar-H). Anal. calcd. for $C_{18}H_{21}N_3$: C, 77.38; H, 7.58; N, 15.04 %. Found: C, 77.45; H, 7.06; N, 15.36 %.

N-Benzyl-N-[(5-methyl-1*H*-1,3-benzimidazol-2-yl)methyl]methanamine (3j): Yield 50 %, m.p. = 88-89 ºC. IR (KBr, ν_{max}, cm^{-1}): 3148, 3038, 2920, 1450, 1300, 804, 700. ^{1}H NMR (DMSO-d_6): δ = 2.39 (bs, 3H, CH_3), 2.65 (bs, 1H, NH), 3.78 (s, 2H, CH_2), 4.02 (s, 2H, CH_2), 6.97-7.47 (m, 8H, Ar-H) 12.55 (bs, 1H, NH). Anal. calcd. for $C_{16}H_{17}N_3$: C, 76.46; H, 6.82; N, 16.72 %. Found: C, 76.81; H, 6.85; N, 16.41 %.

RESULTS AND DISCUSSION

Reaction of appropriate primary amine with 2-chloromethylbenzimidazole and 2-(chloromethyl)-5-methyl-1*H*-3-benzimidazole in ethanol under reflux afforded **3(a-e)** and **3(f-j)**, respectively as shown in **Scheme-I**. However reaction with 2-(chloromethyl)-5-methyl-1*H*-3-benzimidazole proceeded slower due to inductive effect of the methyl group on benzimidazole ring.



(**3a**) G = H, R = propyl (**3b**) G = H, R = butyl (**3c**) G = H, R = 4-MePh
(**3d**) G = H, R = Mesityl (**3e**) G = H, R = benzyl (**3f**) G = CH_3, R = propyl
(**3g**) G = CH_3, R=butyl (**3h**) G = CH_3, R = 4-MePh (**3i**) G = CH_3, R= Mesityl
(**3j**) G = CH_3, R = benzyl

Scheme-I

The structural elucidation of the synthesized compounds was assigned on the basis of their IR and ^{1}H NMR spectral studies. As an example, the IR spectrum of **3a** showed the broad absorption band at 3400-3100 corresponds to two -NH groups. The ^{1}H NMR spectrum of the **3a** is simple and consist of two distinguish aromatic and aliphatic protons signals. The aromatic protons resonate as a multiple signal at 7.13-7.56 ppm. The propyl protons resonate as a multiplet at 0.67-1.65 ppm. However, the two NH protons appear as two different broad signals at 2.73 and 12.40 ppm with equal integration corresponding to NH–R and the NH of imidazole ring. This evidence is in support of a nucleophilic attack on the NH_2 group.

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