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SYNTHESIS OF 2-(1-(4-CHLOROPHENYL) ETHYL)-1-(2-(DIETHYLAMINO) ETHYL)-1H-BENZO[D]IMIDAZOL-5-AMINE

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ABSTRACT
A novel 2-(1-(4-chlorophenyl) ethyl)-1-(2-(diethylamino) ethyl)-1H-benzo[d]imidazol-5-amine is synthesized. The IR, NMR spectroscopy and mass spectrometry were used for the assessment of the structure of the synthesized compounds.
Keywords: Benzimidazole, N^1, N^1-diethylethane-1, 2-diamine, Spectral analysis

INTRODUCTION

Benzimidazole derivatives are usually connected with different types of pharmacokinetic and pharmacodynamic properties. Benzimidazole derivatives possess pharmacological and biological activities[1], including antimicrobial[2], diuretic[3],antidiabetic[4],analgesic[5], antivitral[6], antitumor[7], antiulcer[8], antioxidant[9], anthelmintic[10], anti inflammatory[11] and cysticidal activities[12]. Benzofuran is highly promising pharmacophore for the discovery of drugs, and numerical synthetic methodologies for benzofuran derivatives have been developed over the years. Specifically, vitamin B12[10] constituent of Benzofuran nucleus. The biological significance of the benzimidazole containing moiety is documented[13, 14] well. Albendazole, Mebendazole and Thiabendazole are commonly used as anthelmintic drugs[15].

Benzimidazole derivatives show significance biological activities. Some of the already synthesized compounds from field mentioned above have been to have very strong applications in the field of medicine[16]. The antimicrobial activities resulted in their mode of action, which in turn resulted in the blockage of microtubule in the various nematode, trematode and cystode.

It was obvious from the literature described above that very little work seems to have been done on the reactions of orthophenylenediamine with aromatic acids and their further chemical modifications. Hence, it is thought appropriate to study the condensation of *o*-phenylenediamine analogs with carboxylic acids and further modified the cyclization products to achieve diversity-oriented synthesis. In continuous to our earlier work[17], we report synthesis of 2-(1-(4-chlorophenyl) ethyl)-1-(2-(diethylamino) ethyl)-1H-benzo[d]imidazol-5-amine and 2-(2-(1-(4-chlorophenyl) ethyl)-5-nitro-1H-benzo[d]imidazol-1-yl)-N, N-diethylethanamine as new chemical entities.

EXPERIMENTAL

N^1-(2,4-dinitrophenyl)-N2,N2-diethylethane-1,2-diamine (3)

To a stirred solution of 1-chloro-2,4-dinitrobenzene (15 g, 74.05 mmol) in EtOH (150 mL) was added N^1,N^1-diethylethane-1,2-diamine (12.94 g, 111.08 mmol) at RT, heated to 80 to 85 °C for 16h . Aq NH_4 solution was added solid was formed which was filtered to afford 15 g (72%) of N^1-(2,4-dinitrophenyl)-N^2,N^2-diethylethane-1,2-diamine **(3)** as solid.

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TLC System
EtOAc: pet ether (4: 6); R_f: 0.2
^{1}H NMR (400 MHz, $CDCl_3$):9.15 (d, 1H, J= 2.8 Hz), 9.14 (brs, 1H), 8.26 (dd, 1H, J= 9.6 & 2.4 Hz), 6.87 (d, 1H, J= 9.6 Hz), 3.40 (q, 2H), 2.80 (t, 2H), 2.60 (q, 4H), 1.08 (t, 6H);
Mass: (m/z = 283.1 $(M+H)^+$).

N^1-(2-(diethylamino) ethyl)-4-nitrobenzene-1, 2-diamine (4)
N^1-(2,4-dinitrophenyl)-N^2,N^2-diethylethane-1,2-diamine **(3)** (15 g, 53.19 mmol) was combined with EtOH (150 mL), which was subsequently added to a pre-mixed solution of aqueous; ammonium sulphide (10.8 g, 159.57 mmol) in EtOH (300 mL) and Water (150 mL), at 60 °C for 30 min and the reaction mixture was stirred for 24h at 80 – 85 °C. Completion of the reaction was monitored by TLC. Water was added to the reaction mixture and extracted with DCM. Column chromatography was used for the purification of crude compound over silica gel (100 – 200 mesh) using a solvent gradient of 2 – 3% MeOH in $CHCl_3$ as eluent to afford 11 g (80%) of N^1-(2-(diethylamino)ethyl)-4-nitrobenzene-1,2-diamine **(4)** as solid.

TLC System
MeOH: $CHCl_3$ (1:9); R_f: 0.3
^{1}H NMR (400 MHz, $CDCl_3$): 7.81(dd, 1H, J= 8.8 Hz & 2.0 Hz), 7.60 (d, 1H, J = 2.4 Hz), 6.51 (d, 1H, J = 8.8 Hz), 5.11 (brs, 1H), 3.20 (q, 2H), 2.76 (t, 2H), 2.56 (q, 4H), 1.04 (t, 6H);
Mass: (m/z = 252 $(M+H)^+$).

2-(4-chlorophenyl)-N-(2-(2-(diethylamino) ethylamino)-5-nitrophenyl) propanamide (6)
N^1-(2-(diethylamino)ethyl)-4-nitrobenzene-1,2-diamine **(4)** (11 g, 43.65 mmol) dissolved in DCM (150 mL) was added 2-(4-Chloro-phenyl)-propionic acid **(5)** (11.24 g, 61.11 mmol), EEDQ (10.78 g, 43.65 mmol) at RT heated and refluxed for 24h at 50 to 55 °C. Completion of the reaction was monitored by TLC. To the reaction mixture Aq NH_4 solution was added and extracted with DCM. The column chromatography was used for the purification of crude compound over silica gel (100 – 200 mesh) using a solvent gradient of 1% MeOH in DCM as eluent to afford 6 g (35%) of 2-(4-chlorophenyl)-N-(2-(2-(diethylamino)ethylamino)-5-nitrophenyl)propanamide **(6)** as solid.
^{1}H NMR (400 MHz, $CDCl_3$): 8.04 (d, 1H, J = 9.2 Hz), 8.01 (s, 1H), 7.36 (dd, 4H, J = 8.0 Hz), 6.63 (brs, 1H), 6.57 (d, 1H, J = 8.8 Hz), 5.29 (s, 1H), 3.74 (q, 1H), 3.15 (q, 2H), 2.67 (m, 2H), 2.53 (q, 4H), 1.61 (d, 3H), 1.00 (t, 6H);
Mass: (m/z = 419.1 $(M+H)^+$).

2-(2-(1-(4-chlorophenyl) ethyl)-5-nitro-1H-benzo[d] midazole-1-yl)-N, N-diethylethanamine (7)
To a stirred solution of 2-(4-chlorophenyl)-N-(2-(2-(diethylamino)ethylamino)-5-nitrophenyl)propanamide **(6)** (2.5 g, 5.98 mmol) in $CHCl_3$ (50 mL) was added PCl_5 (4.9 g, 23.92 mmol) at RT heated and refluxed fro overnight . Completion of the reaction mixture was monitored by TLC. Aq NH_4 solution was added to the reaction mixture at 0 °C and extracted with $CHCl_3$. The column chromatography was used for the purification of crude compound over silica gel (100 – 200 mesh) using a solvent gradient of 1 – 1.5% MeOH in $CHCl_3$ as eluent to afford 2 g (83%) of 2-(2-(1-(4-chlorophenyl) ethyl)-5-nitro-1H-benzo[d] midazole-1-yl)-N, N-diethylethanamine **(7)** as solid.
^{1}H NMR (400 MHz, $CDCl_3$): 8.74 (d, 1H, J = 2.4 Hz), 8.20 (dd, 1H, J = 8.8 & 2.0 Hz), 7.33 (d, 1H, J = 9.2 Hz), 7.28 (d, 2H, J = 8.4 Hz), 7.16 (d, 2H, J = 8.4 Hz), 4.50 (q, 1H), 4.00 (t, 2H), 2.57 (m, 1H), 2.51 (m, 1H), 2.39 (m, 4H), 1.83 (d, 3H, j = 5.4 Hz), 0.86 (t, 6H);
Mass: (m/z = 4.1.2 $(M+H)^+$).

2-(1-(4-chlorophenyl)ethyl)-1-(2-(diethylamino)ethyl)-1H-benzo[d]imidazole-5-amine (8)
2-(2-(1-(4-chlorophenyl)ethyl)-5-nitro-1H-benzo[d]imidazole-1-yl)-N,N-diethylethanamine **(7)** (2.4 g, 6.0 mmol) was combined with MeOH (40 mL) which was subsequently added to a prepared solution of saturated Aq; NH_4Cl (20 mL), Zinc powder (4.0 g, 60.0 mmol) at 0 °C and stirred at RT for overnight. Sat $NaHCO_3$ solution was added to the reaction mixture and extracted with EtOAc (2 x 100 mL) The organic layer was concentrated under reduced pressure after it was washed with water, brine and dried over

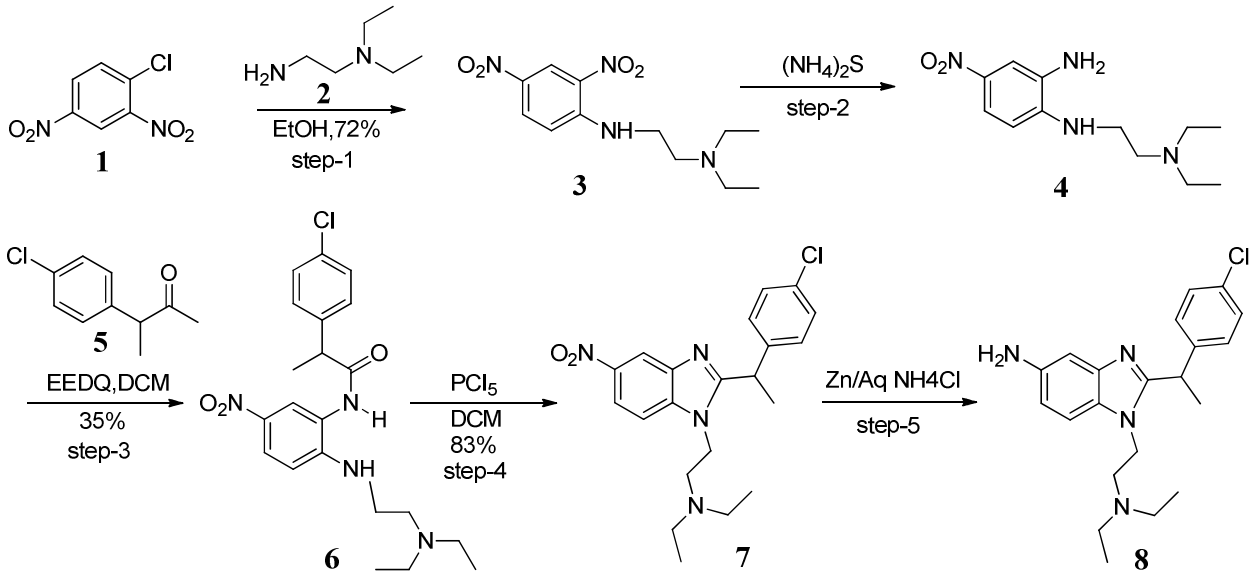
(anhyd.Na_2SO_4). The column chromatography was used for the purification of crude compound over silica gel (100 – 200 mesh) using a solvent gradient of 2 – 2.5% MeOH in $CHCl_3$ as eluent to afford 1.2 g of 2-(1-(4-chlorophenyl) ethyl)-1-(2-(diethylamino) ethyl)-1H-benzo[d]imidazole-5-amine **(8)** as solid.

TLC System

MeOH: $CHCl_3$ (1:9); R_f: 0.3

^{1}H NMR (400 MHz, $CDCl_3$): 7.36 (dd, 4H, J = 8.2 Hz), 7.12 (d, 1H, J = 8.8 Hz), 6.82 (s, 1H), 6.61 (dd, 1H, J = 8.2 & 2.0 Hz) 4.52 (q, 1H), 4.01 (m, 2H), 2.52-2.16 (m, 6H), 1.62 (d, 3H, J = 9.2 Hz), 0.78 (t, 6H);

Mass: (m/z = 370.9 $(M+H)^+$).



Scheme-1

RESULTS AND DISCUSSION

1-chloro-2,4-dinitrobenzene and N^1,N^1-diethylethane-1,2-diamine react to form N-(2-(diethyl amino)ethyl)-2,4-dinitrobenzenamine **(3)**. Compound **3** is treated with ammonium sulphide to give N^1-(2-(diethyl amino) ethyl)-4-nitrobenzene-1,2-diamine **(4)** which on treatment with 3-(4-chlorophenyl)butan-2-one gives N-(2-(2-(diethylamino)ethylamino)-5-nitrophenyl)-2-(4-chlorophenyl)propanamide **(6)**. Compound **6** reacts with PCl_5 to form 2-(2-(1-(4-chlorophenyl)ethyl)-5-nitro-1H-benzo[d]imidazol-1-yl)-N,N-diethylethanamine **(7)** which on reaction with Zn/NH_4Cl gives 2-(1-(4-chlorophenyl)ethyl)-1-(2-(diethylamino)ethyl)-1H-benzo[d]imidazol-5-amine **(8)**.

CONCLUSION

We have presented simple, cost-effective, and practical method for the preparation of 2-(1-(4-chlorophenyl)ethyl)-1-(2-(diethylamino)ethyl)-1H-benzo[d]imidazol-5-amine. This methodology provides an efficient alternative to existing methods for the synthesis of benzo[d]imidazole.

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