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NOTE

Convenient and Improved One Pot Synthesis of Imidazole

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An improved and convenient one pot synthesis of 99 % pure imidazole using (40.0 w/w) glyoxal (1 mol), 25 % aquous ammonia (4 mol) and 35 % formaldehyde (w/w) (1.125 mol) under the temperature conditions of 70-90°C. Various combinations of ammonia, glyoxal and formaldehyde are studied. When the reactions was carried out using ammonia four times of that of glyoxal and formaldehyde 1.125 times to that of glyoxal, it was observed that the better yields of imidazole are obtained with high purity.

Key Words: Synthesis, Imidazole, Heterocycle, Drug intermedicate, Ammonia, Formaldehyde, Glyoxal.

Synthesis of imidazole[1] and its derivatives[2] become very important, since most of the drugs having this moiety (or) its fused analogs possesses pronounced antifungal, antimicrobial, antiviral activities[3]. Even though there were many reports in the literature for the synthesis of imidazoles and its derivatives[4], most of them were either patented or facing difficulties in the reproduction.

Various methods have been reported in the literature are patented and the reaction involves glyoxal, formaldehyde with ammonium cabonate[5], ammonium oxalate[6], liquid ammonia[7] or ammonium sulphate[8]. These combinations under various temperature and pressure conditions reported were not easily reproducible. Methods using glyoxal, ammonia and formaldehyde were also reported[9] with yields varying from 4-9 %. Herein, the optimum reaction condition to produce high yields of imidazole using 4.0 mol of NH_3 1.0 mol of glyoxal and 1.125 mol of formaldehyde under the temperature conditions of 70-90°C is reported.

All the m.ps and m.m.p's were determined in open, capillary tubes, are in.agreement with the literature[10]. IR spectra, (KBr) were recorded on a Perkin-Elmer spectrophotometer and ^{1}H NMR spectra Bruker (300 MHz) spectrophotometer using TMS as internal reference were in agreement with the literature.

Synthesis of imidazole

Method-I: In a 500 mL three necked round bottom flask fitted with two pressure equal dropping funnels, are at each neck and mechanical stirrer to the middle neck, 70 mL of (l.0 mol) ammonia solution (25 %) was stirred at 25°C, glyoxal (40 %) 75g (0.5 mol) and formaldehyde solution (38-40 %). 37.5 g (0.5 mol) were added dropwise through separate dropping funnels over a period of 2 h, with continuous stirring at room temperature (28°C). The reaction mixture was heated at 70°C for 2 h with continuous stirring. The contents of the reaction mixture was distilled off at 130°C under 20 torr pressure. The remaining residue was distilled separately at 210°C under 5 torr pressure gave semi-solid of 5.1 g with 30 % purity. In this method, the purity is not found better, so the method-**II** is opted.

Method-II: In a 500 mL three necked round bottom flask fitted with mechanical stirrer to center neck and two dropping funnel one each to the other two necks, 70 mL of (1.0 mol) of ammonia solution (25 %) was heated to 70°C. To the reaction mixture, glyoxal (40 %) 75 g (0.5 mol) and formaldehyde solution (38-40 %) 37.5 g (0.5 mol) were added drop wise through separate dropping funnels with constant stirring over a period of 1 h at 70°C. The reaction mixture was subjected to vaccum distillation at 130°C and 20 torr pressure and the residue obtained was distilled at 210°C at 5 torr pressure yielded imidazole 25 g with 50 % purity as semi-solid. It was observed that the decrease in product yield was due to the loss of ammonia on heating. So to improve further, the method-**III** is opted for further investigation.

Method-III: In a 500 mL three necked round bottom flask fitted with, mechanical stirrer to the middle neck and two dropping funnels one each to the remaining two necks, 105 mL of (1.5 mol) of ammonia solution (25 %) was heated to 70°C. To the reaction mixture glyoxal (40 %) 75 g (0.5 mol) and formaldehyde solution (38-40%) 37.5 g (0.5 mL) was added dropwise through separate dropping funnels with constant stirring over a period of 1 h at 70°C. The unreacted portion of the reaction mixture was distilled off 130° and 20 torr pressure. The residue obtained was distilled at 210°C and 5 torr pressure to yield imidazole 25.0 g. Of 82 % purity with m.p. 70-72°C (lit. 90-92°C). The improved purity is observed because of excess (3 times to that of glyoxal) aq. ammonia and further investigated the reaction pattern when one more mole aq. ammonia is added in the same reaction which is described in method-**IV**.

Method-IV: In a three necked flask fitted with mechanical stirrer to the middle neck and two dropping funnels one each to the remaining two necks 140 mL of (2.0 mol) ammonia solution (25 %) was heated to 70°C. To the ammonia solution, 75 g (0.5 mol) glyoxal (40 %), 42.2 g (0.5625

mol) and formaldehyde solution (40 %) was added dropwise at 70°C with constant stirring. The reaction became exothermic and the reaction mixture was stirred at 90°C for a period of 3 h. The contents, of the reaction mixture was distilled off at 130°C under 20 mm pressure yielded dark brown coloured residue. The residue obtained was purified by treating with 2 mL of ethylene diamine and heated at 90°C for 1 h. The residue distilled under reduced pressure yielded imidazole 31.0 g 99 % with m.p. 90-92°C, which is in agreement, with the reported in the literature. The spectral and analytical data further supported in the formation of imidazole with high purity.

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