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Synthesis of 2,3-Dihydro-1*H*-benzo[b][1,4]diazepines with Aromatic Diamines and Acetonedicarboxylic Acid

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2,3-Dihydro-1*H*-benzo[b][1,4]diazepines were obtained by the reaction of the corresponding diamines and acetonedicarboxylic acid in various methods. A plausible mechanism for the formation of 1,5-benzodiazepine is also discussed.

Keywords: 1.5-Benzodiazepine, Acetonedicarboxylic acid, Diamines, 1,3-Shift, Structural isomer.

INTRODUCTION

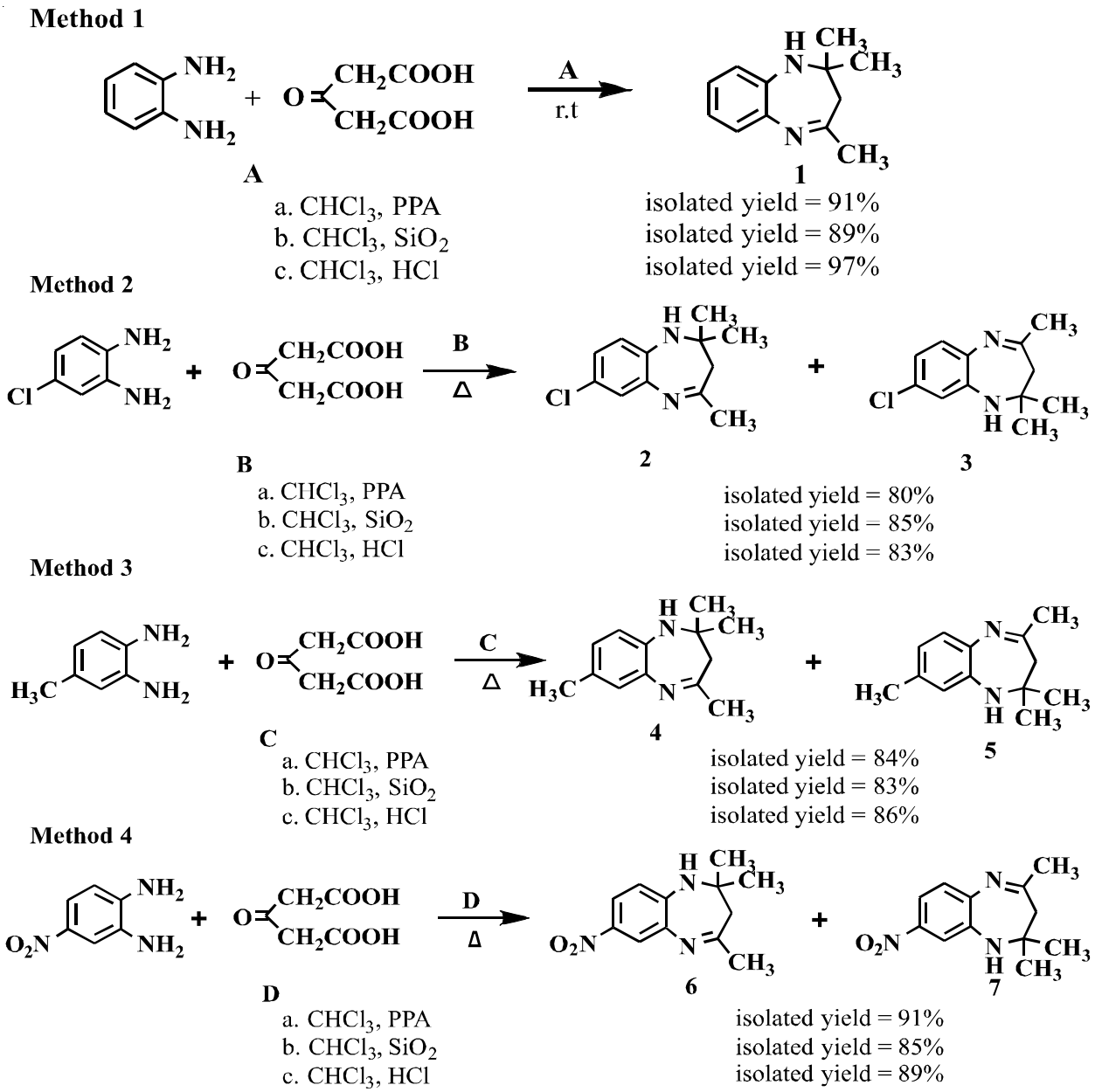
Benzodiazepines are interesting compounds because of their pharmacological properties[1,2]. Many members of this family are, nowadays widely use as tranquilizing and anti-convulsant agents. Although the first benzodiazepine was introduced as a drug nearly 40 years ago[3,4], the research in this area is still very active and is directed towards the synthesis of compounds of enhanced pharmacological activity. 1,5-Benzodiazepines are also used as starting materials for the preparation of some fused ring benzodiazepine derivative, such as triaxol[5] and oxadiazol[6]. Despite their wide range of pharmacological activity, industrial and synthetic applications, the synthesis of 1,5-benzodiazepines has received little attention. Benzodiazepine are generally synthesized by the condensation of *o*-phenylenediamine (OPDA) with α,β-unsaturated carbonyl compounds, β-haloketones, or with ketones[6-9] using acidic catalysts which are critical to enhance the condensation process. Unfortunately, many of these catalysis suffer from one or more limitations, occurrence of several side reactions, drastic reaction conditions, low yields and tedious workup procedure. Merchant and Chotia[10] showed that the reaction of *o*-phenylenediamine with acrylic acid in the presence of poly phosphoric acid (PPA) gave benzodiazepine and pyridobenzodiazepinone. Recently Patar *et al.*[11] and Kalyanam *et al.*[12] reported the correct structure of pyridobenzodiazepinone formed in the reaction of *o*-phenylenediamine with acrylic acid catalyzed by poly phosphoric acid. However the reaction of *o*-phenylenediamine with acrylic acid in the presence of acetonedicarboxylic acid instead of poly phosphoric acid as catalyst only resulted in the formation of 2,4,4,-trimethyl-3*H*-5-hydro-1,5-benzodiazepine. In view of this interesting result, we report the synthesis of 1,5-benzodiazepine derivatives by using acetone dicarboxylic acid in behalf of ketone.

EXPERIMENTAL

Melting points were determined on an electrothermal capillary melting point apparatus and uncorrected and uncorrected. TLC was performed on glass plates coated with silicon oxide (silica gel $60F_{254}$) and compounds were visualized using a UV lamp. Proton nuclear magnetic resonance and ^{13}C NMR spectra were obtained with Bruker AC 200 (200 MHz) and varian Gemini (200 MHz) spectrometers. Mass spectra were measured with HP 5890II GC/Mass (70 eV, EI). The organic solvents and chemicals were obtained from commercial products and purified by the appropriate methods before use.

Reaction of *o*-phenylenediamine with acetone dicarboxilic acid in the presence of poly phosphoric acid (Method 1-A-a) : A solution of *o*-phenylenediamine (5.4 g, 5×10^{-2} mol) and acetonedicarboxylic acid (14.6 g, 10×10^{-2} mol) in chloroform (15 mL) added poly phosphoric acid (1.5 g) was stirred. The reaction mixture was stirred at room temperature for 3 h, diluted with chloroform (3 × 70 mL), the extract washed with water and dried over Na_2SO_4. The organic layer was filtered and concentrated. The residue was chromatographed on a silica gel (*n*-hexane:ethyl acetate = 5: 1, v/v) to yield 2,2,4-trimethyl-2,3-dihydro-1*H*-benzo[b][1,4]diazepine 1 (8.53 g, 91 %) as a yellow solid (**Scheme-I**).

Reaction of *o*-phenylenediamine with acetone dicarboxylic acid in the presence of SiO_2 (Method 1-A-b) : A solution of *o*-phenylenediamine (5.4 g, 5×10^{-2} mol) and acetone dicarboxylic acid (14.6 g, 10×10^{-2} mol) in chloroform (15



Scheme-I

mL) added SiO_2 (0.15 g) was stirred at room temperature for 3 h. The reaction mixture was diluted with water and neutralized with 5 % $NaHCO_3$ (30 mL), then filtered off SiO_2. The aqueous solution was extracted with chloroform (3 × 70 mL). The chloroform extract washed with water (30 mL) and dried over $MgSO_4$. The organic layer was concentrated. Removal of chloroform gave 2,2,4-trimethyl-2,3-dihydro-1*H*-benzo-[b][1,4]diazepine 1 as a yellow solid (8.36 g, 89 %) which crystallized from *n*-hexane (**Scheme-I**).

Reaction of *o*-phenylenediamine with acetone dicarboxylic acid in the presence of HCl (Method 1-A-c): A solution of *o*-phenylenediamine (5.4 g, 5 × 10^{-2} mol) and acetone dicarboxyilc acid (14.6 g, 10 × 10^{-2} mol) in chloroform (15 mL) added 10 % HCl (2 mL) was stirred. The reaction mixture was stirred at room temperature for 8 h . The mixture was extracted with 10 % aq. $NaHCO_3$. The residue was chromatographed on a silica gel (*n*-hexane : ethyl acetate = 5 : 1, v/v) to yield 2,2,4-trimethyl-2,3-dihydro-1*H*-benzo[b][1,4]diazepine (**1**) (9.11 g, 97 %) as a yellow solid (**Scheme-I**).

2,2,4-Trimethyl-2,3-dihydro-1*H*-benzo[b][1,4]diazepine (1): R_f: 0.42 (T.L.C eluent; *n*-hexane : ethyl acetate = 1 : 1, v/v); m.p. 147-148 °C; IR (KBr, ν_{max}, cm^{-1}) : 3275 (s, =N-H), 3055 (aromatic C-H), 2930 (aliphatic C-H), 1660 (S, C=H); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7 (m, ph, 4H), 3 (s, NH, 1H), 2.35 (s, CH_3, 3H), 2.25 (s, CH_2, 2H), 1.35 (s, CH_3, 6H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 172.37, 140.75, 137.85, 126.77, 125.44, 122.04, 121.69, 68.38, 45.02, 30.43, 29.83; Mass (70 eV), *m/z* (rel. Int, %) : 188 (35.6), 173 (100), 158 (0.38), 132 (61.5), 117 (5.8), 92 (11.5), 77 (7.7), 65 (11.5); Elemental analysis (%): (calc./found): C: 76.59, H: 8.51, N: 14.89/C: 76.30, H: 8.63, N: 14.80.

7-Chloro-2,2,4-trimethyl-2,3-dihydro-1H-benzo[b][1,4]diazepine 2: Poly phosphoric acid 3.69 g (83 %), HCl 4.01 g (90 %), SiO_2 3.87 g (87 %) (mixture); R_f: 0.31 (TLC

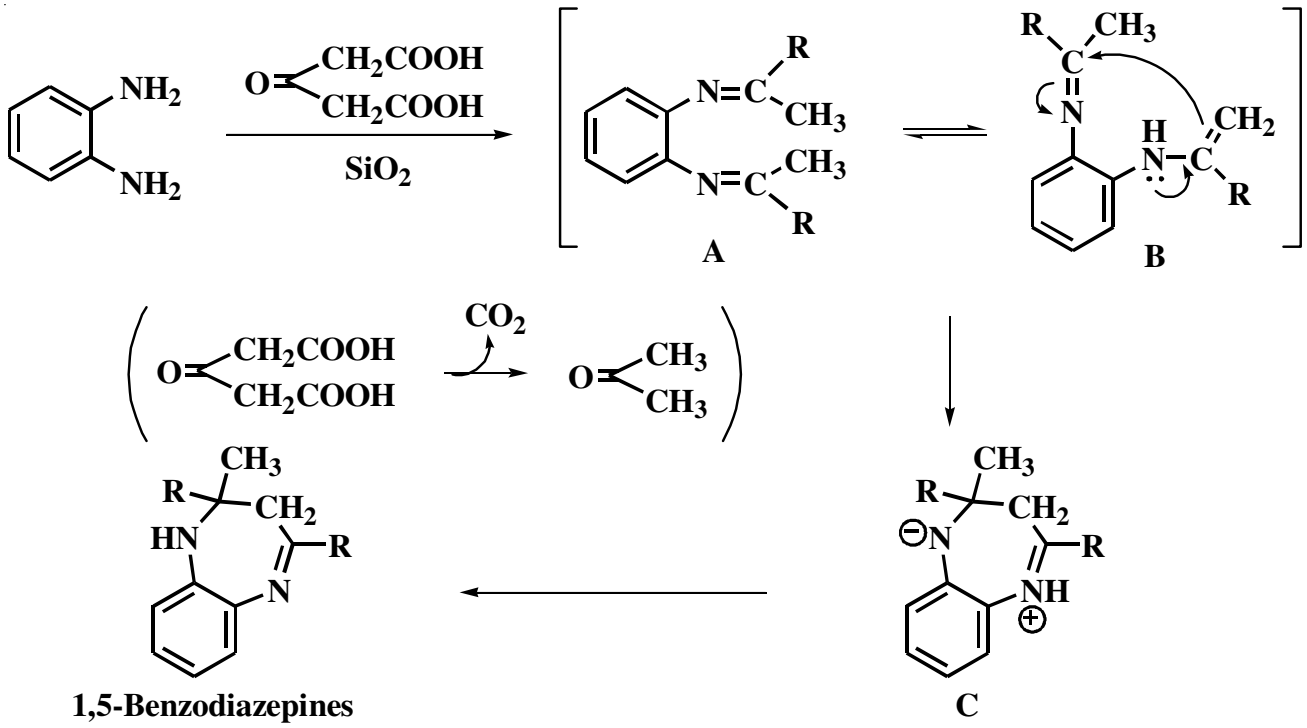


Fig. 1. Possible mechanism for the formation of 1,5-benzodiazepines

eluent; *n*-hexane : ethyl acetone = 3 : 1 v/v); m.p. 151-152 °C; IR (KBr, ν_{max}, cm^{-1}): 3270 (s, =N-H), 3055 (aromatic, C-H), 2930 (aliphatic, C-H), 1660 (s, C=H); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.93 (1H, dd, *J* = 1.2 Hz, *J* = 4.2 Hz), 6.65 (1H, d, *J* = 4.2 Hz), 3.05 (1H, Br), 2.34 (s, CH_3, 3H), 2.25 (s, CH_2, 2H), 1.33 (s, CH_3, 6H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 172.6, 141.8, 139.2, 126.3, 124.7, 122.9, 120.3, 69.8, 45.2, 30.5, 29.7; Mass (70 eV), *m/z* (rel, Int, %): 222 (30), 207 (100), 166 (93.7), 131 (27), 63 (20).

8-Chloro-2,2,4-trimethyl-2,3-dihydro-1*H*-benzo[b][1,4]diazepine (3): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.04 (1H, d, *J* = 4.2 Hz), 6.92 (1H, dd, *J* = 1.1 Hz, *J* = 4.2 Hz), 6.71 (1H, d, *J* = 1.1 Hz), 3.05 (1H, Br), 2.22 (s, CH_3, 3H), 1.34 (s, CH_3, 6H); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 173.5, 141.8, 138.9, 127, 125.8, 123.1, 121.8, 69.2, 45.1, 30.5, 29.9; Mass (70 eV), *m/z* (rel, Int, %): 222 (35.0), 207 (100), 166 (96.2), 131 (23.0) 63 (22).

2,2,4,7-Tetramethyl-2,3-dihydro-1H-benzo[b][1.5]-diazepine (4): Poly phosphoric acid 3.31 g (82 %), HCl 3.43 g (85%), SiO_2 3.27 g (81 %) (mixture); R_f: 0.15 (T.L.C eluent; *n*-hexane: ethyl acetone = 3 : 1, v/v); IR (KBr, ν_{max}, cm^{-1}): 3265 (s, =N=H), 3053 (aromatic, C-H), 2935 (aliphatic, C-H), 1660 (s, C=H); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.01 (1H, d, *J* = 7.9), 6.76 (1H, dd, *J* = 1.2, *J* = 7.9), 6.49 (1H, d, *J* = 1.2, *J* = 7.9), 6.49 (1H, d, *J* = 1.2), 3.01 (1H, Br), 2.31 (3H, s), 2.27 (3H, s), 2.18 (2H, s), 1.28 (6H, s); 13C NMR ($CDCl_3$, 50.32 MHz): δ 171.97, 141.18, 138.41, 135.56, 127.25, 122.90, 122.44, 67.98, 45.64, 30.78, 30.54, 30.00, 21.26; Mass (70 eV), *m/z* (rel, Int, %) 202 (35), 187 (100), 146 (60), 77 (20).

2,2,4,8-Tetramethyl-2,3-dihydro-1*H*-benzo[b][1,5] diazepine (5): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.94 (1H, d, *J* = 1.7), 6.76 (1H, dd, *J* = 1.7, *J* = 7.8), 6.61 (1H, d, *J* = 7.8), 3.01 (1H, Br), 2.32 (3H, s), 2.27 (3H, s), 2.14 (2H, s), 1.27 (6H, s); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 173.13, 138.14, 135.58, 131.93, 127.36, 126.50, 122.25, 68.94, 45.44, 30.88, 30.65, 30.22, 21.07; Mass (70 eV), *m/z* (rel., Int., %) 202 (37), 187 (100), 146 (65), 77 (22).

2,2,4-Trimethyl-7-nitro-2,3-dihydro-1*H*-benzo[b][1,5]-diazepine (6): (Eluent; *n*-hexane: ethyl acetone = 15 : 1, v/v) poly phosphoric acid 4.29 g (yield; 92 %), HCl 4.15 g (yield; 89 %), SiO_2 3.50 g (yield; 75 %) (mixture); R_f: 0.19 (TLC eluent; *n*-hexane : ethyl acetone = 1 : 3, v/v); IR (KBr, ν_{max}, cm^{-1}): 3275 (s, =N=H), 3055 (aromatic, C-H), 2935 (aliphatic, C-H), 1660 (s, C=H); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.02 (1H, d, *J* = 2.6), 7.76 (1H, dd, *J* = 2.6, *J* = 8.8), 6.52 (1H, d, *J* = 8.8), 3.99 (1H, Br), 2.40 (3H, s), 2.28 (2H, s), 1.32 (6H, s); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 172.49, 146.30, 141.50, 135.03, 126.61, 122.34, 119.55, 69.22, 45.77, 31.59, 30.82, 29.75; Mass (70 eV), *m/z* (rel., Int., %) 233 (25), 218 (100), 172 (76), 132 (23), 78 (16).

2,2,4-Trimethyl-8-nitro-2,3-dihydro-1*H*-benzo[b][1,5]-diazepine (7): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.82 (1H, dd, *J* = 2.5, *J* = 8.7), 7.63 (1H, d, *J* = 2.5), 7.20 (1H, d, *J* = 8.7), 4.01 (1H, Br), 2.40 (3H, s), 2.32 (2H, s), 1.39 (6H, s); ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 176.25, 146.27, 145.33, 138.80, 127.71, 117.59, 116.94, 69.22, 45.77, 31.06, 30.42, 30.09; Mass (70 eV), *m/z* (rel, Int, %) 233 (37), 218 (100), 177 (50), 177 (55), 131 (32).

RESULTS AND DISCUSSION

When *o*-phenylenediamine was treated with acetone dicarboxylic acid at room temperature for 3 h, a yellow crystalline solid, 2,4,4-trimethyl-2,3-dihydro-1*H*-benzo[b][1,4] diazepine (**4**) was isolated (86 %) (Method-1). It's structure was assigned on the basis of NMR which showed a singlet at δ 1.33 and δ 2.36 for two methyl protons and one methyl protons respectively. C3-Methylene protons show at δ 2.22 and N5 proton appears at δ 2.97. Mass spectra displayed a protonated molecular

ion at *m/z* 188 corresponding to the molecular formular $C_{12}H_{16}N_2$. From these observations, this product was proposed to have the structure of 2,4,4-trimethyl-2,3-dihydro-1*H*-benzo-[b][1,4]diazepine. These result indicate that acetone dicarboxylic acid is not acid catalyst but reagent because the product is 2,4,4-trimethyl-2,3-dihydro-1*H*-benzo[b][1,4]diazepine formed by acetone as a reagent. Substantially acetone dicaarboxylic acid decompound by hot water, acids or alkalies to CO_2 and acetone. A possible mechanism for the formation of 1,5-benzodiazepine is shown in Fig. 1. Amine of *o*-phenylenediamine attacks carbonyl group of acetone dicarboxylic acid or acetone, giving the intermediate diimine A. A 1,3 shift of the hydrogen attached methyl group then occurs to afford an isomeric enamine B which cyclizes to produce seven-membered ring (Fig. 1).

The reaction of 4-chloro-1,2-phenylenediamine, 3,4-diaminotoluene and 4-nitro-1,2-phenylenediamine as starting materials with acetone dicarboxylic acid were executed in same method (Method 1-4). Products are 7-chloro-2,2,4-trimethyl-2,3-dihydro-1*H*-benzo[b][1,4]diazepine **2**, 8-chloro-2,2,4-trimethyl-2,3-dihydro-1*H*-benzo[b][1,4]diazepine 3, 2,2,4,7-tetramethyl-2,3-dihydro-1*H*-benzo[b][1,4]diazepine **4**, 2,2,4,8-tetramethyl-2,3-dihydro-1*H*-benzo[b][1,5]diazepine **5**, 2,2,4-trimethyl-7-nitro-2,3-dihydro-1*H*-benzo[b][1,5]diazepine **6** and 2,2,4-trimethyl-8-nitro-2,3-dihydro-1*H*-benzo[b][1,4]-diazepine. However we could not separate corresponding structured isomers (**2** and **3**, **4** and **5**, **6** and **7**).

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