

SECTION-I

CHAPTER 4. EXPERIMENTAL

4. EXPERIMENTAL

All the reagents were obtained from commercial sources and used without further purification. Dioxane was freshly distilled over sodium metal.

Melting points were measured using VEEGO Multiprogrammable melting point apparatus and are uncorrected. ¹H-NMR spectra were recorded on Bruker Avance II 400 MHz FT-NMR spectrometer. Chemical shifts are expressed in δ units relative to tetramethylsilane (TMS) signal as internal reference and CDCl₃ as common solvent. IR spectra were recorded on FT-IR system-2000 Bruker spectrometer on KBr pellets. Elemental analyses were performed on ThermoFisher FLASH 2000 Organic elemental analyzer.

The synthetic work as discussed earlier was carried out using different methods. As, the idea was to optimize the method which yielded the maximum product, **Process E** was adopted as a general method for the synthesis of all of the final products (**3a-3m**).

4.1. Synthesis of 1-substituted aryl 3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2-one (3)

4.1.1. Process A: To a solution of N-methylbenzazepin-2-one (1 g, 5.714 mmol) in THF (15 ml) at -70 °C, BuLi (3.5 ml, 11.428 mmol) was added. The reaction mixture was stirred at same temperature for about 30 min. Aryl bromide (11.428 mmol), catalyst Pd₂dba₃ (260 mg, 0.2857 mmol), ligand xantphos (250 mg, 0.426 mmol) and Cu₂I₂ (1.2 g, 6.266 mmol) were added and the reaction mixture was allowed to warm at RT. Progress of the reaction was monitored by TLC. The reaction mixture was quenched by pouring onto crushed ice (100 g) with continuous stirring. The resulting

mixture was extracted with ethyl acetate (50 ml X 3) and the organic phase was evaporated under vacuum. The product so obtained was purified by column chromatography using silica as stationary phase and hexane-ethyl acetate as eluent.

4.1.2. Process B: To a suspension of NaH (545 mg, 14.125 mmol) in dioxane : DMF (5:1) (12 ml) N-methylbenzazepin-2-one (1 g, 5.714mmol) and aryl bromide (11.428 mmol) were added at 0 °C and the reaction mixture was stirred for 30 min. Catalyst Pd₂dba₃ (260 mg, 0.2857mmol), ligand xantphos (250 mg, 0.426 mmol) and Cu₂I₂ (1.2 g, 6.266 mmol) were added and the reaction mixture was allowed to warm at RT in 30 min followed by heating at 100 °C for 12 hr. Progress of the reaction was monitored by TLC. The reaction mixture was quenched by pouring onto crushed ice (100 g) with continuous stirring and the resulting mixture was filtered on celite bed and extracted with ethyl acetate (50 ml X 3). The organic phase was evaporated under vacuum. The product was purified by column chromatography using silica (100-200 mesh) as stationary phase and hexane-ethyl acetate as eluent.

4.1.3. Process C: To a suspension of NaH (545 mg, 14.125 mmol) in dioxane : DMF (5:1) (12 ml) N-methylbenzazepin-2-one (1 g, 5.714mmol) and aryl bromide (11.428 mmol) were added at 0 °C and the reaction mixture was stirred for 30 min. Catalyst PdCl₂ (50 mg, 0.2857mmol), ligand triphenylphosphine (75 mg, 0.426 mmol) and Cu₂I₂ (1.2 g, 6.266 mmol) were added and the reaction mixture was allowed to warm at RT in 30 min followed by heating at 100 °C for 12 hr. Progress of the reaction was monitored by TLC. The reaction mixture was quenched by pouring onto crushed ice (100 g) with continuous stirring and the resulting mixture was filtered on celite bed

and extracted with ethyl acetate (50 ml X 3). The organic phase was evaporated under vacuum. The product was purified by column chromatography using silica (100-200 mesh) as stationary phase and hexane-ethyl acetate as eluent.

4.1.4. Process D: To a suspension of NaH (545 mg, 14.125 mmol) in dioxane : DMF (5:1) (12 ml) N-methylbenzazepin-2-one (1 g, 5.714mmol) and aryl bromide (11.428 mmol) were added at 0 °C and the reaction mixture was stirred for 30 min. Catalyst Pd(OAc)₂ (40 mg, 0.170 mmol), ligand triphenylphosphine (75 mg, 0.285 mmol) and Cu₂I₂ (1.2 g, 6.266 mmol) were added and the reaction mixture was allowed to warm at RT in 30 min followed by heating at 100 °C for 12 hr. Progress of the reaction was monitored by TLC. The reaction mixture was quenched by pouring onto crushed ice (100 g) with continuous stirring and the resulting mixture was filtered on celite bed and extracted with ethyl acetate (50 ml X 3). The organic phase was evaporated under vacuum. The product was purified by column chromatography using silica (100-200 mesh) as stationary phase and hexane-ethyl acetate as eluent.

4.1.5. Process E: To a suspension of NaH (545 mg, 14.125 mmol) in dioxane : DMF (5:1) (12 ml) N-methylbenzazepin-2-one (1 g, 5.714mmol) and aryl bromide (11.428 mmol) were added at 0 °C and the reaction mixture was stirred for 30 min. Catalyst Pd(OAc)₂ (40 mg, 0.170 mmol), ligand triphenylphosphine (75 mg, 0.285 mmol) and Cu₂I₂ (1.2 g, 6.266 mmol) were added and the reaction mixture was exposed to microwave for 10 min at 100 W , 100 °C. Progress of the reaction was monitored by TLC. The reaction mixture was quenched by pouring onto crushed ice (100 g) with continuous stirring and the resulting mixture was filtered on celite bed and extracted

with ethyl acetate (50 ml X 3). The organic phase was evaporated under vacuum. The product was purified by column chromatography using silica (100-200 mesh) as stationary phase and hexane-ethyl acetate as eluent.

4.1.5.1. 1-(3-Methoxyphenyl)-3-methyl-4,5-dihydro-1H-benzo[d]azepin-2(3H)-one (3a)

Process E was used for the synthesis. Compound (**3a**) was obtained as a white solid (1.3 g, 86%), m. p.: 64-66 °C.

Anal.:

IR : 3119, 1648, 1486, 1379, 1212, 1042, 766, 711

¹H-NMR : 8.10-8.12 (d, 1H, *J* = 8.0 Hz), 7.25-7.35 (m, 3H), 7.17-7.21 (t, 1H, *J* = 8.0 Hz), 7.10-7.12 (d, 1H, *J* = 8.0 Hz), 6.79-6.81 (d, 1H, *J* = 8.0 Hz), 6.58-6.62 (t, 1H, *J* = 8.0 Hz), 3.66-3.73 (m, 4H), 3.15 (s, 1H), 3.03-3.10 (m, 1H), 2.88-3.00 (m, 2H)

ESI-MS (m/z) : 282 (*M*⁺+1)

C₁₈H₁₉NO₂ requires C, 76.84; H, 6.81; N, 4.98. Found: C, 76.68; H, 6.51; N, 4.75%

4.1.5.2. 3-Methyl-1-(3-tolyl)-4,5-dihydro-1H-benzo[d]azepin-2(3H)-one (3b)

Process E was used for the synthesis. Compound (**3b**) was obtained as a white solid (1.34 g, 89%), m. p.: 96-98 °C.

Anal.:

IR : 3129, 1635, 1490, 1365, 1210, 750, 730

¹H NMR : 7.19–7.28 (m, 3H), 7.12–7.17 (m, 2H), 7.01–7.03 (d, 1H, $J = 8.0$ Hz), 6.90 (s, 1H), 6.75–6.77 (d, 1H, $J = 8.0$ Hz), 5.24 (s, 1H), 3.70–3.77 (t, 1H, $J = 12.0$ Hz), 3.08–3.16 (m, 1H), 3.05 (s, 3H), 2.92–2.98 (m, 2H), 2.28 (s, 3H)

ESI-MS (m/z) : 266 ($M^+ + 1$)

C₁₈H₁₉NO requires C, 81.47; H, 7.22; N, 5.28. Found: C, 81.64; H, 7.05; N, 5.45%

4.1.5.3. 1-(3-(Trifluoromethyl)phenyl)-3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (3c)

Process E was used for the synthesis. Compound (**3c**) was obtained as a white solid (1.21 g, 72%), m. p.: 139–140 °C.

Anal.:

IR : 3121, 1640, 1433, 1335, 1213, 1128, 754, 702

¹H NMR : 7.41–7.43 (d, 1H, $J = 8.0$ Hz), 7.31–7.35 (t, 1H, $J = 8.0$ Hz), 7.14–7.24 (m, 5H), 7.03–7.05 (d, 1H, $J = 8.0$ Hz), 5.24 (s, 1H), 3.48–3.55 (t, 1H, $J = 8.0$ Hz), 3.05–2.89 (m, 6H)

ESI-MS (m/z) : 320 ($M^+ + 1$)

C₁₈H₁₆F₃NO requires C, 67.70; H, 5.05; N, 4.39. Found: C, 67.52; H, 5.24; N, 4.21%

4.1.5.4. 1-(4-Methoxyphenyl)-3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (3d)

Process E was used for the synthesis. Compound (**3d**) was obtained as an off-white solid (1.41 g, 93%), m. p.: 130-132 °C.

Anal.:

IR : 3124, 1646, 1481, 1342, 1178, 1033, 768, 711

¹HNMR : 8.10-8.12 (d, 1H, *J* = 8.0 Hz), 7.25-7.35 (m, 3H), 7.10-7.12 (d, 1H, *J* = 8.0 Hz), 6.92-6.96 (d, 2H, *J* = 8.0 Hz), 6.77-6.80 (d, 2H, *J* = 8.0 Hz), 3.76 (s, 3H), 3.66-3.73 (t, 1H, *J* = 8.0 Hz), 3.14 (s, 3H), 3.03-3.11 (m, 1H), 2.86-3.00 (m, 2H)

ESI-MS (m/z) : 282 (*M*⁺+1)

C₁₈H₁₉NO₂ requires C, 76.84; H, 6.81; N, 4.98. Found: C, 76.65; H, 6.95;

N, 4.72%

4.1.5.5. 1-(2-Methoxyphenyl)-3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**3e**)

Process E was used for the synthesis. Compound (**3e**) was obtained as an off-white solid (1.21 g, 91%), m. p.: 126-127 °C.

Anal.:

IR : 3129, 1655, 1489, 1354, 1164, 1029, 766, 753

¹HNMR : 8.12-8.15 (d, 1H, *J* = 8.0 Hz), 7.21-7.33 (m, 4H), 7.09-7.11 (d, 1H, *J* = 8.0 Hz), 6.90-6.92 (d, 1H, *J* = 8.0 Hz), 6.74-6.78 (t, 1H, *J* = 8.0 Hz), 6.56-6.59 (d, 1H, *J* = 8.0 Hz), 3.83 (s, 3H), 3.72-3.80 (m, 1H), 3.14-3.19 (m, 1H), 3.11 (s, 3H), 2.932.95 (d, 1H, *J* = 8.0 Hz), 2.76-2.82 (t, 1H, *J* = 8.0 Hz)

ESI-MS (m/z) : 282 (*M*⁺+1)

$C_{18}H_{19}NO_2$ requires C, 76.84; H, 6.81; N, 4.98. Found: C, 76.59; H, 6.92; N, 4.69%

4.1.5.6. 3-Methyl-1-(2-tolyl)-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (3f)

Process E was used for the synthesis. Compound (3f) was obtained as an off-white solid (1.23 g, 88%), m. p.: 140-141 °C.

Anal.:

IR : 3124, 1640, 1481, 1395, 1207, 760, 736

¹HNMR : 7.09-7.27 (m, 6H), 7.02-7.06 (m, 1H), 6.65-6.67 (d, 1H, *J* = 8.0 Hz), 5.24 (s, 1H), 3.95-4.03 (t, 1H, *J* = 16.0 Hz), 3.16-3.25 (t, 1H, *J* = 16.0 Hz), 2.98-3.00 (m, 4H), 2.91-2.97 (m, 1H), 2.45 (s, 3H)

ESI-MS (m/z) : 266 ($M^+ + 1$)

$C_{18}H_{19}NO$ requires C, 81.47; H, 7.22; N, 5.28. Found: C, 81.64; H, 7.43; N, 5.12%

4.1.5.7. 3-Methyl-1-(4-tolyl)-4,5-Dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (3g)

Process E was used for the synthesis. Compound (3g) was obtained as an off-white solid (1.39 g, 93%), m. p.: 120-122 °C.

Anal.:

IR : 3124, 1645, 1487, 1396, 1209, 753, 736

¹HNMR : 7.18-7.26 (m, 3H), 7.11-7.13 (d, 1H, *J* = 8.0 Hz), 7.07-7.09 (d, 2H, *J* = 8.0 Hz), 6.90-6.92 (d, 2H, *J* = 8.0 Hz), 5.24 (s, 1H),

3.69-3.77 (m, 1H), 3.07-3.11 (m, 1H), 3.04 (s, 3H), 2.91-2.98 (m, 2H), 2.30 (s, 3H)

ESI-MS (m/z) : 266 ($M^+ + 1$)

C₁₈H₁₉NO requires C, 81.47; H, 7.22; N, 5.28. Found: C, 81.53; H, 7.34; N, 5.15%

4.1.5.8. 1-(3-Fluorophenyl)-3-methyl-4,5-dihydro-1H-benzo[d]azepin-2(3H)-one (3h)

Process E was used for the synthesis. (3h) was obtained as an off-white solid (1.12 g, 79%), m. p.: 88-90 °C.

Anal.:

IR : 3130, 1655, 1484, 1396, 1215, 1070, 749, 709

¹H NMR : 7.20-7.30 (m, 4H), 7.11-7.13 (d, 1H, $J = 8.0$ Hz), 6.89-6.93 (t, 1H, $J = 8.0$ Hz), 6.84-6.86 (d, 1H, $J = 8.0$ Hz), 6.70-6.74 (d, 1H, $J = 8.0$ Hz), 5.24 (s, 1H), 3.62-3.69 (m, 1H), 3.07-3.15 (m, 1H), 3.05 (s, 3H), 2.91-3.04 (m, 2H)

ESI-MS (m/z) : 270 ($M^+ + 1$)

C₁₇H₁₆FNO requires C, 75.82; H, 5.99; N, 5.20. Found: C, 75.97; H, 5.78; N, 5.12%

4.1.5.9. 1-(4-Fluorophenyl)-3-methyl-4,5-dihydro-1H-benzo[d]azepin-2(3H)-one (3i)

Process E was used for the synthesis. Compound (3i) was obtained as a white solid (1.10 g, 72%), m. p.: 96-98 °C.

Anal.:

IR : 3121, 1635, 1439, 1401, 1165, 1106, 753, 736

¹HNMR : 7.20- 7.29 (m, 3H), 7.10-7.13 (m, 1H), 6.94-7.02 (m, 4H),
5.24 (s, 1H), 3.63-3.70 (m, 1H), 2.91-3.16 (m, 6H)

ESI-MS (m/z) : 270 (M⁺+1)

C₁₇H₁₆FNO requires C, 75.82; H, 5.99; N, 5.20. Found: C, 75.95; H, 5.86;
N, 5.05%

4.1.5.10. 3-Methyl-1-(3,5-dimethylphenyl)-4,5-dihydro-1H-benzo[d]azepin-2(3H)-one (3j)

Process E was used for the synthesis. Compound (**3j**) was obtained as a white solid (1.42 g, 86%), m. p.: 120-121 °C.

Anal.:

IR : 3142, 1652, 1487, 1398, 1211, 775, 735

¹HNMR : 7.19-7.28 (m, 3H), 7.10-7.12 (d, 1H, *J* = 8.0 Hz), 6.84 (s, 1H),
6.63 (s, 2H), 5.20 (s, 1H), 3.75-3.82 (m, 1H), 3.03-3.11 (m, 4H)
2.92-2.98 (m, 2H), 2.23 (s, 6H)

ESI-MS (m/z) : 280 (M⁺+1)

C₁₉H₂₁NO requires C, 81.68; H, 7.58; N, 5.01. Found: C, 81.75; H, 7.45;
N, 5.18%

4.1.5.11. 3-Methyl-1-(1-naphthyl)-4,5-Dihydro-1H-benzo[d]azepin-2(3H)-one (3k)

Process E was used for the synthesis. Compound (**3k**) was obtained as an off-white solid (1.51 g, 93%), m. p.: 205-207 °C.

Anal.:**IR** : 3130, 1640, 1482, 1383, 1207, 782, 748**¹HNMR** : 8.12-8.17 (m, 2H), 7.77-7.79 (d, 1H, $J = 8.0$ Hz), 7.69-7.71 (d, 1H, $J = 8.0$ Hz), 7.39-7.46 (m, 2H), 7.24-7.33 (m, 2H), 7.16-7.18 (t, 1H, $J = 8.0$ Hz), 7.08-7.10 (d, 1H, $J = 8.0$ Hz) 6.77-6.79 (d, 1H, $J = 8.0$ Hz), 5.93 (bs, 1H), 3.40-3.48 (m, 1H), 3.09-3.16 (m, 1H), 3.02 (s, 3H) 2.66-2.76 (m, 2H)**ESI-MS (m/z)** : 302 ($M^+ + 1$)**C₂₁H₁₉NO** requires C, 83.69; H, 6.35; N, 4.65. Found: C, 83.51; H, 6.46;

N, 4.48%

4.1.5.12. 1-(4-Ethylphenyl)-3-methyl-4,5-dihydro-1H-benzo[d]azepin-2(3H)-one (3l)

Process E was used for the synthesis. Compound (**3l**) was obtained as an off-white solid (1.46 g, 92%), m. p.: 77-79 °C.

Anal.:**IR** : 3124, 1635, 1486, 1399, 1210, 752, 697**¹HNMR** : 7.11-7.20 (m, 3H), 7.02-7.09 (m, 3H), 6.86-6.88 (d, 2H, $J = 8.0$ Hz), 5.17 (s, 1H), 3.62-3.70 (m, 1H), 3.00-3.09 (m, 1H), 2.97 (s, 3H), 2.84-2.91 (m, 2H), 2.50-2.56 (q, 2H, $J = 8.0$ Hz), 1.11-1.15 (t, 3H, $J = 8.0$ Hz)**ESI-MS (m/z)** : 280 ($M^+ + 1$)**C₁₉H₂₁NO** requires C, 81.68; H, 7.58; N, 5.01. Found: C, 81.92; H, 7.39;

N, 5.21%

4.1.5.13. 1-(4-Biphenyl)-3-methyl-4,5-dihydro-1H-benzo[d]azepin-2(3H)-one (3m)

Process E was used for the synthesis. Compound (**3m**) was obtained as a white solid (1.62 g, 95%), m. p.: 103-105 °C.

Anal.:

IR : 3127, 1642, 1485, 1392, 1211, 761, 744, 696

¹HNMR : 7.49-7.56 (m, 4H), 7.39-7.43 (t, 2H, $J = 8.0$ Hz), 7.21-7.33 (m, 4H), 7.15-7.17 (d, 1H, $J = 8.0$ Hz), 7.10-7.12 (d, 2H, $J = 8.0$ Hz), 5.32 (s, 1H), 3.73-3.80 (m, 1H), 3.05-3.16 (m, 4H), 2.94-3.03 (m, 2H)

ESI-MS (m/z) : 328 ($M^{+}+1$)

C₂₃H₂₁NO requires C, 84.37; H, 6.46; N, 4.28. Found: C, 84.12; H, 6.58; N, 4.32%

4.2. Synthesis of 1,3-dimethyl-4,5-dihydro-1H-benzo[d]azepin-2(3H)-one (5)

To a suspension of NaH (545 mg, 14.125 mmol) in dioxane : DMF (5:1) (12 ml) N-methylbenzazepin-2-one (1 g, 5.714mmol) was added at 0 °C and the reaction mixture was stirred for 30 min. Catalyst Pd(OAc)₂ (40 mg, 0.170 mmol), ligand triphenylphosphine (75 mg, 0.285 mmol) and NMF (2.9 ml, 8.254 mmol) were added and the reaction mixture was exposed to microwave for 10 min at 100 W , 100 °C. Progress of the reaction was monitored by TLC. The reaction mixture was quenched by pouring on crushed ice (100 g) with continuous stirring and the resulting mixture was filtered on celite bed and extracted with ethyl acetate (50 ml X 3). The organic phase was evaporated under vacuum. The product was purified by column chromatography using silica (100-200 mesh) as stationary phase and hexane-ethyl

acetate as eluent. Product (**5**) was obtained as a white solid (680 mg, 70%), m. p.: 52-53 °C.

Anal.:

IR : 3121, 1647, 1482, 1394, 1207, 762, 745

¹HNMR : 7.03-7.18 (m, 4H), 4.23-4.25 (q, 1H, $J = 8.0$ Hz), 3.94-4.01 (m, 1H), 3.19-3.32 (m, 2H), 3.03-3.07 (m, 1H), 2.89 (s, 3H), 1.47-1.49 (d, 3H, $J = 8.0$ Hz)

ESI-MS (m/z) : 190 ($M^+ + 1$)

C₁₂H₁₅NO requires C, 76.16; H, 7.99; N, 7.40. Found: C, 76.41; H, 7.76; N, 7.55%

4.3. HPLC Analysis

The method and sample preparations were done as reported by Pierson et. al.³⁶

Materials: Acetonitrile (HPLC grade) was purchased from Merck (India). All other chemicals employed were of reagent grade and were used without further purification. The water used was deionized and passed through Phenex 0.45 µm cellulose filters.

Chromatographic system: HPLC experiments were conducted using a LC-20AT Prominence solvent delivery system (Shimadzu Corp., Japan), a Rheodyne fixed-loop injection valve (USA), 20 µl and a SPD-20A Prominence variable-wavelength UV detector (Shimadzu Corp., Japan). The chromatographic conditions were as follows: column: 250 mm x 4.60 mm, 5 micron, Phenomenex Luna C₁₈(2) (Torrance, CA, USA); mobile phase: 5% acetonitrile in 0.1 M phosphate buffer, pH 2.5; flow rate: 1.5 ml/min; temp.: ambient; inj. Vol.: 20 µl. All samples and standards were diluted with 0.1 M phosphate buffer.