Supporting Information

A Facile and simple synthesis of *N*-Alkyl and *N*-Aryl 2-Benzazepines by nucleophilic heteroannulation

Srinivasan A. K,^{*} Rajashekar. K, Shyamapada Banerjee, Syam Kumar. U. K.

Custom Pharmaceutical Services, Dr Reddy's Laboratories Limited, Bollaram Road, Miyapur, Hyderabad,
India.

e-mail: srinivasanak@drreddys.com

Content

1) Content	S2
2) Experimental Section	S3-S13
3) References	S14
4) ^1H , ^{13}C spectra of 2	S15-S16
5) ^1H , ^{13}C and Mass spectra of 3	S16-S17
6) ^1H , ^{13}C and Mass spectra of 4	S18
7) ^1H , ^{13}C and Mass spectra of 6a	S19-S20
8) ^1H , ^{13}C and Mass spectra of 6b	S20-S21
9) ^1H , ^{13}C and Mass spectra of 6c	S22-S23
10) ^1H , ^{13}C and Mass spectra of 6d	S23-S24
11) ^1H , ^{13}C and Mass spectra of 6e	S25-S26
12) ^1H , ^{13}C and Mass spectra of 6f	S26-S27
13) ^1H , ^{13}C and Mass spectra of 6g	S28-S29
14) ^1H , ^{13}C and Mass spectra of 6h	S29-S30
15) ^1H , ^{13}C and Mass spectra of 6i	S31-S32
16) ^1H , ^{13}C and Mass spectra of 6j	S32-S33
17) ^1H , ^{13}C and Mass spectra of 6k	S34-S35
18) ^1H , ^{13}C and Mass spectra of 6l	S35-S36
19) ^1H , ^{13}C and Mass spectra of 7a	S37-S38
20) ^1H , ^{13}C and Mass spectra of 7b	S38-S39
21) ^1H , ^{13}C and Mass spectra of 7c	S40-S41
22) ^1H , ^{13}C and Mass spectra of 7d	S41-S42

EXPERIMENTAL

General methods: All reactions were carried out in oven dried glassware under an atmosphere of N₂. ¹H & ¹³C NMR spectra were recorded in CDCl₃ & DMSO-*d*₆ on Varian Gemini 400 MHz FT spectrometers. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet). Coupling constants (*J*) are given in Hertz. Mass spectra were obtained on a HP-5989A Mass Spectrometer. Thin layer chromatography was performed on silica gel plates (SRL 230-400 mesh). All solvents used are commercially available and were distilled before use.

Procedure for the synthesis of (*E*)-methyl 2-(3-methoxy-3-oxoprop-1-en-1-yl)benzoate (**2**):

To a solution of methyl 2-bromobenzoate (10 g, 46.5 mmol) in 100 mL of toluene was added methyl acrylate (6.03 g, 70.1 mmol) and triethylamine (19.5 mL, 140.0 mmol). The mixture was degassed and then (PPh₃)₂PdCl₂ (1.63 g, 2.3 mmol) was added. The reaction mixture was stirred at 100 °C for 6 h. The reaction mixture was allowed to cool and was diluted with toluene (50 mL). The organic layer was washed with water and brine, dried (MgSO₄) and concentrated under reduced pressure to afford the crude compound and it was purified by column chromatography over silica gel using hexane-ethyl acetate 10:1 to give the pure ester (**2**) as pale brown coloured oil (9.6 g, 94 % yield). ¹H NMR (CDCl₃): δ 8.45 (d, *J* = 15.6 Hz, 1H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 1H), 6.30 (d, *J* = 15.6 Hz, 1H), 3.93 (s, 3H), 3.82 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 51.8, 52.4, 120.7, 127.9, 129.4, 127.8, 130.8, 132.4, 136.4, 143.9, 167.0, 167.1. LRMS (ESI): 221 (M+H)⁺; HRMS (m/z): [M+H]⁺ calcd for [C₁₂H₁₃O₄]⁺: 221.0814, found 221.0815. Spectral data of **2** is in agreement with data given in the lit.¹

Procedure for the synthesis of methyl 2-(3-methoxy-3-oxopropyl)benzoate (3):

To a solution of (*E*)-methyl 2-(3-methoxy-3-oxoprop-1-en-1-yl)benzoate (**2**) (9.0 g) in methanol (100 mL) was added 5 % Pd/C (200 mg) hydrogenated in Parr apparatus with 20 to 30 psi for 1 h. The reaction mixture was filtered through celite and concentrated under reduced pressure to afford the title compound as pale yellow coloured oil. (8.7 g, 96 % yield). IR (cm⁻¹): 3271, 2943, 1637, 1534; ¹H NMR (400 MHz, CDCl₃): δ 7.92 (d, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 6.9 Hz, 1H), 7.26 -7.30 (m, 2H), 3.90 (s, 3H), 3.67 (s, 3H), 3.28 (t, *J* = 7.8 Hz, 2H); 2.67 (t, *J* = 7.8 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 29.9, 35.6, 51.6, 52.0, 126.5, 129.3, 130.9, 131.1, 132.2, 142.5, 167.7, 173.5; LRMS (ESI): 223 (M+H)⁺; HRMS (m/z): [M+H]⁺ calcd for [C₁₂H₁₅O₄]⁺: 223.0970, Found: 223.0961. Spectral data of **3** is in agreement with data given in the lit.²

Procedure for the synthesis of 3-(2-(hydroxymethyl)phenyl)propan-1-ol (4):

To a suspension of LAH (2.56 g, 67.5 mmol) in THF (50 mL) was slowly added a solution of methyl 2-(3-methoxy-3-oxopropyl)benzoate (**3**) (7.5 g, 33.8 mmol) in THF (50 mL) at 0-5 °C under nitrogen atmosphere and stirred for 3 h at room temperature. The reaction mixture was cooled to 0-5 °C temperature and it was quenched with NH₄Cl solution (50 mL). The layers were separated, the aqueous layer was further extracted with ethyl acetate (2 X 100 mL), the organics were washed with water and brine, dried (MgSO₄) and concentrated under reduced pressure to afford the title compound as pale yellow coloured oil (**4**) 5.34 g (95 % yield). IR (cm⁻¹): 3489, 3332, 2965, 1740, 1643, 1533; ¹H NMR

(400 MHz, CDCl₃): δ 7.14-7.33 (m, 4H), 4.62 (s, 2H), 3.50 (t, J = 5.8, 2H), 2.77 (t, J = 7.3 Hz, 2H), 1.81-1.89 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 27.4, 33.5, 60.9, 63.1, 126.1, 128.2, 129.3, 129.3, 138.4, 140.2; LRMS (ESI): 165 (M-H)⁺; HRMS (m/z): [M-H]⁺ calcd for [C₁₀H₁₃O₂]⁺: 165.0916, Found: 165.0913. Spectral data of **3** is in agreement with data given in the lit.³

General procedure for synthesis of *N*-alkyl-2-benzazepine (**6**):

To a solution of 3-(2-(hydroxymethyl)phenyl)propan-1-ol (**4**) (1 g, 6.02 mmol), dichloromethane (20 mL) was added triethylamine (3.4 g, 30.1 mmol). The reaction mixture was cooled to 0 °C; methanesulfonyl chloride (1.72 g, 15.1 mmol) was added at 0 °C and stirred for 3 h. The reaction mixture was washed with water and brine, dried over MgSO₄. To the mesylate solution respective amine (6.3 mmol) was added. Upon reaction completion the reaction mass was washed with water and concentrated under reduced pressure to afford the title compound and the crude product was purified by column chromatography over silica gel using hexane-ethyl acetate.

Procedure for synthesis of 2-benzazepine (**6a**):

To a solution of *in situ* prepared bismesylated compound (**5**) in methanolic ammonia solution (10 mL) was added into a clean parr apparatus, charged with 15 to 20 psi of ammonia pressure. The reaction was maintained for 7 h at room temperature. Upon reaction completion the reaction mixture was concentrated under reduced pressure afforded the title compound as brown syrupy liquid. Yield: 73 %; IR (cm⁻¹): 1514, 1591, 1648, 2025, 2836, 2935, 3311; ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.06-7.17 (m, 4H), 3.99 (s, 2H), 3.20 (t, J = 5.3 Hz, 2H), 2.86-2.93 (m, 2H), 1.74 (t, J = 5.3 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 28.6, 35.2, 53.3, 56.6, 126.3, 127.8, 128.5, 129.1, 142.5, 142.9; LRMS (ESI): 148 (M+H)⁺; HRMS (m/z): [M+H]⁺ calcd for [C₁₀H₁₄N]⁺: 148.1126, Found: 148.1104. Spectral data of **6** is in agreement with data given in the lit.⁴

2-hexyl-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6b):

Pale yellow coloured gummy liquid; Yield: 79; IR (cm^{-1}): 1606, 2072, 2932, 3053, 3444, 3853; ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.09-7.16 (m, 4H), 3.89 (s, 2H) 3.11 (t, $J = 5.2$ Hz, 2H), 2.88 (t, $J = 5.8$, 2H), 2.33 (t, $J = 7.6$ Hz, 2H), 1.72 (p, $J = 5.8$ Hz, 2H), 1.48 (p, $J = 7.3$ Hz, 2H), 1.26 (dt, $J = 5.8$ Hz, 6H), 0.86 (t, $J = 6.7$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 13.7, 22.2, 24.7, 26.7, 27.0, 31.4, 35.8, 52.9, 58.7, 59.0, 125.4, 126.6, 128.2, 129.2, 138.8, 142.3; LRMS (ESI): 232 ($\text{M}+\text{H}$) $^+$; HRMS (m/z): [$\text{M}+\text{H}$] $^+$ calcd for [$\text{C}_{16}\text{H}_{26}\text{N}$] $^+$: 232.2065, Found: 232.2060.

2-cyclopropyl-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6c):

Yellow coloured gummy liquid; Yield: 74%; IR (cm^{-1}): 1509, 1620, 2839, 2941, 3343, 3855; ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.11-7.25 (m, 4H), 3.94 (s, 2H) 3.15 (t, $J = 5.5$ Hz, 2H), 2.90 (t, $J = 5.5$ Hz, 2H), 1.71-1.79 (m, 3H), 0.42 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 6.9, 25.7, 34.4, 35.7, 58.8, 59.9, 125.6, 126.8, 128.4, 129.3, 139.24, 142.4; LRMS (ESI): 188 ($\text{M}+\text{H}$) $^+$; HRMS (m/z): [$\text{M}+\text{H}$] $^+$ calcd for [$\text{C}_{13}\text{H}_{18}\text{N}$] $^+$: 188.1439, Found: 188.1430.

2-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6d):

Brown coloured gummy liquid; Yield: 73 %; IR (cm^{-1}): 1512, 1584, 1656, 2836, 2934, 3070, 3403; ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.23-7.33 (m, 5H), 7.07-7.16 (m, 3H), 6.94 (d, $J = 7.3$ Hz, 1H), 3.87 (s, 2H), 3.53 (s, 2H), 3.11 (t, $J = 5.2$ Hz, 2H), 2.92 (t, $J = 5.5$ Hz, 2H), 1.76 (p, $J = 5.8$ Hz, 2H);

^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 25.2, 36.1, 57.7, 58.7, 59.2, 125.7, 126.8, 127.0, 128.1, 128.7, 128.8, 129.8, 139.2, 139.2, 142.9; LRMS (ESI): 238 ($\text{M}+\text{H}$) $^+$; HRMS (m/z): [$\text{M}+\text{H}$] $^+$ calcd for $[\text{C}_{17}\text{H}_{20}\text{N}]^+$: 238.1596, Found: 238.1603.

(S)-2-(1-phenylethyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6e):

Brown coloured syrupy liquid; Yield: 69 %; IR (cm^{-1}): 1348, 1420, 1584, 1667, 2837, 2936, 3078; ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.21-7.32 (m, 5H), 7.14 (d, $J = 5.5$ Hz, 2H), 7.04-7.12 (m, 1H), 6.83 (d, $J = 7.3$ Hz, 1H), 3.96 (d, $J = 14.7$ Hz, 1H), 3.75 (d, $J = 14.7$ Hz, 1H), 3.57 (q, $J = 6.6$ Hz, 1H), 3.18-3.23 (m, 1H), 3.07-3.11 (m, 1H), 2.89 (t, $J = 5.9$ Hz, 2H), 1.63-1.78 (m, 2H), 1.34 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 20.8, 25.4, 36.5, 56.2, 57.5, 59.4, 125.6, 126.7, 126.9, 127.5, 128.1, 128.7, 130.0, 139.4, 143.1, 144.9; LRMS (ESI): 252 ($\text{M}+\text{H}$) $^+$; HRMS (m/z): [$\text{M}+\text{H}$] $^+$ calcd for $[\text{C}_{18}\text{H}_{22}\text{N}]^+$: 252.1752, Found: 252.1753.

2-(2,6-dichlorobenzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6f):

Yellow coloured gummy liquid; Yield: 71 %; IR (cm^{-1}): 1215, 1436, 1598, 1691, 1740, 2853, 2925, 3141, 3345; ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.39 (dd, $J = 2.1, 19.8$ Hz, 1H), 7.36 (s, 1H), 7.10-7.23 (m, 4H), 6.99 (d, $J = 7.0$ Hz, 1H), 3.87 (s, 2H), 3.56 (s, 2H), 3.12 (t, $J = 5.2$ Hz, 2H), 2.94 (t, $J = 5.5$ Hz, 2H), 1.78 (p, $J = 5.2$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 25.7, 35.9, 54.1, 58.9,

59.6, 125.8, 126.6, 127.1, 128.8, 129.0, 129.6, 131.2, 132.7, 134.5, 135.6, 139.0, 142.8; LRMS (ESI): 306 (M+H)⁺; HRMS (m/z): [M+H]⁺ calcd for [C₁₇H₁₈Cl₂N]⁺: 306.0816, Found: 306.0818.

2-phenyl-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6g):

Brown coloured gummy liquid; Yield: 71 %; IR (cm⁻¹): 1127, 1257, 1479, 1601, 2944, 3332, 3489, 3735; ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.30 (d, *J* = 5.5 Hz, 1H), 7.09-7.18 (m, 5H), 6.79 (d, *J* = 8.0 Hz, 2H), 6.60 (t, *J* = 7.3 Hz, 1H), 4.59 (s, 2H), 3.78 (t, *J* = 5.2 Hz, 2H), 2.98 (td, *J* = 2.9, 5.9 Hz, 2H), 1.89 (p, *J* = 6.2 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 25.8, 35.7, 52.1, 55.0, 112.6, 116.1, 125.7, 127.1, 129.1, 129.4, 129.7, 138.6, 141.6, 147.6; LRMS (ESI): 224 (M+H)⁺; HRMS (m/z): [M+H]⁺ calcd for [C₁₆H₁₈N]⁺: 224.1439, Found: 224.1432.

2-(3-chlorophenyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6h):

Brown coloured thick liquid; Yield: 78 %; IR (cm⁻¹): 1463, 1596, 1652, 1920, 2913, 3342; ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.28-7.30 (m, 1H), 7.11-7.17 (m, 3H), 7.05 (t, *J* = 8.0 Hz, 1H), 6.74 (t, *J* = 2.2 Hz, 1H), 6.66 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.56 (dd, *J* = 7.3, 1.1 Hz, 1H), 4.56 (s, 2H), 3.75 (t, *J* = 5.1 Hz, 2H), 2.97 (t, *J* = 2.6, 5.9 Hz, 2H), 1.88 (p, *J* = 5.9 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 25.8, 35.6, 52.1, 55.0, 110.8, 112.5, 115.9, 125.9, 127.4, 129.4, 129.9, 130.0, 135.0, 138.0, 141.4, 148.8; LRMS (ESI): 258 (M+H)⁺; HRMS (m/z): [M+H]⁺ calcd for [C₁₆H₁₇NCl]⁺: 258.1050, Found: 258.1050.

2-(2-bromophenyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6i):

Dark brown coloured thick liquid; Yield: 75 %; IR (cm^{-1}): 1140, 1231, 1421, 1675, 2838, 2936, 3077, 3248, 3347; ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.44 (dd, $J = 7.7, 1.1$ Hz, 1H), 7.35 (d, $J = 7.3$ Hz, 1H), 7.15-7.29 (m, 4H), 6.58-6.65 (m, 2H), 4.37 (s, 2H), 3.57 (t, $J = 6.6$ Hz, 2H), 2.86 (t, $J = 7.7$ Hz, 2H), 2.11 (p, $J = 7.7$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 29.3, 33.6, 44.4, 45.7, 109.6, 111.4, 117.9, 126.6, 127.7, 128.5, 128.6, 129.6, 132.3, 135.9, 138.9, 144.6; LRMS (ESI): 302, 304 ($\text{M}+\text{H}$) $^+$; HRMS (m/z): [$\text{M}+\text{H}$] $^+$ calcd for $[\text{C}_{16}\text{H}_{17}\text{BrN}]^+$: 302.0544, Found: 302.0539.

2-(3-bromophenyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6j):

Dark brown coloured gummy liquid; Yield: 70 %; IR (cm^{-1}): 1144, 1251, 1471, 1695, 2938, 2986, 3175, 3275, 3387; ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.26-7.29 (m, 1H), 7.15-7.17 (m, 3H), 7.13 (t, $J = 7.3$ Hz, 1H), 6.90 (s, 1H), 6.68-6.74 (m, 2H), 4.55 (s, 2H), 3.74 (t, $J = 5.4$ Hz, 2H), 2.97 (dt, $J = 5.8, 3.4$ Hz, 2H), 1.88 (p, $J = 5.9$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 25.7, 35.5, 52.0, 54.8, 111.1, 115.3, 118.8, 123.4, 125.9, 127.4, 129.4, 129.9, 130.3, 137.9, 141.9, 148.8; LRMS (ESI): 302, 304 ($\text{M}+\text{H}$) $^+$; HRMS (m/z): [$\text{M}+\text{H}$] $^+$ calcd for $[\text{C}_{16}\text{H}_{17}\text{BrN}]^+$: 302.0544, Found: 302.0548.

2-(4-bromophenyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6k):

Dark brown coloured gummy liquid; Yield: 69 %; IR (cm^{-1}): 1095, 1321, 1441, 1683, 2856, 2972, 3117, 3258, 3395; ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.33 (d, $J = 7.7$ Hz, 2H), 7.18-7.23 (m, 5H), 6.50 (dd, $J = 2.2, 6.6$ Hz, 2H), 4.53 (s, 2H), 3.58 (t, $J = 5.9$ Hz, 2H), 2.86 (t, $J = 7.7$ Hz, 2H), 2.10 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 29.3, 33.6, 44.4, 45.9, 109.1, 114.3, 126.7, 127.8, 128.8, 129.6, 131.9, 136.2, 139.0, 147.0; LRMS (ESI): 302, 304 ($\text{M}+\text{H}$) $^+$; HRMS (m/z): [$\text{M}+\text{H}$] $^+$ calcd for $[\text{C}_{16}\text{H}_{17}\text{BrN}]^+$: 302.0544, Found: 302.0534.

2-(4-chloro-2-nitrophenyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6l):

Red coloured gummy liquid; Yield: 61 %; IR (cm^{-1}): 1515, 1583, 1643, 1660, 2833, 2969, 3332, 3489; ^1H NMR (400 MHz, CDCl_3): δ (ppm) 8.21 (d, $J = 2.4$ Hz, 1H), 7.39 (d, $J = 2.4$ Hz, 1H), 7.20-7.37 (m, 4H), 6.80 (d, $J = 9.3$ Hz, 1H), 4.28 (d, $J = 4.9$ Hz, 2H), 3.56 (t, $J = 6.6$ Hz, 2H), 2.85 (t, $J = 7.8$ Hz, 2H), 2.15 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 29.2, 33.4, 44.4, 45.0, 115.4, 120.5, 125.9, 126.9, 128.2, 128.3, 129.8, 129.8, 134.1, 136.4, 138.8, 143.6; LRMS (ESI): 303 ($\text{M}+\text{H}$) $^+$; HRMS (m/z): [$\text{M}+\text{H}$] $^+$ calcd for $[\text{C}_{16}\text{H}_{16}\text{ClN}_2\text{O}_2]^+$: 303.0900, Found: 303.0894.

General procedure for Suzuki coupling reaction (7):

To a solution of 2-(2-bromophenyl)-2, 3, 4, 5-tetrahydro-1*H*-benzo[*c*]azepine (**6i**) (200 mg, 0.66 mmol) in 10 mL of dimethoxyethane was added respective boronic acid (117 mg, 0.76 mmol) and K₃PO₄ tribasic (280 mg, 1.32 mmol). The mixture was degassed and then Pd(PPh₃)₄ (38 mg, 0.03mmol) was added. The reaction mixture was stirred at 90 °C for 12 h. The reaction mixture was cooled to room temperature and filtered on celite bed and washed with EtOAc (20 mL). The organic layer washed with water and brine, dried (MgSO₄) and concentrated under reduced pressure to afford the crude compound and it was purified by column chromatography over silica gel using hexane-ethyl acetate 10:1 to give the pure product as Colourless gummy liquid 190 mg (87 % yield) of the title compound.

2-(4'-methoxy-[1,1'-biphenyl]-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine (7a):

Colourless gummy liquid; Yield: 87 %; IR (cm⁻¹): 1107, 1132, 1264, 1361, 1405, 1595, 1668, 2840, 2937; ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.35 (d, *J* = 8.5 Hz, 1H), 7.14-7.31 (m, 7H), 7.10 (d, *J* = 7.3 Hz, 1H), 6.95 (d, *J* = 8.5 Hz, 1H), 6.78 (d, *J* = 7.3 Hz, 1H), 6.67 (d, *J* = 7.9 Hz, 1H), 4.30 (s, 2H), 3.82 (s, 3H), 3.53 (t, *J* = 6.1 Hz, 2H), 2.81 (t, *J* = 7.3 Hz, 2H), 2.04 (p, *J* = 7.3 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 29.3, 33.5, 44.4, 46.1, 55.2, 110.5, 114.3, 117.2, 126.6, 127.1, 127.4, 128.4, 128.5, 129.4, 130.3, 130.4, 131.5, 132.5, 134.3, 136.6, 138.8, 145.1, 158.8; LRMS (ESI): 330 (M+H)⁺; HRMS (m/z): [M+H]⁺ calcd for [C₂₃H₂₄NO]⁺: 330.1858, Found: 330.1836.

2-(3'-methoxy-[1,1'-biphenyl]-2-yl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (7b):

Colourless gummy liquid; Yield: 86 %; IR (cm^{-1}): 1174, 1215, 1436, 1598, 1691, 1740, 2853, 2925; ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.79 (d, $J = 7.9$ Hz, 1H), 7.66 (d, $J = 7.3$ Hz, 1H), 7.32-7.38 (m, 3H), 7.17-7.31 (m, 4H), 6.74 (t, $J = 6.7$ Hz, 1H), 6.63 (d, $J = 7.9$ Hz, 2H), 4.31 (s, 2H), 3.94 (s, 3H), 3.58 (t, $J = 6.7$ Hz, 2H), 2.87 (t, $J = 7.3$ Hz, 2H), 2.09 (p, $J = 7.1$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 29.7, 33.67, 44.5, 46.0, 52.5, 112.7, 117.6, 126.7, 127.1, 127.7, 129.1, 129.3, 129.6, 131.3, 132.5, 134.3, 139.1, 148.1; LRMS (ESI): 330 ($\text{M}+\text{H}$) $^+$; HRMS (m/z): [$\text{M}+\text{H}$] $^+$ calcd for [$\text{C}_{23}\text{H}_{24}\text{NO}$] $^+$: 330.1858, Found: 330.1828.

2-(4'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (7c):

Pale yellow coloured gummy liquid; Yield: 84 %; IR (cm^{-1}): 1316, 1417, 1595, 1674, 2840, 2937; ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.37 (d, $J = 7.7$ Hz, 1H), 7.17-7.24 (m, 8H), 6.73 (t, $J = 6.2$ Hz, 1H), 6.64 (d, $J = 8.7$ Hz, 2H), 4.31 (s, 2H), 3.56 (t, $J = 6.2$ Hz, 2H), 2.87 (t, $J = 7.7$ Hz, 2H), 2.10 (p, $J = 6.6$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 29.7, 34.5, 47.8, 49.6, 113.6, 125.9, 126.9, 127.0, 127.7, 128.9, 129.5, 129.8, 131.9, 137.0, 141.5; LRMS (ESI): 330 ($\text{M}+\text{H}$) $^+$; HRMS (m/z): [$\text{M}+\text{H}$] $^+$ calcd for [$\text{C}_{23}\text{H}_{21}\text{F}_3\text{N}$] $^+$: 368.1626, Found: 368.1620.

General procedure for Heck coupling reaction (7d):

To a solution of 2-(2-bromophenyl)-2, 3, 4, 5-tetrahydro-1*H*-benzo[c]azepine (**6i**) (200 mg, 0.66 mmol) in 10 mL of toluene was added methyl acrylate (113.6 mg, 1.32 mmol) and K₂CO₃ (228 mg, 1.65 mmol). The mixture was degassed and then (PPh₃)₂PdCl₂ (23 mg, 0.03mmol) was added. The reaction mixture was stirred at 100 °C for 10 h. The reaction mixture was cooled to room temperature and filtered on celite bed and washed with toluene (10 mL). The organic layer was washed with water and brine, dried (MgSO₄) and concentrated under reduced pressure to afford the crude compound which was purified by column chromatography over silica gel using hexane-ethyl acetate 10:1 to give the pure product as an oil 189 mg (93 % yield) of the title compound. Pale yellow coloured gummy liquid; IR (cm⁻¹): 1255, 1387, 1505, 1600, 1650, 2912, 3376; ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.21 (d, *J* = 2.4 Hz, 1H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.20-7.37 (m, 4H), 6.80 (d, *J* = 9.3 Hz, 1H), 4.38 (s, 2H), 3.78 (s, 3H), 3.58 (t, *J* = 6.6 Hz, 2H), 2.88 (t, *J* = 7.6 Hz, 2H), 2.15 (p, *J* = 5.9 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 29.3, 33.6, 44.4, 45.8, 51.6, 111.6, 117.7, 118.1, 119.9, 126.8, 127.9, 128.1, 128.8, 129.7, 131.6, 135.9, 139.0, 140.0, 146.4, 167.6; LRMS (ESI): 308 (M+H)⁺; HRMS (m/z): [M+H]⁺ calcd for [C₂₀H₂₂NO₂]⁺: 308.1651, Found: 308.1644.

References:

1. (a) Patel, B. A.; Ziegler, C. B.; Cortese, N. A.; Plevyak, J. E.; Zebovitz, T. C.; Terpko, P.; Heck, R. F. *J. Org. Chem.* **1977**, 3903-3907; (b) Roberta, B.; Alessandro, P.; Sandro, C.; Giancarlo, F.; Giovanni, F.; Francesco, P.; Sandra, N.; Roser, P.; RosaMaria, S.; Roger, S.; Mar, T.; Adelina, V. *Org. Lett.* **2008**, 4, 561-564; (c) Roberta, B.; Alessandro, P.; Sandro, C.; Giancarlo, F.; Giovanni, F.; Francesco, P.; Sandra, N.; Alexandr, S.; Adelina, V. *Green Chem.* **2010**, 150-158; (d) John, F. P.; David, K. C.; Ewan, K. G.; Paul M.; Jeremy, S. P.; Joseph, B. S. *Org. Process Res. Dev.* **2013**, 17, 397-405.
2. Shibuya, M.; Shibuta, T.; Fukuda, H.; Iwabuchi, Y. *Org. Lett.* **2012**, 14, 5010 – 5013.
3. Miyamoto, K.; Ochiai, M.; Tada, N. *J. Am. Chem. Soc.* **2007**, 129, 2772-2773.
4. (a) Meyers, A. I.; Hutchings, R. H. *Tetrahedron.* **1993**, 49, 1807-1820; (b) Ching, P.; Criscione, K. R.; Dahanukar, V. H.; Grunewald, G. L.; Ching, P. *J. Med. Chem.* **1996**, 39, 3539-3546

¹H NMR of (E)-methyl 2-(3-methoxy-3-oxoprop-1-en-1-yl)benzoate (2):

¹³C NMR of (E)-methyl 2-(3-methoxy-3-oxoprop-1-en-1-yl)benzoate (2):

Mass Spectrum of (E)-methyl 2-(3-methoxy-3-oxoprop-1-en-1-yl)benzoate (2):

¹H NMR of methyl 2-(3-methoxy-3-oxopropyl)benzoate (3):

^{13}C NMR of methyl 2-(3-methoxy-3-oxopropyl)benzoate (3):

TDC-110 CAK-Unkn in CDCl₃
 NMR-400MHz
 AR No: ME0114/518
 Analyst: Ganesh
 Date: 07th Jan. 2014

NUCLEUS : C13
 PRQ (MHz): 100.65
 EXP : s2pul

Mass Spectrum of methyl 2-(3-methoxy-3-oxopropyl)benzoate (3):

¹H NMR of 3-(2-(hydroxymethyl)phenyl)propan-1-ol (4):

TDC-110 CAK/Dlm in CDCl₃
D2O Exchange
NMR-400MHz
AR.No: ME0114/738
Analyst: Haribabu
Date: 09th Jan.2014

NUCLEUS : ¹H
FREQ (MHz): 400.22
EXP : s2pul

¹³C NMR of 3-(2-(hydroxymethyl)phenyl)propan-1-ol (4):

TDC-110 CAK-Diol in CDCl₃
NMR-400MHz
AR.No: ME0114/250
Analyst: Ganesh
Date: 03rd Jan.2014

NUCLEUS : ¹³C
FREQ (MHz): 100.65
EXP : s2pul

¹H NMR of 2-benzazepine (6a):

TDC-110 CAX-BNAZ in CDCl₃

NMR-400MHz
AR.No: ME0114/169
Analyst: Ganesh
Date: 03rd Jan. 2014

NUCLEUS : H1
PRQ (MHz): 400.22
EXP : szpul

¹³C NMR of 2-benzazepine (6a):

TDC-110 CAX-BNAZ in CDCl₃

NMR-400MHz
AR.No: ME0114/376
Analyst: Haribabu
Date: 06th Jan. 2014

NUCLEUS : C13
PRQ (MHz): 100.65
EXP : szpul

Mass Spectrum of 2-benzazepine (6a):

¹H NMR of 2-hexyl-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6b):

¹³C NMR of 2-hexyl-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6b):

750/CAKS/09/13 in CDCl₃
TDC-119

AR.NO:GE1209/52
Analyst:Shruthi
Date: 21st December 2009

AR4D, Aurigene Discovery Technologies Ltd, Hyderabad
Instrument : Mercury Plus (Varian 400MHz)
Date & Time : Tue Dec 22 10:05:27 IST 2009
Recorded By : Shruthi

Mass Spectrum of 2-hexyl-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6b):

CPS,MIYAPUR

Mass Analysis Report

Data Filename	091125033.d	Sample Name	750/CAKS/09/13
Sample Type	Sample	Position	Vial 48
Instrument Name	Instrument 1	User Name	
Acq Method	ESI.m	IRM Calibration Status	Success
DA Method	default.m	Comment	

User Spectra

--- End Of Report ---

¹H NMR of 2-cyclopropyl-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6c):

¹³C NMR of 2-cyclopropyl-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6c):

Mass Spectrum of 2-cyclopropyl-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6c):

CPS,MIYAPUR

Mass Analysis Report

Data Filename	091125030.d	Sample Name	750/CAKS/09/10
Sample Type	Sample	Position	Vial 45
Instrument Name	Instrument 1	User Name	
Acq Method	ESI.m	IRM Calibration Status	Success
DA Method	default.m	Comment

User Spectra

--- End Of Report ---

Page 1 of 1

Printed at: 6:26 PM on:11/25/2009

¹H NMR of 2-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6d):

750/CAKS/09/11 in CDCl₃

TDC-110

AR.No:ME1209/1141
Analyst:Shruthi
Date:22nd Dec. 2009

AR&D, Aurigene Discovery Technologies Ltd, Hyderabad
Instrument : Mercury Plus (Varian 400MHz)
Date & Time : Tue Dec 22 13:26:01 IST 2009
Recorded By : Shruthi. D

^{13}C NMR of 2-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6d):

750/CAKS/09/11 in CDC13
TDC-140

AR.NO:GE1209/59
Analyst:Shruthi
Date: 23rd December 2009

AR&D, Aurigene Discovery Technologies Ltd, Hyderabad
Instrument : Mercury Plus (Varian 400kHz)
Date & Time : Thu Dec 24 17:18:22 IST 2009
Recorded By : Srikanth.A

Handwritten signature
24/12/09

Mass Spectrum of 2-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6d):

CPS,MIYAPUR

Mass Analysis Report

Data Filename	091125031.d	Sample Name	750/CAKS/09/11
Sample Type	Sample	Position	Vial 46
Instrument Name	Instrument 1	User Name	
Acq Method	ESI.m	IRM Calibration Status	Success
DA Method	default.m	Comment

User Spectra

--- End Of Report ---

Handwritten signature
25/11/09

¹H NMR of (S)-2-(1-phenylethyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6e):

¹³C NMR of (S)-2-(1-phenylethyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6e):

Mass Spectrum of (S)-2-(1-phenylethyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6e):

CPS,MIYAPUR

Mass Analysis Report

Data Filename	100208031.d	Sample Name	750/CAK5/09/18
Sample Type	Sample	Position	Vial 58
Instrument Name	Instrument 1	User Name	
Acq Method	ESI.m	IRM Calibration Status	Success
DA Method	default.m	Comment

User Spectra

--- End Of Report ---

Handwritten signature
08/02/10

¹H NMR of 2-(2,6-dichlorobenzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6f):

750-CAK5-09-12 in CDCl₃
TDC-110

AR No:ME1209/659
Analyst:Srikanth.A
Date:14th Dec., 2009

AK&D, Aurigene Discovery Technologies Ltd, Hyderabad
Instrument : Mercury Plus (Varian 400MHz)
Date & Time : Mon Dec 14 15:44:57 IST 2009
Recorded By : Srikanth.A

Handwritten signature
14/12/09

^{13}C NMR of 2-(2,6-dichlorobenzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6f):

Mass Spectrum of 2-(2,6-dichlorobenzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6f):

CPS.MIYAPUR

Mass Analysis Report

Data Filename	091125032.d	Sample Name	750/CAKS/09/12
Sample Type	Sample	Position	Vial 47
Instrument Name	Instrument 1	User Name	
Acq Method	ESI.m	IRM Calibration Status	Success
DA Method	default.m	Comment

User Spectra

--- End Of Report ---

^1H NMR of 2-phenyl-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6g):

750/CAES/10/29 in CDCl₃
TDC-110
AR.NO:ME0310/2003
Analyst: Srikanth.A
Date: 30th March 2010

^{13}C NMR of 2-phenyl-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6g):

750/CAES/10/29 in CDCl₃
TDC-110
AR.NO:0E0410/8
Analyst: Shruthi
Date: 5th April 2010

AK&D, Aurigene Discovery Technologies Ltd, Mysore
Instrument : Gemini 2000 (Varian 200MHz)
Date & Time : Tue Apr 6 08:48:29 GMT 2010
Recorded By : Shruthi.D

Shruthi.D

Mass Spectrum of 2-phenyl-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6g):

CPS,MIYAPUR

Mass Analysis Report

Data Filename	100330006.d	Sample Name	750/CAKS/10/29 Fr-III
Sample Type	Sample	Position	Vial 15
Instrument Name	Instrument 1	User Name	
Acq Method	esi.m	IRM Calibration Status	Success
DA Method	default.m	Comment

User Spectra

--- End Of Report ---

Page 1 of 1

Printed at: 3:31 PM on:3/30/2010

Botreca
30/03/10

¹H NMR of 2-(3-chlorophenyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6h):

¹³C NMR of 2-(3-chlorophenyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6h):

750/CAKS/10/19 in CDCl₃
TQC-110

AR_NO:060410/51
Analyst: Shruthi
Date:10th April 2010

AR&D, Aurigene Discovery Technologies Ltd, Hydera
Instrument : Gemini 2000 (Varian 200MHz)
Date & Time : Sat Apr 17 10:42:32 GMT 2010
Recorded By : Shruthi.D

Handwritten signature and date: 17/4/10

Mass Spectrum of 2-(3-chlorophenyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6h):

CPS,MIYAPUR

Mass Analysis Report

Data Filename 100412012.d
Sample Type Sample
Instrument Name Instrument 1
Acq Method esi.m
DA Method default.m

Sample Name 750/CAKS/10/19
Position Vial 71
User Name
IRM Calibration Status Success
Comment

User Spectra

--- End Of Report ---

Handwritten signature and date: 18/04/10

¹H NMR of 2-(2-bromophenyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6i):

¹³C NMR of 2-(2-bromophenyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6i):

Mass Spectrum of 2-(2-bromophenyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6i):

CPS,MIYAPUR

Mass Analysis Report

Data Filename: 100601001.d
Sample Type: Sample
Instrument Name: Instrument 1
Acq Method: ESI.m
DA Method: default.m

Sample Name: 750/CAKS/10/31
Position: Vial 1
User Name:
IRM Calibration Status: Success
Comment:

User Spectra

--- End Of Report ---

Behera
01/06/10

Page 1 of 1

Printed at: 10:57 AM on:6/1/2010

¹H NMR of 2-(3-bromophenyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6j):

TQC-110 750/CAKS/01/25 1n CDC13
NMR-400
AR: No:ME4311/1222
Analyst: Haribabu.R
Date: 12th March, 2011

^{13}C NMR of 2-(3-bromophenyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6j):

TDC-110 750/CAKS/10/25 Pure In CDC13
 NMR-410
 AR_No:WE0611/523
 Analyst:Heribabu.R
 Date:03rd June. 2011

Mass Spectrum of 2-(3-bromophenyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6j):

CPS,MIYAPUR

Mass Analysis Report

Data Filename	110311019.d	Sample Name	750/CAKS/25
Sample Type	Sample	Position	Vial 3
Instrument Name	Instrument 1	User Name	
Acq Method	ESLM	IRM Calibration Status	Success
DA Method	CEST1_QUANT.m	Comment

User Spectra

--- End Of Report ---

Handwritten signature
 11/03/2011

¹H NMR of 2-(4-bromophenyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6k):

¹³C NMR of 2-(4-bromophenyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6k):

Mass Spectrum of 2-(4-bromophenyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6k):

CPS.MIYAPUR

Mass Analysis Report

Data Filename: 100621018.d
Sample Type: Sample
Instrument Name: Instrument 1
Acq Method: ESI.m
DA Method: default.m

Sample Name: 750/CAKS/10/35
Position: Vial 17
User Name:
IRM Calibration Status: Success
Comment:

User Spectra

--- End Of Report ---

Page 1 of 1

Printed at: 11:40 AM on: 6/21/2010

¹H NMR of 2-(4-chloro-2-nitrophenyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6l):

TDC-110 750-CAKS-10-27-F1 in CDCl₃
NMR-400
AR No: ME0111/826
Analyst: Haribabu.R
Date: 10 th Jan. 2011

^{13}C NMR of 2-(4-chloro-2-nitrophenyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6l):

TDC-110 750/CACS/10/27 In CDCl₃
 NMR-009
 AR.No:UT0111/2308
 Analyst:Haribabu.R
 Date: 25 th Jan. 2011

Mass Spectrum of 2-(4-chloro-2-nitrophenyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (6l):

UT0111_051 8 (0.145) Cm (7.8-57.65)

¹H NMR of 2-(4'-methoxy-[1,1'-biphenyl]-2-yl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (7a):

¹³C NMR of 2-(4'-methoxy-[1,1'-biphenyl]-2-yl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (7a):

Mass Spectrum of 2-(4'-methoxy-[1,1'-biphenyl]-2-yl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (7a):

¹H NMR of 2-(3'-methoxy-[1,1'-biphenyl]-2-yl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (7b):

^{13}C NMR of 2-(3'-methoxy-[1,1'-biphenyl]-2-yl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (7b):

Mass Spectrum of 2-(3'-methoxy-[1,1'-biphenyl]-2-yl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (7b):

CPS,MIYAPUR

Mass Analysis Report

Data Filename	100629019.d	Sample Name	750/CAK5/10/34
Sample Type	Sample	Position	Vial B4
Instrument Name	Instrument 1	User Name	
Acq Method	esi.m	IRM Calibration Status	Success
DA Method	default.m	Comment	

User Spectra

--- End Of Report ---

¹H NMR of 2-(4'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (7c):

750-CAKS-10-32 in CDCl₃
TDC-110

AR.No:ME0610/1566
Analyst:Srikanth
Date:22nd June 2010

AR&D, Aurigene Discovery Technologies Ltd, Hyderabad
Instrument : Mercury Plus (Varian 400MHz)
Date & Time : Tue Jun 22 10:05:37 IST 2010
Recorded By : Haribabu.R

Handwritten signature

¹³C NMR of 2-(4'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (7c):

TDC-110 750/CAKS/11/02-1 in CDCl₃

WHR-000
AR.No:ME0611/1334
Analyst: Haribabu
Date:15th June, 2011

Mass Spectrum of 2-(4'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (7c):

¹H NMR of (E)-methyl 3-(2-(4,5-dihydro-1H-benzo[c]azepin-2(3H)-yl)phenyl)acrylate (7d):

^{13}C NMR of (*E*)-methyl 3-(2-(4,5-dihydro-1*H*-benzo[*c*]azepin-2(3*H*)-yl)phenyl)acrylate (7d):

Mass Spectrum of (*E*)-methyl 3-(2-(4,5-dihydro-1*H*-benzo[*c*]azepin-2(3*H*)-yl)phenyl)acrylate (7d):