Environmentally Benign Nucleophilic Substitution Reaction of Arylalkyl Halides in Water using CTAB as Inverse Phase Transfer Catalyst

Atul K. Godha, Jayaraman Thiruvengadam, Viswanadhan Abhilash, Prajwal Balgi, A. V. Narayanareddy, Kumaresan Vignesh, Amol V. Gadakh,* A. M. Sathiyanarayanan* and Sambasivam Ganesh*

Anthem Biosciences Pvt. Ltd., #49, Canara bank road, Bommasandra Industrial Area, Bommasandra, Bengaluru-560099, Karnataka, India. Tel: +91-80-66724000; Fax: +91-80-66724020

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Experimental Section:

General Materials and Methods:

IR spectra were recorded on Agilent Technologies Cary 630 FTIR. $^1$H (400 MHz, 300 MHz) and $^{13}$C (100 MHz, 75 MHz) spectra were recorded on Bruker Avance 400 or 300 spectrometers. The chemical shifts (δ ppm) and coupling constants (Hz) are reported in the standard fashion with reference to internal tetramethylsilane or residual chloroform or DMSO. In the $^{13}$C NMR spectra, the nature of the carbons (C, CH, CH$_2$ or CH$_3$) are given in parentheses. LCMS analysis were carried out using Agilent Technologies 1200 series instrument using direct inlet mode. Analytical thin-layer chromatography (TLC) were performed on pre-coated 0.2 mm thick Merck 60 F245 silica plates and various combinations of ethyl acetate, CH$_2$Cl$_2$, MeOH and hexanes were used as eluent. Visualization of spots was accomplished by exposure to iodine vapour. All compounds were purified using Teledyne ISCO flash column chromatography and gave spectroscopic data consistent with being ≥95% the assigned structure. All the commercial reagents were used as such without further purification.

Surfactants Used in the Present Study:

- TPGS-750-M
- Triton X-100
- Bis-(2-ethylhexyl)sulfosuccinate sodium salt
- AOT
- Cetyltrimethylammonium bromide (CTAB)
- Brij 58™
Experimental procedure for screening of bases and surfactant for C-benzylation of Ethyl-3-Oxo-3-Phenylpropanoate using CTAB in water:

Synthesis of 2-Benzyl-3-oxo-3-phenyl-propionic acid ethyl ester (3aa) using K₂CO₃:

To the suspension of CTAB (200 mg, 2% w/v) in water (10 mL) was added ethylbenzoyl acetate (1a) (1 g, 5.202 mmol) followed by potassium carbonate (2.15 g, 15.607 mmol) was added. The reaction mixture was allowed to stir at room temperature for 15 min at room temperature. Then benzyl bromide (2a) (0.89 g, 5.202 mmol) was added, the reaction mixture was allowed to stir at 60°C for 16 h. Upon completion (TLC control, 10% EtOAc in n-hexane), the reaction was diluted with water (10 mL). The aqueous layer was extracted with ethyl acetate (2 x 10 mL); combined organic layer was washed with brine and dried (anhdy. Na₂SO₄). Evaporation of solvent followed by purification on Combiflash® purification system using 2-4% ethyl acetate-hexane as an eluent afforded, 2-benzyl-3-oxo-3-phenyl-propionic acid ethyl ester (3aa) (954 mg, 65%) as pale yellow oil.

**IR (KBr):** 2982, 1737, 1597, 1496, 1448, 1368, 1232, 1030, 853 cm⁻¹

**Physical appearance:** pale yellow oil

**¹H NMR (400 MHz, CDCl₃):** δ 8.00 - 7.95 (m, 2H), 7.60 - 7.50 (m, 1H), 7.50 - 7.40 (m, 2H), 7.30 - 7.15 (m, 5H), 4.63 (t, J = 7.2 Hz, 1H), 4.20 – 4.05 (m, 2H), 3.27 (dd, J = 7.2, 2.8 Hz), 1.12 (t, J = 7.2 Hz, 3H).

**¹³C NMR (75 MHz, CDCl₃):** 194.56 (C=O), 169.34 (C=O ester), 138.53 (C), 136.31 (C), 133.58 (CH), 129.01 (CH x 2), 128.85 (CH x 2), 128.72 (CH x 2), 128.59 (CH x 2), 126.70 (CH), 61.54 (CH₂), 56.25 (CH), 34.84 (CH₂), 13.97 (CH₃).

**LCMS (EI, m/z):** calcd for C₁₈H₁₉O₃ [M +H]: 283.13, Found: 283.3

**Note:** The same protocol has been employed with other bases and surfactant following the below general protocol.
**General procedure:** Reaction of the ethylbenzoyl acetate (1a) (1 g, 5.202 mmol) and benzyl bromide (2a) (0.89 g, 5.202 mmol) with appropriate base (15.61 mmol) in appropriate surfactant (200 mg, 2% w/v) in water (10 mL) as described for the synthesis of 2-benzyl-3-oxo-3-phenyl-propionic acid ethyl ester (3aa) using K$_2$CO$_3$ and CTAB. The progress of the reaction was monitored by LCMS/TLC and the extent of conversion was recorded as observed.

**Table-1: Influence of various surfactants/i-PTC catalysts on C-benzylation of Ethyl-3-Oxo-3-Phenylpropanoate using K$_2$CO$_3$ as the base at 60°C**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Surfactant</th>
<th>Yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tween-40</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>AOT</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>CTAB</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>Brij-58</td>
<td>&lt;10</td>
</tr>
<tr>
<td>6</td>
<td>TPGS-750M</td>
<td>&lt;10</td>
</tr>
<tr>
<td>7</td>
<td>TritonX-100</td>
<td>&lt;10</td>
</tr>
<tr>
<td>8</td>
<td>Blank</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

Note: All reactions were carried out on a 1 g scale for 16 h and was monitored by TLC. $^a$ Isolated yield after column purification.
Experimental procedure for synthesis of 2-aralkyl-3-oxo-3-phenyl-propionic acid ethyl ester 3:

Synthesis of 2-(4-Chloro-benzyl)-3-oxo-3-phenyl-propionic acid ethyl ester (3ab):
To the suspension of CTAB (200 mg, 2% w/v) in water (10 mL) was added ethylbenzoyl acetate (1a) (1 g, 5.202 mmol) followed by potassium carbonate (2.15 g, 15.607 mmol) was added. The reaction mixture was allowed to stir at room temperature for 15 min at room temperature. Then 4-chlorobenzyl bromide (2b) (1.1 g, 5.202 mmol) was added, the reaction mixture was allowed to stir at 60°C for 16 h. Upon completion (TLC control, 10 % EtOAc in n-hexane), the reaction mixture was subjected to aqueous work up as mentioned earlier and purified through Combiflash® purification system using 2-4% ethyl acetate-hexane as an eluent afforded, 2-(4-Chloro-benzyl)-3-oxo-3-phenyl-propionic acid ethyl ester (3ab) (935 mg, 57%) as pale yellow oil.

Physical appearance: pale yellow oil

IR (KBr): 2984, 2937, 1735, 1686, 1597, 1493, 1448, 1232, 1094, 1016 cm⁻¹

¹H NMR (400 MHz, CDCl₃): δ 8.00 - 7.95 (m, 2H), 7.65 - 7.55 (m, 1H), 7.50 - 7.40 (m, 2H), 7.25 - 7.20 (m, 2H), 7.20 - 7.15 (m, 2H), 4.59 (t, J = 7.2 Hz, 1H), 4.15 – 4.05 (m, 2H), 3.30 (d, J = 7.2 Hz, 2H), 1.12 (t, J = 6.8 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 194.19 (C=O), 169.90 (C=O, ester), 136.96 (C), 136.11 (C), 133.72 (CH), 132.51 (C), 130.42 (CH×2), 128.81 (CH×3), 128.69 (CH×3), 61.67 (CH₂), 56.00 (CH), 34.08 (CH₂), 13.98 (CH₃).

LCMS (EI, m/z): calcd for C₁₈H₁₈ClO₃ [M+H]: 317.09, Found: 317.2

Synthesis of 2-(4-Iodo-benzyl)-3-oxo-3-phenyl-propionic acid ethyl ester (3ac):
To the suspension of CTAB (200 mg, 2% w/v) in water (10 mL) was added ethylbenzoyl acetate (1a) (1 g, 5.202 mmol) followed by potassium carbonate (2.15 g, 15.607 mmol) was added. The reaction mixture was allowed to stir at room temperature for 15 min at room
temperature. Then 4-iodobenzyl bromide (2c) (1.54 g, 5.202 mmol) was added, the reaction mixture was allowed to stir at 60°C for 16 h. Upon completion (TLC control, 10% EtOAc in n-hexane), the reaction mixture was subjected to aqueous work up as mentioned earlier and purified through Combiflash® purification system using 2-4% ethyl acetate-hexane as an eluent afforded, 2-(4-Iodo-benzyl)-3-oxo-3-phenyl-propionic acid ethyl ester (3ac) (1.34 g, 63%) as an off-white solid.

Physical appearance: Off-white solid

IR (KBr): 2982, 1731, 1675, 1593, 1485, 1239, 1150, 1003 cm⁻¹

¹H NMR (400 MHz, DMSO): δ 8.00 - 7.95 (m, 2H), 7.70 - 7.60 (m, 1H), 7.60 - 7.55 (m, 2H), 7.55 - 7.50 (m, 2H), 7.10 - 7.05 (m, 2H), 5.00 (t, J = 8.0 Hz, 1H), 4.05 – 3.95 (m, 2H), 3.12 (dd, J = 7.2, 1.6 Hz, 2H), 0.98 (t, J = 6.8 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 194.13 (C=O), 169.08 (C=O, ester), 138.17 (C), 137.63 (CH×2), 136.08 (C), 133.75 (CH), 131.12 (CH×2), 128.83 (CH×2), 128.72 (CH×2), 92.07 (C), 61.71 (CH₂), 55.92 (CH), 34.23 (CH₂), 14.02 (CH₃).

LCMS (EI, m/z): calcld for C₁₈H₁₈IO₃ [M+H]: 409.02, Found: 409.2.

HRMS (ESI, m/z): calcld for C₁₈H₁₈IO₃ [M+H]: 409.0295 Found: 409.1875.

Synthesis of 2-(4-Methyl-benzyl)-3-oxo-3-phenyl-propionic acid ethyl ester (3ad):

To the suspension of CTAB (200 mg, 2% w/v) in water (10 mL) was added ethyl benzoyl acetate (1a) (1 g, 5.202 mmol) followed by potassium carbonate (2.15 g, 15.607 mmol) was added. The reaction mixture was allowed to stir at room temperature for 15 min at room temperature. Then 4-methylbenzyl bromide (2d) (0.96 g, 5.202 mmol) was added, the reaction mixture was allowed to stir at 60°C for 16 h. Upon completion (TLC control, 10% EtOAc in n-hexane), the reaction mixture was subjected to aqueous work up as mentioned earlier and purified through Combiflash® purification system using 2-4% ethyl acetate-
hexane as an eluent afforded, 2-(4-Methyl-benzyl)-3-oxo-3-phenyl-propionic acid ethyl ester (3ad) (1.06 g, 69%) as colourless liquid

**Physical appearance:** colourless liquid

**IR (KBr):** 2982, 2933, 1733, 1597, 1392, 1448, 1269, 1023, 853 cm\(^{-1}\).

**\(^1\)H NMR (400 MHz, CDCl\(_3\)):** \(\delta 8.00 - 7.95\) (m, 2H), \(7.60 - 7.55\) (m, 1H), \(7.50 - 7.40\) (m, 2H), \(7.13\) (d, \(J = 8.0\ Hz, 2H\)), \(7.07\) (d, \(J = 7.6\ Hz, 2H\)), \(4.61\) (t, \(J = 7.2\ Hz, 1H\)), \(4.15 - 4.05\) (m, 2H), \(3.35 - 3.25\) (m, 2H), \(2.30\) (s, 3H), \(1.13\) (t, \(J = 7.2, 3H\)).

**\(^{13}\)C NMR (100 MHz, CDCl\(_3\)):** \(\delta 194.61\) (C=O), \(169.39\) (C=O, ester), \(136.27\) (C), \(136.18\) (C), \(135.41\) (C), \(133.56\) (CH), \(129.26\) (CH×2), \(128.86\) (CH×2), \(128.74\) (CH×2), \(128.73\) (CH×2), \(61.52\) (CH\(_2\)), \(56.38\) (CH), \(34.40\) (CH\(_2\)), \(21.08\) (CH\(_3\)), \(14.01\) (CH\(_3\)).

**LCMS (EI, m/z):** calcd for C\(_{19}\)H\(_{21}\)O\(_3\) [M+H]: 297.14, Found: 297.3

**Synthesis of 2-(4-nitro-benzyl)-3-oxo-3-phenyl-propionic acid ethyl ester (3ae):**

To the suspension of AOT (200 mg, 2% w/v) in water (10 mL) was added ethyl benzoyl acetate (1a) (1 g, 5.202 mmol) followed by potassium carbonate (2.15 g, 15.607 mmol) was added. The reaction mixture was allowed to stir at room temperature for 15 min at room temperature. Then 4-nitrobenzyl bromide (2e) (1.2 g, 5.202 mmol) was added, the reaction mixture was allowed to stir at 60°C for 16 h. Upon completion (TLC control, 10% EtOAc in \(n\)-hexane), the reaction mixture was subjected to aqueous work up as mentioned earlier and purified through Combiflash\(^{\text{®}}\) purification system using 2-4% ethyl acetate-hexane as an eluent afforded, 2-(4-nitro-benzyl)-3-oxo-3-phenyl-propionic acid ethyl ester (3ae) (1.04 g, 61%) as pale-yellow solid.

**Physical appearance:** pale yellow solid

**IR (KBr):** 2987, 1733, 1521, 1345, 1254, 1152 cm\(^{-1}\).
1H NMR (400 MHz, CDCl₃): δ 8.15 – 8.10 (m, 2H), 8.00 - 7.95 (m, 2H), 7.65 - 7.55 (m, 1H), 7.50 - 7.45 (m, 2H), 7.45 - 7.40 (m, 2H), 4.64 (t, J = 7.6 Hz, 1H), 4.20 – 4.05 (m, 2H), 3.45 - 3.40 (m, 2H), 1.12 (t, J = 6.8 Hz, 3H).

13C NMR (100 MHz, CDCl₃): δ 193.64 (C=O), 168.75 (C=O, ester), 146.90 (C), 146.30 (C), 135.90 (C), 133.95 (CH), 130.02 (CH×2), 128.90 (CH×2), 128.71 (CH×2), 123.78 (CH×2), 61.91 (CH₂), 55.42 (CH), 34.40 (CH₂), 13.97 (CH₃).

LCMS (EI, m/z): calcd for C₁₉H₁₈NO₅ [M+H]: 328.11, Found: 328.3

Synthesis of 2-(4-bromo-benzyl)-3-oxo-3-phenyl-propionic acid ethyl ester (3af):
To the suspension of CTAB (200 mg, 2% w/v) in water (10 mL) was added ethylbenzoyl acetate (1a) (1 g, 5.202 mmol) followed by potassium carbonate (2.15 g, 15.607 mmol) was added. The reaction mixture was allowed to stir for 15 min at rt. Then 4-bromobenzyl bromide (2f) (1.3 g, 5.202 mmol) was added, the reaction mixture was allowed to stir at 60°C for 16 h. Upon completion (TLC control, 10 % EtOAc in n-hexane), the reaction mixture was subjected to aqueous work up as mentioned earlier and purified through Combiflash® purification system using 2-4% ethyl acetate-hexane as an eluent afforded, 2-(4-Bromo-benzyl)-3-oxo-3-phenyl-propionic acid ethyl ester (3af) (1.33 g, 71%) as pale yellow oil.

Physical appearance: pale yellow oil

IR (KBr): 2980, 1731, 1675, 1595, 1489, 1245, 1152, 811, 686 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ 8.00 - 7.95 (m, 2H), 7.65 - 7.50 (m, 1H), 7.50 - 7.40 (m, 2H), 7.40 - 7.35 (m, 2H), 7.15 - 7.10 (m, 2H), 4.59 (t, J = 7.2 Hz, 1H), 4.15 – 4.05 (m, 2H), 3.28 (d, J = 7.2 Hz, 2H), 1.12 (t, J = 7.2 Hz, 3H).

13C NMR (100 MHz, CDCl₃): 194.14 (C=O), 169.07 (C=O ester), 137.49 (C), 136.08 (C), 133.73 (CH), 131.64 (CH x 2), 130.81 (CH x 2), 128.81 (CH x 2) 128.70 (CH x 2), 120.60 (C), 61.67 (CH x 1), 55.94 (CH₂ x 1), 34.84 (CH₂ x 1), 13.99 (CH₃)

LCMS (EI, m/z): calcd for C₁₉H₁₈BrO₃ [M+H]: 361.04, Found: 361.2
Synthesis of 2-(4-Methoxybenzyl)-3-oxo-3-phenyl-propionic acid ethyl ester (3ag):

To the suspension of CTAB (200 mg, 2% w/v) in water (10 mL) was added ethylbenzoyl acetate (1a) (1 g, 5.202 mmol) followed by potassium carbonate (2.15 g, 15.607 mmol) was added. The reaction mixture was allowed to stir for 15 min at rt. Then 4-methoxy benzyl bromide (2g) (1.04 g, 5.202 mmol) was added, the reaction mixture was allowed to stir at 60°C for 16 h. Upon completion (TLC control, 10% EtOAc in n-hexane), the reaction mixture was subjected to aqueous work up as mentioned earlier and purified through Combiflash® purification system using 2-4% ethyl acetate-hexane as an eluent afforded, 2-(4-Methoxybenzyl)-3-oxo-3-phenyl-propionic acid ethyl ester (3ag) (1.05 g, 65%) as yellow oil.

Physical appearance: yellow oil

IR (KBr): 2982, 2836, 1735, 1686, 1612, 1515, 1448, 1250, 1034, 855 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 8.00 - 7.95 (m, 2H), 7.60 - 7.55 (m, 1H), 7.50 - 7.40 (m, 2H), 7.20 - 7.10 (m, 2H), 6.85 - 6.75 (m, 2H), 4.59 (t, J = 7.2 Hz, 1H), 4.15 - 4.05 (m, 2H), 3.77 (s, 3H), 3.27 (dd, J = 7.6, 2.4 Hz. 2H), 1.13 (t, J = 7.2, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 194.67 (C=O), 169.40 (C=O, ester), 158.37 (C), 136.29 (C), 133.56 (CH), 130.47 (C), 130.01 (CH×2), 128.75 (CH×2), 128.70 (CH×2), 113.97 (CH×2), 61.50 (CH₂), 56.50 (CH₃), 55.25 (CH), 34.00 (CH₂), 14.01 (CH₃).

LCMS (EI, m/z): calcd for C₁₉H₂₀O₄Na [M+Na]: 335.13, Found: 335.3

Synthesis of 2-methyl-3-oxo-3-phenyl-propionic acid ethyl ester (3ah):

To the suspension of CTAB (200 mg, 2% w/v) in water (10 mL) was added ethylbenzoyl acetate (1a) (1 g, 5.202 mmol) followed by potassium carbonate (2.15 g, 15.607 mmol) was added. The reaction mixture was allowed to stir for 15 min at rt. Then methyl iodide (2h) (0.67 mL, 10.404 mmol) was added, the reaction mixture was allowed to stir at 50°C for 16 h. Upon completion (TLC control, 10% EtOAc in n-hexane), the reaction mixture was subjected to aqueous work up as mentioned earlier and purified through Combiflash® purification
system using 1-2% ethyl acetate-hexane as an eluent afforded, 2-methyl-3-oxo-3-phenyl-propionic acid ethyl ester (3ah) as colourless liquid (640 mg, 60%).

**Physical appearance:** colourless liquid

**1H NMR (400 MHz, CDCl₃):** δ 8.05 – 7.95 (m, 2H), 7.65 – 7.55 (m, 1H), 7.55 – 7.45 (m, 2H), 4.38 (q, J = 7.2 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 1.50 (d, J = 7.2 Hz, 3H), 1.17 (t, J = 7.2 Hz, 3H).

**13C NMR (75 MHz, CDCl₃):** δ 195.98 (C=O), 170.95 (C=O, ester), 136.00 (C), 133.51 (CH), 128.80 (CH×2), 128.66 (CH×2), 61.42 (CH₂), 48.50 (CH), 14.03 (CH₃), 13.81 (CH₃).

**LCMS (EI, m/z):** calcd for C₁₂H₁₅O₃ [M+H]: 207.10; Found: 207.2

**Synthesis of 2-propyl-3-oxo-3-phenyl-propionic acid ethyl ester (3ai):**

To the suspension of CTAB (200 mg, 2% w/v) in water (10 mL) was added ethylbenzoyl acetate (1a) (1 g, 5.202 mmol) followed by potassium carbonate (2.15 g, 15.607 mmol) was added. The reaction mixture was allowed to stir for 15 min at rt. Then 1-iodopropane (2i) (1 mL, 10.404 mmol) was added, the reaction mixture was allowed to stir at 50°C for 16 h. Upon completion (TLC control, 10% EtOAc in n-hexane), the reaction mixture was subjected to aqueous work up as mentioned earlier and purified through Combiflash® purification system using 1-2% ethyl acetate-hexane as an eluent afforded, 2-propyl-3-oxo-3-phenyl-propionic acid ethyl ester (3ai) as colourless liquid (850 mg, 70%).

**Physical appearance:** colourless liquid

**1H NMR (400 MHz, CDCl₃):** δ 8.05 – 7.95 (m, 2H), 7.65 – 7.55 (m, 1H), 7.50 – 7.45 (m, 2H), 4.31 (dd, J = 11.6, 6.8 Hz, 1H), 4.20 – 4.10 (m, 2H), 2.05 – 1.95 (m, 2H), 1.45 – 1.35 (m, 2H), 1.18 (t, J = 7.2 Hz, 3H), 0.96 (t, J = 7.6 Hz, 3H).

**13C NMR (75 MHz, CDCl₃):** δ 195.37 (C=O), 170.14 (C=O, ester), 136.44 (C), 133.48 (CH), 128.78 (CH×2), 128.61 (CH×2), 61.33 (CH₂), 54.17 (CH), 31.09 (CH₂), 20.94 (CH₂), 14.06 (CH₃), 13.96 (CH₃).
**LCMS (EI, m/z):** calcd for C_{14}H_{19}O_{3} [M +H]: 235.13 Found: 235.2

**Synthesis of 2-(benzyl)-malonic acid diethyl ester (3ba):**

To the suspension of CTAB (200 mg, 2% w/v) in water (10 mL) was added diethyl malonate (1b) (1 g, 6.25 mmol) followed by potassium carbonate (2.58 g, 18.75 mmol) was added. The reaction mixture was allowed to stir at room temperature for 15 min at room temperature. Then benzyl bromide (2a) (0.75 mL, 6.25 mmol) was added, the reaction mixture was allowed to stir at 60°C for 16 h. Upon completion (TLC control, 10% EtOAc in n-hexane), the reaction mixture was subjected to aqueous work up as mentioned earlier and purified through Combiflash® purification system using 3-5% ethyl acetate-hexane as an eluent afforded, 2-(benzyl)-malonic acid diethyl ester (3ba) (1 g, 65%) as pale yellow oil.

**Physical appearance:** pale yellow oil

**IR (KBr):** 2982, 1735, 1489, 1370, 1228, 1012, 859, 812 cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta \) 7.35 – 7.25 (m, 2H), 7.25 – 7.15 (m, 3H), 4.25 – 4.10 (m, 4H), 3.65 (t, \(J = 8\) Hz, 1H), 3.22 (d, \(J = 8\) Hz, 2H), 1.21 (t, \(J = 6.8\) Hz, 6H).

**LCMS (EI, m/z):** calcd for C_{14}H_{19}O_{4} [M+H]: 251.13 Found: 251.3

**Synthesis of 2-(4-chloro-benzyl)-malonic acid diethyl ester (3bb):**

To the suspension of CTAB (200 mg, 2% w/v) in water (10 mL) was added diethyl malonate (1b) (1 g, 6.25 mmol) followed by potassium carbonate (2.58 g, 18.75 mmol) was added. The reaction mixture was allowed to stir at room temperature for 15 min at room temperature. Then 4-chlorobenzyl bromide (2b) (1.38 g, 6.25 mmol) was added, the reaction mixture was allowed to stir at 60°C for 16 h. Upon completion (TLC control, 10% EtOAc in n-hexane), the reaction mixture was subjected to aqueous work up as mentioned earlier and purified through Combiflash® purification system using 3-5% ethyl acetate-hexane afforded, 2-(4 chloro -benzyl)-malonic acid diethyl ester (3bb) (1.04 g, 59%) as pale yellow oil.

**Physical appearance:** pale yellow liquid
IR (KBr): 2984, 1733, 1495, 1446, 1370, 1228, 1152, 1034, 859, 816 cm⁻¹

¹H NMR (400 MHz, CDCl₃): δ 7.30 – 7.20 (m, 2H), 7.20 – 7.05 (m, 2H), 4.25 – 4.10 (m, 4H), 3.60 (t, J = 8.0 Hz, 1H), 3.18 (d, J = 8.0 Hz, 2H), 1.22 (t, J = 7.2 Hz, 6H).

¹³C NMR (100 MHz, CDCl₃): δ 168.70 (C=O×2, ester), 136.47 (C), 132.67 (C), 130.35 (CH×2), 128.71 (CH×2), 61.64 (CH₂×2), 53.75 (CH), 34.07 (CH₂), 14.10 (CH₃×2).

LCMS (EI, m/z): calcd for C₁₄H₁₈ClO₄ [M+H]: 285.09 Found: 285.3

**Synthesis of 2-(4-iodo-benzyl)-malonic acid diethyl ester (3bc):**

To the suspension of CTAB (200 mg, 2% w/v) in water: THF (10 mL) was added diethyl malonate(1b) (1 g, 6.25 mmol) followed by potassium carbonate (2.58 g, 18.75 mmol) was added. The reaction mixture was allowed to stir at room temperature for 15 min at room temperature. Then 4-iodobenzyl bromide (2c) (1.95 g, 6.25 mmol) was added, the reaction mixture was allowed to stir at 60°C for 16h. Upon completion (TLC control, 10% EtOAc in n-hexane), the reaction mixture was subjected to aqueous work up as mentioned earlier and purified through Combiflash® purification system using 3-5% ethyl acetate-hexane as an afforded, 2-(4-iodo-benzyl)-malonic acid diethyl ester (3bc) (1.3 g, 55%) as pale yellow solid.

**Physical appearance:** pale yellow solid

IR (KBr): 2984, 1733, 1487, 1444, 1401, 1370, 1338, 1230, 1060, 1034, 859, 811 cm⁻¹

¹H NMR (400 MHz, CDCl₃): δ 7.65 – 7.55 (m, 2H), 7.00 – 6.95 (m, 2H), 4.25 – 4.15 (m, 4H), 3.60 (t, J = 8.0 Hz, 1H), 3.15 (d, J = 7.6 Hz, 2H), 1.22 (t, J = 7.2 Hz, 6H).

¹³C NMR (100 MHz, CDCl₃): δ 168.63 (C=O×2, ester), 137.63 (C), 130.10 (CH×4), 92.16 (C), 61.63 (CH₂×2), 53.60 (CH), 34.19 (CH₂), 14.09 (CH₃×2).

LCMS (EI, m/z): calcd for C₁₄H₁₈IO₄ [M+H]: 377.02 Found: 377.2
Synthesis of 2-(4-methyl-benzyl)-malonic acid diethyl ester (3bd):

To the suspension of CTAB (200 mg, 2% w/v) in water: THF (8.5:1.5), (10 mL) was added diethyl malonate (1b) (1 g, 6.25 mmol) followed by potassium carbonate (2.58 g, 18.75 mmol) was added. The reaction mixture was allowed to stir at room temperature for 15 min at room temperature. Then 4-methylbenzyl bromide (2d) (1.15 g, 6.25 mmol) was added, the reaction mixture was allowed to stir at 60°C for 16 h. Upon completion (TLC control, 10% EtOAc in n-hexane), the reaction mixture was subjected to aqueous work up as mentioned earlier and purified through Combiflash® purification system using 3-5% ethyl acetate-hexane as an eluent, 2-(4-methyl-benzyl)-malonic acid diethyl ester (3bd) (0.99 g, 60%) as colourless oil.

**Physical appearance**: colourless oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.15 – 7.05 (m, 4H), 4.25 – 4.10 (m, 4H), 3.62 (t, $J$ = 8.0 Hz, 1H), 3.18 (d, $J$ = 8.0 Hz, 2H), 2.31 (s, 3H), 1.25-1.15 (m, 6H).

**LCMS (EI, m/z)**: calcd for C$_{15}$H$_{21}$O$_4$ [M+H]: 265.14 Found: 265.3

Synthesis of 2-(4-nitro-benzyl)-malonic acid diethyl ester (3be):

To the suspension of AOT (200 mg, 2% w/v) in water (10 mL) was added diethyl malonate (1b) (1 g, 6.25 mmol) followed by potassium carbonate (2.58 g, 18.75 mmol) was added. The reaction mixture was allowed to stir at room temperature for 15 min at room temperature. Then 4-nitrobenzyl bromide (2e) (1.35 g, 6.25 mmol) was added, the reaction mixture was allowed to stir at 60°C for 16 h. Upon completion (TLC control, 10% EtOAc in n-hexane), the reaction mixture was subjected to aqueous work up as mentioned earlier and purified through Combiflash® purification system using 3-5 % ethyl acetate-hexane as an eluent, 2-(4-nitro-benzyl)-malonic acid diethyl ester (3be) (550 mg, 30%) as pale yellow solid.

**Physical appearance**: pale yellow solid

**IR (KBr)**: 2987, 2939, 1735, 1608, 1524, 1347, 1280, 1232, 1180, 1027, 852, 749 cm$^{-1}$
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.20 – 8.10 (m, 2H), 7.45 – 7.35 (m, 2H), 4.25 – 4.15 (m, 4H), 3.66 (t, $J$ = 8.0 Hz, 1H), 3.32 (d, $J$ = 7.6 Hz, 2H), 1.23 (t, $J$ = 7.2 Hz, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 168.30 (C=O×2, ester), 147.00 (C), 145.72 (C), 129.90 (CH×2), 123.77 (CH×2), 61.84 (CH$_2$×2), 53.15 (CH), 34.36 (CH$_2$), 14.05 (CH$_3$×2).

LCMS (EI, m/z): calcld for C$_{14}$H$_{18}$NO$_6$ [M+H]: 296.11 Found: 296.2

**Synthesis of 2-(4-bromo-benzyl)-malonic acid diethyl ester (3bf):**

To the suspension of CTAB (200 mg, 2% w/v) in water (10 mL) was added diethyl malonate (1b) (1 g, 6.25 mmol) followed by potassium carbonate (2.58 g, 18.75 mmol) was added. The reaction mixture was allowed to stir at room temperature for 15 min at room temperature. Then 4-bromobenzyl bromide (2f) (1.56 g, 6.25 mmol) was added, the reaction mixture was allowed to stir at 60°C for 16 h. Upon completion (TLC control, 10% EtOAc in n-hexane), the reaction mixture was subjected to aqueous work up as mentioned earlier and purified through Combiflash® purification system using 4-5% ethyl acetate-hexane afforded, 2-(4 bromo -benzyl)-malonic acid diethyl ester (3bf) (1.20 g, 58%) as pale yellow oil.

**Physical appearance:** pale yellow oil

**IR (KBr):** 2982, 1735, 1489, 1370, 1228, 1034, 1012, 859, 813 cm$^{-1}$

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.45 – 7.35 (m, 2H), 7.15 – 7.05 (m, 2H), 4.25 – 4.10 (m, 4H), 3.60 (t, $J$ = 7.6 Hz, 1H), 3.17 (d, $J$ = 8.0 Hz, 2H), 1.22 (t, $J$ = 7.2 Hz, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 168.98 (C=O×2, ester), 138.01 (C), 128.96 (CH×2), 128.60 (CH×2), 126.83 (CH), 61.56 (CH$_2$×2), 53.97 (CH), 34.80 (CH$_2$), 14.12 (CH$_3$×2).

LCMS (EI, m/z): calcld for C$_{14}$H$_{18}$BrO$_4$ [M+H]: 329.03 Found: 329.3

**Synthesis of 2-(4-methoxy-benzyl)-malonic acid diethyl ester (3bg):**

To the suspension of CTAB (200 mg, 2% w/v) in water (10 mL) was added diethyl malonate (1b) (1 g, 6.25 mmol) followed by potassium carbonate (2.58 g, 18.75 mmol) was added. The reaction mixture was allowed to stir at room temperature for 15 min at room temperature.
Then 4-methoxybenzyl bromide (2g) (0.9 mL, 6.25 mmol) was added, the reaction mixture was allowed to stir at 60°C for 16 h. Upon completion (TLC control, 10% EtOAc in n-hexane), the reaction mixture was subjected to aqueous work up as mentioned earlier and purified through Combiflash® purification system using 3-5% ethyl acetate-hexane as an eluent afforded, 2-(4-methoxy-benzyl)-malonic acid diethyl ester (3bg) (1.08 g, 62%) as colourless oil.

**Physical appearance:** colourless oil

**IR (KBr):** 2984, 1731, 1612, 1515, 1466, 1444, 1370, 1250, 1111, 1034, 859, 824 cm⁻¹

**¹H NMR (400 MHz, CDCl₃):** δ 7.13 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.4 Hz, 2H), 4.25 – 4.10 (m, 4H), 3.78 (s, 3H), 3.60 (t, J = 8.0 Hz, 1H), 3.16 (d, J = 8.0 Hz, 2H), 1.22 (t, J = 7.2 Hz, 6H).

**¹³C NMR (75 MHz, CDCl₃):** δ 168.95 (C=O×2), 136.24 (C), 134.87 (C), 129.20 (CH×2), 128.74 (CH×2), 61.42 (CH₂×2), 54.03 (CH), 34.33 (CH₂), 21.05 (CH₃), 14.05 (CH₃×2).

**LCMS (EI, m/z):** calcd for C₁₅H₂₁O₅ [M +H]: 281.13 Found: 281.3.

**“One-pot” Synthesis of 2-Phenyl-quinoline-3-carboxylic acid ethyl ester:**

To the suspension of CTAB (400 mg, 2% w/v) in water (20 mL) was added 3-Oxo-3-phenyl-propionic acid ethyl ester (1a) (2 g, 0.010 mol) followed by potassium carbonate (4.14 g, 0.03 mol). The reaction mixture was allowed to stir at room temperature for 15 min at room temperature. Then 1-Bromomethyl-2-nitro-benzene (2j) (2.47 g, 0.011 mol) was added, the reaction mixture was allowed to stir at 60°C for 16 h. The progress of the reaction was monitored using LCMS. Upon completion, the reaction mixture was cooled to rt then added Zn dust (980 mg, 0.015 mol) and NH₄Cl (2.4 g, 0.045 mol) and stirred the RM for 16h at 60°C, after completion of reaction, the RM was diluted with EtOAc and Water, filtered through Celite and separated the layers of filtrate, the organic layer was washed with brine and dried (anhyd. Na₂SO₄). Evaporation of solvent followed by purification on Combiflash®
purification system using 2-10% ethyl acetate-hexane as an eluent afforded, 2-Phenyl-
quinoline-3-carboxylic acid ethyl ester (9aj) (1.10 g, 40%) as Yellow viscous oil.

**Physical appearance:** Yellow viscous oil

**$^1$H NMR (400 MHz, CDCl$_3$):** $\delta$ 8.69 (s, 1H), 8.30-8.20 (m, 1H), 7.95 (d, $J = 8.0$ Hz, 1H), 7.84 (dt, $J = 8.0$, 1.2 Hz, 1H), 7.70-7.60 (m, 3H), 7.60-7.40 (m, 3H), 4.20 (q, $J = 7.2$ Hz, 2H), 1.09 (t, $J = 7.2$ Hz, 3H).

**$^{13}$C NMR (100 MHz, CDCl$_3$):** $\delta$ 168.06 (C), 158.22 (C), 148.39 (C), 140.80 (C), 139.21 (CH), 131.66 (CH), 129.58 (CH), 128.68 (CH), 128.32 (CH x 3), 128.28 (CH x 2), 127.34 (CH), 125.95 (C), 125.62 (C), 61.63 (CH$_2$), 13.78 (CH$_3$).

**IR (KBR):** $\nu$ 3060, 3029, 2980, 2928, 2853, 1720, 1620, 1595, 1556, 1487, 1455, 1373, 1267, 1232, 1100, 1036, 803, 771, 699 cm$^{-1}$.

**LCMS (EI, m/z):** calcd for C$_{18}$H$_{16}$NO$_2$ [M+H]: 278.33, Found: 278.10.
Table-2: Screening of Bases for Regioselective N-Alkylation of 2-pyridones

\[
\text{N} \quad \text{O} \quad \text{B} \quad \text{N} \quad \text{O} \\
\text{B} \quad \text{r} \quad \text{N} \quad \text{O} \\
\text{A} \\ \text{T} \\ \text{B} \quad \text{(} \quad \text{1.5} \quad \text{equiv.)} \\
\text{C} \quad \text{T} \quad \text{A} \quad \text{B} \quad \text{(} \quad \text{2} \quad \% \quad \text{w/w in} \text{H}_2\text{O}) \\
\text{50°C, 16 h} \\
\]

After 3 h

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Experimental procedure for N-benzylation of 2-pyridone using CTAB in water:

Synthesis of 1-Benzyl-1H-pyridin-2-one (11a) using K$_2$CO$_3$:

To the suspension of CTAB (100 mg, 2% w/v) in water (5 mL) was added 1H-Pyridin-2-one (10) (500 mg, 5.257 mmol) followed by potassium carbonate (1.08 g, 7.885 mmol). The reaction mixture was allowed to stir at room temperature for 15 min at room temperature. Then benzyl bromide (2a) (0.89 g, 5.257 mmol) was added, the reaction mixture was allowed to stir at 60°C for 16 h. Upon completion (TLC/LCMS control), the reaction mixture was diluted with water (10 mL). The aqueous layer was extracted with ethyl acetate (2 x 10 mL); combined organic layer was washed with brine, dried (anhyd. Na$_2$SO$_4$), concentrated to get the crude. The crude was purified by column using 2-4% ethyl acetate-hexane as an eluent afforded, 1-Benzyl-1H-pyridin-2-one (11a) (800 mg, 82%) as off-white solid.

$^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 7.78 (ddd, $J$ = 6.8, 2, 0.8 Hz, 1H), 7.42 (ddd, $J$ = 9.2, 6.8, 2.4 Hz, 1H), 7.40 - 7.25 (m, 5H), 6.45 – 6.35 (m, 1H), 6.23 (ddd, $J$ = 8, 1.2, 1.2 Hz, 1H), 5.09 (s, 2H).

$^{13}$C NMR (100 MHz, DMSO-d$_6$): 161.40 (C), 140.04 (CH), 139.12 (CH), 137.43 (C), 128.52 (CH x 2), 127.62 (CH x 2), 127.45 (CH), 119.88 (CH) 105.49 (CH), 51.04 (CH$_2$).

IR (KBR): $\nu$ 3110, 3075, 3030, 1655, 1578, 1539, 1433, 1346, 1142, 1081, 770 cm$^{-1}$.

LCMS (EI, $m/z$): calcd for C$_{12}$H$_{12}$NO [M +H]: 186.23, Found: 186.2

Synthesis of 1-(4-Chloro-benzyl)-1H-pyridin-2-one (11b)

To a solution of CTAB (100 mg, 2% w/v) in water (5 mL) was added 1H-Pyridin-2-one (10) (500 mg, 5.257 mmol) followed by potassium carbonate (1.08 g, 7.886 mmol). The reaction mixture was allowed to stir at room temperature for 15 min at room temperature. Then 4-chlorobenzylbromide (2b) (1.18 g, 5.783 mmol) was added, the reaction mixture was allowed to stir at 50°C for 16 h. Upon completion (TLC/LCMS control), the reaction mixture was diluted with water (10 mL). The aqueous layer was extracted with ethyl acetate (2 x 10 mL);
combined organic layer was washed with brine and dried (anhyd. Na₂SO₄). Evaporation of solvent followed by purification on Combiflash® purification system using 2-4% ethyl acetate-hexane as an eluent afforded, 1-(4-Chloro-benzyl)-1H-pyridin-2-one (11b) (875 mg, 76%) as off-white solid.

**1H NMR (400 MHz, DMSO-d₆):** δ 7.80 (ddd, J = 6.8, 2, 0.4, Hz, 1H), 7.50 – 7.35 (m, 3 H), 7.35 – 7.25 (m, 2 H), 6.41 (dd, J = 9.2, 0.4 Hz, 1H), 6.25 (td, J = 6.8, 1.6 Hz, 1H), 5.08 (s, 2 H).

**13C NMR (100 MHz, CDCl₃):** δ 162.66 (C), 139.66 (CH), 137.20 (CH), 135.05 (C), 134.06 (C), 129.59 (CH x 2), 129.14 (CH x 2), 121.51 (CH), 106.48 (CH), 51.54 (CH₂).

**IR (KBR):** ν 3051, 3030, 2974, 1651, 1584, 1534, 1437, 1344, 1156, 1018, 861, 766 cm⁻¹.

**LCMS (EI, m/z):** calcd for C₁₂H₁₁ClNO [M+H]: 220.05 Found: 220.1

**Synthesis of 1-(4-Iodo-benzyl)-1H-pyridin-2-one (11c):**

To a solution of CTAB (100 mg, 2% w/v) in water (5 mL) was added 1H-Pyridin-2-one (10) (500 mg, 5.257 mmol) followed by potassium carbonate (1.08 g, 7.886 mmol). The reaction mixture was allowed to stir at room temperature for 15 min at room temperature. Then 4-iodo benzyl bromide (2c) (1.72 g, 5.7827 mmol) was added, the reaction mixture was allowed to stir at 50°C for 16 h. Upon completion (TLC/LCMS control), the reaction mixture was diluted with water (10 mL). The aqueous layer was extracted with ethyl acetate (2 x 10 mL); combined organic layer was washed with brine and dried (anhyd. Na₂SO₄). Evaporation of solvent followed by purification on Combiflash® purification system using 2-4% ethyl acetate-hexane as an eluent afforded 1-(4-Iodo-benzyl)-1H-pyridin-2-one (11c) (1.40 g, 86%) as off-white solid.

**1H NMR (400 MHz, CDCl₃):** δ 7.66 (dt, J = 8.4, 2.4 Hz, 2H), 7.40-7.30 (m,1H), 7.29-7.20 (m, 1H), 7.05 (dt, J = 6.8, 1.2 Hz, 2H), 6.61 (dq, J = 8.8, 0.8 Hz, 1H), 6.16 (td, J = 6.4, 1.2 Hz, 1H), 5.08 (s, 2 H),
$^{13}$C NMR (100 MHz, CDCl$_3$): δ 162.61 (C), 139.68 (CH), 138.00 (CH x 2), 137.20 (CH), 136.17 (C), 130.05 (CH x 2), 121.42 (CH), 106.49 (CH), 93.73 (C), 51.65 (CH$_2$).

LCMS (EI, m/z): calcd for C12H11INO [M+H]: 312.1 Found: 312.1

Synthesis of 1-(4-methyl-benzyl)-1$H$-pyridin-2-one (11d):
To a solution of CTAB (300 mg, 2% w/v) in water (15 mL) was added 1$H$-Pyridin-2-one (10) (1.5 g, 15.773 mmol) followed by potassium carbonate (3.27 g, 23.66 mmol). The reaction mixture was allowed to stir at room temperature for 15 min at room temperature. Then 4-methyl benzyl bromide (2d) (3.21 g, 17.35 mmol) was added, the reaction mixture was allowed to stir at 50°C for 16 h. The progress of the reaction was monitored using LCMS. Upon completion, the reaction mixture was diluted with water (30 mL). The aqueous layer was extracted with ethyl acetate (3 x 30 mL); combined organic layer was washed with brine and dried (anhyd. Na$_2$SO$_4$). Evaporation of solvent followed by purification on Combiflash® purification system using 2-4% ethyl acetate-hexane as an eluent afforded 1-(4-methyl-benzyl)-1$H$-pyridin-2-one (11d) (2.69 g, 86%) as off-white solid.

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.35-7.20 (m, 2H), 7.20 (dd, $J = 8.0$ Hz, 2H), 7.15 (dd, $J = 8.0$ Hz, 2H), 6.62 (d, $J = 9.2$ Hz, 1H), 6.13 (td, $J = 6.8$, $1.6$ Hz, 1H), 5.11 (s, 2H), 2.33 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 162.74 (C), 139.38 (CH), 137.86 (C), 137.22 (CH), 133.42 (C), 129.61 (CH x 2), 128.30 (CH x 2), 121.20 (CH), 106.22 (CH), 51.66 (CH$_2$), 21.17 (CH$_3$).

IR (KBR): ν 3066, 3028, 2950, 2928, 1951, 1662, 1582, 1541, 1515, 1435, 1351, 1144, 1027, 937, 851, 762 cm$^{-1}$.

LCMS (EI, m/z): calcd for C$_{13}$H$_{14}$NO [M+H]: 200.15 Found: 200.25.

Synthesis of 1-(4-Nitro-benzyl)-1$H$-pyridin-2-one (11e):
To a solution of CTAB (100 mg, 2% w/v) in water (5 mL) was added 1$H$-Pyridin-2-one (10) (500 mg, 5.257 mmol) followed by potassium carbonate (1.08 g, 7.886 mmol). The reaction
mixture was allowed to stir at room temperature for 15 min at room temperature. Then 4-
nitrobenzylbromide (2e) (1.25 g, 5.783 mmol) was added, the reaction mixture was allowed
to stir at 50°C for 16 h. The progress of the reaction was monitored using LCMS. Upon
completion, the reaction mixture was diluted with water (10 mL). The aqueous layer was
extracted with ethyl acetate (2 x 10 mL); combined organic layer was washed with brine and
dried (anhyd. Na₂SO₄). Evaporation of solvent followed by purification on Combiflash®
purification system using 2-4% ethyl acetate-hexane as an eluent afforded 1-(4-Nitro-benzyl)-
1H-pyridin-2-one (11e) (908 mg, 75%) as off-white solid.

¹H NMR (400 MHz, DMSO- d₆): δ 8.25-8.15 (m, 2H), 7.85 (dd, J = 6.8, 1.2 Hz, 1H), 7.55 –
7.40 (m, 3 H), 6.44 (d, J = 9 Hz, 1H), 6.29 (td, J = 6.8, 1.2 Hz, 1H), 5.23 (s, 2 H),

¹³C NMR (100 MHz, DMSO- d₆): δ 161.39 (C), 146.78 (C), 145.12 (C), 140.52 (CH),
139.27 (CH), 128.58 (CH x 2), 123.69 (CH x 2), 119.99 (CH), 105.84 (CH), 50.96 (CH₂).

IR (KBR): ν 3110, 3064, 3084, 2850, 1664, 1586, 1539, 1519, 1433, 1346, 1142, 1098, 945,
842, 807, 770 cm⁻¹.

LCMS (EI, m/z): calcd for C₁₂H₁₁N₂O₃ [M+H]: 231.07 Found: 231.1

Synthesis of 1-(4-bromo-benzyl)-1H-pyridin-2-one (11f):

To a solution of CTAB (300 mg, 2% w/v) in water 15 mL) was added 1H-Pyridin-2-one (10)
(1.5 g, 15.77 mmol) followed by potassium carbonate (3.27 g, 23.66 mmol). The reaction
mixture was allowed to stir at room temperature for 15 min at room temperature. Then 4-
bromo benzyl bromide (2f) (4.34 g, 17.35 mmol) was added, the reaction mixture was
allowed to stir at 50°C for 16 h. The progress of the reaction was monitored using LCMS.
Upon completion, the reaction mixture was diluted with water (30 mL). The aqueous layer
was extracted with ethyl acetate (2 x 30 mL); combined organic layer was washed with brine
and dried (anhyd. Na₂SO₄). Evaporation of solvent followed by purification on Combiflash®
purification system using 2-4% ethyl acetate-hexane as an eluent afforded 1-(4-bromo-
benzyl)-1H-pyridin-2-one (11f) (3.55 g, 85%) as off-white solid.

^1H NMR (400 MHz, CDCl$_3$): δ 7.50-7.45 (m, 2H), 7.40-7.30 (m, 1H), 7.30-7.25 (m, 1H),
7.25-7.15 (m, 2H), 6.66 (d, J = 9.2 Hz, 1H), 6.19 (dt, J = 6.4, 1.2 Hz, 1H), 5.10 (s, 2 H)

^13C NMR (100 MHz, CDCl$_3$): δ 162.68 (C), 139.80 (CH), 137.22 (CH), 135.48 (C), 132.13
(CH x 2), 129.92 (CH x 2), 122.22 (C), 121.46 (CH), 106.71 (CH), 51.68 (CH$_2$).

LCMS (EI, m/z): calcd for C$_{12}$H$_{11}$BrNO [M+2]: 266.0 Found: 266.0

Synthesis of 1-(2-Nitro-benzyl)-1H-pyridin-2-one (11j):

To a solution of CTAB (200 mg, 2% w/v) in water (10 mL) was added 1H-Pyridin-2-one (10)
(1 g, 10.52 mmol) followed by potassium carbonate (2.18 g, 15.77 mmol). The reaction
mixture was allowed to stir at room temperature for 15 min at room temperature. Then 1-
Bromomethyl-2-nitro-benzene (2j) (2.5 g, 11.57 mmol) was added, the reaction mixture was
allowed to stir at 50°C for 16 h. Upon completion (LCMS/TLC control), the reaction mixture
was diluted with water (20 mL). The aqueous layer was extracted with ethyl acetate (2 x 20
mL); combined organic layer was washed with brine and dried (anhyd. Na$_2$SO$_4$). Evaporation
of solvent followed by purification on Recrystallization using 2:8 DCM-Hexane obtained 1-
(2-Nitro-benzyl)-1H-pyridin-2-one (11j) (1.82 g, 75%) as yellow solid.

^1H NMR (400 MHz, CDCl$_3$): δ 8.11 (dd, J = 8, 0.8 Hz, 1H), 7.57 (td, J = 7.6, 1.2 Hz, 1H),
7.52-7.37 (m, 2H), 7.33 (dd, J = 6.8, 1.6 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 6.65 (d, J = 8.8
Hz, 1H), 6.25 (td, J = 6.4, 1.2 Hz, 1H), 5.52 (s, 2 H)

^13C NMR (100 MHz, CDCl$_3$): δ 162.74 (C), 148.10 (C), 140.24 (CH), 138.04 (CH), 134.13
(CH), 132.00 (CH), 129.10 (CH), 128.74 (CH), 125.40 (CH), 121.58 (CH), 106.85 (CH),
50.16 (CH$_2$)

IR (KBR): ν 3080, 3024, 1664, 1589, 1573, 1532, 1446, 1336, 1148, 971, 889, 766 cm$^{-1}$.

LCMS (EI, m/z): calcd for C$_{12}$H$_{11}$N$_2$O$_3$ [M+H]: 231.07 Found: 231.1
Synthesis of 1-(3-Chloro-benzyl)-1H-pyridin-2-one (11k):

To a solution of CTAB (100 mg, 2% w/v) in water (5 mL) was added 1H-Pyridin-2-one (10) (500 mg, 5.257 mmol) followed by potassium carbonate (1.08 g, 7.886 mmol). The reaction mixture was allowed to stir at room temperature for 15 min at room temperature. Then 3-chlorobenzylbromide (2k) (0.76 mL, 5.783 mmol) was added, the reaction mixture was allowed to stir at 50°C for 16 h. The progress of the reaction was monitored using LCMS. Upon completion, the reaction mixture was diluted with water (10 mL). The aqueous layer was extracted with ethyl acetate (2 x 10 mL); combined organic layer was washed with brine and dried (anhyd. Na₂SO₄). Evaporation of solvent followed by purification on Combiflash® purification system using 2-4% ethyl acetate-hexane as an eluent afforded, 1-(3-Chloro-benzyl)-1H-pyridin-2-one (11k) (808 mg, 70%) as off-white solid.

1H NMR (400 MHz, CDCl₃): δ 7.40-7.30 (m, 1H), 7.30 - 7.25 (m, 4H), 7.25 – 7.15 (m, 1H), 6.63 (dd, \(J = 9.2, 0.4\) Hz, 1H), 6.18 (td, \(J = 6.4, 1.2\) Hz, 1H), 5.12 (s, 2H).

13C NMR (100 MHz, CDCl₃): δ 162.62 (C), 139.75 (CH), 138.47 (C), 137.27 (CH), 134.81 (C), 130.25 (CH), 128.31 (CH), 128.11 (CH), 126.26 (CH), 121.50 (CH), 106.57 (CH), 51.57 (CH₂).

IR (KBR): ν 3066, 3023, 2960, 1660, 1584, 1538, 1476, 1433, 1344, 1142, 952, 859 cm⁻¹.

LCMS (EI, m/z): calcd for C₁₂H₁₁ClNO [M+H]: 220.05 Found: 220.1

Synthesis of 1-(3-Nitro-benzyl)-1H-pyridin-2-one (11l)

To a solution of CTAB (100 mg, 2% w/v) in water (5 mL) was added 1H-Pyridin-2-one (10) (500 mg, 5.257 mmol) followed by potassium carbonate (1.08 g, 7.886 mmol). The reaction mixture was allowed to stir at room temperature for 15 min at room temperature. Then 3-nitrobenzylbromide (2l) (1.24 g, 5.783 mmol) was added, the reaction mixture was allowed to stir at 50°C for 16 h. The progress of the reaction was monitored using LCMS. Upon completion, the reaction mixture was diluted with water (10 mL). The aqueous layer was
extracted with ethyl acetate (2 x 10 mL); combined organic layer was washed with brine and
dried (anhyd. Na₂SO₄). Evaporation of solvent followed by purification on Combiflash®
purification system using 2-4% ethyl acetate-hexane as an eluent afforded, 1-(3-Nitro-
benzyl)-1H-pyridin-2-one (11I) (846 mg, 70%) as off-white solid.

**1H NMR (400 MHz, DMSO- d₆):** δ 8.20-8.10 (m, 2H), 7.91 (ddd, J = 6.8, 2, 0.4 Hz, 1H),
7.80 – 7.75 (m, 1H), 7.70 – 7.60 (m, 1H), 7.46 (ddd, J = 9.2, 6.8, 2.4 Hz, 1H), 6.44 (dd, J =
9.2, 0.8 Hz, 1H), 6.29 (td, J = 6.8, 1.2 Hz, 1H), 5.22 (s, 2 H).

**13C NMR (100 MHz, CDCl₃):** δ 162.58 (C), 148.60 (C), 140.08 (CH), 138.58 (C), 137.27
(CH), 134.30 (CH), 130.06 (CH), 123.15 (CH), 122.77 (CH), 121.74 (CH), 106.89 (CH),
51.93 (CH₂).

**IR (KBR):** ν 3077, 3064, 2956, 1660, 1586, 1524, 1478, 1429, 1354, 1142, 911, 870 cm⁻¹.

**LCMS (EI, m/z):** calcd for C₁₂H₁₁N₂O₃ [M+H]: 231.07 Found: 231.1

**HRMS (ESI, m/z):** calcd for C₁₂H₁₀N₂NaO₃ [M+Na]: 253.05 Found: 253.06

**Synthesis of 1-(2,4,6-Trimethyl-benzyl)-1H-pyridin-2-one (11p):**

To a solution of CTAB (200 mg, 2% w/v) in water (10 mL) was added 1H-Pyridin-2-one (10)
(1 g, 10.52 mmol) followed by potassium carbonate (2.18 g, 15.78 mmol). The reaction
mixture was allowed to stir at room temperature for 15 min at room temperature. Then 2-
Bromomethyl-1,3,5-trimethyl-benzene (2p) (2.46 g, 11.57 mmol) was added, the reaction
mixture was allowed to stir at 50°C for 16 h. The progress of the reaction was monitored
using LCMS. Upon completion, the reaction mixture was diluted with water (20 mL). The
aqueous layer was extracted with ethyl acetate (2 x 20 mL); combined organic layer was
washed with brine and dried (anhyd. Na₂SO₄). Evaporation of solvent followed by
purification on Combiflash® purification system using 30-50-% ethyl acetate-hexane as an
eluent of 1-(2,4,6-Trimethyl-benzyl)-1H-pyridin-2-one (11p) (1.5 g, 63%) as off-white solid.
1H NMR (400 MHz, CDCl₃): δ 7.40-7.25 (m, 1H), 6.95 (s, 2H), 6.72 (dd, J = 6.8, 1.6 Hz, 1H), 6.70-6.60 (m, 1H), 6.05 (td, J = 6.8, 1.6 Hz, 1H), 5.12 (s, 2 H), 2.31 (s, 3 H), 2.20 (s,6H)

13C NMR (100 MHz, CDCl₃): δ 163.26 (C), 139.07 (CH), 138.71 (C), 138.63 (CH), 134.48 (C x 2), 129.65 (CH x 2), 127.96 (C), 120.30 (CH), 106.08 (CH), 45.52 (CH₂), 21.11 (CH₃), 19.72 (CH₃ x 2).

IR (KBR): ν 2965, 2918, 1664, 1578, 1533, 1472, 1265, 1157, 1096, 870, 852, 766 cm⁻¹.

LCMS (EI, m/z): calcd for C₁₅H₁₈NO₃ [M+H]: 228.2 Found: 228.2

Synthesis of 1-(2-Oxo-2-phenyl-ethyl)-1H-pyridin-2-one (11q):
To a solution of CTAB (200 mg, 2% w/v) in water (10 mL) was added 1H-Pyridin-2-one (10) (1 g, 10.52 mmol) followed by potassium carbonate (2.18 g, 15.78 mmol). The reaction mixture was allowed to stir at room temperature for 15 min at room temperature. Then phenacyl bromide (2q) (2.3 g, 11.57 mmol) was added, the reaction mixture was allowed to stir at 50°C for 16 h. The progress of the reaction was monitored using LCMS. Upon completion, the reaction mixture was diluted with water (20 mL). The aqueous layer was extracted with ethyl acetate (2 x 20 mL); combined organic layer was washed with brine and dried (anhyd. Na₂SO₄). Evaporation of solvent followed by purification on Combiflash® purification system using 2-4% ethyl acetate-hexane as an eluent afforded 1-(2-Oxo-2-phenyl-ethyl)-1H-pyridin-2-one (11q) (1.61 g, 72%) as off-white solid.

1H NMR (400 MHz, CDCl₃): δ 8.06 (d, J = 8.4 Hz, 2H), 7.72 (t, J = 14.8, 7.2 Hz, 1H), 7.64 (dd, J = 6.8, 1.6 Hz, 1H), 7.60 (t, J = 15.2, 8.0 Hz, 2H), 7.48 (m, 1H), 6.42 (d, J = 8.8 Hz, 1H), 6.27 (td, J = 6.8, 1.2 Hz, 1H), 5.39 (s, 2 H).

13C NMR (100 MHz, CDCl₃): δ 192.37 (C), 162.48 (C), 140.25 (CH), 138.44 (CH), 134.75 (C), 134.15 (CH), 128.98 (CH x 2), 128.25 (CH x 2), 120.87 (CH), 106.20 (CH), 54.37 (CH₂)

IR (KBR): ν 3060, 3028, 2943, 1698, 1664, 1586, 1539, 1448, 1351, 1230, 1178, 997, 887, 781, 758 cm⁻¹.
LCMS (EI, m/z): calcd for C₁₃H₁₂NO₂ [M+H]: 214.1 Found: 214.1

Synthesis of 1- Allyl-1H-pyridin-2-one (11r):

To a solution of CTAB (300 mg, 2% w/v) in water (15 mL) was added 1H-Pyridin-2-one (10) (1.5 g, 15.78 mmol) followed by potassium carbonate (3.27 g, 23.66 mmol). The reaction mixture was allowed to stir at room temperature for 15 min at room temperature. Then 3-Bromo-propene (2r) (4.1 mL, 47.34 mmol) was added, the reaction mixture was allowed to stir at 50°C for 16 h. IPC-LCMS indicated the presence of unreacted pyridone 10 in ~30%. The reaction mixture was diluted with water (30 mL). The aqueous layer was extracted with ethyl acetate (2 x 30 mL); combined organic layer was washed with brine and dried (anhyd. Na₂SO₄). Evaporation of solvent followed by purification on Combiflash® purification system using 2-4% ethyl acetate-hexane as an eluent of 1-allyl-1H-pyridin-2-one (11r) (1.32 g, 62%; 87% yield Based on unreacted 10) as pale yellow liquid.

$^1$H NMR (400 MHz, CDCl₃): δ 7.65-7.55 (m, 1H), 7.45-7.35 (m, 1H), 6.38 (dt, J = 9.2, 0.4 Hz, 1H), 6.22 (td, J = 6.4, 1.2 Hz, 1H), 6.00-5.80 (m, 1H), 5.16 (dd, J = 11.6, 1.6 Hz, 1H), 5.05 (dd, J = 18.8, 1.6 Hz, 1H), 4.49 (dt, J = 5.2, 1.6 Hz, 2H).

$^{13}$C NMR (100 MHz, CDCl₃): δ 162.44 (C), 139.52 (CH), 137.14 (CH), 132.53 (CH), 121.07 (CH), 118.43 (CH₂), 106.15 (CH), 50.99 (CH₂).

LCMS (EI, m/z): calcd for C₈H₁₀NO [M+H]: 136.07 Found: 135.94

Synthesis of 1-Pentyl-1H-pyridin-2-one (11s):

To a solution of CTAB (300 mg, 2% w/v) in water (15 mL) was added 1H-Pyridin-2-one (10) (1.5 g, 15.78 mmol) followed by potassium carbonate (3.27 g, 23.66 mmol). The reaction mixture was allowed to stir at room temperature for 15 min at room temperature. 1-iodo-pentane (2s) (6.20 mL, 47.34 mmol) was added, the reaction mixture was allowed to stir at 50°C for 16 h. The progress of the reaction was monitored using LCMS. Upon completion, the reaction mixture was diluted with water (30 mL). The aqueous layer was extracted with
ethyl acetate (2 x 30 mL); combined organic layer was washed with brine and dried (anhyd. 
Na$_2$SO$_4$). Evaporation of solvent followed by purification on Combiflash® purification 
system using 2-4% ethyl acetate-hexane as an eluent of 1-Pentyl-1H-pyridin-2-one (**11s**) (1.8 
g, 69%) as brown colour liquid.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.35-7.25 (m, 1H), 7.26-7.20 (m, 1H), 6.56 (dd, $J = 9.2, 0.4$ 
Hz, 2H), 6.15 (td, $J = 6.4, 1.2$ Hz, 1H), 3.92 (t, $J = 7.2$ Hz, 1H), 1.80-1.68 (m, 2 H), 1.50-1.30 
(m, 4H), 0.90 (t, $J = 6.8$ Hz, 3 H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 162.71 (C), 139.29 (CH), 137.61 (CH), 121.12 (CH), 
105.93 (CH), 49.91 (CH), 28.82 (CH$_2$), 22.38 (CH$_2$), 13.97 (CH$_3$).

LCMS (EI, m/z): calcd for C$_{10}$H$_{16}$NO [M+H]: 166.12 Found: 166.05.
Fig. 1 $^1$H NMR of 3aa

Fig. 2 $^{13}$C NMR of 3aa
Fig. 3 $^1$H NMR of 3ab

Fig. 4 $^{13}$C NMR of 3ab
Fig. 5 $^1$H NMR of 3ac

Fig. 6 $^{13}$C NMR of 3ac
Fig. 7: $^1$H NMR of 3ad

Fig. 8: $^{13}$C NMR of 3ad
Fig. 9 $^1$H NMR of 3ae

Fig. 10 $^{13}$C NMR of 3ae
Fig. 11 $^1$H NMR of 3af

Fig. 12 $^{13}$C NMR of 3af
Fig. 13 $^1$H NMR of 3ag

Fig. 14 $^{13}$C NMR of 3ag
Fig. 15 $^1$H NMR of 3ah

Fig. 16 $^{13}$C NMR of 3ah
Fig. 17 $^1$H NMR of 3ai

Fig. 18 $^{13}$C NMR of 3ai
Fig. 19 $^1$H NMR of 3ba

Fig. 20 $^{13}$C NMR of 3ba
**Fig. 21** $^1$H NMR of 3bb

**Fig. 22** $^{13}$C NMR of 3bb
Fig. 23 $^1$H NMR of 3bc

Fig. 24 $^{13}$C NMR of 3bc
Fig. 25 $^1$H NMR of 3be

Fig. 26 $^{13}$C NMR of 3be
Fig. 27 $^1$H NMR of 3bf

Fig. 28 $^{13}$C NMR of 3bf
Fig. 29 $^1$H NMR of 3bg

Fig. 30 $^{13}$C NMR of 3bg
Fig. 31: $^1$H NMR of 9aj

Fig. 32: $^{13}$C NMR of 9aj
Fig. 33 $^1$H NMR of 11a

Fig. 34 $^{13}$C NMR of 11a
Fig. 35 $^1H$ NMR of 11b

Fig. 36 $^{13}C$ NMR of 11b
Fig.37 $^1$H NMR of 11c

Fig.38 $^{13}$C NMR of 11c
Fig. 39 $^1$H NMR of 11d

Fig. 40 $^{13}$C NMR of 11d
Fig. 41 $^1$H NMR of 11e

Fig. 42 $^{13}$C NMR of 11e
Fig. 43 COSY Spectra of 11e

Fig. 44 NOESY Spectra of 11e
Fig. 45 $^1$H NMR of 11f

Fig. 46 $^{13}$C NMR of 11f
Fig. 47 $^1$H NMR of 11j

Fig. 48 $^{13}$C NMR of 11j
Fig. 49 $^1$H NMR of 11k

Fig. 50 $^{13}$C NMR of 11k
Fig. 51 $^1$H NMR of 11l

Fig. 52 $^{13}$C NMR of 11l
Fig. 53 $^1$H NMR of 11p

Fig. 54 $^{13}$C NMR of 11p
Fig. 55 $^1$H NMR of 11q

Fig. 56 $^{13}$C NMR of 11q
Fig. 57 $^1$H NMR of 11r

Fig. 58 $^{13}$C NMR of 11r
Fig. 59 $^1$H NMR of 11s

Fig. 60 $^{13}$C NMR of 11s
Application of the methodology for large scale:

**Optimized procedure for the synthesis of 2-(4-nitro-benzyl)-3-oxo-3-phenyl-propionic acid ethyl ester (3ae):**

To the suspension of AOT (2 g, 2% w/v) in water (100 mL) was added ethyl benzoyl acetate (1a) (10.0 g, 52.02 mmol) followed by potassium carbonate (21.5 g, 156.07 mmol) was added. The reaction mixture was allowed to stir at room temperature for 15 min at room temperature. Then 4-nitrobenzyl bromide (2e) (10.2 g, 46.82 mmol) was added, the reaction mixture was allowed to stir at 55°C for 4 h (*IPC-LCMS indicated presence of 15% of unreacted 2e*). The reaction mixture cooled to RT, diluted with ice cold water (150 mL) and the above aqueous layer was decanted. The oily sediment obtained was stirred with 200 mL water at 50°C for 1 h to procure a pale pink precipitate (*15.6 g, 90% purity by LCMS*), which was digested with hexane (50 mL) for 15 min. The residue was then filtered and dried to get 2-(4-nitro-benzyl)-3-oxo-3-phenyl-propionic acid ethyl ester (3ae) as off-white solid (*11.1 g, Yield - 85% based on the unreacted 2e*). **Purity:** 99.03% (by LCMS)

![](image)

**1H NMR Spectrum for 3ae (10 g scale)**
LCMS Spectrum for 3ae (10 g scale)
Optimized procedure for the synthesis of 1-(4-Nitro-benzyl)-1H-pyridin-2-one (11e):

To a solution of CTAB (2 g, 2% w/v) in water (10 mL) was added 1H-Pyridin-2-one (10 g, 105.15 mmol) followed by potassium carbonate (21.807 g, 157.73 mmol). The reaction mixture was allowed to stir at room temperature for 15 min at room temperature. Then 1-bromomethyl-4-nitro-benzene (2e) (24.98 g, 115.67 mmol) was added, the reaction mixture was allowed to stir at 50°C for 16 h. The progress of the reaction was monitored using LCMS. Upon completion, the reaction mixture was slowly brought to rt then filtered, the solid was washed with water (2 x 20 mL) and dried the solid to get 1-(4-nitro-benzyl)-1H-pyridin-2-one (11e) (22 g, 91%) as off-white solid.

Purity by LCMS – 96%

\[ \text{1}^1\text{H NMR Spectrum for 11e (10 g scale)} \]
LCMS Spectrum for 11e (10 g scale)