Electronic Supplementary Information (ESI)

An efficient strategy for the general synthesis of 3-aryl substituted pyrazolo[5,1-c][1,4]benzoxazines and pyrazolo[1,5-a][1,4]benzodiazepin-6(4H)-ones
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1. General Information:

The palladium catalysed and cycloaddition reactions were carried out under argon atmosphere using dry solvents; otherwise all the reactions were run under open atmosphere using commercial grade solvents. Petroleum ether refers to fraction boiling in the range 60-80 °C. DMF was dried over CaH\textsubscript{2}, distilled, and stored over 3Å molecular sieves in sealed container. THF was distilled over sodium and benzophenone. Analytical thin-layer chromatography (TLC) was performed on silica gel G coated aluminium sheets. Visualization of the developed chromatogram was done by UV absorbance. For purification, column chromatography was performed using silica gel (60-120 or 100-200 mesh). \textsuperscript{1}H and \textsuperscript{13}C NMR spectra were recorded using 300 or 600 MHz NMR instrument using tetramethylsilane (TMS) as internal standard. Chemical shifts (\(\delta\)) are given from TMS (\(\delta=0.00\)) in parts per million (ppm) with the residual signals of deuterated solvent used as standards [CDCl\textsubscript{3}: \textsuperscript{1}H NMR \(\delta = 7.26\) ppm (s); \textsuperscript{13}C NMR \(\delta = 77.0\) ppm (t)]. Coupling constants (\(J\)) are expressed in hertz (Hz) and spin multiplicities are given as s (singlet), d (doublet), dd (double doublet), ddd (doublet of double doublet), t (triplet), m (multiplet) and br (broad). All \textsuperscript{13}C NMR spectra were obtained with complete proton decoupling. Mass spectra were performed using ESI-TOF, EI or FAB ionization mode. Infrared spectra were obtained on FT-IR spectrometer in neat condition or as KBr plate. Melting points were uncorrected.

2. X-Ray Crystallographic Informations of Product 3j:

Single crystal of product 3j was obtained through slow evaporation (at room temperature) of a solution of dichloromethane-petroleum ether (1:1; v/v). A single crystal of 3j was attached to a glass fiber with epoxy glue and transferred to a Brüker SHELXL-97 X-ray diffractometer, equipped with a graphite-monochromator. Diffraction data of product 3j was measured with MoK\(\alpha\) radiation (\(\lambda = 0.71073\) Å) at 296(2) K. Computing cell refinement and data reduction were carried out at APEX 2 Brüker Kappa. The structures were solved by direct methods using the SHELXS-97 program.\textsuperscript{1a} Refinements were carried out with a full matrix least squares method against \(R^2\) using SHELXL-97.\textsuperscript{1b} The non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms...
were included in geometric positions and given thermal parameters equivalent to 1.2 times those of the atom to which they were attached. The important crystal data of product 3j are given below.

**Table 1: Important crystal data of product 3j**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Empirical formula</td>
<td>C_{20}H_{17}N_{3}O_{5}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>379.37</td>
</tr>
<tr>
<td>Temperature</td>
<td>296(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Triclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P-1</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 9.3525(4) Å, b = 10.0265(5) Å, c = 10.8420(5) Å</td>
</tr>
<tr>
<td></td>
<td>α = 113.426(2)°, β = 96.914(2)°, γ = 97.590(2)°</td>
</tr>
<tr>
<td>Volume</td>
<td>907.85(7) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.388 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.102 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>396</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.28 x 0.24 x 0.2 mm³</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>2.09 to 25.00°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-8 &lt;= h &lt;= 11, -11 &lt;= k &lt;= 11, -12 &lt;= l &lt;= 12</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>13611</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>3186 [R(int) = 0.0219]</td>
</tr>
<tr>
<td>Completeness to theta = 25.00°</td>
<td>99.8%</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>multi-scan</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.9949 and 0.9819</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>3186 / 0 / 255</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>0.674</td>
</tr>
<tr>
<td>Final R indices [I&gt;2sigma(I)]</td>
<td>R1 = 0.0477, wR2 = 0.1255</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0540, wR2 = 0.1369</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.434 and -0.280 e.Å⁻³</td>
</tr>
</tbody>
</table>

For details please see the corresponding CIF file, attached with the supporting information. The crystal data of Product 3j has already been deposited at Cambridge Crystallographic Data Centre and the CCDC reference no is 838046.
3. Preparation of Starting Materials 7a and 7b:

3.1 Synthesis of 2-(prop-2-ynyloxy)aniline (7a):

\[
\text{NO}_2 \quad \text{OH} \quad \text{Fe/AcOH} \quad \text{rt, 8 h} \quad \text{NH}_2 \quad \text{O} \quad \text{7a}
\]

\[\text{NO}_2 \quad \text{O} \quad \text{o-Nitrophenol} \quad \text{i) K}_2\text{CO}_3, \text{Acetone, rt, 3 h} \quad \text{ii) Propargyl bromide, reflux, 9 h} \]

Synthesis of 2-(prop-2-ynyloxy)aniline (7a) was carried out according to the literature procedure, starting with commercially available o-nitrophenol (Scheme 1).

3.2 Synthesis of 2-amino-N-methyl-N-(prop-2-ynyl) benzamide (7b)\(^3\)

\[
\text{NH}_2 \quad \text{Me} \quad \text{ Nev} \quad \text{N} \quad \text{O} \quad \text{Dioxane} \quad 100^\circ\text{C, 3 h} \quad \text{7b}
\]

\[\text{H} \quad \text{H} \quad \text{Me} \quad \text{isatoic anhydride} \quad \text{190 mg, 2.75 mmol} \quad \text{300 mg, 1.84 mmol} \quad \text{10 mL} \quad \text{3 h} \quad \text{50 mL} \quad \text{5% NaOH} \quad \text{3 × 150 mL} \quad \text{N}_2\text{SO}_4 \quad \text{81% yield} \]

N-Methylpropargylamine (190 mg, 2.75 mmol) was added to a solution of isatoic anhydride (300 mg, 1.84 mmol) in dioxane (10 mL) and the mixture was heated under reflux for 3 h. It was then poured into ice-water (50 mL), adjusted to pH 9 with 5% NaOH and extracted with ethyl acetate (3 × 150 mL). The organic layer was washed with water, dried over Na\(_2\)SO\(_4\), filtered, and evaporated under reduced pressure. The crude product was purified by silica gel (60-120 mesh) column chromatography to furnish the product 7b (81% yield).
4. General procedure for the preparation of 2-(3-arylprop-2-ynyloxy)aniline (8) under Sonogashira reaction conditions:

\[
\begin{align*}
\text{Ar} & \quad \text{Pd(PPh}_3\text{)}_2\text{Cl}_2, \text{CuI} \quad \text{Et}_3\text{N, rt, 2-6 h} \\
7a & \quad + \quad 6 \quad \rightarrow \quad 8
\end{align*}
\]

Scheme 3

Pd(PPh\(_3\))\(_2\)Cl\(_2\) (21 mg, 0.03 mmol) and CuI (9.5 mg, 0.05 mmol) were added to aryl iodide 6 (1.0 mmol) dissolved in dry Et\(_3\)N (5 mL) and the mixture was stirred under argon atmosphere for 20 minutes. Next, 2-(prop-2-ynyloxy)aniline 7a (176 mg, 1.2 mmol) dissolved in dry Et\(_3\)N (1 mL) was added drop wise to the reaction mixture and flushed carefully with argon. The whole reaction mixture was allowed to stir for 2-6 hours (except the product 8l for which 15 h stirring was required) at room temperature. After completion of the reaction (TLC), the solvent was removed \textit{in vacuo} and the residue was poured into 30 mL of water. The aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organic extracts were dried over anhydrous Na\(_2\)SO\(_4\), filtered and concentrated under reduced pressure. The resulting residue was purified through silica gel (100-200 mesh) column chromatography using 3-25\% EtOAc in petroleum ether (v/v) as eluent.

4.1 Selected spectral data of alkynes 8 (8a-e, 8h-l):

2-(3-Phenylprop-2-ynyloxy)aniline\(^2\) (8a): Yield: 89\%; oil; IR (liquid film): 3462, 3375, 2237, 1613 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 3.84 (br s, 2H), 4.93 (s, 2H), 6.71-6.87 (m, 3H), 6.94-7.00 (m, 1H), 7.25-7.45 (m, 5H); \(^13\)C NMR (CDCl\(_3\), 150 MHz): \(\delta\) 57.2, 84.2, 87.0, 112.7, 115.4, 118.3, 122.1, 122.3, 128.2, 128.6, 131.7, 136.7, 145.5; ESI-MS: m/z 246.13 [M+Na]\(^+\).
2-[3-(Naphthalene-1-yl)prop-2-ynyloxy]aniline (8b): Yield: 81%; oil; IR (liquid film): 3462, 3376, 2227, 1611 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 3.87 (br s, 2H), 5.09 (s, 2H), 6.78-6.89 (m, 3H), 7.09 (d, $J = 7.5$ Hz, 1H), 7.41 (t, $J = 7.7$ Hz, 1H), 7.49-7.52 (m, 2H), 7.67 (d, $J = 6.9$ Hz, 1H), 7.83 (d, $J = 7.8$ Hz, 2H), 8.21 (d, $J = 6.9$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 57.4, 85.2, 88.9, 113.0, 115.5, 118.4, 119.9, 122.2, 125.0, 126.0, 126.4, 126.8, 128.2, 129.1, 130.7, 133.0, 133.2, 136.8, 145.4; ESI-MS: m/z 296.13 [M+Na]$^+$; Anal. Calcd. for C$_{19}$H$_{15}$NO: C, 83.49; H, 5.53; N, 5.12. Found: C, 83.45; H, 5.51; N, 5.17.

2-[3-(Pyridine-3-yl)prop-2-ynyloxy]aniline (8c): Yield: 92%; oil; IR (liquid film): 3453, 3362, 1616 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 3.85 (br s, 2H), 4.95 (s, 2H), 6.72-6.77 (m, 2H), 6.83-6.88 (m, 1H), 6.97 (d, $J = 7.5$ Hz, 1H), 7.23-7.26 (m, 1H), 7.72 (d, $J = 7.8$ Hz, 1H), 8.67 (s, 1H); $^{13}$C NMR (CDCl$_3$, 150 MHz): $\delta$ 56.9, 83.7, 87.6, 112.6, 115.5, 118.3, 119.4, 122.2, 122.9, 136.7, 138.7, 145.3, 148.9, 152.3; ESI-MS: m/z 247.13 [M+Na]$^+$; Anal. Calcd. for C$_{14}$H$_{12}$N$_2$O: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.93; H, 5.44; N, 12.56.

2-[3-(2-Thienyl)prop-2-ynyloxy]aniline (8d): Yield: 83%; oil; IR (liquid film): 3377, 2224, 1606 cm$^{-1}$; $^1$H NMR CDCl$_3$, 300 MHz): $\delta$ 3.84 (br s, 2H), 4.93 (s, 2H), 6.69-6.76 (m, 2H), 6.84 (t, $J = 7.4$ Hz, 1H), 6.94-6.98 (m, 2H), 7.22-7.27 (m, 2H); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 57.2, 80.3, 88.1, 112.7, 115.4, 118.3, 122.08, 122.1, 126.9, 127.6, 132.7, 136.7, 145.4; ESI-MS: m/z 252.09 [M+Na]$^+$; Anal. Calcd. for C$_{13}$H$_{11}$NOS: C, 68.09; H, 4.84; N, 6.11. Found: C, 68.13.; H, 4.87; N, 6.08.
2-[3-(4-Methylphenyl)prop-2-ynyloxy]aniline² (8e): Yield: 69%; oil; IR (liquid film): 3482, 3384, 2230, 1609 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 2.34 (s, 3H), 3.84 (br s, 2H), 4.92 (s, 2H), 6.71-6.76 (m, 2H), 6.81-6.86 (m, 1H), 6.98 (d, J = 7.5 Hz, 1H), 7.11 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 7.8 Hz, 2H); ¹³C NMR (CDCl₃, 75 MHz): δ 21.4, 57.3, 83.5, 87.2, 112.8, 115.4, 118.3, 119.2, 122.0, 129.0, 131.6, 136.7, 138.8, 145.6; ESI-MS: m/z 260.13 [M+Na]⁺.

2-[3-(4-Methoxyphenyl)prop-2-ynyloxy]aniline² (8h): Yield: 70%; oil; IR (liquid film): 3480, 3375, 2224, 1606 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 3.80 (s, 3H), 3.84 (br s, 2H), 4.91 (s, 2H), 6.71-6.75 (m, 2H), 6.81-6.86 (m, 3H), 6.97-6.99 (m, 1H), 7.38 (d, J = 8.7 Hz, 2H); ¹³C NMR (CDCl₃, 75 MHz): δ 55.2, 57.3, 82.8, 86.9, 112.7, 113.8, 114.3, 115.3, 118.2, 121.9, 133.2, 136.7, 145.5, 159.8; ESI-MS: m/z 276.12 [M+Na]⁺.

2-[3-(2,4-Dimethoxy-5-pyrimidinyl)prop-2-ynyloxy]aniline² (8i): Yield: 84%; sticky oil; IR (liquid film): 3417, 3305, 2233, 1599 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 3.82 (br s, 2H), 3.98 (s, 3H), 4.01 (s, 3H), 4.93 (s, 2H), 6.68-6.73 (m, 2H), 6.79-6.84 (m, 1H), 6.96 (d, J = 7.8 Hz, 1H), 8.29 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz): δ 54.4, 55.1, 57.2, 78.6, 90.5, 99.1, 112.8, 115.4, 118.2, 122.1, 136.6, 145.3, 161.7, 164.2, 170.6; ESI-MS: m/z 308.13 [M+Na]⁺.
2-[3-(2-Methyl-4-nitrophenyl)prop-2-ynyloxy]aniline (8j): Yield: 96%; sticky oil; IR (liquid film): 3468, 3380, 2250, 1612, 1511, 1344 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz):  δ 2.46 (s, 3H), 3.84 (br s, 2H), 5.01 (s, 2H), 6.71-6.77 (m, 2H), 6.84-6.89 (m, 1H), 6.98 (d, J = 7.8 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.97-8.06 (m, 2H); ¹³C NMR (CDCl₃, 150 MHz):  δ 20.7, 56.9, 84.3, 93.1, 112.8, 115.6, 118.3, 120.7, 122.4, 124.2, 128.9, 132.7, 136.7, 142.1, 145.2, 147.1; ESI-MS: m/z 305.11 [M+Na]⁺; Anal. Calcd. for C₁₆H₁₄N₂O₃: C, 68.07; H, 5.00; N, 9.92. Found: C, 68.12; H, 5.04; N, 9.86.

2-[3-(4-Carbomethoxyphenyl)prop-2-ynyloxy]aniline (8k): Yield: 89%; gummy solid, IR (KBr): 3479, 3376, 1716, 1608 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz):  δ 3.85 (br s, 2H), 3.91 (s, 3H), 4.95 (s, 2H), 6.72-6.77 (m, 2H), 6.83-6.88 (m, 1H), 6.98 (d, J = 7.5 Hz, 1H), 7.49 (d, J = 7.8 Hz, 2H), 7.98 (d, J = 8.1 Hz, 2H); ¹³C NMR (CDCl₃, 75 MHz):  δ 52.2, 56.9, 86.2, 87.1, 112.6, 115.4, 118.3, 122.2, 126.8, 129.4, 129.8, 131.6, 136.6, 145.3, 166.3; ESI-MS: m/z 304.14 [M+Na]⁺; Anal. Calcd. for C₁₇H₁₅NO₃: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.53; H, 5.42; N, 4.92.

1,2-Bis[(3´-phenyl-2´-ynyloxy)-2´-amino-phenyl]benzene² (8l): Yield 51%, oil, IR(liquid film): 3459, 3371, 1612 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz):  δ 3.83 (br s, 4H), 4.84 (s, 4H), 6.73 (t, J = 6.9 Hz, 4H), 6.79-6.85 (m, 2H), 6.99 (d, J = 7.8 Hz, 2H), 7.24-7.27 (m, 2H), 7.40-7.43 (m, 2H); ¹³C NMR (CDCl₃, 150 MHz):  δ 57.0, 85.3, 88.3, 112.7, 115.4, 118.3, 121.9, 124.9, 128.3, 131.9, 136.6, 145.5; ESI-MS: m/z 391.15 [M+Na]⁺.
5. General procedure for the preparation of 2-amino-N-methyl-N-(3-aryl-prop-2-ynyl)benzamides (9) under Sonogashira reaction conditions:\(^4\):

![Scheme-4](image)

To a well stirred solution of aryl iodide 6 (1.45 mmol) and Et$_3$N (10.15 mmol) in DMF (3 mL), PdCl$_2$(PPh$_3$)$_2$ (41 mg, 0.058 mmol) was added. The whole reaction mixture was allowed to stir at room temperature for 10 min under argon atmosphere. Next, CuI (16 mg, 0.087 mmol) was added followed by drop wise addition of a solution of amine 7b (286 mg, 1.52 mmol) in DMF (1.0 mL). The resulting reaction mixture was allowed to stir at room temperature for 2 h. The reaction was monitored through TLC to ensure complete consumption of the starting materials. It was then extracted with ethyl acetate (3 × 50 mL). The combined ethyl acetate extracts were washed successively with brine (30 mL) and water (30 mL), dried over Na$_2$SO$_4$, and filtered. The solvent was evaporated under reduced pressure and the resulting residue was purified by column chromatography over silica gel (100-200 mesh) using 20-30% ethyl acetate in hexane (v/v) to afford the product 9.

The spectral data of products 9a-f has been reported\(^5\) earlier.

5.1 Spectral Data of alkynes 9:

2-Amino-N-methyl-N-[3-[(2,4-dimethoxy)pyrimidine-5-yl]prop-2-ynyl]benzamide

(9g): Yield 74%; Oil; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.17 (s, 3H), 4.01 (s, 3H), 4.05 (s, 3H), 4.42 (br s, 2H), 4.48 (br s, 2H), 6.71-6.76 (m, 2H), 7.16-7.22 (m, 2H), 8.33 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 34.6 (br), 39.9 (br), 54.2, 54.8, 75.6, 90.1, 99.0, 116.3, 116.8, 118.6, 127.7, 130.5, 145.6, 161.2, 163.8, 170.4, 170.6; IR (neat, cm$^{-1}$) 3460, 3355, 2999, 2956, 1622, 1593, 1550, 1471, 1398, 1323, 1238, 1074; MS (EI) (m/z) 326, 206, 120. Anal. Calcd. for C$_{17}$H$_{18}$N$_4$O$_3$: C, 62.57; H, 5.56; N, 17.17. Found: C, 62.51; H, 5.60; N, 17.12.

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2-Amino-N-methyl-N-[3-(4-nitro-2-methylphenyl)prop-2-ynyl]benzamide (9h):
Yield 80%; Solid, mp 86-88 °C; 1H NMR (300 MHz, CDCl3) δ 2.54 (s, 3H), 3.20 (s, 3H), 4.43 (s, 2H), 4.53 (s, 2H), 6.71-6.76 (m, 2H), 7.17-7.23 (m, 2H), 7.54 (d, J = 8.7 Hz, 1H), 8.01 (dd, J = 8.4, 1.8 Hz, 1H), 8.09 (s, 1H); 13C NMR (75 MHz, CDCl3) δ 20.5, 35.0 (br), 39.5 (br), 81.2, 93.1, 116.5, 116.9, 118.4, 120.4, 123.9, 127.7, 128.9, 130.8, 132.4, 141.7, 145.7, 146.7, 170.8; IR (KBr, cm⁻¹) 3433, 3347, 3232, 3078, 2923, 1611, 1509, 1339, 1282, 1078; MS (EI) (m/z) 323, 203, 120.

6. Screening Studies about the optimisation of reaction conditions for the synthesis of product 3a (condition A):

Initially, we carried out diazotisation (NaNO₂/HCl) followed by Japp-Klingemann reaction (ethyl 2-chloroacetoacetate and sodium acetate) on 2-(3-phenylprop-2-ynyloxy)aniline 8a in one pot and isolated the crude product 10a by usual work-up. This crude (without chromatographic purification) intermediate 10a was used directly for optimisation studies of the cycloaddition reactions (Table 2) varying with different solvents and bases. All the reactions were carried out at reflux temperature of the solvent employed. Our investigation started with earlier reported reaction conditions using Et₃N (10.0 equiv.) in toluene which led to the formation of product 3a in 46% yield after prolonged (18 h) heating as shown in entry 1 of Table 2. The observation with such sluggish reaction prompted us to screen different bases and high boiling solvents in order to attain the appropriate reaction conditions. Thus, replacement of the solvent from toluene to xylene gave an encouraging result wherein a dropping of the reaction time from 18 h to 6 h with slightly higher yield (49%) was observed (Table 2, entry 2).
Table 2: Optimisation of the reaction conditions (condition A) for the cycloaddition of crude intermediate 10a

- **Reaction conditions:** Crude hydrazonoyl chloride 10a (205 mg derived from 0.5 mmol of 8a) and base (2.0-10.0 equiv.) in dry solvent (6 mL) was heated under reflux until the complete consumption of the starting materials (TLC).
- **Base (equiv.)** was employed with respect to starting amine 8a.
- Chromatographically isolated pure products and yields were calculated based on the amine 8a.
- Tetrabutylammonium bromide (0.1 equiv.) was used as phase transfer catalyst.
- No phase transfer catalyst (tetrabutylammonium bromide) was used.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Amount of base (equiv.)</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield(%) of 3a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et3N</td>
<td>10.0</td>
<td>Toluene</td>
<td>18.0</td>
<td>46</td>
</tr>
<tr>
<td>2</td>
<td>Et3N</td>
<td>5.0</td>
<td>Xylene</td>
<td>6.0</td>
<td>49</td>
</tr>
<tr>
<td>3</td>
<td>2,6-Lutidine</td>
<td>2.0</td>
<td>Xylene</td>
<td>5.0</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>DMAP</td>
<td>2.5</td>
<td>Xylene</td>
<td>1.0</td>
<td>26</td>
</tr>
<tr>
<td>5d</td>
<td>K2CO3</td>
<td>4.0</td>
<td>Xylene</td>
<td>3.0</td>
<td>44</td>
</tr>
<tr>
<td>6d</td>
<td>Cs2CO3</td>
<td>4.0</td>
<td>Xylene</td>
<td>1.5</td>
<td>33</td>
</tr>
<tr>
<td>7d</td>
<td>NaOAc</td>
<td>4.0</td>
<td>Xylene</td>
<td>2.0</td>
<td>52</td>
</tr>
<tr>
<td>8e</td>
<td>NaOAc</td>
<td>4.0</td>
<td>Xylene</td>
<td>8.0</td>
<td>51</td>
</tr>
<tr>
<td>9d</td>
<td>NaOAc</td>
<td>4.0</td>
<td>Chlorobenzene</td>
<td>0.5</td>
<td>53</td>
</tr>
<tr>
<td>10</td>
<td>DBU</td>
<td>2.0</td>
<td>Xylene</td>
<td>3.0</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

*Reactions with no phase transfer catalyst (tetrabutylammonium bromide) were performed.*
Next, we used 2, 6-lutidine as base and to our surprise, it did not yield any desired product 3a; starting materials were only recovered in this case. We then examined a variety of bases (DMAP, K$_2$CO$_3$, Cs$_2$CO$_3$, NaOAC etc.) in refluxing xylene (Table 2, entries 4-8). Pleasingly, reaction was found to be complete within two hours (52% yield) by the employment of NaOAC and catalytic amount of n-tetrabutylammonium bromide (TBAB) as shown in entry 7 of Table 2. Interestingly, omission of TBAB made the cycloaddition slower moving (Table 2, entry 8). Gratifyingly, replacement of xylene by chlorobenzene led to completion of the cycloaddition within 30 min only (Table 2, entry 9). Further, change of bases like DBU resulted in a tarry mixture with no sign of the product formation. Thus, reaction conditions of entry 9 of Table 2 appeared to be the optimum and therefore, we decided to employ chlorobenzene and NaOAc as solvent and base (condition A) in the following cycloaddition reactions of crude intermediate 10.

7. General procedure (condition A) for the synthesis of 2-carbethoxy-4$H$-pyrazolo[5,1-c][1,4]benzoxazines 3:

![Chemical Structure](image)

To an ice-cooled (0-5°C) solution of 8 (0.85 mmol) in MeOH (1.5 mL), 6 M hydrochloric acid (0.5 mL) and NaNO$_2$ (117 mg, 1.70 mmol) were added successively and the reaction mixture was allowed to stir at this temperature for one hour. The acidity of the medium was then adjusted to pH 5 by careful addition of sodium acetate. Next, a solution of ethyl 2-chloroacetoacetate (0.12 mL, 0.85 mmol) in MeOH (1 mL) was added drop wise and the reaction mixture was allowed to stir vigorously at room temperature. After completion (4 h) of the reaction the solvent was removed under reduced pressure and the residue was extracted with EtOAc (2×15 mL). The organic extracts were washed with saturated aqueous NaHCO$_3$ solution (15 mL) followed by water (15 mL), dried over anhydrous
Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude intermediate 10 was then used directly. Thus, a solution of the product 10 in chlorobenzene (4 mL) was refluxed in the presence of NaOAc (278 mg, 3.39 mmol) and n-Bu₄NBr (27 mg, 0.085 mmol) until complete consumption of the starting material (TLC). After removal of the solvent, it was extracted with ethyl acetate (3 x 20 mL) and the combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Finally, the crude residue was purified by silica gel (100-200 mesh) column chromatography using 4-30% EtOAc in petroleum ether (v/v) as eluent.

7.1 Spectral Data of 3-aryl substituted 2-carbethoxy-4H-pyrazolo-[5,1-c][1,4]benzoxazines 3:

2-Carbethoxy-3-(pyridine-3-yl)-4H-pyrazolo[5,1-c][1,4]benzoxazine (3c): Yield: 45%; solid, m.p.: 170-172 °C; IR (KBr): 2981, 1715, 1604, 1479, 1365, 1233, 1162, 861 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 1.30 (t, J = 7.2 Hz, 3H), 4.36 (q, J = 7.1 Hz, 2H), 5.25 (s, 2H), 7.08-7.17 (m, 2H), 7.21-7.27 (m, 1H), 7.36-7.40 (m, 1H), 7.76-7.79 (m, 1H), 8.05 (dd, J = 1.4, 7.7 Hz, 1H), 8.53 (s, 1H), 8.61-8.63 (m, 1H); ¹³C NMR (CDCl₃, 75 MHz): δ 14.0, 61.3, 61.8, 116.7, 117.6, 117.9, 122.91, 122.97, 125.7, 126.6, 127.9, 132.6, 137.4, 141.8, 146.4, 148.9, 149.9, 161.8; ESI-MS: m/z 344.15 [M+Na]⁺; HRMS (EI, 70 eV) calcd for C₁₈H₁₃N₃O₃ [M⁺] 321.1113, found 321.1103.
2-Carbethoxy-3-(2-thienyl)-4H-pyrazolo[5,1-c][1,4]benzoxazine (3d): Yield: 46%; solid, m.p.: 119-122 °C; IR (KBr): 2985, 1721, 1506, 1364, 1235, 1179, 862 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 1.37 (t, J = 7.1 Hz, 3H), 4.41 (q, J = 7.1 Hz, 2H), 5.34 (s, 2H), 7.06-7.26 (m, 5H), 7.39 (d, J = 4.8 Hz, 1H), 8.02 (d, J = 7.8 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz): δ 14.1, 61.2, 62.1, 114.3, 116.5, 117.4, 122.7, 125.6, 126.2, 127.0, 127.8, 128.4, 130.3, 132.5, 141.7, 146.3, 161.8; ESI-MS: m/z 349.07 [M+Na]+; Anal. Calcd. for C₁₇H₁₄N₂O₃S: C, 62.56; H, 4.32; N, 8.58. Found: C, 62.52; H, 4.37; N, 8.64.

2-Carbethoxy-3-(4-methylphenyl)-4H-pyrazolo[5,1-c][1,4]benzoxazine (3e): Yield: 43%; solid, m.p.: 105-108 °C; IR (KBr): 2976, 1720, 1601, 1497, 1360, 1215, 1152, 820 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 1.32 (t, J = 7.2 Hz, 3H), 2.40 (s, 3H), 4.36 (q, J = 7.1 Hz, 2H), 5.23 (s, 2H), 7.05-7.15 (m, 2H), 7.18-7.23 (m, 5H), 8.04 (dd, J = 1.1, 7.9 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz): δ 14.1, 21.2, 60.9, 62.0, 116.5, 117.4, 121.6, 122.7, 125.9, 127.1, 127.5, 128.8, 129.5, 131.9, 137.5, 141.6, 146.4, 162.1; ESI-MS: m/z 357.10 [M+Na]+; Anal. Calcd. for C₂₀H₁₈N₂O₃: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.90; H, 5.37; N, 8.32.

2-Carbethoxy-3-(4-trifluoromethylphenyl)-4H-pyrazolo[5,1-c][1,4]benzoxazine (3f): Yield: 51%; solid, m.p.: 133-135 °C; IR (KBr): 2990, 1716, 1618, 1502, 1447, 1391, 1324, 1229, 864 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 1.31 (t, J = 7.2 Hz, 3H), 4.36 (q, J = 7.2 Hz, 2H), 5.23 (s, 2H), 7.09 (td, J = 1.3, 7.4 Hz, 1H), 7.16 (dd, J = 1.5, 7.8 Hz, 1H), 7.22 (dd, J = 1.5, 7.8 Hz, 1H), 7.47 (d, J = 7.8 Hz, 2H), 7.69 (d, J = 8.1 Hz, 2H), 8.05 (dd, J = 1.4, 7.9 Hz, 1H); ¹³C NMR (CDCl₃, 150 MHz): δ 14.1, 61.4, 61.9, 116.8, 117.6, 120.4, 123.1, 124.1 (q, J = 270.4 Hz), 125.1 (q, J = 3.75 Hz), 125.8, 128.0, 129.9 (q, J = 32.3 Hz), 130.2, 132.5, 134.2, 141.7, 146.5, 161.9; ESI-MS: m/z 411.18 [M+Na]+; HRMS (EI, 70 eV) calcd for C₂₀H₁₅F₃N₂O₃ [M⁺]: 388.1035; found 388.1017.

S-15
2-Carbethoxy-3-(4-methoxyphenyl)-4H-pyrazolo[5,1-c][1,4]benzoxazine (3h): Yield: 47 %; solid, m.p.: 134-136 °C; IR (KBr): 2976, 1717, 1606, 1493, 1383, 1250, 1172, 858 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 1.32 (t, J = 7.1 Hz, 3H), 3.85 (s, 3H), 4.36 (q, J = 7.1 Hz, 2H), 5.23 (s, 2H), 6.96 (d, J = 8.7 Hz, 2H), 7.08 (td, J = 1.2, 7.1 Hz, 1H), 7.12-7.15 (m, 1H), 7.19 (dd, J = 1.4, 7.7 Hz, 1H), 7.23-7.28 (m, 2H), 8.04 (dd, J = 1.4, 7.7 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz), δ 14.1, 55.2, 61.0, 62.1, 113.5, 116.6, 117.5, 121.4, 122.4, 122.8, 125.9, 127.6, 130.9, 131.9, 141.6, 146.4, 159.1, 162.1; ESI-MS: m/z 373.05 [M+Na]⁺; HRMS (EI, 70 eV) calcd for C₂₀H₁₈N₂O₄ [M⁺] 350.1267, found 350.1283.

2-Carbethoxy-3-(2,4-dimethoxy-5-pyrimidinyl)-4H-pyrazolo[5,1-c][1,4]benzoxazine (3i): Yield: 44%; solid, m.p.: 200-202 °C; IR (KBr): 2990, 1713, 1565, 1467, 1378, 1228, 1181, 861 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 1.31 (t, J = 7.1 Hz, 3H), 3.97 (s, 3H), 4.05 (s, 3H), 4.35 (q, J = 7.1 Hz, 2H), 5.15 (s, 2H), 7.08 (td, J = 1.2, 7.1 Hz, 1H), 7.14 (dd, J = 1.1, 7.9 Hz, 1H), 7.22 (td, J = 1.4, 7.7 Hz, 1H), 8.03 (dd, J = 1.5, 7.8 Hz, 1H), 8.25 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz): δ 14.2, 54.1, 54.9, 61.2, 62.4, 105.3, 111.9, 116.7, 117.5, 122.9, 125.9, 127.9, 133.2, 142.5, 146.3, 159.2, 161.9, 165.1, 168.2; ESI-MS: m/z 405.14 [M+Na]⁺; HRMS (EI, 70 eV) calcd for C₁₉H₁₈N₄O₅ [M⁺] 382.1277, found 382.1269.
1,2-Bis[2’-carbethoxy-3’-phenyl-4’H-pyrazolo[5’,1’-c][1,4]benzoxazinyl]benzene \( (3l) \):
Yield: 36%; solid, m.p.: 186-188 °C; IR (KBr): 2991, 1720, 1604, 1490, 1380, 1226, 1160, 1021, 864 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz): \( \delta \) 1.23 (t, \( J = 7.1 \) Hz, 6H), 4.29 (q, \( J = 6.9 \) Hz, 4H), 4.83 (d, \( J = 14.1 \) Hz, 2H), 5.06 (d, \( J = 14.1 \) Hz, 2H), 6.99-7.08 (m, 4H), 7.16 (t, \( J = 7.4 \) Hz, 2H), 7.31-7.34 (m, 2H), 7.44-7.47 (m, 2H), 7.91 (d, \( J = 7.2 \) Hz, 2H); \(^{13}\)C NMR (CDCl\(_3\), 150 MHz): \( \delta \) 13.9, 61.1, 62.0, 116.6, 117.5, 120.3, 122.7, 125.8, 127.8, 128.1, 130.7, 130.8, 133.1, 141.7, 146.5, 161.9; ESI-MS: \( m/z \) 585.27 [M+Na]\(^+\); Anal. Calcd. for C\(_{32}\)H\(_{26}\)N\(_4\)O\(_6\): C, 68.32; H, 4.66; N, 9.96. Found: C, 68.37; H, 4.63; N, 9.99.

8. General procedure (condition B) for the synthesis of 2-carbethoxy-5-methyl-3-aryl-pyrazolo[1,5-a][1,4]benzodiazepin-6(4\( H \))-ones \( 4 \):

To a well stirred and cooled (0-3 °C) solution of \( 9 \) (0.50 mmol) in 2 M hydrochloric acid (8.0 mL) was added a solution of NaNO\(_2\) (48 mg, 0.70 mmol) in 2 mL H\(_2\)O drop wise during 45 min and the reaction mixture was allowed to stir for another 30 min at the same temperature. Ethyl 2-chloroacetoacetate (90 mg, 0.55 mmol) was added drop wise during 2-3 min at 0-3 °C. The temperature of the reaction mixture was then allowed to attain room temperature (rt) and stirred for another 5 h. It was then extracted with ethyl acetate (2 \( \times \) 20 mL). The organic extracts were washed with water, dried over Na\(_2\)SO\(_4\), filtered and concentrated in vacuo. The resulting crude product was refluxed (138-140 °C) in xylene (5.0 mL) in the presence of triethylamine (0.42 mL, 3.0 mmol) for few hours. Upon completion of the reaction (TLC), the solvent was removed in vacuo and extracted...
with ethyl acetate (2 × 20 mL). The combined organic extracts were washed with water (20 mL), dried over Na₂SO₄, filtered and concentrated. The resulting crude product was purified through silica gel (100-200 mesh) column chromatography (40-50% ethyl acetate in hexane, v/v) to furnish the desired product 4.

8.1 Spectral data of the products 4:

2-Carbethoxy-5-methyl-3-(2-methylphenyl)-pyrazolo[1,5-α][1,4]benzodiazepin-6(4H)-one (4c): Yield 45%; Solid, mp 180-182 °C; ¹H NMR (300 MHz, CDCl₃) δ 1.17 (t, J = 7.05 Hz, 3H), 2.15 (s, 3H), 3.10 (s, 3H), 4.12-4.32 (m, 4H), 7.14 (d, J = 7.2 Hz, 1H), 7.24-7.37 (m, 3H), 7.50 (t, J = 7.65 Hz, 1H), 7.67 (t, J = 7.8 Hz, 1H), 8.04 (t, J = 8.1 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 13.7, 20.1, 35.6, 42.1, 60.8, 121.9, 122.8, 125.4, 127.4, 127.9, 128.3, 129.7, 130.0, 130.3, 131.6, 132.3, 135.3, 137.6, 139.5, 142.4, 161.6, 166.6; IR (KBr, cm⁻¹) 2982, 2931, 1723, 1643, 1479, 1346, 1274, 1171; MS (ESI) (m/z) 398.13 (M+Na⁺).


2-Carbethoxy-5-methyl-3-(4-fluorophenyl)-pyrazolo[1,5-α][1,4]benzodiazepin-6(4H)-one (4e): Yield 40%; Solid, mp 76-78 °C; ¹H NMR (300 MHz, CDCl₃) δ 1.27 (t, J = 7.2 Hz, 3H), 3.14 (s, 3H), 4.24 (s, 2H), 4.32 (q, J = 7.1 Hz, 2H), 7.17 (t, J = 8.55 Hz, 2H), 7.31-7.44 (m, 2H), 7.51 (t, J = 7.5 Hz, 1H), 7.69 (td, J = 7.8 Hz, 1H), 8.02 (t, J = 8.1 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 13.9, 35.6, 42.2, 61.0, 115.2 (d, J = 21.75 Hz), 121.8, 122.8, 126.5 (d, J = 6.0 Hz), 127.4, 128.0, 131.6, 131.7 (d, J = 8.25 Hz), 132.4, 135.2, 139.6, 142.2, 161.7, 162.4 (d, J = 246 Hz), 166.5; IR (KBr, cm⁻¹) 2983, 2936, 1723, 1643, 1481, 1388, 1289, 1225, 1167; MS (ESI) (m/z) 402.09 (M+Na⁺).

Anal. Calcd. for C₂₁H₁₈FN₃O₃: C, 66.48; H, 4.78; N, 11.08. Found: C, 66.44; H, 4.80; N, 11.03.

S-18
2-Carbethoxy-5-methyl-3-(4-nitro-2-methylphenyl)-pyrazolo[1,5-a][1,4]benzodiazepine-6(4H)-one (4h): Yield 37%; Solid, mp 85-87 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.17 (t, \(J = 7.05\) Hz, 3H), 2.28 (s, 3H), 3.10 (s, 3H), 4.15 (br s, 2H), 4.24-4.34 (m, 2H), 7.34 (d, \(J = 8.1\) Hz, 1H), 7.54 (td, \(J = 7.5\) Hz, 1H), 7.70 (td, \(J = 7.8\) Hz, 1H), 8.02-8.06 (m, 2H), 8.16 (d, \(J = 8.1\) Hz, 1H), 8.21 (s, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 13.9, 20.3, 35.7, 42.1, 61.2, 119.8, 120.6, 122.8, 124.5, 127.4, 128.3, 131.1, 131.7, 132.5, 134.9, 137.7, 139.5, 140.0, 142.3, 147.7, 161.3, 166.5; IR (KBr, cm\(^{-1}\)) 2986, 2932, 1723, 1643, 1518, 1479, 1386, 1346, 1289, 1173; MS (ESI) (m/z) 443.15 (M+Na\(^+\)). Anal. Calcd. for C\(_{22}\)H\(_{20}\)N\(_4\)O\(_5\): C, 62.85; H, 4.79; N, 13.33; Found: C, 62.89; H, 4.77; N, 13.37.

9. References:
10. NMR Spectra of Compounds 8 and 3:

**$^1$H NMR (300 MHz) SPECTRUM of 8c:**

$^{13}$C NMR (150 MHz) SPECTRUM of 8c:
$^1$H NMR (300 MHz) SPECTRUM of 8k:

KB-2-102  $^1$H in CDC13

$^{13}$C NMR (75 MHz) SPECTRUM of 8k:

KB-2-102P  $^{13}$C in CDC13
$^1$H NMR (300 MHz) SPECTRUM of 3a:

$^{13}$C NMR (75 MHz) SPECTRUM of 3a:
$^1$H NMR (600 MHz) SPECTRUM of 3b:

$^{13}$C NMR (150 MHz) SPECTRUM of 3b:
HSQC SPECTRUM of 3b:

A Part of HSQC Spectrum of 3b:
$^1$H NMR (300 MHz) SPECTRUM of 3c:

$^{13}$C NMR (75 MHz) SPECTRUM of 3c:
$^1$H NMR (300 MHz) SPECTRUM of 3d:

13C NMR (75 MHz) SPECTRUM of 3d:
**1H NMR (300 MHz) SPECTRUM of 3e:**

**13C NMR (75 MHz) SPECTRUM of 3e:**
$^{1}H$ NMR (300 MHz) SPECTRUM of 3f:

$^{13}C$ NMR (150 MHz) SPECTRUM of 3f:
$^1$H NMR (300 MHz) SPECTRUM of 3g:

$^{13}$C NMR (75 MHz) SPECTRUM of 3g:
$^1$H NMR (300 MHz) SPECTRUM of 3h:

KB-2-130B$^*$  1H in CDCl$_3$

\[ \begin{array}{cccccc}
6.01 & 7.00 & 7.06 & 7.08 & 7.11 & 7.13 \\
5.29 & 4.37 & 6.37 & 4.37 & 4.31 & 1.05 \\
4.31 & 1.83 & 1.29 & 1.29 & 1.29 & 1.29
\end{array} \]

$^{13}$C NMR (75 MHz) SPECTRUM of 3h:

KB-2-130B  13C in CDCl$_3$

\[ \begin{array}{cccccc}
141.14 & 139.14 & 141.14 & 141.14 & 141.14 & 141.14 \\
71.90 & 71.90 & 71.90 & 71.90 & 71.90 & 71.90 \\
42.28 & 42.28 & 42.28 & 42.28 & 42.28 & 42.28 \\
61.31 & 61.31 & 61.31 & 61.31 & 61.31 & 61.31
\end{array} \]
**¹H NMR (300 MHz) SPECTRUM of 3i:**

![¹H NMR Spectrum](image1)

**¹³C NMR (75 MHz) SPECTRUM of 3i:**

![¹³C NMR Spectrum](image2)
$^1$H NMR (600 MHz) SPECTRUM of 3j:

KB-2-139P  $^1$H-NMR in CDCl$_3$

$^{13}$C NMR (75 MHz) SPECTRUM of 3j:

KB-2-139P  $^{13}$C in CDCl$_3$
HSQC SPECTRUM of 3j:

A Part of HSQC SPECTRUM of 3j:
$^1$H NMR (300 MHz) SPECTRUM of 3k:

$^{13}$C NMR (75 MHz) SPECTRUM of 3k:
$^1$H NMR (300 MHz) SPECTRUM of 3l:

R = CO$_2$Et

$^{13}$C NMR (150 MHz) SPECTRUM of 3l:
11. NMR Spectra of Compounds 4, 12 and 13:

$^1$H NMR (300 MHz, CDCl$_3$) of 4a

$^{13}$C NMR (75 MHz, CDCl$_3$) of 4a
$^1$H NMR (300 MHz, CDCl$_3$) of 4b

$^{13}$C NMR (75 MHz, CDCl$_3$) of 4b
$^1$H NMR (300 MHz, CDCl$_3$) of 4c

$^{13}$C NMR (75 MHz, CDCl$_3$) of 4c
$^1$H NMR (300 MHz, CDCl$_3$) of 4d

$^{13}$C NMR (75 MHz, CDCl$_3$) of 4d
$^1$H NMR (300 MHz, CDCl$_3$) of 4e

![NMR spectrum of 4e](image1)

$^{13}$C NMR (75 MHz, CDCl$_3$) of 4e

![NMR spectrum of 4e](image2)
$^1$H NMR (300 MHz, CDCl$_3$) of 4f

$^{13}$C NMR (75 MHz, CDCl$_3$) of 4f
$^1$H NMR (300 MHz, CDCl$_3$) of 4g

$^{13}$C NMR (75 MHz, CDCl$_3$) of 4g
$^1$H NMR (300 MHz, CDCl$_3$) of 4h

$^{13}$C NMR (75 MHz, CDCl$_3$) of 4h
$^{1}H$ NMR (300 MHz) SPECTRUM of 12:

KB-2-152  1H in DMSO-d$_6$

$^{13}C$ NMR (75 MHz) SPECTRUM of 12:

KB-2-152  13C in DMSO-d$_6$
$^1$H NMR (600 MHz, DMSO-d$_6$) of 13

$^{13}$C NMR (150 MHz, DMSO-d$_6$) of 13