Supplementary Information

Synthesis of pyrazoles through catalyst-free cycloaddition of diazo compounds to alkynes

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General methods:

$^1$H and $^{13}$C NMR spectra were obtained on a Brücker 300. Chemical shifts $\delta$ are given in ppm relative to TMS as internal standard. Coupling constant $J$ are measured in Hz. Mass analyses were obtained on an ESQUIRE-LC Brücker.

Materials:

All chemicals were used as provided without further purification.

Monitoring of the reactions:

The conversion of the substrate into product was measured by integration in the $^1$H NMR spectra directly from the reaction mixture.

Experimental procedures:

*Methyl phenyldiazoacetate 1b*

To a mixture of methyl phenylacetate (1.5 g, 10 mmol) and tosyl azide (2 g, 10 mmol) in MeCN (25 mL) at room temperature was added DBU (2 g, 13 mmol). After stirring for 16 h, the reaction mixture was quenched with an aqueous solution of satd NH$_4$Cl (25 mL) and extracted with CH$_3$Cl$_2$ (3×30 mL). The combined organic phases were washed with brine (30 mL), dried over MgSO$_4$ and the solvents were removed in vacuo. The residue was purified through column chromatography over silica gel (cyclohexane/AcOEt, 90:10) to afford 1b as an orange liquid (60% yield).

$^1$H NMR (CDCl$_3$, 200 MHz), $\delta$: 3.89 (s, 3H); 7.20 (m, 1H); 7.40 (m, 2H); 7.47 (m, 2H)

$^{13}$C NMR (CDCl$_3$, 75 MHz), $\delta$: 52.0; 124.0; 125.5; 125.8; 128.6; 128.9; 165.6
To an ice-cooled solution of MeONa (1.08 g, 20 mmol) and ethyl formate (1.48 g, 20 mmol) in benzene (20 mL) was added dropwise a solution of α-tetralone (1.72 g, 10 mmol) in benzene (20 mL). The mixture was stirred overnight at room temperature. The reaction was quenched with ice-water and then acidified with aqueous HCl (3.0 M). The mixture was extracted with Et$_2$O and the combined organic phases were washed with brine and water, dried over MgSO$_4$, filtered and the filtrate was evaporated in vacuum to afford the corresponding α-formyl ketone that was used in the next step without further purification.

To a stirred solution of the above α-formyl ketone and tosyl azide (2.17 g, 11 mmol) in Et$_2$O (20 mL) was added dropwise diethylamine (1.46 g, 20 mmol) at 0 ºC. The mixture was allowed to warm to room temperature. After 2 hours, water was added and the mixture was extracted with Et$_2$O, washed with brine, dried on MgSO$_4$, filtered and the filtrate was evaporated in vacuum. The crude product was purified by chromatography on silica gel (CH$_2$Cl$_2$) to afford the α-diazo ketone 1c as a red solid (40% yield); mp 50-51 ºC (litt. 2 48-49 ºC).

$^1$H NMR (CDCl$_3$, 300 MHz), $\delta$: 2.87 (m, 4H); 7.08 (d, J=7.5, 1H); 7.20 (t, J=7.5, 1H); 7.30 (t, J=7.5, 1H); 7.88 (d, J=7.5, 1H)

$^{13}$C NMR (CDCl$_3$, 75 MHz), $\delta$: 20.2; 27.3; 62.2; 125.3; 126.5; 127.9; 132.1; 132.8; 139.8; 183.1

IR ($\nu$, cm$^{-1}$): 1624, 2074

2-Diazo-1-tetralone 1b

According to the procedure used for 1c: 63% yield, orange solid; mp 86 ºC (lit. 3 86.5-88.5 ºC).

$^1$H NMR (CDCl$_3$, 300 MHz), $\delta$: 4.02 (s, 2H); 7.39 (t, J=7.2, 1H); 7.40 (d, J=7.3, 1H); 7.54 (t, J=7.2, 1H); 7.73 (d, J=7.3, 1H)

$^{13}$C NMR (CDCl$_3$, 75 MHz), $\delta$: 28.6; 122.6; 125.3; 127.8; 133.1; 137.3; 143.2; 188.4

IR ($\nu$, cm$^{-1}$): 1717, 2071
Ethyl 3-(4-chlorophenyl)-2-diazo-3-hydroxypropanoate 1e

To a mixture of 4-chlorobenzaldehyde (1.4 g, 10 mmol) and ethyl diazoacetate (1.4 g, 12 mmol) in CH₂Cl₂ (8 mL) was added a solution of DBU (152 mg, 1 mmol) in CH₂Cl₂ (2 mL). After stirring during 16 h, the solvent was evaporated and the residue was purified through column chromatography over silica gel (cyclohexane/Et₂O, 80:20) to afford 1e as a yellow liquid (60% yield).

^1H NMR (CDCl₃, 300 MHz), δ: 1.30 (t, J=7.1, 3H); 2.98 (s br, 1H); 4.27 (q, J=7.1, 2H); 5.89 (d, J=3.6, 1H); 7.37 (s, 4H)

^13C NMR (CDCl₃, 75 MHz), δ: 14.3; 61.3; 67.9; 68.0; 127.1; 128.8; 134.0; 137.5; 166.3

IR (ν, cm⁻¹): 1664, 2094, 3247

Ethyl 2-diazo-3-oxopropanoate 1f

According to the procedure used for 1b: 60% yield, yellow oil.

^1H NMR (CDCl₃, 300 MHz), δ: 1.25 (t, J=7.1, 3H); 2.42 (s, 3H); 4.24 (q, J=7.1, 2H)

^13C NMR (CDCl₃, 75 MHz), δ: 14.1; 27.9; 61.2; 76.0; 161.1; 189.9

IR (ν, cm⁻¹): 1656, 1713, 2135

General procedure for the 1,3-dipolar cycloaddition of diazo compounds 1a-f to alkynes:

A 5 mL round-bottom flask equipped with a reflux condenser was charged with the diazo compound and the alkyne (1 mmol of the heaviest reagent / 1.1 mmol of the most volatile one) and was heated at 80 °C. After completion of the reaction (see Table 2 in the article), the excess of reagent was evaporated under vacuum to afford the corresponding pyrazole as pure solid.

Diethyl 1H-pyrazole-3,5-dicarboxylate: 95% yield (from 1a), 86% (from 1e, after column chromatography, cyclohexane/AcOEt, 7:3), white crystals; mp 54 °C (lit. 5 54-55 °C)

^1H NMR (CDCl₃, 300 MHz), δ: 1.26 (t, J=7.1, 6H); 4.30 (q, J=7.1, 4H); 7.23 (s, 1H); 13.02 (s br, 1H)

^13C NMR (CDCl₃, 75 MHz), δ: 13.8; 61.3; 111.0; 139.6; 160.3
Triethyl 1H-pyrazole-3,4,5-tricarboxylate: 95% yield, pale yellow crystals; mp 92 °C (lit. 70-91 °C)

Ethyl-5-(trimethylsilyl)-1H-pyrazole-3-carboxylate: 90% yield, white crystals; mp 142 °C (lit. 143-144 °C)

Ethyl-5-phenyl-1H-pyrazole-3-carboxylate: 93% yield, white solid; mp 137 °C
3-Ethyl-5-methyl-4-phenyl-1H-pyrazole-3,5-dicarboxylate: 60% yield (after column chromatography, cyclohexane/AcOEt, 7:3), white solid; mp 107-109 °C

\[
\begin{align*}
\text{HN} & \text{N} \\
\text{Ph} & \text{CO}_2\text{Et} \\
\text{MeO}_2\text{C} & \text{Ph}
\end{align*}
\]

$^1$H NMR (CDCl$_3$, 300 MHz), $\delta$: 1.34 (t, J=7.1, 3H); 3.83 (s, 3H); 4.35 (q, J=7.1, 2H); 7.42 (m, 3H); 7.60 (m, 2H); 11.51 (s br, 1H) 
$^{13}$C NMR (CDCl$_3$, 75 MHz), $\delta$: 13.8; 52.2; 61.4; 112.8; 127.8; 128.2; 128.6; 129.3; 141.1; 146.9; 160.7; 164.4
APCI m/z (rel.int.): 273 [M-H]$^+$ (100%)
IR ($\nu$, cm$^{-1}$): 1727, 2982

Ethyl 4,9-dihydro-9-oxopyrazolo[1,5-b]isoquinoline-2-carboxylate: 90% yield, yellow crystals; mp 171 °C

\[
\begin{align*}
\text{O} & \text{N} \text{N} \\
\text{CO}_2\text{Et} & \text{CO}_2\text{Et}
\end{align*}
\]

$^1$H NMR (CDCl$_3$, 300 MHz), $\delta$: 1.41 (t, J=7.1, 3H); 4.43 (q, J=7.1, 2H); 4.47 (s, 2H); 6.88 (s, 1H); 7.46 (d, J=7.9, 1H); 7.52 (t, J=7.9, 1H); 7.68 (t, J=7.9, 1H); 8.43 (d, J=7.9, 1H) 
$^{13}$C NMR (CDCl$_3$, 75 MHz), $\delta$: 14.2; 27.1; 61.6; 107.9; 125.4; 127.9; 128.4; 130.0; 134.3; 136.6; 142.7; 148.3; 157.6; 161.9
APCI m/z (rel.int.): 257 [M+H]$^+$ (100%)
IR ($\nu$, cm$^{-1}$): 1719

Diethyl 4,9-dihydro-9-oxopyrazolo[1,5-b]isoquinoline-2,3-dicarboxylate: 85% yield, white solid; mp 115 °C

\[
\begin{align*}
\text{O} & \text{N} \text{N} \\
\text{CO}_2\text{Et} & \text{CO}_2\text{Et}
\end{align*}
\]

$^1$H NMR (CDCl$_3$, 300 MHz), $\delta$: 1.38 (t, J=7.1, 3H); 1.41 (t, J=7.1, 3H); 4.37 (q, J=7.1, 2H); 4.45 (q, J=7.1, 2H); 4.68 (s, 2H); 7.53 (d, J=7.7, 1H); 7.56 (t, J=7.6, 1H); 7.73 (t, J=7.6, 1H); 8.45 (d, J=7.7, 1H) 
$^{13}$C NMR (CDCl$_3$, 75 MHz), $\delta$: 14.1; 14.2; 28.1; 61.2; 62.3; 112.2; 124.8; 128.3; 128.6; 130.0; 134.7; 136.5; 146.9; 148.5; 157.3; 161.5; 162.2
APCI m/z (rel.int.): 329 [M+H]$^+$ (100%)
IR ($\nu$, cm$^{-1}$): 1705, 1729
**Ethyl 10-oxo-5,10-dihydro-4H-pyrazolo[1,5-b][2]benzazepine-2-carboxylate**: 88% yield, red solid; mp: 115-116 °C

![](image)

$^1$H NMR (CDCl₃, 300 MHz), δ: 1.41 (t, J=7.2, 3H); 3.15 (t, J=5.2, 2H); 3.19 (t, J=5.2, 2H); 4.42 (q, J=7.2, 2H); 6.71 (s, 1H); 7.28 (d, J=7.5, 1H); 7.43 (t, J=7.5, 1H); 7.54 (t, J=7.5, 1H); 8.25 (d, J=7.5, 1H)

$^{13}$C NMR (CDCl₃, 75 MHz), δ: 14.0; 26.8; 32.6; 61.3; 109.6; 127.3; 129.1; 130.1; 133.8; 133.9; 140.7; 146.6; 147.0; 161.5; 163.5

APCI m/z (rel.int.): 271 [M+H]$^+$ (100%)

IR (ν, cm$^{-1}$): 1705

**Diethyl 10-oxo-5,10-dihydro-4H-pyrazolo[1,5-b][2]benzazepine-2,3-dicarboxylate**: 85% yield, red oil

$^1$H NMR (CDCl₃, 300 MHz), δ: 1.35 (t, J=7.2, 3H); 1.41 (t, J=7.2, 3H); 3.15 (t, J=5.2, 2H); 3.52 (t, J=5.2, 2H); 4.33 (q, J=7.2, 2H); 4.43 (q, J=7.2, 2H); 7.31 (d, J=7.5, 1H); 7.42 (t, J=7.5, 1H); 7.57 (t, J=7.5, 1H); 8.19 (d, J=7.5, 1H)

$^{13}$C NMR (CDCl₃, 75 MHz), δ: 13.7; 13.8; 25.6; 31.9; 60.9; 61.9; 112.8; 127.4; 129.0; 129.8; 133.6; 134.2; 140.5; 147.4; 149.7; 161.6; 162.0; 163.4

APCI m/z (rel.int.): 343 [M+H]$^+$ (100%)

IR (ν, cm$^{-1}$): 1715

**2-Phenyl-4,5-dihydro-10H-pyrazolo[1,5-b][2]benzazepin-10-one**: 40% yield (after column chromatography, cyclohexane/AcOEt, 7:3), red solid; mp: 159-160 °C

$^1$H NMR (CDCl₃, 300 MHz), δ: 3.14 (t, J=5.2, 2H); 3.19 (t, J=5.2, 2H); 6.57 (s, 1H); 7.26 (d, J=7.5, 1H); 7.43 (m, 4H); 7.52 (t, J=7.5, 1H); 7.95 (m, 2H); 8.29 (d, J=7.5, 1H)

$^{13}$C NMR (CDCl₃, 75 MHz), δ: 27.4; 29.7; 106.9; 126.7; 127.4; 128.6; 129.0; 129.3; 131.1; 131.5; 133.4; 134.0; 140.8; 146.8; 155.1; 164.0

APCI m/z (rel.int.): 275 [M+H]$^+$ (100%)
General procedure for the 1,3-dipolar cycloaddition of trimethylsilyl diazomethane to alkynes:

A 5 mL round-bottom flask was charged with trimethylsilyl diazomethane (2M solution in hexane; 0.55 mL, 1.1 mmol) and the alkyne (1 mmol). The mixture was stirred at room temperature (80 ºC for phenyl acetylene). After the reaction completion, the excess of reagent and the hexane were evaporated under vacuum to afford the corresponding pyrazole.

Ethyl 1H-pyrazole-3-carboxylate \(^\text{10}\) : 93% yield, white crystals; mp 158 ºC (lit. 158-160 ºC)

\[
\begin{align*}
\text{HN} & \text{N} \\
\text{CO}_2\text{Et} \\
\end{align*}
\]

\(^1\)H NMR (CDCl\(_3\), 300 MHz), \(\delta\): 1.41 (t, J=7.1, 3H); 4.43 (q, J=7.1, 2H); 6.84 (d, J=2.3, 1H); 7.85 (d, J=2.3, 1H); 12.96 (s br, 1H)

\(^{13}\)C NMR (CDCl\(_3\), 75 MHz), \(\delta\): 14.4; 60.9; 107.5; 131.6; 142.4; 162.4

ESI m/z (rel.int.): 163 [M+23]\(^+\) (100%)

IR (v, cm\(^{-1}\)): 1698, 3247

Diethyl 1H-pyrazole-3,4-dicarboxylate \(^\text{10}\) : 86% yield, pale yellow crystals, mp 70 ºC (lit. 69-70 ºC)

\[
\begin{align*}
\text{HN} & \text{N} \\
\text{CO}_2\text{Et} & \text{O}_2\text{C} \\
\end{align*}
\]

\(^1\)H NMR (CDCl\(_3\), 300 MHz), \(\delta\): 1.34 (t, J=7.1, 3H); 1.39 (t, J=7.1, 3H); 4.31 (q, J=7.1, 2H); 4.44 (q, J=7.1, 2H); 8.23 (s, 1H); 13.88 (s br, 1H)

\(^{13}\)C NMR (CDCl\(_3\), 75 MHz), \(\delta\): 14.1; 14.2; 60.7; 61.7; 114.7; 135.3; 142.2; 162.0

ESI m/z (rel.int.): 235 [M+23]\(^+\) (50%), 447 [2M+23]\(^+\)

IR (v, cm\(^{-1}\)): 1716, 2985

3-phenyl-1H-pyrazole \(^\text{11}\) : 87% yield, pale yellow solid; mp100 ºC (lit. 102-104 ºC)
\[ \text{HN} \text{N} \text{Ph} \]

$^1$H NMR (CDCl$_3$, 300 MHz), $\delta$: 6.62 (d, J=2.2, 1H); 7.37 (tt, J=8.2 and 1.5, 1H); 7.41 (tt, J=8.2 and 1.4, 2H); 7.61 (d, J=2.2, 1H); 7.79 (dd, J=8.2 and 1.4, 2H); 11.71 (s br, 1H)

$^{13}$C NMR (CDCl$_3$, 75 MHz), $\delta$: 102.5; 125.8; 127.9; 128.7; 132.1; 133.2; 149.0

APCI $m/z$ (rel.int.): 145 [M+H]$^+$ (100%)

IR ($\nu$, cm$^{-1}$): 2964

8 M. Barnes, R. Conory, D. J. Miller, J. Miles, J. G. Montana, P. K. Pooni, G. A. Showell, L. M. Walsh and J. B. H. Warneck, *Bioorg. Med. Chem. Lett.*, 2007, 17, 354-357. Some differences were observed in $^{13}$C NMR when compared to this article: the signal at 143.7 ppm was not reported.
9 T. T. Dang, T. T. Dang, C. Fischer, H. Görls and P. Langer, *Tetrahedron*, 2008, 64, 2207-2215. This product was described as an oil, and the signal at 105.3 ppm was reported at 116.5 ppm.