Supplementary Material (ESI) for Green Chemistry

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 δ 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:

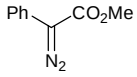
All chemicals were used as provided without further purification.

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***[1]



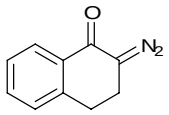
To a mixture of methyl phenylacetate (1.5 g, 10 mmol) and tosyl azide (2 g, 10 mmol) in MeCN (25 mL) at room temperature was added DBU (2 g, 13 mmol). After stirring for 16 h, the reaction mixture was quenched with an aqueous solution of satd NH_4Cl (25 mL) and extracted with CH_2Cl_2 (3×30 mL). The 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), δ: 3.89 (s, 3H); 7.20 (m, 1H); 7.40 (m, 2H); 7.47 (m, 2H)

^{13}C NMR ($CDCl_3$, 75 MHz), δ: 52.0; 124.0; 125.5; 125.8; 128.6; 128.9; 165.6

IR (ν, cm^{-1}) : 1698, 2081

2-Diazo-1-tetralone ***1c*** [2]



To an ice-cooled solution of MeONa (1.08 g, 20 mmol) and ethyl formate (1.48 g, 20mmol) 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_2O 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_2O (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_2O, 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_2Cl_2) to afford the α-diazo ketone **1c** as a red solid (40% yield); mp 50-51 °C (litt. [2] 48-49 °C).

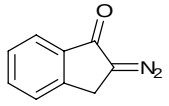
^{1}H NMR ($CDCl_3$, 300 MHz), δ: 2.87 (m, 4H); 7.08 (d, J=7.5, 1H); 7.20 (t, J=7.5, 1H); 7.30 (t, J=7.5, 1H); 7.88 (d, J=7.5, 1H)

^{13}C NMR ($CDCl_3$, 75 MHz), δ: 20.2; 27.3; 62.2; 125.3; 126.5; 127.9; 132.1; 132.8; 139.8; 183.1

IR (ν, cm^{-1}): 1624, 2074

2-Diazo-1-indanone ***1b***

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

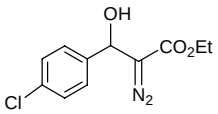


^{1}H NMR ($CDCl_3$, 300 MHz), δ: 4.02 (s, 2H); 7.39 (t, J=7.2, 1H); 7.40 (d, J=7.3, 1H); 7.54 (t, J=7.2, 1H); 7.73 (d, J=7.3, 1H)

^{13}C NMR ($CDCl_3$, 75 MHz), δ: 28.6; 122.6; 125.3; 127.8; 133.1; 137.3; 143.2; 188.4

IR (ν, cm^{-1}) : 1717, 2071

Ethyl 3-(4-chlorophenyl)-2-diazo-3-hydroxypropanoate ***1e***[4]



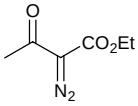
To a mixture of 4-chlorobenzaldehyde (1.4 g, 10 mmol) and ethyl diazoacetate (1.4 g, 12 mmol) in CH_2Cl_2 (8 mL) was added a solution of DBU (152 mg, 1 mmol) in CH_2Cl_2 (2 mL). After stirring during 16 h, the solvent was evaporated and the residue was purified through column chromatography over silica gel (cyclohexane/Et_2O, 80:20) to afford **1e** as a yellow liquid (60% yield).

^{1}H NMR ($CDCl_3$, 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)

^{13}C NMR ($CDCl_3$, 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*** [5]



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

^{1}H NMR ($CDCl_3$, 300 MHz), δ: 1.25 (t, J=7.1, 3H); 2.42 (s, 3H); 4.24 (q, J=7.1, 2H)

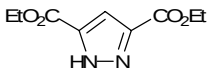
^{13}C NMR ($CDCl_3$, 75 MHz), δ: 14.1; 27.9; 61.26; 76.0; 161.1; 189.9

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 ºC. 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 ºC (lit.[6] 54-55 °C)



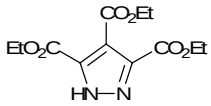
^{1}H NMR ($CDCl_3$, 300 MHz), δ: 1.26 (t, J=7.1, 6H); 4.30 (q, J=7.1, 4H); 7.23 (s, 1H); 13.02 (s br, 1H)

^{13}C NMR ($CDCl_3$, 75 MHz), δ: 13.8; 61.3; 111.0; 139.6; 160.3

APCI *m/z* (rel.int.): 213 $[M+H]^+$ (60%), 425 $[2M+H]^+$ (100%)

IR (ν, cm^{-1}): 1719, 2984

Triethyl 1H-pyrazole-3,4,5-tricarboxylate: 95% yield, pale yellow crystals; mp 92 ºC (lit.[7] 90-91 ºC)



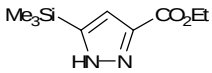
^{1}H NMR ($CDCl_3$, 300 MHz), δ: 1.30 (t, J=7.1, 6H); 1.34 (t, J=7.1, 3H); 4.33 (q, J=7.1, 4H); 4.37 (q, 7.1, 2H); 12.55 (s br, 1H)

^{13}C NMR ($CDCl_3$, 75 MHz), δ: 13.8; 13.9; 61.9; 62.0; 119.5; 137.1; 159.1; 163.1

APCI *m/z* (rel.int.): 285 $[M+H]^+$ (100%)

IR (ν, cm^{-1}): 1717, 2985

Ethyl-5-(trimethylsilyl)-1H-pyrazole-3-carboxylate[8]*:* 90% yield, white crystals; mp 142 ºC (lit. 143-144 ºC)



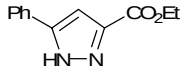
^{1}H NMR ($CDCl_3$, 300 MHz), δ: 0.24 (s, 9H); 1.23 (t, J=7.0, 3H); 4.29 (q, J=7.0, 2H); 6.89 (s, 1H); 12.60 (s br, 1H)

^{13}C NMR ($CDCl_3$, 75 MHz), δ: -1.5; 14.1; 60.6; 115.1; 143.7; 144.2; 162.6

APCI *m/z* (rel.int.): 213 $[M+H]^+$ (90%), 425 $[2M+H]^+$ (100%)

IR (ν, cm^{-1}): 1726, 2986

Ethyl-5-phenyl-1H-pyrazole-3-carboxylate[9]*:* 93% yield, white solid; mp 137 ºC



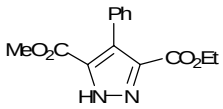
^{1}H NMR ($CDCl_3$, 300 MHz), δ: 1.32 (t, J=7.1, 3H); 4.31 (q, J=7.0, 2H); 7.06 (s, 1H); 7.38 (m, 3H); 7.74 (d, J=6.9, 2H); 12.13 (s br, 1H)

^{13}C NMR ($CDCl_3$, 75 MHz), δ: 14.1; 61.2; 105.3; 125.6; 128.5; 128.8; 130.5; 139.5; 148.8; 160.8

APCI *m/z* (rel.int.): 217 $[M+H]^+$ (100%), 433 $[2M+H]^+$ (30%)

IR (ν, cm^{-1}): 1724, 2963

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



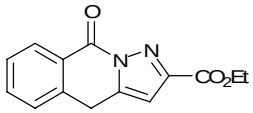
^{1}H NMR ($CDCl_3$, 300 MHz), δ: 1.34 (t, J=7.1, 3H); 3.83 (s, 3H); 4.35 (q, J=7.1, 2H); 7.42 (m, 3H); 7.60 (m, 2H); 11.51 (s br, 1H)

^{13}C NMR ($CDCl_3$, 75 MHz), δ: 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 (ν, cm^{-1}): 1727, 2982

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



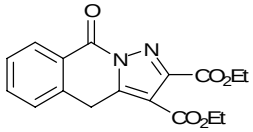
^{1}H NMR ($CDCl_3$, 300 MHz), δ: 1.41 (t, J=7.1, 3H); 4.43 (q, J=7.1, 2H); 4.47 (s, 2H); 6.88 (s, 1H); 7.46 (d, J=7.9, 1H); 7.52 (t, J=7.9, 1H); 7.68 (t, J=7.9, 1H); 8.43 (d, J=7.9, 1H)

^{13}C NMR ($CDCl_3$, 75 MHz), δ: 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 (ν, cm^{-1}): 1719

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



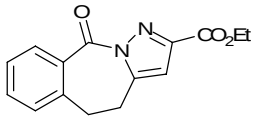
^{1}H NMR ($CDCl_3$, 300 MHz), δ: 1.38 (t, J=7.1, 3H); 1.41 (t, J=7.1, 3H); 4.37 (q, J=7.1, 2H); 4.45 (q, J=7.1, 2H); 4.68 (s, 2H); 7.53 (d, J=7.7, 1H); 7.56 (t, J=7.6, 1H); 7.73 (t, J=7.6, 1H); 8.45 (d, J=7.7, 1H)

^{13}C NMR ($CDCl_3$, 75 MHz), δ: 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 (ν, 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



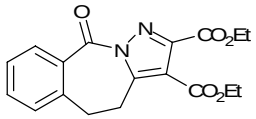
^{1}H NMR ($CDCl_3$, 300 MHz), δ: 1.41 (t, J=7.2, 3H); 3.15 (t, J=5.2, 2H); 3.19 (t, J=5.2, 2H); 4.42 (q, J=7.2, 2H); 6.71 (s, 1H); 7.28 (d, J=7.5, 1H); 7.43 (t, J=7.5, 1H); 7.54 (t, J=7.5, 1H); 8.25 (d, J=7.5, 1H)

^{13}C NMR ($CDCl_3$, 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



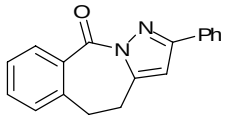
^{1}H NMR ($CDCl_3$, 300 MHz), δ: 1.35 (t, J=7.2, 3H); 1.41 (t, J=7.2, 3H); 3.15 (t, J=5.2, 2H); 3.52 (t, J=5.2, 2H); 4.33 (q, J=7.2, 2H); 4.43 (q, J=7.2, 2H); 7.31 (d, J=7.5, 1H); 7.42 (t, J=7.5, 1H); 7.57 (t, J=7.5, 1H); 8.19 (d, J=7.5, 1H)

^{13}C NMR ($CDCl_3$, 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 ($CDCl_3$, 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 ($CDCl_3$, 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

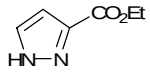
APCI *m/z* (rel.int.): 275 $[M+H]^+$ (100%)

IR (ν, cm^{-1}): 1693

General procedure for the 1,3-dipolar cycloaddition of trimethylsilyl diazomethane to alkynes:

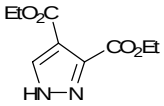
A 5 mL round-bottom flask was charged with trimethylsilyl diazomethane (2M solution in hexane; 0.55 mL, 1.1 mmol) and the alkyne (1 mmol). The mixture was stirred at room temperature (80 ºC for phenyl acetylene). After the reaction completion, the excess of reagent and the hexane were evaporated under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

Ethyl 1H-pyrazole-3-carboxylate[10] *:* 93% yield, white crystals; mp 158 ºC (lit. 158-160 ºC)



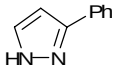
^{1}H NMR ($CDCl_3$, 300 MHz), δ: 1.41 (t, J=7.1, 3H); 4.43 (q, J=7.1, 2H); 6.84 (d, J=2.3, 1H); 7.85 (d, J=2.3, 1H); 12.96 (s br, 1H)
^{13}C NMR ($CDCl_3$, 75 MHz), δ: 14.4; 60.9; 107.5; 131.6; 142.4; 162.4
ESI *m/z* (rel.int.): 163 $[M+23]^+$ (100%)
IR (ν, cm^{-1}): 1698, 3247

Diethyl 1H-pyrazole-3,4-dicarboxylate[10] *:* 86% yield, pale yellow crystals, mp 70 ºC (lit. 69-70 ºC)



^{1}H NMR ($CDCl_3$, 300 MHz), δ: 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), δ: 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 (ν, cm^{-1}): 1716, 2985

3-phenyl-1H-pyrazole[11] : 87% yield, pale yellow solid; mp100 ºC (lit. 102-104 ºC)



^{1}H NMR ($CDCl_3$, 300 MHz), δ: 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), δ: 102.5; 125.8; 127.9; 128.7; 132.1; 133.2; 149.0

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

IR (ν, cm^{-1}): 2964

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