Rhodium-Catalyzed Intermolecular Reaction of Alkyl Azides with Diazo(aryl)acetates

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General.

$^1$H NMR (at 400 MHz) and $^{13}$C NMR (at 100 MHz) spectra were all obtained as solutions in CDCl$_3$. The infrared (IR) spectra were determined as neat oils. High resolution mass spectra (HRMS) were obtained by electro spray ionization (ESI) and the errors between observed and theoretical monoisotopic molecular masses were less than 5 ppm. The reactions were determined by thin layer chromatography (TLC) on 2.5 x 10 cm, 250 μm analytical plates coated with silica gel 60 F254. Column chromatography was carried out by using silica gel 60 particle size 40 – 63 μm or 5 - 20 μm. All glassware was oven dried and reactions were carried out under a flow of nitrogen, and all the solvents were distilled according to the general methods before use.
Representative Procedure for Intermolecular Reaction of Benzyl Azide 2a with Ethyl Diazophenylacetate 1a. To a stirred solution of Rh\(_2\)(Oct)_4 (2.7 mg, 0.003 mmol) in DCM (1.0 mL) was added a mixture of ethyl diazophenylacetate 1a (95 mg, 0.5 mmol) and benzyl azide 2a (133 mg, 1.0 mmol) in DCM (3.0 mL) during a period of 30 min. The reaction mixture was kept at 10-15 °C for 30 min, then 2 M HCl (0.5 mL) was added and the mixture was kept for another 45 min, and then water (5 mL) was added. The mixture was extracted with DCM (10 mL*3) and washed by water (10 mL*2). The organic phase was dried over Na\(_2\)SO\(_4\) and concentrated. The residue was purified by flash chromatography to afford the aryl α-keto ester 3a\(^2\)\(^-\)\(^4\) as a slight yellow oil (88 mg, 99% yield). The aryl α-keto ester 3a was also prepared from ethyl diazophenylacetate 1a (95 mg, 0.5 mmol) and azide 2b (129 mg, 1.0 mmol) in 73% yield (65 mg) or from ethyl diazophenylacetate 1a (95 mg, 0.5 mmol) and azide 2c (141 mg, 1.0 mmol) in 82% yield (73 mg); TLC R\(_f\) (ethyl acetate/petroleum ether = 1/10) = 0.52; \(^1\)H NMR (CDCl\(_3\), 400 MHz) δ: 1.43 (t, \(J = 7.2\) Hz, 3 H), 4.46 (q, \(J = 7.2\) Hz, 2 H), 7.50-7.54 (m, 2 H), 7.64-7.69 (m, 1 H), 8.00-8.03 (m, 2 H); \(^13\)C NMR (CDCl\(_3\), 100 MHz) δ: 14.1, 62.3, 128.9 (2), 130.0 (2), 132.4, 134.9, 163.8, 186.4.

methyl 2-oxo-2-phenylacetate (3b).\(^4\)\(^-\)\(^5\) The aryl α-keto ester 3b was prepared by the same procedure for aryl α-keto ester 3a from the diazo ester 1b (173 mg, 1.0 mmol) and benzyl azide 2a (266 mg, 2.0 mmol) in 93% yield (80 mg) as a faint yellow oil: TLC R\(_f\) (ethyl acetate/petroleum ether = 1/10) = 0.38; \(^1\)H NMR (CDCl\(_3\), 400 MHz) δ: 3.98 (s, 3 H), 7.49-7.54 (m, 2 H), 7.64-7.69 (m, 1 H),
ethyl 2-oxo-2-p-tolylacetate (3e).\textsuperscript{2,3} The aryl α-keto ester 3e was prepared by the same procedure for aryl α-keto ester 3a from the diazo ester 1c (102 mg, 0.5 mmol) and benzyl azide 2a (133 mg, 1.0 mmol) in 95% yield (91 mg) or from the diazo ester 1c (102 mg, 0.5 mmol) and azide 2b (129 mg, 1.0 mmol) in 74% yield (71 mg) as a faint yellow oil: TLC $R_f$ (ethyl acetate/petroleum ether = 1/10) = 0.47; $^1$H NMR (CDCl$_3$, 400 MHz) δ: 1.42 (t, $J = 7.2$ Hz, 3 H), 2.44 (s, 3 H), 4.44 (q, $J = 7.2$ Hz, 2 H), 7.31 (dd, $J = 1.6$ Hz and 6.8 Hz, 2 H), 7.91 (dd, $J = 1.6$ Hz and 6.8 Hz, 2 H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ: 14.3, 22.1, 62.4, 129.8 (2), 130.1, 130.3 (2), 146.4, 164.2, 186.3.

ethyl 2-(4-methoxyphenyl)-2-oxoacetate (3d).\textsuperscript{2,3} The aryl α-keto ester 3d was prepared by the same procedure for aryl α-keto ester 3a from the diazo ester 1d (110 mg, 0.5 mmol) and benzyl azide 2a (133 mg, 1.0 mmol) in 99% yield (103 mg) as a yellow oil: TLC $R_f$ (ethyl acetate/petroleum ether = 1/10) = 0.23; $^1$H NMR (CDCl$_3$, 400 MHz) δ: 1.41 (t, $J = 7.2$ Hz, 3 H), 3.89 (s, 3 H), 4.43 (q, $J = 7.2$ Hz, 2 H), 6.97 (dd, $J = 2.0$ Hz and 7.2 Hz, 2 H), 8.00 (dd, $J = 2.0$ Hz and 7.2 Hz, 2 H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ: 14.3, 55.8, 62.3, 114.3 (2), 125.6, 132.7 (2), 164.3, 165.1, 185.0.

ethyl 2-(4-chlorophenyl)-2-oxoacetate (3e).\textsuperscript{3,6} The aryl α-keto ester 3e was prepared by the same procedure for aryl α-keto ester 3a from the diazo ester 1e (111 mg, 0.5 mmol) and benzyl azide 2a (133 mg, 1.0 mmol) in 92% yield (97 mg) or from the diazo ester 1e (111 mg, 0.5 mmol) and azide 2b (129 mg, 1.0 mmol) in 76% yield (80 mg) as a faint yellow oil: TLC $R_f$ (ethyl acetate/petroleum ether = 1/10) = 0.48; $^1$H NMR (CDCl$_3$, 400 MHz) δ: 1.43 (t, $J = 7.2$ Hz, 3 H), 4.45 (q, $J = 7.2$ Hz, 2 H), 7.48-7.51 (m, 2 H), 7.97-8.00 (m, 2 H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ:
The aryl α-keto ester 3f was prepared by the same procedure for aryl α-keto ester 3a from the diazo ester 1f (135 mg, 0.5 mmol) and benzyl azide 2a (133 mg, 1.0 mmol) in 92% yield (119 mg) or from the diazo ester 1f (135 mg, 0.5 mmol) and azide 2c (141 mg, 1.0 mmol) in 86% yield (111 mg) as a faint yellow oil: TLC Rf (ethyl acetate/petroleum ether = 1/10) = 0.47; 1H NMR (CDCl3, 400 MHz) δ: 1.41 (t, J = 7.2 Hz, 3 H), 4.43 (q, J = 7.2 Hz, 2 H), 7.63-7.66 (m, 2 H), 7.87-7.90 (m, 2 H); 13C NMR (CDCl3, 100 MHz) δ: 14.2, 62.7, 130.6, 131.4, 131.6 (2), 132.4 (2), 163.2, 185.2.

The aryl α-keto ester 3g was prepared by the same procedure for aryl α-keto ester 3a from the diazo ester 1g (126 mg, 0.5 mmol) and benzyl azide 2a (133 mg, 1.0 mmol) in 87% yield (104 mg) as a faint yellow oil: TLC Rf (ethyl acetate/petroleum ether = 1/10) = 0.38; 1H NMR (CDCl3, 400 MHz) δ: 5.42 (s, 2 H), 7.38-7.51 (m, 7 H), 7.64-7.67 (m, 1 H), 7.96-7.98 (m, 2 H); 13C NMR (CDCl3, 100 MHz) δ: 67.9, 128.77 (2), 128.89 (2), 128.97, 129.04 (2), 130.2 (2), 132.5, 134.6, 135.1, 163.8, 186.2.

The aryl α-keto ester 3h was prepared by the same procedure for aryl α-keto ester 3a from the diazo ester 1h (140 mg, 0.5 mmol) and benzyl azide 2a (133 mg, 1.0 mmol) in 85% yield (115 mg) or from the diazo ester 1h (140 mg, 0.5 mmol) and azide 2c (141 mg, 1.0 mmol) in 87% yield (117 mg) as a yellow oil: TLC Rf (ethyl acetate/petroleum ether = 1/10) = 0.22; 1H NMR (CDCl3, 400 MHz) δ: 3.88 (s, 3 H), 5.40 (s, 2 H), 6.93-6.97 (m, 2 H), 7.34-7.46 (m, 5 H), 7.94-7.95 (m, 2 H); 13C NMR (CDCl3, 100 MHz) δ: 55.7,
The aryl \( \alpha \)-keto ester \( 3i \) was prepared by the same procedure for aryl \( \alpha \)-keto ester \( 3a \) from the diazo ester \( 1i \) (166 mg, 0.5 mmol) and benzyl azide \( 2a \) (133 mg, 1.0 mmol) in 84\% yield (132 mg) or from the diazo ester \( 1i \) (166 mg, 0.5 mmol) and azide \( 2c \) (141 mg, 1.0 mmol) in 81\% yield (128 mg) as a faint yellow solid: TLC \( R_f \) (ethyl acetate/petroleum ether = 1/10) = 0.50; \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \): 5.41 (s, 2 H), 7.36-7.46 (m, 5 H), 7.62-7.65 (m, 2 H), 7.83-7.84 (m, 2 H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \): 68.1, 128.8 (2), 128.9 (2), 129.1, 130.8, 131.3, 131.6 (2), 132.5 (2), 134.5, 163.1, 184.9.

The aryl \( \alpha \)-keto ester \( 3j \) was prepared by the same procedure for aryl \( \alpha \)-keto ester \( 3a \) from the diazo ester \( 1j \) (166 mg, 0.5 mmol) and benzyl azide \( 2a \) (133 mg, 1.0 mmol) in 86\% yield (138 mg) or from the diazo ester \( 1j \) (166 mg, 0.5 mmol) and azide \( 2b \) (129 mg, 1.0 mmol) in 74\% yield (120 mg) as a colorless solid: TLC \( R_f \) (ethyl acetate/petroleum ether = 1/10) = 0.36; mp 65.7 °C; \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \): 5.36 (s, 2 H), 7.33 (d, \( J = 8.4 \) Hz, 2 H), 7.48-7.54 (m, 4 H), 7.64-7.68 (m, 1 H), 7.95-7.98 (m, 2 H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \): 66.9, 123.0, 129.0 (2), 130.1 (2), 130.3 (2), 131.9 (2), 132.3, 133.6, 135.1, 163.5, 185.8; IR (film) 1738, 1658 cm\(^{-1}\); HRMS (ESI) calcd for C\(_{15}\)H\(_{11}\)BrNaO\(_3\) (M\(^+\) + Na) 340.9784, found 340.9776.

The aryl \( \alpha \)-keto ester \( 3k \) was prepared by the same procedure for aryl \( \alpha \)-keto ester \( 3a \) from the diazo ester \( 1k \) (284 mg, 1.0 mmol) and benzyl azide \( 2a \) (266 mg, 2.0 mmol) in 87\% yield (237 mg) or from the diazo ester \( 1k \) (140 mg, 0.5 mmol) and
azide 2b (129 mg, 1.0 mmol) in 62% yield (84 mg) as a yellow solid: TLC R<sub>f</sub> (ethyl acetate/petroleum ether = 1/10) = 0.33; mp 53.6 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ: 3.82 (s, 3 H), 5.36 (s, 2 H), 6.92 (dd, J = 2.0 Hz and 6.8 Hz, 2 H), 7.40 (dd, J = 2.0 Hz and 6.8 Hz, 2 H), 7.48 (dd, J = 2.0 Hz and 6.8 Hz, 2 H), 7.62-7.66 (m, 1 H), 7.94-7.96 (m, 2 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ: 55.4, 67.8, 114.1 (2), 126.7, 129.0 (2), 130.1 (2), 130.7 (2), 132.4, 135.0, 160.1, 163.8, 186.3; IR (film) 1516, 1688 cm<sup>-1</sup>; HRMS (ESI) calcd for C<sub>16</sub>H<sub>14</sub>NaO<sub>4</sub> (M<sup>+</sup> + Na) 293.0784, found 293.0776.

benzyl 2-(naphthalen-3-yl)-2-oxoacetate (3l)<sup>4,6</sup> The aryl α-keto ester 3l was prepared by the same procedure for aryl α-keto ester 3a from the diazo ester 1l (151 mg, 0.5 mmol) and benzyl azide 2a (133 mg, 1.0 mmol) in 93% yield (135 mg) or from the diazo ester 1l (151 mg, 0.5 mmol) and azide 2c (141 mg, 1.0 mmol) in 83% yield (121 mg) as a faint yellow solid: TLC R<sub>f</sub> (ethyl acetate/petroleum ether = 1/10) = 0.40; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ: 5.48 (s, 2 H), 7.48-7.51 (m, 2 H), 7.55-7.59 (m, 1 H), 7.63-7.67 (m, 1 H), 7.87-7.93 (m, 3 H), 8.02 (dd, J = 1.6 Hz and 8.4 Hz, 1 H), 8.43 (d, J = 1.6 Hz, 1 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ: 68.0, 124.0, 127.3, 128.1, 128.86 (2), 128.92 (2), 129.0, 129.1, 129.8, 129.9, 130.1, 132.4, 133.8, 134.8, 136.5, 163.9, 186.1.

benzyl 2-(naphthalen-4-yl)-2-oxoacetate (3m)<sup>4</sup> The aryl α-keto ester 3m was prepared by the same procedure for aryl α-keto ester 3a from the diazo ester 1m (151 mg, 0.5 mmol) and benzyl azide 2a (133 mg, 1.0 mmol) in 86% yield (125 mg) as a yellow oil: TLC R<sub>f</sub> (ethyl acetate/petroleum ether = 1/10) = 0.36; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ: 5.47 (s, 2 H), 7.37-7.44 (m, 3 H), 7.48-7.51 (m, 3 H), 7.55-7.61 (m, 1 H), 7.66-7.76 (m, 1 H), 7.89-7.93 (m, 2 H), 8.09 (d, J = 8.4 Hz, 1 H), 9.06 (d, J = 8.8 Hz, 1 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ: 67.9, 124.4, 125.6, 127.1, 128.0, 128.72 (2), 128.82 (2), 128.88, 129.4, 131.0, 133.9, 134.3, 134.6, 136.0, 164.5, 188.5.
Intermolecular reaction of azido amine 5 with diazophenylacetates 1a

\[
\begin{array}{c}
\text{N}_2 \\
\text{CO}_2\text{Et} + \\
\text{NHT}_{\text{Ts}} \\
\text{N}_3 \\
\text{CO}_2\text{Et} \\
\text{Rh}_2(\text{Oct})_4 \\
\text{NHT}_{\text{Ts}} \\
\text{73%}
\end{array}
\]

To a stirred mixture of Rh₂(Oct)₄ (2.7 mg, 0.003 mmol) and azido amine 5 (133 mg, 1.0 mmol) in DCM (2.0 mL) was added a solution of ethyl diazophenylacetate 1a (95 mg, 0.5 mmol) in DCM (3.0 mL) over a period of 30 min. The reaction mixture was kept at 10-15 °C for 30 min. The reaction mixture was concentrated and purified by flash chromatography to afford the ethyl 2-(3-(tosylamino)propylimino)-2-phenylacetate (6) as a yellow oil (146 mg, 73% yield from diazophenylacetate 1a): TLC R_f (ethyl acetate/petroleum ether = 1/5) = 0.16; '^H NMR (CDCl₃, 400 MHz) δ: 1.38 (t, J = 7.2 Hz, 3 H), 1.86-1.92 (m, 2 H), 2.37 (s, 3 H), 3.07-3.11 (m, 2 H), 3.55 (t, J = 6.0 Hz, 2 H), 4.43 (q, J = 7.2 Hz, 2 H), 5.58 (t, J = 6.0 Hz, 1 H), 7.22 (d, J = 8.4 Hz, 2 H), 7.40-7.47 (m, 3 H), 7.63 (d, J = 8.4 Hz, 2 H), 7.70 (d, J = 8.4 Hz, 2 H); '^C NMR (CDCl₃, 100 MHz) δ: 14.4, 21.6, 29.8, 42.0, 52.5, 61.8, 127.13 (2), 127.15 (2), 128.8 (2), 129.7 (2), 131.4, 133.8, 137.0, 143.2, 161.0, 165.5; IR (film) 3422, 1731, 1633, 1311, 1159 cm⁻¹; HRMS (ESI) calcd for C₂₀H₂₅N₂O₄S (M⁺ + H) 389.1530, found 389.1527.

Hydrogenation of the crude mixture of imino ester 4a.

\[
\begin{array}{c}
\text{N}_2 \\
\text{O} \\
\text{O} \\
\text{H} \\
\text{N} \\
\text{O} \\
\text{CO}_2\text{Et}
\end{array}
\]

To a stirred solution of Rh₂(Oct)₄ (2.7 mg, 0.003 mmol) in DCM (0.5 mL) was added a mixture of ethyl diazophenylacetate 1a (95 mg, 0.50 mmol) and benzy1 azide 2a (74 mg, 0.55 mmol) in DCM (2.0 mL) in 30 min. The reaction mixture was kept at 10-15 °C for 30 min, then the mixture was concentrated and diluted in MeOH (2 mL) in an autoclave. Then the Ru/C (5%, 27 mg) was added, hydrogen gas was charged. The reaction was stirred under H₂ (6.0 Mpa) for 3 h at room temperature. The hydrogen gas was released carefully and slowly. The mixture was filtered, and then concentrated to afford the amino ester 8 as a slight yellow oil (NMR pure, 101 mg, 75% yield):
TLC Rf (ethyl acetate/petroleum ether = 1/5) = 0.38; 1H NMR (CDCl₃, 400 MHz) δ: 1.22 (t, J = 7.2 Hz, 3 H), 2.42 (bs, 1 H), 3.76 (s, 2 H), 4.11-4.23 (m, 2 H), 4.40 (s, 1 H), 7.26-7.43 (m, 10 H); 13C NMR (CDCl₃, 100 MHz) δ: 14.2, 51.4, 61.2, 64.4, 127.1, 127.6 (2), 128.1, 128.4 (2), 128.5 (2), 128.7 (2).

References:
