Copper-mediated synthesis of aryl α-keto amides from epoxide derivatives

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Table of content

General methods.................................................................................................................................S1

General procedure for copper-mediated synthesis of aryl α-ketoamides from epoxide derivatives..............................S2

NMR data for products.......................................................................................................................S2

References...........................................................................................................................................S6

Copies of NMR spectra of products..................................................................................................S7
**General methods**

1,4-dioxane, toluene, DCE and DMF were purchased from domestic corporations and used without purification. Copper catalysts were purchased from Alfa. Analytical thin layer chromatography (TLC) plates, preparative TLC and the silica gel for column chromatography were phased from Qingdao Haiyang Chemical and Special Silica Gel Co, Ltd.

High-resolution LC-MS was carried out by Agilent LC/MSD TOF using a column of Agilent ZORBAX SB-C18 (rapid resolution, 3.5 μm, 2.1 × 30 mm) at a flow of 0.40 mL/min. The solvent was MeOH/water (75:25 (v/v)), containing 5 mmol/L ammonium formate. The ion source is electrospray ionization (ESI).

Proton nuclear magnetic resonance (1H NMR) and carbon nuclear magnetic resonance (13C NMR) spectroscopy were performed on Bruker Advance 400M and 500 M NMR spectrometers. Chemical shifts of 1H NMR spectra are reported as in units of parts per million (ppm) downfield from SiMe4 (δ 0.0) and relative to the signal of chloroform-d (δ = 7.260, singlet) and DMSO-d6 (δ = 2.500, quintet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublet of doublets); m (multiplets), etc. The number of protons (n) for a given resonance is indicated by nH. Carbon nuclear magnetic resonance spectra (13C NMR) are reported as in units of parts per million (ppm) downfield from SiMe4 (δ 0.0) and relative to the signal of chloroform-d (δ = 77.230, triplet) and DMSO-d6 (δ = 39.510, septet).
General procedure for copper-mediated synthesis of aryl α-ketoamides from epoxide derivatives

The mixture of epoxide (1.0 mmol), Cu(OAc)$_2$ (2.0 mmol) in DMF (2.0 mL) was stirred at 120°C under an atmosphere of O$_2$ overnight, then cooled to room temperature and diluted with ethyl acetate. H$_2$O was added and the mixture was extracted by ethyl acetate. The organic layer was washed with brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified with flash column chromatography to afford the desired product.

N,N-dimethyl-2-oxo-2-phenylacetamide (3a) ¹

Oil, 133 mg, 75% yield, R$_f$ = 0.5 (EtOAc/Petroleum ether = 1:3). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.12 – 7.84 (m, 2H), 7.72 – 7.57 (m, 1H), 7.57 – 7.41 (m, 2H), 3.08 (s, 3H), 2.93 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 191.9, 167.2, 134.9, 133.2, 129.8, 129.1, 37.2, 34.1.

N,N-dimethyl-2-oxo-2-(p-tolyl)acetamide (3b) ¹

Oil, 124 mg, 65% yield, R$_f$ = 0.5 (EtOAc/Petroleum ether = 1:3). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.79 (d, $J$ = 8.2 Hz, 2H), 7.26 (d, $J$ = 7.9 Hz, 2H), 3.06 (s, 3H), 2.90 (s, 3H), 2.39 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 191.7, 167.4, 146.1, 130.8, 130.0, 129.9, 37.2, 34.1, 22.0.

2-(4-(tert-butyl)phenyl)-N,N-dimethyl-2-oxoacetamide (3c) ²
Oil, 145 mg, 62% yield, Rf = 0.5 (EtOAc/Petroleum ether = 1:3). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.81 (d, $J = 8.6$ Hz, 2H), 7.63 (d, $J = 8.6$ Hz, 2H), 3.01 (s, 3H), 2.86 (s, 3H), 1.30 (s, 9H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 191.7, 166.5, 158.3, 130.2, 129.2, 126.2, 36.4, 35.1, 33.1, 30.6.

2-(4-bromophenyl)-N,N-dimethyl-2-oxoacetamide (3d) ²

Oil, 156 mg, 61% yield, Rf = 0.5 (EtOAc/Petroleum ether = 1:3). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.93 – 7.73 (m, 2H), 7.72 – 7.55 (m, 2H), 3.11 (s, 3H), 2.96 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 190.7, 166.6, 132.6, 131.3, 130.4, 128.1, 37.3, 34.3.

2-(4-chlorophenyl)-N,N-dimethyl-2-oxoacetamide (3e) ¹

Oil, 131 mg, 62% yield, Rf = 0.5 (EtOAc/Petroleum ether = 1:3). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.88 (d, $J = 8.6$ Hz, 2H), 7.68 (d, $J = 8.6$ Hz, 2H), 3.01 (s, 3H), 2.87 (s, 3H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 190.8, 165.9, 140.0, 131.3, 131.1, 129.6, 36.4, 33.3.

2-(4-fluorophenyl)-N,N-dimethyl-2-oxoacetamide (3f) ¹

Oil, 133 mg, 68% yield, Rf = 0.5 (EtOAc/Petroleum ether = 1:3). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.97 – 7.93 (m, 2H), 7.17 – 7.12 (m, 2H), 3.08 (s, 3H), 2.93 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 190.2, 166.9 (d, $J = 258.8$ Hz), 132.7 (d, $J = 9.7$ Hz), 128.1 (d, $J = 7.3$ Hz), 116.5 (d, $J = 22.3$ Hz), 115.6 (d, $J = 21.5$ Hz), 37.3, 34.3.

N,N-dimethyl-2-oxo-2-(4-(trifluoromethyl)phenyl)acetamide (3g) ⁴
Oil, 152 mg, 62% yield, Rf = 0.5 (EtOAc/Petroleum ether = 1:3). 1H NMR (400 MHz, CDCl3) δ 8.05 (dd, J = 8.8, 0.6 Hz, 2H), 7.74 (dd, J = 8.7, 0.5 Hz, 2H), 3.08 (s, 3H), 2.93 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 190.4, 166.2, 135.9, 135.8 (q, J = 33.0 Hz), 130.2, 126.2 (q, J = 3.7 Hz), 124.9, 122.2, 37.2, 34.3.

**N,N-dimethyl-2-(4-nitrophenyl)-2-oxoacetamide (3h)**

Oil, 100 mg, 45% yield, Rf = 0.5 (EtOAc/Petroleum ether = 1:3). 1H NMR (400 MHz, CDCl3) δ 8.29 (d, J = 9.0 Hz, 2H), 8.09 (d, J = 9.0 Hz, 2H), 3.10 (s, 3H), 2.96 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 189.4, 165.8, 137.6, 130.9, 127.2, 124.2, 37.2, 34.4.

**N,N-dimethyl-2-oxo-2-(o-tolyl)acetamide (3i)**

Oil, 138 mg, 72% yield, Rf = 0.5 (EtOAc/Petroleum ether = 1:3). 1H NMR (400 MHz, CDCl3) δ 7.69 – 7.65 (m, 1H), 7.49 – 7.41 (m, 1H), 7.33 – 7.26 (m, 2H), 3.08 (s, 3H), 2.95 (s, 3H), 2.64 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 193.9, 168.0, 141.7, 133.9, 132.8, 132.8, 131.7, 126.4, 37.2, 34.2, 21.9.

**2-(2-chlorophenyl)-N,N-dimethyl-2-oxoacetamide (3j)**

Oil, 106 mg, 50% yield, Rf = 0.5 (EtOAc/Petroleum ether = 1:3). 1H NMR (400 MHz, CDCl3) δ 7.86 (dd, J = 7.7, 1.7 Hz, 1H), 7.50 – 7.46 (m, 1H), 7.43 – 7.35 (m, 2H), 3.04 (s, 3H), 3.05 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 190.4, 167.1, 134.5, 133.9, 133.7, 132.5, 131.0, 127.5, 37.3, 34.7.
N,N-dimethyl-2-oxo-2-(m-tolyl)acetamide (3k)

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\begin{align*}
\text{Oil, 141 mg, 74% yield, } R_f &= 0.5 \text{ (EtOAc/Petroleum ether = 1:3). }^3 \\
^1H \text{ NMR (400 MHz, CDCl}_3\right) &\delta 7.72 - 7.67 (m, 2H), 7.40 (d, J = 7.6 Hz, 1H), 7.38 - 7.31 (m, 1H), 3.07 (s, 3H), 2.90 (s, 3H), 2.36 (s, 3H). \\
^13C \text{ NMR (101 MHz, CDCl}_3\right) &\delta 192.2, 167.3, 139.1, 135.7, 133.2, 130.1, 129.0, 127.1, 37.2, 34.1, 21.4.
\end{align*}
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2-(2,5-dimethylphenyl)-N,N-dimethyl-2-oxoacetamide (3l)

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\begin{align*}
\text{Oil, 105 mg, 51% yield, } R_f &= 0.5 \text{ (EtOAc/Petroleum ether = 1:3). }^3 \\
^1H \text{ NMR (400 MHz, DMSO-d}_6\right) &\delta 7.43 (s, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.30 (d, J = 7.7 Hz, 1H), 3.00 (s, 3H), 2.89 (s, 3H), 2.51 (s, 3H), 2.33 (s, 3H). \\
^13C \text{ NMR (101 MHz, DMSO-d}_6\right) &\delta 194.0, 167.0, 137.1, 135.7, 134.6, 132.4, 132.2, 131.2, 36.4, 33.3, 20.6, 20.3.
\end{align*}
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N,N-diethyl-2-oxo-2-phenylacetamide (3m)

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\begin{align*}
\text{Oil, 103 mg, 50% yield, } R_f &= 0.5 \text{ (EtOAc/Petroleum ether = 1:3). }^3 \\
^1H \text{ NMR (400 MHz, CDCl}_3\right) &\delta 7.94 - 7.90 (m, 2H), 7.65 - 7.57 (m, 1H), 7.52 - 7.46 (m, 2H), 3.55 (q, J = 7.2 Hz, 2H), 3.23 (q, J = 7.1 Hz, 2H), 1.30 - 1.25 (m, 3H), 1.14 (t, J = 7.1 Hz, 3H). \\
^13C \text{ NMR (101 MHz, CDCl}_3\right) &\delta 191.6, 166.7, 134.6, 133.3, 129.7, 129.0, 42.1, 38.8, 14.1, 12.9.
\end{align*}
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References:


