Palladium-Catalysed Carbonylative α-Arylation of Nitromethane

Zhong Lian, Stig D. Friis and Troels Skrudstrup*

Carbon Dioxide Activation Center (CADIAC), Department of Chemistry and the Interdisciplinary Nanoscience Center, Aarhus University, Gustav Wieds Vej 14, 8000 Aarhus C, Denmark

ts@chem.au.dk

Supporting Information

Table of contents

General methods S2

General procedure A: Carbonylative α-arylation of nitromethane (Scheme 2) S2

General procedure B: [3+2] Dipolar cycloaddition of α-nitroketones (Scheme 3) S9

Pyrrole Synthesis from α-nitroketones (Scheme 4) S10

References S11

NMR spectra S12
General Method

All reactions were setup using the commercially available COware two chamber system, with self-sealing PTFE/silicon septa. All purchased chemicals were used as received without further purification. Chemicals were purchased from Sigma-Aldrich. All Dry solvents were afforded by adding activated 4Å molecular sieves and purging rigorously with argon. HPLC grade solvents were purchased from Sigma-Aldrich. CHCl₃ (ethanol-free) was filtered through a short pad of potassium carbonate prior to use. Flash chromatography was carried out on silica gel 60 (230–400 mesh). ¹H NMR spectra were recorded at 400 MHz, ¹³C NMR spectra were recorded at 100 MHz and ¹⁹F NMR spectra were recorded at 376 MHz on a Bruker Ascend 400 spectrometer. Chemical shifts were reported in ppm downfield to TMS (δ = 0) and referenced to the solvent residual peak, using the following peak pattern abbreviations: br, broad; s, single; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; dt, doublet of triplets; dm, doublet of multiplets; td, triplet of doublets. MS spectra were recorded on a LC TOF (ESI) apparatus.

General procedure A: Carbonylative α-arylation of nitromethane

Chamber 1: In an argon filled glovebox, to chamber 1 of a COware two-chamber system, was added aryl iodides 1 (0.40 mmol), Pd(OAc)₂ (4.5 mg, 0.02 mmol), XantPhos (11.6 mg, 0.02 mmol), MgCl₂ (46 mg, 0.48 mmol), nitromethane (4.0 mL) and triethylamine (0.22 mL, 1.60 mmol) in that order. The chamber was sealed with a screwcap fitted with a Teflon seal. Chamber 2 (2.5 equiv CO): To chamber 2 of the two-chamber system was added 9-methylfluorene-9-carbonyl chloride (243 mg, 1.0 mmol), Pd(dba)₂ (29 mg, 0.05 mmol), HBF₄•P(PrBu)₃ (29 mg, 0.10 mmol), anisole (4.0 mL) and triethylamine (0.33 mL, 2.4 mmol) in that order. The chamber was sealed with a screwcap fitted with a Teflon seal. The loaded two-chamber system was removed from the glovebox and stirred at 60 °C for 16 h. After this period, the reaction (chamber 1) was quenched with 10% aqueous CH₃COOH (3 mL) and stirred at room temperature for 1 h. The mixture was extracted with CH₂Cl₂ and dried over anhydrous Na₂SO₄. The volatiles were removed under reduced pressure. The crude residue was subjected to flash column chromatography using pentane/ethyl acetate (0.1% CH₃COOH) as eluent to afford the desired products 2.

1-(4-methoxyphenyl)-2-nitroethan-1-one (2a)

Prepared according to procedure A; isolated as white solid (62 mg, 80%) using pentane/ethyl acetate (4:1, 0.1% CH₃COOH) as eluent. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.86 (d, J=9.0 Hz, 2H), 7.00 (d, J=9.0 Hz, 2H), 5.84 (s, 2H), 3.90 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 183.9, 165.0, 130.7 (2C), 126.4, 114.5 (2C), 81.0, 55.7. HRMS C₉H₈NO₄ [M+H]⁺; calculated 196.0610, found: 196.0603.

1-(3-methoxyphenyl)-2-nitroethan-1-one (2b)

Prepared according to procedure A; isolated as white solid (51 mg, 66%) using pentane/ethyl acetate (4:1, 0.1% CH₃COOH) as eluent. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.47-7.40 (m, 2H), 7.40-7.35 (m, 1H), 5.88 (s, 2H), 3.90 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 185.6, 160.2, 134.6, 130.3, 121.6, 120.6, 112.4, 81.3, 55.6. HRMS C₉H₈NO₄ [M+H]⁺; calculated 196.0610, found: 196.0603.
1-(2-methoxyphenyl)-2-nitroethan-1-one (2c)

Prepared according to procedure A; isolated as white solid (41 mg, 53%) using pentane/ethyl acetate (4:1, 0.1% CH₃COOH) as eluent. $^1$H NMR (400 MHz, CDCl₃) $\delta$ (ppm) 7.99 (dd, $J=8.0$, 2.0 Hz, 1H), 7.64-7.56 (m, 1H), 7.12-7.05 (m, 1H), 7.02 (d, $J=8.0$ Hz, 1H), 5.78 (s, 2H), 3.95 (s, 3H). $^{13}$C NMR (100 MHz, CDCl₃) $\delta$ (ppm) 185.9, 159.6, 136.3, 131.4, 123.3, 121.4, 111.8, 85.3, 55.7. HRMS C₉H₉NO₄ [M+H]$^+$; calculated 196.0610, found: 196.0604.

1-(3,4-dimethoxyphenyl)-2-nitroethan-1-one (2d)

Prepared according to procedure A; isolated as white solid (70 mg, 78%) using pentane/ethyl acetate (2:1, 0.1% CH₃COOH) as eluent. $^1$H NMR (400 MHz, CDCl₃) $\delta$ (ppm) 7.50 (d, $J=2.0$ Hz, 1H), 7.42 (dd, $J=8.4$, 2.1 Hz, 1H), 6.94 (d, $J=8.4$ Hz, 1H), 5.88 (s, 2H), 3.99 (s, 3H), 3.95 (s, 3H). $^{13}$C NMR (100 MHz, CDCl₃) $\delta$ (ppm) 184.1, 154.9, 149.7, 126.6, 123.1, 110.3, 110.1, 81.0, 56.2, 56.1. HRMS C₁₀H₁₁NO₅ [M+H]$^+$; calculated 226.0715, found: 226.0712.

1-(4-(methylthio)phenyl)-2-nitroethan-1-one (2e)

Prepared according to procedure A; isolated as white solid (61 mg, 72%) using pentane/ethyl acetate (4:1, 0.1% CH₃COOH) as eluent. $^1$H NMR (400 MHz, CDCl₃) $\delta$ (ppm) 7.78 (d, $J=8.4$ Hz, 2H), 7.32 (d, $J=8.4$ Hz, 2H), 2.56 (s, 3H). $^{13}$C NMR (100 MHz, CDCl₃) $\delta$ (ppm) 185.0, 149.6, 129.8, 129.0 (2C), 125.6 (2C), 81.6, 15.0. HRMS C₉H₉NSO₃ [M+H]$^+$; calculated 212.0381, found: 212.0375.

1-(4-(2,5-dimethyl-1H-pyrrol-1-yl)phenyl)-2-nitroethan-1-one (2f)

Prepared according to procedure A; isolated as white solid (68 mg, 66%) using pentane/ethyl acetate (4:1, 0.1% CH₃COOH) as eluent. $^1$H NMR (400 MHz, CDCl₃) $\delta$ (ppm) 8.04 (d, $J=8.5$ Hz, 2H), 7.43 (d, $J=8.5$ Hz, 2H), 5.98 (s,
$^2$H, 5.97 (s, 2H), 2.10 (s, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 185.0, 145.0, 132.1, 129.3 (2C), 128.9 (2C), 128.5 (2C), 107.2 (2C), 81.2, 13.1 (2C). HRMS C$_{14}$H$_{14}$N$_2$O$_3$ [M+H]$^+$; calculated 259.1083, found: 259.1077.

2-nitro-1-(p-tolyl)ethan-1-one (2g)

\[
\begin{array}{c}
\text{O} \\
\text{NO}_2 \\
\text{Ph}
\end{array}
\]

Prepared according to procedure A; isolated as white solid (58 mg, 81%) using pentane/ethyl acetate (4:1, 0.1% CH$_3$COOH) as eluent. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.77 (d, $J$=8.0 Hz, 2H), 7.33 (d, $J$=8.0 Hz, 2H), 5.86 (s, 2H), 2.45 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 185.2, 146.4, 131.0, 130.0 (2C), 128.3 (2C), 81.2, 21.8. HRMS C$_9$H$_9$NO$_3$ [M+H]$^+$; calculated 180.0661, found: 180.0654.

2-nitro-1-phenylethan-1-one (2h)

\[
\begin{array}{c}
\text{O} \\
\text{NO}_2 \\
\text{Ph}
\end{array}
\]

Prepared according to procedure A; isolated as white solid (54 mg, 72%). Alternatively, starting from 4-bromoanisole: According to procedure A, albeit at a reaction temperature of 85 °C; isolated as white solid (15 mg, 23%). Purified using pentane/ethyl acetate (4:1, 0.1% CH$_3$COOH) as eluent. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.88 (dd, $J$=8.3, 1.1 Hz, 2H), 7.69 (dd, $J$=10.7, 4.2 Hz, 1H), 7.54 (t, $J$=7.8 Hz, 2H), 5.90 (s, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 185.7, 135.1, 133.4, 129.3 (2C), 128.2 (2C), 81.3. HRMS C$_8$H$_7$NNaO$_3$ [M+Na]$^+$; calculated 188.0324, found: 188.0318.

1-(4-chlorophenyl)-2-nitroethan-1-one (2i)

\[
\begin{array}{c}
\text{Cl} \\
\text{O} \\
\text{NO}_2 \\
\text{Ph}
\end{array}
\]

0.5 mmol scale: Prepared according to procedure A; isolated as white solid (56 mg, 70%) using pentane/ethyl acetate (4:1, 0.1% CH$_3$COOH) as eluent. 4.0 mmol scale: Under an ambient atmosphere, Pd(OAc)$_2$ (46 mg, 0.20 mmol), XantPhos (116 mg, 0.20 mmol), anhydrous MgCl$_2$ (457 mg, 4.8 mmol) and 1-chloro-4-iodobenzene (954 mg, 4.0 mmol) was weighed into chamber 1 of a COware two-chamber system (total volume 400 mL). 9-Methylfluorene-9-carbonyl chloride (2427 mg, 10.0 mmol), Pd(dba)$_2$ (23.0 mg, 0.04 mmol) and HBF$_4$•P(tBu)$_3$ (11.6 mg, 0.04 mmol) was weighed into chamber 2. The two-chamber system was taken into an argon filled glovebox where nitromethane (40 mL) and triethylamine (2.23 mL, 16.0 mmol) was added to chamber 1. Anisole (40 mL) and triethylamine (3.34 mL, 24 mmol) was added to chamber 2 before the system was closed with Teflon-seal fitted screwcap, removed from the glovebox and stirred for 16 h at 60 °C. After this period, the reaction (chamber 1) was quenched with 10% aqueous CH$_3$COOH (30 mL) and stirred at room temperature for 1 h. The mixture was extracted with CH$_2$Cl$_2$ and dried over anhydrous MgSO$_4$, before the volatiles were removed under reduced pressure. The crude residue was subjected to flash column chromatography using a gradient of ethyl acetate (20-25%) in pentane with 0.1% HCOOH as eluent to afford the desired products 2i as a colorless crystalline solid (578 mg, 72%).
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.76 (d, $J=8.6$ Hz, 2H), 7.46 (d, $J=8.6$ Hz, 2H), 5.78 (s, 2H). Minor tautomer observed in some cases, inter alia (characteristic peaks) 13.73 (s, 1H), 7.68 (d, $J=8.7$ Hz, 2H), 7.42 (d, $J=8.7$ Hz, 2H), 7.34 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 184.5, 141.9, 131.7, 129.7 (2C), 129.6 (2C), 81.0; minor tautomer inter alia (characteristic peaks) 129.5 (2C), 128.1 (2C).

HRMS C$_8$H$_6$ClNO$_3$ [M+H]$^+$; calculated 200.0114, found: 200.0102.

1-(2-chlorophenyl)-2-nitroethan-1-one (2j)

Prepared according to procedure A; isolated as white solid (41 mg, 52%) using pentane/ethyl acetate (4:1, 0.1% CH$_3$COOH) as eluent. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.80 (d, $J=7.6$ Hz, 1H), 7.61 – 7.41 (m, 3H), 5.93 (s, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 187.3, 134.4, 134.2, 132.3, 131.2, 131.0, 127.6, 83.6. HRMS C$_8$H$_6$ClNO$_3$ [M+H]$^+$; calculated 200.0114, found: 200.0114.

4-(2-nitroacetyl)phenyl 4-methylbenzenesulfonate (2k)

Prepared according to procedure A; isolated as white solid (88 mg, 66%) using pentane/ethyl acetate (4:1, 0.1% CH$_3$COOH) as eluent. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.83 (d, $J=8.8$ Hz, 2H), 7.72 (d, $J=8.2$ Hz, 2H), 7.34 (d, $J=8.2$ Hz, 2H), 7.18 (d, $J=8.8$ Hz, 2H), 5.84 (s, 2H), 2.46 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 184.4, 154.3, 146.1, 131.9, 131.8, 130.1 (2C), 130.0 (2C), 128.4 (2C), 123.2 (2C), 81.0, 21.7. HRMS C$_{15}$H$_{13}$NNaO$_6$S [M+Na]$^+$; calculated 358.0361, found: 358.0360.

1-(2-fluorophenyl)-2-nitroethan-1-one (2l)

Prepared according to procedure A; isolated as white solid (33 mg, 45%) using pentane/ethyl acetate (5:1, 0.1% CH$_3$COOH) as eluent. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 8.05 (td, $J=7.7$, 1.8 Hz, 1H), 7.68 (dd, $J=8.4$, 7.2, 5.3, 1.9 Hz, 1H), 7.38 – 7.31 (m, 1H), 7.22 (dd, $J=11.5$, 8.4, 0.8 Hz, 1H), 5.81 (d, $J=3.5$ Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 183.5 (d, $J=3.7$ Hz), 162.3 (d, $J=254.4$ Hz), 137.0 (d, $J=9.5$ Hz), 131.1 (d, $J=1.9$ Hz), 125.4 (d, $J=3.2$ Hz), 121.7 (d, $J=12.3$ Hz), 116.8 (d, $J=23.4$ Hz), 84.4 (d, $J=12.8$ Hz). $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ (ppm) -109.5 (m). HRMS C$_8$H$_6$FNO$_3$ [M+H]$^+$; calculated 184.0410, found: 184.0404.
**1-(3-acetylphenyl)-2-nitroethan-1-one (2m)**

![Chemical Structure](image)

Prepared according to procedure A; isolated as white solid (52 mg, 63%) using pentane/ethyl acetate (2:1, 0.1% CH₃COOH) as eluent. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.41 (t, J=1.6 Hz, 1H), 8.26 – 8.22 (m, 1H), 8.09 (ddd, J=7.8, 1.7, 1.2 Hz, 1H), 7.67 (t, J=7.8 Hz, 1H), 5.97 (s, 2H), 2.66 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 196.6, 185.4, 141.6, 136.3, 129.0 (2C), 128.5 (2C), 81.2, 26.9. HRMS C₁₀H₉NO₄ [M+H]⁺; calculated 208.0610, found: 208.0606.

**1-(4-acetylphenyl)-2-nitroethan-1-one (2n)**

![Chemical Structure](image)

Prepared according to procedure A; isolated as white solid (51 mg, 62%). Alternatively, starting from 4-bromoacetophenone: According to procedure A, albeit at a reaction temperature of 85 °C; isolated as white solid (20 mg, 25%). Purified using pentane/ethyl acetate (4:1, 0.1% CH₃COOH) as eluent. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.09 (d, J=8.6 Hz, 2H), 7.97 (d, J=8.6 Hz, 2H), 5.91 (s, 2H), 2.67 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 196.9, 185.3, 141.6, 136.3, 129.0 (2C), 128.5 (2C), 81.2, 26.9. HRMS C₁₀H₉NO₄ [M]⁺; calculated 207.0532, found: 207.0531.

**ethyl 4-(2-nitroacetyl)benzoate (2o)**

![Chemical Structure](image)

Prepared according to procedure A; isolated as white solid (57 mg, 61%) using pentane/ethyl acetate (4:1, 0.1% CH₃COOH) as eluent. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.17 (d, J=8.6 Hz, 2H), 7.93 (d, J=8.6 Hz, 2H), 5.93 (s, 2H), 4.41 (q, J=7.1 Hz, 2H), 1.41 (t, J=7.1 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 185.5, 165.2, 136.4, 136.0, 130.4 (2C), 128.2 (2C), 81.4, 61.8, 14.3. HRMS C₁₁H₁₁N⁺NaO₅ [M+Na]⁺; calculated 260.0535, found: 260.0529.

**4-(2-nitroacetyl)benzonitrile (2p)**

![Chemical Structure](image)

Prepared according to procedure A; isolated as white solid (36 mg, 47%). Alternatively, starting from 4-bromobenzonitrile: According to procedure A, albeit at a reaction temperature of 85 °C; isolated as white solid (23
mg, 30%). Purified using pentane/ethyl acetate (4:1, 0.1% CH₃COOH) as eluent. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.00 (d, J=8.6 Hz, 2H), 7.86 (d, J=8.6 Hz, 2H), 5.89 (s, 2H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 184.7, 133.1 (2C), 132.8, 128.7 (2C), 118.4, 117.2, 80.9. HRMS C₉H₆N₂O₃ [M+H]+; calculated 191.0457, found: 191.0454.

1-(naphthalen-1-yl)-2-nitroethan-one (2q)

\[
\begin{align*}
\text{1H NMR (400 MHz, CDCl}_3\text{) } & \delta \text{ (ppm) 8.86 (d, } J=8.7 \text{ Hz, 1H), 8.13 (d, } J=8.2 \text{ Hz, 1H), 7.92 (d, } J=8.1 \text{ Hz, 1H), 7.83 (dd, } J=7.3 \text{, 1.0 Hz, 1H), 7.69 (ddd, } J=8.6 \text{, 6.9, 1.4 Hz, 1H), 7.62 (dd, } J=8.1 \text{, 1.1 Hz, 1H), 7.58 – 7.51 \text{ (m, 1H), 5.97 (s, 2H); minor tautomer inter alia (characteristic peaks) 13.8 (s, 1H), 8.22 (d, } J=8.4 \text{ Hz, 1H), 7.97 (d, } J=8.2 \text{ Hz, 1H). ¹³C NMR (100 MHz, CDCl}_3\text{) } & \delta \text{ (ppm) 187.8, 135.5, 134.1, 130.5, 130.4, 129.4, 129.2, 128.7, 127.3, 125.5, 124.1, 82.7; minor tautomer inter alia (characteristic peaks) 133.0, 128.8, 127.9, 127.8, 126.9, 124.8, 124.7. HRMS C₁₂H₉NO₃ [M+H]+; calculated 216.0661, found: 216.0669.}
\end{align*}
\]

1-(naphthalen-2-yl)-2-nitroethan-one (2r)

\[
\begin{align*}
\text{1H NMR (400 MHz, CDCl}_3\text{) } & \delta \text{ (ppm) 8.32 (s, 1H), 7.92 (dd, } J=13.4 \text{, 12.9, 6.6 Hz, 4H), 7.71 – 7.64 \text{ (m, 1H), 7.64 – 7.58 (m, 1H), 6.03 (s, 2H). ¹³C NMR (100 MHz, CDCl}_3\text{) } & \delta \text{ (ppm) 178.1, 139.9, 136.7, 133.6, 128.8, 129.7, 129.4, 128.0, 127.5, 123.0, 81.4. HRMS C₁₂H₉NO₃ [M+H]+; calculated 216.0661, found: 216.0656.}
\end{align*}
\]

2-nitro-1-(thiophen-2-yl)ethan-one (2s)

\[
\begin{align*}
\text{1H NMR (400 MHz, CDCl}_3\text{) } & \delta \text{ (ppm) 7.84 (dd, } J=4.9 \text{, 1.0 Hz, 1H), 7.73 (dd, } J=3.9 \text{, 1.1 Hz, 1H), 7.22 (dd, } J=4.9 \text{, 3.9 Hz, 1H), 5.77 (s, 2H). ¹³C NMR (100 MHz, CDCl}_3\text{) } & \delta \text{ (ppm) 178.1, 139.9, 136.7, 133.6, 128.8, 80.7. HRMS C₈H₆SNO₃ [M+H]+; calculated 172.0068, found: 172.0064.}
\end{align*}
\]

2-nitro-1-(thiophen-3-yl)ethan-one (2t)

\[
\begin{align*}
\text{HRMS C₈H₆SNO₃ [M+H]+; calculated 172.0068, found: 172.0064.}
\end{align*}
\]
Prepared according to procedure A; isolated as white solid (46 mg, 67%) using pentane/ethyl acetate (4:1, 0.1% CH₃COOH) as eluent. "H NMR (400 MHz, CDCl₃) δ (ppm) 8.13 (s, 1H), 7.55 (s, 1H), 7.44 (s, 1H), 5.76 (s, 2H). "C NMR (100 MHz, CDCl₃) δ (ppm) 179.5, 138.1, 134.0, 127.9, 126.5, 81.5. HRMS C₆H₅SNO₃ [M+H]⁺; calculated 172.0068, found: 172.0060.

2-nitro-1-(pyridin-2-yl)ethan-1-one (2u)

Prepared according to procedure A; isolated as white solid (32 mg, 48%) using pentane/ethyl acetate (4:1, 0.1% CH₃COOH) as eluent. "H NMR (400 MHz, CDCl₃) δ (ppm) 8.70 (d, J=4.6 Hz, 1H), 8.14 (d, J=7.8 Hz, 1H), 7.95 (td, J=7.7, 1.6 Hz, 1H), 7.61 (ddd, J=7.6, 4.8, 1.1 Hz, 1H), 6.15 (s, 2H). "C NMR (100 MHz, CDCl₃) δ (ppm) 187.6, 150.4, 149.4, 137.5, 128.8, 122.6, 81.4. HRMS C₇H₆N₂O₃ [M+H]⁺; calculated 167.0457, found: 167.0450.

1-(1-methyl-1H-indol-5-yl)-2-nitroethan-1-one (2v)

Prepared according to procedure A; isolated as white solid (61 mg, 70%) using pentane/ethyl acetate (4:1, 0.1% CH₃COOH) as eluent. "H NMR (400 MHz, CDCl₃) δ (ppm) 8.15 (d, J=1.5 Hz, 1H), 7.79 (dd, J=8.7, 1.8 Hz, 1H), 7.40 (d, J=8.7 Hz, 1H), 7.20 (d, J=3.2 Hz, 1H), 6.66 (dd, J=3.2, 0.6 Hz, 1H), 5.98 (s, 2H). "C NMR (100 MHz, CDCl₃) δ (ppm) 185.3, 139.9, 131.3, 128.1, 125.4, 123.2, 121.5, 109.9, 103.4, 81.4, 33.1. HRMS C₁₁H₁₀N₂O₃ [M+H]⁺; calculated 219.0770, found: 219.0165.

13C-labelled 1-(4-methoxyphenyl)-2-nitroethan-1-one (13C-2a)

Prepared according to procedure A; isolated as white solid (61 mg, 78%) using pentane/ethyl acetate (4:1, 0.1% CH₃COOH) as eluent. "H NMR (400 MHz, CDCl₃) δ (ppm) 7.88 (d, J=4.7, 2H), 7.02 (d, J=8.3, 2H), 5.87 (d, J=4.1, 2H), 3.93 (s, 3H). "C NMR (100 MHz, CDCl₃) δ (ppm) 183.9 (13C), 169.6, 130.7 (d, J=3.1 Hz, 2C), 126.3 (d, J=61.3 Hz), 114.5 (d, J=4.6 Hz, 2C), 81.0 (d, J=39.6 Hz), 55.7. HRMS C₉₁₃H₉N₂O₄ [M+H]⁺; calculated 197.0643, found: 197.0640.

13C-labelled 2-nitro-1-phenylethan-1-one (13C-2h)
Prepared according to procedure A; isolated as white solid (47 mg, 71%) using pentane/ethyl acetate (4:1, 0.1% CH$_3$COOH) as eluent. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.91 (ddd, $J$=8.5, 4.2, 1.2 Hz, 2H), 7.72 (t, $J$=7.4 Hz, 1H), 7.57 (t, $J$=7.6 Hz, 2H), 5.92 (d, $J$=4.8 Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 185.6, 135.1, 133.7 (d, $J$=6.1 Hz), 129.3 (d, $J$=6.1 Hz), 129.3 (d, $J$=4.4 Hz, 2C), 128.2 (d, $J$=2.9 Hz, 2C), 81.2 (d, $J$=39.7 Hz). HRMS C$_7$H$_{13}$NO$_3$ [M+H]$^+$; calculated 167.0538, found: 167.0533.

**General procedure B: Cyclization of Benzylnitromethane with Dipolarophile**

Based on the procedure by Machetti.$^3$ A solution of benzylnitromethane (1.0 mmol), 1-methylimidazole (0.2 mmol) and the dipolarophile (0.4 mmol) in anhydrous and ethanol-free chloroform (1.4 mL) was stirred for 40 h in a sealed vial at 60 °C. The solvent was then removed. The residue was dissolved in diethyl ether and washed with brine, NaOH (1 M) and brine again. The organic layer was dried (sodium sulfate), filtered and concentrated under reduced pressure. The residue was subjected to flash column chromatography using pentane/ethyl acetate (20:1) as eluent to afford the desired products 3 and 4.

**phenyl(4-phenyl-4,5-dihydroisoxazol-3-yl)methanone (3)**

Prepared according to procedure B and using styrene as dipolarophile; isolated as clear oil (95 mg, 95%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 8.31 – 8.26 (m, 2H), 7.64 (ddd, $J$=6.9, 4.1, 1.3 Hz, 1H), 7.55 – 7.49 (m, 2H), 7.47 – 7.37 (m, 5H), 5.81 (dd, $J$=11.5, 8.8 Hz, 1H), 3.82 (dd, $J$=17.7, 11.5 Hz, 1H), 3.43 (dd, $J$=17.7, 8.8 Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 186.2, 157.4, 139.7, 135.8, 133.6, 130.3 (2C), 128.9(2C), 128.6, 128.4 (2C), 125.9 (2C), 84.2, 41.8. HRMS C$_{16}$H$_{13}$NO$_2$ [M+H]$^+$; calculated 252.1025, found: 252.1019.

**$^{13}$C-labelled phenyl(4-phenyl-4,5-dihydroisoxazol-3-yl)methanone ($^{13}$C-3)**

Prepared according to procedure B and using styrene as dipolarophile; isolated as clear oil (94 mg, 94%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 8.20 – 8.14 (m, 2H), 7.54 (t, $J$=7.4 Hz, 1H), 7.42 (t, $J$=7.8 Hz, 2H), 7.30 (dd, $J$=9.2, 3.9, 2.2 Hz, 5H), 5.71 (dd, $J$=11.5, 8.8 Hz, 1H), 3.77 – 3.67 (m, 1H), 3.37 – 3.27 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 186.2 ($^{13}$C), 157.4 (d, $J$=63.0 Hz), 139.7, 135.7 (d, $J$=58.3 Hz), 133.7, 130.4 (d, $J$=2.7 Hz, 2C), 128.9 (2C), 128.6, 128.4 (d, $J$=4.3 Hz, 2C), 125.9 (2C), 84.2, 41.9 (d, $J$=58.3 Hz). HRMS C$_{15}$H$_{13}$NO$_2$ [M+H]$^+$; calculated 253.1058, found: 253.1054.

**phenyl(4-phenylisoxazol-3-yl)methanone (4)**

![Diagram](image-url)
Prepared according to procedure B and using phenylacetylene as dipolarophile; isolated as slight yellow oil (67 mg, 68%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 8.27 (dd, $J$=5.2, 3.4 Hz, 2H), 7.80 – 7.75 (m, 2H), 7.62 – 7.54 (m, 1H), 7.49 – 7.40 (m, 5H), 6.97 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 185.8, 170.8, 162.4, 135.7, 134.0, 130.8, 130.7 (2C), 129.1 (2C), 128.6 (2C), 126.7, 126.0 (2C), 100.2. HRMS C$_{16}$H$_{11}$NO$_2$ [M+H]$^+$; calculated 250.0868, found: 250.0862.

$^3$C-labelled phenyl(4-phenylisoxazol-3-yl)methanone ($^{13}$C-4)

Prepared according to procedure B and using phenylacetylene as dipolarophile; isolated as slight yellow oil (66 mg, 66%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 8.32 – 8.24 (m, 2H), 7.79 (dd, $J$=7.7, 1.9 Hz, 2H), 7.59 (t, $J$=7.4 Hz, 1H), 7.50 – 7.41 (m, 5H), 6.99 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 185.8 ($^{13}$C), 170.8, 162.4 (d, $J$=62.4 Hz), 135.7 (d, $J$=58.5 Hz), 134.1, 130.8, 130.7 (d, $J$=3.0 Hz, 2C), 129.1 (2C), 128.6 (d, $J$=4.4 Hz, 2C), 126.7, 126.0 (2C), 100.2 (d, $J$=4.4 Hz). HRMS C$_{15}$H$_{11}$NO$_2$ [M+H]$^+$; calculated 251.0902, found: 251.0900.

Pyrrole Synthesis from $\alpha$-nitroketones

2-amino-1-(4-chlorophenyl)ethanone hydrochloride salt (5)

1-(4-chlorophenyl)-2-nitroethan-1-one (272 mg, 1.36 mmol) was dissolved in 99% EtOH (10 mL) before sulfide platinum on carbon (5%, 50 mg) was added. The flask was flushed with argon and then with H$_2$ from a balloon. After 5 min the exit needle was removed, concentrated hydrochloric acid (0.5 mL) was added and the reaction was heated to 50 °C. Complete conversion was observed by TLC after 2 h. Excess hydrogen was flushed from flask with argon and the reaction was cool to rt. The catalyst was removed by filtration and washed with methanol. After concentration under reduced pressure to approximately 15 mL and addition of acetone (10 mL) the product could be collected by filtration. A second crop of crystals was collected after concentration, dissolution in methanol and trituration with Et$_2$O. The two crops were dried under vacuum to provide the product as colorless needles (212 mg, 76%). $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ (ppm) 8.49 (s, 3H), 8.04 (d, $J$=8.4 Hz, 2H), 7.67 (d, $J$=8.4 Hz, 2H), 4.58 (s, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 192.6, 139.8, 132.9, 130.6 (2C), 129.6 (2C), 45.3. HRMS C$_8$H$_9$Cl$_2$NO [M-CI]$^+$; calculated 170.0373, found: 170.0368.

ethyl 4-(4-chlorophenyl)-2-methyl-1H-pyrrole-3-carboxylate (6)
2-amino-1-(4-chlorophenyl)ethanone hydrochloride salt (103 mg, 0.50 mmol), ethyl acetoacetate (75 µL, 0.59 mmol) and sodium acetate (248 mg, 3.0 mmol) was weighed into a flask and dissolved in mixture of water (10 mL) and 96% EtOH (5 mL). The resulting red solution was heated to reflux (oil-bath at 85 °C) for 3 h before water (10 mL) and saturated NaHCO$_3$ (5 mL) was added. Extraction with CH$_2$Cl$_2$, drying of the organic phases over MgSO$_4$ and concentration under reduced pressure provided the crude product as a red solid. Flash column chromatography using an eluent of 0-1 % Et$_2$O in CH$_2$Cl$_2$ afforded the pure product as a slightly yellow crystalline solid (111 mg, 84%).

$^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 8.34 (br s, 1H), 7.32 (d, $J$=8.8 Hz, 2H), 7.28 (d, $J$=8.8 Hz, 2H), 6.54 (d, $J$ = 2.5 Hz, 1H), 4.18 (q, $J$=7.1 Hz, 2H), 2.53 (s, 3H), 1.19 (t, $J$=7.1 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ (ppm) 165.6, 136.3, 134.3, 132.1, 130.6 (2C), 127.6 (2C), 126.1, 115.5, 110.0, 59.5, 14.2, 14.0. HRMS C$_{14}$H$_{14}$ClNO$_2$ [M+H]$^+$; calculated 264.0791, found: 264.0787.

References

1. A detailed description of how to use the COware two chamber system can be found on the www.sytracks.com.
NMR spectra

2a
$^{13}$C-2a
$^{13}$C-4