Supplement

Efficient Synthesis of Pharmaceutically Relevant Prochiral Heterocyclic Aminoketones

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General
All chemicals were purchased from Acros Organics (Queluz, Portugal), Aldrich (St. Louis, Missouri, United States), Alfa Aesar (Haverhill, Massachusetts, United States), Merck (Darmstadt, Germany) and Eurisotop (Saint-Aubin, France) and were used as received.

All reactions were monitored by TLC and the precoated TLC plates (Silica gel 60 F254) were visualized by exposure to ultraviolet light and/or ninhydrin stain.

General procedures
To a solution of morpholine (1000 µL, 11.6 mmol) in MTBE (10 mL) was added chloroacetone (0.5 equiv.) at room temperature. The reaction was stirred for 48 hours, then filtered and solvent was removed under reduced pressure. The residue was treated with MTBE and the precipitate was filtered, then the solvent was removed under reduced pressure to afford the crude mixture as a yellow liquid (Scheme S1).

To a solution of 4a-i (1000 µL) in MTBE (10 mL) was added potassium carbonate (1.5 equiv.) and chloroacetone (1.1 equiv.) at room temperature. The reaction was refluxed until completion (followed by TLC DCM:MeOH 9:1+0.1 % NH4OH), then filtered and the solvent and excess of chloroacetone removed under reduced pressure (10 mbar) by keeping the water bath at 70 °C. The residue was treated with MTBE and the precipitate was removed by filtration. The solvent was removed under reduced pressure to afford 6a-i (Scheme S2).

To a solution of 4a-i (1000 µL) in MTBE (10 mL) was added chloroacetone (0.6 equiv.) at room temperature. The reaction was refluxed until completion (followed by TLC DCM:MeOH 9:1+0.1 % NH4OH), then filtered and the solvent and excess of chloroacetone removed under reduced pressure (10 mbar) by keeping the water bath at 70 °C. The residue was treated with MTBE and the precipitate was removed by filtration. The solvent was removed under reduced pressure to afford 6a-i (Scheme S3).

Piperazine (1000 mg, 11.6 mmol) was dissolved in MTBE (10 mL) at reflux temperature, then chloroacetone (0.5 equiv.) was added and the reaction was refluxed until completion (followed by TLC DCM:MeOH 9:1+0.1 % NH4OH). The precipitation was filtered off, and the solvent evaporated to yield a yellow oil that was treated with MTBE. After filtration the solvent was evaporated to yield the crude mixture of 6i and 4i (Scheme S4).

Piperazine (1000 mg, 11.6 mmol) was dissolved in MTBE (10 mL) at reflux temperature, then potassium carbonate (3 equiv.) and chloroacetone (2.1 equiv.) was added and the reaction was refluxed until completion (followed by TLC DCM:MeOH 9:1+0.1 % NH4OH). The mixture was filtered and

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Scheme S1 Alkylation of morpholine (4a) at room temperature

Scheme S2 General procedure for alkylation of amine heterocycles (4a-i) with external base K2CO3

Scheme S3 General procedure for alkylation of amine heterocycles (4a-i) without external base

Scheme S4 Monoalkylation of piperazine (4j)
the solvent and excess chloroacetone removed under reduced pressure (10 mbar) by keeping the water bath at 70 °C to yield 6k (Scheme S5).

The solution of 6a-g in MTBE was treated with 4N HCl in dioxane (1.05 equiv.) under nitrogen atmosphere. The forming crystals were triturated and filtered under N₂ atm. to afford 7a-g. If the hydrochloride was not forming properly, the MTBE was evaporated and the residue was taken up in EtOH, then the hydrochloride was recrystallized by addition of MTBE (Scheme S6).

The solution of 6h,i,k in MTBE was treated with 4N HCl in dioxane (2.05 equiv.) under nitrogen atmosphere. The forming crystals were triturated and filtered under N₂ atm to afford 7h,i,k (Scheme S7).

The solution of 6j in MTBE was treated with 4N HCl in dioxane (1.05 equiv.) under nitrogen atmosphere. The forming crystals were triturated and filtered under N₂ atm. to afford 7j (Scheme S8).

Regeneration of 4i
The filter cake of the respective preparation of 6i with external base was dissolved in aqueous 1N NaOH solution (20 mL, pH > 10) and extracted with ethyl acetate. The organic phases were combined and dried on sodium sulfate. The solvent was evaporated to yield 4i as a colorless liquid.

Characterization of compounds
All melting points (mp) were determined on TA Instruments DSC250 calorimeter and are uncorrected. NMR spectra (Fig. S1–Fig. S36) were obtained with a Bruker Fourier 300 spectrometer, or a Magritec Spinsolve Benchtop NMR spectrometer at room temperature. Proton NMR spectra were recorded at 43 or 300 MHz, $^{13}$C NMR spectra were recorded at 75 MHz. Chemical shifts are given in ppm units, (1H NMR in DMSO-$d_6$; δ 2.50 ppm, or D$_2$O; δ = 4.79; $^{13}$C NMR in DMSO-$d_6$; δ = 39.5). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Spin-spin coupling constants (J) were given in Hz units. Infrared spectra (IR) of solid samples were recorded on a Nicolet Avatar 360 Fourier Transform Infrared spectrometer, of oils spectra were recorded on a Shimadzu IRAffinity-1 FTIR spectrometer. High-resolution mass spectra (HRMS) were recorded on an AB Sciex TripleTOF® 6600 System mass spectrometer.
Fig. S1 $^1$H NMR of 1-morpholinopropan-2-one (6a)

Fig. S2 $^{13}$C NMR of 1-morpholinopropan-2-one (6a)
Fig. S3 $^1$H NMR of 1-thiomorpholinopropan-2-one (6b)

Fig. S4 $^{13}$C NMR of 1-thiomorpholinopropan-2-one (6b)
Fig. S5 $^1$H NMR of 1-(4-methylpiperidin-1-yl)propan-2-one (6c)

Fig. S6 $^{13}$C NMR of 1-(4-methylpiperidin-1-yl)propan-2-one (6c)
Fig. S7 $^1$H NMR of 1-(4-benzylpiperidin-1-yl)propan-2-one (6d)

Fig. S8 $^{13}$C NMR of 1-(4-benzylpiperidin-1-yl)propan-2-one (6d)
Fig. S9 $^1$H NMR of 1-(2-oxopropyl)piperidine-4-carboxylate (6e)

Fig. S10 $^{13}$C NMR of 1-(2-oxopropyl)piperidine-4-carboxylate (6e)
Fig. S11 $^1$H NMR of 1-(pyrrolidin-1-yl)propan-2-one (6f)

Fig. S12 $^{13}$C NMR of 1-(pyrrolidin-1-yl)propan-2-one (6f)
Fig. S13 $^1$H NMR of 1-(azepan-1-yl)propan-2-one (6g)

Fig. S14 $^{13}$C NMR of 1-(azepan-1-yl)propan-2-one (6g)
Fig. S15 $^1$H NMR of 1-(4-methylpiperazin-1-yl)propan-2-one (6h)

Fig. S16 $^{13}$C NMR of 1-(4-methylpiperazin-1-yl)propan-2-one (6h)
**Fig. S17** $^1$H NMR of 1-(4-phenylpiperazin-1-yl)propan-2-one (6i)

**Fig. S18** $^{13}$C NMR of 1-(4-phenylpiperazin-1-yl)propan-2-one (6i)
Fig. S19 1H NMR of 1,1′-(piperazine-1,4-diyl)bis(propan-2-one) (6k)

Fig. S20 13C NMR of 1,1′-(piperazine-1,4-diyl)bis(propan-2-one) (6k)
Fig. S21 $^1$H NMR of 1-morpholinopropan-2-one hydrochloride (7a)

Fig. S22 $^{13}$C NMR of 1-morpholinopropan-2-one hydrochloride (7a)
Fig. S23 ¹H NMR of 1-thiomorpholinopropan-2-one hydrochloride (7b)

Fig. S24 ¹³C NMR of 1-thiomorpholinopropan-2-one hydrochloride (7b)
Fig. S25 ¹H NMR of 1-(4-methylpiperidin-1-yl)propan-2-one hydrochloride (7c)

Fig. S26 ¹³C NMR of 1-(4-methylpiperidin-1-yl)propan-2-one hydrochloride (7c)
Fig. S27 $^1$H NMR of 1-(azepan-1-yl)propan-2-one hydrochloride (7g)

Fig. S28 $^{13}$C NMR of 1-(azepan-1-yl)propan-2-one hydrochloride (7g)
Fig. S29 $^1$H NMR of 1-(4-methylpiperazin-1-yl)propan-2-one hydrochloride (7h)

Fig. S30 $^{13}$C NMR of 1-(4-methylpiperazin-1-yl)propan-2-one hydrochloride (7h)
Fig. S31 $^1$H NMR of 1-(4-phenylpiperazin-1-yl)propan-2-one hydrochloride (7i)

Fig. S32 $^{13}$C NMR of 1-(4-phenylpiperazin-1-yl)propan-2-one hydrochloride (7i)
Fig. S33 $^1$H NMR of 4-(2-oxopropyl)piperazin-1-ium hydrochloride (7j)

Fig. S34 $^{13}$C NMR of 4-(2-oxopropyl)piperazin-1-ium hydrochloride (7j)
Fig. S35 ¹H NMR of 1,1'-(piperazine-1,4-diyl)bis(propan-2-one) hydrochloride (7k)

Fig. S36 ¹³C NMR of 1,1'-(piperazine-1,4-diyl)bis(propan-2-one) hydrochloride (7k)
Yellow oil. **TLC** \((R_f)\) 0.69 (DCM:MeOH 9:1+0.1 % NH\(_2\)OH); **\(^1\)H NMR** (\(\delta\), 300 MHz, DMSO-\(d_6\)) 3.61 – 3.52 (m, 4H), 3.16 (s, 2H), 2.43 – 2.33 (m, 4H), 2.07 (s, 3H); **\(^13\)C NMR** (75 MHz, DMSO-\(d_6\)) \(\delta\) 207.08, 68.10, 66.57, 53.56, 28.01; **IR** (cm\(^{-1}\)): 3441, 2965, 2920, 2858, 2816, 1722, 1714, 1651, 1456, 1356, 1298, 1244, 1152, 1115, 1070, 1015, 869; **HRMS** (ESI\(^+\)) \([M+H]^+\) C\(_{13}\)H\(_{16}\)NO \(\text{calcd.}\) 232.1701, found: 232.1730 (Scheme S12).

Orange oil. **TLC** \((R_f)\) 0.67 (DCM:MeOH 9:1+0.1 % NH\(_2\)OH); **\(^1\)H NMR** (\(\delta\), 300 MHz, DMSO-\(d_6\)) 3.81 – 3.74 (m, 4H), 3.16 (s, 2H), 2.61 – 2.53 (m, 4H), 2.04 (s, 3H), 1.80 (d, \(J = 7.1\) Hz, 3H), 1.52 (t, \(J = 5.2\) Hz, 4H), 2.05 (s, 3H), 1.63 – 1.49 (m, 8H); **\(^13\)C NMR** (75 MHz, DMSO-\(d_6\)) 207.80, 174.74, 68.29, 60.22, 52.82, 40.32, 28.39, 27.87, 14.53; **IR** (cm\(^{-1}\)): 2943, 2806, 1706, 1715, 1645, 1447, 1393, 1356, 1287, 1260, 1182, 1115, 1049, 1028, 868; **HRMS** (ESI\(^+\)) \([M+H]^+\) C\(_{13}\)H\(_{20}\)NO \(\text{calcd.}\) 214.1443, found: 214.1462 (Scheme S13).

Brown oil. **TLC** \((R_f)\) 0.58 (DCM:MeOH 9:1+0.1 % NH\(_2\)OH); **\(^1\)H NMR** (\(\delta\), 300 MHz, DMSO-\(d_6\)) 3.29 (s, 2H), 2.47 (t, \(J = 2.6\) Hz, 4H), 2.07 (s, 3H), 1.72 – 1.63 (m, 4H); **\(^13\)C NMR** (75 MHz, DMSO-\(d_6\)) 206.82, 65.44, 53.55, 27.53, 23.36; **IR** (cm\(^{-1}\)): 3478, 2967, 2803, 1722, 1715, 1651, 1607, 1549, 1524, 1504, 1462, 1352, 1150; **HRMS** (ESI\(^+\)) \([M+H]^+\) C\(_{13}\)H\(_{12}\)NO \(\text{calcd.}\) 128.1075, found: 128.1080 (Scheme S14).

**Scheme S9** 1-morpholino propan-2-one (6a)

**Scheme S10** 1-thiomorpholino propan-2-one (6b)

**Scheme S11** 1-(4-methylpiperidin-1-yl)propan-2-one (6e)

**Scheme S12** 1-(4-benzylpiperidin-1-yl)propan-2-one (6d)

**Scheme S13** 1-(2-oxopropyl)piperidine-4-carboxylate (6d)

**Scheme S14** 1-(pyrrolidin-1-yl)propan-2-one (6f)

**Scheme S15** 1-(azepan-1-yl)propan-2-one (6g)
Orange oil. **TLC** ($R_f$) 0.56 (DCM:MeOH 9:1+0.1% NH$_3$OH); **$^1$H NMR** ($\delta$, 300 MHz, DMSO-$_d_6$) 3.12 (s, 2H), 3.17 (ddd, $J_{1,2} = 13.3$ Hz, 2H), 2.32 (s, 3H), 2.22 – 2.09 (m, 4H), 1.73 – 1.55 (m, 4H); **$^{13}$C NMR** ($\delta$, 75 MHz, DMSO-$_d_6$) 206.62, 150.96, 128.85, 118.76, 115.34, 67.32, 52.64, 48.13, 27.59; **IR (cm$^{-1}$)**: 3421, 2946, 2848, 2645, 2539, 1728, 1713, 1599, 1504, 1454, 1385, 1352, 1234, 1146, 1015, 926, 760, 692; **HRMS (ESI$^+$)** [M+H]$^+$ C$_{11}$H$_{14}$N$_2$O calcd. 199.1479, found: 199.1470 (Scheme S17).

Yellow oil. **TLC** ($R_f$) 0.62 (DCM:MeOH 9:1+0.1% NH$_3$OH); **$^1$H NMR** ($\delta$, 300 MHz, DMSO-$_d_6$) 3.17 (s, 2H), 2.43 (s, 8H), 2.06 (s, 6H); **$^{13}$C NMR** ($\delta$, 75 MHz, DMSO-$_d_6$) 206.71, 162.79, 52.51, 27.59; **IR (cm$^{-1}$)**: 3418, 2938, 2816, 1722, 1715, 1697, 1651, 1462, 1427, 1385, 1360, 1296, 1238, 1161, 1016, 978, 825; **HRMS (ESI$^+$)** [M+H]$^+$ C$_{10}$H$_{14}$NO calcd. 141.0925, found: 141.0917 (Scheme S18).

Faint-yellow solid. **Mp**: 191 °C; **$^1$H NMR** ($\delta$, 300 MHz, Deuterium Oxide) 4.44 (s, 2H), 4.06 (br, 4H), 3.46 (br, 4H), 2.33 (s, 3H); **$^{13}$C NMR** ($\delta$, 75 MHz, Deuterium Oxide) 201.86, 63.56, 63.32, 52.32, 26.74; **IR (cm$^{-1}$)**: 3418, 2923, 2640, 1728, 1630, 1449, 1400, 1360, 1270, 1128, 1037, 879; **HRMS (ESI$^+$)** [M+H]$^+$ C$_{10}$H$_{14}$N$_2$O calcd. 144.1025, found: 144.1017 (Scheme S19).

White solid. **Mp**: 185 °C; **$^1$H NMR** ($\delta$, 300 MHz, Deuterium Oxide) 4.30 (s, 2H), 3.49 (s, 4H), 2.96 (s, 4H), 2.22 (s, 3H); **$^{13}$C NMR** ($\delta$, 75 MHz, Deuterium Oxide) 201.95, 63.96, 54.72, 26.83, 23.96; **IR (cm$^{-1}$)**: 3428, 2946, 2848, 2645, 2539, 1725, 1395, 1340, 1188, 933, 625; **HRMS (ESI$^+$)** [M+H]$^+$ C$_{10}$H$_{16}$NO calcd. 160.0796, found: 160.0785 (Scheme S20).

Yellow solid. **Mp**: 167 °C; **$^1$H NMR** ($\delta$, 300 MHz, Deuterium Oxide) 4.33 (s, 2H), 3.56 (d, $J = 12.5$ Hz, 2H), 3.33 (br, 1H), 3.08 (t, $J = 13.1$ Hz, 2H), 2.32 (s, 3H), 1.97 (d, $J = 14.8$ Hz, 2H), 1.76 (br, 1H), 1.57 (t, $J = 13.3$ Hz, 2H), 1.03 (d, $J = 6.4$ Hz, 3H); **$^{13}$C NMR** ($\delta$, 75 MHz, Deuterium Oxide) 202.33, 63.78, 54.03, 30.71, 27.72, 26.79, 20.18; **IR (cm$^{-1}$)**: 3446, 2957, 2663, 1729, 1639, 1394, 1365, 1188, 1064, 952; **HRMS (ESI$^+$)** [M+H]$^+$ C$_{10}$H$_{16}$NO calcd. 156.1388, found: 156.1384 (Scheme S21).

**Scheme S19** 1-morpholinopropan-2-one hydrochloride (7a)

**Scheme S20** 1-thiomorpholinopropan-2-one hydrochloride (7b)

**Scheme S21** 1-(4-methylpiperidin-1-yl)propan-2-one hydrochloride (7e)

**Scheme S22** 1-(4-azepan-1-yl)propan-2-one hydrochloride (7g)
Faint-yellow solid. **Mp**: 197 °C; $^1$H NMR ($\delta$, 300 MHz, Deuterium Oxide) 4.43 (s, 2H), 3.70 (br, 10H), 3.08 (s, 3H), 2.32 (s, 3H); $^{13}$C NMR ($\delta$, 75 MHz, Deuterium Oxide) 202.33, 63.28, 50.16, 49.29, 42.89, 26.87; IR (cm$^{-1}$): 3446, 2992, 2806, 2694, 2610, 2430, 1731, 1635, 1474, 1436, 1410, 1371, 1288, 1188, 1034, 985, 656, 591; HRMS (ESI+) [$M+H$] C$_{8}$H$_{17}$N$_{2}$O calcd. 157.1341, found: 157.1328 (Scheme S23).

Faint-yellow solid. **Mp**: 198 °C; $^1$H NMR ($\delta$, 300 MHz, Deuterium Oxide) 7.51 (d, $J$ = 7.7 Hz, 1H), 7.52 – 7.27 (m, 1H), 7.33 – 7.17 (m, 3H), 4.49 (s, 2H), 3.77 – 3.53 (m, 11H), 2.33 (s, 3H); $^{13}$C NMR ($\delta$, 75 MHz, Deuterium Oxide) 202.30, 146.82, 130.37, 125.13, 118.77, 66.94, 51.98, 48.28, 27.25; IR (cm$^{-1}$): 3429, 3015, 2966, 2849, 2360, 2332, 1733, 1597, 1495, 1446, 1231, 1364, 1271, 1186, 762, 695, 540; HRMS (ESI+) [$M+H$] C$_{13}$H$_{19}$N$_{2}$O calcd. 219.1497, found: 219.1497 (Scheme S24).

Faint-yellow solid. **Mp**: 116 °C; $^1$H NMR ($\delta$, 300 MHz, Deuterium Oxide) 3.67 (s, 2H), 3.35 (t, $J$ = 5.3 Hz, 4H), 2.87 (t, $J$ = 5.3 Hz, 4H), 2.20 (s, 3H); $^{13}$C NMR ($\delta$, 75 MHz, Deuterium Oxide) 208.83, 65.26, 48.79, 42.75, 27.02; HRMS (ESI+) [$M+H$] C$_{7}$H$_{15}$N$_{2}$O calcd. 143.1184, found: 143.1167 (Scheme S25).

Faint-yellow solid. **Mp**: 232 °C; $^1$H NMR ($\delta$, 300 MHz, Deuterium Oxide) 4.49 (s, 4H), 3.74 (s, 8H), 2.33 (s, 6H); $^{13}$C NMR ($\delta$, 75 MHz, Deuterium Oxide) 201.97, 63.17, 49.00, 26.70; IR (cm$^{-1}$): 3444, 3026, 2917, 2394, 1732, 1490, 1458, 1436, 1367, 1345, 1184, 1110, 1006, 545; HRMS (ESI+) [$M+H$] C$_{10}$H$_{19}$N$_{2}$O$_{2}$ calcd. 199.1447, found: 199.1426 (Scheme S26).

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**Scheme S23** 1-(4-methylpiperazin-1-yl)propan-2-one hydrochloride (7h)

**Scheme S24** 1-(4-phenylpiperazin-1-yl)propan-2-one hydrochloride (7i)

**Scheme S25** 4-(2-oxopropyl)piperazin-1-ium hydrochloride (7j)

**Scheme S26** 1,1’-(piperazine-1,4-diyl)bis(propan-2-one) hydrochloride (7k)