Supporting Information

Synthesis of 1-*tert*-butyl-4-chloropiperidine: Generation of an *N*-*tert*-butyl group by the reaction of a dimethyliminium salt with methylmagnesium chloride

Joseph S. Amato,[†] John Y. L. Chung,[†] Raymond J. Cvetovich,[†] Xiaoyi Gong,[‡] Mark McLaughlin,*[,†] and Robert A. Reamer[†]

Department of Process Research[†] and Department of Analytical Research,[‡] Merck Research Laboratories, P.O. Box 2000, Rahway, NJ 07065 USA

Contents: Experimental procedures and analytical data for the following compounds are presented – **1, 3, 5, 6, 7, 8, 11, 12, 13, 14, 15, 16, 18, 19.**

1-*tert*-Butyl-4-chloropiperidine (1):

A slurry of tetrabutylammonium chloride (TBAC) (2.473 kg, 8.9 mol, 50 mol%) in dry toluene (35 L, 0.25 M, KF <50 μg/mL) was heated to 85 ºC in a 100 L flask. The mixture was colorless and homogeneous at 85 ºC (KF increased to 500-1000 μg/mL due to Bu_4NCl). Neat thionyl chloride (4.235 kg, 2.582 L, 35.6 mol, 200 mol%) was added, producing a yellow coloration. Next, a solution of 1-*tert*-butylpiperidin-4-ol **6** (2.8 kg, 17.8 mol, 100 mol%) in toluene (22 L, 0.81 M) was slowly added. A gummy precipitate developed as the solution of **6** was added and sulfur dioxide was evolved (scrubbed through aq. NaOH). Following completion of the addition, the mixture was stirred for a further 30 min before it was concentrated *in vacuo* to remove the bulk of the toluene and any excess thionyl chloride. The residue was partitioned between water (30 L) and

MTBE (11 L). The organic phase was extracted a second time with more water (20 L), then the combined aqueous phase was treated with MTBE (30 L). The stirred two-phase system is chilled to 5 ºC then made basic (pH 11) by the careful addition of solid potassium carbonate (10.9 kg, 78.9 mol). After separation of the MTBE layer, a second extraction with MTBE (30 L) was carried out. The combined organic phase was then washed with saturated brine (20 L). The organic phase was filtered and concentrated at no higher than 25 ºC (operating range of vacuum 70-200 mmHg) to leave 1-*tert*-butyl-4-chloropiperidine **1** as a pale yellow liquid. GC analysis indicated only 2% of the olefin **7** was present and gave a corrected assay yield of 85% for 1-*tert*-butyl-4-chloropiperidine **1**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (s, 9H), 1.84-1.94 (m, 2H), 2.06-2.14 (m, 2H), 2.30-2.39 (m, 2H), 2.85-2.93 (m, 2H), 3.96-4.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2 (CH_3), 36.6 (CH_2), 44.1 (CH_2), 53.9, (C), 58.1 (CH).

Olefin (**7**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (s, 9H), 2.15-2.21 (m, 2H), 2.64 (t, J = 5.6 Hz, 2H), 3.12-3.16 (m, 2H), 5.68-5.73 (m, 1H), 5.75-5.79 (m, 1H).

1-*tert*-Butyl-4-chloropiperidine (1) via addition of MeMgCl:

A slurry of iminium bromide **19** (12.74 g, 52.9 mmol, 100 mol%) in THF (110 mL, 0.58 M) was cooled to -15 ºC. A 3.0 M solution of MeMgCl in THF (25.4 mL, 76.2 mmol, 120 mol%) was added slowly over 1 h using a syringe pump. The resultant slurry was aged for 6 h at -15 ºC before it was allowed to slowly warm to room temperature. After stirring for 1 h at room temperature the mixture was colorless and homogeneous. The mixture was poured into MTBE (200 mL) and water (150 mL). GC and ^{1}H NMR

analysis of the MTBE phase indicated the presence of a small amount of secondary amine **8** (<5%), produced via the enamine formation/hydrolysis pathway. Amine **8** was conveniently removed by washing the separated MTBE phase with 0.25 M aqueous NH_4Cl (100 mL). The organic phase was then washed with brine (100 mL) and the aqueous phases were further extracted with more MTBE (100 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated to leave the product as a near colorless liquid (8.83 g, 95%, purity of 99.1 A% by GC assay). Data in agreement with that reported above.

Optimized through process from 4-chloro-1-methylpiperidine hydrochloride:

4-Chloro-1-methylpiperidine hydrochloride **10** (3.47 g, 20.4 mmol, 100 mol%) was converted to the free-base **8** through treatment with 2 M aqueous K_2CO_3 (20 mL) and extracted into 1,2-DCE (3 × 20 mL). The organic phase was dried over Na_2SO_4 and filtered into the reaction flask. 4 Å Molecular sieves were added directly to the 1,2-DCE solution of **8** until the water content (KF titration) was <50 μg/mL. The mixture was cooled in an ice-bath and treated with neat ACE-Cl (2.33 mL, 21.4 mmol, 105 mol%), maintaining the internal temperature <5 ºC. The resultant pale yellow mixture was stirred on ice for a further 30 min before it was allowed to warm to room temperature. Once at room temperature, the mixture was heated to 80 ºC for 3 h on a mantle. After cooling to room temperature, the resultant orange slurry was concentrated *in vacuo* and the residue was re-dissolved in MeOH (50 mL) and heated under reflux for 2 h. After cooling to room temperature, the orange mixture was filtered to remove the sieves. Next, NaBr (2.52 g, 24.5 mmol, 120 mol%) was added to the MeOH solution and the mixture was

stirred at room temperature for 18 h. After this time, the resultant slurry was solvent switched into MeCN (40 mL final volume) then 2,2-dimethoxypropane (40 mL) was added and the mixture was heated to 73 ºC using a distillation set-up with a short column. This temperature was sufficient to boil the mixture but the rate of heating was controlled such that distillation did not occur. After 18 h, the rate of heating was then increased to initiate steady distillation, which was conducted until the batch volume had been reduced by approximately one third. At this stage, the now brownish slurry was allowed to cool to room temperature before it was filtered. The cake was washed with MTBE and briefly dried using an N_2-sweep before it was re-slurried in THF (60 mL, KF 15 μg/mL) and cooled to -15 ºC. A 3.0 M solution of MeMgCl in THF (10.0 mL, 30.0 mmol, 150 mol%) was added slowly over 1 h using a syringe pump. The resultant slurry was aged for 6 h at -15 ºC before it was allowed to slowly warm to room temperature. After stirring for 1 h at room temperature the mixture was pale yellow and contained a fine solid. The mixture was poured into MTBE (200 mL) and water (200 mL). The organic phase was then washed with brine (150 mL) and the aqueous phases were further extracted with more MTBE (200 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated to leave the product as a yellow liquid (2.50 g, 71% overall yield from **10**). Analytical data in accord with those described above.

1,1-Dimethyl-4-oxopiperidinium iodide (3):

To a stirred solution of 1-methyl-4-piperidone **2** (4.100 kg, 36.2 moles, 100 mol%) in acetone (60 L, 0.6 M) at 25-30 °C was added methyl iodide (2.5 L, 40.0 moles, 111 mol%) over 60 minutes. Ice water was used for external cooling (T < 30 °C). After

aging at ambient temperature for 1 h, the precipitated crystalline quaternary salt (92 : 8 hydrate : keto-form) was filtered, washed with acetone (20 L) and dried with a nitrogen stream (9.1 kg, 92% yield based on starting piperidone → hydrate). Hydrate NMR data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.86 (br t, J = 5.6 Hz, 4H), 3.10 (s, 6H), 3.24 (br t, J = 5.6 Hz, 4H), 5.94 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 35.3 (CH_3), 51.1 (CH_2), 60.4 (CH_2), 89.4 (C). Keto-form NMR data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.71 (br t, J = 6.4 Hz, 4H), 3.28 (s, 6H), 3.76 (br t, J = 6.4 Hz, 4H).

1-*tert*-Butylpiperidin-4-one (5):

To a solution of acrylic acid (176 g, 2.50 mol) in water (500 mL) was slowly added 10 N aqueous NaOH (230 mL, 2.30 mol). 1,1-Dimethyl-4-oxopiperidinium iodide **3** (92 : 8 hydrate : keto-form) (136 g, 0.50 mol) and *tert*-butylamine **4** (1 L) were added and the resulting solution was heated at reflux (65 °C) for 90 min. The conversion was monitored by GC assay and typically peaked after 90 min. After complete conversion, the excess *tert*-butylamine **4** was distilled out (25 °C/40 mmHg). The concentrated mixture was extracted with EtOAc (500 mL) then the aqueous phase was further extracted with more EtOAc (2 × 250 mL). The combined organic phase was washed with brine (2 × 200 mL) and concentrated *in vacuo* (25 °C/40 mmHg) to give the piperidone as a colorless oil (70.0 g, 87% assay yield, purity of 96.5 wt% and 99.7 A% by GC assay). An analytically pure sample (99.94 GC%) was obtained by distillation (~109 °C/~50 torr or ~58 °C/~1 torr; lit. bp 92-94 °C/9 mm.): ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.07 (s, 9H), 2.29 (t, J = 6.1 Hz, 4H), 2.76 (t, J = 6.1 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.1, 41.7, 45.6, 53.5, 208.8.

1-*tert*-Butylpiperidin-4-ol (6):

1-*tert*-Butylpiperidin-4-one **5** (2.8 kg 18.0 moles) was dissolved in ethanol (18 L, 1.0 M) and the solution was subjected to hydrogen at 40 psi in the presence of Raney-Nickel (950 g). After the theoretical amount of hydrogen had been absorbed, the catalyst was removed by filtration and GC assay indicated a yield of 99%. The ethanol solution was then turned over into toluene until GC assay indicated less than 0.1% ethanol remained. A final volume of 22 L (0.81 M) was achieved. A small aliquot was removed and concentrated to afford material for characterization: mp 59-60 °C (lit. mp 60-61 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.98 (s, 9H), 1.24-1.35 (m, 2H), 1.64-1.72 (m, 2H), 2.07 (dt, J = 11.2, 2.4 Hz, 2H), 2.74-2.82 (m, 2H), 3.31-3.40 (m, 1H), 4.42 (d, J = 4.4 Hz, 1H).

4-Chloropiperidine hydrochloride (11):

4-Chloro-1-methylpiperidine hydrochloride **10** (303.6 g, 1.78 mol, 100 mol%) was converted to the free-base through treatment with 2 M aqueous K_2CO_3 (1.3 L) and extracted into 1,2-DCE (3 × 700 mL). The organic phase was dried over Na_2SO_4 and filtered into the reaction flask.

Free-base NMR data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85-1.95 (m, 2H), 2.04-2.12 (m, 2H), 2.14-2.25 (m, 2H), 2.26 (s, 3H), 2.62-2.74 (m, 2H), 3.97-4.08 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.6 (CH_2), 46.1 (CH_3), 53.2 (CH_2), 56.8 (CH).

4 Å Molecular sieves were added directly to the 1,2-DCE solution of 4-chloro-1-methylpiperidine until the water content (KF titration) was <100 μg/mL. The mixture (2.1 L, 0.85 M) was cooled in an ice-bath and treated with neat ACE-Cl (209 mL, 1.92 mol, 108 mol%), maintaining the internal temperature <5 ºC. The resultant pale yellow mixture was stirred on ice for a further 30 min before it was allowed to warm to room temperature. Once at room temperature, the mixture was heated to 80 ºC for 3 h on a mantle. After cooling to room temperature, the resultant orange slurry was concentrated *in vacuo* and the residue was re-dissolved in MeOH (1 L) and heated under reflux for 2 h. After cooling to room temperature, the orange mixture was concentrated *in vacuo* to leave an orange solid. This solid was slurried in MeCN (250 mL), collected by filtration and washed with more MeCN then MTBE. The 4-chloropiperidine hydrochloride was obtained as a white crystalline solid (250.7 g, 90%) mp 203-204 ºC (lit. mp 202-203 ºC). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.88-1.98 (m, 2H), 2.16-2.26 (m, 2H), 2.94-3.03 (m, 2H), 3.09-3.18 (m, 2H), 4.38-4.45 (m, 1H), 9.36 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 31.9 (CH_2), 41.3 (CH_2), 55.0 (CH). Anal. Calcd. for $C_5H_{11}Cl_2N$: C, 38.48; H, 7.10; N, 8.98. Found: C, 38.59; H, 7.13; N, 8.88.

Note: (For large scale work a more appropriate method of drying the 4-chloro-1-methylpiperidine free-base before treatment with ACE-Cl involves extraction into MTBE, followed by azeotropic drying at 25 ºC and 40 mmHg until the KF was <100 μg/mL. Approximately 10% of material is lost to the distillate under these conditions but this may be recovered efficiently as the hydrochloride salt by treatment of the distillate with HCl.)

General procedure for the conversion of HCl salt (11) into alternative salt derivatives:

The HCl salt **11** of 4-chloropiperidine (100 mol%) was broken between 2 M aqueous K_2CO_3 (200 mol%) and MTBE. The aqueous phase was extracted with a second portion of MTBE then the combined organic phase was washed with brine, dried over $MgSO_4$ and filtered. The MTBE solution of free-base was cooled on ice and treated with the appropriate acid (100 mol%). Following precipitation, the product salt was collected by filtration, washed with more MTBE and dried in a vacuum oven at 40 ºC.

4-Chloropiperidine trifluoromethanesulfonate (12):

Starting with 4-chloropiperidine hydrochloride **11** (5.0 g, 32.0 mmol) the salt was obtained as a fluffy white solid (7.95 g, 92%), mp 91-92 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.80-1.90 (m, 2H), 2.12-2.21 (m, 2H), 2.98-3.06 (m, 2H), 3.16-3.24 (m, 2H), 4.35-4.42 (m, 1H), 8.34 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 32.1 (CH_2), 41.7 (CH_2), 54.5 (CH), 121.2 (q, J_{CF} = 322 Hz, CF_3). Anal. Calcd. for $C_6H_{11}ClF_3NO_3S$: C, 26.72; H, 4.11; N, 5.19. Found: C, 26.78; H, 3.94; N, 5.12.

4-Chloropiperidine hydrobromide (13):

A 0.9 M solution of HBr in MeOH was prepared by adding AcBr (54.1 g, 0.44 mol) to MeOH (500 mL) at 0 ºC. This acid solution was added to the MTBE solution of free-base **8** then the mixture was concentrated to dryness and the resulting solid residue re-slurried in MTBE for collection by filtration. Starting with 4-chloropiperidine hydrochloride **11**

(5.0 g, 32.0 mmol) the salt was obtained as a white crystalline solid (5.77 g, 90%), mp 188-189 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.84-1.95 (m, 2H), 2.16-2.25 (m, 2H), 2.99-3.09 (m, 2H), 3.14-3.23 (m, 2H), 4.38-4.47 (m, 1H), 8.69 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 31.9 (CH_2), 41.5 (CH_2), 54.8 (CH). Anal. Calcd. for $C_5H_{11}BrClN$: C, 29.95; H, 5.53; N, 6.99. Found: C, 30.05; H, 5.36; N, 6.95.

4-Chloropiperidine methanesulfonate (14):

Starting with 4-chloropiperidine hydrochloride **11** (5.0 g, 32.0 mmol) the salt was obtained as a white crystalline solid (6.28 g, 91%), mp 88-89ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.84-1.93 (m, 2H), 2.14-2.23 (m, 2H), 2.39 (s, 3H), 2.96-3.06 (m, 2H), 3.14-3.24 (m, 2H), 4.34-4.44 (m, 1H), 8.60 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 32.0 (CH_2), 40.2 (CH_3), 41.6 (CH_2), 54.8 (CH). Anal. Calcd. for $C_6H_{14}ClNO_3S$: C, 33.41; H, 6.54; N, 6.49. Found: C, 33.50; H, 6.45; N, 6.38.

4-Chloropiperidine trifluoroacetate (15):

Starting with 4-chloropiperidine hydrochloride **11** (5.0 g, 32.0 mmol) the salt was obtained as a fluffy white solid (6.65g, 89%), mp 86-87 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.82-1.93 (m, 2H), 2.14-2.23 (m, 2H), 2.99-3.06 (m, 2H), 3.17-3.24 (m, 2H), 4.37-4.43 (m, 1H), 9.01 (br s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 32.1 (CH_2), 41.5 (CH_2), 54.8 (CH), 117.5 (q, J_{CF} = 298 Hz, CF_3), 159.4 (q, J_{CF} = 32 Hz, C). Anal. Calcd. for $C_7H_{11}ClF_3NO_2$: C, 35.99; H, 4.75; N, 6.00. Found: C, 35.99; H, 4.64; N, 5.90.

4-Chloropiperidine *p*-toluenesulfonate (16):

Starting with 4-chloropiperidine hydrochloride **11** (5.0 g, 32.0 mmol) the salt was obtained as a white crystalline solid (8.40 g, 90%), mp 156-157 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.69-1.78 (m, 2H), 2.12-2.22 (m, 2H), 2.26 (s, 3H), 2.98-3.08 (m, 2H), 3.16-3.24 (m, 2H), 4.33-4.42 (m, 1H), 7.11 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 8.50 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.3 (CH_3), 32.1 (CH_2), 41.7 (CH_2), 54.7 (CH), 126.0 (CH), 128.7 (CH), 138.5 (C), 145.6 (C). Anal. Calcd. for $C_{12}H_{18}ClNO_3S$: C, 49.39; H, 6.22; N, 4.80. Found: C, 49.27; H, 6.15; N, 4.77.

Iminium triflate (18):

A slurry of 4-chloropiperidine trifluoromethanesulfonate **12** (0.65 g, 2.41 mmol) in 2,2-dimethoxypropane (25 mL) was heated until slow distillation was achieved (75-79 ºC). The mixture became homogeneous quickly as the temperature reached >50 ºC. After 3 h, an aliquot was removed and concentrated *in vacuo*. The residue was dissolved in dry DMSO-d_6 and ^{1}H NMR indicated complete conversion to the iminium triflate species. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.98-2.07 (m, 2H), 2.26-2.36 (m, 2H), 2.48 (s, 6H), 3.88-3.95 (m, 2H), 4.05-4.14 (m, 2H), 4.54-4.60 (m, 1H).

Iminium bromide (19):

A slurry of 4-chloropiperidine hydrobromide **13** (12.12 g, 60.4 mmol) in a mixture of MeCN (124 mL) and 2,2-dimethoxypropane (124 mL) was heated to 73 ºC using a distillation set-up with a short column. This temperature was sufficient to boil the mixture but the rate of heating was controlled such that distillation did not occur. After

approximately 1 h the mixture became homogeneous and remained so for a further 1 h before a white precipitate began to re-appear. The resultant slurry was further heated for a total of 18 h. After this time a small amount of distillate had collected (<10 mL). The rate of heating was then increased to initiate steady distillation, which was conducted until the batch volume had been reduced by approximately one third. At this stage, the now brownish slurry was allowed to cool to room temperature before it was filtered. The cake was washed with MTBE and briefly dried using an N_2-sweep before it was transferred to an appropriate container for drying in a vacuum oven (40 ^oC). The iminium bromide was obtained as a white solid (12.99 g, 89%). ^1H NMR (400 MHz, DMSO-d_6) δ 1.98-2.07 (m, 2H), 2.29-2.36 (m, 2H), 2.50 (s, 6H), 3.91-3.98 (m, 2H), 4.07-4.14 (m, 2H), 4.57-4.64 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 25.6 (CH_3), 34.8 (CH_2), 50.5 (CH_2), 55.1, (CH), 188.2 (C).