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Synthesis of 3-Substituted 4-Piperidinones via a One-Pot Tandem Oxidation−Cyclization−Oxidation Process: Stereodivergent Reduction to 3,4-Disubstituted Piperidines

Perdip S. Bahia and John S. Snaith*

School of Chemistry, The University of Birmingham, Edgbaston, Birmingham, B15 2TT, United Kingdom

j.s.snaith@bham.ac.uk

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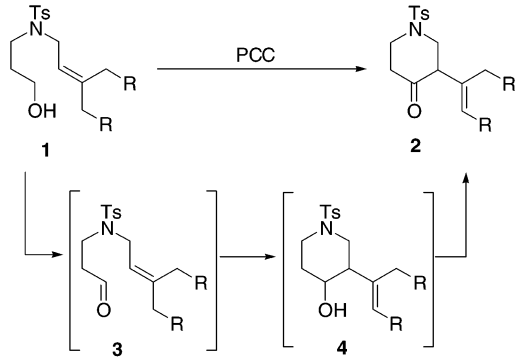
Abstract: A novel approach to 3-substituted 4-piperidinones is described. The one-pot tandem oxidation−cyclization−oxidation of unsaturated alcohols **1a**−**e** by PCC or PCC and trifluoromethanesulfonic acid affords piperidinones **2a**−**e** in good yield. Reduction of **2a**−**e** by L-Selectride gives the corresponding cis 3,4-disubstituted piperidines with diastereomeric ratios of >99:1. By contrast, reduction of **2a**−**e** by *Al*-isopropoxydiisobutylalane gives the trans products with diastereomeric ratios of up to 99:1.

The importance of the piperidine ring system in natural products[1] and synthetic pharmaceuticals[2] has resulted in the development of a large number of synthetic approaches to these heterocycles.[3] Nevertheless, the variety of functionality and substitution patterns found in piperidine targets continues to drive the search for new methodologies.[4]

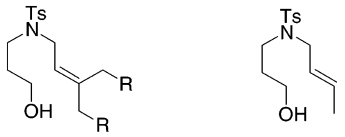
Piperidinones frequently serve as versatile intermediates in the synthesis of functionalized piperidines. We envisaged a concise route whereby unsaturated alcohols **1** were converted into 3-substituted 4-piperidinones **2**, the key step being the formation of the C3−C4 bond via a one-pot tandem oxidation−cyclization−oxidation by PCC (Scheme 1). Tandem oxidation−cyclization reactions by PCC to form six-membered rings were first reported by Corey;[5] application to the construction of heterocycles has not been explored.

The cyclization precursors **1a**−**e** (Figure 1) were synthesized in two steps from 3-aminopropanol as previously described.[6] Alcohol **1f** was prepared by the same route in an overall yield of 67%.

SCHEME 1. One-Pot Tandem Oxidation−Cyclization−Oxidation of Unsaturated Alcohols 1 to Piperidinones 2 by PCC[a]



[a] Aldehyde **3** and piperidine **4** are nonisolated intermediates.



1a R = H
1b R = CH_3
1c R = —$(CH_2)_2$—
1d R = —$(CH_2)_3$—
1e R = —$(CH_2)_4$—

1f

FIGURE 1. Cyclization precursors **1a**−**f**.

The tandem cyclization process was initially attempted with PCC without any additives (Table 1). Treatment of the alcohols **1c** and **1e** with 2.5 equiv of PCC led smoothly to the piperidinones **2c** and **2e** within 24 h. In the other cases reaction stopped at the corresponding aldehyde **3**, with subsequent cyclization−oxidation being extremely slow. Presumably the strain imposed on the double bonds by the five- and seven-membered rings in **1c** and **1e** increases the reactivity of these alkenes toward cyclization. In an effort to accelerate the remaining cyclizations, we increased the number of equivalents of PCC and extended the reaction time. Alcohols **1a**, **1b**, and **1d** were found to cyclize under the extremely forcing conditions of 15 equiv of PCC for 10 days, affording the piperidinones **2a**, **2b**, and **2d**, respectively. Alcohol **1f** resisted even these conditions, most likely as a result of the less electron rich monosubstituted double bond.

Clearly such conditions were unacceptable, and so we sought alternative methods to accelerate the process. Initial oxidation to the aldehyde was rapid, and it appeared that the rate-limiting step was cyclization to the piperidine **4** via a carbonyl-ene type process.

Since such carbonyl-ene reactions are known to be catalyzed by Brønsted acids, we explored the addition of various acids to the reaction mixture. Unfortunately, the addition of either concentrated hydrochloric acid or

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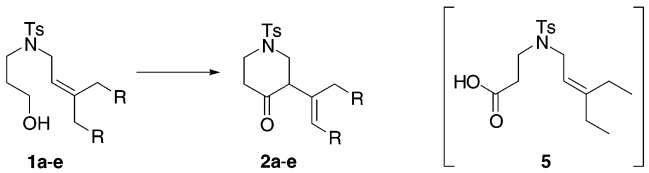
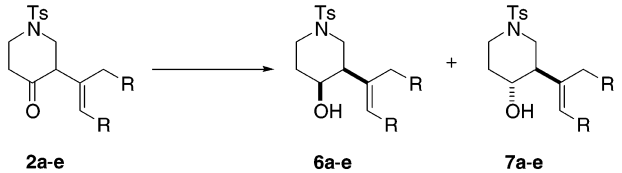
TABLE 1. Cyclizations of Alcohols 1a−e



entry	alcohol	PCC equiv[a]	time (h)	yield (%)[b] **2a−f**	acid[c]
1	**1c**	2.5	24	62	
2	**1e**	2.5	24	65	
3	**1a**	15	240	64	
4	**1b**	15	240	62[d]	
5	**1d**	15	240	71	
6	**1f**	15	240	—[e]	
7	**1b**	2.5	24	—[f]	HCl
8	**1b**	2.5	24	—[f]	H_2SO_4
9	**1a**	5	24	61	CF_3SO_3H
10	**1b**	5	24	67[d]	CF_3SO_3H
11	**1d**	5	24	59	CF_3SO_3H
12	**1f**	5	24	—[e]	CF_3SO_3H

[a] Reactions performed in CH_2Cl_2 at 25 °C. [b] Isolated yields following chromatography. [c] 1.5 equiv. [d] Formed as a 2:1 mixture of *E*:*Z* isomers. [e] Aldehyde obtained. [f] Carboxylic acid **5** was the sole product.

TABLE 2. Reduction of 4-Piperidinones 2a−e



entry	ketone	reducing agent[a]	time (h)	**6**:**7**[b]	yield (%)[c] **6a-e**
1	**2a**	L-Selectride	3	99:1	85
2	**2b**	L-Selectride	3	99:1	82[d]
3	**2c**	L-Selectride	3	99:1	86
4	**2d**	L-Selectride	3	99:1	70
5	**2e**	L-Selectride	3	99:1	79
6	**2a**	^{i}Bu$_2$AlO^{i}Pr	6	1:99	79
7	**2b**	^{i}Bu$_2$AlO^{i}Pr	6	1:99	74[d]
8	**2c**	^{i}Bu$_2$AlO^{i}Pr	6	2:98	70
9	**2d**	^{i}Bu$_2$AlO^{i}Pr	6	4:96	73
10	**2e**	^{i}Bu$_2$AlO^{i}Pr	6	1:99	87

[a] L-Selectride reductions performed in tetrahydrofuran at −78 °C; ^{i}Bu$_2$AlO^{i}Pr reductions performed in toluene at 25 °C. [b] Ratio determined by HPLC of crude reaction product. [c] Isolated yields following chromatography. [d] Formed as a 2:1 mixture of *E*:*Z* isomers.

sulfuric acid to a solution of **1b** and PCC resulted in overoxidation to the carboxylic acid **5**, without any cyclization occurring. Happily, changing the acid to trifluoromethanesulfonic acid resulted in an acceleration of the desired cyclization reaction without any of the competing carboxylic acid formation. Thus, treatment of alcohols **1a**, **1b**, and **1d** with PCC (5 equiv) and trifluoromethanesulfonic acid (1.5 equiv) in dichloromethane for 24 h gave piperidinones **2a**, **2b**, and **2d** as the sole product in each case, in isolated yields of 59−67% after chromatography. The less electron rich **1f** afforded only the corresponding aldehyde under these conditions.

Support for the mechanism proposed in Scheme 1 came from the isolation of small amounts (<5%) of the intermediate piperidines on two occasions, during the preparation of **2b** and **2e**, when the reaction was stopped too soon. Simply extending the reaction time resulted in complete conversion to the piperidinones.

With the piperidinones in hand, we went on to explore their stereoselective reduction to 4-hydroxypiperidines. A number of *cis*- and *trans*-3,4-disubstituted piperidines have potent biological activity,[7] and so we sought conditions which would allow us to access both stereoisomers. Methods for the reduction of six-membered cyclic ketones to the thermodynamically less stable stereoisomer are well developed, with the Selectride reagents of Brown most notable among the methods for achieving this transformation.[8] Troin[9] employed the L-Selectride reduction of a 2,3-disubstituted 4-piperidinone to set the cis stereochemistry between positions 3 and 4 in the total synthesis of Dienomycin-C.

Comins[10] has used K-Selectride for the stereoselective reduction of 2-substituted 4-piperidinones to the thermodynamically less stable isomer. Treatment of piperidinones **2a**−**e** with L-Selectride resulted in complete conversion to the *cis*-3-substituted 4-hydroxypiperidines **6a**−**e**, with diastereomeric ratios determined by HPLC in excess of 99:1 (Table 2).

The products were isolated as crystalline solids after chromatography. Single crystals of **6a** were grown from petroleum ether and ethyl acetate, and X-ray analysis confirmed the cis relationship between the two substituents (Figure 2).

Methods for the reduction of six-membered cyclic ketones to the thermodynamically more stable stereoisomer are rather less well developed.

Cha and Kwon[11] recently reported a new method for the reduction of cyclic ketones to the thermodynamically more stable alcohols using a diethyl ether solution of *Al*-isopropoxydiisobutylalane, a reagent readily prepared by the addition of 2-propanol to diisobutylaluminum hydride. The authors propose that the reduction proceeds through a Meerwein−Ponndorf−Verley (MPV)-type mechanism, supported by the fact that the proportion of the thermodynamically more stable alcohol increases with time. The stereocontrol is good to excellent, although a drawback is that long reaction times are required to achieve this, typically between 5 and 7 days.

The rates of MPV reductions have been reported to exhibit significant solvent effects,[12] being fastest in nonpolar solvents and slowest in solvents such as ether

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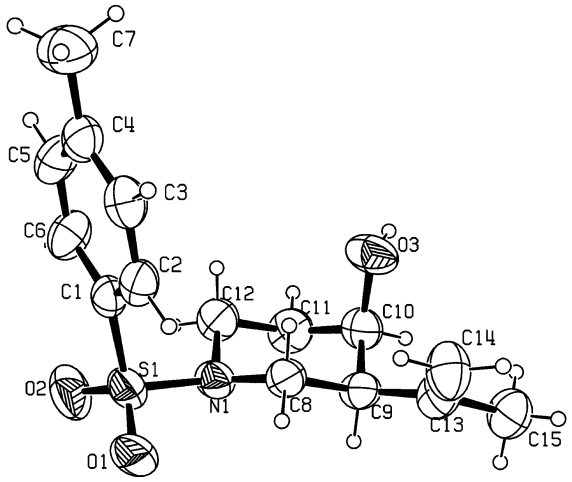

FIGURE 2. ORTEP representation of **6a**; ellipsoids are drawn at the 30% probability level.

and THF, which are capable of acting as donor ligands to the aluminum.

Paralleling these findings, we found the production of *trans*-piperidin-4-ols **7** to be sluggish in ether. In an effort to accelerate the reductions, we adapted the Cha and Kwon procedure to use toluene as the solvent. The change in solvent was found to markedly increase the rate of reaction. Thus, treatment of piperidinones **2a**−**e** with *Al*-isopropoxydiisobutylalane (1 equiv) in toluene for 6 h led to formation of the *trans*-3-substituted 4-hydroxypiperidines **7a**−**e**, with diastereomeric ratios of between 96:4 and 99:1 (HPLC) and with isolated yields of 70−87% after chromatography (Table 2).

In summary, we have discovered a concise synthesis of 3-substituted 4-piperidinones via the tandem oxidation−cyclization−oxidation of simple precursors. Reduction of the piperidinones can be controlled by appropriate choice of reducing agent to afford either the *cis*- or *trans*-3,4-disubstituted piperidines with high diastereoselectivity. Application to the synthesis of more complex molecules is currently under investigation and will be reported in due course.

Experimental Section

Typical Procedure for the Tandem Oxidation−Cyclization: Preparation of 3-Isopropenyl-1-(toluene-4-sulfonyl)-piperidin-4-one (2a). Triflic acid (0.08 mL, 0.9 mmol) was added to a suspension of pyridinium chlorochromate (0.65 g, 3.0 mmol) in CH_2Cl_2 (15 mL), which was then stirred for 5 min before being cooled to 0 °C. The *N*-alkylated sulfonamide **1a** (0.18 g, 0.6 mmol) in CH_2Cl_2 (5 mL) was then added in one portion to the reaction mixture. After the mixture was warmed to room temperature and stirred for 24 h, $NaHSO_4$ (1.78 g) and ether (25 mL) were added, then the solution was vigorously stirred for 15 min. After filtering through silica, the residue was washed with ether (200 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash column chromatography of the colorless oil (silica; eluent 1:3 ethyl acetate:petroleum ether) afforded 3-isopropenyl-1-(toluene-4-sulfonyl)piperidin-4-one (**2a**) (0.11 g, 61%) as a white crystalline solid: mp 82−83 °C; R_f 0.40; IR 2924, 1721, 1598, 1342, 1166 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.72 (s, 3H), 2.44 (s, 3H), 2.55−2.60 (m, 2H), 3.04−3.23 (m, 3H), 3.63−3.71 (m, 2H), 4.90 (s, 1H), 5.01−5.03 (m, 1H), 7.35 (d, J = 8.1 Hz, 2H), 7.68 (d, J = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 23.0, 41.2, 47.6, 50.9, 57.7, 116.5, 128.8, 131.2, 134.9, 140.9, 146.4, 206.1; MS (electrospray) *m*/*z* 316 (100%, $[M + Na]^+$). Anal. Calcd for $C_{15}H_{19}NO_3S$: C, 61.41; H, 6.53; N, 4.78. Found: C, 61.3; H, 6.3; N, 4.6.

3-[(3-Ethylpent-2-enyl)(toluene-4-sulfonyl)amino]propanoic Acid (5). Concentrated hydrochloric acid (0.044 mL, 0.45 mmol) was added to a suspension of pyridinium chlorochromate (0.32 g, 1.5 mmol) in CH_2Cl_2 (10 mL), which was then stirred for 5 min before being cooled to 0 °C. The *N*-alkylated sulfonamide **1b** (0.098 g, 0.3 mmol) in CH_2Cl_2 (5 mL) was then added in one portion to the reaction mixture. After the mixtue was warmed to room temperature and stirred for 24 h, $NaHSO_4$ (0.89 g) and ether (15 mL) were added, then the solution was vigorously stirred for 15 min. After filtering through silica, the residue was washed with ether (100 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash column chromatography of the colorless oil (silica; eluent 1:3 ethyl acetate:petroleum ether) afforded 3-[(3-ethylpent-2-enyl)(toluene-4-sulfonyl)amino]propanoic acid (**5**) (0.068 g, 67%) as a colorless oil: R_f 0.29; IR 2969, 1713, 1600, 1342, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87−0.95 (m, 6H), 1.94−2.05 (m, 4H), 2.42 (s, 3H), 2.69−2.73 (m 2H), 3.35 (t, J = 7.5 Hz, 2H), 3.84 (d, J = 7.0 Hz, 2H), 4.90 (t, J = 6.7 Hz, 1H), 7.30 (d, J = 8.1, 2H), 7.69 (d, J = 8.1, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.2, 14.0, 23.4, 24.2, 29.8, 35.1, 43.6, 47.0, 117.5, 128.2, 130.6, 138.1, 144.7, 149.2, 177.9; MS (electrospray) *m*/*z* 362 (100%, $[M + Na]^+$).

Typical Procedure for the L-Selectride Reduction: Preparation of (3*R,4*S**)-3-Isopropenyl-1-(toluene-4-sulfonyl)piperidin-4-ol (6a).** L-Selectride (1 M solution in THF, 0.157 mL, 0.157 mmol) was added to **2a** (46 mg, 0.157 mmol) in THF (20 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 3 h and then allowed to warm to room temperature before being hydrolyzed with water (4 mL) and ethanol (15 mL). The organoborane was oxidized by stirring it along with 6 M NaOH (10 mL) and 30% hydrogen peroxide (15 mL) at room temperature for 1 h. The organic phase was separated, and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash column chromatography (silica; eluent 2:1 petroleum ether:ethyl acetate) afforded (3*R**,4*S**)-3-isopropenyl-1-(toluene-4-sulfonyl)-piperidin-4-ol (**6a**) (39 mg, 85%) as a white crystalline solid: mp 89−91 °C (from petroleum ether/ethyl acetate); R_f 0.36; IR 3519, 2920, 2904, 1651, 1597, 1447, 1323, 1304, 1157 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.50 (br s, 1H), 1.77 (s, 3H), 1.81−1.95 (m, 2H), 2.37 (d, J = 12.1 Hz, 1H), 2.42 (s, 3H), 2.55−2.62 (m, 2H), 3.55−3.59 (m, 2H), 3.96 (d, J = 2.2 Hz, 1H), 4.58 (s, 1H), 4.96 (s, 1H), 7.31 (d, J = 8.1 Hz, 2H), 7.64 (d, J = 8.1 Hz, 2H); ^{13}C NMR(125 MHz, $CDCl_3$) δ 21.5, 22.8, 31.1, 40.5, 43.5, 46.7, 63.0, 112.2, 127.6, 129.6, 133.4, 143.4, 143.8; MS (CI) *m*/*z* 296 ($[M + H]^+$, 100%), 278 (4), 257 (5), 189 (8), 143 (13), 124 (15), 105 (4), 79 (11). Anal. Calcd for $C_{15}H_{21}NO_3S$: C, 60.99; H, 7.17; N, 4.74. Found: C, 61.0; H, 7.1; N, 4.6.

Preparation of DIBAO*i*Pr in Toluene. Isopropyl alcohol (0.81 mL, 10.5 mmol) was added dropwise to diisobutylauminium hydride (1 M solution in toluene, 10 mL, 10 mmol) at 0 °C. After the evolution of hydrogen had ceased, the reagent solution was stirred at room temperature for 1 h to give a solution of DIBAO*i*-Pr (0.93 M) in toluene.

Typical Procedure for DIBAO*i*Pr Reduction: Preparation of (3*R,4*R**)-3-Isopropenyl-1-(toluene-4-sulfonyl)piperidin-4-ol (7a).** DIBAO*i*Pr (0.93 M solution in toluene, 0.169 mL, 0.157 mmol) was added to **2a** (46 mg, 0.157 mmol) in toluene (10 mL) and the reaction mixture was stirred at room temperature for 24 h. Then 3 M HCl (1.5 mL) and ether (10 mL) were added, and the mixture was allowed to stir for 30 min, after which 3 M NaOH (5 mL) was added, and this solution was allowed to stir for 1 h. The organic layer was separated, the aqueous phase was extracted with ether (3 × 20 mL), and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash column chromatography (silica; eluent 2:1 petroleum ether:ethyl acetate) afforded (3*R**,4*R**)-3-isopropenyl-1-(toluene-4-sulfonyl)piperidin-4-ol (**7a**) (37 mg, 79%) as a white crystalline solid: mp 149−151 °C (from petroleum ether/ethyl acetate); R_f 0.24; IR 3391, 2920,

2904, 1647, 1597, 1458, 1334, 1304, 1157 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.58−1.68 (m, 1H), 1.71 (s, 3H), 1.85 (br s, 1H), 2.01−2.06 (m, 1H), 2.17−2.27 (m, 2H), 2.37 (dt, J = 2.8, 12.4 Hz, 1H), 2.43 (s, 3H), 3.44 (dt, J = 4.5, 10.1 Hz, 1H), 3.75−3.77 (m, 1H), 3.81−3.86 (m, 1H), 4.89 (s, 1H), 5.01 (s, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 8.0 Hz, 2H); ^1H NMR (125 MHz, $CDCl_3$) δ 20.6, 21.5, 32.5, 45.0, 48.8, 51.6, 69.4, 114.7, 127.6, 129.7, 133.6, 142.4, 143.6; MS (CI) m/z 296 ($[M + H]^+$, 100%), 278 (4), 247 (5), 189 (5), 143 (10), 124 (8), 79 (4), 69 (10). Anal. Calcd for $C_{15}H_{21}NO_3S$: C, 60.99; H, 7.17; N, 4.74. Found: C, 61.0; H, 7.1; N, 4.6.

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Supporting Information Available: Experimental procedures and full characterization for piperidinones **2a**−**e** and piperidine-4-ols **6a**−**e** and **7a**−**e**, as well as the CIF file for **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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