C(6)-Alkylation of 3-Hydroxypiperidine via Reductive and Homolytic Cleavage of N,S-Acetals

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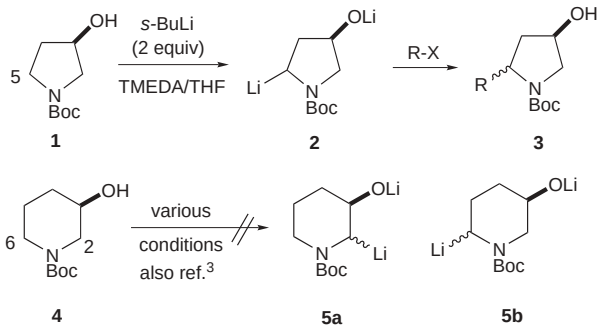
Abstract: *N*-Carboxymethyl 3-hydroxypiperidine (**6**) undergoes substitution at C(6) via reductive cleavage of N,S-acetal **8a** with lithium naphthalenide (LN) and trapping of the resulting carbanionic intermediate **9** with different electrophiles to give adducts **10**. N,S-Acetal **8a** also undergoes C–S homolysis and trapping of the resulting radical provides an alternative entry to 2-substituted-5-hydroxypiperidines.

Key words: piperidines, alkylation, anodic oxidation, radical

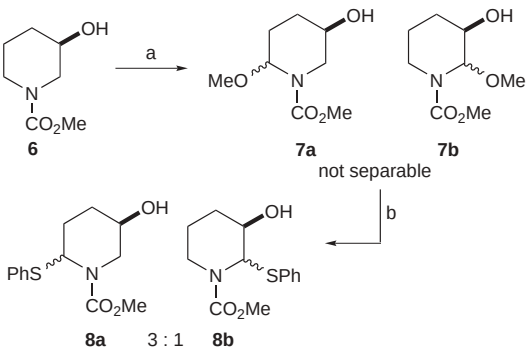
Hydroxylated pyrrolidines and piperidines[1] are found within a range of natural products and an ability to introduce these fragments directly via functionalization of an appropriate intact heterocyclic unit is a synthetically attractive option. We have previously described the regioselective lithiation of *N*-Boc 3-hydroxypyrrolidine (**1**), which undergoes preferential deprotonation at C(5) to give **2**, thereby providing access to 2-substituted 4-hydroxypyrrolidines **3** (Scheme 1).[2]



Scheme 1

Generating a disubstituted piperidine via a similar approach is attractive but Beak[3] has reported that *N*-Boc 3-hydroxypiperidine (**4**) does not undergo lithiation at either C(2) or C(6) to give **5a** and **5b**, respectively. In light of our ability to produce and characterize **2**, we have also examined deprotonation of **4** under a variety of conditions, but without success. In this paper we describe an alternative entry to an α-lithiated 3-hydroxypiperidine (cf. **5b**) based on a regioselective oxidation of the piperidine nucleus that enables subsequent metalation by reductive lithiation rather than deprotonation.

N-Carboxymethyl 3-hydroxypiperidine (**6**) was subjected to anodic oxidation[4] in methanol to provide a 53% yield of the N,O-acetals **7a** and **7b** as an inseparable mixture of regio and *cis*/*trans* diastereoisomers (Scheme 2).[5] This reaction was also investigated using the corresponding *N*-tosyl and *N*-Boc piperidines, but these were less efficient substrates for the oxidation process. In addition, the oxidation of **6** was best carried out using graphite rather than platinum electrodes[6] as the latter produced significant amounts of overoxidized material.



Scheme 2 *Reagents*: (a) 5 mol% Et_4NOTs, carbon electrodes, MeOH, 8 h, r.t., 2.34 $Fmol^{-1}$ (53%); (b) PhSH, *p*-TsOH, CH_2Cl_2, 2 h, 0 °C (3:1 ratio of **8** and **9**, 80% total yield).

Exposure of **7a**,**b** to PhSH under acidic conditions provided the corresponding N,S-acetals **8a**,**b**, which were readily separable and the desired C(6)-regioisomer **8a** was isolated in 61% yield.[7,8]

Reductive lithiation of **8a** (as a mixture of *cis*/*trans* diastereomers) was achieved using (i) BuLi (to generate the corresponding alkoxide) followed by (ii) freshly prepared lithium naphthalenide (LN, 4 equiv). Addition of an appropriate electrophile to the putative α-lithiated piperidine **9** gave the *N*-Boc 2-substituted-5-hydroxypiperidines **10a**–**c** in moderate yields (Scheme 3, Table 1).[9]

Products **10a**–**c** were all obtained as *cis* and *trans* isomers, which were separable. In each case, the major component was the *trans* isomer (however, see below and ref.[11]) and ^1H NMR (NOE and in particular the signal associated with H_{6ax}) was especially helpful in making this assignment. In the case of *cis*/*trans*-**10a**, this product was converted by hydrogenation to **11**, the *cis* and *trans* isomers

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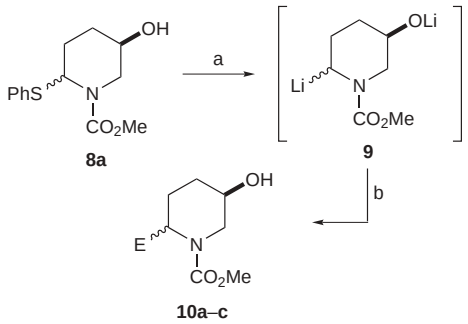
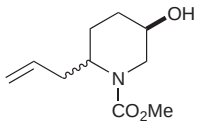
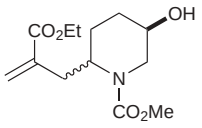
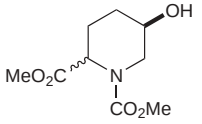
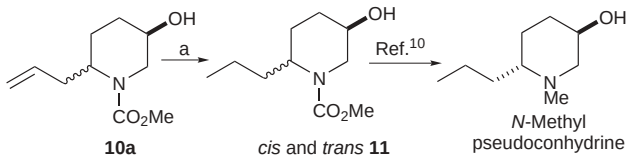


Scheme 3 *Reagents*: (a) *n*-BuLi, THF, –78 °C, 2 min then LN (1 M in THF, 4 equiv), 2 min; (b) electrophile (see Table 1).

Table 1 Reaction of the Electrophile with α-Lithiated Piperidine **9**

Electrophile	2-Substituted-5-hydroxypiperidine **10**	Yield (%) *trans*:*cis*
Br	 **10a**	60 3.3:1
CO_2Et Br	 **10b**	49 3.0:1
MeOCOCl	 **10c**	38 2.0:1

of which were individually characterized (Scheme 4). *Trans*-**11** is a known intermediate in the synthesis of *N*-methyl pseudoconhydrine **12** and both *cis*- and *trans*-**11** have been described previously.[10]

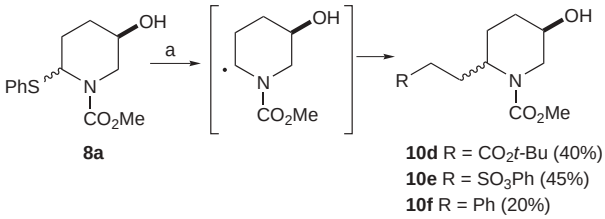


Scheme 4 *Reagents*: (a) H_2, 5% Pd/C, MeOH (96%).

Two issues currently present themselves. Firstly, an excess of LN is required to achieve fast conversion of **8a**, and this limits the nature of the electrophile that can be used to trap **9**. Attempts to capture **9** with, for example, PhCHO failed as benzyl alcohol was formed by rapid competitive reduction. Also PhS^- is generated by reduction of **8a**, and this can lead to the formation of by-products; when allyl bromide was used, phenyl allyl sulfide was also detected.

These issues not withstanding, reductive cleavage of N,S-acetal **8a** does provide for the first time a route to a 3-hydroxypiperidine moiety nucleophilic at C(6). Intermediate **9** has been trapped with synthetically useful electrophiles, and studies are underway to address the practical issues that have been highlighted above. It is also appropriate to recognize that the reactivity associated with **8a** when coupled to **9** complements the well known electrophilic profile associated with N-acyl imimium ions, which provides an alternative method for substitution adjacent to nitrogen.[11]

In addition to undergoing reductive lithiation, N,S-acetal **8a** undergoes homolytic cleavage. Keck allylation (allyl tributylstannane, AIBN, PhMe, reflux) of **8a** gave **10a** in 33% yield but as a 5:1 mixture of *cis* and *trans* isomers. Note under these conditions the *cis* isomer predominated. Using Bu_3SnH and AIBN, the resulting α-aza radical was also trapped by a series of alkenes to provide the corresponding 2-substituted-5-hydroxypiperidines **10d**–**f** in moderate yields and as *cis*/*trans* mixtures (Scheme 5).[12,13]



Scheme 5 *Reagents*: (a) Bu_3SnH, AIBN, PhMe, reflux, $RCH{=}CH_2$.

In summary, N,S-acetal **8a** provides access to nucleophilic reactivity using two complementary methods based on either (i) reductive lithiation or (ii) C-S homolysis. Both methods can be utilized to generate a range of N-protected 2-substituted-5-hydroxypiperidines.

Acknowledgment

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(7) **Procedure for Electrochemical Oxidation of 6 to 7a,b and Conversion of 7a,b to 8a,b:**
A solution of *N*-methoxycarbonyl-3-hydroxypiperidine (**6**, 2.0 g, 12.60 mmol) and tetraethylammonium tosylate (189 mg, 0.63 mmol, 5 mol%) in dry MeOH (20 mL) was placed into a beaker-type undivided electrolysis cell equipped with a graphite anode and cathode. A constant current of 0.1 A (10–12 V) was passed through the solution at 15 °C until 2.34 $Fmol^{-1}$ of electricity had passed (approx. 8 h). The electrolyzed solution was concentrated in vacuo and the crude product purified by flash chromatography (silica gel; hexane–EtOAc 3:1) to give **7a**,**b** (1.26 g, 53%) as a pale yellow oil.
A mixture of **7a**,**b** (1.0 g, 5.40 mmol) in CH_2Cl_2 (35 mL) was cooled to 0 °C and $TsOH·H_2O$ (1.1 g, 5.90 mmol) was added followed by thiophenol (0.74 mL, 7.00 mmol). After 2 h at 0 °C, the mixture was quenched with H_2O (30 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo and the residue was purified by flash chromatography (hexane–EtOAc 3:2) to afford 2-phenylthio-*N*-carbomethoxy-3-hydroxypiperidine (**8b**, 275 mg, 19%) as a mixture of diastereoisomers and as colorless oil. Continued elution gave 2-phenylthio-*N*-carbomethoxy-5-hydroxypiperidine (**8a**, 880 mg, 61%) as a mixture of diastereoisomers and as a colorless oil.

(8) ^{1}H NMR and ^{13}C NMR data for the *cis* and *trans* isomers of **8a** are presented here, and ^{1}H NMR assignments are based on a COSY analysis. While it was possible to separate the *cis* and *trans* isomers of **8a**, but we have been unable to individually and unambiguously assign configurations to these compounds. **Isomer A**: ^{1}H NMR (300 MHz, $CDCl_3$, some doubling due to rotameric populations): δ = 1.72–2.12 (4 H, m, 3-H_2 and 4-H_2), 3.10–3.32 (4 H, m, 6-H and OMe), 3.61 (1 H, m, 5-H), 3.99, 4.31 (1 H, br s, 6-H), 5.66, 6.08 (1 H, br s, 2-H), 7.21–7.56 (5 H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.8, 29.2, 44.8, 45.5, 52.5, 61.1, 62.1, 66.8, 128.8, 132.6, 133.8, 135.3, 155.5. **Isomer B**: ^{1}H NMR (300 MHz, $CDCl_3$, some doubling due to rotameric populations): δ = 1.47–2.50 (4 H, m, 3-H_2 and 4-H_2), 3.02–3.81 (5 H, m, 6-H and OMe), 3.89, 4.12 (1 H, br s, 6-H), 5.79, 6.10 (1 H, br s, 2-H), 7.26–7.51 (5 H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.4, 25.9, 44.4, 44.9, 52.4, 62.1, 63.1, 63.8, 127.9, 128.8, 131.9, 132.7, 156.4. Both isomers of **8a** gave satisfactory HRMS data.
^{1}H NMR and ^{13}C NMR data for **8b** (mixture of diastereomers): ^{1}H NMR (300 MHz, $CDCl_3$, also some doubling due to rotameric populations): δ = 7.72–7.19 (10 H, m, Ar), 6.15–5.49 (2 H, 4 × br s, 2-H), 4.24–3.51 (6 H, m, 3-H and 6-H_2), 3.23 (6 H, br s, OCH_3) and 2.15–1.48 (8 H, m, 4-H_2 and 5-H_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.4, 155.5, 135.0, 134.6, 133.3, 132.9, 129.3, 129.0, 128.9, 127.5, 72.2, 70.7, 69.3, 67.3, 52.9, 52.4, 39.3, 38.3, 29.4, 23.9, 23.4. Compound **8b** also gave satisfactory HRMS data.

(9) **Typical Experimental Procedure:** N,S-Acetal **8a** (149 mg, 0.56 mmol) in THF (5 mL) was cooled to –78 °C and BuLi (0.28 mL, 2 M in hexanes, 0.56 mmol) was added slowly followed after 2 min by freshly prepared lithium naphthalenide (2.23 mL, 1 M in THF, 2.23 mmol) [prepared from Li metal (70.0 mg, 10.0 mmol) and naphthalene (1.28 g, 10.0 mmol) in THF (10 mL)]. After 2 min, allyl bromide (0.24 mL, 338 mg, 2.79 mmol) was added and the mixture was stirred for 1 h at –78 °C, then slowly warmed to r.t. After addition of 10 mL of H_2O, the organic layer was separated and the aqueous layer extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), concentrated and the residue was purified by flash chromatography (silica gel, hexane–EtOAc 5:1) to give *trans*-**10a** (52 mg, 46%) and *cis*-**10a** (16 mg, 14%). *trans*-**10a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.08–1.38 (4 H, m, 3-H_2 and 4-H_2), 2.24 (1 H, m, 1′-H) 2.38 (1 H, m, 1′-H), 3.04 (1 H, dd, *J* = 14.1 and 1.2 Hz, 6-H_{ax}), 3.69 (3 H, s, OCH_3), 3.96 (1 H, br s, 5-H), 4.06 (1 H, br d, *J* = 14.6 Hz, 6-H_{eq}), 4.32 (1 H, br s, 2-H), 5.10–5.01 (2 H, m, 3′-H_2) and 5.73 (1 H, ddd, *J* = 17.2, 10.5 and 7.1 Hz, 2′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0, 28.5, 34.1, 45.6, 49.4, 52.6, 67.2, 117.2, 134.8, 156.4. MS (CI): *m/z* calcd for $C_{10}H_{18}NO_3$ [MH^+]: 200.1287; found: 200.1277. *cis*-**10a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.92–1.42 (4 H, m, 3-H_2 and 4-H_2), 2.25 (1 H, m, 1′-H), 2.39 (1 H, m, 1′-H), 2.62 (1 H, dd, *J* = 13.1 and 10.9 Hz, 6-H_{ax}), 3.60 (1 H, m, 5-H), 3.68 (3 H, s, OCH_3), 4.31–4.08 (2 H, m, 6-H_{eq} and 2-H), 5.14–4.98 (2 H, m, 3′-H_2) and 5.17 (1 H, ddt, *J* = 17.2, 10.5 and 7.2 Hz, 2′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 25.5, 34.0, 45.1, 50.8, 52.7, 64.4, 117.1, 135.0, 157.0. MS (CI): *m/z* calcd for $C_{10}H_{18}NO_3$ [MH^+]: 200.1287; found: 200.1283. The environment (chemical shift and coupling constants) associated with 6-H_{ax} is a useful diagnostic probe for *cis*/*trans* stereochemistry in this and related disubstituted piperidines.[10]

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(11) N,S-Acetal **8a** also provided access to the corresponding N-acyl imimium ion under Lewis acid-mediated conditions. Accordingly, reaction of **8a** with allyl trimethylsilane in the presence of TMSOTf gave **10a** as a 6:1 mixture of *cis* and *trans* isomer in a combined yield of 77%. Note that under these conditions, *cis*-**10a** predominated.

(12) Radical addition adducts **10d**–**f** were obtained as approx. 1:1 mixtures of *cis* and *trans* isomers which were separable by chromatography. Styrene is generally a poor trap for nucleophilic radicals, and the major byproduct in this case was **6**.

(13) The N,Se-acetal corresponding to **8a** is generated from **7a**,**b** under similar conditions to those used for **8a** and **8b** and has also been used as a source of a nucleophilic α-aza radical by C-Se homolysis to provide **10d**–**f** in similar yields to those obtained from **8a**. The use of an N,Se-acetal as a source of nucleophilic radical reactivity adjacent to nitrogen within a pyrrolidine framework has been described. See: Barrett, A. G. M.; Pilipauskas, D. *J. Org. Chem.* **1991**, *56*, 2787.