



Directed lithiation on the quinuclidine ring system: the synthesis of 2,3-difunctionalised quinuclidines

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ABSTRACT

Lithiation of 3-methoxymethyl quinuclidine *N*-oxide occurs regioselectively to generate the 2-lithio 3-methoxymethyl derivative which can be trapped out with non-enolisable electrophiles to give 2,3-disubstituted quinuclidine *N*-oxide derivatives in good yield.

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The quinuclidine ring system is found in a number of natural products including the cinchona alkaloids as exemplified by quinine¹ and quinidine, and in pharmacologically active compounds such as CP-96,345,² which is an NK₁-receptor antagonist, and the dopamine transporter inhibitor shown in Figure 1, which has potential use in the treatment of cocaine addiction (Fig. 1).³ Modified derivatives of quinine and quinidine are amongst the most widely used and successful ligands in asymmetric synthesis.⁴ However, methods for the synthesis of novel functionalised quinuclidines remain scarce, and to date most of them rely on the ring closure of an appropriately functionalised piperidine derivative, as exemplified

in Stork's synthesis of quinine.⁵ Historically, 2,3-disubstituted quinuclidine systems have been synthesised from 3-quinuclidinone via its base-catalysed condensation with a variety of aromatic aldehydes.⁶ These reactions invariably occur with concomitant dehydration to afford the corresponding α,β -unsaturated 3-quinuclidinone systems, which then have to be manipulated in various ways to incorporate further functionality.

As part of a programme directed towards new methods for the synthesis of polyfunctionalised quinuclidines, we report a directed lithiation on a functionalised quinuclidine *N*-oxide which gives direct access to 2,3-difunctionalised quinuclidines. The lithiation of

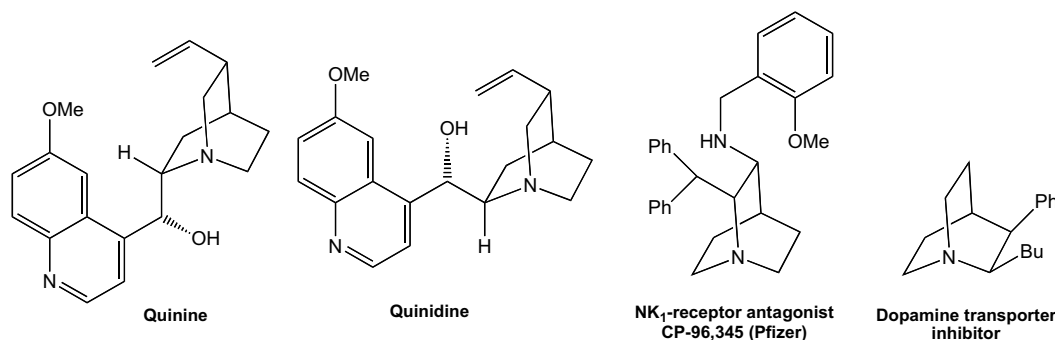
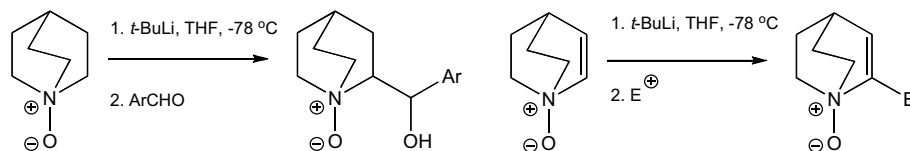


Figure 1.

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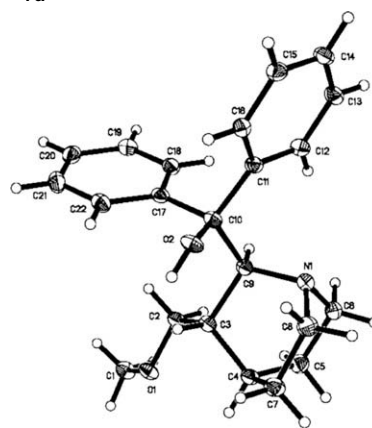
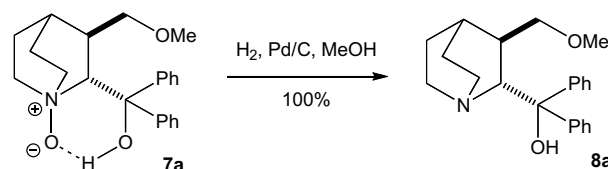
Scheme 1.

quinuclidine *N*-oxide was reported first by Barton et al.⁷ Treatment of anhydrous quinuclidine *N*-oxide with *tert*-butyllithium gave the 2-lithio derivative, which was trapped out with a range of aromatic aldehydes. We have recently extended this methodology to the lithiation and functionalisation of quinuclidine enamine *N*-oxide, which underwent selective deprotonation at the C-2 vinylic position.⁸ The resulting carbanion could be trapped out with a range of electrophiles (Scheme 1). Furthermore, we have also shown that 2-lithio quinuclidine *N*-oxide can serve as a base/HMPA mimetic in a number of important reactions.⁹

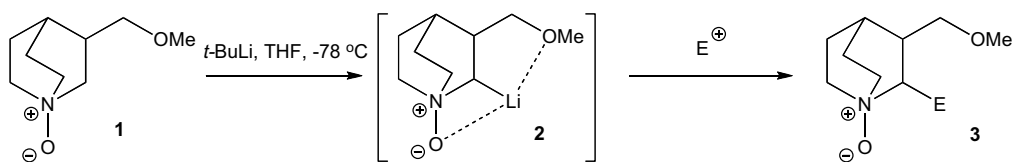
It was envisaged that treatment of a quinuclidine *N*-oxide **1**, bearing a methoxymethyl group at the C-3 position, with *tert*-butyllithium would result in lithiation occurring at the C-2 carbon adjacent to the *N*-oxide and the methoxymethyl group, as a consequence of a directed lithiation effect, and in subsequent stabilisation of the organolithium intermediate **2** by intramolecular or intermolecular chelation.¹⁰ The resulting carbanion could then be trapped out with an appropriate electrophile to give the 2,3-disubstituted quinuclidine *N*-oxide **3** directly (see Scheme 2).

The route to the required 3-methoxymethyl quinuclidine *N*-oxide (**1**) is shown in Scheme 3. Treatment of 3-ketoquinuclidine (**4**) with the ylide derived from methoxymethylene triphenylphosphonium chloride gave the methyl enol ether **5** as a 2:1 mixture of geometric isomers in 76% yield. Reduction of the enol ether **5** with hydrogen in the presence of palladium on carbon gave the 3-methoxymethyl derivative **6**. Conversion of tertiary amine **6** to the desired *N*-oxide **1** was achieved using ozone in Et₂O at -78 °C. This is a superior method for the synthesis of quinuclidine

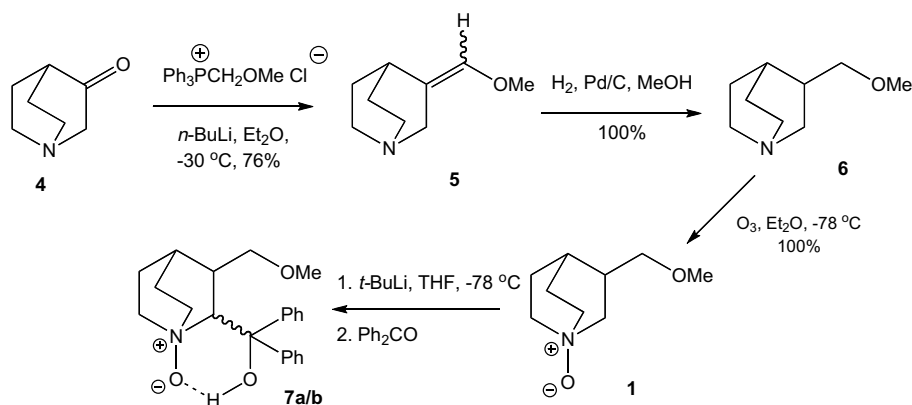
N-oxide as the product is produced in an anhydrous state with no need for further purification.⁹ The Et₂O solvent was removed in vacuo, anhydrous THF was added, and after brief sonication, addition of *tert*-butyllithium at -78 °C resulted in lithiation at the desired



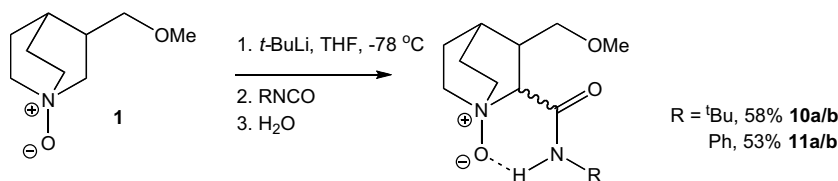
Scheme 4.



Scheme 2.



Scheme 3.



Scheme 5.

C-2 position. This carbanion was trapped out initially with benzophenone to give the products **7a/b** as a 1:1 mixture of diastereoisomers in 95% yield. We did not observe any deprotonation at the other N-CH₂ positions.

The product diastereoisomers **7a/b** were separable by flash chromatography, and the less polar isomer **7a** was subjected to catalytic hydrogenation using Pd/C in MeOH to give the parent tertiary amine **8a**, which was crystalline (Scheme 4). X-ray analysis confirmed the structure of the product as the *anti*-diastereoisomer.

The carbanion **2** was also trapped out with a number of other electrophiles. The adduct with fluoren-9-one was obtained in 84% yield, again as a 1:1 mixture of diastereoisomers **9a/b**. Quenching the carbanion with non-enolisable aromatic aldehydes, such as benzaldehyde, gave the corresponding adducts as complex mixtures of diastereoisomers, which were inseparable by chromatography. With *tert*-butyl and phenylisocyanate, the corresponding amides **10a/b** and **11a/b** were generated in 58% and 53% yields, respectively, after aqueous work-up, as 1:1 mixtures of diastereoisomers (Scheme 5).

In summary, we have shown that functionalised 2,3-quinuclidines can be prepared by the directed lithiation of 3-methoxymethyl quinuclidine *N*-oxide in good to excellent yields. To the best of our knowledge, this is the first report of a directed lithiation α to a tertiary amine *N*-oxide.

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