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Novel chemoselective reduction of the tetrahydro-4-pyridyl versus indole moiety governed by electron donation: first X-ray evidence for indolopiperidyl–borane complexation

Alfio Borghese,[a,*] Luc Antoine[a] and Gregory Stephenson[b]

[a]*Chemical Process Research and Development, Lilly Development Centre SA, 1348 Mont-Saint-Guibert, Belgium*
[b]*Material Science and Physical Characterization, Eli Lilly & Co, Indianapolis, IN, USA*

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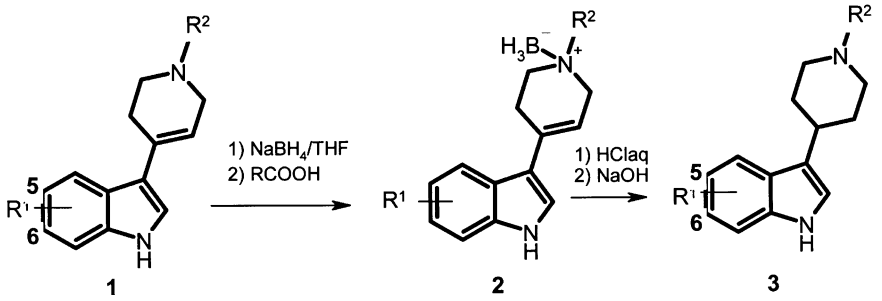
Abstract—A series of amino–borane complexes of structure type **2** are the key intermediates in the preparation of 3-(piperidyl) indole derivatives. The selective reduction of the tetrahydro-4-pyridyl double bond via **2** under strongly acidic conditions is feasible only when the pyridyl double bond is conjugated with electron rich substituents, such as indoles. This reduction methodology allows the presence of reducible and hydrogenolizable functional groups. An improved process to prepare **2** by treatment of the 3-(tetrahydro-4-pyridyl) indole derivatives with $NaBH_4$ in THF under acidic conditions (AcOH or CF_3COOH) is also described.

The 3-(piperidyl) indole derivative **3** are common building blocks found in many pharmaceutical compounds having interesting serotoninergic activity.[1] These pharmacophores are usually prepared by catalytic hydrogenation of 3-(tetrahydro-4-pyridyl) indole derivatives **1** (Scheme 1). Silane reduction[2] (Et_3SiH/CF_3COOH) in acidic media is preferred when substituents susceptible to hydrogenolysis are present. Bonjoch et al. reported[3] one example on the reduction of 3-(tetrahydro-4-pyridyl) indole to the corresponding 3-(piperidyl) derivative by using $NaBH_4/BF_3$–Et_2O in THF, speculating the tetrahydropyridine–borane complex as an intermediate. The same reduction reaction applied to the 3-(tetrahydro-2-pyridyl) indoles lead only to the indolines derivatives. In general,[5,6] when indoles are treated with $NaBH_4$ or $NaBH_3CN$ in acidic media as well as BH_3–THF in TFA, indolines are formed. In neat AcOH, the corresponding indolines are further 1-N alkylated.[7] Also, borane reduction of indole derivatives bearing amino substituents yields the corresponding indoline derivatives.[8]

In this paper, we report that the synthesis of 3-(piperidyl) derivatives **3**, via the formation of the isolable key amino–borane intermediate **2** from 3-(tetrahydro-4-pyridyl) derivatives **1** (Scheme 1) is feasible when the pyridyl double bond is conjugated to an electron rich indole. Strong acid treatment of **2** yields the desired 3-(piperidyl) indole derivative **3** in excellent yields (Table 1). Indeed, when we replaced the indole sub-



Scheme 1.

* Corresponding author. Tel.: +32(0)10 476309; fax: +32(0)10 476315; e-mail: a.borghese@lilly.com

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Table 1. Reduction of 3-(tetrahydro-4-pyridyl) indoles

Entry	R^1	R^2	Salt	Yield[b]
1	5-Br	Me		96
2	5-NH_2	Me		83
3	5-NO_2	Me		66
4	6-F	H		93
5	6-F	**4**		78
6	6-F	**5**		63
7	5-BnO	Me		92
8	5-NO_2	Me	Acetate	88
9	6-F	H	Hydrochloride	98
10	6-F	**4**	Phosphate	93
11	6-F	**5**	L-Tartrate	>99[a]

[a] Isolated as hydrochloride salt.
[b] Isolated crude yields with ^{1}H NMR analysis.

stituent with 2-naphthyl or 5-benzothiophene moieties, the reaction failed to furnish the reduced compound despite the formation of the amino–borane complex.[4] In this case, strong acid treatment of the amino–borane complex restored the starting material.

An improved process to prepare the amino–boranes **2** by treating **1** with $NaBH_4$ in THF under mildly acidic conditions (AcOH or TFA) is also reported. BH_3–THF could be employed without hydroboration of the tetrahydro-4-pyridyl double bond under these conditions. However, use of the $NaBH_4$–RCOOH couple overcomes significant scale up and equipment issues associated with the use of BF_3–Et_2O, BH_3–THF or Et_3SiH/CF_3COOH, and was thus the method of choice.

Most significantly, no reduction of the tetrahydro-4-pyridyl double bond occurred prior to strong acid (HCl) treatment of the reaction mixture.[9] This complex **2** could be isolated in almost quantitative yield as a crystalline, stable solid and was characterized by XRD[10] (Fig. 1), ^{1}H NMR and mass spectral analysis. The reduction of the 3-(tetrahydro-4-pyridyl) indole double bond with $NaBH_4$ under neutral conditions was also attempted in THF, as the tetrahydropyridine double bond might be considered activated through conjugation with the indole ring. Under these conditions, only starting materials were recovered unchanged.

This novel operating procedure was applied successfully to several 3-(tetrahydro-4-pyridyl) indole derivatives bearing hydrogenolizable or easily reducible (catalytic hydrogenation) functional groups (Table 1, entries 1–7), demonstrating the generality and the high chemoselectivity of the reaction. In each case the key amino–borane complex **2** was formed as an intermediate in the course of the reduction reaction. More highly functionalized molecules (Table 1, entries 5, 6, Scheme 2) also bearing uniquely reducible functional groups were selectively transformed to the corresponding piperidine derivatives in high yield.

Table 1 contains several examples performed with the $NaBH_4$/AcOH protocol to illustrate the selectivity of the operating procedure. AcOH was selected for convenience, as it was found equally effective to CF_3COOH. The last four entries are examples of the reduction using preformed salts of the 3-(tetrahydro-4-pyridyl) indole derivatives. More interesting, when various salts of **1** (Table 1, entries 8, 9, 10, 11) were used, the reaction with $NaBH_4$ afforded the amino–borane complex **2** directly without the need for addition of an external acid, leading to **3** after strong acid treatment of the reaction mixture. It is noteworthy that in general, a better yield was obtained when the salts of **1** were used (compare entries 3 with 8, 5 with 10, 6 with 11, Table 1). Moreover, the detrimental effect of the strong electron withdrawing group NO_2 (entries 3 and 8, Table 1) on the yield should be noted, indicating the importance of the electronic effect on the efficiency of that reaction.

The observation that the amine–borane derivative was formed in almost quantitative yield demonstrated that a

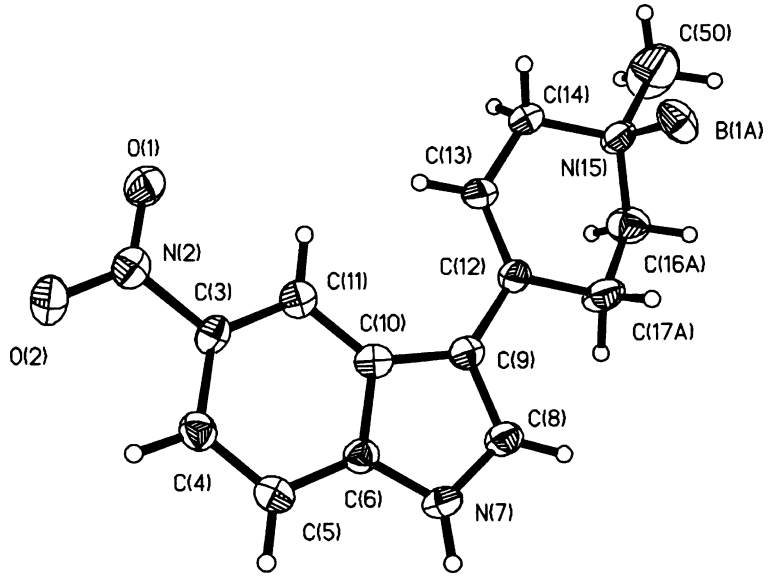
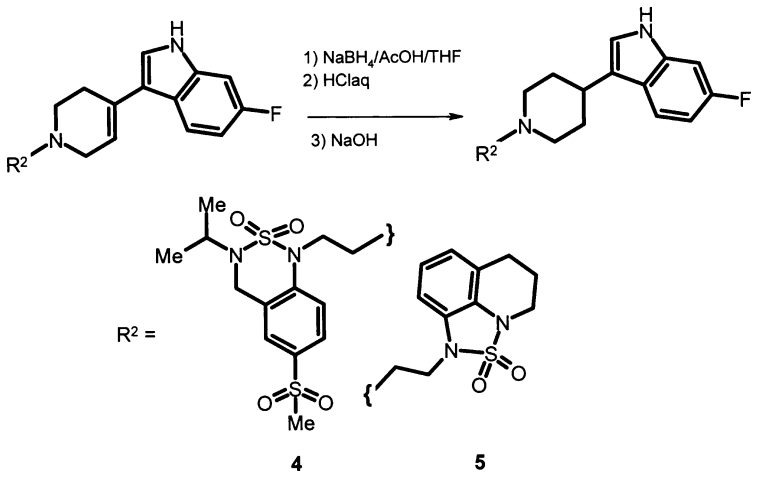


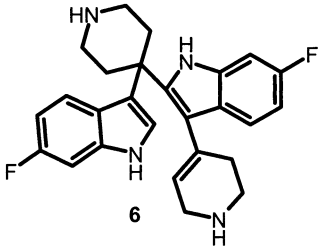
Figure 1. ORTEP view of **2** (entry 3, Table 1).



Scheme 2.

borane surrogate was generated in situ. Indeed, the $NaBH_4/RCO_2H$ mixture was previously used by Hach and by Marshall[11] to perform the hydroboration of olefins. Masamune[12] also reported the in situ generation of borane by reaction of $NaBH_4$ with HCl, $MeSO_3H$ or H_2SO_4. These results might explain the formation of **2** when salts of **1** are used with $NaBH_4$. The salt positions the requisite acid at the site of complexation. When carboxylic acids (RCOOH) are used in combination with $NaBH_4$, sodium acyloxyborohydrides species $(NaBH_x(OCOR)_y$ or $NaBH_3(OCOR)$ are formed, and these are thought to be the reactive species.[13] In our case,[14] we believe that if $NaBH_3(OCOCH_3)$ forms, it reacts rapidly with the amine to form the amine–borane **2** before further reaction with AcOH to form the triacetoxy species. We have demonstrated that the reduction of **1** with $NaBH(OCOCH_3)_3$ failed to give the desired **3**.

Under our experimental conditions, no indoline derivatives have been formed, indicating that the selectivity of the reduction process is in favor of the formation of the (piperidyl) indole derivatives. This reactivity is very likely due to the vinylogous nature of the tetrahydro-4-pyridyl double bond, conjugated through the indole moiety. The fact that strong acid treatment of **2** is needed to perform the reduction supports a mechanistic notion that a tertiary carbocation is generated by double bond protonation in **2**. This is in agreement with previous reported observations.[3] Indirect evidence for the proposed protonation of the double bond is given by the formation of compound **6** when HCl is added to a THF solution of **1**. The formation of **6** also demonstrates the acid sensitivity of this conjugated species. The cation could react intramolecularly with amine–BH_3 hydride, forming a six-membered ring transition state (cf. **7**), although definitive evidence is not available.



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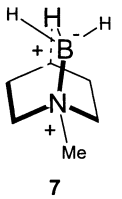

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In conclusion, these results demonstrated the generality of $NaBH_4$/organic acid in reducing the 3-(tetrahydro-4-pyridyl) indole derivatives to the corresponding piperidyl derivatives and the selective application to indole substituted derivatives. The amino–borane complex is the key intermediate in these reduction reactions. The fact that no indoline is formed during the reduction process in acidic media demonstrated the high chemoselectivity of this reaction. Moreover, this reduction protocol can be extended to 3-(tetrahydro-4-pyridyl) indoles bearing hydrogenolizable substituents on the indole ring. The same experimental protocol has also been successfully extended to other 3-(tetrahydro-3-pyridyl) indole derivatives. In addition, from a large-scale synthesis perspective, this reduction procedure is very attractive as it can be performed without the need of highly corrosive or reactive reagents.

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4. In these examples the *N*-methyl, 2-methyl pyridyl derivatives were used.
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9. ^{1}H NMR of the isolated **2** (entry 4) confirmed the presence of the piperidyl double bond. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 1.46 (s (br), 3 H), 2.61 (m, 3 H), 3.19 (m, 2 H), 3.51 (dm, $J=17.72$ Hz, 1 H), 6.10 (s, 1 H), 6.24 (s (br), 1 H), 6.90 (td, $J=9.23$, 2.21 Hz, 1 H), 7.17 (dd, $J=10.09$, 2.22 Hz, 1 H), 7.43 (s, 1 H), 7.79 (dd, $J=8.61$, 5.66 Hz, 1 H), 11.39 (s, 1 H).
10. Crystallographic data (excluding structure factors) for **2** (entry 3) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 182427. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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14. Experimental procedure: To a suspension of $NaBH_4$ (2.6 g, 68.7 mmol; 2.0 equiv.) and 6-fluoro-3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1*H*-indole (7.4 g, 34.3 mmol, 1.0 equiv.) in THF (100 ml) is slowly added glacial CH_3COOH (6.0 ml, 104.8 mol; 3.0 equiv.), while keeping the temperature below 30°C. Stirring of the reaction mixture was continued at room temperature for 0.5 h. A 37% HCl solution (10 ml) was slowly added to the reaction mixture, and the mixture stirred for 0.5 h at room temperature. H_2O (100 ml) was added and the THF removed from the reaction mixture by distillation under atmospheric pressure. The reaction mixture is cooled to room temperature and neutralized with a 30% NaOH solution (20 ml) until pH>12. The resulting suspension was stirred for 1 h at room temperature. The precipitate was filtered, washed with H_2O (50 ml) and dried under reduced pressure at 50°C to yield 6.97 g (93.3%) of 6-fluoro-3-piperidin-4-yl-1*H*-indole.