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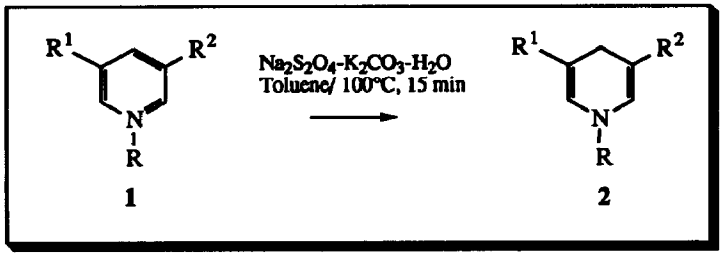
1,4-Dihydropyridines from Dithionite Reduction of Pyridinium Salts without Electron-Withdrawing Groups as Substituents

Yung-Sing Wong, Christian Marazano,* Dino Gnecco† and Bhupesh C. Das

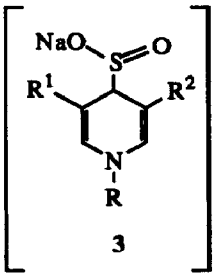
Institut de Chimie des Substances Naturelles, C.N.R.S., 91198 Gif-sur-Yvette Cedex, France

Abstract: Conditions have been established for the sodium dithionite ($Na_2S_2O_4$) reduction of pyridinium salts **1** lacking electron-withdrawing substituents to their corresponding 1,4-dihydropyridines (1,4-DHPs) **2**, a reaction which was previously reported to fail. The importance of hydrophobic effects for this reduction to take place could be recognized from the results obtained. The present procedure offers a very convenient route to a number of 1,4-DHPs **2**, in particular, a series of chiral derivatives such as **5** and **9**.

The sodium dithionite reduction of *N*-alkyl pyridinium salts **1** (Scheme 1) bearing electron-withdrawing substituents R^1 and/or R^2 to give 1,4-DHPs **2** is a long-known and well-established procedure which has received much attention, especially for studies of NADH coenzyme models.[1] The mechanism of this reduction has also been investigated.[2] In addition to the use of an inexpensive reducing agent, other advantages to obtaining 1,4-dihydropyridines by this reaction are simple experimental conditions and a complete regioselectivity for 4-H substituted pyridinium salts. However, an apparent limitation of this procedure was the reported failure of the sodium dithionite reduction when *N*-alkyl pyridinium salts are not substituted with electron-withdrawing groups at position 3 (and/or 5) of the ring.[1a,3]



	R	R^1	R^2	% yield of **2**
a	Me	H	H	0
b	-$(CH_2)_n$-Me	H	H	0 (n=1-3) 50 (n=4) 80 (n=5-11)
c	-CH_2Ph	H	H	80
d	-CH_2Ph	Me	H	80
e	-CH_2Ph	Me	Me	80



Scheme 1

† *Universidad Autonoma de Puebla, Institudo de Ciencias, Centro de Quimica, Puebla, Mexico.*

Presumably for this reason, alternative approaches toward 3-unsubstituted or 3-alkyl substituted 1,4-DHPs, consisting mainly in a Birch-type reduction of the corresponding pyridinium salts, have been devised.[4] The synthetic interest of these 1,4-DHPs as useful 1,5-diketone equivalents has been pointed out.[5]

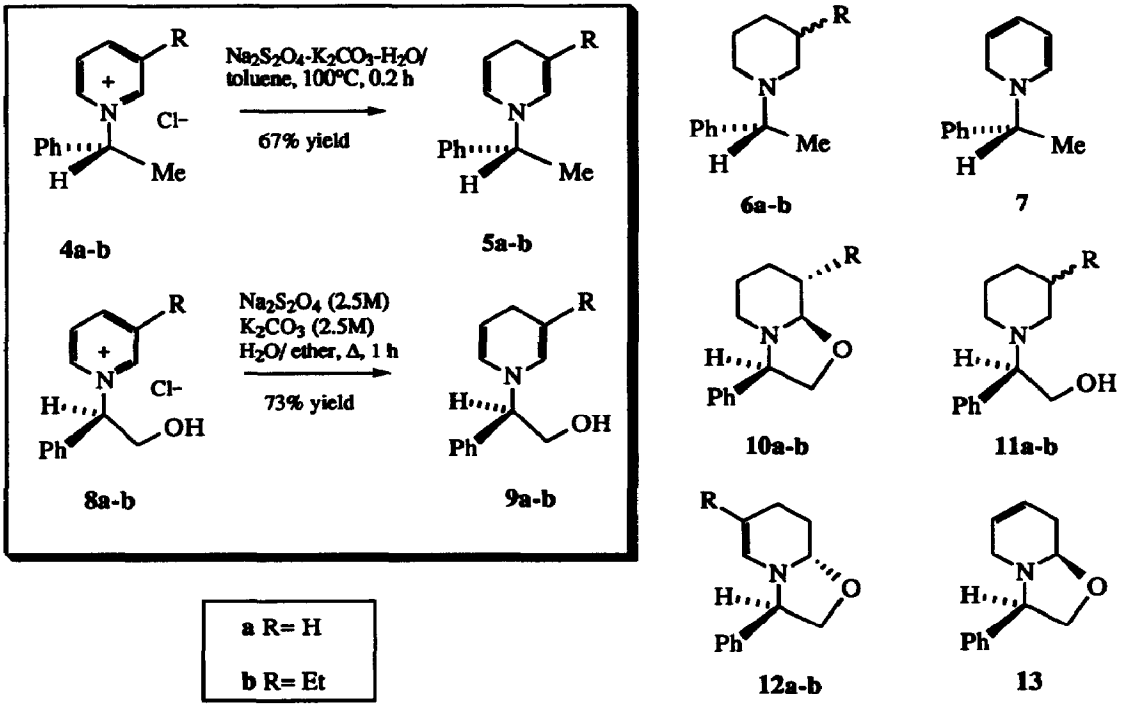
In the course of our studies on the asymmetric synthesis of alkaloids from chiral pyridinium salts[6] *via* chiral dihydropyridine derivatives,[7] we needed a simple procedure for reduction of these salts to the corresponding 1,4-DHPs which could subsequently cyclize to give synthetically useful oxazolidine intermediates.[8] Thus, with the ease of the dithionite procedure in mind, we decided to reinvestigate the reduction of pyridinium salts devoid of electron-withdrawing substituents. We now report the essential features of this reduction which in fact provides a very convenient access to 1,4-DHPs. The reduction proceeded successfully with a large variety of pyridinium salts, in particular those obtained recently in our laboratory using Zincke's reaction with chiral primary amines.[6]

Our initial attempts to reduce *N*-methyl substituted salt **1a** in a two-phase system (H_2O–K_2CO_3–$Na_2S_2O_4$/toluene at 100°C) proved unsuccessful, inasmuch as no organic product could be extracted from the aqueous phase. This was seemingly a confirmation of the reported failure of the reaction in the absence of electron-withdrawing substituents at position 3 (and/or 5) of the ring. However, in sharp contrast, we observed that, after 10 min under the same conditions, long-chain substituted salt **1b** (n=11) gave the corresponding 1,4-DHP which was recovered in 80% yield after simple decantation and evaporation of the organic layer. By varying the length of the alkyl chain of **1b** and using the same conditions, no reaction was found to occur with n=1, 2 or 3, but with n=4, the corresponding 1,4-DHP could be obtained in approximately 50% yield after 10 min. Synthetically more useful 1,4-DHP **1c** was obtained in high yield (>80%) under these conditions. Alkyl substituents at positions 3 or 3,5 did not affect the yield of the reaction as shown by the reduction of salts **1d** and **1e**. These results demonstrated the determining role of hydrophobic interactions for the reaction to take place, the likely role of these interactions being the destabilization of the intermediate sulfinate adduct **3** in the aqueous phase.

With this background information in hand, we carried out detailed studies on the dithionite reduction of the chiral pyridinium salts **4** and **8**[6] (Scheme 2). Reduction of **4a** and **4b** gave the corresponding 1,4-DHPs **5a** and **5b** in good yields in the toluene-water system at 100°C (see experimental for a typical procedure). Noteworthy is the fact that at low salt concentration (concentration of sodium dithionite and potassium carbonate ranging from 0.25M to 0.75 M) a significant proportion (up to 40%) of the isomeric piperidines **6a-6b** was obtained. Formation of these by-products was completely suppressed using salt concentration above 1M. As expected, these 1,4-DHPs were relatively stable, contrasting with the very high instability of their 1,2-dihydro counterparts such as **7** obtained by the $NaBH_4$ reduction of **4a** in alkaline medium.[7a]

Attempts to obtain 1,4-DHP **9a** under the conditions found for the synthesis of **5a-b** were disappointing, the predominant product of the reaction being the piperidine **11a** along with small amounts of oxazolidine **10a**. Similar results were obtained during the reduction of salt **8b** which led to **11b** as the major compound, again accompanied with a minor amount of **10b**. The presence of a hydroxyl group in these molecules was very likely favourable for an overreduction of the intermediate 1,4-DHP in the water phase.

We therefore sought new conditions which could ensure a rapid transfer of the DHP **9a** or **9b** from the aqueous to the organic phase as soon as it was formed, in order to prevent these overreduction phenomena. Since it was not possible to increase the hydrophobic character of the starting pyridinium salt, we decided to work with a *saturated* aqueous solution of sodium dithionite (≥ 2.5M) and potassium carbonate (≥ 2.5M), having in mind the role of salt concentration in the reduction of **4a-b** (*vide supra*). Finally, under these conditions, using refluxing ether as organic solvent, 1,4-DHP **9a**[9] was extracted in ether and recovered in 73% yield. The formation of the products **10a** and **11a** was completely suppressed under these conditions. This was demonstrated by recording the NMR spectra of the crude product obtained immediately after removal of the solvent (see experimental).



Scheme 2

Compared to 1,4-DHPs **5a**, 1,4-DHP **9a** proved to be very unstable, turning into tars within a few hours at ambient temperature. Again, the presence of the hydroxyl group was responsible for the instability of the compound, presumably catalysing dimerization and polymerization *via* very reactive immonium intermediates. During this process, the initial formation of oxazolidine **12a** (scheme 2) was observed. The behaviour of 1,4-DHP **9a** thus contrasted with that of the corresponding regioisomeric 1,2-DHP which, as we have recently shown,[8] gave spontaneously the corresponding oxazolidine **13**. Noteworthy is the presence of a very reactive enamine in **12a** and not in **13**. Finally, it is important to point out that, in contrast to unsubstituted 1,4-DHP **9a**, 3-alkyl substituted 1,4-DHPs such as **9b** gave useful oxazolidine intermediate **12b** in good yield.

Detailed studies on the application of these oxazolidines toward asymmetric synthesis of a number of natural products will be disclosed separately.

Experimental (typical procedures):

(+)-1-[(1*R*)-1-Phenylethyl]- 1,4-dihydropyridine (5a). To a two-phase solution of toluene (150 mL) and water (170 mL) containing sodium dithionite (30g) and potassium carbonate (24 g) was added pyridinium salt **4a** (6.2 g, 28.2 mmol) in water (20 mL). The mixture was heated at 100°C during 0.2 h under vigorous stirring. The organic phase was collected, washed with an aqueous solution of sodium bicarbonate, and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure and filtration over alumina (30 g) with pentane – AcOEt (1:1) as eluant gave pure 1,4-dihydropyridine **5a** (3.5 g, 18.9 mmol, 67% yield) as a pale yellow oil. This compound decomposes on standing in air but could be stored at –20°C over KOH pellets; $[\alpha]_D$ +3 (*c* 1.2, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 7.15–7.33 (5H,.m), 5.77 (2H, dt, *J* = 1.2 Hz, *J* = 8.3 Hz), 4.35 (2H, dt, *J* = 3, *J* = 8.3 Hz), 4.18 (3H, q, *J* = 7 Hz), 2.96 (2H, m), 1.47 (3H, d, *J* = 7 Hz); ^{13}C NMR (50.2 MHz, $CDCl_3$): 19.2, 23.0, 59.9, 98.1 (2C), 126.7 (2C), 127.1, 128.4 (2C), 129.9 (2C), 142.9; HRMS (EI): calcd for $C_{13}H_{15}N$ *m/z* 185.1204, obsd *m/z* 185.1211

(–)-1-[(2*R*)-2-Phenylethanol]-1,4-dihydropyridine (9a). To a biphasic solution of diethyl ether (500 mL) and water (90 mL) containing sodium dithionite (60 g) and potassium carbonate (48 g) was added pyridinium salt **8a** (12.2 g, 51.8 mmol) in water (30 mL). The mixture was refluxed during 1 h under vigorous stirring. The ethereal phase was decanted and washed with an aqueous solution of sodium bicarbonate, dried over anhydrous Na_2SO_4 and concentrated. The residue was dissolved in pentane and filtered over celite to give pure 1,4-dihydropyridine **9a** (7.58 g, 37.7 mmol, 73% yield) as an oil which decomposed very rapidly; $[\alpha]_D$ –49 (*c* 1.7, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 7.20–7.38 (5H,.m), 5.83 (2H, d, *J* = 8.3 Hz), 4.36 (2H, dt, *J* = 3 Hz, *J* = 8.3 Hz), 4.15 (1H, dd, *J* = 6.2 Hz, *J* = 7.8 Hz), 3.92 (1H, d, *J* = 6.2 Hz), 3.91 (2H, m), 2.96 (m, 2H); ^{13}C NMR (50.2 MHz, $CDCl_3$): 22.8, 62.6, 66.3, 98.1 (2C), 126.9 (2C), 127.3, 128.3 (2C), 130.0 (2C), 138.7; HRMS (EI): calcd for $C_{13}H_{15}N$ *m/z* 201.1154, obsd *m/z* 201.1146.

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