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Reduction of Isoquinoline and Pyridine-containing Heterocycles with Lithium Triethylborohydride (Super-Hydride®)

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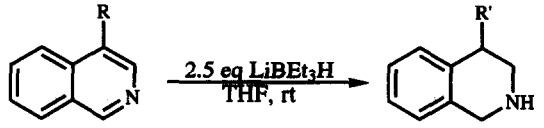
Abstract: Isoquinolines, quinoline and pyridines are effectively reduced to 1,2,3,4-tetrahydroisoquinolines, 1,2,3,4-tetrahydroquinolines and piperidines respectively with lithium triethylborohydride (Super-Hydride®). The mechanism of the reduction was explored by reduction of isoquinoline and pyridine with lithium triethylborodeuteride (Super-Deuteride®).

As part of our program directed toward the synthesis of PCP-like ligands, we required a method to selectively reduce 4-allylisoquinoline (**1e**) to its 1,2,3,4-tetrahydro analog.[1] Two reported methods for the selective reduction of isoquinolines (**1**) to 1,2,3,4-tetrahydroisoquinolines (**2**) are hydride addition[2] and catalytic hydrogenation.[3] Reduction of the heterocyclic ring of **1e** with sodium cyanoborohydride in acid was successful, but we were surprised to observe concurrent olefin reduction which is normally suppressed under these conditions. Since hydrogenation would cause the same undesirable side reaction neither of the two known methods were applicable. An alternate route involved conversion of **1e** to the quaternary salt with methyl iodide, followed by sodium borohydride reduction to the N-methyl-1,2,3,4-tetrahydroisoquinoline and then N-demethylation. The first two steps proceeded smoothly; however, removal of the N-methyl group was complicated by the competing cleavage of the benzylic C-N bond. In this study, we report the selective direct reduction of isoquinolines (**1**) to 1,2,3,4-tetrahydroisoquinolines (**2**) using lithium triethylborohydride (Super-Hydride®). In addition, the application of this method to other heterocycles is presented.

In 1988, a report by Minter outlined the use of sodium triethylborohydride in a reaction with isoquinolines as an approach to 4-alkylisoquinolines.[4] After the initial addition of one equivalent of hydride, an aldehyde was added to the mixture which underwent nucleophilic attack by a boron-activated enamine. The secondary alcohol then eliminated and the olefin isomerized into conjugation providing the desired 4-alkylisoquinolines. We reasoned that since the postulated reactive intermediate was an enamine, it may tautomerize to an imine and allow the addition of a second equivalent of hydride. Indeed, reaction of 4-allylisoquinoline (**1e**) with 2.2 equivalents of lithium triethylborohydride afforded 4-allyl-1,2,3,4-tetrahydroisoquinoline (**2e**) in 93% yield. After one hydride equivalent, the reaction mixture became dark and after the second equivalent the mixture cleared to a pale yellow. Reduction was also successful with 1 equivalent of Super-Hydride® followed by 1 equivalent of lithium aluminum hydride; however only in 54% yield. The yield of the latter reaction was low because extraction of the resulting amines out of the aluminum salts was difficult. No such problem exists when using only Super-Hydride® since the triethylborane by-product can be extracted out of an acidified crude layer with ether.

Table 1. Super-Hydride® Reduction of Isoquinolines

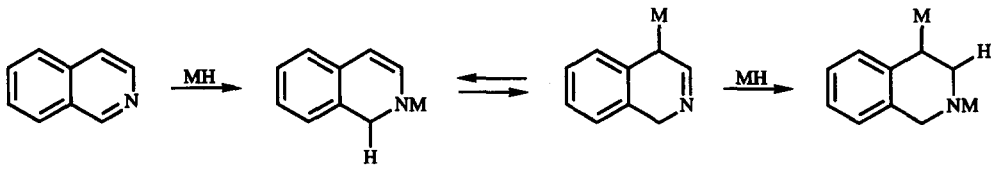


1 2

Compound	R	R'	Yield %
a	H	H	85%
b	Me	Me	82%
c	Et	Et	88%
d	$CH{=}CH_2$	Et	74%
e	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	93%
f	Ph	Ph	79%

The high yield and general ease of this reduction suggested that it might have wider applicability. Table 1 lists the results obtained with isoquinolines (**1a-f**). Starting isoquinolines were either purchased or made from 4-bromoisoquinoline via a nickel catalyzed Grignard[5] or a palladium catalyzed stannane[6] coupling. These two coupling reactions were remarkably complimentary. The nickel reaction was superior when coupling alkyl Grignards with aryl bromide while the palladium coupling was efficient with activated stannanes such as allyl stannane. Each subsequent reduction provided a highly pure product which could be readily isolated via column chromatography or crystallization. The only anomaly encountered was in the reduction of 4-vinylisoquinoline (**1d**) which reduced to 4-ethyl-1,2,3,4-tetrahydroisoquinoline (**2d**).

Reductions of isoquinoline with deuterated reagents were conducted in order to determine the order and location of hydride addition. All results were based on peak shifts and relative peak integrations of ^1H NMR spectra. Reaction of isoquinoline with Super-Deuteride® introduced deuteriums at C-1 and C-3. Reaction with Super-Hydride® followed by quenching with CD_3OD resulted in deuterium introduction at C-4 only. As would be expected, reaction of isoquinoline with Super-Deuteride® followed by quenching with CD_3OD resulted in deuterium incorporation at all three sites. Reaction of isoquinoline with one equivalent of hydride produced a 1:1 mixture of starting material and product which indicates that the second addition is much faster than the first. Mechanistically, these observations suggest that hydride addition initially occurs at C-1 providing an anion at C-4 which then allows the second equivalent to react with the imine at C-3, Scheme 1.

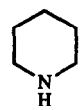
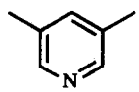
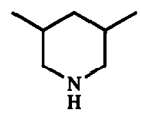
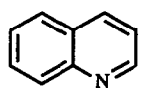
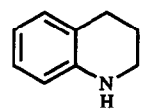
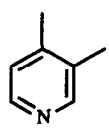
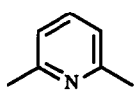


Scheme 1

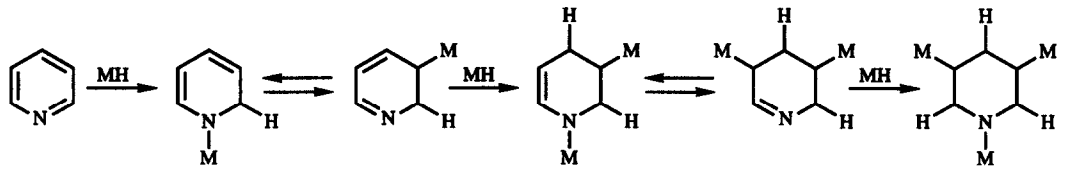
We then applied these conditions to the reduction of pyridine. In 1980, Brown et al. reported the reduction of pyridine to tetrahydropyridine with two equivalents of lithium triethylborohydride in tetrahydrofuran.[7] Addition of a third equivalent, presumably to form piperidine, was "quite slow and incomplete." We were therefore surprised to find that in our hands the addition of three equivalents of hydride to pyridine was rapid. As before,

the solution changed colors, from yellow to orange to reddish orange, then back to light orange; however, the changes were different from those reported by Brown et al.[7] They observed a change from yellowish green to orange and back to yellowish green. Only after six hours did they observe a re-emergence of the orange color.[8] Due to this discrepancy, we decided to explore the reduction of additional pyridine compounds. Table 2 lists the results obtained from other pyridines.[9] 3,5-Lutidine reduced to a 1:1 mixture of cis and trans 3,5-lupetidines and quinoline reduced to 1,2,3,4-tetrahydroquinoline with relative ease. Other pyridines were not reduced as efficiently. 3,4-Lutidine reduced to a mixture of tetrahydropyridines and both 2,6-lutidine and 2-(3-pentenyl)-pyridine were totally inert to these conditions.

Table 2. Super-Hydride® Reduction of Pyridines

Reactant	Product	Yield %
		81%
		84%
		40%
	mixture of tetrahydropyridines	-
	starting material	-

A similar set of mechanistic experiments were conducted in the reduction of pyridine as was described for isoquinoline. Deuteriums were incorporated at C-2, C-4 and C-6 of piperidine when Super-Deuteride® was added to pyridine. Reaction of pyridine with Super-Hydride® followed by quenching with CD_3OD resulted in deuterium introduction at C-3 and C-5. Reduction of pyridine with Super-Deuteride® followed by quenching with CD_3OD introduced a deuterium at every position. Combined, these experiments suggest that hydride initially adds at C-2, Scheme 2. This intermediate then tautomerizes, allowing 1,4 hydride addition at C-4. The second intermediate can also tautomerize which allows the final equivalent of hydride to add at C-6. The incomplete reduction of 3,4-lutidine and the inertness of 2,6-lutidine to Super-Hydride® could be due to steric hindrance, or alternatively, the reduction could be inhibited by deprotonation of the more acidic 4-methyl and 2,6-dimethyl groups of 3,4-lutidine and 2,6-lutidine, respectively. The observation that reaction of 2,6-lutidine with Super-Hydride® followed by quenching with CD_3OD resulted in no apparent deuterium incorporation in the methyl groups argues against the latter explanation.



Scheme 2

TYPICAL EXPERIMENTAL

To a stirred solution of 1.44 g (8.46 mmol) of 4-allylisoquinoline (**1e**) in 22 mL of dry tetrahydrofuran at room temperature was added 18.6 mL (18.6 mmol) of 1.0M lithium triethylborohydride in tetrahydrofuran dropwise. The solution turned reddish brown after one equivalent and cleared to a pale yellow after a second addition. The mixture was allowed to stir for 0.5 h and quenched with 10 mL methanol dropwise. The solution was diluted with diethyl ether and 1N aqueous hydrochloric acid. Triethylborane was extracted out with ethyl ether. The pH of the aqueous layer was raised to 8 and the layer was extracted with methylene chloride. The combined methylene chloride layers were dried over sodium sulfate and concentrated under reduced pressure. The thick yellow oil was purified by flash chromatography on silica gel. Elution with 8:1 ether-hexane afforded 1.35 g (93%) of 4-allyl-1,2,3,4-tetrahydroisoquinoline (**2e**).

ACKNOWLEDGMENT

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8. The difference in reactivity may be a result of reagent preparation. Brown et al. prepared their lithium triethylborohydride themselves prior to use while ours was purchased from Aldrich Chemical Company, Milwaukee, WI.
9. All piperidines were isolated as their HCl salt.

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