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Reduction of Quinolines to 1,2,3,4-Tetrahydro Derivatives Employing a Combination of $NaCNBH_3$ and $BF_3.OEt_2$#

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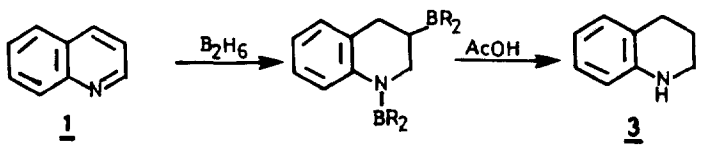
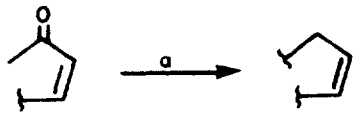
Abstract: A regiospecific reduction of quinolines (and 1,10-phenanthroline) into the corresponding 1,2,3,4-tetrahydro derivatives using a combination of sodium cyanoborohydride and boron trifluoride etherate in refluxing methanol is described. Under the same conditions indole and acridine reduced to the corresponding dihydroderivatives, whereas acyl group transfer from oxygen to nitrogen atom is also noticed in the case of 8-acyloxyquinolines.

Regioselective reduction of nitrogen containing heterocyclic compounds, *e.g.* quinoline, isoquinoline etc., into the corresponding tetrahydro derivatives is an important transformation in organic synthesis, since they serve as key synthetic intermediates for drugs, agrochemicals, dyes, higher alkaloids etc.[1] Among the several methods developed for the conversion of various quinolines to the corresponding tetrahydro derivatives, Fish and coworkers[2] employed a high pressure (500 psi, 80°C) homogeneous catalytic hydrogenation, whereas Murahashi *et al.*[1] used the rhodium catalysed hydrogenation employing carbon monoxide and water. Keller and coworkers[3] studied the use of diborane for the conversion of quinolines and several related compounds into the corresponding tetrahydro derivatives via the acid mediated hydrolysis of the borane intermediate formed by the hydroboration of the initially formed 1,2-dihydro derivatives (eqn. 1). Whereas Kudo and coworkers[4] examined the transition metal salt catalysed reductions using either sodium borohydride or diborane, Gribble and coworkers[5] generated the corresponding N-alkylated derivatives using sodium borohydride in the presence of appropriate carboxylic acids, and Hutchins and Natale[6] reported the reduction of quaternised pyridines to the N-alkylated tetrahydro compounds employing sodium cyanoborohydride. Recently Blough and Carroll[7] reported the use of super hydride for the conversion of isoquinolines and pyridines to the corresponding tetrahydro derivatives, whereas quinoline was reduced to tetrahydroquinoline in low yield. We have recently discovered[8,9] that sodium cyanoborohydride in the presence of boron



1 **3** (eqn. 1)

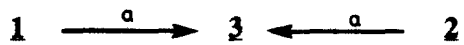
#Dedicated to Professor U.R. Ghatak on the occasion of his 65th Birthday.



(eqn. 2)

a. $NaCNBH_3$, $BF_3.OEt_2$, THF

trifluoride etherate in tetrahydrofuran is an efficient ionic hydrogenation combination, and its use in several deoxygenation reactions was explored. Since it was already established[9] that sodium cyanoborohydride in the presence of boron trifluoride etherate chemoselectively deoxygenates α,β-unsaturated carbonyl compounds to olefins (eqn. 2) without any observable amount of 1,4-reduction, we anticipated that this combination may reduce the quinolines to the corresponding 1,2-dihydro derivatives. However, herein we report, in contrast to our expectation, a regiospecific reduction of quinolines and related compounds to the corresponding tetrahydro derivatives employing sodium cyanoborohydride in the presence of boron trifluoride etherate in refluxing methanol.



(a. $NaCNBH_3$, $BF_3.OEt_2$)

Reaction of quinoline (1) in dry tetrahydrofuran containing two equivalents each of boron trifluoride etherate and sodium cyanoborohydride for twelve hours at room temperature, instead of the expected dihydro derivative 2, furnished the 1,2,3,4-tetrahydroquinoline (3) in low yield along with substantial amount (60%) of unreacted quinoline. However, change of the reaction conditions to refluxing methanol dramatically increased the efficiency of the reaction and the tetrahydroquinoline 3 was obtained in 90% yield. The formation of the tetrahydroquinoline 3 can be rationalised in two ways (scheme 1); 1,4 reduction of BF_3-quinoline complex followed by the reduction of the resultant 1,4-dihydroquinoline, an enamine, as claimed in several earlier methods (path A); alternatively first 1,2 reduction of the BF_3-quinoline complex followed by the reduction of the resultant 1,2-dihydroquinoline 2 via the carbonium ion 4 analogous to the enamine reductions[10] (path B). In order to establish the mechanism, the reaction was carried out with 1,2-dihydroquinoline (2) which was freshly prepared by reduction[11] of quinoline with lithium aluminium hydride. Interestingly reaction of 1,2-dihydroquinoline (2) with sodium cyanoborohydride and boron trifluoride etherate either in refluxing THF or methanol cleanly furnished the tetrahydroquinoline 3 (entry 2).

SCHEME 1

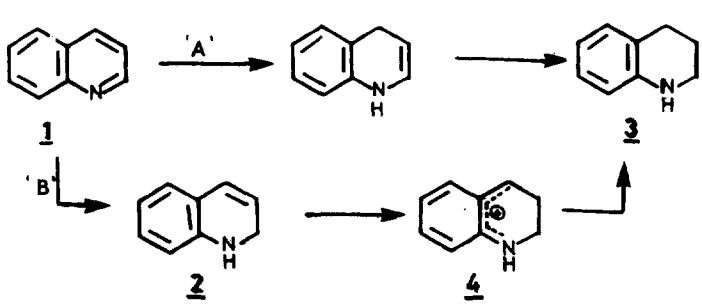
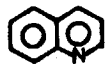
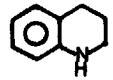
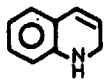
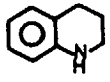
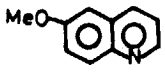
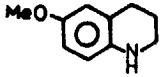
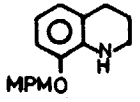
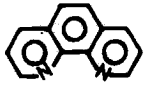
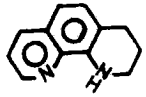
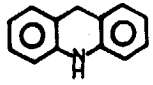
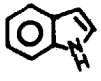
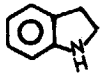
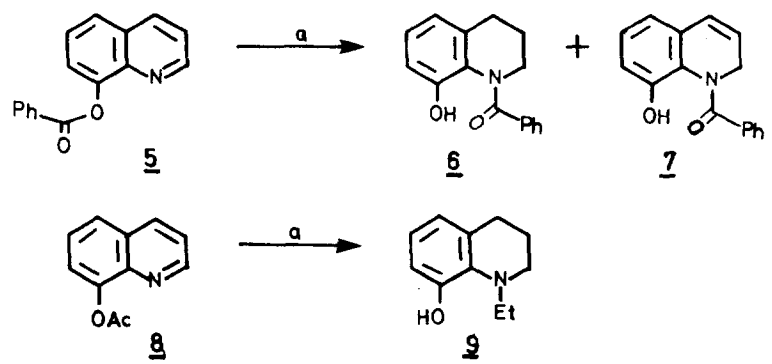


Table: Reduction of quinolines using $NaCNBH_3$ and $BF_3.OEt_2$

entry	Substrate	Product[a]	m.p. °C	in THF time hr	in THF yield %	in MeOH time hr	in MeOH yield %	^1H NMR spectral data of the products (90 MHz, $CDCl_3$) δ ppm
1			b	12	15[c]	3	90	6.35-7.1 (4H, m), 3.62 (1H, brs), 3.25 (2H, t, J=8Hz), 2.72 (2H, t, J=8Hz), 1.92 (2H, quintet, J=8Hz).
2				4	68	8	83	
3			46[d]	12	5	4	88	6.35-6.7 (3H, m), 3.7 (3H, s), 3.25 (2H, t, J=7.5Hz), 2.75 (2H, t, J=7.5Hz), 2.6 (1H, brs), 1.9 (2H, quintet, J=7.5Hz).
4			75	1	76	5	77	7.35 and 6.9 (4H, 2 x ABq, J=9 Hz), 6.4-6.8 (3H, m), 4.98 (2H, s), 3.85 (3H, s), 3.28 (2H, t, J= 7.5Hz), 2.78 (2H, t, J=7.5Hz), 1.94 (2H, quintet, J=7.5Hz), 1.5 (1H, brs).
5			b	3	70	4	33	8.65 (1H, dd, J=5.2 and 2.5Hz), 8.0 (1H, dd, J=9 and 2.5Hz), 7.28 (1H, dd, J=9 and 5.2 Hz), 7.15 and 6.95 (2H, ABq, J=9 Hz), 3.5 (2H, t, J=6.5Hz), 2.9 (2H, t, J=6.5 Hz), 2.02 (2H, quintet, J=6.5Hz).
6			166-69[e]	8	98	8	92	6.5-7.3 (8H, m), 5.9 (1H, brs), 4.0 (2H, s).
7			b	3	50	3	87	6.9-7.3 (2H, m), 6.7 (2H, t, J=9 Hz), 3.55 (2H, t, J=9Hz), 3.0 (2H, t, J=9Hz), 2.85 (1H, brs).

(a) Yields (unoptimised) refer to isolated and chromatographically pure compounds. (b) liquid. (c) Reaction was carried out at room temperature, in addition 62% of starting material was also recovered. At reflux temperature very poor yields were obtained without recovery of any starting material. (d) lit.[12b] 42-43°C. (e) lit.[12b] 169°C.

Formation of the tetrahydroquinoline **3** from the dihydroquinoline **2**, and isolation of the dihydro derivative in one more example (eqn. 3) established the mechanism of the reaction as proceeding via 1,2-reduction (path B). To test the generality of this reaction various quinolines were reduced employing sodium cyanoborohydride and boron trifluoride etherate both in refluxing THF as well as in reluxing methanol. The results are summarised in the table along with the ^{1}H NMR spectral data of the products. Structures of the products were established, wherever possible, by comparing NMR spectral data with those reported in the literature.[12] Interestingly the 1,10-phenanthroline resulted in tetrahydroderivative (entry 5), and it is worth mentioning that using the diborane methodology[3] 1,10-phenanthroline was reported to generate a complex mixture. Quite expectedly acridine resulted only the 9,10-dihydroacridine (entry 6) and indole resulted in dihydroindole (entry 7). Even though the normal p-methoxybenzyl (MPM) ethers are known to cleave under these conditions,[13] the MPM ether of 8-quinolinol cleanly furnished the corresponding tetrahydro derivative (entry 4) without effecting the MPM ether moiety, obviously due to the preferential complexation of BF_3 to nitrogen atom. In contrast to the MPM ether, the benzoate of the 8-quinolinol **5** resulted in the intramolecular transfer of the benzoyl group from oxygen atom to nitrogen atom furnishing the amide[14] **6**. Even though yield was low, the reaction was found to be clean in refluxing THF furnishing only the tetrahydro derivative **6**, whereas in refluxing methanol varying amount (5-50%) of the corresponding dihydro derivative **7** was also observed. Surprisingly under the same conditions, the corresponding acetate, 8-acetyloxyquinoline **8**, both in refluxing THF as well as in refluxing methanol, furnished the 1-ethyl-1,2,3,4-tetrahydro-8-quinolinol **9**, m.p. 59-62°C,[15] in 25 and 37% yields respectively. The structure of the product **9** was established from its spectral data and further confirmed by ^{1}H NMR double irradiation experiments (see experimental). The formation of the compound **9** can be explained, analogous to the benzoyl migrated product **6**, migration of the acetyl group from oxygen atom to nitrogen atom followed by redution of the amide group, perhaps assisted by the proximal hydroxy group. Probably the steric crowding due to phenyl group might be responsible for the stability of the amide **6** towards further reduction.



(eqn. 3)

a. $NaCNBH_3$, $BF_3.OEt_2$

In conclusion, a new methodology for the efficient transformation of quinolines and related compounds into the corresponding tetrahydro derivatives is discovered employing a combination of sodium cyanoborohydride and boron trifluoride etherate in refluxing methanol.

EXPERIMENTAL SECTION

Melting points are recorded in capillaries and are not corrected. Boron trifluoride etherate was obtained from E-Merck and sodium cyanoborohydride was obtained from Fluka and used as such. Dry THF was obtained by distilling over sodium benzophenone ketyl and dry methanol was obtained by distilling over magnesium methoxide. 8-Quinolinol MPM ether (m.p. 120°C) was prepared from 8-quinolinol and freshly prepared p-methoxybenzyl bromide using potassium carbonate as base in refluxing acetone.

General procedure for the reduction of quinolines:

A solution of a quinoline (0.5 mmol), sodium cyanoborohydride (1 mmol) and boron trifluoride etherate (1-1.5 mmol) in either dry THF or dry methanol (2 ml) was refluxed for the time specified in the table. The reaction mixture was cooled, treated with 25% aqueous ammonia (5 ml) and extracted with ether (3 x 5 ml). The ether extract was washed with brine and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by purification of the residue over a silica gel (*ca* 8 g) column furnished the product.

1-Benzoyl-1,2,3,4-tetrahydro-8-quinolinol (6):

Reaction of 8-benzoyloxyquinoline (5) with five equivalents each of sodium cyanoborohydride and boron trifluoride etherate in refluxing THF for 3 h as described above furnished the amide 6 in 21% yield. m.p. 175°C (lit.[14] 180°C). IR (neat): ν_{max} 3100 (br), 1620 (C=O), 1590, 1570, 1400 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 7.5 (5 H, m, Ph), 7.17 (1 H, t, J=7.9 Hz, H-6), 6.96 (1 H, d, J=7.5 Hz, H-5), 6.82 (1 H, d, J=7.1 Hz, H-7), 3.71 (2 H, t, J=7 Hz, H-2), 2.92 (2 H, t, J=7.1 Hz, H-4), 2.01 (2 H, q, J=6.5 Hz, H-3).

Reaction of the benzoate 5 with five equivalents each of boron trifluoride etherate and sodium cyanoborohydride in refluxing methanol for 12 h furnished a *ca*. 1:1 mixture of the amides 6 and 7 in 75% yield. ^1H NMR (90 MHz, $CDCl_3$) peaks due to the dihydro compound 7: δ 6.5-8.0 (m, aromatic and H-4), 6.02 (1 H, t of d, J=10 and 5 Hz, H-3), 4.24 (2 H, d with structure, J=5 Hz, H-2).

Same reaction in refluxing methanol with addition of boron trifluoride etherate and sodium cyanoborohydride in two batches (2.5 equivalents of each) at 4 h interval followed by refluxing further 12 h furnished *ca*. 1:8 mixture of the amides 6 and 7 in ≈70% yield.

1-Ethyl-1,2,3,4-tetrahydro-8-quinolinol (9):

Reaction of 8-acetyloxyquinoline (8) with five equivalents each of sodium cyanoborohydride and boron trifluoride etherate in refluxing THF for 3 h furnished the tetrahydro compound 9 in 25% yield; and in refluxing methanol for 12 h furnished the same compound 9 in 40% yield. m.p. 59-62°C.[15] IR (neat): ν_{max} 3000 (br), 1590, 1350, 1180, 760 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 6.89 (1 H, t, J=7.7 Hz, H-6), 6.75 (1 H, d, J=5.4 Hz, H-5), 6.62 (1 H, d, J=7.5 Hz, H-7), 3.07 (2 H, t, J=5.4 Hz, H-2), 2.7-2.9 (4 H, q and t overlapped, H-4 and N-CH_2), 1.84 (2 H, quintet, J=5.4 Hz, H-3), 1.24 (3 H, t, J=7.2 Hz, CH_3). Irradiation of the signal at δ 1.25 changed the signal at δ 2.7-2.9 into a singlet and a triplet, whereas irradiation of the signal at δ 1.84 changed the signal at δ 2.7-2.9 into a quartet and a singlet, and the signal at δ 3.07 into a singlet.

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