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REGIOSELECTIVE REDUCTION OF QUINOLINES AND RELATED SYSTEMS TO 1,2,3,4-TETRAHYDRO DERIVATIVES WITH ZINC BOROHYDRIDE

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ABSTRACT : A simple and convenient procedure for the reduction of quinolines, isoquinoline and other related systems to the corresponding 1,2,3,4-tetrahydro derivatives has been developed in the presence of catalytic amount of *N,N*-dimethyl aniline under sonication.

Reduction of quinoline and related heterocyclic compounds to the corresponding tetrahydro derivatives is an important transformation in organic synthesis as they have gained considerable importance in the total synthesis of natural products[1] as well as in medicinal chemistry.[2] Several methods, e.g. high pressure hydrogenation,[3] rhodium catalyzed hydrogenation using carbon monoxide

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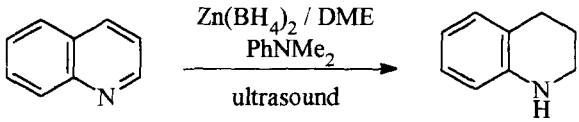
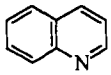
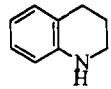
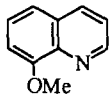
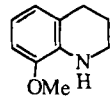
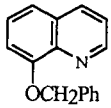
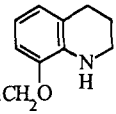
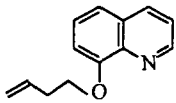
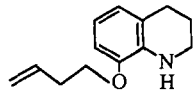
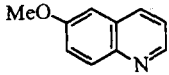
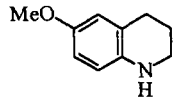
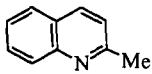
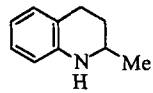
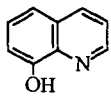
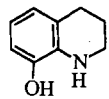
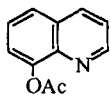
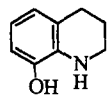
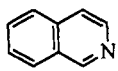
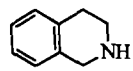
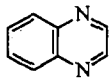
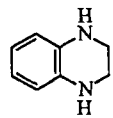
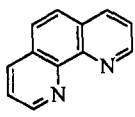
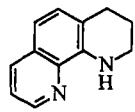
and water,[4] reduction by pyridine-borane,[5] sodium borohydride in acidic media,[6] ammonium formate-palladium on carbon,[7] and recently sodium cyanoborohydride in presence of boron trifluoride etherate[8] have been developed for this purpose. Although, these reagents are satisfactory for the reduction of simple quinolines, these methods have limited use for quinolines containing sensitive functionalities like olefinic double bond and acid labile moiety. Lithium triethylborohydride (super hydride) is reported to be used for the reduction of isoquinolines containing double bond; but reduction of quinoline is accomplished in low yield.[9] Our recent experience on the reduction of various functionalities with zinc borohydride[10] prompted us to investivate this useful transformation. We have observed that quinolines are regioselectively reduced to the corresponding 1,2,3,4-tetrahydro derivatives with zinc borohydride in the presence of a catalytic amount of *N, N*-dimethylaniline under sonication.



In a typical procedure, a mixture of quinoline and a solution of zinc borohydride in DME was sonicated in the presence of a catalytic amount of N,N-dimethyl aniline. The product was isolated by simple extraction with diethyl ether after decomposition with water. The results are reported in Table 1. Several structurally varied quinolines underwent regioselective reductions to the

Table-1. Reduction of Quinolines to Corresponding Tetrahydroderivatives.

Entry	Substrate	Time(h)	Product	Yield(%)[a]
1		24		80
2		24		70
3		24		75
4		6		85
5		24		78
6		40		65
7		12		45
8		12		42
9		30		75
10		10		90
11		20		80

[a]The yield was calculated on the basis of the isolated pure products

corresponding 1,2,3,4-tetrahydro quinolines in reasonably good yields by this procedure. The reaction condition is mild enough not to affect olefinic double bond (entry 4), benzyl ether (entry 3) and methyl ether (entries 2,5) moieties. 8-Acetoxy quinoline (entry 8)also underwent reduction without any rearrangement,[8] although acetate group was cleaved under this condition as observed by us earlier.[10d] The yields of reduction of both 8-hydroxy and 8-acetoxy quinolines (entries 7,8) are relatively low possibly because of the formation of some polymeric compounds (considerable amount of tarry materials were found). Reductions of isoquinoline (entry 9) and other related heterocyclic systems, quinoxaline (entry 10) and 1,10-phenanthroline (entry 11) were also achieved by this procedure. In all the cases, it is the heterocyclic ring which underwent reduction. In phenthroline only one ring was reduced (entry 11).

Without sonication the reaction is very slow and in absence of *N,N*-dimethylaniline the progress of reaction is badly affected. Acceleration of reduction by *N,N*-dimethylaniline, though interesting, was observed previously by us[10d] and other group.[11]

In conclusion, the present procedure using zinc borohydride in presence of *N,N*-dimethylaniline provides an efficient regioselective reduction of quinoline, isoquinoline and related heterocyclic systems to the corresponding 1,2,3,4-tetrahydro derivatives through a mild and simple operation. This procedure offers significant improvements over other methods[1-7] being general and compatible with a number of sensitive functionalities. Besides, this procedure does not involve any

toxic chemicals. We believe, this methodology will certainly find suitable and significant application in the field of organic synthesis.

EXPERIMENTAL SECTION

General : Zinc borohydride in 1,2-dimethoxyethane (DME) was prepared from zinc chloride and sodium borohydride following a reported procedure[12] and was used without any purification from a stock solution preserved in the refrigerator. Quinoloines are mostly commercial materials and a few derivatives were prepared by standard procedures. The quinolines and *N,N*-dimethylaniline were distilled before use.An ultrasonic cleaner (USR 3, Julabo, Germany) was used for sonication.

General Procedure for Reduction : A mixture of quinoline (258 mg, 2 mmol) and zinc borohydride (6 mmol) in DME (6 ml)[12] was sonicated in presence of *N,N*-dimethylaniline (3-4 drops) in an ultrasonic cleaner for a certain period of time as required to complete the reaction (TLC). [After each 6h a fresh solution (2 ml) of zinc borohydride was added). The reaction mixture was then decomposed with careful dropwise addition of water and filtered. The residue was washed with diethyl ether and the combined washings and filtrate was washed with brine, dried(Na_2SO_4). Evaporation of solvent furnished the crude product which was further purified through column chromatography over silica gel to produce 212 mg (80%) of pure 1,2,3,4-tetrahydroquinoline.

The products are mostly known compounds[3,8,13,14] except those in entries 3 and 4 and are easily identified by comparison of their spectra. The spectral and analytical data for those products in entries 3 and 4 are as follows: **3:** ^{1}H NMR (60 MHz, CCl_4) : δ 1.63-2.06 (2H, m), 2.7 (2H, t, J=6 Hz), 3.23 (2H, t, J=6 Hz), 4.1 (1H, broad), 4.9 (2H, s), 6.33-6.56 (3H, m), 7.1-7.36 (5H, m). Anal. cald. for $C_{16}H_{17}NO$: C, 80.29; H,7.17; N, 5.85. Found: C, 80.10; H, 7.34, N, 6.06. **4:** ^{1}H NMR (60 MHz, CCl_4) : δ 1.13-2.1 (4H, m), 2.73 (2H, t, J=6 Hz), 3.33 (2H, t, J=6 Hz), 3.83-4.1 (3H, m), 4.96-5.26 (3H, m), 6.33-6.56 (3H, m). Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.79; H, 8.44; N, 6.88. Found: C,76.56; H, 8.86; N, 6.85.

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