SYNTHESIS OF DIHYDROISOQUINOLINES AND 1-SUBSTITUTED TETRAHYDROISOQUINOLINES

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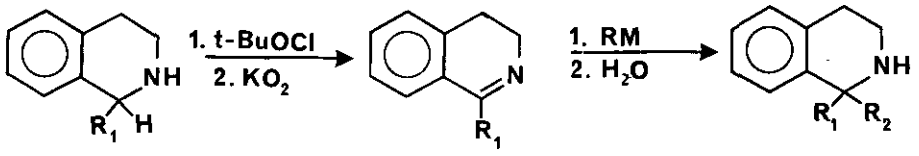
Abstract—A simple synthesis of three dihydroisoquinolines and five 1-substituted tetrahydroisoquinolines from the parent compound involves N-chlorination/dehydrochlorination with KO_2 and subsequent organometallation.

Syntheses of 1-substituted tetra- or dihydroisoquinolines generally employ cyclization of an appropriate phenethylamine precursor.[1-5] Various methods, however, suffer from low yields, harsh reaction conditions, unique structural requirements, or lack of generality to analogous compounds. By contrast, manipulation of an intact tetrahydroisoquinoline ring provides simplicity and flexibility of synthetic design lacking in these other approaches.

Recently, we reported that KO_2 dehydrohalogenates organic N-chloramines in an aprotic medium.[6] The method was used to advantage in the one-pot regioselective 2-alkylation of piperidine and pyrrolidine.[7] We wish to report here the application of this reaction to the regiospecific synthesis of 1-alkyltetra- and dihydroisoquinolines in high yield.

Compounds 1 can be converted to their N-chloro derivatives with tert-butyl hypochlorite in



1a,b,c 2a,b,c 3a - 7a

a. R_1 = H-
b. R_1 = Ph-
c. R_1 = CH_3-

3a. R_2 = CH_3-
4a. R_2 = CH_3CH_2-
5a. R_2 = n-Bu-
6a. R_2 = Ph-
7a. R_2 = $PhCH_2$-

ether. The N-chloramines cannot be isolated without their decomposition. However, their ether solutions can be washed of tert-butyl alcohol and any unreacted amine and dried before being dehydrohalogenated with KO_2 to produce the corresponding 2 in high yield.

The chlorination/dechlorination sequence is carried out in a manner similar to that described in our earlier report.[6] In a typical procedure 1,2,3,4-tetrahydroisoquinoline (4.0 g, 30 mmol), anhydrous ether (150 ml), and $NaHCO_3$ (2 g) are mixed in a round bottomed flask. The flask is immersed in an ice bath and tert-butyl hypochlorite (3.4 ml, 30 mmol) is added dropwise at a rate slow enough to maintain the solution temperature below 10°C. When addition is complete, the solution is filtered, washed with water (40 ml), 1.5M sulfuric acid (40 ml), and water (2 x 40 ml). The ether solution is then dried for at least 1 hour over anhydrous K_2CO_3 and molecular sieves before being filtered. It is then reacted with powdered KO_2 (4.7 g, 66 mmol) and 18-crown-6 ether (80 mg) in a dry atmosphere for about 4.5 hours or until the bright yellow color of KO_2 fades to a cream white and oxygen evolution subsides. If the product mixture is allowed to stir over the resulting peroxide salts longer than needed for complete reaction, the solution becomes dark yellow, yields are reduced, and a polymeric residue is left on distillation of the dihydroisoquinoline. After filtration and concentration in vacuo 3,4-dihydroisoquinoline, 2a, is distilled and collected as an oil at 59-65°C (0.8 - 1.3mm) in 94 - 96% yield. On prolonged standing in the dark below - 15°C, the oil crystallizes, m.p. 35 - 36°C (lit.[4] mp 33 - 36°C). The 3,4-dihydroisoquinolines synthesized in this manner are listed in Table I.

Table I. Yields of 3,4-Dihydroisoquinolines

3,4-Dihydroisoquinoline[a]	Isolated Yield, %
3,4-Dihydroisoquinoline (2a)	95
1-Phenyl-3,4-dihydroisoquinoline (2b)	88
1-Methyl-3,4-dihydroisoquinoline (2c)	85

[a]All compounds were characterized by I.R., ^1H and ^{13}C-NMR. Correct C,H, and N analyses to within 0.3% were obtained for all compounds.

There are two previous reports of conversion of an intact tetrahydroisoquinoline ring to a 3,4-dihydroisoquinoline.[8,12] However, yields are either considerably lower or very sensitive to substitution at the 1-position. Whereas these methods require more extensive clean-up procedures, work-up of the reaction described in this paper simply involves filtration of the inorganic salts, concentration of the solvent, and distillation of the desired product.

The simplest member of this series, 2a, is a useful intermediate for the preparation of 1-alkyl-1,2,3,4-tetrahydroisoquinolines (3a - 7a) since it can be reacted with an excess of a Grignard or organolithium reagent in high yield (Table II). An advantage of using the organolithium reagent is that it will add rapidly to the dihydroisoquinoline at or below room temperature, whereas the Grignard reagent requires reaction times at room temperature of 24 hours or longer. Benzyllithium can be prepared in THF by the method of Gilman[13] and 7a is prepared by addition of an ether solution of 2a to the benzyllithium at -78°C followed by stirring for 3 hours. Aqueous work-up and distillation provides good yields of 3a, 5a, and 7a. The solid 6a is purified by sublimation. Work-up of the Grignard reaction requires continuous liquid-liquid extraction of the aqueous layer to increase the isolated yields.

Because the conditions (KO_2/ether) used in the formation of the 3,4-dihydroisoquinolines are dry, the solution is suitable for direct addition to a solution of an organometallic without inter-

Table II. Yields of 1-Alkyl-1,2,3,4- tetrahydroisoquinolines

Tetrahydroisoquinoline[a]	Isolated Yield, %
1-Methyl-1,2,3,4-tetrahydroisoquinoline (3a)	82
1-Ethyl-1,2,3,4-tetrahydroisoquinoline (4a)	78
1-n-Butyl-1,2,3,4-tetrahydroisoquinoline (5a)	85
1-Phenyl-1,2,3,4-tetrahydroisoquinoline (6a)	85
1-Benzyl-1,2,3,4-tetrahydroisoquinoline (7a)	86[b]

[a]All compounds were characterized by I.R., ^1H and ^{13}C-NMR. Correct C,H, and N analyses to within 0.3% were obtained for all compounds. Compounds 3a, 5a, 6a, and 7a were formed from the appropriate organolithium reagent; compound 4a was formed from ethylmagnesium bromide.

[b]There is a small amount of unreacted starting material isolated in this reaction. This yield is based on reacted starting material only. Otherwise yield is 77%.

mediate isolation of the [illegible]quinoline. Thus, the "one-pot" regioselective arylation of 1a yields 74% isolated 6a by the reaction sequence outlined in this paper.

Valentine has provided evidence that unlike its action as a weak acid in water ($pk_a = 4.8$)[9], superoxide acts as a powerful base in an aprotic solvent because of poor solvation[10]. Other data from our lab supports this mechanism for the dehydrohalogenation of N-chloramines as outlined in this paper.[11]

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