Regioselective Synthesis of 8-Hydroxytetrahydroquinolines by the Cyclization of *m*-Hydroxyphenethyl Ketone *O*-2,4-Dinitrophenyloximes

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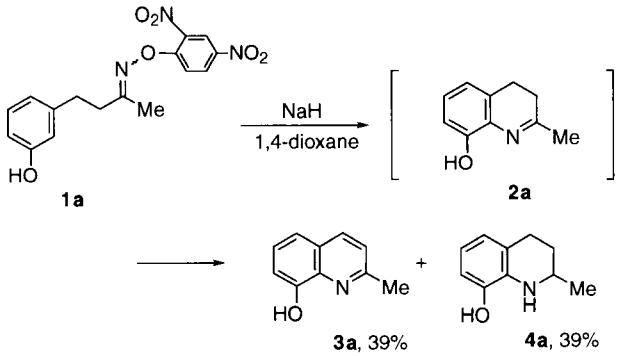
8-Hydroxy-1,2,3,4-tetrahydroquinolines are synthesized from *m*-hydroxyphenethyl ketone *O*-2,4-dinitrophenyloximes by the cyclization on the sp^2 nitrogen atom of the oxime derivatives using sodium hydride and sodium cyanoborohydride.

Many synthetic methods have been developed toward the construction of 1,2,3,4-tetrahydroquinolines,[1] due to the interesting biological properties of tetrahydroquinoline alkaloids. Most of the synthetic methods are based on the reduction of the corresponding quinoline derivatives or the derivation from aniline derivatives.[1] Only few methods have been reported for the construction of tetrahydroquinoline skeleton by the formation of N-C(8a) bond as a key step; for example, the electrophilic amination of *N*-acetoxy-3-phenylpropanamide with $FeCl_3$[2] and aminyl radical cyclization of *N*-chloro-*N*-methyl-3-phenylpropylamine with $FeSO_4$.[3]

Recently we have reported the intramolecular cyclization of phenethyl ketone oxime derivatives between the sp^2 nitrogen atom and the aryl group.[4] For example, treatment of 4-(*m*-hydroxyphenyl)butan-2-one *O*-2,4-dinitrophenyloxime (**1a**) with sodium hydride in 1,4-dioxane at 50 °C gave 8-hydroxy-2-methylquinoline (**3a**) and 8-hydroxy-2-methyl-1,2,3,4-tetrahydroquinoline (**4a**) in 39% and 39% yield, respectively.[4a] The formation of equal amounts of the quinoline **3a** and the tetrahydro derivative **4a** suggests the generation of 3,4-dihydroquinoline **2a** as a primary product, which is disproportionated to **3a** and **4a**. It was expected that tetrahydroquinoline **4a** would be synthesized if the intermediate 3,4-dihydroquinoline **2a** could be reduced.



The cyclization of *O*-2,4-dinitrophenyloxime **1a**[5] was investigated in the presence of sodium hydride and reducing reagents. Among several reducing reagents examined,[6] sodium cyanoborohydride was found to be a suitable one. When the oxime **1a** was treated with sodium hydride and sodium cyanoborohydride in 1,4-dioxane at 50 °C, 8-hydroxytetrahydroquinoline **4a** was obtained in 78% yield without forming the quinoline **3a** and the Beckmann rearrangement product. Furthermore, the other regioisomer, 6-hydroxytetrahydroquinoline, was not obtained.

The reductive cyclization of several *m*-hydroxyphenethyl ketone *O*-2,4-dinitrophenyloxime derivatives **1** was attempted and the results are listed in Table 1. In all reactions, 8-hydroxytetrahydroquinoline derivatives **4** were obtained in good yield without formation of the possible regioisomers. A styryl ketone oxime **1c** cyclized to 2-styryltetrahydroquinoline (**4c**) in 64% yield. The reaction of a β-substituted ketone oxime **1d** gave 8-hydroxy-2,4-dimethyltetrahydroquinoline (**4d**) in 83% yield with a predominant formation of the *cis* isomer (*cis*:*trans*=5:1).[7] Though secondary alkyl ketone oximes tend to suffer the Beckmann rearrangement,[4c] a secondary alkyl ketone *O*-2,4-dinitrophenyloxime **1e** cyclized to 2-ethyl-3-methyltetrahydroquinoline **4e** in 71% yield as a mixture of *cis* and *trans* isomers (diastereomer ratio = 1:1.8) without the formation of the Beckmann rearrangement product. 5-Bromo-8-hydroxy-2-methyltetrahydroquinoline (**4f**) was obtained from 4-(6-bromo-3-hydroxyphenyl)butan-2-one *O*-2,4-dinitrophenyloxime (**1f**) in 92% yield. As shown in Entries 5 and 6, the (*E*)-isomer of **1e** and a 2:1 mixture of the (*E*) and (*Z*)-isomers gave the cyclized product **4e** in the same yield with the same diastereomer ratio. Therefore, separation of the stereoisomers of oximes is not required from the synthetic point of view.

This cyclization reaction is applied to the synthesis of tricyclic compounds, namely octahydrophenanthridine and 3,4-cyclopenteno-1,2,3,4-tetrahydroquinoline. *cis*-2-(*m*-Hydroxyphenyl)cyclohexyl methyl ketone *O*-2,4-dinitrophenyloxime (**5**)[8] cyclized at room temperature in 5 h to afford (6*R**,6a*R**,10a*S**)-

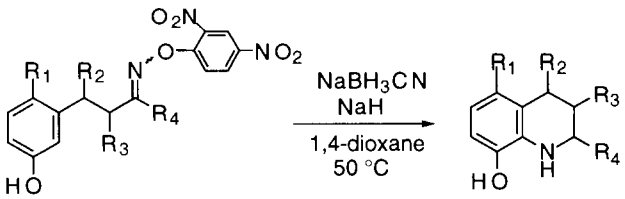


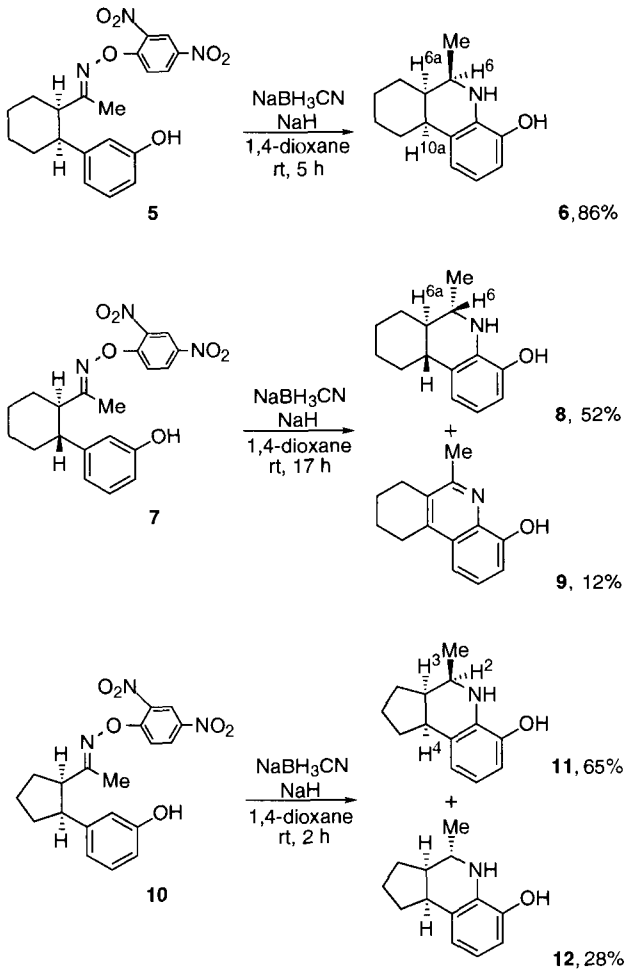
Table 1. Cyclization of *O*-2,4-dinitrophenyloximes **1**

Entry	Oxime 1[b]	R^1	R^2	R^3	R^4	Yield/%	
1	**1a**	H	H	H	Me	78	**4a**
2	**1b**	H	H	H	*i*-Pr	83	**4b**
3	**1c**	H	H	H	PhCH=CH	64	**4c**
4[a]	**1d**	H	Me	H	Me	83[d]	**4d**
5[a]	**1e**	H	H	Me	Et	71[e]	**4e**
6	**1e**[c]	H	H	Me	Et	70[e]	**4e**
7	**1f**	Br	H	H	Me	92	**4f**

[a] Reactions were carried out at room temperature.
[b] (*E*)-Isomer was employed unless otherwise noted.
[c] A mixture of (*E*) and (*Z*)-isomers of **1** (*E*:*Z*=2:1) was employed.
[d] *cis*:*trans*=5:1
[e] Diastereomer ratio=1:1.8

4-hydroxy-6-methyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridine (**6**)[9] stereoselectively in 86% yield without formation of the other stereoisomer. The reaction of the corresponding *trans* cyclohexyl derivative **7**[8] proceeded more slowly (17 h at room temperature) as compared to that of the *cis* isomer **5**, giving (6*S**,6a*R**,10a*R**)-phenanthridine derivative **8**[10] stereoselectively in 52% yield along with 4-hydroxy-6-methyl-7,8,9,10-tetrahydrophenanthridine (**9**) in 12% yield.

Cyclopentenotetrahydroquinoline skeleton can also be constructed by applying this method. That is, *cis*-2-(*m*-hydroxyphenyl)cyclopentyl methyl ketone *O*-2,4-dinitrophenyloxime (**10**) cyclized at room temperature to afford 8-hydroxy-2-methyl-3,4-cyclopenteno-1,2,3,4-tetrahydroquinoline **11** and **12** in 93% yield in 2.3:1 diastereomer ratio.[11]



General experimental procedure is as follows (Table 1, Entry 1): To a 1,4-dioxane (10 ml) suspension of sodium hydride (10.1 mmol) and sodium cyanoborohydride (5.1 mmol) was added a 1,4-dioxane (10 ml) solution of the *O*-2,4-dinitrophenyloxime **1a** (1.0 mmol) at room temperature. After the mixture was stirred for 10 h at 50 °C, the reaction was quenched by adding 1 mol dm^{-3} HCl solution until the reaction mixture became acidic (pH 1). After being stirred for 0.5 h, the mixture was neutralized with sodium bicarbonate and the organic materials were extracted with ethyl acetate and dried over sodium sulfate. The crude products were purified by thin-layer chromatography (Silica gel, hexane:ethyl acetate=4:1) to afford the tetrahydroquinoline **4a** (0.78 mmol, 78%).

As for the reaction mechanism, the cyclization proceeds not by the S_N2 substitution reaction on the oxime nitrogen atom[4b,c,d,e] but by an alkylideneaminyl radical intermediate generated by intramolecular electron transfer. The precise reaction mechanism has been intensively studied, which will be reported in a full paper.

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References and Notes

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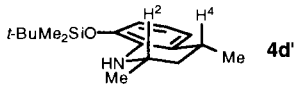
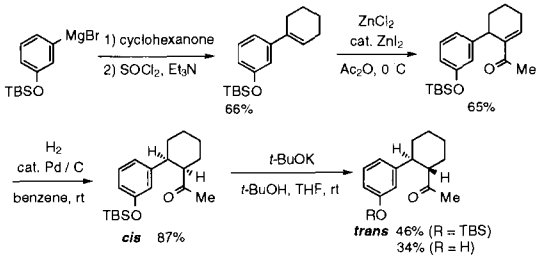
5 2,4-Dinitrophenyloxime **1a** was prepared by the reported procedure. M. J. Miller and G. M. Loudon, *J. Org. Chem.*, **40**, 126 (1975). The *E*-isomer, separated by HPLC from the *Z*-isomer, was employed in the experiments.
6 Sodium borohydride, zinc borohydride, sodium triacetoxyborohydride, and lithium tri-*tert*-butoxyaluminum hydride were examined as reducing reagents. In each reaction, the tetrahydroquinoline **4a** was obtained in less than 30% yield.
7 The stereochemistry was determined by the observation of NOE between H^2 and H^4 protons of the major isomer after conversion of **4d** to the corresponding *t*-butyldimethylsilyl ether **4d'**.



4d'

8 The oximes **5** and **7** were prepared from the corresponding *cis*- and *trans*-(*m*-hydroxyphenyl)cyclohexyl methyl ketones which were prepared as follows.



9 The stereochemistry was determined by the differential NOE experiments (H^6 and H^{6a} 6.4%, H^6 and H^{10a} 6.5%) after conversion of **6** to the corresponding *t*-butyldimethylsilyl ether.
10 The coupling constant between H^6 and H^{6a} ($J_{H6\text{-}H6a}$=9.6 Hz) suggested the stereochemistry as shown in **8**.
11 The stereochemistry of the major isomer **11** was determined by the differential NOE experiments (H^2 and H^3 7.4%, H^2 and H^4 3.2%) after conversion of **11** to the corresponding *t*-butyldimethylsilyl ether.