

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

Katsuya Uchiyama, Yujiro Hayashi, and Koichi Narasaka*

Department of Chemistry, Graduate School of Science, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113, Japan

Received 8 October 1996

Dedicated to Professor E. J. Corey in recognition of his outstanding contributions to the art of organic synthesis

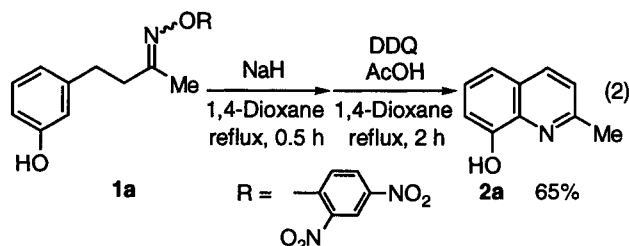
Abstract: 8-Hydroxyquinolines are synthesized from *O*-2,4-dinitrophenyloximes of *m*-hydroxyphenethyl ketones by the treatment with sodium hydride, and then with 2,3-dichloro-4,5-dicyano-*p*-benzoquinone (DDQ).

Quinoline alkaloids have been targets for medicinal chemistry due to their interesting biological properties.¹ Among them are known several 8-hydroxyquinoline derivatives, such as tridennic acid² and yukocitrine.³ Recently, we have reported that the intramolecular cyclization of phenethyl ketone oximes proceeds by the catalytic use of tetrabutylammonium perchlorate and trifluoromethanesulfonic acid to afford quinolines⁴ and azaspirodienones.⁵ In this reaction, intramolecular substitution of the oxime hydroxy group with the phenyl group occurs on the nitrogen atom without the Beckmann rearrangement.⁶

To explore the scope of this substitution reaction on the nitrogen atom of oximes, the cyclization was examined by using various derivatives of 4-(3-hydroxyphenyl)butan-2-one oximes, such as *O*-2-chlorobenzoyl, 2,6-dichlorobenzoyl, methylsulfonyl, and 2,4-dinitrophenyl oximes. Examination of the cyclization with these oxime derivatives revealed that the 2,4-dinitrophenyl derivative **1a**⁷ is suitable for the cyclization. The treatment of a 1:1 mixture of *E* and *Z*-isomers of **1a** with sodium hydride⁸ in refluxing 1,4-dioxane afforded 8-hydroxy-2-methylquinoline **2a** and 8-hydroxy-2-methyl-1,2,3,4-tetrahydroquinoline **3** in 37% and 33% yields, respectively (Eq. 1). In this reaction, the 8-hydroxy quinoline derivatives **2a** and **3** were obtained regioselectively and the corresponding 6-hydroxy isomer, 6-hydroxy-2-methylquinoline, was not detected which was the major product (20% yield) in the cyclization of the corresponding methylsulfonyl oxime.⁹

Each of the *E* and *Z* isomers of the *O*-2,4-dinitrophenyloxime **1a**, separated by HPLC, was found to cyclize smoothly under the above reaction conditions, providing the quinoline **2a** and the tetrahydroquinoline **3** in almost the same yield (Table 1). Accordingly, the separation of the *E* and *Z* isomers of the starting oximes is not required for the synthesis of 8-hydroxyquinolines. In the above reactions of *E*-**1a** and *Z*-**1a**, the isomerization of the *E* and *Z*-oximes was observed; when each reaction was quenched at about 40% conversion, the recovered *E* or *Z*-**1a** was contained 6% or 12% of the other isomers, respectively.

Synthetically it is desirable to obtain the cyclized products as a sole substance. The dihydroquinoline, which is the preliminary product of the cyclization, is expected to be converted to the quinoline **2a** by the oxidation with 2,3-dichloro-4,5-dicyano-*p*-benzoquinone (DDQ). In fact, when the reaction mixture was treated with 0.5 equiv. amount of DDQ¹⁰ and acetic acid for 2 h after the cyclization reaction, the quinoline **2a** was obtained in 65% yield without the formation of the tetrahydroquinoline **3** (Eq. 2).



The cyclization of several *O*-2,4-dinitrophenyloximes of *m*-hydroxyphenethyl ketone derivatives was attempted and the results are listed in Table 2. In every reaction except for that of an aldoxime **1f**, the cyclization proceeds to provide 8-hydroxyquinolines in good to moderate yield, and a small amount of the ketones were formed as a side product. It is noteworthy that possible products, such as 6-hydroxyquinoline derivatives or Beckmann rearrangement products, were not formed. As well as 4-(3-hydroxyphenyl)butan-2-one *O*-2,4-dinitrophenyloxime (**1a**), a 4-methyl derivative **1b** cyclized to a 2,4-dimethylquinoline **2b** in 63% yield (Entry 2). A 1-(3-hydroxyphenyl)-2-methylpentan-3-one oxime **1c** was cyclized to 2-ethyl-3-methyl-8-hydroxyquinoline (**2c**) in 55% yield (Entry 3). Introduction of a bromo atom on the *m*-hydroxyphenyl group of **1a** increased the yield of quinoline; the treatment of an oxime **1d** with NaH gave 5-bromo-8-hydroxy-2-methylquinoline (**2d**) in 82% yield (Entry 4). A styryl ketone derivative **1e** cyclized to a quinoline **2e** in 58% yield, which has a styryl moiety at 2 position (Entry 5). The cyclization of an aldoxime **1f**, however, did not proceed but the Beckmann fragmentation occurred to afford 3-(3-hydroxyphenyl)propionitrile in 68% yield (Entry 6).

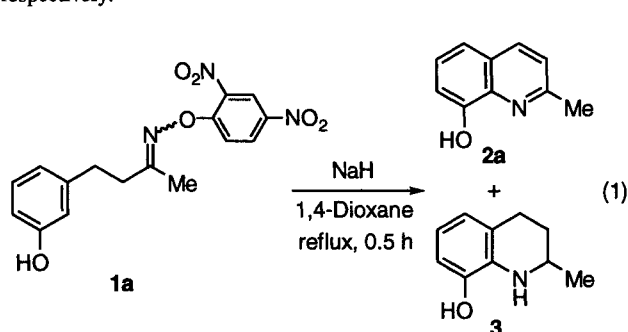


Table 1. Reaction of **1a** with sodium hydride

1a <i>E</i> : <i>Z</i> ratio	Yield / % ^{a)}	
	2a	3
50 : 50	37	33
100 : 0	37	33
0 : 100	34	34

a) Isolated yield

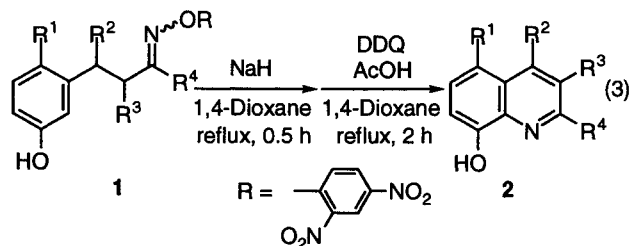
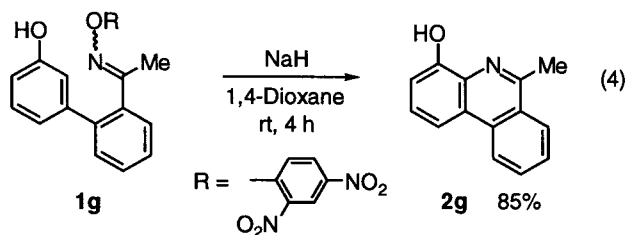


Table 2. Cyclization of *O*-2,4-dinitrophenyloximes **1**

Entry		R ¹	R ²	R ³	R ⁴		Yield / % ^{a)}
1	1a	H	H	H	Me	2a	65
2	1b	H	Me	H	Me	2b	63
3	1c	H	H	Me	Et	2c	55
4	1d	Br	H	H	Me	2d	82
5	1e	H	H	H	PhCH=CH	2e	58
6	1f	H	H	H	H	2f	0

a) Isolated yield

In addition to 8-hydroxyquinoline skeleton, 10-hydroxy-phenanthridine framework can be constructed. 2-(3-Hydroxyphenyl)-acetophenone *O*-2,4-dinitrophenyloxime (**1g**) was converted to 10-hydroxy-2-methylphenanthridine **2g** in 85% yield even at room temperature by applying the above procedure (Eq. 4).



Representative experimental procedure is as follows (Table 2, Entry 1): To a 1,4-dioxane suspension (2 ml) of sodium hydride (240 mg, 10.0 mmol) was added a 1,4-dioxane solution (3 ml) of 4-(3-hydroxyphenyl)butan-2-one *O*-2,4-dinitrophenyloxime (**1a**), (345 mg, 1.0 mmol) and the mixture was immediately heated to reflux. After 0.5 h, the reaction mixture was cooled to room temperature. Acetic acid (900 mg, 15.0 mmol) and 1,4-dioxane solution (5 ml) of DDQ (114 mg, 0.5 mmol) was added to the reaction mixture. After refluxing for 2 h, the reaction was quenched by adding saturated sodium bicarbonate solution, and the organic materials were extracted with ethyl acetate. After evaporation of the solvent, the crude products were purified by thin-layer chromatography (silica gel, hexane : ethyl acetate = 1 : 1) to afford 8-hydroxy-2-methylquinoline (**2a**), (104 mg, 65% yield).

References and Notes

- (1) Michael, J. P., *Nat. Prod. Rep.*, **1995**, 465, and the references cited therein.
- (2) Silva, E. D.; Miao, S.; Andersen, R. J.; Schultz, L. W.; Clardy, J., *Tetrahedron Lett.*, **1992**, 33, 2917.
- (3) Takemura, Y.; Uchida, H.; Ju-ichi, M.; Omura, M.; Ito, C.; Nakagawa, K.; Ono, T.; Furukawa, H., *Heterocycles*, **1992**, 34, 2123.
- (4) Kusama, H.; Yamashita, Y.; Narasaka, K., *Chem. Lett.*, **1995**, 5.
- (5) Kusama, H.; Uchiyama, K.; Yamashita, Y.; Narasaka, K., *Chem. Lett.*, **1995**, 715.
- (6) a) There are several examples in which nucleophiles substitute formally with the hydroxy group on the nitrogen atom of oximes, see; Erdik, E.; AY, Mehmet., *Chem. Rev.*, **1989**, 89, 1947. b) Griot, T.; Wagner-Jauregg, T., *Helv. Chim. Acta*, **1958**, 41, 867; **1959**, 42, 121. c) Schinzer, D.; Bo, Y., *Angew. Chem., Int. Ed. Engl.*, **1991**, 30, 687.
- (7) Miller, M. J.; Loudon, G. M., *J. Org. Chem.*, **1975**, 40, 126.
- (8) The reaction conditions were screened in detail in the cyclization of **1a**. After screening several bases such as Na_2CO_3 , NaOH, KOH, $\text{NaO}-t\text{-Bu}$, $\text{KO}-t\text{-Bu}$, $(n\text{-Bu})_4\text{NF}$, NaNH_2 , $\text{NaN}(\text{SiMe}_3)_2$, NaH, KH, and LiH, NaH gave the best results.
- (9) In the case of the methylsulfonyl oxime of 4-(3-hydroxyphenyl)-butan-2-one, the 6- and 8-hydroxy quinolines were obtained in 20% and 7% yield, respectively.
- (10) When an equimolar amount of DDQ was used, the yield of the quinoline **2a** decreased to 49%.