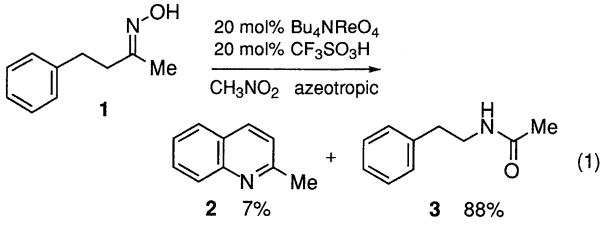
Synthesis of Quinolines *via* Intramolecular Cyclization of Benzylacetone Oxime Derivatives Catalyzed with Tetrabutylammonium Perrhenate(VII) and Trifluoromethanesulfonic Acid

Hiroyuki Kusama, Yuko Yamashita, and Koichi Narasaka*
Department of Chemistry, Graduate School of Science, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113

(Received September 26, 1994)

Intramolecular cyclization reaction on the nitrogen atom of benzylacetone oxime derivatives, which have electron donating group(s) on the phenyl group, proceeds by treatment with tetrabutylammonium perrhenate, trifluoromethanesulfonic acid, and 4-chloranil in refluxing 1,2-dichloroethane to afford quinoline derivatives in good yield.

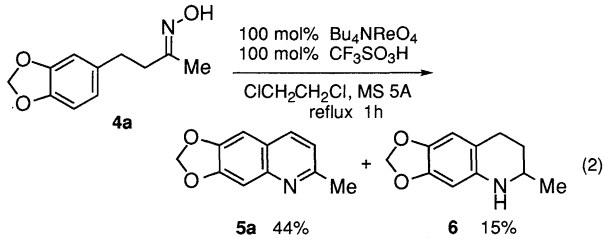
Recently, we have reported that the catalytic Beckmann rearrangement proceeds by the combined use of tetrabutylammonium perrhenate (Bu_4NReO_4) and trifluoromethanesulfonic acid (CF_3SO_3H).[1] During the course of this study, it was found that the intramolecular cyclization reaction proceeded on the nitrogen atom of benzylacetone oxime (**1**) by treatment with 0.2 molar amount of Bu_4NReO_4 and 0.2 molar amount of CF_3SO_3H to give the 2-methylquinoline (**2**) in 7% yield along with the Beckmann rearrangement product, *N*-phenethylacetamide (**3**), in 88% yield (eq. 1).



(1)

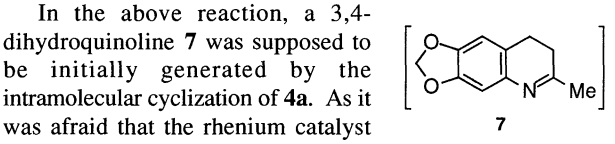
Nitrilium ions generated by the Beckmann rearrangement of oximes have been utilized as synthetic intermediates in the syntheses of isoquinolines,[2] pyridines,[3] and azepines.[4] On the contrary, there have been only a few examples that the substitution reaction of the hydroxyl group proceeds directly on the nitrogen atom of oximes prior to the Beckmann rearrangement; for instance, the cyclization reaction of 2-cyclopentenylacetone oxime with zinc in acetic acid gives a pyrrolidine derivative,[5] and a cyclohexanone oxime mesylate having an allylsilane moiety cyclizes to afford a piperidine derivative by treatment with diisobutylaluminum hydride.[4] Since 2-methylquinoline (**2**) was obtained as a direct substitution product of oxime hydroxyl group, the improvement of the above reaction was investigated by using the rhenium catalyst.

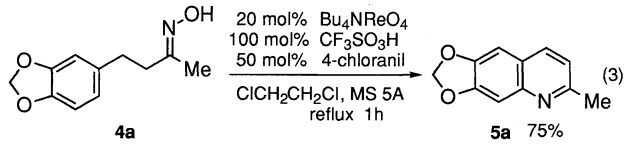
In order to increase the nucleophilicity of the phenyl group, the reaction was examined by employing a benzylacetone oxime derivative having methylenedioxyl group on its phenyl group. Treatment of 4-(3,4-methylenedioxyphenyl)butan-2-one oxime (**4a**) with equimolar amounts of Bu_4NReO_4 and CF_3SO_3H, and Molecular Sieves 5A[6] in refluxing 1,2-dichloroethane[7] gave the desired product, 2-methyl-6,7-methylenedioxyquinoline (**5a**) in 44% yield along with 2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroquinoline (**6**) in 15% yield (eq. 2). In this reaction, the Beckmann rearrangement product was not detected at all.



(2)

In the above reaction, a 3,4-dihydroquinoline **7** was supposed to be initially generated by the intramolecular cyclization of **4a**. As it was afraid that the rhenium catalyst was consumed for the oxidation of the 3,4-dihydroquinoline **7** into the quinoline **5a**, the above reaction was tried in the presence of various oxidizing agents. When the reaction was carried out by using 2,3,5,6-tetrachloro-*p*-benzoquinone (4-chloranil), Bu_4NReO_4, and CF_3SO_3H, the quinoline **5a** was obtained in 75% yield without formation of the tetrahydroquinoline **6** (eq. 3).[8]


7

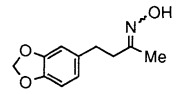
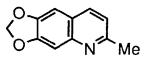
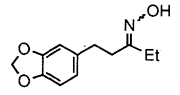
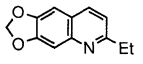
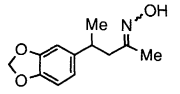
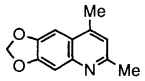
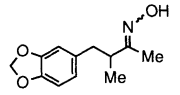
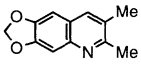
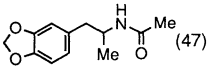
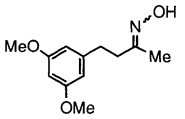
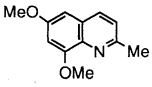
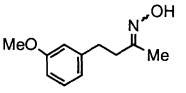
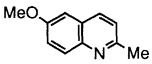
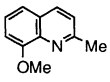
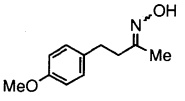
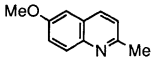
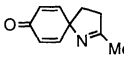
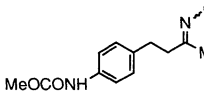
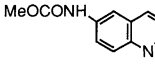


(3)

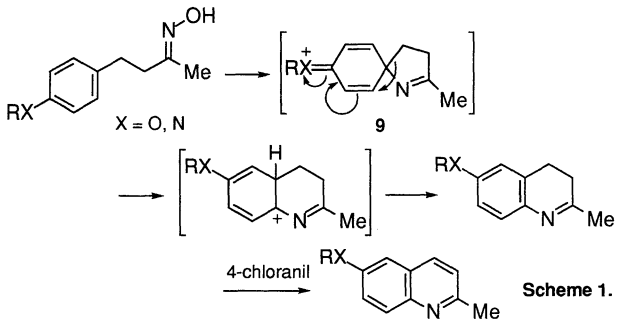
The cyclization reactions of several benzylacetone oxime derivatives[9] were attempted and the results were listed in Table 1.[10,11] As well as the methyl ketone oxime **4a**, an ethyl ketone oxime **4b** cyclized to a 2-ethylquinoline **5b** in 89% yield (Entries 1, 2). The reaction of the β-methyl piperonylacetone oxime **4c** gave a 2,4-dimethylquinoline **5c** in 83% yield (Entry 3), while the cyclization and the Beckmann rearrangement occurred concurrently in the reaction of the α-methyl piperonylacetone oxime **4d**, which was a α-secondary alkyl ketone oxime, to afford a quinoline **5d** (49%) and an amide (47%) (Entry 4). Oximes **4e** and **4f** which have *m*-methoxyl group(s) on their phenyl groups also cyclized to quinolines **5e** and **5f**, respectively, in good yield (Entries 5, 6). The reaction of *p*-methoxybenzylacetone oxime **4g** gave an azaspirodienone **8** (76%) with a small amount of a 6-methoxy quinoline **5f-1** (Entry 7), however, the reaction of a *p*-aminobenzyl derivative **4h** gave a 6-amino quinoline **5h** (not a 7-amino quinoline) in 76% yield (Entry 8). The last two results strongly indicated that the cyclization reaction of an oxime initially occurred at ipso position to give a spirocyclic cationic intermediate **9**. Then dienone-phenol rearrangement[12] of **9** proceeded to afford a dihydroquinoline, as shown in scheme 1. The azaspirodienone **8** was thought to be formed by hydrolysis of the oxonium ion intermediate **9** (X=O) (Entry 7), while the iminium ion **9** (X=N)

was not hydrolyzed but rearranged to the quinoline **5h** (Entry 8). In the reactions of the meta methoxy derivatives **4e** and **4f**, the formation of the 6,8-dimethoxyquinoline **5e** and the 6- and 8-methoxyquinolines **5f** revealed that the cyclization reaction proceeded directly at the ortho position without formation of the spirocyclic intermediates because of the orientation effect of *m*-methoxyl group(s) (Entries 5, 6).

Table 1. Cyclization of Several Benzylacetone Oximes[a]

Entry	Oxime	Time / h	Product (Yield / %)
1	 **4a**	1	 **5a** (75)
2	 **4b**	1.5	 **5b** (89)
3	 **4c**	1	 **5c** (83)
4	 **4d**	1.5	 **5d** (49)
			 (47)
5	 **4e**	2	 **5e** (74)
6	 **4f**	2	 **5f-1** (51)
			 **5f-2** (15)
7[b]	 **4g**	1	 **5f-1** (4)
			 **8** (76)
8	 **4h**	2	 **5h** (76)

[a]The reactions were carried out by using 20 mol% of Bu_4NReO_4, 100 mol% of CF_3SO_3H, 50 mol% of 4-chloranil, and MS 5A in refluxing 1,2-dichloroethane. [b]The reaction was carried out in the absence of 4-chloranil because the formation of azaspirodienone **8** required no oxidation process. The reaction in the presence of 4-chloranil gave **8** in lower yield.



Scheme 1.

Representative experimental procedure is as follows (Table 1, Entry 1): To a 1,2-dichloroethane suspension (6 ml) of 4-(3,4-methylenedioxyphenyl)butan-2-one oxime (**4a**) (203 mg, 0.98 mmol), 4-chloranil (126 mg, 0.51 mmol), tetrabutylammonium perrhenate (98 mg, 0.20 mmol), and Molecular Sieves 5A (100 mg), was added a 1,2-dichloroethane solution (4 ml) of trifluoromethanesulfonic acid (150 mg, 1.0 mmol); the mixture was immediately heated to reflux. After 1 h, the reaction was quenched by saturated aqueous sodium hydrogencarbonate and the resulting inorganic materials were filtered off through Celite. Organic materials were extracted with dichloromethane. After evaporation of the solvent, the crude products were purified by thin-layer chromatography (silica gel, hexane : ethyl acetate = 2 : 1) to afford the quinoline **5a** (137 mg, 75% yield).

References and Notes

1 a) K. Narasaka, H. Kusama, Y. Yamashita, and H. Sato, *Chem. Lett.*, **1993**, 489; b) H. Kusama, Y. Yamashita, and K. Narasaka, *Bull. Chem. Soc. Jpn.*, in press.

2 G. Jones, "Pyridines and their Benzo Derivatives: (V) Synthesis," in "Comprehensive Heterocyclic Chemistry," ed by A. R. Katritzky, Vol. 2, p 395, Pergamon Press, Oxford (1984); S. Goszczynski and A. I. Kucherenko, *Zh. Org. Khim.*, **8**, 2586 (1972).

3 S. Sakane, Y. Matsumura, Y. Yamamura, Y. Ishida, K. Maruoka, and H. Yamamoto, *J. Am. Chem. Soc.*, **105**, 672 (1983); S. Sakane, K. Maruoka, and H. Yamamoto, *Tetrahedron Lett.*, **24**, 943 (1983).

4 D. Schinzer and Y. Bo, *Angew. Chem., Int. Ed. Engl.*, **30**, 687 (1991).

5 R. Griot and T. Wagner-Jauregg, *Helv. Chim. Acta*, **41**, 867 (1958); **42**, 121 (1959).

6 In the absence of Molecular Sieves 5A, 4-(3,4-methylenedioxyphenyl)butan-2-one was obtained in 40% yield by hydrolysis of the oxime **4a** along with the quinoline **5a** in 45% yield.

7 The reaction in 1,2-dichloroethane gave the best result (**5a**, 45% yield) as compared with the reactions in other solvents, such as nitromethane (20%), acetonitrile (31%), and toluene (29%).

8 The reaction was also examined in the presence of other oxidizing agents, such as 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, nitrobenzene, manganese dioxide, cupric chloride, *t*-butylhydroperoxide, and oxygen, but the yield of **5a** was not satisfactory.

9 Mixtures of *E* and *Z* oximes were employed as starting materials. The ratio of *E* and *Z* did not influence the yield of quinolines because the isomerization of oximes proceeded under these reaction conditions. See ref. 1b).

10 The products were characterized by ^1H, ^{13}C NMR, and IR analyses, and their spectral data were in good agreement with those of the authentic samples which were prepared by condensation reaction of appropriate aniline derivatives with α,β-unsaturated aldehydes or acetylacetone. For the preparation of quinolines, see; C. M. Leir, *J. Org. Chem.*, **42**, 911 (1977); R. Adams and J. Campbell, *J. Am. Chem. Soc.*, **72**, 1021 (1950).

11 In most cases, the Beckmann rearrangement did not proceed at all, but small amounts of ketones were produced by hydrolysis of oximes.

12 D. A. Whiting, "Dienone-Phenol Rearrangement and Related Reactions," in "Comprehensive Organic Synthesis," ed by B. M. Trost, Vol. 3, p 803, Pergamon Press, Oxford (1991).