Synthesis of Azaspirodienones *via* Intramolecular Cyclization of *p*-Hydroxybenzylacetone Oximes and Their Transformation into Quinolines

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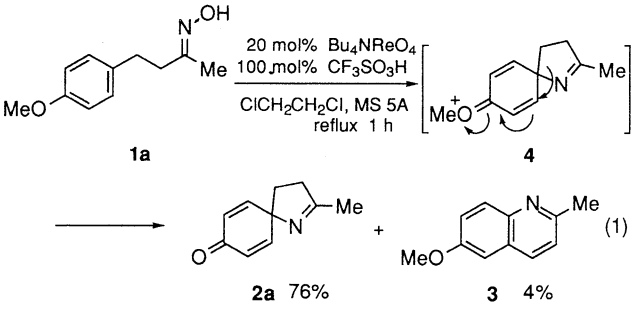
Intramolecular cyclization reaction on the nitrogen atom of oximes of *p*-hydroxybenzylacetone derivatives proceeds by the treatment with tetrabutylammonium perrhenate and trifluoromethanesulfonic acid in refluxing 1,2-dichloroethane to afford azaspirodienones in good yield. The azaspirodienones are transformed into quinolines *via* dienone-phenol rearrangement.

Recently, we have reported that the intramolecular cyclization on the nitrogen atom of oximes of benzylacetone derivatives proceeds by the treatment with tetrabutylammonium perrhenate (Bu_4NReO_4), trifluoromethanesulfonic acid (CF_3SO_3H), and 4-chloranil, affording quinoline derivatives.[1] In this reaction, benzylacetone oximes having an electron-donating group, such as methylenedioxyl, *m*-methoxyl, or *p*-carbamoyl group, on the phenyl group could be converted to the corresponding quinolines in good yield.

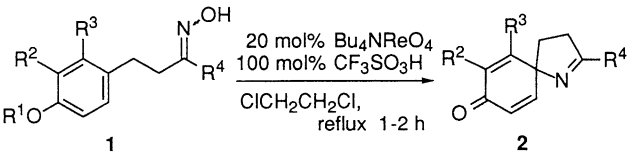
The cyclization reaction of *p*-methoxybenzylacetone oxime (**1a**) gave a 1-azaspiro[4.5]decatrienone derivative **2a** in 76% yield along with a small amount (4%) of a quinoline **3** (eq. 1).[1] It is thought that the cyclization occurs at the *ipso* position to form a spiro cationic intermediate **4**. Then the azaspirodienone **2a** is produced by cleavage of Me–O bond and the quinoline **3** is formed by dienone-phenol rearrangement[2] of **4**.



1a **4** **2a** 76% **3** 4%

This result prompted us to examine the formation of spiro-compounds in detail. In this report is described a novel method for synthesis of azaspirodienones by means of the intramolecular cyclization reaction of *p*-hydroxy (or *p*-alkoxy) benzylacetone oxime derivatives.

To facilitate the formation of the azaspirodienone **2a**, the cyclization reaction was tried by employing *p*-hydroxybenzylacetone oxime (**1b**) instead of the *p*-methoxy derivative **1a**. Treatment of **1b** with a 0.2 molar amount of Bu_4NReO_4 and an equimolar amount of CF_3SO_3H in refluxing 1,2-dichloroethane[3] gave **2a** in 91% yield without formation of a quinoline (Table 1, Entries 1 and 2). The reaction of oxime **1c** also afforded an azaspirodienone **2c** having a methoxyl group on C-7 in 46% yield along with 10% of 2-methyl-6,7-dimethoxyquinoline, while that of *p*-hydroxy-*m*-methoxy derivative **1d** gave **2c** in 75% yield without formation of a quinoline (Entries 3 and 4). In addition, *o*-methoxy derivative **1e** cyclized to give the corresponding azaspirodienone **2e** in 89% yield (Entry 5). Introduction of an electron-withdrawing *N,N*-diethylaminocarbonyl group, did not disturb the cyclization reaction; treatment of an oxime **1f** with the catalysts gave a 6-*N,N*-diethylaminocarbonyl-substituted azaspirodienone **2f** in 52% yield (Entry 6). Cylization of an aldoxime **1g** did not proceed but the Beckmann fragmentation occurred to afford 3-(4-hydroxyphenyl)propiononitrile in 36% yield (Entry 7).

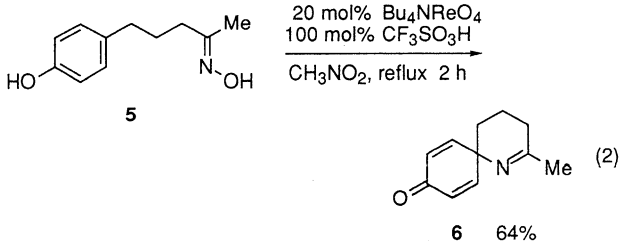


1 **2**

Table 1. Cyclization of Oximes **1**[4,5,6]

Entry	Oxime	R^1	R^2	R^3	R^4	Yield / %
1	**1a**	Me	H	H	Me	**2a** 76
2	**1b**	H	H	H	Me	**2a** 91
3	**1c**	Me	OMe	H	Me	**2c** 46
4	**1d**	H	OMe	H	Me	**2c** 75
5	**1e**	H	H	OMe	Me	**2e** 89
6	**1f**	H	$CONEt_2$	H	Me	**2f** 52
7	**1g**	H	H	H	H	**2g** 0

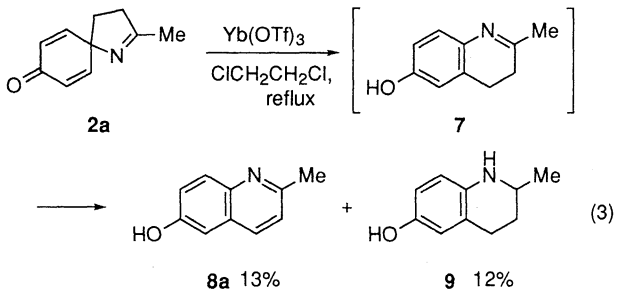
As well as *p*-hydroxybenzylacetone oximes, 5-(4-hydroxyphenyl)pentan-2-one oxime (**5**) which is a one-carbon elongated compound cyclized to afford a 1-azaspiro[5.5]undecatrienone **6** in 64% yield (eq. 2).[7]



5 **6** 64%

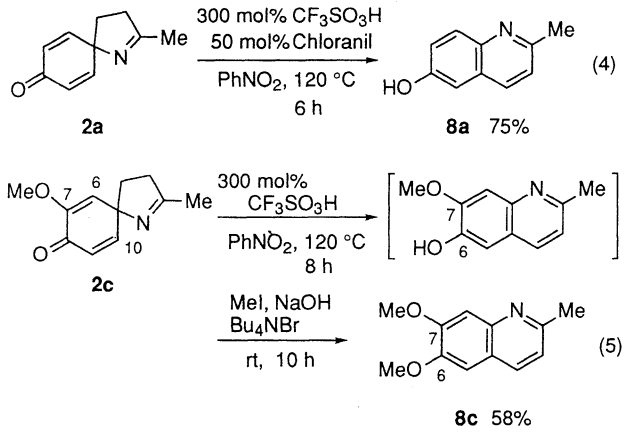
Transformation of the 1-azaspiro[4.5]decatrienones into quinoline derivatives was investigated by applying dienone-phenol rearrangement. It has been known that dienone-phenol rearrangement of carbocyclic spirodienones proceeds by the

treatment with Brønsted acid or Lewis acid, such as hydrochloric acid, trifluoroacetic acid, and borontrifluoride etherate.[2,8] The reaction of **2a** with borontrifluoride etherate in refluxing toluene resulted in a complex mixture, and that with ytterbium trifluoromethanesulfonate gave rearranged products, a quinoline **8a** and a tetrahydroquinoline **9**, in 13 and 12% yields, respectively (eq. 3).



(3)

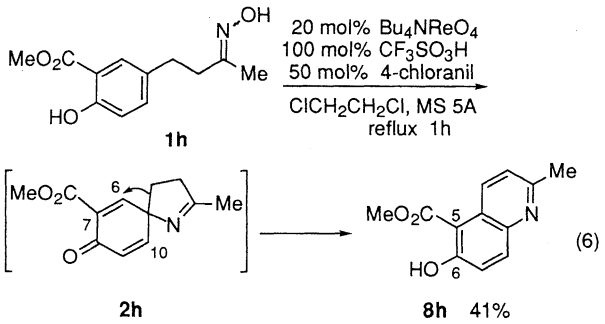
The reaction was carried out under more vigorous conditions in the presence of an oxidizing agent. Treatment of the azaspirodienone **2a** with 3 molar amounts of trifluoromethanesulfonic acid and a 0.5 molar amount of 4-chloranil in nitrobenzene at 120 °C afforded a quinoline **8a** in good yield without formation of a tetrahydroquinoline (eq. 4). Although the reaction of **2c** gave a complex mixture under the above conditions, the reaction took place cleanly in the absence of 4-chloranil. After treating the reaction mixture with methyl iodide, tetrabutylammonium bromide, and an aqueous sodium hydroxide, a quinoline was isolated as a 6,7-dimethoxy derivative **8c** in 58% yield (eq. 5).



(4)

(5)

During the course of the study for the synthesis of azaspirodienones, it was found that the reaction of an oxime **1h**, which have an electron-withdrawing methoxycarbonyl group on *m*-position, directly gave 5-methoxycarbonyl-6-hydroxyquinoline **8h** in 41% yield (eq. 6). In this reaction, an azaspirodienone **2h** was supposed to be initially formed by the *ipso*-cylization, and then an alkyl group of **2h** rearranged toward C-6, giving the quinoline **8h**. The above rearrangement reactions indicate that the rearrangement of an azaspirodienone having an electron-donating group on C-7 proceeds toward C-10 to give a 6,7-substituted quinoline, while an electron-withdrawing group-substituted azaspirodienone rearranges to afford a 5,6-substituted quinoline. This regioselectivity is explained by the fact that the migration of the alkyl group proceeds toward more cationic center.



(6)

Although azaspiro moieties are found in some alkaloids, such as erythrina alkaloids[9] and historionicotoxins,[10] multi-step sequences are normally required for the construction of azaspiroskeletons.[10] Hence, the present cyclization reaction of oximes provides a convenient method for their syntheses.

Representative experimental procedure for the synthesis of azaspirodienones is as follows (Table 1, Entry 2): To a 1,2-dichloroethane solution (8 ml) of the oxime **1b** (209 mg, 1.17 mmol) and Bu_4NReO_4 (115 mg, 0.23 mmol) was added a 1,2-dichloroethane solution (2 ml) of CF_3SO_3H (177 mg, 1.18 mmol), and the mixture was immediately heated to reflux for 1.5 h. After the usual work-up, the azaspirodienone **2a** was obtained in 91% yield (171 mg).

References and Notes

1 H. Kusama, Y. Yamashita, and K. Narasaka, *Chem. Lett.*, **1995**, 5.

2 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).

3 The reaction of **1b** in nitromethane gave **2a** in 86% yield, but Michael addition reaction of nitromethane to **2a** was accompanied to give a small amount of a nitromethyl-substituted azaspiroketone.

4 Mixtures of *E* and *Z* oximes were employed as starting materials. The ratio of *E* and *Z* did not influence the yield of azaspirodienones because the isomerization of oximes proceeded under these reaction conditions. See, H. Kusama, Y. Yamashita, and K. Narasaka, *Bull. Chem. Soc. Jpn.*, **68**, 373 (1995).

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

6 The structure of azaspirodienones was characterized by ^1H and ^{13}C NMR, IR, MS analyses, and was also confirmed by the formation of quinolines by the dienone-phenol rearrangement.

7 The reaction in 1,2-dichloroethane gave a complex mixture.

8 It has been reported that borontrifluoride etherate promotes the dienone-phenol rearrangement of a phenyl group substituted diazaspirodienone under toluene reflux reaction conditions; M. Kobayashi, K. Uneyama, N. Hamada, and S. Kashino, *Tetrahedron Lett.*, **35**, 5235 (1994).

9 K. W. Bentley, *Natural Product Reports*, **9**, 365 (1992).

10 J. W. Daly, *Progress in the Chemistry of Organic Natural Products*, **41**, 205 (1982).