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# Cyclization of *O*-Acetoacetylbenzamide Oxime Derivatives[1,2]

Katsumi Tabei,*,[a] Etsuko Kawashima,[a] Toyozo Takada,[a] and Tetsuzo Kato[b]

*Tokyo College of Pharmacy,[a] Horinouchi 1432-1, Hachioji Tokyo 192-03, Japan and Pharmaceutical Institute, Tohoku University,[b] Aobayama, Sendai 980, Japan*

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*O*-Acetoacetylbenzamide oxime derivatives (**2**) were prepared from benzamide oxime derivatives (**1**) and diketene at low temperature in almost quantitative yields. Cyclization of **2** in the presence of a strong base proceeded with elimination of acetone to afford 3-aryl-1,2,4-oxadiazolin-5-one derivatives (**4**) in 77—95% yields. However, in the cases of the *o*-, *m*-, and *p*-nitrobenzamide oxime derivatives (**2f—h**), the reaction proceeded with dehydration even in the presence of a strong base to afford 5-acetonyl-3-aryl-1,2,4-oxadiazole derivatives (**3f—h**) in moderate yields.

Possible mechanisms of these cyclization are discussed.

**Keywords**——benzamide oxime; *O*-acetoacetylbenzamide oxime; 3-aryl-1,2,4-oxadiazolin-5-one; cyclization; elimination of acetone; retro-Claisen condensation

Early in 1969, Sasaki *et al.* reported that the reaction of aromatic amide oxime with diketene in refluxing toluene afforded 5-acetonyl-3-aryl-1,2,4-oxadiazole derivatives in quantitative yields.[3] However, they did not isolate the intermediate *O*-acetoacetylamide oxime derivatives except for *O*-acetoacetyl-5-nitrofuramide oxime, which was obtained by treatment of 5-nitro-2-furamide oxime with diketene in acetic acid or in pyridine at room temperature. In the present paper, we report the preparation of *O*-acetoacetylbenzamide oxime derivatives and their cyclization in the presence of a strong base.

Benzamide oxime (**1a**, R=H) was treated with diketene in dry chloroform at 0—5°C to give *O*-acetoacetylbenzamide oxime (**2a**), $C_{11}H_{12}N_2O_3$, mp 122°C, in 91% yield. The structure of **2a** was confirmed by comparison of its spectral data with those of *O*-acetoacetyl-5-nitro-2-furamide oxime; the infrared (IR) spectrum of **2a** showed characteristic stretching bands at 3400 and 3320 $cm^{-1}$ ($NH_2$), 1762 $cm^{-1}$ (OC=O), 1700 $cm^{-1}$ (keto C=O), and 1640 $cm^{-1}$ (C=N). The nuclear magnetic resonance (NMR) spectrum of **2a** showed characteristic signals at 2.30 ppm (3H, singlet, acetyl $CH_3$), 3.68 ppm (2H, singlet, $COCH_2CO$), 5.30 ppm (2H, broad, disappeared on addition of $D_2O$, $NH_2$), and 7.20—7.70 ppm (5H, multiplet, aromatic H).

Next, the cyclization of **2a** in the presence of base was studied. When compound **2a** was treated with pyridine or triethylamine in refluxing toluene, the reaction proceeded with dehydration to afford 5-acetonyl-3-phenyl-1,2,4-oxadiazole (**3a**), mp 89°C in 60 and 63% yields, respectively. Benzamide oxime (**1a**), which was derived from **2a** by hydrolysis, was also obtained in 39 and 33% yields, respectively. Compound **3a** was also obtained by thermolysis of **2a** at 130—150°C in 77% yield. The identity of **3a** was confirmed by mixed melting point determination with an authentic sample obtained from **1a** and ethyl acetoacetate.[4]

On the other hand, when compound **2a** was treated with sodium methoxide in refluxing toluene, the reaction proceeded with elimination of acetone to afford a colorless precipitate, which on acidification with dilute hydrochloric acid afforded colorless needles of mp 208°C (**4a**), $C_8H_6N_2O_2$, in 90% yield. The structure of compound **4a** was assumed to be 3-phenyl-1,2,4-oxadiazolin-5-one on the basis of spectral and mass spectral data, and this was finally confirmed by mixed melting point determination with an authentic sample prepared from **1a** and ethyl chlorocarbonate.[5]

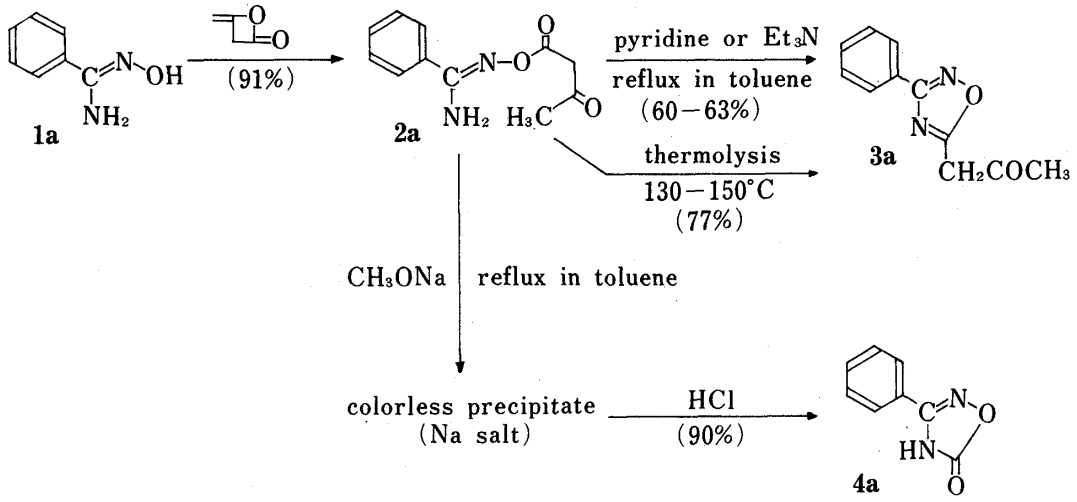
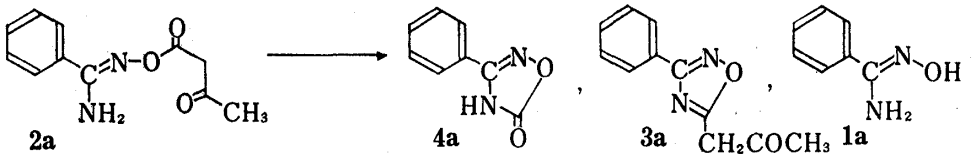



Chart 1

Some strong bases were used as catalysts in place of sodium methoxide, and the results are summarized in Table I. Thus, compound **4a** was obtained in good yields (85—95%) as a sole product by using sodium hydride, lithium hydride, or diethyl sodiomalonate in toluene. When compound **2a** was treated with sodium hydroxide in toluene, however, the yield of **4a** decreased (39%) and an appreciable amount of benzamide oxime (**1a**) was obtained (45%). Compound **3a** was also obtained in 14% yield. Similarly, when ethanol was used as a solvent, the reaction proceeded with ethanolysis of the starting material (**2a**) to give **1a** and **3a** in 69 and 21% yields, respectively. Ethyl acetoacetate was detected in the reaction medium.

TABLE I. Cyclization of **2a** with Anionic Nucleophiles

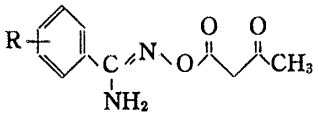



| Exp. No. | Solvent | Nucleophile (eq mol) | Product (Yield %) |
|---|---|---|---|
| 1 | Toluene | $CH_3ONa$ (1.1) | **4a** (90) |
| 2 | Toluene | NaH (2.5) | **4a** (95) |
| 3 | Toluene | LiH (2.5) | **4a** (85) |
| 4 | Toluene | NaCH $(COOEt)_2$ (1.1) | **4a** (92) |
| 5 | Toluene | NaOH (1.1) | **4a** (39), **3a** (14), **1a** (45) |
| 6 | EtOH | $CH_3ONa$ (1.1) | **3a** (21), **1a** (69) |
| 7 | Pyridine | $CH_3ONa$ (1.1) | **4a** (97) |

The above results show that compound **2a** was dehydrated in the presence of an amine, cyclizing to 5-acetonyl-3-phenyl-1,2,4-oxadiazole (**3a**). On the other hand when a strong base such as sodium methoxide, sodium hydride, lithium hydride or diethyl sodiomalonate was used as a catalyst, the cyclization of **2a** occurred with elimination of acetone affording 3-phenyl-1,2,4-oxadiazolin-5-one (**4a**).

Subsequently, we investigated the influence of substituents on the present cyclization. That is to say, seven kinds of substituted benzamide oxime derivatives (**1b**—**h**) were allowed to react with diketene at low temperature, giving the corresponding *O*-acetoacetylbenzamide oxime derivatives (**2b**—**h**) in almost quantitative yields. The reaction conditions and results are summarized in Table II.

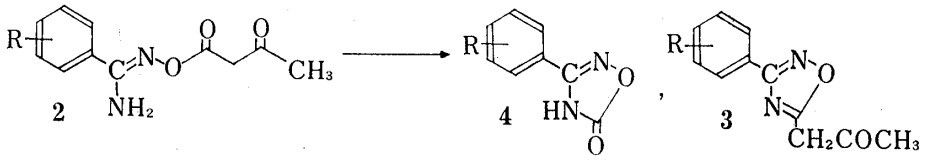
Table II. *O*-Acetoacetylbenzamide Oxime Derivatives (**2**)



| 2[a] | R | mp (°C) (Recryst. solvent) | Reaction conditions | | | Yield (%) |
|---|---|---|---|---|---|---|
| | | | Solvent | Temp. (°C) | Time (h) | |
| **a** | H | 122 (Benzene) | $CHCl_3$ | 0—5 | 1.5 | 91 |
| **b** | *p*-$CH_3$ | 131 (Benzene) | $CHCl_3$ | 0—5 | 1 | 96 |
| **c** | *m*-$CH_3$ | 77 (EtOH) | $CHCl_3$ | 0—5 | 1 | 94 |
| **d** | *o*-$CH_3$ | Viscous oil | $CHCl_3$ | 0—5 | 1.5 | 91 |
| **e** | *p*-$OCH_3$ | 147 (EtOAc) | $CHCl_3$ | 0—5 | 1 | 94 |
| **f** | *p*-$NO_2$ | 142 (EtOH) | THF | r. t. | 48 | 96 |
| **g** | *m*-$NO_2$ | 106 ($CHCl_3$) | THF | r. t. | 24 | 98 |
| **h** | *o*-$NO_2$ | 110 ($CHCl_3$) | $CHCl_3$ | r. t. | 12 | 97 |

*a*) *Anal.* Calcd (Found): **2a** ($C_{11}H_{12}N_2O_3$): C, 59.99; H, 5.49; N, 12.72 (C, 59.84; H, 5.51; N, 12.66); **2b** ($C_{12}H_{14}N_2O_3$): C, 61.52; H, 6.02; N, 11.96 (C, 61.73; H, 6.10; N, 12.03); **2c** ($C_{12}H_{14}N_2O_3$): C, 61.52; H, 6.02; N, 11.96 (C, 61.58; H, 6.11; N, 11.99); **2e** ($C_{12}H_{14}N_2O_4$): C, 57.59; H, 5.64; N, 11.20 (C, 57.51; H, 5.78; N, 11.29); **2f** ($C_{11}H_{11}N_3O_5$): C, 49.81; H, 4.18; N, 15.84 (C, 49.45; H, 4.15; N, 16.06); **2g** ($C_{11}H_{11}N_3O_5$): C, 49.81; H, 4.18; N, 15.84 (C, 49.71; H, 4.22; N, 16.13); **2h** ($C_{11}H_{11}N_3O_5$): C, 49.81; H, 4.18; N, 15.84 (C, 49.64; H, 4.11; N, 16.07).

Table III. Cyclization of **2a**—**h** by Using Anionic Nucleophiles



| 2 | R | Reaction conditions | | | | Product* mp (°C) and (yield, %) |
|---|---|---|---|---|---|---|
| | | Solvent | Nucleophile | Temp. | Time (h) | |
| **a** | H | Toluene | NaH | Reflux | 3 | **4a** (208°C,[a] 95%) |
| **b** | *p*-$CH_3$ | Toluene | NaH | Reflux | 3.5 | **4b** (229°C, 85%) |
| **c** | *m*-$CH_3$ | Toluene | NaH | Reflux | 3 | **4c** (156°C, 83%) |
| **d** | *o*-$CH_3$ | Pyridine | $CH_3ONa$ | 110°C | 3 | **4d** (147°C, 85%) |
| **e** | *p*-$OCH_3$ | Toluene | NaH | Reflux | 3 | **4e** (217°C, 77%) |
| **f** | *p*-$NO_2$ | Pyridine | $CH_3ONa$ | 110°C | 3 | **3f** (144°C,[b] 59%) |
| **g** | *m*-$NO_2$ | Toluene–THF | $CH_3ONa$ | 50°C | 3.5 | **3g** (152°C,[c] 43%) |
| **h** | *o*-$NO_2$ | Toluene–THF | $CH_3ONa$ | Reflux | 3.5 | **3h** (78°C, 49%) |

* *Anal.* Calcd (Found): **4b** ($C_9H_8N_2O_2$): C, 61.36; H, 4.58; N, 15.90 (C, 61.56; H, 4.65; N, 15.98); **4c** ($C_9H_8N_2O_2$): C, 61.36; H, 4.58; N, 15.90 (C, 61.09; H, 4.52; N, 15.81): **4d** ($C_9H_8N_2O_2$); C, 61.36; H, 4.58; N, 15.90 (C, 61.21; H, 4.55; N, 15.95); **4e** ($C_9H_8N_2O_3$): C, 56.25; H, 4.20; N, 14.58 (C, 56.33; H, 4.21; N, 14.72); **3h** ($C_{11}H_9N_3O_4$): C, 53.44; H, 3.67; N, 17.00 (C, 53.29; H, 3.62; N, 16.93).

*a*) Lit. mp 204°C; Ref. 5.
*b*) Lit. mp 143—144°C; Ref. 3.
*c*) Lit. mp 150—151°C; Ref. 3.

Seven kinds of *O*-acetoacetylbenzamide oxime derivatives (**2b**—**h**) were subjected to cyclization in the presence of a strong base, and the results are summarized in Table III.

In the case of **2b**—**e**, the reaction proceeded in the same way as with compound **2a**, and the corresponding 3-aryl-1,2,4-oxadiazolin-5-one derivatives (**4b**—**e**) were obtained in 77—85% yields. On the other hand, the cyclization of **2f**—**h** proceeded along another pathway to give 5-acetonyl-3-(nitrophenyl)-1,2,4-oxadiazole derivatives (**3f**—**h**) even in the presence of a strong base.

We suggest the following mechanisms for these cyclizations: thus, the formation of compound **3** can be explained by the intermediate formation of the cyclo-adduct (**A**), and the

subsequent stage involves dehydration to form the 1,2,4-oxadiazole structure (**3**). When a strong base such as sodium methoxide is added as a catalyst, on the other hand, the intermediate would exist in an enol form (**B**). The reaction might then proceed with elimination of acetone, by a retro-Claisen condensation mechanism,[6] as shown in Chart 2, to afford the sodium salt of the 4-hydroxy-1,2,4-oxadiazole which, on acidification with hydrochloric acid, affords the 3-aryl-1,2,4-oxadiazolin-5-one derivative (**4**).

In the case of *O*-acetoacetylnitrobenzamide oxime (**2f—h**), however, the elimination of water from an enol intermediate might occur in preference to that of acetone, even in the presence of a strong base, resulting in the formation of the acetonyl derivative (**3**).

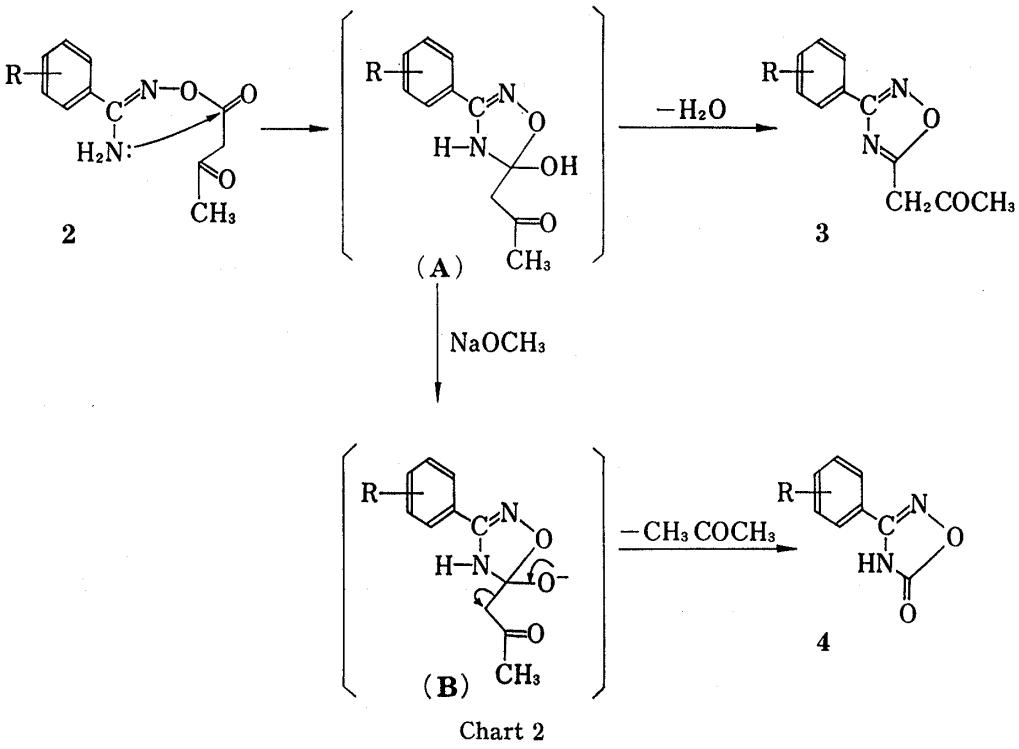



Chart 2

## Experimental

Melting points were determined with a hot-stage microscope and are uncorrected. IR spectra were obtained with a Hitachi 215 spectrometer. NMR spectra were recorded on a JEOL PS-100 spectrometer at 100 MHz with TMS as an internal standard. Mass spectra were recorded on a Hitachi RMU-7 mass spectrometer.

The starting materials, benzamide oxime derivatives (**1a—h**), were prepared from the corresponding benzonitrile derivatives and hydroxylamine following the method described in the literature.[7]

**Preparation of *O*-Acetoacetylbenzamide Oxime Derivatives (2a—h)**——General Procedure: A solution of 1.1 eq mol of diketene in 10 ml of $CHCl_3$ was added in small portions to a solution of **1a—h** (0.01 mol) in 30—50 ml of $CHCl_3$ at 0—5°C under vigorous stirring. After being stirred for 1—1.5 h at that temperature, the mixture was concentrated under reduced pressure. The resulting residue was recrystallized from the solvent cited in the table, except in the case of **2d**, which was obtained as a viscous oil. The results and reaction conditions are listed in Table II.

In the case of **2f—h**, the reaction was carried out at room temperature for 12—48 h.

**Cyclization of 2a in the Presence of Organic Bases**——A mixture of *O*-acetoacetylbenzamide oxime (**2a**) (0.001 mol, 220 mg) and 1 mol eq of pyridine (80 mg) or $Et_3N$ (100 mg) was allowed to react in refluxing toluene (20—30 ml) for 3 h. After removal of the solvent, the residue was subjected to flash chromatography on a silica gel column.[8] Elution with EtOAc–hexane (3: 1) mixture gave colorless needles of 5-acetonyl-3-phenyl-1,2,4-oxadiazole (**3a**), mp 89°C (60 and 63%) and benzamidoxime (**1a**) (25 and 29% yields, respectively).

**Cyclization of 2a in the Presence of an Anionic Nucleophile**——A solution of **2a** (0.001 mol, 220 mg) and 1.1—2.5 mol eq of an anionic nucleophile in 20—30 ml of toluene was refluxed for 3—3.5 h. After

removal of the solvent, the residue was diluted with water, acidified with 5% HCl, and extracted with EtOAc. The EtOAc solution was washed with water and dried over $Na_2SO_4$. After removal of the solvent, the residue was subjected to flash chromatography on a silica gel column. Elution with EtOAc–hexane (3: 1) mixture gave 3-phenyl-1,2,4-oxadiazolin-5-one (**4a**), mp 208°C, 5-acetonyl-3-phenyl-1,2,4-oxadiazole (**3a**), and/or benzamide oxime (**1a**). The yields and reaction conditions are listed in Table I.

In Exp. 6 and 7, with EtOH and pyridine as solvents, the mixture was worked up as described above.

**Cyclization of 2b—h in the Presence of an Anionic Nucleophile**——A mixture of **2b—h** (0.001 mol) and 1.1 mol equivalent of $CH_3ONa$ or 2.5 mol eq of NaH in 30 ml of toluene, pyridine, or a mixture of toluene–THF (1: 1) was refluxed (or stirred) at 110°C for 3—3.5 h. After removal of the solvent by evaporation, the residue was diluted with water, acidified with 5% HCl, and extracted with EtOAc. The EtOAc solution was washed with water and dried over $Na_2SO_4$. After removal of the solvent, the residue was subjected to flash chromatography on a silica gel column. Elution with EtOAc–hexane (3: 1) mixture gave 3-aryl-1,2,4-oxadiazolin-5-one (**4b—e**) or 5-acetonyl-3-aryl-1,2,4-oxadiazole (**3f—h**). The results and reaction conditions are listed in Table III.

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## References and Notes

1) This work was presented at the 100th Annual Meeting of the Pharmaceutical Society of Japan (April 1981, Kumamoto).
2) This paper forms Part IV of "Reaction of $\gamma$-Bromoacetoacetyl Bromide with *N*-Phenylhydroxylamine Derivatives." Part III: K. Tabei, E. Kawashima, and T. Kato, *Chem. Pharm. Bull.*, **29**, 244 (1981).
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6) E.S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Comp. Inc., New York, 1959, p. 337.
7) D. Krug, *Chem. Ber.*, **18**, 1053 (1885).
8) Flash chromatography was carried out on a Kimura Kagaku flash chromatography apparatus with Kieselgel 60 (Merck, 230—400 mesh) under the elution conditions described in the literature: W.C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).