Reaction of 3,4-Diaroyl-1,2,5-oxadiazole-2-oxide with Hydrazine Hydrate

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Reaction of 3,4-di (m- or p-substituted benzoyl) -1,2,5-oxadiazole-2-oxide with hydrazine hydrate in acetic acid gave 4,7-diaryl-1,2,5-oxadiazolo[3,4-d]pyridazine and/or its 1-oxide, depending upon a reaction temperature, an amount of hydrazine used, and the substituent of the substrate.

Introduction

Previously, 2,5-diphenylpyridines, which is annelated at 3 and 4 positions with a heteroaromatic ring such as 1,2,5-oxa-, 1,2,5-thia-, and 1,2,5-selena-diazole, thiophene, N-methylpyrrole, 1,2,3-triazole, pyrazole, imidazole, pyridine, and pyrazine, were prepared. These compounds are fluorescent in a solid state and are of interest as a light emitting material for an electroluminescence device5).

Earlier, it was reported that the reaction of 3,4-dibenzoyl-1,2,5-oxadiazole-2-oxide (1a) with hydrazine dihydrochloride in refluxing methanol gave 1,2,5-oxadiazolo[3,4-d]pyridazine-1-oxide 2a3). In the reaction with an excess amount of hydrazine, it was expected that the deoxygenation of 1-oxide 2 might occur to afford 1,2,5-oxadiazolo[3,4-d]pyridazine 3, which is an aza analogue of strongly fluorescent 4,7-diaryl-1,2,5-oxadiazolo[3,4-d]pyridine3).

In the present article, it is described the reaction of 3,4-diaroyl-1,2,5-oxadiazole-2-oxide 1 with hydrazine hydrate in acetic acid, giving 4,7-diaryl-1,2,5-oxadiazolo[3,4-d]pyridazine-1-oxide 2 and/or oxadiazolo[3,4-d]pyridazine 3.

Results and Discussion

According to the method6) reported previously, 3,4-diaroyl-1,2,5-oxadiazole-1-oxides 1a-f were prepared by the oxidative coupling reaction of the corresponding acetophenones with nitric acid (Scheme 1). Similarly, 2-acetylthiophene and acetylnaphthalenes gave the desired 1g-i, however the treatment of 4- and 2-acetylpypyridine, 2-acetylfuran, and 2-acetylpypyrole with nitric acid did not give the expected 1,2,5-oxadiazoles and produced only tarry materials.

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Table 1  Preparation of 4,7-diaryl-1,2,5-oxadiazolo[3,4-d]pyridazine-1-oxide 2 and 4,7-diaryl-1,2,5-oxadiazolo[3,4-d]pyridazine 3.

<table>
<thead>
<tr>
<th>l</th>
<th>Reaction temp.*</th>
<th>Reaction time (h)</th>
<th>N₂H₄ • H₂O/1 (mol/mol)</th>
<th>Product (Yield, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>90°C reflux</td>
<td>24</td>
<td>2</td>
<td>2a (24), 3a (16)</td>
</tr>
<tr>
<td>b</td>
<td>90°C reflux</td>
<td>24</td>
<td>2.5</td>
<td>2b (40), 3b (42)</td>
</tr>
<tr>
<td>c</td>
<td>90°C reflux</td>
<td>48</td>
<td>1</td>
<td>2c (+), 3c (+)</td>
</tr>
<tr>
<td>d</td>
<td>80°C reflux</td>
<td>1</td>
<td>3.5</td>
<td>2d (71), 3d (14)</td>
</tr>
<tr>
<td>e</td>
<td>reflux</td>
<td>24</td>
<td>4</td>
<td>3e (8)</td>
</tr>
<tr>
<td>f</td>
<td>80°C reflux</td>
<td>4</td>
<td>4</td>
<td>2e (82), 2e (20)</td>
</tr>
<tr>
<td>g</td>
<td>reflux</td>
<td>24</td>
<td>4</td>
<td>3f (3)</td>
</tr>
<tr>
<td>h</td>
<td>90°C reflux</td>
<td>2</td>
<td>2</td>
<td>3g (3), 3g (+)</td>
</tr>
<tr>
<td>i</td>
<td>reflux</td>
<td>24</td>
<td>4</td>
<td>3h (25)</td>
</tr>
</tbody>
</table>

a) Reaction was carried out in acetic acid.
b) Compound 1h was recovered in 74% yield.

The reaction of 1 with hydrazine hydrate was carried out in acetic acid and the results are shown in Scheme 2 and Table 1.

The reaction of 3,4-dibenzoyl-1,2,5-oxadiazole-2-oxide (1a) with two folds amount of hydrazine hydrate was carried out in acetic acid at 90°C and 2a was produced in 24% yield. The reaction with four equivalents of hydrazine hydrate in acetic acid under reflux afforded the deoxygenated product 3a in 16% yield, as a major product. The similar reaction of p-methylbenzoyl derivative 1b afforded the corresponding 2b and 3b in 40% and 42% yields, respectively, depending upon the reaction temperature. Di-p-methoxybenzoyl-1,2,5-oxadiazole 1c gave 2c and/or 3c in poor yields when four folds of hydrazine hydrate was used. Yield of 3c was improved to 42% by using ten equivalent amount of hydrazine hydrate in refluxing acetic acid for 48h. The reaction of di-m-nitrobenzoyl derivative 1d at 80°C gave 2d in a good yield. Deoxygenated product 3d was obtained in the reaction in refluxing acetic acid. p-Nitrobenzoyl derivative 1e afforded 3e in a poor yield.

Deoxgenation reaction of 2b and 2d with hydrazine hydrate took place in refluxing acetic acid, affording the corresponding 3b and 3d in 10% and 8% yields, respectively. Although the formation pathway of 3 is not known, the analysis of the reaction mixture of 1
and hydrazine hydrate by means of mass spectroscopic method showed the peak which is
ascribed to the corresponding 4,5-diaryloxydiazole dioxime A. Intermediate A may cy-
clize with a loss of water, giving 1,2,5-oxadiazolo[3,4-d]pyridine 3, as shown in Scheme 2.

Contrary to 1a-1d, 3,4-di-p-bromobenzoylloxadiazole-2-oxide 1e afforded only 2e; The
reaction carried out at 80°C gave 2e in 82% yield and the reaction in refluxing acetic acid
also gave 2e in a deceased yield (20%). Indeed, 2e was treated with an excess amount of
hydrazine hydrate in refluxing acetic acid and unchanged 2e was recovered in a quantitative
yield.

Compounds 3g and 3h were obtained, respectively, in the reaction of 1g and 1h with
hydrazine hydrate and their yields are poor. 2-Naphthoyl compound 1i gave 3i in 25% yield.
In these reactions, the corresponding 1-oxides 2 were not obtained.

Finally, 1,2,5-oxadiazolo[3,4-d]pyrazines 3 prepared in this study are only weakly
fullorescent in a solid state.

**Experimental**

**General.** Melting points were determined on a Yanagimoto micro melting point appa-
ratus and are uncorrected. IR spectra were recorded on a Nippon Bunko A-102 and IR
Report-100 spectro-photometer as a KBr pellets. Mass spectra were measured on a JMS
AX 505-HA spectrometer at 70 eV. 1H NMR spectra were obtained on JEOL JSX-270 in
deuteriochloroform using tetramethylsilane as an internal standard. Column chromato-
graphy was carried out on silica gel (Wako gel, C-300).

3,4-Dibenzoyl-1,2,5-oxadiazole-2-oxide (1a): mp 85-86°C (lit.2 87°C).
3,4-Di-p-methylbenzoyl-1,2,5-oxadiazole-2-oxide (1b): mp 121-124°C (lit.3 123-125°C).
3,4-Di-p-methoxybenzoyl-1,2,5-oxadiazole-2-oxide (1c): mp 139-140°C (lit.2 139-140°C).
3,4-Di-p-nitrobenzoyl-1,2,5-oxadiazole-2-oxide (1d): mp 128-135°C (lit.5 150°C).
3,4-Di-p-nitrobenzoyl-1,2,5-oxadiazole-2-oxide (1e): mp 154-155°C (lit.3 154°C).
3,4-Di-p-bromobenzoyl-1,2,5-oxadiazole-2-oxide (1f): mp 138-141°C (lit.6 128°C).
3,4-Di(2-thienyl)1,2,5-oxadiazole-2-oxide (1g). To a mixture of 2-acetylthiophene
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(19g) in acetic acid (80ml), a mixture of sodium nitrite (3.7g) and nitric acid (90ml) in acetic acid (200ml) was added dropwise for 10 min. at room temperature. After the mixture was stirred at 65°C for 3h, it was allowed to stand at room temperature overnight and was poured into a large excess of water. The precipitates formed were filtered and recrystallized to give 1g (16.1g, 70%): pale yellow prisms (ethanol); mp 111.5-113°C; IR 1638cm⁻¹; ¹H-NMR δ = 7.10 - 7.38 (2H, m), 7.71 (1H, d, J = 5.4 Hz), 7.80 - 8.02 (2H, m), 8.03 (2H, d, J = 5.4 Hz); MS m/z (rel intensity, %) 306 (M⁺, 0.8), 111 (100). Anal. Found: C, 46.87; H, 2.17; N, 8.96%. Calcd for C₁₂H₆N₂O₄S₂: C, 47.05; H, 1.97; N, 9.15%.

3,4-Di-(1-naphthoyl)-1,2,5-oxadiazole-2-oxide (1h). A mixture of sodium nitrite (8g) and nitric acid (d₂o = 1.42, 80ml) in acetic acid (160ml) was added at room temperature to a mixture of 1-acetylnaphtalene (26g) in acetic acid (80ml) for 10-20 minutes. During the addition, the mixture spontaneously warmed up to about 40°C. After the reaction mixture was stirred at room temperature for 24h, the precipitates formed were filtered and recrystallized to give 1h (20.5g, 68%): yellow prisms (benzene); mp 157-159°C; IR 1640 cm⁻¹; ¹H-NMR δ = 7.20 - 7.67 (6H, m), 7.72 - 8.23 (6H, m), 8.45 - 8.81 (2H, m); MS m/z (rel intensity, %) 394 (M⁺, 7), 172 (100), 155 (85). Anal. Found: C, 72.99; H, 3.80; N, 6.62%. Calcd for C₂₄H₁₄N₂O₄: C, 73.03; H, 3.58; N, 7.10%.

The filtrate was poured into a large excess of water, affording naphthalene-1-carboxylic acid (3.9g 15%).

3,4-Di-(2-naphthoyl)-1,2,5-oxadiazole-2-oxide (1i). A mixture of 2-acetylnaphthalene (30g) in acetic acid (160 ml) was treated with a mixture of sodium nitrite (8g) in acetic acid (100ml) and worked up as described above, giving naphthalene-2-carboxylic acid (2.1g 7%) and 1i (22.5g, 65%): yellow prisms (ethanol); mp 152-153°C; IR 1680 cm⁻¹; ¹H-NMR δ = 7.36 - 7.80 (4H, m), 7.80 - 8.26 (8H, m), 8.38 (IH, s), 8.89 (IH, s); MS m/z (rel intensity, %) 394 (M⁺, 3), 172 (93), 155 (100). Anal. Found: C, 72.68; H, 3.81; N, 6.62%. Calcd for C₂₄H₁₄N₂O₄: C, 73.09; H, 3.58; N, 7.10%.

General procedure for the reaction of 1 with hydrazine hydrate. A mixture of 1 (1.00g) and a specified amount of hydrazine hydrate in acetic acid (50ml) was stirred at the reaction temperature for the reaction time given in Table 1. The mixture was condensed in vacuo to about 5ml and the condensate was chromatographed. Compounds 2 and 3 were obtained from the fractions eluted with benzene.

4,7-Diphenyl-1,2,5-oxadiazolo [3,4-d] pyridazine-1-oxide (2a): mp 214-215°C (lit. ² 210°C).

4,7-Di-p-tolyl-1,2,5-oxadiazolo [3,4-d] pyridazine-1-oxide (2b): pale orange needles (ethanol); mp 208-212°C; MS m/z (rel intensity, %) 318 (M⁺, 38), 230 (100). Anal. Found: C, 68.22; H, 4.54; N, 17.67%. Calcd for C₁₉H₁₄N₂O₂: C, 67.92; H, 4.43; N, 17.60%.

4,7-Di-p-methoxyphenyl-1,2,5-oxadiazolo [3,4-d] pyridazine-1-oxide (2c): red plates (ethanol); mp 175-179°C; MS m/z (rel intensity, %) 350 (M⁺, 10), 262 (100), 176 (90). Anal. Found: C, 62.18; H, 4.22; N, 16.37%. Calcd for C₁₉H₁₄N₂O₄: C, 61.71; H, 4.03; N, 15.99.

4,7-Di-m-nitrophenyl-1,2,5-oxadiazolo [3,4-d] pyridazine-1-oxide (2d): yellow
needles (toluene); mp 252-252.5°C (decomp.) (lit.2 251°C).

4,7-Di-p-bromophenyl-1,2,5-oxadiazolo[3,4-d]pyridazine-1-oxide (2e): dark orange needles (toluene); mp 256-257°C (decomp.); MS m/z (rel. intensity, %) 450 (M+, 18), 448 (M+, 35), 446 (M+, 18), 360 (100). Anal. Found: C, 43.15; H, 1.90; N, 12.66%. Calcd for C16H8Br2N4O2: C, 42.85; H, 1.78; N, 12.50.

4,7-Diphenyl-1,2,5-oxadiazolo[3,4-d]pyridazine (3a): orange needles (hexane); mp 191-192.5°C (lit.2 sublimed at 170°C); MS m/z (rel. intensity, %) 274 (M+, 62), 141 (100), 77 (77). Anal. Found: C, 70.03; H, 3.83; N, 20.25%. Calcd for C16H10N4O: C, 70.07; H, 3.67; n, 20.43.

4,7-Di-p-tolyl-1,2,5-oxadiazolo[3,4-d]pyridazine (3b): orange needles (toluene); mp 251-253°C; MS m/z (rel. intensity, %) 302 (M+, 100). Anal. Found: C, 71.69; H, 4.67; N, 18.46%. Calcd for C16H14N4O: C, 71.51; H, 4.67; N, 18.53%.

4,7-Di-p-methoxyphenyl-1,2,5-oxadiazolo[3,4-d]pyridazine (3c): reddish brown needles (benzene); mp 216-217°C; MS m/z (rel. intensity, %) 358 (M+, 56) 186 (33) 76 (100). Anal. Found: C, 53.08; H, 2.49; N, 23.29%. Calcd for C16H14N4O3: C, 52.76; H, 2.21; N, 23.07%.

4,7-Di-p-nitrophenyl-1,2,5-oxadiazolo[3,4-d]pyridazine (3d): orange needles (ethanol); mp 269-270°C; MS m/z (rel. intensity, %) 364 (M+, 100). Anal. Found: C, 53.01; H, 2.47; N, 22.85%. Calcd for C16H14N4O: C, 52.76; H, 2.21; 23.07%.

4,7-Di-(1-thienyl)-1,2,5-oxadiazolo[3,4-d]pyridazine (3f): orange needles (ethanol); mp 246-247°C; MS m/z (rel. intensity, %) 374 (M+, 100); 1H-NMR δ = 7.11 - 7.39 (2H, m), 7.63 (2H, d, J = 6.1 Hz), 8.45 (2H, d, J = 6.1 Hz). Anal. Found: C, 50.50; H, 2.36; N, 19.08%. Calcd for C12H6N4O3: C, 50.33; H, 2.11; N, 19.57%.

4,7-Di-(1-naphtyl)-1,2,5-oxadiazolo[3,4-d]pyridazine (3g): red plates (ethanol); mp 246-247°C; MS m/z 374 (M+). Anal. Found: C, 77.42; H, 4.43; N, 14.96%. Calcd for C24H14N4O: C, 76.99; H, 3.77; N, 14.94%.

4,7-Di-(2-naphtyl)-1,2,5-oxadiazolo[3,4-d]pyridazine (3h): golden plates (dioxane); mp 265-166°C; MS m/z (rel. intensity, %) 374 (M+, 100). Anal. Found: C, 76.78; H, 4.05; N, 14.55%. Calcd for C24H14N4O: C, 76.99; H, 3.77; N, 14.96%.

References


4) T. Okuda, Yakugaku Zasshi, 78, 808 (1958).