Synthesis of 5,5’-(1,2-Ethanediyl)-bis[3-(Aryl)-1,2,4-Oxadiazoles] and 3-[3-(Aryl)-1,2,4-Oxadiazol-5-yl] Propionic Acids.

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São descritas as sínteses dos compostos 3a-f, a partir dos ácidos 3-[3-(aryl)-1,2,4-oxadiaxol-5-il] propiónicos, 1a-f, e ariamidoximas, 2a-f. O uso de síntese induzida por micro-ondas dos ácidos, 1a-f, com alto rendimento é também descrita.

The synthesis of title compounds, 3a-f, from 3-[3-(aryl)-1,2,4-oxadiiazol-5-yl] propionic acids, 1a-f, and arylamidoximes, 2a-f, is reported. The use of microwave-induced synthesis of the starting acids, 1a-f, in high yields is also described.

**Key words:** oxadiazoles; propionic acids derivatives; synthesis.

**Introduction**

A literature survey showed that only one bis-1,2,4-oxadiazole of the type 5,5’-(1,2-ethanediyl)-bis[3-(phenyl)-1,2,4-oxadiazole] was prepared from succinic acid and bezamidoxime. Besides its spectroscopic studies, no other work has been done. We became interested in these products because of their centro-symmetric nature. Since only little is known about these compounds, this series holds future promise for chemical studies. We herein describe the synthesis of 3a-f starting from 3-[3-(aryl)-1,2,4-oxadiazol-5-yl] propionic acids, 1a-f, and an arylamidoxime, 2. Compounds 3b-f are new products.

During our attempts to improve the yields of the above starting acids, we discovered that a mixture of arylamidoxime and succinic anhydride react in a domestic microwave oven in 10 min. to provide 1a-f in high yields. Such a method is reported for the first time for the preparation of acids, 1a-f. Very recently, 1a, has been found to possess significant peripheral analgesic and anti-inflammatory properties. This is the first examples of this series to have such biological activities. Because of this, these acids are important and could prove as potential drugs against pain and inflammation.

**Results and Discussion**

Reaction of 1a-f, α-dicyclohexylcarbodiimide, and the appropriate arylamidoxime, 2, in dry dioxane at reflux tempera-
ture followed by work-up afforded bis-oxadiazoles, 3a-f (Scheme 1). Their structures were inferred by infrared and nmr spectra. The mechanism of formation of 3 by the reaction of 1 and 2 needs comment. It has been established earlier \(^7\) that the hydroxyl oxygen of arylamidoximes is more nucleophilic than nitrogen of NH\(_2\) function. Therefore, it is assumed that intermediate 6 is formed and this cyclizes to 3 on heating. But the amide 7 (vide infra) would also lead to 3.

\[
\begin{align*}
\text{Ar} & \quad \text{N} \quad \text{C} \quad \text{O} \quad \text{H}_2\text{O} \quad \Delta \quad 3 \\
\text{Ar} & \quad \text{N} \quad \text{C} \quad \text{N} \quad \text{O} \quad \text{C} \quad \text{N} \quad \text{N} \quad \text{H}_2\text{O} \\
\text{Ar} & \quad \text{N} \quad \text{C} \quad \text{N} \quad \text{O} \quad \text{C} \quad \text{N} \quad \text{N} \quad \text{H}_2\text{O}
\end{align*}
\]

Next, we diverted our attention to improve the yields of starting acids, 1a-f. We succeeded in developing three methods to prepare these acids in higher yields. These are as follows:

1. The reaction of arylamidoximes, 2a-f, with succinic anhydride, 4, was reported\(^8\) to yield 1a-f in poor to moderate yields. By heating an appropriate arylamidoxime and succinic anhydride, we have been able to detect, by tlc, three products instead of only one, 1, as described earlier. Their separation was achieved on a silica gel column. The products were identified as 5a-f (R\(_f\) = 0.8), 3a-f (R\(_f\) = 0.5) and 1a-f (R\(_f\) = 0.1). Components 5 and 3 were minor ones, whereas 1 was the major one (70-75%) (Table). If the quantities of 1, 3 and 5 are summed up, we get a yield of 85% or more.

2. We have further improved the yields of 1a-f by performing the reaction in refluxing dioxane. Thus, heating a mixture of 2a-f and 4 in dioxane at reflux temperature followed by work-up and chromatography provided 80-92% of compounds 1a-e and 68% of 1f (Table). Small quantities of 3a-f & 5a-f were also isolated.

3. Another fast and efficient synthesis of 1a-f was found. When an intimate mixture of the appropriate arylamidoxime and succinic anhydride was heated in a microwave oven (80% potency) for 10 min, compound 1 was obtained as the major product and 3 and 5 as minor components. Separation by column chromatography provided the pure acids in high yields (Table) except in the case of 1b. Thus, it is clear that microwave heating is more efficient than conventional heating for dry organic reactions. The method allows rapid synthesis and cleaner products because of a shorter residence time.

Regarding the real reaction in microwave, it is hard to explain at the moment because of many contradictory results in the literature. Recently, Laurent et al.\(^9\) performed experiments to clarify the difference between conventional heating and microwave irradiation, but suggested for more studies to answer the question.

The formation of small quantity of 3 in the reaction of an arylamidoxime 2 and succinic anhydride 4 is interesting and requires clarification. The acid 1 formed initially reacts with another molecule of amidoxime to give 3. The intermediate may be an ester 6 or an amide 7 which cyclizes to 3.

The formation of 5 appears to be due to the reaction between two molecules of arylamidoximes under heating conditions. Compounds 5a-d,f were found to be identical with authentic samples, which were obtained by heating individual amidoxime as described earlier\(^10,11\). The mechanism of formation of bisaryl-1,2,4-oxadiazoles has already been discussed in detail\(^11\). Oxadiazole 5e is unknown, and therefore, its properties are described in the experimental section.

**Experimental**

Melting points are uncorrected. IR spectra were run on a Perkin-Elmer spectrophotometer, model 237B. \(^1\)H-NMR spectra were recorded with a Varian EM 390 Instrument using TMS as internal reference. Sanyo microwave oven (2450 MHz and 1350 Watts) was used for the preparation of 2a-f. Elemental analyses were performed by Dr. Luzia E. Narimatsu, Instituto de Química, Universidade de São Paulo, S.P. TLC were done on silica gel with fluorescent indicator (PF\(_254\)) and eluted with chloroform unless stated.

**Synthesis of 3,5-(1,2-Ethenediy)-bis[3-(aryl)-1,2,4-oxadiazoles] (3a-f) from (1a-f) and (2a-f).** The appropriate 3-(3-aryl)-1,2,4-oxadiazol-5-yl)propionoic acid, 1 (1.92 mmol), dicyclohexylcarbodiimide (1.92 mmol) and the suitable benzamidoxime, 2 (1.92 mmol) in dried and freshly distilled dioxane (ca. 10 ml) were stirred at room temperature under nitrogen for 2h followed by 4 h of reflux. TLC (CHCl\(_3\)-EtOAc, 1:1) showed four spots in each case. The R\(_f\) values of the products in the reaction of 1a and 2a were: 0.88 (DCC), 0.77 (3a), 0.47 (2a, trace), and 0.02 (dicyclohexylurea) respectively. The reaction of 2b-f and 1b-f showed similar tlc, i.e., four spots in each case. Solvent vaporization afforded a solid mass, which was separated over silica gel packed column. The details are given below:

**5,5-(1,2-Ethenediy)-bis[3-(phenyl)-1,2,4-oxadiazole] (3a).** After chromatography, the pure material weighed 0.49g (81%). Recrystallization from ethanol-water gave a product, mp 163 °C (lit. [2], m.p. 163-164 °C). \(^1\)H NMR (CDCl\(_3\)): \(\delta = 3.58\) (s, 4H, 2CH\(_2\)), 7.27-7.70 (m, 6H, meta and para aromatic protons), 7.90-8.27 (m, 4H, ortho aromatic protons).

**5,5-(1,2-Ethenediy)-bis[3-(o-tolyl)-1,2,4-oxadiazole] (3b).** Column chromatography afforded 0.53g (80%) of 3b. Crystallization either from chloroform-n-hexane or ethanol-water provided crystals, mp 149-150 °C. \(^1\)H NMR (CDCl\(_3\)): \(\delta = 2.60\) (s, 6H, 2CH\(_3\)), 3.53 (s, 4H, 2CH\(_2\)), 7.10-7.65 (m, 6H, 7.27-7.70 (m, 6H, meta and para aromatic protons), 7.90-8.27 (m, 4H, ortho aromatic protons).
meta and para protons), 7.78-8.20 (narrow multiplet, 2H, ortho protons).

C₆H₁₁Na₂O₇ calculated C 69.35 H 5.24 N 16.17
(346.34) found 69.26 5.27 16.07

5.5'-[1,2-Ethenediyl]-bis[3-(p-toluyl)-1,2,4-oxadiazole] (3c). Recrystallization from ethanol gave 0.45 g of 3c (69%) m.p. 111-112 °C. 1H NMR (CDCl₃): δ = 2.42 (s, 6H, 2CH₃), 3.5 (s, 4H, 2CH₂), 6.98-7.45 (4H, unresolved narrow multiplet, meta and para protons), 7.61-8.00 (broad and unresolved ortho protons, 4H).

C₆H₁₈Na₂O₇ calculated C 69.35 H 5.24 N 16.17
(346.34) found 69.09 5.09 15.99

5.5'-[1,2-Ethenediyl]-bis[3-(p-toluyl)-1,2,4-oxadiazole] (3d). After chromatographic separation, the compound was recrystallized from ethanol to give 0.51 g (77%) of 3d, m.p. 172-173 °C. 1H NMR (CDCl₃): δ = 2.42 (s, 6H, 2CH₃), 3.57 (s, 4H, 2CH₂), 7.65 (AA'BB' system, 8H).

C₆H₁₈Na₂O₇ calculated C 69.35 H 5.24 N 16.17
(346.34) found 69.07 5.25 16.31

5.5'-[1,2-Ethenediyl]-bis[3-(p-chlorophenyl)-1,2,4-oxadiazole] (3e). Usually chromatographic and work-up followed by crystallization from ethyl acetate furnished 0.45g (58%) of 3e, m.p. 234-236 °C. This compound is almost insoluble in most cold organic solvents. It is only sparingly soluble in a mixture of dimethylsulfoxide and aceton at room temperature.

1H NMR (CDCl₃-DMSO-d₆, 1/1): δ = 3.70 (s, 4H, 2CH₂), 7.80 (AA'BB' system, 8H).

C₆H₁₁Cl₂Na₂O₇ calculated C 55.83 H 3.13 N 14.16
(387.18) found 55.57 3.14 14.23

5.5'-[1,2-Ethenediyl]-bis[3-(p-bromophenyl)-1,2,4-oxadiazole] (3f). This product 0.59 g (69%) was obtained as colorless crystals. Similar solubility problem, as observed for 3e, has been encountered in this case as well. Because of this, the 1H NMR spectrum was not obtained. Crystallization and recrystallization from a large quantity of hot ethyl acetate provided crystals, m.p. 222-223 °C.

C₁₅H₁₈Br₂N₂O₇ calculated C 45.39 H 2.54 N 11.76
(476.28) found 45.63 2.63 12.02

Reaction of Arylamidoximes, 2a-f, with Succinic Anhydride. General Procedure A. The appropriate arylamidoxime (7.35mmol) and succinic anhydride (8.00 mmol) were triturated and put in a test tube. The test tube was dipped in a preheated oil bath at 130 °C. After 40 min, the same was removed. Tlc showed four spots corresponding to compounds (Rf values in parentheses): 5 (0.8), 3 (0.5), 2 (0.3), and 1 (0.1). The mixture was chromatographed over silica gel using initially n-hexane and then gradually increasing the polarity by adding chloroform. This separated compounds 5 and 3. Elution of 1 was possible only with a mixture of chloroform and ethyl acetate. A little of a polar compound remained on the column which could be eluted only with methanol. This products presumably impure succinic acid. The details are given below:

3,3'-Bisaryl-1,2,4-oxadiazoles 5a-f. Rf ≈ 0.8. Compounds 5a-d,f were identical with those prepared earlier. Their yields are given in parentheses: 5a (6.1%), 5b (1.4%), 5c (11.2%), 5d (2.9%), and 5f (9.9%). The product 5e melted at 179-8 °C, after recrystallization from ethanol-water, yield (11.5%).

1H NMR (CDCl₃-DMSO-d₆, 9.90/1): δ = 7.55 (d, 2H), 7.63 (d, 2H), 8.17 (d, 2H), and 8.27 (d, 2H). These doublets have J value of about 8.5 Hz.

Table 1. Melting points and yields of products 1a-f.

<table>
<thead>
<tr>
<th>Compound</th>
<th>M. P. (°C)</th>
<th>Yield (%)</th>
<th>GP A</th>
<th>GP B</th>
<th>GP C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>present</td>
<td>Lit. 6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>119-120</td>
<td>118-120</td>
<td>70.2</td>
<td>92.0</td>
<td>73.3</td>
</tr>
<tr>
<td>1b</td>
<td>102</td>
<td>103-104</td>
<td>74.9</td>
<td>83.0</td>
<td>25.0</td>
</tr>
<tr>
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<td>101-102</td>
<td>98-100</td>
<td>74.5</td>
<td>91.0</td>
<td>76.4</td>
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<tr>
<td>1d</td>
<td>145</td>
<td>138.5</td>
<td>74.8</td>
<td>86.0</td>
<td>67.7</td>
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<tr>
<td>1e</td>
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<td>145-146</td>
<td>72.5</td>
<td>80.0</td>
<td>83.1</td>
</tr>
<tr>
<td>1f</td>
<td>157-158</td>
<td>149-150</td>
<td>73.6</td>
<td>68.0</td>
<td>76.5</td>
</tr>
</tbody>
</table>

*GP A, B and C represent General procedures A, B and C.

Compounds with R value ≈ 0.5. After chromatography over silica gel followed by work-up provided pure compounds. The tlc, melting point and 1H-NMR spectra of these products agreed with 3a-f. The yields are given in parentheses: 3a (8.9%), 3b (12%), 3c (11.6%), 3d (4.4%), 3e (8.8%), 3f (10.5%).

3-[3-(Aryl)-1,2,4-oxadiazol-5-y] propionic acids (1a-f). The melting points as well as the yields of compounds 5a-f are compiled in the Table 1. General Procedure B. The appropriate arylamidoxime, 2 (3.67mmol) and succinic anhydride (3.67 mmol) in dry dioxane (ca. 10 ml) were refluxed for 4 h under nitrogen atmosphere. Tlc of the mixture of this reaction had the same Rf values as described above. Solvent removal followed by liquid chromatography over silicagel using solvents as described in procedure A, afforded the desired products. The yields of 1a-f are summarized in the Table 1.

General Procedure C. Arylamidoxime (3.7 mmol) and succinic anhydride (4.06mmol) were intimately mixed, and heated in a microwave oven at 80% potency for 5 min. Initially, and later on another 5 min. Tlc showed similar results as shown in procedures A or B. Compound 1b reacted poorly underthese conditions. Therefore, this product was heated at maximum potency for 10 min. For the reaction to complete. The products were cromatographed over silica gel column. The yields are given in the Table 1. Acknowledgement

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References


