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-(aril)- 1,2,4-oxadiazol-5-il] propiônicos, **1a-f**, e arilamidoximas, 2a-f. O uso de síntese induzida por micro-ondas dos ácidos, **1a-f**, com alto rendimento é também descrita.

Thesynthesis of title compounds, **3a-f**, from 3-[3-(aryl)- 1,2,4-oxadiazol-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.*

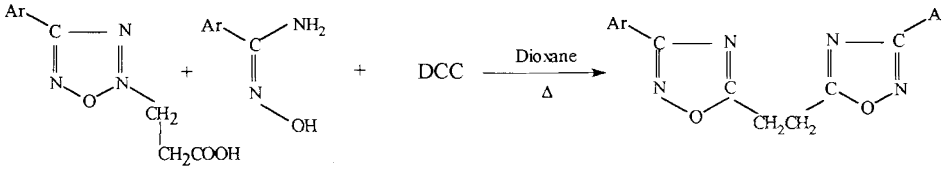
Introduction

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[2] from succinic acid and bezamidoxime. Besides its spectroscopic studies[3,4], 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.

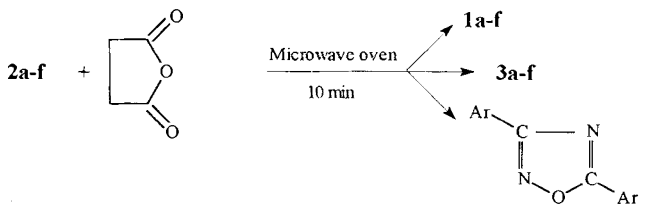
During our attempts to improve the yields of the above starting acids, we discovered that a mixture of arylamidoxime and succinic anhydride react in a domestic microwave oven in 10 min. to provide **1a-f** in high yields. Such a method is reported for the first time for the preparation of acids, **1a-f**. Very recently, **1a,** has been found to possess significant peripheral analgesic and anti-inflammatory properties[5]. 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**,[6] dicyclohexylcarbodiimide, and the appropriate arylamidoxime, **2**, in dry dioxane at reflux tempera-

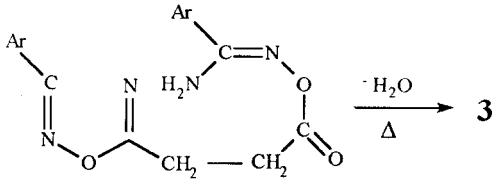


1a-f **2a-f** **3a-f**



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.**



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:

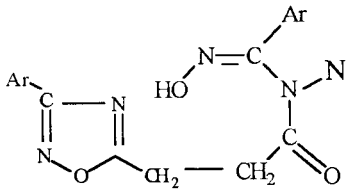
1. The reaction of arylamidoximes, **2a-f,** with succinic anhydride, **4**, was reported[6] to yield **1a-f** in poor to moderate yields. By heating an appropriate arylamidoxime and succinic anhydride, we have been able to detect, on tlc, three products instead of only one, **1**, as described earlier. Their separation was achieved on a silica gel column. The products were identified as **5a-f** ($R_f \approx 0.8$), **3a-f** ($R_f \approx .5$) and **1a-f** ($R_f \approx 0.1$). 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, itis clear that microwave heating is more efficient than coventional 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 anhydrid **4** is interesting



andrequires 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 ciclizes 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 arylamidoxime 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 Quí mica, Universidade de São Paulo, S.P. TLC were done on silica gel with flourescent indicator (PF_{254}) and eluted with chloroform unless stated.

*Synthesis of 5,5'-(1,2-Ethanediyl)-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]propionicacid, **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. Solvente vaporation afforded a solid mass, which was separated over silica gel packed column. The details are given below:

5,5'-(1,2-Ethanediyl)-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 ($CDCl_3$):δ = 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-Ethanediyl)-bis[3-(o-tolu)-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 ($CDCl_3$): δ = 2.60 (s, 6H, $2CH_3$), 3.53 (s, 4H, $2CH_2$),7.10-7.65 (m, 6H,

meta and *para* protons), 7.78-8.20 (narrow multiplet, 2H, *ortho* protons).

$C_{20}H_{18}N_4O_2$ calc. C 69.35 H 5.24 N 16.17
(346.34) found 69.26 5.27 16.07

5,5'-(1,2-Ethanediyl)-bis[3-(m-tolu)-1,2,4-oxadiazole] (3c). Recrystallization from ethanol gave 0.45 g of **3c** (69%) m.p. 111-112 °C. ^{1}H NMR ($CDCl_3$): δ = 2.4 (s, 6H, 2CH3), 3.5 (s, 4H, $2CH_2$), 6.98-7.45 (4H, unresolved narrow multiplet, *meta* and *para* protons), 7.61-8.00 (broad and unresolved *ortho* protons, 4H).

$C_{20}H_{18}N_4O_2$ calc. C 69.35 H 5.24 N 16.17
(346.34) found 69.09 5.09 15.99

5,5'-(1,2-Ethanediyl)-bis[3-(p-tolu)-1,2,4-oxadiazole] (3d). After chrmatografic separation, the compound was recrystallized from ethanol to give 0.51 g (77%) of **3d**, m.p. 172-173 °C. ^{1}H-NMR ($CDCl_3$): δ = 2.42 (s, 6H, $2CH_3$), 3.57 (s, 4H, $2CH_2$), 7.65 (AA'BB' system, 8H).

$C_{20}H_{18}N_4O_2$ calc. C 69.35 H 5.24 N 16.17
(346.34) found 69.07 5.25 16.31

5,5'-(1,2-Ethanediyl)-bis[3-(p-chlorophenyl)-1,2,4-oxadiazole] (3e). Usual chromatography and work-up followed by crystallization from ethyl acetate furnished 0.43g (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 acetone at room temperature. ^{1}H NMR (CD_3COCD_3DMSO-d_6, 1/1): δ = 3.70 (s, 4H, $2CH_2$),7.80(AA'BB' system, 8H).

$C_{18}H_{12}Cl_2N_4O_2$ calc.C 55.83 H 3.13 N 14.16
(387.18) found 55.57 3.14 14.23

5,5'-(1,2-Ethanediyl)-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 ^{1}H NMR spectrum was not obtained. Crystallization and recrystallization from a large quantity of hot ethyl acetate provided crystals, m.p. 222-223 °C.

$C_{18}H_{12}Br_2N_4O_2$ calc.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[6]. General Procedure A. The appropriate arylamidoxime (7.35mmol) and succinic anhydride (8.09 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 (R_f values in parenthses): **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 clhoroform. This separeted 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 productis presumably impure succinic acid. The details are given below:

3,5-Bisaryl-1,2,4-oxadiazoles 5a-f, $R_f \approx 0.8$. Compunds **5a-d,f** were identical with those prepared earlier[10,11].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%).

^{1}H NMR ($CDCl_3$-DMSO-d_6, 9.9/0.1): δ = 7.55 (d, 2H), 7.63 (d, 2H),8.17 (d, 2H), and 8.27 (d, 2H). These doublets have J valueofabout 8.5 Hz.

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

Compound	M. P. (°C) present	M. P. (°C) Lit.[6]	Yields (%)* present GP A	Yields (%)* present GP B	Yields (%)* present GP C	Yields (%) Lit.[6]
1a	119-120	118-120	70.2	92.0	73.3	55.0
1b	102	103-104	74.9	83.0	25.0	25.0
1c	101-102	98-100	74.5	91.0	76.4	53.0
1d	145	138.5	74.8	86.0	67.7	54.0
1e	153-154	145-146	72.5	80.0	83.1	58.0
1f	157-158	149-150	73.6	68.0	76.5	40.0

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

$C_{14}H_8Cl_2N_2O$ calc. C 57.74 H 2.77 N 9.62
found 57.45 2.62 9.32

Compounds with R value ≈ 0.5. After cromatography over silica gel followed by work-up provided pure compounds. The tlc, mixture melting pointsand the NMR spectra of these products agreed with **3a-f**. The yields are given inparentheses: **3a** (8.9%), **3b** (12%), **3c** (11.6%), **3d** (4.4%), 3**e** (8.8%), **3f** (10.5%).

3-[3-(Aryl)-1,2,4-oxadiazol-5-yl] propionic acids (**1a-f**). The melting points as well as the yields ofcompounds **5a-f** are compiled in the Table 1. General Procedure B. The appropriate arylamidoxime, 2 (3.67 mmol) 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 R_f 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.

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