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Article

Preparation and Reactions of 3-[3-(Aryl)-1,2,4-Oxadiazol-5-yl] Propionic Acids[1]

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Neste artigo descrevemos as sínteses dos ácidos 3-[3-(aril)-1,2,4-oxadiazol-5-il] propiônicos **3a-g**, com alto rendimento, a partir das arilamidoximas **1a-g** e do anidrido succínico. Os 1,2,4-oxadiazóis **3a-f** também foram obtidos fazendo-se a reação em um forno de microondas doméstico. Avaliações farmacológicas preliminares demonstraram que os compostos **3b-e** possuem propriedades analgésicas. Cálculos *ab-initio* com base sto-3g foram realizados com os compostos **3a**, **4a**, **5a** e **6a.**

The synthesis of title compounds **3a-g**, from arylamidoximes **1a-g** and succinic anhydride in high yields is described. 1,2,4-Oxadiazoles **3a-f** were also obtained by carrying out the reaction in a domestic microwave oven. Preliminary pharmacological evaluations demonstrated that **3b-e** possess analgesic properties. *Ab initio* molecular orbital calculations of the type STO-3G have been performed for compounds **3a**, **4a**, **5a** and **6a**.

Keywords: *arylamidoximes, bis-1,2,4-oxadiazoles, diaryl-1,2,4-oxadiazoles,* ab-initio *sto-3g calculations*

Introduction

Although the synthesis of acids **3a-g** have been described, their yields were rather low[2-4]. In an attempt to improve the yields of these acids, we discovered that heating a mixture of arylamidoximes **1a-f** and succinic anhydride **2** in a domestic microwave oven for 10 min provides **3a-f** in high yield (Scheme 1). These acids are important because 3-[3-(phenyl)-1,2,4-oxadiazol-5-yl] propionic acid (**3a**) has been found to possess significant peripheral analgesic and anti-inflammatory properties[5]. Compounds **3b-e**, in a preliminary screening, showed some analgesic property; in fact, **3b** and **3d** have slightly better activity than dipyrone. Acid **3b** also showed anti-inflammatory property but 30 percent less than indomethacine[6].

During the preparation of **3a-g**, we carefully investigated two minor products and identified them as **4a-f** and **5a-f** respectively. We synthesised **4a-f** from **3a-f** in order to verify their identities. The literature reports the synthesis of only **4a**, from benzamidoxime and succinic anhydride[7], and its spectroscopic properties[8,9]. Besides this, no more information was available on this class of compounds. Next we transformed acids, **3a-g** to their methyl esters, **6a-g**. None of the methyl esters were known. Therefore, this paper describes the improved synthesis of **3a-f** and the preparations of **4a-f** from **3a-f**, and of **6a-g** from **3a-g**, respectively.

Results and Discussion

The reaction of arylamidoximes **1a-f** with succinic anhydride **2** was reported to yield **3a-f** in poor to moderate yields[4]. Repeating this method under improved conditions and examining the products carefully by thin layer chromatography (TLC), we detected two fast running minor components. Their separation was achieved on a silica gel column. The products were identified as **3a-f** (R_f = 0,1), **4a-f** (R_f = 0,5) and **5a-f** (R_f = 0,8) respectively. Acids **3a-f** were the major products (70-75%) whereas **4a-f** and **5a-f** were the minor ones. If the quantities of all three products are summed up, a yield of 85% was obtained. Table 1 lists the yields of **3a-f** obtained by heating **1** and **2** in a preheated oil bath (GPA), in dioxane (GPB) or in a microwave oven (GPC).

Table 1. Melting points and yields of products 3a-f.

Compound	MP (°C)		Yields (%)			
	Present	Lit.[4]	Present*			Lit.[4]
			GPA	GPB	GPC	
3a	119-120	118-120	70.2	92.0	73.3	55.0
3b	102	103-104	74.9	83.0	25.0	25.0
3c	101-102	98-100	74.5	91.0	76.4	53.0
3d	145	138.5	74.8	86.0	67.7	54.0
3e	153-154	145-146	72.5	80.0	83.1	58.0
3f	157-158	149-150	73.6	68.0	76.5	40.0

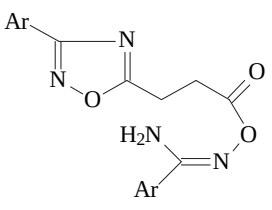
*GP A, B and C represent General Procedures A, B and C.

The yields of acids **3a-f** have been slightly improved by refluxing the arylamidoxime and succinic anhydride in dioxane (GPB). This experiment also gave the two minor products.

Another fast and efficient synthesis of **3a-f** was found. When an intimate mixture of an appropriate arylamidoxime and succinic anhydride was heated in a domestic microwave oven (80% potency) for 10 min (GPC), compound **3** was obtained as the major product and **4** and **5** as the minor products. Separation by column chromatography provided pure acids in high yields except in the case of **3b** (Table 1). Thus, it is clear that microwave heating is more efficient than conventional heating for dry organic reactions[10]. The method allows rapid synthesis and cleaner products because of a shorter residence time.

The formation of a small quantity of **4** in the reaction of an arylamidoxime **1** and succinic anhydride **2** is interesting and requires comment. The acid **3** formed initially reacts with another molecule of amidoxime to give **4**. This was proved experimentally by carrying out this preparation from **1** and **3**, as shown in Scheme 1, item B. Either **7** or **8** could be the intermediate, which cyclizes to **4** on heating**.** However, intermediate **7** is more likely since, as has been established earlier,[11] the hydroxyl oxygen of arylamidoxime is more nucleophilic than the -NH_2 nitrogen, supporting the intermediate **7**.

The formation of **5** is due to the reaction between two molecules of arylamidoximes under the reaction conditions. Compounds **5a-d**,**f** were identical with authentic samples[12,13]. Oxadiazole **5e** was not found in the literature and, therefore, its properties are described in the experimental section.



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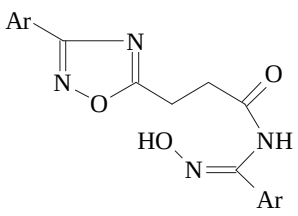

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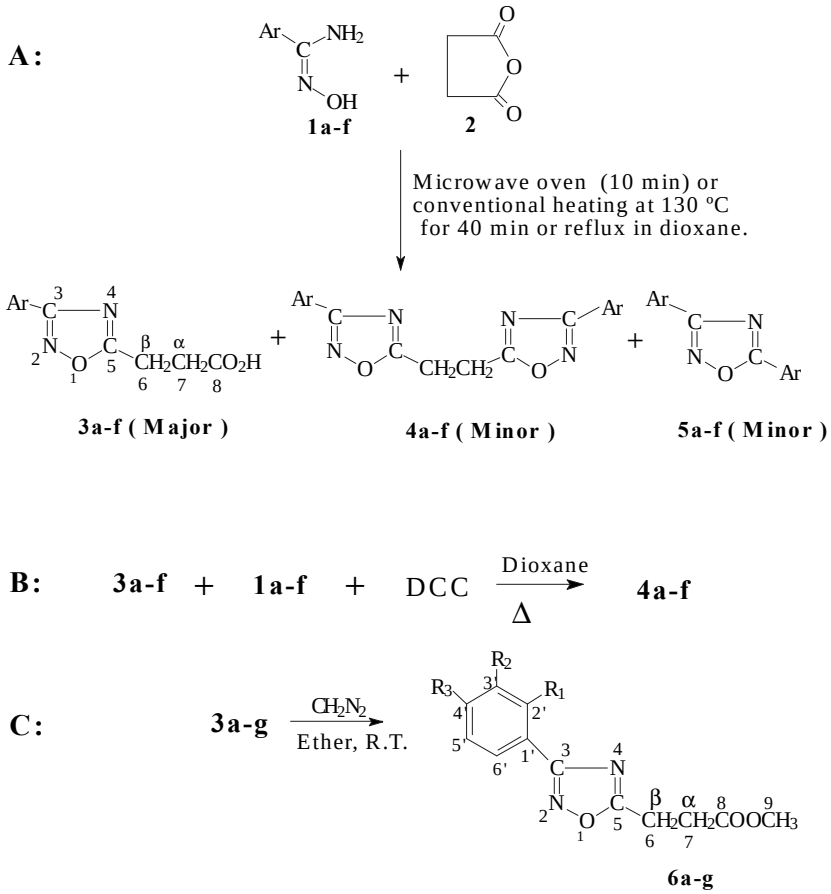
Next, we tried to transform **3a-g** to their methyl esters. Acids **3a-f** were synthesised by the reported procedure[1b], and acid **3g** was obtained likewise[1a]. Addition of diazomethane to an ethereal solution of these acids afforded methyl 3-[3-(aryl)-1,2,4-oxadiazol-5-yl] propionates **6a-g** in almost quantitative yield. All seven esters were new.

The IR spectra of **6a-g** showed a strong absorption around 1735 cm^{-1} for the ester carbonyl function. The other absorptions were similar to those of the 1,2,4-oxadiazole ring reported earlier[14,15]. The UV spectra had absorptions characteristic of a 1,2,4-oxadiazole ring[16]. Table 2 lists the UV spectra of compounds **6a-g**.

The 90 MHz ^{1}H-NMR Spectrum of **6a** showed a multiplet between δ 2.70-3.43 ppm for the methylene protons ($2CH_2$), but the 200 MHz proton magnetic resonance spectrum produced two well defined triplets at δ 2.94 and 3.25 ppm respectively, the *J* values in both cases were 7.0 Hz. The former and latter are assigned as α and β methylene protons respectively. This assumption is based on our work for 3-[3-(phenyl)-1,2,4-oxadiazol-5-yl] propionic acid.[4] The other products **6b-g** showed similar triplets having almost the same chemical shifts (Table 3).

^{13}C-NMR spectra

In 1989, the methyl substituent effects on the phenyl ring of 3-phenyl- and 5-methyl-3-phenyl-1,2,4-oxadiazoles were studied[17]. This paper describes the study of methyl, methoxy, chloro and bromo substituent effects on the phenyl ring of methyl 3-[3-(phenyl)-1,2,4-oxadiazol-5-yl] propionates, **6a-g**. The ^{13}C substituent effects of monosubstituted benzenes were obtained from the published data[18], and the values added to the phenyl carbons of **6a**. The additivity holds good



Ar	Ar		
a: Ph	**e:** *p*-ClPh	**a:** $R_1 = R_2 = R_3 = H$	**e:** $R_1 = R_2 = H$; R_3 =Cl
b: *o*-CH_3Ph	**f:** *p*-BrPh	**b:** $R_1 = CH_3$; $R_2 = R_3 = H$	**f:** $R_1 = R_2 = H$; R_3 =Br
c: *m*-CH_3Ph	**g:** *p*-CH_3OPh	**c:** $R_1 = R_3 = H$; $R_2 = CH_3$	**g:** $R_1 = R_2 = H$; R_3 =OCH_3
d: *p*-CH_3Ph		**d:** $R_1 = R_2 = H$; $R_3 = CH_3$	

Scheme 1.

for all compounds except in the case of **6b** especially for 2' and 6' carbons. This kind of discrepancy has been observed earlier17 (Table 4). Initially, we faced some difficulty in assigning the C-6 and C-7 signals. However, we overcame this problem in the following manner.

As described in the section dealing with the proton spectra of these compounds, we assigned the α and β methylene protons at δ 2.94 and 3.25ppm respectively. Selective irradiation of the triplet at δ 3.27 ppm of **6b** changed the methylene carbon as a singlet at 30.31 ppm confirming it as C-6. Similarly, irradiation of the triplet at δ 2.94 produced a singlet at 21.95 ppm indicating clearly that it is due to C-7. In the totally proton decoupled spectrum of **6b**, it was difficult to locate C-1'. However, the Attached Proton Test (APT) technique indicated that C-1' had almost the same chemical shift as C-5'. Varying the delay time of the pulse sequence of the APT experiment gave the all quaternary carbon spectrum where C-1' appeared at δ 126.04 ppm, thus confirming its identity.

There seems to be no effect on C-3 of the 1,2,4-oxadiazole ring when the substituent changes from phenyl to *m*-, *p*-tolyl or *p*-anisyl. However, a small downfield shift (~ +0.65 ppm) is observed when the subsitituent at C-3 is a *o*-tolyl group. A *p*-chlorophenyl or *p*-bromophenyl substituent at C-3 produced a small uplield shift (-0.73 & -0.64 ppm).

In summary, the additivity rule for the substituents on the phenyl ring holds good in all compounds except in **6b**. Table 4 lists the ^{13}C chemical shifts of compounds **6a-g**.

Appearance of C-3 (δ 167.19-168.88 ppm) and C-5 (δ 176.19-178.53) signals in the ^{13}C spectrum of compounds **6a-g** can be correlated with the calculated charges

of these carbons obtained for **6a** (Table 5). The positive charges are 0.146548 e.u. and 0.231096 e.u. for C-3 and C-5. The former is lower than the latter and, therefore, the chemical shifts and the calculated values agree with the assignment. This can be justified by considering the electronegativity of two nitrogens attached on C-3 *vs.* one nitrogen and one oxygen on C-5.

Table 2. The ultraviolet spectra of compounds **6a-g** obtained in 95% ethanol.

Compound	$\lambda_{max.}$ (nm)	∈	Compound	λ_{max} (nm)	∈
6a	286	634.3	**2e**	290	617.3
	274	740.0		276	1,111.0
	240	10,993.7		249	18,271.6
6b	283	1,087.4	**2f**	290	593.5
	241	9,381.7		281	1,038.6
				253	18,694.4
6c	289	1,194.0			
	284	1,368.2	**2g**	293	2,124.7
	245	10,945.3		262	18,413.6
6d	288	592.4			
	276	1,066.3			
	249	14,761.9			

Computational Method

The *ab initio* Hartree-Fock Self-Consistent Field (HF-SCF) molecular orbital calculations were performed by using the Gaussian 92 Program[19] on an IBM RISC 6000 computer of our Department.

Ab initio calculations

In order to gain more insight about these molecules, we carried out *ab initio* molecular orbital calculations of compounds **3a**, **4a**, **5a** and **6a** using STO-3G basis set for geometry optimisation. It was not possible to do calculations for all compounds because of the computer time. The literature doesn't record any theoretical work on these molecules. The results obtained are discussed in the following paragraphs, and the principal values are listed in Tables 5 and 6. Figure 1 shows a schematic picture of the most stable conformations found for each molecule.

First, we examined the acid **3a.** Although, semi-empirical calculations have been performed on the oxadiazoles[20,21], no work was found in the literature on 3-[3-(phenyl)-1,2,4-oxadiazol-5-yl] propionic acid **3a.** The calculations show that both phenyl and oxadiazole rings are coplanar. Further, C-6, C-7 and carbonyl carbon are in the plane of the oxadiazole ring. We did not examine the dimer of this acid. The dimer might show a somewhat different conformation of the side-chain. The calculated bond lengths and bond angles are very close to the experimental values for 2-(3-*p*-chlorophenyl[1,2,4]-oxadia-

Table 3. Chemical shifts (in ppm) of protons of oxadiazoles 6a-g[a].

Compound	Ar	α-CH_2 (t)	βCH_2 (t)	AR-CH_3 (s)	-$COOCH_3$ (s)
6a	7.27-7.60 m (3H)	2.94	3.25	-	3.67
	7.80-8.20 m (2H)				
6b	7.03-7.37 m (2H)	2.94	3.27	2.55	3.63
	7.70-8.03 m[b] (2H)				
6c	7.05-7.38 m[b] (2H)	2.94	3.25	2.37	3.67
	7.55-7.91 m[b] (2H)				
6d	[7.20d (2H); 7.88d (2H)][c]	2.93	3.25	2.37	3.68
6e	[7.37d (2H);7.83d (2H)][c]	2.94	3.25	-	3.68
6f	[7.59d (2H);7.90 (2H)][d]	2.94	3.26	-	3.70
6g[e]	[7.20d (2H); 8.05 (2H)][c]	2.93	3.24	-	3.70

[a]90 MHz, Solvent: $CDCl_3$. The values of α & β-CH_2 protons are from 200 MHz NMR spectra with *J* values = 7.0 Hz.
[b]Narrow multiplet.
[c] AA'BB' system (*J* = 8.0 Hz).
[d] AA'BB'system (*J* = 9.0 Hz).
[e]Ar $0CH_3$ protons appeared at δ 3.83 ppm as a singlet.

Table 4. ^{13}C-NMR Chemical shift assignments of compounds **6a-g***.

	Carbons												
Compounds	3	5	6	7	8	9	1'	2'	3'	4'	5'	6'	Ar-CH_3
6a	168.23	176.19	30.27	22.02	171.64	52.01	126.71	127.35	128.73	131.06	128.73	127.35	
6b	168.88	177.26	30.33	21.96	171.75	52.06	126.04	138.18	129.99	131.31	125.89	130.49	22.06
calcd.$^+$							127.41	136.25	129.43	130.96	125.83	127.25	
6c	168.28	178.07	30.21	21.96	171.59	51.93	126.52	127.83	138.48	131.80	128.61	124.42	21.18
calcd$^+$							126.61	128.05	137.63	131.76	128.63	124.45	
6d	168.26	178.02	30.28	22.02	171.69	51.99	123.70	127.29	129.46	141.40	129.46	127.29	21.47
calcd.$^+$							123.81	127.25	129.43	139.96	129.43	127.25	
6e	167.50	178.50	30.23	22.02	171.64	52.08	125.26	128.71	129.12	137.27	129.12	128.71	
calcd.$^+$							124.81	128.65	129.13	137.26	129.13	128.65	
6f	167.59	178.53	30.24	22.02	171.64	52.08	125.69	128.90	132.09	125.69	132.09	128.90	
calcd.$^+$							125.11	129.05	132.13	125.56	132.13	129.05	
6g**	168.25	177.68	30.30	21.99	171.68	52.00	119.17	128.94	114.15	161.64	114.15	128.94	
calcd.$^+$							119.01	128.35	114.33	162.46	114.33	128.35	

* Spectra obtained in $CDCl_3$

** Methoxy carbon absorption appeared at δ 55.20 ppm.

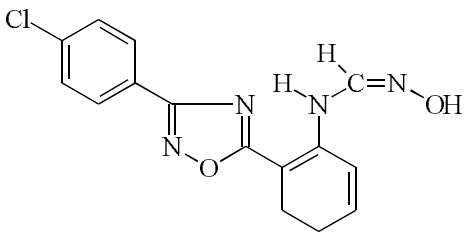
+Calculated by adding the known values of the substituents (Ref. 18) to the phenyl carbons of **6a**.

zol-5-yl)-3,4-dihydro-1-naphthylaminoformaldehyde oxime **9** obtained by X-ray crystallography[22]. The bond distances, bond angles and electronic charges on each atom of the heterocyclic ring are given in Table 5. Dipole moments and HOMO energies are listed in Table 6.

Next, we examined the methyl ester **6a** of acid **3a**. To our surprise, the ester shows the same conformation as that of the parent acid, indicating that substitution of the hydrogen atom by the methyl group did not affect the conformation.

Oxadiazole **5a** shows that all three rings lie in the same plane. The literature does not report any work about this compound. As expected the atomic charge at C-5 is slightly less than when there is an alkyl substituent. This also supports that the C-5 phenyl ring and the heterocyclic ring are conjugated.

Examination of **4a** shows that the phenyl rings still remain in the same plane as the oxadiazole ring and the molecule as a whole, in it's most stable conformation, is practically planar, with a dihedral angle of 179.9° between the two ring oxygens. A second stable structure was found with the phenyl-oxadiazol-5-yl groups connected via the ethylene function forming a torsion angle of about 66° from one another. This structure was found to be about 0.22 kcal/mol higher in energy than the former. The values in Table 5 for compound **4a** refer to the most stable conformation (the planar one). We can note, that the calculated values for **4a** are also in good agreement with the available experimental data[22].



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Experimental

Melting points are uncorrected. IR spectra were recorded with a Perkin-Elmer spectrophotometer, model 237B grating instrument and UV spectra with a Beckman Model DB spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were obtained with a EM-390 90 MHz and with a Bruker AC 200 MHz spectrophotometers using TMS as an internal standard. A solution (0.3M) of compounds **6a-g** in $CDCl_3$ in a 5 mm sample tube was used for measuring the ^{13}C spectra. Sanyo microwave oven (2450 MHz and 1350 watts) was employed for the preparation of **3a-f**. Dr. Luzia E. Narimatsu of the "Instituto de Química, Universidade de São Paulo, SP," performed the elemental analyses. Thin layer chromatography (TLC) was carried out on silica gel coated plates

with fluorescent indicator (PF_{254}) and eluted with chloroform unless otherwise stated.

*Reaction of Arylamidoximes **1a-f** with Succinic Anhydride*[4]

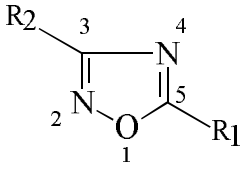
General procedure A

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 ($CHCl_3$, R_f values in pa-

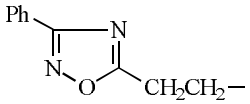
Table 6. Dipole moments and HOMO energies for the calculated compounds

Molecule	μ (D)	ε_{HOMO} (eV)
3a	1.6453	-7.3318
6a	1.8771	-7.3210
5a	1.7362	-7.1084
4a	0.0017	-7.3833

Table 5. Atomic charges on the oxadiazole ring, bond distances and angles of compounds **3a**, **6a**, **5a** and **4a** obtained from the sto-3g calculations.



3a: $R_2 = Ph$; $R_1 = CH_2CH_2CO_2H$
6a: $R_2 = Ph$; $R_1 = CH_2CH_2CO_2CH_3$
5a: $R_1 = R_2 = Ph$
4a: $R_2 = Ph$; $R_1 =$



Molecule	Atomic Charges				
	O_1	N_2	C_3	N_4	C_5
3a	-0.142152	-0.127994	0.146668	-0.283339	0.231073
6a	-0.142247	-0.128213	0.146548	-0.283413	0.231096
5a	-0.142979	-0.128931	0.146663	-0.280646	0.226245
4a	-0.141209	-0.126912	0.147286	-0.283669	0.230706
	Bond Distances (Å)				
	O_1-N_2	N_2-C_3	C_3-N_4	N_4-C_5	C_5-O_1
Experimental [a]	1.410	1.300	1.358	1.306	1.374
3a	1.392	1.321	1.424	1.306	1.374
6a	1.392	1.321	1.424	1.306	1.374
5a	1.390	1.322	1.420	1.312	1.375
4a	1.392	1.321	1.425	1.306	1.374
	Bond Angles (degrees)				
	O_1-N_2-C_3	N_2-C_3-N_4	C_3-N_4-C_5	N_4-C_5-O_1	C_5-O_1-N_2
Experimental [a]	103.1	115.0	103.8	111.4	106.7
3a	104.75	113.35	101.88	113.39	106.63
6a	104.75	113.34	101.89	113.38	106.63
5a	104.72	113.50	101.92	113.10	106.75
4a	104.78	113.33	101.86	113.45	106.57

[a] The values were obtained from the x-ray data of the compound 2-(3-*p*-chlorophenyl[1,2,4]-oxadiazol-5-yl)-3,4-dihydro-1-naphthylaminoformaldehyde oxime[22].

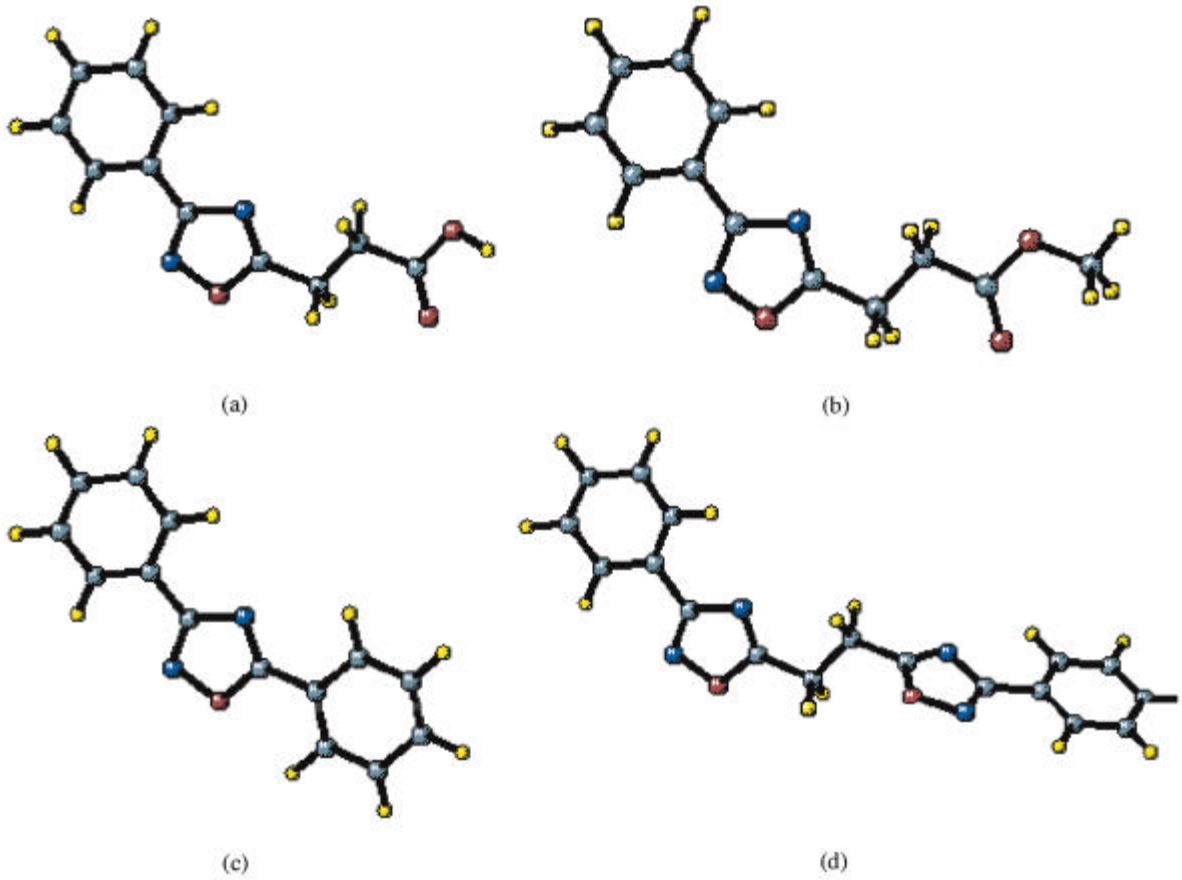


Figure 1. Conformations obtained from sto-3g calculations for: (a) 3-[3-(phenyl)-1,2,4-oxadiazol-5-yl] propionic acid - **3a**; (b) methyl 3-[3-(phenyl)-1,2,4-oxadiazol-5-yl] propionate - **6a**; (c) 3,5-bisphenil-1,2,4-oxadiazole - **5a**; (d) 5,5'-(1,2-ethanediyl)-bisphenyl-1,2,4-oxadiazole - **4a**.

rentheses): **5** (0.8), **4**, (0.5), **1** (0.3), and **3** (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 **4**. Elution of **3** 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 product is presumably the impure succinic acid. The details are given below:

3,5-Bisaryl-1,2,4-oxadiazoles (**5a-f**, $R_f \approx 0.8$). Compounds **5a-d**, **f** were identical with those prepared earlier.[12,13] Their yields are given in parentheses: **5a** (6.1%), **5b** (1.4%), **5c** (11,2%), **5d** (2.9%), and **5f** (9.9%). The new product **5e** melted at 179-8 °C, after recrystallization from ethanol-water, yield (11,5%). Its NMR data and elemental analysis are given below:

^{1}H-NMR ($CDCl_3$-DMSO-d_6, 9.9/0.1): $\delta = 7.55$ (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.

$C_{14}H_8Cl_2N_20$	Calc.	C 57.74	H 2.77	N 9.62
(291.10)	Found	57.45	2.62	9.32

Compounds with R_f value ≈ 0,5. The TLC, mixture melting points and the NMR spectra of these products agreed with **4a-f**, isolated earlier or prepared independently. The yields are given in parentheses: **4a** (8.9%), **4b** (12%), **4c** (11.6%), **4d** (4.4%), **4e** (8.8%), **4f** (10.5%).

3-[3-(Aryl)-1,2,4-oxadiazol-5-yl] propionic acids (**3a-f**). The melting points as well as the yields of compounds **3a-f** are compiled in Table 1.

General procedure B

The appropriate arylamidoxime **1** (3.67 mmol) and succinic anhydride **2** (3.67 mmol) in dioxane (10 mL) were refluxed for 4 h under nitrogen atmosphere. TLC of the reaction mixture had the same R_f values as described above. Solvent removal followed by liquid chromatography over silica gel, using solvents as described in procedure A, afforded the desired products. The yields of **3a-f** are summarised in Table 1.

General procedure C

Arylamidoxime (3.7 mmol) and succinic anhydride (4.06 mmol) were intimately mixed, and heated initially in a microwave oven at 80% power for 5 min, and after a few minutes the same mixture was heated for an additional

5 min. TLC showed similar results as observed in procedures A or B. Compound **1b** reacted poorly under these conditions. Therefore, this product was heated at maximum power for 10 min without interruption. The products were cromatographed by silica gel chromatography. The yields are given in Table 1.

Synthesis of 5,5'-(1,2-Ethanediyl)-bis[3-(aryl)-1,2,4-oxadiazoles] (**4a-f**) *from* (**3a-f**) *and* (**1a-f**). The appropriate 3-[3-(aryl)-1,2,4-oxadiazol-5-yl] propionic acid, **3a-f** (1.92 mmol), dicyclohexylcarbodiimide (1.92 mmol) and the appropriate benzamidoxime **1a-f** (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 ($CHCl_3$-Et0Ac, 1/1) showed four spots in each case. The R_f values of the reaction products of **3a** and **1a** were: 0.88 (DCC), 0.77 (**4a**), 0.47 (**1a**, trace), and 0.02 (dicyclohexylurea) respectively. The reaction of **1b-f** and **3b-f** gave similar TLC results, *i.e.* four spots in each case. Solvent evaporation afforded a solid mass, which was separated using a silica gel packed column. The details are given below:

5,5'-(1,2-Ethanediyl)-bis[3-(phenyl)-1,2,4-oxadiazole] (**4a**). After chromatography, the pure material weighed 0.49 g (81%). Recrystallization from ethanol-water gave a product, mp 163 °C (lit.[7], 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-tolyl)-1,2,4-oxadiazole] (**4b**). Column chromatography afforded 0.53 g (80%) of **4b**. Crystallisation 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-tolyl)-1,2,4-oxadiazol e] (**4c**). Recrystallization from ethanol gave 0.45 g of **4c** (69%) m.p. 111-112°. ^{1}H-NMR ($CDCl_3$): δ = 2.4 (s, 6H, $2CH_3$), 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'-(1,4-Ethanediyl)-bis[3-(p-tolyl)-1,2,4-oxadiazole] (**4d**). After chromatographic separation, the compound was recrystallised from ethanol to give 0.51 g (77%) of **4d**, 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)-l,2,4-oxadiazole] (**4e**). Usual chromatography and work-up followed by crystallisation from ethyl acetate furnished 0.43 g (58%) of **4e**, 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_3-DMSO-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 (**4f**). This product 0.59 g (69%) was obtained as colourless crystals. A similar solubility problem, as observed for **4e**, was encountered. Because of this, the ^{1}H-NMR spectrum was not obtained. Crystallisation 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

Methyl 3-[3-(Aryl)-1,2,4-oxadiazol-5-yl] propionates. (**6a-g**). To the appropriate acid **3a-g** in ether, a freshly prepared ethereal solution of diazomethane[23] was added dropwise until the nitrogen evolution ceased and the yellow colour of diazomethane persisted. Solvent removal, after half hour of standing at room temperature, provided an almost quantitative yield of **6a-g**. The details of the individual compounds are given below:

Methyl 3-[3-(phenyl)-1,2,4-oxadiazol-5-yl] propionate (**6a**). Recrystallisation from ethanol-water afforded colourless crystals, m.p. 49 °C.

$C_{12}H_{12}N_2O_3$	Calc.	C 62.06	H 5.21	N 12.06
(232.09)	Found	62.41	5.35	12.17

Methyl 3-[3-(o-tolyl)-1,2,4-oxadiazol-5-yl] propionate (**6b**). The ester obtained was yellow in colour. Liquid chromatography over a short silica gel column removed the coloured impurities. This compound could not be crystallised, but the colourless oil analysed correctly for **6b**.

$C_{13}H_{14}N_2O_3$	Calc.	C 63.41	H 5.73	N 11.37
(246.24)	Found	63.46	6.14	11.19

Methyl 3-[3-(m-tolyl)-1,2,4-oxadiazol-5-yl] propionate (**6c**). The liquid obtained was purified as described for **6b**. The spectral results agreed with the structure of **6c**.

$C_{13}H_{14}N_2O_3$	Calc.	C 63.41	H 5.73	N 11.37
(246.24)	Found	63.43	5.88	11.73

Methyl 3-[3-p-tolyl)-1,2,4-oxadiazol-5-yl] propionate (**6d**). Crystallisation and recrystallization of the product from ethanol-water gave colourless crystals m.p. 63-64 °C.

$C_{13}H_{14}N_20_3$	Calc.	C 63.41	H 5.73	N 11.37
(246.24)	Found	63.88	5.92	11.17

Methyl 3-[3-(p-chlorophenyl)-1,2,4-oxadiazol-5-yl] propionate (**6e**). Crystallisation from ethanol afforded a colourless solid, m.p. 92 °C. The spectroscopic data confirmed the structure as **6e**.

$C_{12}H_{11}N_20_3Cl$	Calc.	C 54.07	H 4.16	N 10.63
(266.66)	Found	53.92	4.01	10.63

Methyl 3-[3-(p-bromophenyl)-1,2,4-oxadiazol-5-yl] propionate (**6f**). The compound after recrystallization from ethanol-water melted at 100 °C.

$C_{12}H_{11}N_20_3Br$	Calc.	C 46.31	H 3.57	N 9.00	Br 25.71
(311.21)	Found	46.48	3.89	8.74	25.62

Methyl 3-[3-(p-anisyl)-1,2,4-oxadiazol-5-yl] propionate (**6g**). This compound was also crystallised from ethanol-water, and melted at 59.5 °C.

$C_{13}H_{14}N_20_4$	Calc.	C 59.53	H 5.38	N 10.67
(262.24)	Found	59.36	5.30	10.43

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