

# Methyl 3-[3-(Aryl)-1,2,4-Oxadiazol-5-Yl]Propionates.

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Descreve-se a preparação de sete 3-[3-(aril)-1, 2, 4-oxadiazol-5-il] propionatos de metila, 2a-g, e suas propriedades espectroscópicas (IV, UV,  $^1\text{H}$  e  $^{13}\text{C}$ NMR).

Preparation of seven methyl 3-[3-(aryl)-1,2,4-oxadiazol-5-yl] propionates, 2a-g, and their spectroscopic properties (IR, UV,  $^1\text{H}$  and  $^{13}\text{C}$  NMR) are described.

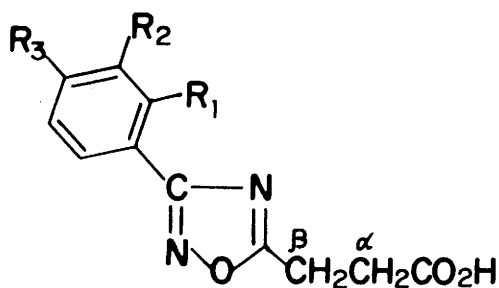
**Key words:** propionic acids; oxadiazol.

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## Introduction

Although 3-[3-(aryl)-1,2,4-oxadiazol-5-yl] propionic acids, 1a-g, have been synthesized<sup>1-3</sup>, only one ester (ethyl ester) of 1a is known<sup>1</sup>. For transforming the carboxylic acid moiety of 1a-g to other functional groups, we needed their esters. This paper, therefore, reports the preparation and spectroscopic studies of methyl 3-[3-(aryl)-1,2,4-oxadiazol-5-yl] propionates, 2a-g (Scheme). All seven esters are new.

## Scheme



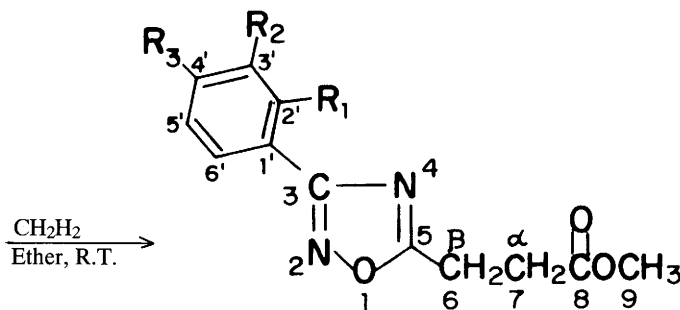
1a - g

- a:  $\text{R}_1 = \text{R}_2 = \text{R}_3 = \text{H}$
- b:  $\text{R}_1 = \text{CH}_3$ ;  $\text{R}_2 = \text{R}_3 = \text{H}$
- c:  $\text{R}_1 = \text{R}_3 = \text{H}$ ;  $\text{R}_2 = \text{CH}_3$
- d:  $\text{R}_1 = \text{R}_2 = \text{H}$ ;  $\text{R}_3 = \text{CH}_3$

## Results and Discussion

Addition of diazomethane to an ethereal solution of acids, 1a-g, afforded methyl 3-[3-(aryl)-1,2,4-oxadiazol-5-yl]propionates, 2a-g, in almost quantitative yield.

The IR spectra of 2a-g showed a strong absorption around 1735  $\text{cm}^{-1}$  for the ester carbonyl function. The other absorptions were similar to those of 1,2,4-oxadiazole ring reported earlier<sup>4,5</sup>. The UV spectra had the absorptions characteristic of



2a - g

- e:  $\text{R}_1 = \text{R}_2 = \text{H}$ ;  $\text{R}_3 = \text{OCH}_3$
- f:  $\text{R}_1 = \text{R}_2 = \text{H}$ ;  $\text{R}_3 = \text{Cl}$
- g:  $\text{R}_1 = \text{R}_2 = \text{H}$ ;  $\text{R}_3 = \text{Br}$

1,2,4-oxadiazoles<sup>4,6</sup>. Table 1 lists the UV spectra of compounds **2a-g**.

**Table 1.** The spectra were obtained in 95% ethanol.

Compound	max (NM)	S	Compound	max (nm)	S
<b>2a</b>	286	634.3	<b>2e</b>	293	2,124.7
	274	740.0		262	18,413.6
	240	10,993.7		<b>2f</b>	290
<b>2b</b>	283	1,087.4	276		1,111.0
	241	9,381.7	<b>2g</b>	249	18,271.6
<b>2c</b>	289	1,194.0		290	593.5
	284	1,368.2		281	1,038.6
	245	10,945.3		253	18,694.4
<b>2d</b>	288	592.4			
	276	1,066.3			
	249	14,761.9			

The 90 MHz <sup>1</sup>H-NMR spectrum of **2a** showed a multiplet between δ 2.70-3.43 for the methylene protons (2CH<sub>2</sub>), but the 200MHz spectrum produced two well defined triplets at δ 2.94 and 3.25; the J values in both cases were ~ 7.0 Hz. The former and the latter are assigned as a and b methylene protons respectively. This assumption is based on our work for 3-[3-(phenyl)-1,2,4-oxadiazol-5-yl]propionic acid<sup>3</sup>. The other products, **2b-g**, showed similar triplets having almost the same chemical shifts (Table 2).

90 MHz, Solvent: CDCl<sub>3</sub>. The values of a- & b-CH protons are from 200MHz NMR spectra. The J values are ~ 7.0 Hz. Narrow multiplet. AA'BB' system (J ~ 8.0 Hz). ArOCH protons appeared at δ 3.83 ppm as a singlet. AA'BB' system (J ~ 9.0 Hz).

**Table 3.** Chemical shift assignments of compounds **2a-g**.\*

Com- pounds	Carbons						Ar-CH <sub>3</sub>						
	2	5	6	7	8	9							
<b>2a</b>	168.23	176.19	30.27	22.02	171.64	52.01	126.71	127.35	128.73	131.06	128.73	127.35	
<b>2b</b> calcd. <sup>+</sup>	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
							127.41	136.25	129.43	130.96	125.83	127.25	
<b>2c</b> calcd. <sup>+</sup>	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
							126.61	128.05	137.63	131.76	128.63	124.45	
<b>2d</b> calcd. <sup>+</sup>	168.26	178.02	30.28	22.02	171.69	51.99	123.70	127.29	129.46	141.30	129.46	127.29	21.47
							123.81	127.25	129.43	139.96	129.43	127.25	
<b>2e</b> <sup>**</sup> calcd. <sup>+</sup>	168.25	177.68	30.30	21.99	171.68	52.00	119.17	128.94	114.15	161.64	114.15	128.94	-
							119.01	128.35	114.33	162.46	114.33	128.35	
<b>2f</b> calcd. <sup>+</sup>	167.50	178.50	30.23	22.02	171.64	52.08	125.26	128.71	129.12	137.27	129.12	128.71	-
							124.81	128.65	129.13	137.26	129.13	128.65	
<b>2g</b> calcd. <sup>+</sup>	167.59	178.53	30.24	22.02	171.64	52.08	125.69	128.80	132.09	125.69	132.09	128.90	-
							125.11	129.05	132.13	125.56	132.13	129.05	

\* Spectra obtained in CDCl<sub>3</sub>

\*\* Methoxy carbon absorption appeared at δ 55.29 ppm.

<sup>+</sup> Calculated by adding the known values of the substituents (Ref. 8, p.111) to phenyl carbons of **2a**.

**Table 2.** Chemical shifts (in ppm) of protons of oxadiazoles **2a-g**<sup>a</sup>.

Com- pound	Ar	α-CH <sub>2</sub> t	βCH <sub>2</sub> t	Ar-CH <sub>3</sub> s	-COCH <sub>3</sub> O s
<b>2a</b>	7.27-7.60 m (3H)	2.94	3.25		7.67
	7.80-8.20 m (2H)				
<b>2b</b>	7.03-7.37 m (2H)	2.94	3.27	2.55	3.63
	7.70-8.03 m <sup>b</sup> (2H)				
<b>2c</b>	7.05-7.38 m <sup>b</sup> (2H)	2.94	3.25	2.37	3.67
	7.55-7.91 m <sup>b</sup> (2H)				
<b>2d</b>	[7.20d (2H); 7.88d (2H)] <sup>c</sup>	2.93	3.25	2.37	3.68
<b>2e</b> <sup>d</sup>	[7.20d (2H); 8.05 (2H)] <sup>c</sup>	2.93	3.24	-	3.70
<b>2f</b>	[7.37d (2H); 7.83d (2H)] <sup>c</sup>	2.94	3.25	-	3.68
<b>2g</b>	[7.59d (2H); 7.90 (2H)] <sup>c</sup>	2.94	3.26	-	3.70

<sup>a</sup> 90 MHz, Solvent: CDCl<sub>3</sub>. The values of α- & b-CH<sub>2</sub> protons are from 200 MHz NMR spectra. The J values are ~ 7.0 Hz.

<sup>b</sup> Narrow multiplet.

<sup>c</sup> AA'BB' system (J ~ 8.0 Hz)

<sup>d</sup> Ar OCH<sub>3</sub> protons appeared at δ 3.83 ppm as a singlet.

<sup>e</sup> AA'BB' system (J ~ 9.0 Hz).

#### 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<sup>7</sup>. This paper describes the study of methyl, methoxy, chloro and bromo substituents' effects on the phenyl ring of 3-[3-(phenyl)-1,2,4-oxadiazol-5-yl]propionates, **2a-g**. The C substituent effects of monosubstituted benzenes were obtained from the published data<sup>8</sup>, and the values added to the phenyl carbons of **2a**. The additivity holds good for all compounds except in the case of **2b** especially for 2' and 6' carbons. This kind of discrepancy has been observed earlier<sup>7</sup> (Table 3). In-

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 a and b methylene protons at  $\delta$  2.94 and 3.25 respectively. Selective irradiation of the triplet at  $\delta$  3.27 ppm of **2b** changed the methylene carbon as a singlet at 30.31 ppm confirming it as C-6. Similarly, irradiation of the triplet at  $\delta$  2.94 produced a singlet at 21.95 ppm indicating clearly that is due to C-7. In the normal spectrum of **2b**, it was difficult to locate the C-1'. However, on the heteronuclear decoupled spectrum, C-1' gave a weak signal which appeared well in the quaternary carbons only spectrum. Thus it is clear that C-1' and C-5' overlap in the normal spectrum. There seems no effect at C-3 of the 1,2,4-oxadiazole ring when the substituent changes from phenyl to m-, p-tolyl or p-anisyl group. However, a small downfield shift ( $\sim +0.65$  ppm) is observed when the substituent at C-3 is a o-tolyl group. Chlorophenyl or p-bromophenyl substituent at C-3 produced a little upfield 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 **2b**. Table 3 lists the C data of compounds **2a-g**.

### Experimental

All melting points are uncorrected. IR spectra were recorded with a Perkin-Elmer Model 237B grating instrument and UV spectra with a Beckman Model DB spectrophotometer. H-NMR spectra were determined with a EM-390 90 MHz instrument using TMS as internal reference. C-NMR spectra were recorded on a Bruker AC 200 spectrometer. A solution  $\sim 0.3M$  of compounds **2a-g** in  $CDCl_3$  was used in 5mm sample tubes with TMS as an internal standard for measuring the C spectra.

*Methyl 3-[3-(Aryl)-1,2,4-oxadiazol-5-yl] propionate (2a-g):* 3-[3-(Aryl)1,2,4-oxadiazol-5-yl] propionic acids (1a-g) were synthesized by the method [9] developed in our laboratory. To the appropriate acid in ether, a freshly prepared [10] ethereal solution of diazomethane was added dropwise until the nitrogen evolution ceased, and the yellow color of diazomethane persisted. Solvent removal, after 1/2 h of standing at room temperature, provided almost a quantitative yield of **2a-g**. The details of the individual compound are given below.

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

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

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

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

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

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

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

$C_{13}H_{14}N_2O_3$  Calcd. C 63.41; H 5.73; N 11.37  
(246.24) Found C 63.88; H 5.92; N 11.17

*Methyl 3-[3-(p-anisyl)-1,2,4-oxadiazol-5-yl] propionate (2e):* this compound was also crystallized from ethanol-water, and melted at 59.5°C.

$C_{13}H_{14}N_2O_4$  Calcd. C 59.53; H 5.38; N 10.67  
(262.24) Found C 59.36; H 5.30; N 10.43

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

$C_{12}H_{11}N_2O_3Cl$  Calcd. C 54.07; H 4.16; N 10.63  
(266.66) Found C 53.92; H 4.01; N 10.63

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

$C_{12}H_{11}N_2O_3Br$  Calcd. C 46.31; H 3.57; N 9.00 Br 25.71  
(311.21) Found C 46.48; H 3.89; N 8.74 Br 25.62

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