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SYNTHESIS OF DERIVATIVES OF 1,3,4-OXADIAZOLES BASED ON MONOHYDRAZIDES OF 2-ARYL-4-METHYL-4-CYCLOHEXEN-1,2-DICARBOXYLIC ACIDS

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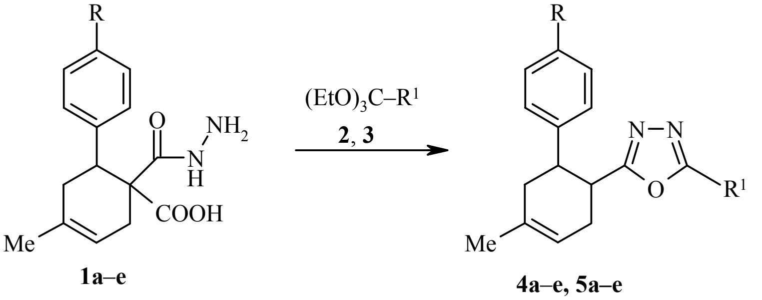
The corresponding derivatives of 1,3,4-oxadiazoles have been synthesized by the reaction of monohydrazides of 2-aryl-4-methyl-4-cyclohexen-1,1-dicarboxylic acids with triethyl orthoformate or triethyl orthoacetate.

Keywords: 2-(2-aryl)-4-methycyclohexen-4-yl)-[1,3,4]oxadiazoles, 1,3,4-oxadiazoles, monohydrazides of 2-aryl-4-methyl-4-cyclohexen-1,1-dicarboxylic acids, triethyl orthoformate, triethyl orthoacetate.

Some derivatives of 1,3,4-oxadiazoles possess anti-inflammatory, analgesic, antiviral, and antibacterial activity [1-3]. These compounds are also used in the dyestuffs industry [4], in thermostable polymeric materials [5], and in scintillation techniques [6].

Information on methods of synthesis of compounds containing the 1,3,4-oxadiazole ring and on starting materials for their synthesis is very limited in the literature [7]. Therefore we have studied more deeply the possibility of synthesizing derivatives of 1,3,4-oxadiazole from monohydrazides of 2-aryl-4-methyl-4-cyclohexen-1,1-dicarboxylic acid **1a-e** which we synthesized previously [8].

One of the methods to prepare 1,3,4-oxadiazoles is the interaction of hydrazides of carboxylic acids with an excess of triethyl orthoformate (**2**) [9, 10]. The preparation of 2-aryl-substituted 1,3,4-oxadiazoles by boiling the corresponding hydrazides for 15-20 h with ester **2** [11].



1, **4**, **5** **a** R = H; **b** R = F; **c** R = Cl; **d** R = Br; **e** R = NO_2; **2**, **4** R^1 = H; **3**, **5** R^1 = Me

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TABLE 1. Characteristics of Compounds **4a-e** and **5a-e**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	N	Hal		
4a	$C_{15}H_{16}N_2O$	75.04 74.97	6.90 6.71	11.73 11.66		93-95	66
4b	$C_{15}H_{15}FN_2O$	69.61 69.75	5.93 5.85	10.72 10.85		95-97	73
4c	$C_{15}H_{15}ClN_2O$	65.69 65.57	5.61 5.50	10.31 10.20	13.01 12.90	92-94	74
4d	$C_{15}H_{15}BrN_2O$	56.62 56.44	4.61 4.74	8.65 8.78	25.16 25.03	69-72	67
4e	$C_{15}H_{15}N_3O_3$	63.38 63.15	4.27 5.30	14.68 14.73		97-99	64
5a	$C_{16}H_{18}N_2O$	75.48 75.56	7.20 7.13	10.97 11.01		61-62	70
5b	$C_{16}H_{17}FN_2O$	70.42 70.57	6.38 6.29	10.34 10.29		44-46	53
5c	$C_{16}H_{17}ClN_2O$	66.69 66.55	6.01 5.93	9.80 9.70	12.36 12.28	94-95	60
5d	$C_{16}H_{17}BrN_2O$	57.58 57.67	5.06 5.14	8.48 8.41	24.02 23.98	71-73	56
5e	$C_{16}H_{17}N_3O_3$	64.31 64.20	5.81 5.72	9.28 9.36		107-109	52

We have found that monohydrazides of aryl-substituted cyclohexendicarboxylic acids **1a-e** react with triethyl orthoformate **2** considerably faster. The corresponding 1,3,4-oxadiazoles **4a-e** were isolated from the reaction mixture after boiling the components for 3 h.

Under analogous conditions we also obtained derivatives of 5-methyl-substituted 1,3,4-oxadiazoles **5a-e**, the formation of which occurred still more rapidly on boiling the hydrazide starting materials **1a-e** with triethyl orthoacetate (**3**) for 1 h.

TABLE 2. ^{1}H NMR Spectra of Compounds **4a-e** and **5a-e**

Compound	Chemical shifts, δ, ppm. (*J*, Hz)
4a	1.73 (3H, s, CH_3); 2.45 (4H, m, $2CH_2$); 3.51 (2H, m, 2CH); 5.48 (1H, m, =CH); 6.78-7.24 (5H, m, C_6H_5); 8.18 (1H, s, N=CH)
4b	1.74 (3H, s, CH_3); 2.42 (4H, m, $2CH_2$); 3.45 (2H, m, 2CH); 5.43 (1H, m, =CH); 6.73 (4H, m, C_6H_4); 8.05 (1H, s, N=CH)
4c	1.75 (3H, s, CH_3); 2.42 (4H, m, $2CH_2$); 3.53 (2H, m, 2CH); 5.55 (1H, m, =CH); 6.93 (2H, m, ^3J = 8, C_6H_4); 7.22 (2H, m, ^3J = 8, C_6H_4); 8.26 (1H, s, N=CH)
4d	1.74 (3H, s, CH_3); 2.42 (4H, m, $2CH_2$); 3.43 (2H, m, 2CH); 5.37 (1H, m, =CH); 6.67 (2H, m, ^3J = 8, C_6H_4); 7.26 (2H, m, ^3J = 8, C_6H_4); 8.05 (1H, s, N=CH)
4e	1.77 (3H, s, CH_3); 2.48 (4H, m, $2CH_2$); 3.57 (2H, m, 2CH); 5.61 (1H, m, =CH); 7.22 (2H, m, ^3J = 9, C_6H_4); 8.01 (2H, m, ^3J = 9, C_6H_4); 8.26 (1H, s, N=CH)
5a	1.71 (3H, s, CH_3); 2.29 (3H, s, CH_3); 2.44 (4H, m, $2CH_2$); 3.42 (2H, m, 2CH); 5.48 (1H, m, =CH); 6.89-7.29 (5H, m, C_6H_5)
5b	1.68 (3H, s, CH_3); 2.33 (3H, s, CH_3); 2.38 (4H, m, $2CH_2$); 3.42 (2H, m, 2CH); 5.49 (1H, m, =CH); 6.91 (4H, m, C_6H_4)
5c	1.71 (3H, s, CH_3); 2.32 (4H, m, $2CH_2$); 2.36 (3H, s, CH_3); 3.44 (2H, m, 2CH); 5.48 (1H, m, =CH); 6.91 (2H, m, ^3J = 8, C_6H_4); 7.11 (2H, m, ^3J = 8, C_6H_4)
5d	1.73 (3H, s, CH_3); 2.33 (3H, s, CH_3); 2.38 (4H, m, $2CH_2$); 3.42 (2H, m, 2CH); 5.49 (1H, m, =CH); 6.84 (2H, m, ^3J = 8, C_6H_4); 7.29 (2H, m, ^3J = 8, C_6H_4)
5e	1.75 (3H, s, CH_3); 2.31 (3H, s, CH_3); 2.48 (4H, m, $2CH_2$); 3.31 (2H, m, 2CH); 5.55 (1H, m, =CH); 7.20 (2H, m, ^3J = 9, C_6H_4); 8.10 (2H, m, ^3J = 9, C_6H_4)

The synthesized 2-hexenyl derivatives of 1,3,4-oxadiazole are colorless crystalline substances with comparatively low melting points.

The structures and composition of the compounds obtained were confirmed ^{1}H NMR data and elemental analyses.

EXPERIMENTAL

^{1}H NMR spectra of $CDCl_3$ solutions with HMDS internal standard (δ 0.055) were recorded on a Bruker WH 90/DS (90 MHz) spectrometer. The purity of the compounds synthesized was confirmed by TLC on Silufol strips with solvent systems ethyl acetate–benzene (1:2) for **4a,e** and **5a**, chloroform–methanol (9:1) for **4c,d** and **5d,e**, and chloroform–methanol–acetic acid (95:5:3) for **4b** and **5b,c.**

Characteristics of the compounds synthesized are given in Tables 1 and 2.

2-[4-Methyl-2-(4-R-phenyl)-4-cyclohexen-1-yl][1,3,4-]oxadiazoles 4a-e. Hydrazides **1a-e** (1 mmol) and triethyl orthoformate (2 ml) were refluxed for 3 h. The excess ester **2** was evaporated, the residue was cooled and triturated with hexane (**4a-d**) or methanol (**4e**). The solid was filtered off and recrystallized from 1:1 methanol–water (**4a,c,e**) or 1:1 ethanol–water (**4b,d**).

2-[4-Methyl-2-(4-R-phenyl)-4-cyclohexen-1-yl]-5-methyl[1,3,4-]oxadiazoles 5a-e. Hydrazides **1a-e** (1 mmol) and triethyl orthoacetate (2 ml) were refluxed for 1 h. The excess ester **2** was evaporated, the residue was cooled and triturated with hexane (**5a,c**), petroleum ether (**5d),** or methanol (**5e**). The solid was filtered off and recrystallized from 1:1 methanol–water. Compound **5b** was isolated by addition of water to the residue after evaporation of the excess ester **3**, extraction with ethyl acetate, drying of the extract with anhydrous magnesium sulfate and evaporation of the solvent.

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