MICROWAVE IRRADIATION PROMOTED REACTIONS OF ORTHOESTERS WITH CARBOXYLIC ACID HYDRAZIDES. PREPARATION OF 1,3,4-OXADIAZOLES☆

Khajavi, Mohammad Sadegh; Sadat Hosseini, Seyed Saheb and Sefidkon, Fatemeh*
Department of Chemistry, Faculty of Science, Shahid Beheshti University, Tehran, I.R. Iran.

ABSTRACT: *Rapid and highly efficient synthesis of 2- or 2,5-substituted 1,3,4-oxadiazoles by the condensation of aryl carboxylic acid hydrazides and orthoesters can be achieved under microwave irradiation using an unmodified commercial oven in unsealed vessels.*

KEY WORDS: *Microwave irradiation, Orthoesters, Acid hydrazides, 1,3,4-Oxadiazoles.*

INTRODUCTION

The potential of microwave assisted organic reactions has been extensively studied and exploited as an expeditious technique in organic synthesis [1-6]. We have recently described an efficient and rapid synthesis of a variety of heterocyclic compounds under microwave irradiation in an unmodified commercial microwave oven [7-9]. We wish to report now the utility of microwave irradiation by the synthesis of a number of various substituted 1,3,4-oxadiazoles from aryl carboxylic acid hydrazides and orthoesters.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on either a Bruker AC 80 or JEOL EX-90 instrument. IR spectra were recorded as KBr pellets on a Shimadzu IR-470 spectrophotometer. Microwave irradiations were carried out in a National oven, Model 5250 at 2450 MHz. Orthoesters **2a-c** and **3a-c**, N,N-dimethylacetamide dimethyl acetal and 2-furoic-hydrazide were purchased from *Fluka* and used without further purification. Compounds **1a-d** [10] and the authentic samples of products [11] were prepared according to reported procedures. The products were identified by their spectroscopic properties and by comparison with authentic samples.

Caution! All domestic microwave ovens are equipped with fans which can efficiently remove vapors from the microwave cavity. For safety all the experiments should be performed in an efficient hood in order to avoid the contact of vapors.

☆ *Dedicated to Professor Abbas Shafiee on the occasion of his 60th birthday.*

* *To whom correspondence should be addressed*

1021-9986/97/2/68 4/$/2.40

Preparation of 2-substituted and 2,5-disubstituted-1,3,4-oxadiazoles

Method A

For low boiling orthoesters **2a-b** , **3a** , **3c** and **7** is illustrated with 2-(*p*-chlorophenyl)-1,3,4- oxadiazole (**4a**). To a mixture of 4-chlorobenzoic acid hydrazide (3.42 g, 20 mmol) and trimethyl orthoformate (5.3 g, 50 mmol) contained in a tall beaker (100 mL), a catalytic amount of *p*-toluenesulfonic acid monohydrate (0.02 g) was added. The beaker was covered with a stemless funnel and placed in the microwave oven and subjected to irradiation at 210 Watts for 4 minutes. After 5 minutes, as it was cooled to room temperature, trimethyl orthoformate (3.18 g, 30 mmol) was added and this mixture was irradiated again for 6 minutes at 490 Watts. The resulting reaction mixture was allowed to cool to room temperature and the excess trimethyl orthoformate was removed under reduced pressure. The crude product recrystallized from ethanol to give colourless needless of the pure product (**4a**) in 97% yield. mp 133-134 °C (lit [11], 134-135 °C); IR(KBr), 1598, 1571, 1475, 1056, 727, 690 cm^{-1}. ^1H NMR($CDCl_3$), δ , 7.15 (d, 2H, Ar-H), 7.95(d, 2H, Ar-H), 8.43(S, 1H, C_5 -H).

Method B

For high boiling orthoesters **2c** and **3b** is illustrated with 2,5-diphenyl-1,3,4-oxadiazole (**4f**). A mixture of benzoic hydrazide (2.72 g, 20 mmol), triethyl orthobenzoate (8.96 g, 40 mmol) and TSOH (0.02 g) was irradiated first for 5 minutes at 385 Watts and then for another 5 minutes at 490 Watts. The reaction mixture was allowed to cool to room temperature and the excess orthobenzoate was removed. The resulting residue was recrystallized from ethanol to afford the pure product (**4f**) in 88% yield. mp 138-139 °C (lit [12], 138-139, lit [13], 139-140 °C); IR(KBr), 1544, 1478, 1343, 1068, 781, 709, 685 cm^{-1}. ^1H NMR($CDCl_3$), δ , 7.43-8.35(m, 10H, Ar-H).

Compounds **4d** and **4e** were identical with authentic samples prepared by the reported procedures [11], **4d**; IR(KBr), 3015, 2983, 1575, 1558, 1470, 1085, 710, 670 cm^{-1}. ^1H NMR($CDCl_3$), δ , 1.06(t, 3H, CH_3), 1.85 (sextet, 2H, CH_2), 2.83(t, 2H, CH_2), 7.42(d, 2H, Ar-H), 7.95(d, 2H, Ar-H). **4e**; IR(KBr), 3021, 2950, 1598, 1571, 1474, 1085, 730, 670 cm^{-1}; ^1H NMR ($CDCl_3$), δ , 0.98(t, 3H, CH_3), 1.18-1.95 (m, 4H, CH_2CH_2), 2.85(t, 2H, CH_2), 7.45(2H, d, Ar-H), 7.92 (2H, d, Ar-H).

RESULTS AND DISCUSSION

Many compounds containing 1,3,4-oxadiazole nucleus have been used as important substances in drugs or pesticides because of their broad spectrum of biological activities [14,15]. A number of synthetic methods for the preparation of 1,3,4-oxadizaole derivatives have been described: (i) dehydration of 1,2-diacylhydrazines [16-18]; (ii) electrochemical oxidation of aldehyde N-acylhydrazones [13]; (iii) oxidative cyclization of N-acylhydrazones by a number of oxidizing agents such as lead tetraacetate [19] or phenyliodine (III) diacetate [20]. *Ainsworth* [11] had discovered that the reaction of aryl carboxylic acid hydrazides with excess orthoesters at reflux over a period of 24 hours led to substituted 1,3,4-oxadiazoles in 63-92% yields.

Initial attempts on the preparation of 1,3,4-oxadiazole derivatives by Ainsworth method under microwave irradiation resulted in disappointing yields of desired products or in several cases the isolation of the intermediate. However, it was found that by addition of a catalytic amount of *p*-toluenesulfonic-acid (TSOH), the condensation of carboxylic acid hydrazides **1a-d** with orthoesters **2a-c** or **3a-c** results in the rapid formation of 1,3,4-oxadiazoles **4a-l** in high yields when the reactions were conducted in open vessels in a microwave oven. Thus treatment of 4-chlorobenzoic acid hydrazide (**1a**) with excess of trimethyl orthoformate (**2a**) in a beaker covered with a stemless funnel in presence of TSOH and irradiation for 10 minutes, after usual work-up gives 2-(*p*-chlorophenyl)-1,3,4-oxadiazole (**4a**) in 98% yield.

Table 1 shows the variety of aryl carboxylic acid hydrazides that readily reacted with orthoesters to give 2- or 2,5-substituted 1,3,4-oxadiazoles. In general, the reaction in the microwave oven was highly accelerated and in all cases provides products in high yields with simple work-up of the reaction mixtures.

This reaction proceeds without organic solvent (energy-transfer medium) and without some type of solid material as either a promoter or as a support.

Furthermore, not unexpectedly, changing the acid catalyst from TSOH to camphorsulfonic acid (CSA) or pyridinium *p*-toluenesulfonate (PPTS) had no effect on the irradiation time for complete reaction to occur.

In order to find the best reaction conditions, mixtures of acid hydrazides and orthoesters were irradiated for variable times, molar ratios of reactants and microwave power. The results are summarized in Table 1.

Interestingly, when the reaction of acid hydrazide **1a** with trimethyl orthoformate (**2a**) in presence of a

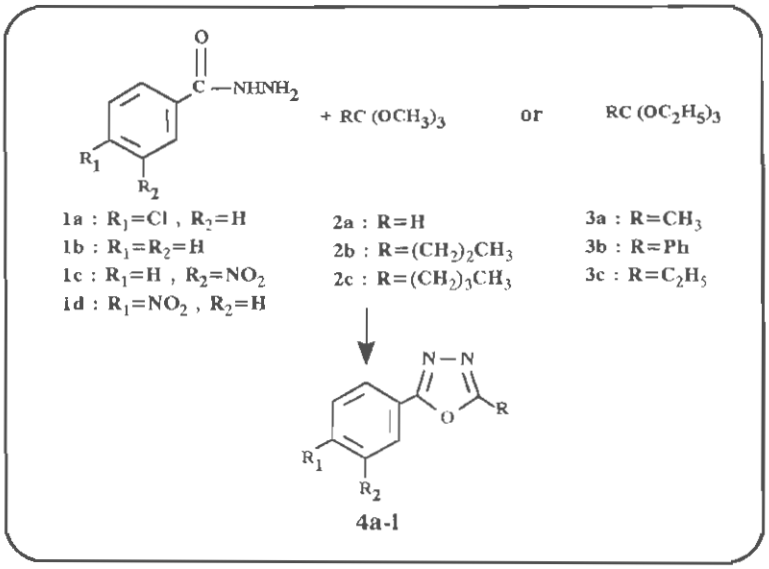


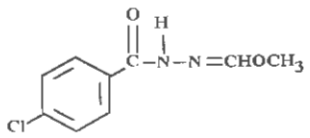
Table 1: Products of the reaction of aryl carboxylic acid hydrazides with orthoesters

Entry	Product	R_1	R_2	R	Orthoesters (equiv)	Irradiation conditions[a]				yield[b] (%)	mp (°C)	lit. mp (°C)
						(1)P/W	t/min	(2)P/W	t/min			
1	4a	Cl	H	H	4	210	4	490	6	97	133-134	134-135[11]
2	4b	Cl	H	Ph	2	385	5	490	5	98	157-158	156-157[21]
3	4c	Cl	H	C_2H_5	3	385	4	490	5	92	92-94	93-94[11]
4	4d	Cl	H	$(CH_2)_2CH_3$	3	385	4	490	5	94	76-78	–
5	4e	Cl	H	$(CH_2)_3CH_3$	3	385	4	490	5	83	69-71	–
6	4f	H	H	Ph	2	385	5	490	5	88	138-139	139-140[13] 138-139[12]
7	4g	H	H	H	4	210	3	490	6	85	34-36	34-35[11]
8	4h	H	H	CH_3	3	210	4	490	6	90	67-68	67-69[13]
9	4i	H	NO_2	Ph	2	385	5	490	5	96	149-151	147[22]
10	4j	NO_2	H	Ph	2	385	5	490	5	98	209-211	210-212[23]
11	4k	NO_2	H	H	4	210	4	490	5	94	156-157	156-157[11]
12	4l	NO_2	H	C_2H_5	3	385	3	490	6	96	132-134	133-134[11]
13	6	H	H	2-Furyl	2	210	4	490	3	78	103	103-103.5[16]

a : To control the reaction, the irradiation period was carried out in two stages, with a cooling time between each irradiation.

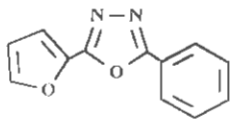
b : Yield of pure, isolated product based on acid hydrazide.

catalytic amount of TSOH was irradiated for 4 minutes at 210 Watts the intermediate (**5**) was formed in nearly quantitative yield. This was irradiated further (7 minutes at 490 Watts) to give oxadiazole **4a** .



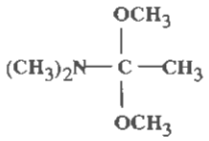
5

2-Furoic hydrazide and orthoester **3b** also gave a good yield of the desired oxadiazole **6** in nearly the same length of time (Table 1).



6

A good yield of oxadiazole (4 hours) from N,N-dimethylacetamide dimethylacetal (**7**) and hydrazide **1b** was achieved (3 minutes at 210 Watts and 5 minutes at 490 Watts) in 87% yield.



7

To summarize, for the synthesis of 1,3,4-oxadiazole derivatives from acid hydrazides and orthoesters microwave irradiation is an advantageous new procedure. The especial features of this new process are the high purity of products, high yields and simple work-up with reduced reaction time (10 minutes). In these reactions, orthoesters serve as a "one-atom linchpin" to form the corresponding oxadiazole. Further applications of these reagents will be reported in due course.

Received, 12th January 1997 ; Accepted, 3rd March 1997

REFERENCES

[1] Bose, A. K., Banik, B. K. and Manhas, M. S., *Tetrahedron Lett.,* **36,** 213(1995) and references cited therein.

[2] Oussaid, B., Moeini, L., Martin, B., Villemin, D. and Garrigues, B., *Synth. Commun.,* **25,** 1451 (1995).

[3] Alajarin, R., Jordan, P., Vaquero, J. J. and Alvarez-Builla, J., *Synthesis,* 389(1995).

[4] Abramovitch, R. A. and Bulman, A., *Synlett.,* 795(1992).

[5] Jones, G. B. and Chapman, B. J., *J. Org. Chem.,* **58,** 5558(1993).

[6] For the latest review of the microwave assisted organic reactions see *S. Caddick, Tetrahedron,***51,** 10403 (1995).

[7] Khajavi, M. S., Hajihadi, M. and Naderi, R., *J. Chem. Res.(S),* 92(1996).

[8] Khajavi, M. S., Hajihadi, M. and Nikpour, F., *J. Chem. Res.(S),* 94(1996).

[9] Khajavi, M. S., Nikpour, F. and Hajihadi, M., *J. Chem. Res.(S),* 96(1996).

[10] Rabini, T. and Vita, G., *J. Org. Chem.,* **30,** 2486(1965).

[11] Ainsworth, C., *J. Am. Chem. Soc.,* **77,** 1148(1955).

[12] Gillis, B. T. and La Montagne, M. P., *J. Org. Chem.,* **32,** 3318(1967).

[13] Chiba, T. and Okimoto, M., *J. Org. Chem.,* **57,** 1375(1992).

[14] Giri, S., Singh, H. and Yadav, L. D. S., *Agric. Biol. Chem.,* **40,** 17(1976).

[15] Hetzheim, A. and Mockel, K., *Adv. Heterocycl. Chem.,* 7, 183(1966).

[16] Hayes, F. N., Rogers, B. S. and Ott, D. G., *J. Am. Chem. Soc.,* **77,** 1850(1955).

[17] Perez, M. A. and Bermejo, J. M., *J. Org. Chem.,* **58,** 2628(1993).

[18] Goddard, C. J., *J. Heterocycl. Chem.,* **28,** 17(1991).

[19] Gladstone, W. A. F., Aylward, J. B. and Norman, R. O. C., *J. Chem. Soc. C,* 2587(1969).

[20] Yang, R. Y. and Dai, L. X., *J. Org. Chem.,* **58,** 3381(1993).

[21] Popp, F. D., *J. Chem. Soc.,* 3503(1964).

[22] Grekov, A P. and Azen, R. S., *Zh. Obshch. Khim.,* **31,** 1919(1961); CA, 55, 272791(1961).

[23] Walker, C. C. and Shechter, H., *J. Am. Chem. Soc.,* **90,** 5626(1968).