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AN EXPEDITIOUS, SOLVENT-FREE SYNTHESIS OF SOME 5-ARYL-2-(2-HYDROXY-PHENYL)-1,3,4-OXADIAZOLES

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An efficient, rapid, microwave-accelerated one-step synthesis of some 5-aryl-2-(2-hydroxy-phenyl)-1,3,4-oxadiazoles by reaction of salicylic hydrazide with carboxylic acids in the presence of thionyl chloride under neat conditions is described.

Keywords: 1,3,4-oxadiazoles, salicylic hydrazide, microwave acceleration.

The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic in nature. 1,3,4-Oxadiazoles are non-naturally occurring five-membered aromatic heterocycles with great utility in synthetic, medicinal, and material chemistry. The oxadiazole nucleus is present in antihypertensive dugs such as *tiodazosin* [1] and *nesapidil* [2] and antibiotics such as *furamizole* [3]. Biologically active molecules containing the oxadiazole motif include the HIV integrase inhibitor [4] and the angiogenesis inhibitor [5]. The widespread use of 1,3,4-oxadiazoles as a scaffold in medicinal chemistry is demonstrated by the following examples. 2-Amino-1,3,4-oxadiazoles exhibit muscle relaxant [6] and antimitotic activity [7] while 2,5-diaryl-1,3,4-oxadiazoles are platelet aggregation inhibitors [8]. 5-Aryl-2-hydroxymethyl-1,3,4-oxadiazoles display diuretic, analgesic, anti-inflammatory, anticonvulsive, and antiemetic properties [9], and 2-hydroxyphenyl-1,3,4-oxadiazoles act as hypnotics and sedatives [10]. Symmetrical 2,5-bis(2,4-dichlorophenyl)-1,3,4-oxadiazole and its analogues are effective insecticides toward houseflies, faceflies, and hornflies and are shown to inhibit chitin synthesis in *Drosophila* and in *Musca domestica*. 2-[2,2-Dimethyl-3-(2,2-dichlorovinyl)cyclopropyl]-5-substituted 1,3,4-oxadiazoles and 2-substituted-phenoxymethyl-5-substituted aryl-1,3,4-oxadiazoles showed good insecticidal activities against larvae of armyworm (*Pseudaletia separata* Walker) [11].

2,5-Disubstituted 1,3,4-oxadiazoles have also attracted significant interest due to their applications in organic light emitting diodes, photoluminescence, polymers, and material science [12-14].

In view of the great medicinal significance and material applications a number of synthetic routes have been developed for 1,3,4-oxadiazoles. The majority of them are based upon cyclodehydration of diacylhydrazines using different reagents including hexamethyldisilazane [15], boron trifluoride etherate [16], triflic anhydride [17], phosphorus pentoxide [18], thionyl chloride [19], phosphorus oxychloride [20], sulfuric acid [21], and polyphosphoric acid [22]. One-pot syntheses of 1,3,4-oxadiazoles include synthesis by reaction of hydrazine with carboxylic acids [23], condensation of acyl hydrazides and aromatic aldehydes in the presence of ceric ammonium nitrate [24], cyclodehydration of carboxylic acids and acyl hydrazides with triphenyl phosphine and carbon tetrabromide [25], and reaction of carboxylic acids with amidoximes using polymer-supported reagents [26].

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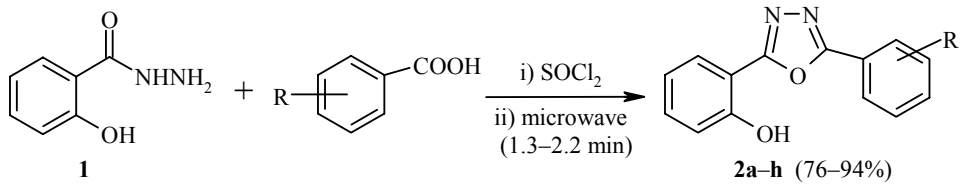
Salicylate derivatives are well known for their anti-inflammatory activity [27] and anticancer efficacy [28, 29]. The idea was to append the salicylate moiety to oxadiazole nucleus in order to combine their beneficial effects in a single structure with expected bioactivities, including anticancer activity. Herein, we report a simple method for the synthesis of 1,3,4-oxadiazoles having a phenolic group.

Salicylic hydrazide was synthesized from methyl salicylate; the latter was prepared from commercial salicylic acid according to standard procedures. Reaction of salicylic hydrazide **1** with some readily available carboxylic acids in the presence of thionyl chloride under microwave irradiation gave 1,3,4-oxadiazoles **2a**-**h** in good yields, thus, saving time, solvent, and workup compared to their synthesis under conventional thermal heating conditions.

TABLE 1. Compounds **2a-h**

Com-pound	mp, °C	Reaction time, min	^{1}H NMR, δ, ppm (*J*, Hz)	MS, *m*/*z*, %	Yield, %
2a	165	1.30	7.07-8.18 (9H, m, Ar); 10.19 (1H, s, OH)	238 $[M]^+$ (22), 181 (74), 121 (100), 105 (82), 91 (73), 77 (43)	94
2b	163	2.0	2.54 (3H, s, $ArCH_3$); 7.1-8.2 (4H, m, Ar); 7.49 (2H, d, *J* = 7.2, Ar); 7.79 (2H, d, *J* = 8.1, Ar); 10.2 (1H, s, OH)	252 $[M]^+$ (42), 121 (100), 119 (69), 91 (77), 77 (40)	88
2c	102	2.20	3.89 (3H, s, CH_3O); 7.05-7.8 (4H, m, Ar); 7.84 (2H, d, *J* = 9.1, Ar); 8.1 (2H, d, *J* = 7.2, Ar); 10.38 (1H, s, OH)	268 $[M]^+$ (31), 135 (64), 121 (100), 91 (72), 77 (68)	91
2d	127	1.50	3.97 (3H, s, CH_3O); 3.98 (3H, s, CH_3O); 7.21-8.20 (7H, m, Ar); 10.5 (1H, s, OH)	298 $[M]^+$ (22), 165 (82), 121 (100), 91 (64), 77 (41)	87
2e	145	1.30	3.89 (3H, s, CH_3O); 3.97 (3H, s, CH_3O); 3.98 (3H, s, CH_3O); 7.23-8.08 (6H, m, Ar); 10.5 (1H, s, OH)	328 $[M]^+$ (14), 181 (86), 196 (84), 121 (100), 91 (81)	90
2f	84	1.50	7.23-7.4 (4H, m, Ar); 7.47 (1H, m, Ar); 7.53 (1H, m, Ar); 7.97 (1H, m, Ar); 8.09 (1H, m, Ar); 10.31 (OH)	274, 272 $[M]^+$ (22), 181 (86), 140 (74), 121 (100), 91 (49), 77 (43)	82
2g	111	1.30	7.2-7.4 (4H, m, Ar); 7.42 (1H, ddd, *J* = 7.4, *J* = 1.2, *J* = 1.2, Ar); 7.49 (1H, ddd, *J* = 7.7, *J* = 7.7, *J* = 1.8, Ar); 7.56 (1H, m, Ar); 8.0 (1H, dd, *J* = 7.8, *J* = 2.0, Ar); 10.4 (OH)	317, 315 $[M]^+$, 181 (86), 140 (48) 121 (100), 91 (68)	83
2h	97	2.20	3.87 (3H, s, CH_3O); 4.07 (2H, s, CH_2); 7.1-7.56 (4H, m, Ar); 7.42 (4H, m, Ar); 7.60 (2H, d, *J* = 2.35, Ar); 7.64 (1H, d, *J* = 7.4, Ar); 10.34 (OH)	282 $[M]^+$ (22), 181 (86), 149 (67), 121 (100), 91 (71), 77 (61)	76



1 **2a–h** (76–94%)

2 a R = H, **b** R = 4-Me, **c** R = 4-MeO, **d** R = 3,4-$(MeO)_2$, **e** R = 3,4,5-$(MeO)_3$,
f R = 3-Cl, **g** R = 2-Br, **h** RC_6H_4 = 3-$MeOC_6H_4CH_2$

Formation of 1,3,4-oxadiazoles **2a-h** was confirmed by the absence of the N–H and carbonyl absorptions of chelated hydrazide at 3268 and 1642 cm^{-1} respectively and by the appearance of very strong absorption maxima at 1677-1686 cm^{-1} for C=N, at 1265-1270 and 1026-977 cm^{-1} for characteristic stretching vibrations of the =COC= fragment of the oxadiazole ring [30] in addition to three characteristic "stepwise" absorptions of increasing intensity at 3553, 3477, 3414 cm^{-1} for the phenolic hydroxyl observed in each case in the IR spectra. The structures were further confirmed by ^1H NMR where, besides the peaks for aromatic protons in the region of 6.97-8.22, the phenolic hydroxyl was observed at δ 10.2-10.4 ppm. In the mass spectra, in addition to the molecular ion, the base peak was observed at *m/z* 121 in each case (Table 1).

In conclusion, we have developed a simple, rapid, one-step method for the preparation of substituted 1,3,4-oxadiazoles from the corresponding acyl hydrazides. The salient features of our method, which distinguishes it from previous such synthesis [31], include crucial shortening of irradiation time, use of less expensive thionyl chloride, lack of use of alumina support, and lack of aqueous workup, which makes it an attractive protocol for rapidly generating these important building blocks.

EXPERIMENTAL

Melting points were recorded using a digital Gallenkamp (SANYO) model MPD BM 3.5 apparatus and are uncorrected. ^1H NMR spectra were determined as $CDCl_3$ solutions at 300 MHz using a Bruker AM-300 spectrophotometer. FT IR spectra were recorded using an FTS 3000 MX spectrophotometer; mass spectra (EI, 70eV) on a GC-MS instrument. The reactions were carried out in an unmodified domestic microwave oven (MW 900 W, frequency 2450 MHz, Power level 1, Dawlance, Pakistan). All compounds were purified by thick layer chromatography using silica gel from Merck.

Preparation of 1,3,4-oxadiazoles 2ah (General Method). A homogenized mixture of salicylic hydrazide (1 mmol) and carboxylic acid (1 mmol) in thionyl chloride (1-2 drops) was irradiated for 1.3-2.2 min in an alumina bath inside a microwave oven (Table 1). On completion of the reaction, followed by TLC examination using hexane–ethyl acetate (9 : 1), the reaction mixture was diluted with ethyl acetate and subjected directly to thick layer chromatography on silica gel, then recrystallized using ethyl acetate to afford the 1,3,4-oxadiazoles **2a-j**.

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