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"EFFICIENT SYNTHESIS OF 2, 5-DISUBSTITUTED 1,3,4-OXADIAZOLE DERIVATIVES "

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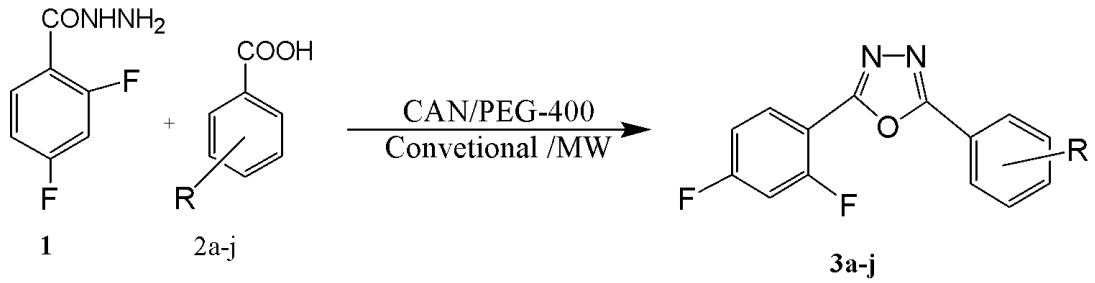
Abstract: A rapid and efficient microwave-accelerated synthesis of fluorinated 2,5-disubstituted 1,3,4-oxadiazole derivatives was synthesized by 2,4-difluoro benzo hydrazide with substituted benzoic acid in the presence of Ceric ammonium nitrate in PEG. The structural elucidation of these compounds is based on their spectral data (IR, ^{1}H NMR, and MS). The advantage of the method is good for the excellent yield of the product and the process is rapid.

Keywords: Microwave irradiation, Ceric ammonium nitrate, Polyethylene glycol (PEG-400), Cyclization.

Introduction:

In recent years, significant interest has been devoted to finding a new methodology for the synthesis of 1,3,4-oxadiazole containing pyridine moiety. 1,3,4-oxadiazoles are five-membered aromatic heterocycles with great utility in synthetic, medicinal, and material chemistry. They have been reported to possess significant biological activities such as antimicrobial [I-III], antiviral [IV, V], antifungal [VI, VII], anticancer [VIII, X], antitumor [XI], anti-inflammatory [XII-XIII], anti-diabetic [XIV], antibacterial [XV-XVI], antioxidant [XVII-XIV], analgesic [XX], anti-tubercular [XXI], anti-HIV [XXII] and cytotoxic activities [XXIII]. Searching for simple and efficient methods for the generation of libraries of novel heterocyclic compounds is in demand. A methodology using several approaches, some of the more popular being the cyclization with a variety of reagents such as Catalytic NaOH−DMSO [*XIV*], TsCl base [XV], Heteropoly acid [XVI], and transition-metal-free conditions [XVII]. Because of the great medicinal significance and material applications, we have developed a mild and convenient one-pot protocol for the synthesis of fluorinated 1,3,4-oxadiazoles from fluorinated acid hydrazides with substituted benzoic acid in presence of ceric ammonium nitrate in PEG under microwave irradiation. Microwave accelerated synthesis is also promising as a powerful tool for high-throughput organic synthesis. It has been confirmed that the use of microwave heating can significantly short reaction times and increase product yield.

Reaction Scheme



1 2a-j **3a-j**

R= H,4-NO_2,3-NO_2,4-OCH_3, 4-Cl,
2-Cl,3-OH,4-CH_3,4-OH,4-NH_2

Result and Discussion.

In search of the best reaction conditions for the synthesis of 2,4-Difluoro-phenyl-5-(substituted phenyl)-[1,3,4]-oxadiazoles synthesized by the reaction of 2,4-difluorobenzohydrazide with substituted benzoic acid in presence of ceric ammonium nitrate in PEG-400 under conventional and microwave irradiation method.

Table 1. Synthesis of fluorinated 2,5-disubstituted 1,3,4-oxadiazoles at different solvent conditions.

Entry	Solvent	Time h	Temperature	% yield
1	Toluene	20	110 ^{0}C	50
2	**PEG-400**	**10**	**120 ^{0}C**	**65**
3	Methanol	30	Reflux	46
4	Glycerol	15	120 ^{0}C	58
5	Acetonitrile	20	Reflux	47

In order to investigate the reaction conditions for the synthesis of fluorinated disubstituted 1,3,4-oxadiazole, we studied reaction at the varied temperature, different mmol % of CAN, and different types of solvents. The reaction of 2,4-difluoro benzo hydrazide (1mmol) (**1**) and benzoic acid (1mmol) **(2a-j**) was performed in a conventional organic solvent like toluene, methanol, ethanol, glycerol, and acetonitrile in an appropriate amount of CAN **(Table 1)**. The reaction mixture was stirred and heated at 5 h to 30 h at reflux temperature to obtain 35 % to 50% yield of fluorinated 1,3,4-oxadiazole (**3a**). By using PEG as a solvent in the above reaction, a significant improvement was observed and the yield of (**3a)** radically increased to 65% after stirring the reaction mixture heated at 120^0C for only 10 h in the 1mmol of CAN. Synthesis of fluorinated acid was carried in a different time with different yields in different conditions. We are reporting yield in toluene about 50 % after heating for 20 h. Yield increases to 65 % when the reaction is carried out in PEG-400 after heating for 10 h. Interestingly, the expected fluorinated 1,3,4- oxadiazole (3**a)** was obtained in 65 % yield after 10 h (**Table 1, entry 2**). Similarly in method, while yield obtained 65 % when reaction carried out in PEG-400 for 10 h. Hence we conclude that PEG is a good medium for the current reaction scheme.

Table 2: Enhancement on the formation of disubstituted 1, 3, 4- oxadiazole in the presence of the various amount of CAN [a]

Entry	CAN (mmol %)	Time (h)	% yield [b]
1	2	12	68
2	4	12	72
3	**5**	**10**	**80**
4	8	12	74

In an optimized reaction condition, CAN be added to a mixture of (**1)** and (**2a)** in PEG to attain maximum yield. 2 % of CAN was added and the mixture was stirred and reflux for 12 h, affording fluorinated 1,3,4-oxadiazole (**3a**) in 68 % yield. To further improve the yield and to optimize the reaction conditions, the same reaction was carried out in the presence of 4 and 5 mmol % of CAN under similar conditions. With this optimistic result in hand, we further investigated the best reaction conditions by using different amounts of CAN. An enhancement in the quantity of CAN from 2 to 5 mol % not only decreased the reaction time from 12 h to 10 h but also increased the product yield slightly from 68 to 80 %. An increase in the quantity of CAN from 5 to 8 mol % neither improved the product yield nor decreased the reaction time. Hence we observed that amount catalyst consequence on the product yield. The reaction was carried out in a range of solvents at varied temperatures and resulted in poor to moderate yields of the corresponding synthesis fluorinated 1,3,4-oxadiazole. The best results in terms of yields were obtained by heating 2, 4-difluoro benzo hydrazide **(1)** with benzoic acid with (**2a)** in 5 % mmol of CAN in PEG at 120 ^{0}C for 10 h (**Table 2, entry 3**). To circumvent the poor yields observed in the conventional heating, it was considered worthwhile to attempt the microwave promoted synthesis of fluorinated 1,3,4-oxadiazole. The reaction between 2, 4-difluoro benzo hydrazide **(1),** and benzoic acid **(2a**) was chosen as a model reaction for optimizing reaction conditions. The best result in terms of yield was obtained using 5 % mmol of CAN at 110^0C oven temperature for 15 min under microwave radiation. Having determined suitable reaction conditions, the developed strategy was next explored with an of 2,4-difluorobenzo hydrazide **(1)** and benzoic acid (**2a**) affording facile synthesis of a library of fluorinated 2,5-disubstituted1,3,4-oxadiazoles (**2a)** with excellent yields. Based on the above observations, we conducted the same reactions using various

carboxylic acids **(2a-j**) under similar conditions, and as expected satisfactory results were observed. (**Table 3**). We are reporting fluorinated 1,3,4-oxadiazole derivatives the first time. The structure elucidations of the synthesized compounds were carried out by different spectroscopic techniques like FTIR, ^{1}H NMR, and LC-MS. The structure of compound **3 (a-j)** was confirmed by the absence of hydrazide protons at δ 4.80 (NH_2) and δ 10.10 (NH) in the ^{1}H NMR spectrum. Compound **3(a-j)** displayed multiplets in the region between δ 7.07–8.9 for different aromatic protons. In IR spectra of compound **3a,** the absorption band has been observed at 1604 cm^{-1} indicates the –C=N vibrations, which confirmed the formation of the oxadiazole ring. Stretching at 1146 cm^{-1} represents C–O–C bending vibration. Mass spectra of compound **3a** displayed a molecular ion base peak at m/z 259, which supports the structure of compound **3a**.

Table 3. Physical data of synthesized compounds 3 (a-j) using conventional and microwave irradiation.

Entry	Compound	R	Microwave Irradiation		Conventional method		M.P.(^{0}C)
			ReactionTime (min)	Yield (%)	Reaction Time (h)	Yield (%)	
1	5a	H	15	91	10	80	125
2	5b	4-NO_2	15	94	9	82	205
3	5c	3-NO_2	15	93	9	83	252
4	5d	4-OCH_3	15	89	10	75	139
5	5e	4-Cl	15	93	10	76	155-160
6	5f	4-NH_2	15	91	10	75	87
7	5g	4-CH_3	15	92	9	72	235
8	5h	2-Cl	15	89	9	71	128
9	5i	4-OH	15	90	10	74	191
10	5j	3-OH	15	91	10	73	155-157

In the present study, we observed that the use of microwaves enhances the yield in a short reaction time of 15 min. The 94 % yield is obtained for the electron-withdrawing group while in electron-donating yield is slightly lower. It is very significantly high as compared to conventional heating techniques. In this maximum yield obtained is 83 %

Experimental

All solvents and reagents were obtained Ana lR Grade from Aldrich and used without further purification. All reactions and purity of synthesized compound was checked by thin layer chromatography (TLC) using aluminum plates coated with silica gel (Merck) using (40:60) ethyl acetate and n-hexan. Microwave experiments were carried out using catalyst microwave synthesizer (model No.13060295)

Procedure for Synthesis of fluorinated 1,3,4-oxadiazoles 3 (a-j) (Conventional Method)

A mixture of 2,4-difluorobenzohydrazide (1mmol) with substituted benzoic acid **(2 a-j)**

(1mmol) and ceric ammonium nitrate suspended in PEG-400 was heated at 110 ^{0}C for 9-10 h. The completion of the reaction was monitored by TLC. After completion of the reaction the reaction mixture was cooled and poured on to crushed ice drop wise with continuous stirring, left overnight at room temperature. The resulting solid thus obtained was collected by filtration, washed well with cold water, dried and recrystallized from absolute ethanol.

Procedure for Synthesis of fluorinated 1,3,4-oxadiazoles 3 (a-j) (under microwave)

A mixture of 2,4-difluorobenzohydrazide (1mmol), Substituted benzoic acid (1mmol) in PEG 400 in RBF and was added ceric ammonium nitrate. The mixture was irradiated under microwave irradiation at 120 ^{0}C for the different time interval. (**Table1**). The completion of the reaction was

monitored by TLC. After completion of the reaction the RBF was removed from the oven. The reaction mixture was poured on to crushed ice drop wise with continuous stirring, left overnight for room temperature. The resulting solid thus obtained was collected by filtration, washed well with cold water, dried and recrystallized from absolute ethanol.

2-(2,4-Difluoro-phenyl)-5-phenyl-[1,3,4]oxadiazole (5a)

Yield 91%, m.p.125°C; IR (KBr) cm^{-1}: 1604 (C=N stretching),1146(C–O–C stretching), 3061 (Ar–CH stretching.) ; 1546(C=C Ar stretching), ^{1}H NMR (DMSO d6) δ:7.077 (2H, Ar–H),7.55 (2H, Ar–H), 8.15 (H, Ar–H), 8.20 (H, Ar–H), (MS *m/z*: 259 (M^+)

2-(2,4-Difluoro-phenyl)-5-(4-nitro-phenyl)-[1,3,4]oxadiazole (5b)

Yield92%,m.p.205°C; IR (KBr) cm−1: 1631 (C=N stretching), 1185(C–O–C stretching) 1527(C=CAr stretching),1451(N-O stretching); ^{1}H NMR (DMSO d6) δ:7.75 (2H, Ar–H), 7.72 (2H, Ar–H), 7.05.(2H, Ar–H), 8.19 (H,Ar–H),MS *m/z*: 305 (M^+).

2-(2,4-Difluoro-phenyl)-5-(3-nitro-phenyl)-[1,3,4]oxadiazole (5c)

Yield 91%, m.p.252 °C; IR (KBr,cm−^{1}): 1593 (C=N stretching), 1177(C–O–C stretching), 1531 (C=C stretching aromatic ring), 1450(N-O stretching); ^{1}H NMR (400 MHz, $CDCl_3$):δ 7.43 ((d,H, Ar–H),7.88 (s,1H, Ar–H),8.01(d,2H Ar–H), 8.62 (d,1H, Ar–H), 9.01(d,1H, Ar–H) , MS *m/z*: 305 (M^+

2-(2,4-Difluoro-phenyl)-5-(4-methoxy-phenyl)-[1,3,4]oxadiazole (5d)

Yield89%, m.p.139°C; IR (KBr,cm−^{1}):1606 (C=N stretching),995(C–O–C stretching),1507(C=C stretching, aromatic ring), 2853(C-OC $_3$ stretching);^{1}H NMR (400 MHz, $CDCl_3$) δ:3.89 (s,3H,OCH_3),7.048 (d,2H,Ar–H), 7.26(d,2H, Ar–H), 8.073 (s,2H, Ar–H), 8.17(d,2H, Ar–H), MS *m/z*: 289 (M^+).

(4-Chloro-phenyl)-5-(2,4-difluoro-phenyl)-[1,3,4]oxadiazole (5e)

Yield 93%, m.p.155-160 °C; IR (KBr) cm−1: 1600(C=N), 996(C–O–C), 1496 (C=C Ar),; ^{1}H NMR (DMSO d6) δ:7.36 (2H, Ar–H), 7.40 (H, Ar–H), 8.38 (H, Ar–H), 8.44 (2H, Ar–H), MS *m/z* 293(M^+)

4-[5-(2,4-Difluoro-phenyl)-[1,3,4]oxadiazol-2-yl]-phenylamine (3f)

Yield 91%, m.p.87°C; IR (KBr) cm−1: 1596 (C=N), 1174(C–O–C), 1545 (C=C Ar), 3369 (NH_2),;^{1}H NMR (DMSO d6) δ: 2.17 (2H, Ar–NH_2), 7.43 (d,2H, Ar–H), 7.52 (d,2H, Ar–H), 7.8 (s,H, Ar–H), 8.1 (d.2H, Ar–H) MS *m/z*: 274(M^+).

2-(2,4-Difluoro-phenyl)-5-p-tolyl-[1,3,4]oxadiazole (5g)

Yield92%,m.p.235°CIR(KBr,cm−^{1}):1601(C=Nstretching),1173(C–O–Cstretching),1492(C=C stretchingaromatic),;(

CH_3groupstretching,),^{1}HNMR(400MHz,$CDCl_3$dppm):δ:2.45(s,3H,CH_3),7.34(d,2H,Ar–H),

7.36 (s,H, Ar–H),8.02 (d,2H, Ar–H), 8.57 (s,2H, Ar–H), 8.90 (d,2H, Ar–H), MS *m/z*: 273(M^+).

2-(3-Chloro-phenyl)-5-(2,4-difluoro-phenyl)-[1,3,4]oxadiazole (5h)

Yield 89 %, m.p.128°C; IR (KBr,cm−^{1}):1605(C=N stretching),1106(C–O–C stretching),1482 (C=Cstretching),3260;(O-H stretching aromatic):;^{1}H NMR (400 MHz, $CDCl_3$ dppm):

δ:6.57(d,2H,Ar–H), 6.58(s,H,Ar–H),7.81(d,H, Ar–H),8.16(m,H, Ar–H), 8.45 (d,H, Ar–H), MS *m/z*: 293(M^+).

4-[5-(2,4-Difluoro-phenyl)-[1,3,4]oxadiazol-2-yl]-phenol (5i)

Yield 90 %, m.p.191°C; IR (KBr) cm^{-1}:160(C=N stretching),1107(C–O–C stretching),1482 (C=C stretching),3377;(O-H stretching aromatic):^{1}H NMR (400 MHzCDCl$_3$ dppm): *δ*:7.51(s,Ar-OH),7.54(d,H,Ar–H),7.82(d,2H, Ar–H),8.16 (s,H, Ar–H),8.72-8.84 (d,3H, Ar–H), MS *m/z*: 275(M^+).

3-[5-(2,4-Difluoro-phenyl)-[1,3,4]oxadiazol-2-yl]-phenol (3j)

Yield91% m.p.155-157 ℃; IR (KBr) cm−1:1607(C=N stretching),1164 (C–O–C stretching), 1487 (C=C Aromatics stretching),; ^{1}H NMR (DMSO d6) *δ*: 7.38 ((s,Ar-OH),7.40 (d,2H, Ar–H), 7.73-7.75 (d,3H, Ar–H) , 7.9 (d, H, Ar–H), 8.09 (d,H, Ar–H)MS *m/z*: 275 (M^+).

Conclusion.

In summary, we have developed a rapid and efficient one-pot method for the synthesis of fluorinated disubstituted 1,3,4-oxadiazoles in high yields using 2,4-difluorobenzo hydrazide and substituted carboxylic acids under mild reaction conditions. The use of ceric ammonium nitrate in PEG in combination with microwave heating significantly easy the purification process, and allowed us to quickly identify the optimal reaction condition and obtain excellent yields and operational efficiency. The structures of all the title products were elucidated by spectroscopic data, IR, ^{1}H NMR, and mass analyses.

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