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Solvent-free microwave-assisted synthesis of oxadiazoles containing imidazole moiety

PRIYA V FRANK, K S GIRISH and BALAKRISHNA KALLURAYA
Department of Studies in Chemistry, Mangalore University, Mangalagangothri, Mangalore 574 219
e-mail: bkalluraya_2001@yahoo.com

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Abstract. Microwave-assisted as well as conventional synthesis of 5-substituted-2-(2-methyl-4-nitro-1-imidazomethyl)-1,3,4-oxadiazoles containing the nitroimidazole moiety is carried out and their antibacterial, antifungal and anti-inflammatory activity is reported.

Keywords. Microwave synthesis; imidazole derivatives; 1,3,4-oxadiazoles; biological activity; anti-inflammatory activity.

1. Introduction

Use of microwave technology in organic and inorganic reactions is reported in a number of publications and reviews.[1–3] In the last few years, there has been increasing interest in the use of environmentally benign reagents and conditions[4–6] particularly in solvent-free procedures.[7] In dry media, reactions occur rapidly and the method avoids hazards associated with solvents especially in sealed vessels. The absence of solvent reduces reaction time and always improves yield. Using microwaves with proper control of power and reaction temperature is more efficient than conventional heating. In this context, we planned to prepare oxadiazoles under eco-friendly and environmentally benign solvent-free conditions, wherein several disadvantages like long reaction time and tedious work-up can be overcome.

The imidazole nucleus appears in a number of naturally occurring products like the amino acids, histidine and purines which comprise many of the most important bases in nucleic acids. Imidazole derivatives possess a broad spectrum of pharmacological activities such as anticonvulsant,[8] anti-parkinson[9] and monoamineoxidase (MAO) inhibitory[10] activity.

The oxadiazole chemistry has been developed extensively and is still developing. Presently there are a number of drugs used clinically, which comprise oxadiazole moiety in association with various heterocyclic rings. In view of these, a project was undertaken to synthesise a new series of 1,3,4-oxadiazoles containing the 4-nitroimidazole moiety by microwave irradiation and to evaluate the new compounds for their pharmacological activity.

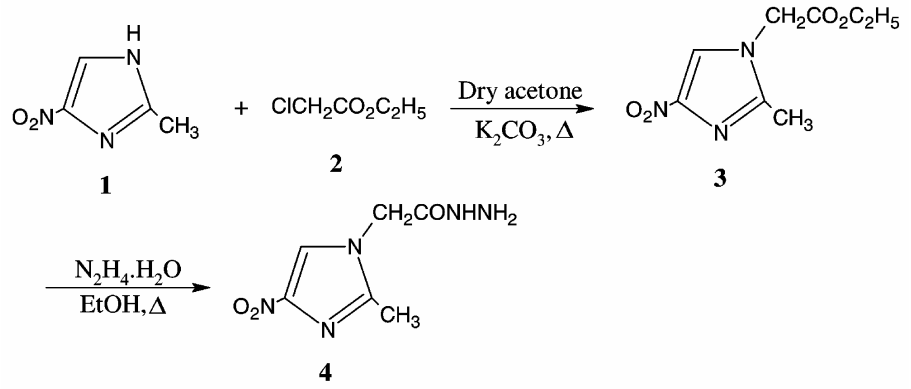
2. Results and discussion

The starting material 2-methyl-4-nitro-imidazole[11] **1** employed in the preparation of hydrazide **3** is obtained commercially and is used after purification by recrystallization. Ethylchloroacetate **2** was procured from Ranbaxy and was purified by distillation. The imidazole hydrazide **3** was obtained by refluxing the starting material **1** with ethylchloroacetate in dry acetone in the presence of potassium carbonate and subsequent hydrazinolysis with hydrazine hydrate (scheme 1).

The aryloxy acetic acids **5a–e** were prepared according to the method reported in the literature by the reaction of phenols with chloroacetic acid employing sodium hydroxide base and subsequent neutralization with hydrochloric acid (scheme 2) and were identified by their sharp melting point and reference to literature[12]. The characterization data of these newly synthesized aryloxyacetic acids are given in table 1.

The 5-aryl-2-(2-methyl-4-nitro-1-imidazomethyl)-1,3,4-oxadiazoles **7a–l** were prepared by the microwave irradiation of 2-methyl-4-nitro-1-imidazo acethydrazide **4** with appropriate carboxylic acids in the presence of phosphorous oxy chloride (scheme 3). Similarly, the reaction was also carried out by the

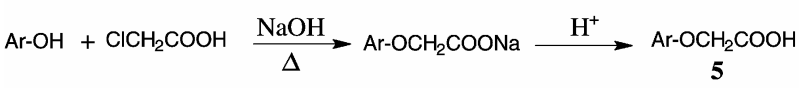
*For correspondence



Scheme 1.

Table 1. Physical and analytical data of compounds **5a–e**.

Compound	Ar	Melting point (°C)	Yield (%)	Molecular formula
5a	Phenyl	97–99	80	$C_8H_8O_3$
5b	*p*-Tolyl	150–152	63	$C_9H_{10}O_3$
5c	*o*-Tolyl	141–142	77	$C_9H_{10}O_3$
5d	*p*-Chlorophenyl	155–157	62	$C_8H_7ClO_3$
5e	*p*-Chloro-*m*-tolyl	176–178	70	$C_9H_9ClO_3$

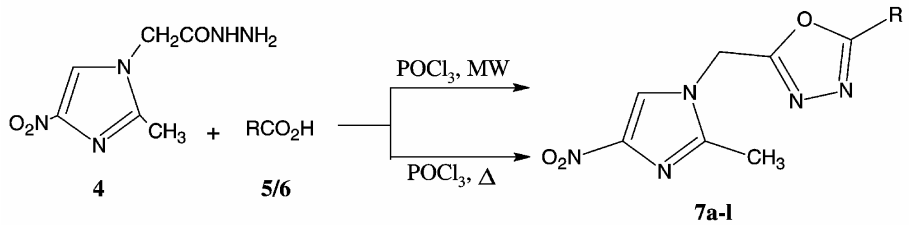


5a: Ar = C_6H_5 **5d:** Ar = 4-ClC_6H_4

5b: Ar = 4-$CH_3C_6H_4$ **5e:** Ar = 4-Cl-2-CH_3-C_6H_3

5c: Ar = 2-$CH_3C_6H_4$

Scheme 2.



7a: R = C_6H_5 **7g:** R = 2-C_4H_3O

7b: R = 4-$CH_3C_6H_4$ **7h:** R = C_6H_5-OCH_2

7c: R = 4-$OCH_3C_6H_4$ **7i:** R = 4-CH_3-C_6H_4-OCH_2

7d: R = 4-ClC_6H_4 **7j:** R = 2-CH_3-C_6H_4-OCH_2

7e: R = 2-$CH_3C_6H_4$ **7k:** R = 4-Cl-C_6H_4-OCH_2

7f: R = C_5H_4N **7l:** R = 4-Cl-2-CH_3-C_6H_3-OCH_2

Scheme 3.

conventional method by refluxing an intimate mixture of hydrazide **4** with appropriate carboxylic acid in phosphorous oxy chloride in an oil bath. The physical constants, yield and analytical data of 5-substituted-2-(2-methyl-4-nitro-1-imidazomethyl)-1,3,4-oxadiazoles **7a–l** are given in table 2.

3. Biological activity

3.1 *Antibacterial activity*

Studies on the antibacterial activity of synthesized compounds **7** have been carried out against four pathogenic organisms, viz., *Staphylococcus aureus* (G^+), *Klebsiella pneumoniae* (G^-), *Escherichia coli* (G^-) and *Pseudomonas aeruginosa* (G^-). The antibacterial activity of the newly synthesized compounds in the present investigation was assessed by the cup-plate method.[13] The results of the antibacterial studies are shown in table 3. Among the compounds tested, **7e** and **7l** showed good activity against the bacteria *E. coli*, *P. aeruginosa* and *K. pneumoniae* and moderate activity against *S. aureus*. Compound **7h** showed good activity against *E. coli* and *P. aeruginosa* and moderate activity against *K. pneumoniae* and *S. aureus*. Compound **7i** showed good activity against *P. aeruginosa* and *K. pneumoniae* and moderate activity against *S. aureus*. Compound **7j** showed good activity against *K. pneumoniae* and moderate activity against *S. aureus*.

3.2 *Antifungal activity*

The antifungal activity studies of the newly synthesized oxadiazole derivatives have been carried out against the fungi *Aspergillus flavus*, *A. fumigatus*, *Penicillium* and *Trichophyton* by the cup-plate method.[13] The results of the antifungal studies are shown in table 4. Among the compounds tested, **7d** showed good activity against all the fungi. Compound **7f** showed good activity against the fungi *A. flavus* and *Penicillium*. Compounds **7b** and **7c** showed good activity against the fungus *A. flavus* and moderate activity against *Penicillium*. Compound **7j** showed good activity against the fungus *A. fumigatus* and moderate activity against *Trichophyton*,

Table 2. Physical and analytical data of compounds **7a–l**.

Compd	R	Melting point (°C)	(%) Yield microwave (traditional)	Time (min)	Molecular formula	Elemental analysis Found (calculated) (%) C	H	N
7a	Phenyl	174	66 (56)	1·5	$C_{13}H_{11}N_5O_3$	54·52 (54·74)	3·91 (3·86)	24·62 (24·56)
7b	*p*-Tolyl	164	65 (50)	3	$C_{14}H_{13}N_5O_3$	56·28 (56·19)	4·29 (4·35)	23·50 (23·41)
7c	*p*-Anisyl	172	54 (40)	2	$C_{14}H_{13}N_5O_4$	53·42 (53·33)	4·08 (4·13)	22·31 (22·22)
7d	*p*-Chlorophenyl	212	56 (50)	4	$C_{13}H_{10}N_5O_3Cl$	48·99 (48·90)	3·05 (3·13)	21·86 (21·94)
7e	*o*-Tolyl	157	67 (55)	2	$C_{14}H_{13}N_5O_3$	56·25 (56·19)	4·29 (4·35)	23·36 (23·41)
7f	3-Pyridyl	269	63 (55)	2	$C_{12}H_{10}N_6O_3$	50·41 (50·35)	3·55 (3·49)	29·28 (29·37)
7g	2-Furyl	247	66 (48)	2	$C_{11}H_9N_5O_4$	48·11 (48·00)	3·33 (3·27)	25·36 (25·45)
7h	*p*-Phenoxy methyl	207	75 (60)	5	$C_{14}H_{13}N_5O_4$	53·42 (53·33)	4·09 (4·13)	22·16 (22·22)
7i	*p*-Cresyloxy methyl	201	75 (62)	5	$C_{15}H_{15}N_5O_4$	54·65 (54·71)	4·62 (4·56)	21·19 (21·18)
7j	*o*-Cresyloxy methyl	249	71 (54)	5	$C_{15}H_{15}N_5O_4$	54·66 (54·71)	4·49 (4·56)	21·35 (21·28)
7k	*p*-Chloro-phenoxymethyl	234	75 (62)	4	$C_{14}H_{12}N_5O_4Cl$	48·09 (48·14)	3·49 (3·44)	20·11 (20·06)
7l	*p*-Chloro-*m*-cresyloxy methyl	239	68 (52)	5	$C_{15}H_{14}N_5O_4Cl$	49·65 (49·59)	3·93 (3·86)	19·20 (19·28)

Solvent of crystallization: DMF + ethanol

Table 3. Antibacterial screening for compounds **7**.

Compd	Diameter of zone of inhibition (mm) at 10 mg/ml concentration			
	E. coli	*P. aeruginosa*	*K. pneumoniae*	*S. aureus*
7b	–	–	–	–
7d	–	–	–	–
7e	25	28	26	18
7f	–	–	–	–
7h	25	24	12	12
7i	–	28	28	16
7j	–	–	26	14
7k	–	–	–	–
7l	24	26	26	15
Ciprofloxacin (std)*	20	22	22	20
Solvent control (DMF)	–	–	–	–

*std = standard

Table 4. Antifungal screening for compounds **7**.

Compd	Diameter of zone of inhibition (mm) at 10 mg/mL concentration			
	A. flavus	*A. fumigatus*	*Penicillium*	*Trichophyton*
7b	26	–	14	–
7c	28	–	18	–
7d	28	26	28	28
7e	–	–	–	–
7f	26	–	26	–
7g	–	–	12	–
7i	–	–	–	12
7j	–	24	–	14
7l	–	–	–	–
Ciclopiroxolamine (std)*	22	22	20	20
Solvent control (DMF)	–	–	–	–

*std = standard

whereas compounds **7g** and **7i** showed moderate activity against the fungi *Penicillium* and *Trichophyton* respectively.

3.3 *Anti-inflammatory activity*

The method of Winter *et al*[14] was followed to study the anti-inflammatory activity of the oxadiazoles with slight modification. Formalin-induced oedema test was employed. The rat paw volume was measured by using the apparatus of Buttle *et al*[15], which was again modified by Singh and Ghosh.[16] The results obtained are represented in table 5. All the tested compounds have anti-inflammatory activity at a dose of 50 mg/kg. The anti-inflammatory activity of **7b**, **7c** and **7d** is comparable to that of indomethacin at a dose of 1·5 mg/kg.

4. Experimental section

4.1 *General*

All reagents and solvents were procured from Ranbaxy. The reactions were carried out under microwave irradiation at 160 W. TLC was used to monitor the progress of the reaction. The melting points of the newly synthesised compounds were determined in open capillaries and are uncorrected. The IR spectra were recorded on a Perkin–Elmer 983 IR spectrophotometer or Jasco FT IR 430 spectrophotometer as KBr pellet. The ^{1}H-NMR spectra were recorded on a Bruker AC 300F (300 MHz) NMR spectrometer using DMSO-d_6 or $CDCl_3$ as solvent and TMS as internal standard. All chemical shift values are expressed in the δ scale downfield from TMS and proton signals are indicated as *s* = singlet, *d* = doublet,

Table 5. Anti-inflammatory screening for compounds **7**.

		Paw volume (mL) after	Percentage inhibition of oedema after
Compd	Dose (mg/kg)	3 h	3 h
7b	50	0·29	50
7c	50	0·23	60
7d	50	0·26	55
7e	50	0·36	38
7j	50	0·39	33
Control	10 ml/kg	0·58	–
Standard	1·5	0·20	65

t = triplet, *m* = multiplet. Mass spectra of the compounds were recorded on a Jeol JMS-D300 mass spectrometer by operating at 70 eV.

4.2 *2-Methyl-4-nitro-1-imidazo-ethylacetate* (**3**)

A mixture of 2-methyl-4-nitro-imidazole **1** (127 g, 1 mol), ethyl chloroacetate **2** (122 g, 1 mol) and potassium carbonate (147 g, 1·5 mol) in dry acetone (500 mL) was refluxed for 50 h. The reaction mixture was filtered hot and the solvent was distilled off from the filtrate. The crude ester thus obtained was purified by recrystallization from ethanol, m.p. 96°C (lit.[17] m.p. 95°C), yield 106 g (50%).

4.3 *2-Methyl-4-nitro-1-imidazo-acethydrazide* (**4**)

A mixture of 2-methyl-4-nitro-1-imidazo-ethylacetate **3** (106 g, 0·5 mol) and hydrazine hydrate (99%, 25 g, 0·5 mol) in ethanol (100 mL) was refluxed for 8 h. The solution on cooling gave a solid mass of hydrazide **4**, which was collected by filtration, and recrystallized from ethanol, m.p. 189°C, yield 107 g (54%).

Analysis (found): C, 36·37; H, 4·29; N, 35·46%; (calculated for $C_6H_9N_5O_3$): C, 36·18; H, 4·52; N, 35·18%.

MS: *m*/*z* 199 (*M*+, 70), 183 (02), 168 (48), 153 (20), 141 (100), 111 (05).

4.4 *Aryloxy acetic acids* (**5a–e**)

To a mixture of appropriate phenol (0·1 mol) and 35 mL of 33% sodium hydroxide, in a round-bottom flask, 25 mL of 50% chloroacetic acid solution was added. Water was added if necessary to dissolve the salt of phenol. The flask is stoppered loosely and heated on a boiling water bath for an hour. It is cooled, diluted with 100 mL of water, acidified to congo red with dilute hydrochloric acid and extracted with 300 mL of ether. The ethereal extract was washed with water and the aryloxyacetic acid was extracted with sodium carbonate (5%, 250 mL) solution. The sodium carbonate extract was acidified with dilute hydrochloric acid to congo red, the crystals formed were collected and recrystallized from water or aqueous ethanol to yield **5a–e**.

4.5 *5-Substituted-2-(2-methyl-4-nitro-1-imidazomethyl)-1,3,4-oxadiazoles* (**7a–l**)

Method I: A mixture of substituted carboxylic acid (0·01 mol) and hydrazide **4** (0·01 mol) was ground in a mortar using a pestle for uniform mixing. This mixture was taken in a 50 mL beaker and 5–6 drops of phosphorous oxychloride was added. The beaker was kept inside a microwave oven operating at 160 W for about 5 min. The completion of the reaction was checked by TLC. The product was poured to crushed ice. It was then neutralized by 5% sodium bicarbonate. The solid obtained was filtered, dried and recrystallized from a mixture of ethanol–DMF to give **7a–l**.

Method II: To a mixture of substituted carboxylic acid (0·01 mol) and hydrazide **4** (0·01 mol), phosphorous oxychloride (5 mL) was added. The reaction mixture was refluxed for 4–5 h on an oil bath, the contents were cooled to room temperature and poured onto crushed ice. It was then neutralized by 5% sodium bicarbonate solution. The solid that separated was collected by filtration through a Büchner funnel and dried. Further purification was done by recrystallization from a mixture of ethanol–

DMF to give **7a–l**. A few typical compounds are described below.

5-Phenyl-2-(2-methyl-4-nitro-1-imidazomethyl)-1,3,4-oxadiazoles (**7a**)

m.p.: 172–74°C; yield: 56%.
IR (KBr) ν_{max}: 2991–3066, 1598, 1506, 1328 cm^{-1}.
^1H NMR ($CDCl_3$): δ 2·46 (*s*, 3H, CH_3); 4·77 (*s*, 2H, NCH_2); 7·61–8·00 (*m*, 5H, ArH); 8·48 (*s*, 1H, imidazole H).

5-(2-Furyl)-2-(2-methyl-4-nitro-1-imidazomethyl)-1,3,4-oxadiazoles (**7g**)

m.p.: 246–48°C; yield: 48%.
IR (KBr) ν_{max}: 2966–3051, 1595, 1508, 1336 cm^{-1}.
^1H NMR ($CDCl_3$): δ 2·32 (*s*, 3H, CH_3); 4·94 (*s*, 2H, NCH_2); 8·32 (*s*, 1H, imidazole H); 6·65–6·68 (*m*, 1H, furan-4H); 7·22–7·23 (*m*, 1H, furan-3H); 7·901–7·907 (*m*, 1H, Furan-5H).

5-o-Cresyloxymethyl-2-(2-methyl-4-nitro-1-imidazomethyl)-1,3,4-oxadiazoles (**7j**)

m.p.: 245–47°C; yield: 54%.
IR (KBr) ν_{max}: 2958–3055, 1625, 1542, 1334 cm^{-1}.
^1H NMR ($CDCl_3$): δ 2·21 (*s*, 3H, CH_3); 2·29 (*s*, 3H, CH_3 protons of *o*-tolyl); 4·63 (*s*, 2H, NCH_2); 4·89 (*s*, 2H, OCH_2); 8·30 (*s*, 1H, imidazole H); 6·84–7·15 (*m*, 4H, Ar-H).

5-p-Chlorophenoxymethyl-2-(2-methyl-4-nitro-1-imidazomethyl)-1,3,4-oxadiazoles (**7k**)

m.p.: 231–34°C; yield: 62%.
IR (KBr) ν_{max}: 2922–3014, 1542, 1494, 1332 cm^{-1}.
^1H NMR ($CDCl_3$): δ 2·30 (*s*, 3H, CH_3); 4·63 (*s*, 2H, NCH_2); 4·90 (*s*, 2H, OCH_2); 8·30 (*s*, 1H, imidazole H); 7·00 (*d*, 2H, Ar-H), 7·34 (*d*, 2H, Ar-H).

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