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ONE-POT SYNTHESIS OF 1,2,4-OXADIAZOLES MEDIATED BY MICROWAVE IRRADIATION UNDER SOLVENT-FREE CONDITION

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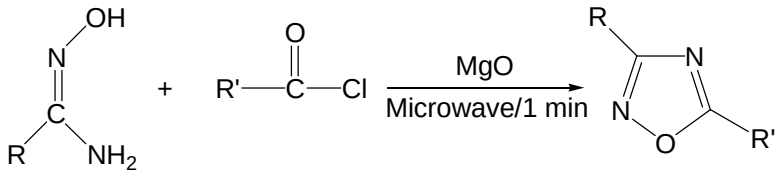
Abstract – Microwave-assisted synthesis of 1,2,4-oxadiazoles of amidoximes under solvent free conditions was found to be an efficient method for one-pot synthesis of 1,2,4-oxadiazole derivatives from amidoximes and acyl chlorides. This method is an easy, rapid, and high-yielding reaction for the synthesis of 1,2,4-oxadiazoles.

The oxadiazole [1] nucleus is a well-studied traditional pharmacophoric scaffold that has emerged as a core structural unit of various muscarinic agonists,[2] benzodiazepine receptor partial agonists,[3] dopamine transporters,[4] antirhinovirals,[5] growth hormone secretagogous,[6] and 5-HT agonists.[7] Among the oxadiazoles, 1,2,4-oxadiazole derivatives are gaining in interest in medicinal chemistry.[8] Several methods have been reported in the literature for synthesis of 1,2,4-oxadiazoles. [9-15] In general, synthesis of 1,2,4-oxadiazoles involves first the *O*-acylation step of an amidoxime by an activated carboxylic acid derivatives, followed by cyclodehydration.[16] It has found that cyclization could be effected by treating an *O*-acylamidoxime with NaH or NaOEt [17a-c] at room temperature, pyridine with heating, [17d,e] tetrabutylammonium fluoride as catalyst[18] and using of solid support techniques[19] for the preparation of 1,2,4-oxadiazoles. The application of microwave energy to accelerate organic reactions is of increasing interest and offers several advantages over conventional techniques.[20] As a part of our efforts to explore the novel utilities of microwave-assisted and surface-mediated reactions for the synthesis of heterocyclic compounds[21, 22] we describe here a new method for one-pot synthesis 1,2,4-oxadiazoles from amidoximes and acyl chlorides under solvent free condition. It is found that magnesia under solvent-free conditions was capable of producing high yields of 1,2,4-oxadiazoles by reaction from amidoximes with acyl chloride under mild reaction conditions in 67-91% yields under microwave irradiation (Scheme 1, Table 1).



1 **2** **3**

Scheme 1

Table 1. Reaction of amidoximes with acyl halides in the presence of magnesia under microwave irradiation.

Product **3**	R- **1**	R' **2**	Yield[a] (%)	Product **3**	R- **1**	R' **2**	Yield[a] (%)
a[17b]	C_6H_5-	Me	81	**f**	C_6H_5-CH=CH-	C_6H_5-	78
b	*m*-ClC_6H_4-	Me	91	**g**	C_6H_{11}-	C_6H_5-	76
c	*p*-ClC_6H_4-	Me	80	**h**[17b]	C_6H_5-	C_6H_5-	67
d	2, 4-$Cl_2C_6H_3$-	Me	74	**i**	*p*-$ClC_6H_4CH_2$-	*p*-$O_2NC_6H_4$-	86
e	*p*-$ClC_6H_4CH_2$-	C_6H_5-	72	**j**	*m*-ClC_6H_4-	*p*-$O_2NC_6H_4$-	70

a. Isolated Yield.

As shown Table 1, bezamidoxime (**1a**) in the presence of mixture of acetyl chloride (**2a**) afforded 3-phenyl-5-methyl-1,2,4-oxadiazole (**3a**) in 81% yield. The other derivatives of bezamidoximes (**1b-1d**) also react with acethyl chloride in the presence of magnesia under microwave irradiation, to give the desired compounds (**3b-3d**) in moderate to high yields. The reaction also proceeds with moderate yield with benzoyl chloride and *p*-nitrobenzoyl chloride as acylating agents affords the desired products (**3e-3j**) in good yield. Alumina is not as effective as magnesia and usually gives *O*-acylamidoximes as major product.

In summary, simple work-up, low consumption of solvent, fast reaction rates, mild reaction condition, good to moderate yields, and selectivity of the reaction make this method an attractive and a useful contribution to present methodologies.

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EXPERIMENTAL

General: All chemicals were commercial products and distilled or recrystallized before use. All melting points were obtained by a Buchi 510 and are uncorrected. A commercially available pulse microwave at 2450 MHz (900 W) was used in all experiments. IR spectra were determined using a FT-IR Brucker-Vector 22.

NMR spectra were taken with a DMX-500 Bruker Avance instrument with the chemical shifts being reported as δ ppm and couplings expressed in Hertz. Silica gel column chromatography was carried out with Silica gel 100 (Merck No. 10184). Merck Silica-gel 60 F254 plates (No. 5744) were used for the preparative TLC.

Preparation of Amidoximes (1):

General Procedure: To a solution of 0.01 mol of nitrile in 200 mL of ethanol was added a solution of 0.695 g (0.01 mol) of hydroxylamine hydrochloride in 10 mL of water, followed by the further addition of 0.420 g (0.005 mol) of sodium carbonate in 10 mL of water. The reaction mixture was stirred overnight at rt. The mixture was then concentrated to small volume under vacuum, diluted with cold water, and placed in refrigerator overnight. The precipitate that formed was recovered and recrystallized from ethanol. All amidoximes were known and characterized by comparison of their physical data with those prepared in accordance with literature procedures. [17, 23a-c]

Preparation of *p*-Chlorobenzamidoxime (1c): To a solution of 2.75 g (0.02 mol) of *p*-chlorobenzonitrile in 50 mL of ethanol was added a solution of 1.39 g (0.02 mol) of hydroxylamine hydrochloride in 5 mL of water, followed by the further addition of 1.68 g (0.02 mol) of sodium bicarbonate in 5 mL of water. The reaction mixture was stirred overnight at rt. The mixture was then concentrated to small volume under vacuum, diluted with cold water, and placed in refrigerator overnight. The precipitate that formed was recovered and recrystallized from ethanol to give *p*-chlorobenzamidoxime 3.2 g (94%). [23a] mp 132-134°C, ^{1}H-NMR, δ_H ($CDCl_3$, TMS): 4.98 (s, 2H, -NH_2), 7.38-7.64 (m, 4H), 8.89 (s, 1H, -OH); 172 (M^++2, 30), 170 (M^+, 100), 153 (75), 111 (40), 75 (65) 50 (50), 30 (35).

Preparation of 1, 2, 4-oxadiazoles:

General Procedure: This solvent-free method has operationally simple procedure. A 5 mmol of the amidoxime (finely ground) was added to magnesia 1 g (25 mmol, grinded in a mortar and pestle). The acyl chloride (7 mmol) was added to this mixture and the mixture was shacked for 5 min and irradiated by microwave for 1 min using 630 W (A kitchen-type microwave was used in all experiments). The reaction mixture was grinded in a mortar and pestle until a fine, homogeneous, powder is obtained. Homogeneous mixture was chromatographed on silica gel (Hexane:EtOAc=95:5) to give pure product in 67-91 % yield. All products gave satisfactory spectral data in accord with the assigned structures and literature reports. [17b] For new compounds spectral data are reported as following:

3-(*m*-Chlorophenyl)-5-methyl-1, 2, 4-oxadiazole (3b):

5 mmol (0.85 g) of the *m*-chlorobenzamidoxime (**1b**, finely ground) was added to magnesia 1 g (25 mmol), grinded in a mortar and pestle). The acethyl chloride (0.7 mL, 10 mmol) was added to this mixture and shacked

for 5 min and was irradiated by microwave for 1 min using 630 W (A kitchen-type microwave was used in all experiments). The reaction mixture was grinded in a mortar and pestle until a fine, homogeneous, powder is obtained. Homogeneous mixture was chromatographed on silica gel (Hexane:EtOAc=95:5) to give pure product 0.89 g (91 %). mp 143-145°C (ethanol); IR (KBr): 3050, 2980, 1660, 1649 cm^{-1}; ^{1}H-NMR, δ_H ($CDCl_3$, TMS): 2.68 (s, 3H), 7.39-8.05 (m, 4H): ^{13}C-NMR, δ_c ($CDCl_3$, TMS): 12.31, 125.34, 127.4, 128.52, 130.10, 131.08, 134.89, 167.37, 176.78; MS *m/z*: 196 (M^++2, 20), 194 (M^+, 60), 153 (100), 125, 90, 43 (80). Anal. Calcd for $C_9H_7N_2OCl$: C, 55.54; H, 3.63; N, 14.38. Found: C, 55.22; H, 3.82; N, 14.40.

3-(*p*-Chlorophenyl)-5-methyl-1, 2, 4-oxadiazole (3c) :

This oxadiazole was prepared in the general way and had mp 140-143°C (ethanol). IR (KBr): 3030, 2891, 1674, 1653 cm^{-1}; ^{1}H-NMR, δ_H ($CDCl_3$, TMS): 2.63 (s, 3H), 7.44 (dd, 2H, J=8 Hz and J=2 Hz), 7.98 (dd, 2H, J=8 Hz and J=2 Hz): ^{13}C-NMR, δ_c ($CDCl_3$, TMS): 12.33, 125.32, 128.62, 129.14, 137.25, 167.59, 176.70; MS *m/z*: 196 (M^++2, 30), 194 (M^+, 100), 153 (75), 125, 90, 43 (65). Anal. Calcd for $C_9H_7N_2OCl$: C, 55.54; H, 3.63; N, 14.38. Found: C, 55.28; H, 3.76; N, 14.24.

3-(2, 4-Dichlorophenyl)-5-methyl-1, 2, 4-oxadiazole (3d) :

This oxadiazole was prepared in the general way and had mp 150-152° C (ethanol). IR (KBr): 3010, 2931, 1660, 1640 cm^{-1}; ^{1}H-NMR, δ_H ($CDCl_3$, TMS): 2.67 (s, 3H), 7.36 (dd, 1H, J=8 Hz and J=2 Hz), 7.55 (d, 1H, J=2 Hz), 7.86 (d, 1H, J=8 Hz); ^{13}C-NMR, δ_c ($CDCl_3$, TMS): 12.35, 124.73, 127.35, 130.87, 132.41, 134.26, 137.24, 166.58, 176.26; MS *m/z*: 230 (M^++2, 40), 228 (M^+, 65), 187 (73), 124 (60), 43 (100). Anal. Calcd for $C_9H_6N_2OCl_2$: C, 47.19; H, 2.64; N, 12.23. Found: C, 46.90; H, 2.85; N, 12.20.

3-(4-Chlorophenylmethyl)-5-phenyl-1, 2, 4-oxadiazole (3e):

This oxadiazole was prepared in the general way and had mp 76-78° C (ethanol). IR (KBr): 3020, 2910, 1655, 1635 cm^{-1}; ^{1}H-NMR, δ_H ($CDCl_3$, TMS): 4.10 (s, 2H), 7.28-7.35 (m, 4H), 7.46-7.55 (m, 3H), 8.09 (d, 2H, J=8 Hz); ^{13}C-NMR, δ_c ($CDCl_3$, TMS): 31.73, 124.02, 128.02, 128.97, 129.05, 129.23, 130.33, 131.10, 132.70, 132.97, 133.94, 169.63, 175.81. Anal. Calcd for $C_{15}H_{11}N_2OCl$: C, 66.55; H, 4.10; N, 10.35. Found: C, 66.38; H, 4.36; N, 9.89.

3-(2-Phenylvinyl)-5-methyl-1, 2, 4-oxadiazole (3f) :

This oxadiazole was prepared in the general way and had mp 131-133°C (ethanol). IR (KBr): 3040, 2970, 1677, 1652, 1610 cm^{-1}; ^{1}H-NMR, δ_H ($CDCl_3$, TMS): 2.30 (s, 3H), 6.64 (d, 1H, J=16 Hz), 7.31-7.47 (m, 6H); ^{13}C-NMR, δ_c ($CDCl_3$, TMS): 27.20, 126.86, 127.98, 130.22, 134.15, 143.06, 197.93; MS *m/z*: 186 (M^+, 20), 149 (50), 128 (45), 77 (32), 43 (100). Anal. Calcd for $C_{16}H_{12}N_2O$. C, 77.40; H, 4.87; N, 11.29. Found: C, 77.21; H, 4.65; N, 10.96.

3-Cyclohexyl-5-phenyl-1, 2, 4-oxadiazole (3g):

This oxadiazole was prepared in the general way and had mp 159-161°C (ethanol). IR (KBr): 3072, 2931, 1663, 1643 cm^{-1}; ^{1}H-NMR, δ_H ($CDCl_3$, TMS): 1.20 (tt, 1H, J=13 Hz and J=3 Hz), 1.21 (tq, 2H, J=13 Hz and

J=3 Hz), 1.43 (dq, 2H, J=13 Hz and J=3 Hz), 1.65-1.67 (m, 1H), 1.76 (td, 2H, J=13 Hz and J=3 Hz), 1.81-1.84 (m, 2H), 3.20 (tt, 1H, J=13 Hz and J=3 Hz) 7.37 (t, 2H, J=7 Hz), 7.45 (t, 1H, 7 Hz), 7.88 (d, 1H, 8 Hz); ^{13}C-NMR, δ_c ($CDCl_3$, TMS): 25.56, 25.73, 29.16, 45.26, 127.94, 128.28, 132.40, 136.07, 203.31; MS *m/z*: 228 (M^+, 30), 125 (80), 123 (75), 109 (70), 105 (100), 83 (65). Anal. Calcd for $C_{14}H_{16}N_2O$. C, 73.65; H, 7.06; N, 12.27. Found: C, 73.39; H, 6.85; N, 12.10.

3-(4-Chlorophenylmethyl)-5-(4-nitrophenyl)-1, 2, 4-oxadiazole (3i) :

This oxadiazole was prepared in the general way and had mp 132-134° C (ethanol). IR (KBr): 3015, 2920, 1632, 1625 cm^{-1}; ^{1}H-NMR, δ_H ($CDCl_3$, TMS): 4.13 (s, 2H), 7.20-7.35(m, 4H), 8.27 (d, 2H, J=4.6 Hz), 8.34 (d, 2H, J=4.6 Hz); ^{13}C-NMR, δ_c ($CDCl_3$, TMS): 31.58, 124.21, 125.43, 128.54, 129.18, 129.25, 130.41, 133.46, 150.12, 170.17, 173.75. Anal. Calcd for $C_{15}H_{10}N_3O_3Cl$: C, 57.06; H, 3.19; N, 13.31. Found: C, 57.40; H, 3.25; N, 13.20.

3-(3-Chlorophenyl)-5-(4-nitrophenyl)-1, 2, 4-oxadiazole (3j):

This oxadiazole was prepared in the general way and had mp 190-192° C (ethanol). IR (KBr): 3025, 2960, 1630, 1620 cm^{-1}; ^{1}H-NMR, δ_H ($CDCl_3$, TMS): 7.47 (d, 2H, J=5.8 Hz), 8.09 (d, 1H, J=5.8 Hz), 8.30-8.39 (m, 4H); ^{13}C-NMR, δ_c ($CDCl_3$, TMS): 124.29, 124.71, 125.12, 127.21, 128.75, 129.12, 129.23, 130.41, 137.72, 150.17, 168.51, 173.72. Anal. Calcd for $C_{14}H_8N_3O_3Cl$: C, 55.73; H, 2.67; N, 13.93. Found: C, 55.36; H, 2.85; N, 13.58.

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