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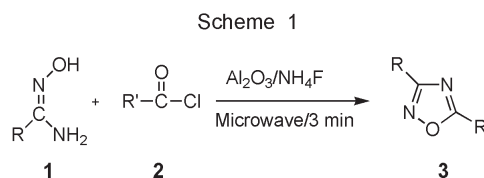
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Alumina supported ammonium fluoride was found as an efficient reagent for the synthesis of 1,2,4-oxadiazoles of amidoximes under solvent free conditions using microwave irradiation. This method is a one-pot, easy, rapid, and high-yielding reaction for the synthesis of 1,2,4-oxadiazole derivatives from amidoximes and acyl chlorides. Reaction of amidoximes with acylchlorides in the presence of alumina without ammonium fluoride gave only the corresponding *O*-acylamidoximes as major product.

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Oxadiazoles have been used as bioisosteres for amides and esters. The oxadiazole moiety is an important structure unit in drugs and chemical materials [1-7]. 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 the 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 been 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 use 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]. In recent years, microwave irradiation has been reported for the synthesis of 1,2,4-oxadiazoles and 1,3,4-oxadiazoles in the presence of solvent or solvent-free conditions [21-24]. However, using microwave irradiation in the presence of alumina under solvent-free conditions, gave a low yield of 1,2,4-oxadiazoles [21]. Moreover, often when carrying out a reaction in a microwave oven the use of a solvent can sometimes be avoided, which is important in order to make the synthesis more environmentally friendly ('green chemistry'). These observations led us to investigate the possibility of improving the meth-



ods used for the synthesis of 1,2,4-oxadiazoles use microwave irradiation. As a part of our efforts to explore the novel utilities of solid supported reactions for the synthesis of heterocyclic compounds [25,26] we describe here a new method for one-pot synthesis 1,2,4-oxadiazoles from amidoximes and acyl chlorides under solvent free condition using microwave irradiation. It is found that alumina supported ammonium fluoride 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 71-90% yields under microwave irradiation (Scheme 1, Table 1).

As shown Table 1, benzamidoxime (**1a**) in the presence of a mixture of benzoyl chloride (**2a**) afforded 3,5-diphenyl-1,2,4-oxadiazole (**3a**) in 90% yield. The other derivatives of amidoximes (**1b-1e**) also react with benzoyl chloride in the presence of alumina supported ammonium fluoride under microwave irradiation, to give the desired compounds (**3b-3e**) in moderate to high yields. The reaction also proceeds with moderate yield with *p*-methoxy and *p*-nitrobenzoyl chloride as acylating agents affords the

Table 1

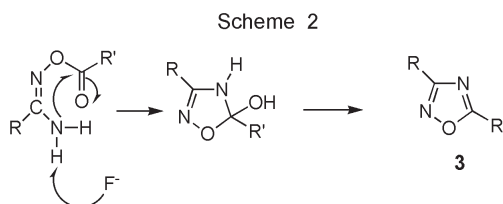
Reaction of amidoximes with acyl chlorides in the presence of alumina supported ammonium fluoride under microwave irradiation.

Product 3	R- 1	R' 2	Yield [a] (%)	Product 3	R- 1	R' 2	Yield [a] (%)
a [17b]	C ₆ H ₅ -	C ₆ H ₅ -	90	f [17b]	C ₆ H ₅ -	<i>p</i> -CH ₃ OC ₆ H ₄ -	78
b [27a]	<i>p</i> -ClC ₆ H ₄ CH ₂ -	C ₆ H ₅ -	86	g	2, 4-Cl ₂ C ₆ H ₃ -	<i>p</i> -CH ₃ OC ₆ H ₄ -	71
c	<i>p</i> -ClC ₆ H ₄ -	C ₆ H ₅ -	87	h	<i>p</i> -ClC ₆ H ₄ CH ₂ -	<i>p</i> -O ₂ NC ₆ H ₄ -	80
d	2, 4-Cl ₂ C ₆ H ₃ -	C ₆ H ₅ -	75	i	<i>p</i> -ClC ₆ H ₄ -	<i>p</i> -O ₂ NC ₆ H ₄ -	86
e	C ₆ H ₁₁ -	C ₆ H ₅ -	85	j	C ₆ H ₁₁ -	<i>p</i> -O ₂ NC ₆ H ₄ -	82

[a] Isolated Yield.

desired products (**3f-3j**) in good yields. Alumina without supported ammonium fluoride is not as effective and gives *O*-acylamidoximes as major product. Ammonium chloride (NH_4Cl) and bromide (NH_4Br) was not as effective as ammonium fluoride and failed to give the required product. The reaction gave low yields of 1,2,4-oxadiazoles with using of alumina supported potassium fluoride.

Since the procedure described herein proceeds at solvent-free conditions, NH_4F is likely functioning as a strong base. Fluoride ion promotes the cyclization by acting as a strongly basic reagent (Scheme 2) [28].



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

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 [17,27a-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%) [**27a**]; mp 132-134 °C, $^1\text{H-NMR}$, δ_{H} (CDCl_3 , TMS): 4.98 (s, 2H, $-\text{NH}_2$), 7.38-7.64 (m, 4H), 8.89 (s, 1H, $-\text{OH}$); 172 ($\text{M}^{+}+2$, 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. The reagent (5 mmol) was prepared by the combination of ammonium fluoride (5 mmol, finely ground) and alumina (Al_2O_3 , acidic, 2 g) in a mortar and pestle by grinding them together until a fine, homogeneous, powder was obtained (5-10 min). A 5 mmol of the amidoxime (finely ground) was added to this mixture. The acyl chloride (7 mmol) was then added and the mixture was shaken for 5 min and irradiated by microwave for 3 min using 600 W (A kitchen-type microwave was used in all experiments). The reaction mixture was ground in a mortar and pestle until a fine, homogeneous, powder is obtained. The homogeneous mixture was chromatographed on silica gel (Hexane:EtOAc=95:5) to give pure product in 71-90 % yield. All products gave satisfactory spectral data in accord with the assigned structures and literature reports [17b,26b]. For new compounds spectral data are reported as follows:

3-(4-Chlorophenylmethyl)-5-phenyl-1,2,4-oxadiazole (**3b**).

This oxadiazole was prepared using the general procedure and has mp 76-78 °C (ethanol); $^1\text{H-NMR}$, 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); $^{13}\text{C-NMR}$, 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 $\text{C}_{15}\text{H}_{11}\text{ClN}_2\text{O}$: C, 66.55; H, 4.10; N, 10.35. Found: C, 66.38; H, 4.36; N, 9.89.

3-(2, 4-Dichlorophenyl)-5-phenyl-1,2,4-oxadiazole (**3d**).

This oxadiazole was prepared in the general way and has mp 140-142 °C (ethanol); $^1\text{H-NMR}$, δ_{H} (CDCl_3 , TMS): 7.41 (dd, 2H, $J=8.4$ Hz and $J=1.7$ Hz), 7.52-7.68 (m, 4H), 8.02 (d, 1H, $J=8.4$ Hz), 8.21(d, 2H, $J=7.2$ Hz); $^{13}\text{C-NMR}$, δ_{C} (CDCl_3 , TMS): 123.85, 124.76, 127.26, 128.14, 129.09, 130.78, 132.48, 132.90, 134.28, 137.18, 166.97, 175.28.

Anal. Calcd for $\text{C}_{14}\text{H}_8\text{Cl}_2\text{N}_2\text{O}$: C, 57.73; H, 2.74; N, 9.62. Found: C, 57.48; H, 2.86; N, 9.30.

3-Cyclohexyl-5-phenyl-1,2,4-oxadiazole (**3e**).

This oxadiazole was prepared in the general way and has mp 159-161 °C (ethanol); $^1\text{H-NMR}$, 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); $^{13}\text{C-NMR}$, δ_{C} (CDCl_3 , TMS): 25.56, 25.73, 29.16, 45.26, 127.94, 128.28, 132.40, 136.07, 203.31.

Anal. Calcd for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.39; H, 6.85; N, 12.10.

3-(2, 4-Dichlorophenyl)-5-(*p*-methoxyphenyl)-1,2,4-oxadiazole (**3g**).

This oxadiazole was prepared in the general way and has mp 139-141 °C (ethanol); ¹H-NMR, δ_H (CDCl₃, TMS): 3.91 (s, 3H), 7.04 (d, 2H, J=8.9 Hz), 7.40 (dd, 1H, J=8.4 Hz and J=2.0 Hz), 7.57 (d, 1H, J=1.9 Hz), 8.00 (d, 1H, J=8.4 Hz), 8.21 (d, 2H, J=8.8 Hz); ¹³C-NMR, δ_C (CDCl₃, TMS): 55.45, 114.50, 116.37, 124.95, 127.21, 130.06, 130.72, 132.46, 134.25, 137.04, 163.28, 166.81, 175.15.

Anal. Calcd for C₁₅H₁₀Cl₂N₂O₂: C, 56.07; H, 3.11; N, 8.723. Found: C, 55.83; H, 3.18; N, 8.38.

3-(4-Chlorophenylmethyl)-5-(4-nitrophenyl)-1, 2, 4-oxadiazole (**3h**).

This oxadiazole was prepared in the general way and has mp 132-134 °C (ethanol); ¹H-NMR, δ_H (CDCl₃, 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); ¹³C-NMR, δ_C (CDCl₃, 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 C₁₅H₁₀ClN₃O₃: C, 57.06; H, 3.19; N, 13.31. Found: C, 57.40; H, 3.25; N, 13.20.

3-(4-Chlorophenyl)-5-(4-nitrophenyl)-1,2,4-oxadiazole (**3i**).

This oxadiazole was prepared in the general way and has mp 163-165 °C (ethanol); ¹H-NMR, δ_H (CDCl₃, TMS): 7.54 (d, 2H, J=5.8 Hz), 8.14 (d, 1H, J=5.8 Hz), 8.30-8.45 (m, 4H); ¹³C-NMR, δ_C (CDCl₃, TMS): 124.31, 128.78, 129.14, 129.25, 129.36, 129.47, 137.74, 150.20, 168.54, 173.75.

Anal. Calcd for C₁₄H₈ClN₃O₃: C, 55.73; H, 2.67; N, 13.93. Found: C, 55.42; H, 2.87; N, 13.63.

3-Cyclohexyl-5-(4-nitrophenyl)-1,2,4-oxadiazole (**3j**).

This oxadiazole was prepared in the general way and has mp 101-103 °C (ethanol); ¹H-NMR, δ_H (CDCl₃, TMS): 1.26-1.50 (m, 3H), 1.65 (dq, 2H, J=13 Hz and J=3 Hz), 1.71-1.78 (m, 1H), 1.89 (td, 2H, J=13 Hz and J=3 Hz), 1.97-2.11 (m, 2H), 2.91 (tt, 1H, J=13 Hz and J=3 Hz), 8.32 (d, 2H, J=8.9 Hz), 8.39 (d, 2H, J=8.9 Hz); ¹³C-NMR, δ_C (CDCl₃, 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 C₁₄H₁₅N₃O₃: C, 61.53; H, 5.49; N, 15.38. Found: C, 61.28; H, 5.65; N, 15.10.

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