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Magnesia-supported hydroxylamine hydrochloride in the presence of sodium carbonate as an efficient reagent for the synthesis of 1,2,4-oxadiazoles from nitriles

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Abstract—An efficient one-pot method has been developed for the synthesis of 1,2,4-oxadiazoles through a one-pot reaction of nitriles with hydroxylamine hydrochloride in the presence of magnesia-supported sodium carbonate followed by reaction with acyl halides under solvent-free conditions using microwave irradiation. This method is easy, rapid and good yielding.
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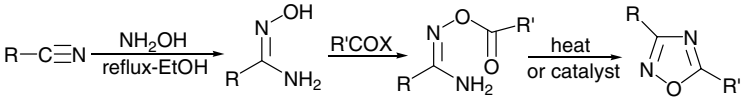
Many heterocyclic compounds are pharmaceutically important natural and synthetic materials. The remarkable ability of heterocyclic nuclei to serve both as biomimetics and active pharmacophores has largely contributed to their unique value as traditional key elements of numerous drugs.[1] The oxadiazole nucleus is a well studied 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] a growth hormone secretagogue,[6] and 5-HT agonists.[7] Among oxadiazoles, 1,2,4-oxadiazole derivatives have gained importance in medicinal chemistry. In the literature, 1,2,4-oxadiazoles have shown affinities for serotonin and norepinephrine transporters.[4] The 1,2,4-oxadiazole ring system has also been used as a urea bioisostere in β_3 adrenergic receptor agonists.[8] Several methods have been reported in the literature for the synthesis of 1,2,4-oxadiazoles.[9–15] In general 1,2,4-oxadiazoles are prepared in two steps by *O*-acylation of an amidoxime with an activated carboxylic acid derivative, typically an active acyl chloride, followed by cyclodehydration (Scheme 1).[16] Cyclization can be effected by treating an *O*-acylamidoxime with bases such as NaH or NaOEt at room temperature, or pyridine with heating.[17] Recently, the use of tetrabutylammonium fluoride as catalyst and solid support has been reported for the cyclization of *O*-acylamidoximes to 1,2,4-oxadiazoles.[18,19]

The development of simple and general synthetic routes for widely used organic compounds from readily available reagents is one of the major challenges in organic synthesis. In recent years, the use of reagents and catalysts immobilised on solid supports has received considerable attention.[20] Such reagents not only simplify purification processes but also help prevent release of reaction residues into the environment. Reagents supported on organic polymers and within and/or on the surface of inorganic matrices have all been reported. The application of microwave energy to accelerate organic reactions is of increasing interest and offers several advantages over conventional techniques.[21] Syntheses that normally require lengthy periods, can be achieved conveniently and very rapidly in a microwave oven. In



Scheme 1.

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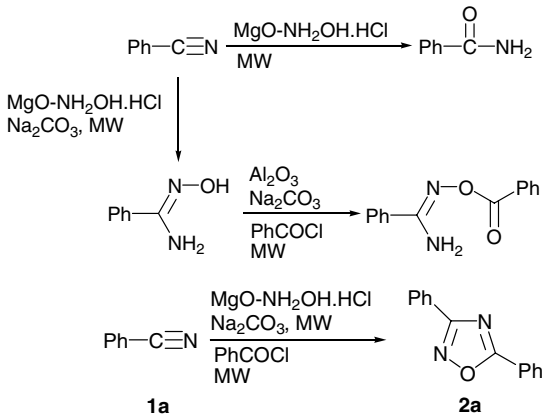
recent years, microwave irradiation has been reported for the synthesis of 1,2,4-oxadiazoles in the presence of solvent or under solvent-free conditions.[22] However, often when carrying out a reaction in a microwave oven the use of a solvent can sometimes be avoided, which is important in order to make the synthesis more environmentally friendly ('green chemistry'). Moreover, all of the above methods are not one-pot methods and require amidoximes as starting materials. These observations led us to investigate the possibility of improving the methods used for the synthesis of 1,2,4-oxadiazoles under microwave irradiation. As part of our efforts to explore the utility of solid-supported reagents for the synthesis of heterocyclic compounds under microwave irradiation,[23] we report a new method for the synthesis of 1,2,4-oxadiazoles from nitriles through a one-pot reaction of nitriles with hydroxylamine hydrochloride in the presence of magnesia-supported sodium carbonate followed by reaction with acyl halides under solvent-free conditions (Scheme 2, Table 1).

Initially, we carried out the reaction of benzonitrile **1a** in a mixture of magnesia-supported hydroxylamine hydrochloride under microwave irradiation to afford the corresponding benzamide in 80% yield after 2 min. When

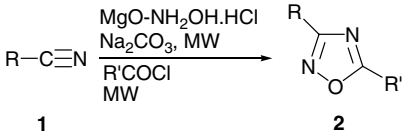


Scheme 2.

Table 1. Reaction of nitriles with hydroxylamine hydrochloride in the presence of magnesia-supported sodium carbonate followed by reaction with acyl halides under solvent-free conditions using microwave irradiation

Entry	R **1**	R′	Reaction time (min)	Yield[a] (%) **2**
a	C_6H_5–	C_6H_5–	3	50
b	C_6H_5–	*p*-$CH_3OC_6H_4$–	3	42
c	C_6H_5–	*p*-$O_2NC_6H_4$–	3	43
d	*p*-$ClC_6H_4CH_2$	C_6H_5–	4	40
e	*p*-$ClC_6H_4CH_2$	*p*-$O_2NC_6H_4$–	4	46
f	*p*-ClC_6H_4–	C_6H_5–	2	53
g	*p*-ClC_6H_4–	*p*-$CH_3OC_6H_4$–	2	42
h	2,4-$Cl_2C_6H_3$–	C_6H_5–	2	46
i	2,4-$Cl_2C_6H_3$–	*p*-$O_2NC_6H_4$–	2	41
j	2,4-$Cl_2C_6H_3$–	*p*-$CH_3OC_6H_4$–	2	40
k	*m*-ClC_6H_4–	C_6H_5–	2	70
l	Cyclohexyl	C_6H_5–	5	44

[a] Yield (over two steps, based on nitrile) refers to total isolated yield by column chromatography.



Scheme 3.

this reaction was carried out in the presence of sodium carbonate for 2 min, it afforded the corresponding benzamidoxime in 78% yield. Reaction of the benzamidoxime, without separation, with benzoyl chloride under solvent-free conditions using microwave irradiation, gave 3,5-diphenyl-1,2,4-oxadiazole (**2a**) in 50% yield (over two steps, based on benzonitrile). Reaction of the benzamidoxime with benzoyl chloride in the presence of alumina-supported sodium carbonate gave only the corresponding *O*-acylamidoxime as the major product (Scheme 2). Sodium bicarbonate ($NaHCO_3$) was not as effective as sodium carbonate and gave very low yields of the required product.

These results prompted us to extend this process to other nitriles. Interestingly, nitriles reacted smoothly with hydroxylamine hydrochloride in the presence of magnesia-supported sodium carbonate followed by reaction with acyl halides under solvent-free conditions using microwave irradiation to produce the corresponding 1,2,4-oxadiazoles in good yields (Table 1 and Scheme 3). As shown in Table 1, benzonitrile (**1a**) in the presence of *p*-methoxybenzoyl chloride afforded 3-phenyl-5-(*p*-methoxyphenyl)-1,2,4-oxadiazole (**2b**) in 42% yield. Other benzonitriles also reacted with hydroxylamine hydrochloride in the presence of magnesia-supported sodium carbonate under microwave irradiation followed by reaction with acyl halides to give the desired compounds in good yields.[24]

In summary, the rapid reaction rates, mild reaction conditions, moderate to good yields and the relatively clean reactions make this method an attractive and useful contribution to present methodologies for the synthesis of 1,2,4-oxadiazoles.

Acknowledgement

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24. The supported reagent was prepared by combination of hydroxylamine hydrochloride (5 mmol, finely ground), sodium carbonate (5 mmol) and magnesia (2 g) in a mortar and pestle by grinding them together until a fine, homogeneous, powder was obtained (5–10 min). Nitrile (5 mmol, finely ground for solid nitriles) was added to this mixture. The reaction mixture was irradiated with microwaves for 3 min at 180 W. The acyl chloride (7 mmol) was then added and the mixture was shaken for 5 min and irradiated for 2–5 min at 600 W (a kitchen-type Samsung microwave oven, model number CE290DN, was used in all experiments). The reaction mixture was ground in a mortar and pestle until a fine, homogeneous, powder was obtained. The mixture was chromatographed on silica gel (hexane–EtOAc 95:5) to give the pure product in 40–70% yield. All products gave satisfactory spectral data in accord with the assigned structures and literature reports.[17,22,23c,d] For new compounds, spectral data are reported as follows:

3-(4-Chlorophenylmethyl)-5-phenyl-1,2,4-oxadiazole (**2d**): Mp 76–78 °C (ethanol). IR (KBr): 3020, 2910, 1655, 1635 cm^{-1}; ^1H NMR, δ_H ($CDCl_3$, TMS-500 MHz): 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-125 MHz): 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 $C_{15}H_{11}ClN_2O$: C, 66.55; H, 4.10; N, 10.35. Found: C, 66.38; H, 4.36; N, 9.89.

3-(4-Chlorophenylmethyl)-5-(4-nitrophenyl)-1,2,4-oxadiazole (**2e**): Mp 132–134 °C (ethanol). IR (KBr): 3015, 2920, 1632, 1625 cm^{-1}; ^1H NMR, δ_H ($CDCl_3$, TMS-500 MHz): 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-125 MHz): 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 $C_{15}H_{10}ClN_3O_3$: C, 57.06; H, 3.19; N, 13.31. Found: C, 57.40; H, 3.25; N, 13.20.

3-(2,4-Dichlorophenyl)-5-phenyl-1,2,4-oxadiazole (**2h**): Mp 140–142 °C (ethanol). ^{1}H NMR, δ_H ($CDCl_3$, TMS-500 MHz): 7.41 (dd, 1H, $J = 8.4$ 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}C NMR, δ_C ($CDCl_3$, TMS-125 MHz): 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 $C_{14}H_8Cl_2N_2O$: C, 57.73; H, 2.74; N, 9.62. Found: C, 57.48; H, 2.86; N, 9.30.

3-(2,4-Dichlorophenyl)-5-(p-methoxyphenyl)-1,2,4-oxadiazole (**2j**): Mp 139–141 °C (ethanol). ^{1}H NMR, δ_H ($CDCl_3$, TMS-500 MHz): 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); ^{13}C NMR, δ_C ($CDCl_3$, TMS-125 MHz): 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 $C_{15}H_{10}Cl_2N_2O_2$: C, 56.07; H, 3.11; N, 8.72. Found: C, 55.83; H, 3.18; N, 8.38.

3-Cyclohexyl-5-phenyl-1,2,4-oxadiazole (**2l**): Mp 159–161 °C (ethanol). IR (KBr): 3072, 2931, 1663, 1643 cm^{-1}; ^{1}H NMR, δ_H ($CDCl_3$, TMS-500 MHz): 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, $J = 7$ Hz), 7.88 (d, 2H, $J = 8$ Hz); ^{13}C NMR, δ_C ($CDCl_3$, TMS-125 MHz): 25.56, 25.73, 29.16, 45.26, 127.94, 128.28, 132.40, 136.07, 203.31; EI–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.