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Organic reactions in water: an efficient method for the synthesis of 1,2,4-oxadiazoles in water

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ABSTRACT

A simple and efficient process has been developed for the synthesis of 1,2,4-oxadiazoles in good yields through the reaction of amidoximes with anhydrides under catalyst-free conditions in water.

Heterocyclic compounds are valuable natural and synthetic materials that have been used as intermediates and solvents in pharmaceutical, chemical, textile, dye-stuff, petroleum, and photography industries. The remarkable ability of the heterocyclic nuclei to serve both as biomimetics and active pharmacophores has largely contributed to their 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. 1,2,4-Oxadiazoles have shown affinities for serotonin, norepinephrine transporters,[4] and have also been used as a urea bioisostere in β_3 adrenergic receptor agonists.[8] The 1,2,4-oxadiazole motif is found in several drugs including the potent S1P1 agonist **I** and the metabotropic glutamate subtype 5 (mGlu5) receptor antagonist **II** (Fig. 1).[9] Recently, the anticancer activities of a library of 1,2,4-oxadiazoles were studied by Kumar et al.[10] Several methods have been reported for the synthesis of 1,2,4-oxadiazoles.[11–17] In general, the two most common routes are: (i) 1,3-dipolar cycloaddition of nitriles to nitrile oxides; (ii) cyclization of amidoxime derivatives.[18] In the second method, 1,2,4-oxadiazoles are prepared in two steps by O-acylation of an amidoxime, which can be easily prepared by the reaction of nitriles with hydroxylamine, with an activated carboxylic acid derivative, typically an active acyl chloride, followed by cyclodehydration (Scheme 1). Cyclization can be achieved by treating the *O*-acylamidoxime with bases such as NaH or NaOEt at room temperature, or pyridine on heating.[19] Cyclization of the *O*-acyl amidoxime formed from the reaction of an amidoxime with an acyl chloride is generally the most difficult and time-consuming step and often requires sealed tube conditions and long reaction times. Recently, the use of tetrabutylammonium fluoride as a catalyst and solid support was reported for the cyclization of *O*-acylamidoximes into 1,2,4-oxadiazoles.[20] In an attempt to improve on these procedures, microwave-assisted methods for this cyclization have recently been reported.[21]

The development of simple and general routes for widely used organic compounds from the readily available reagents is one of the major challenges in organic synthesis. Organic reactions in aqueous media have attracted much recent attention.[22] Water is an abundant, cheap, and environmentally friendly solvent. Indeed water exhibits unique reactivity and selectivity, which is different

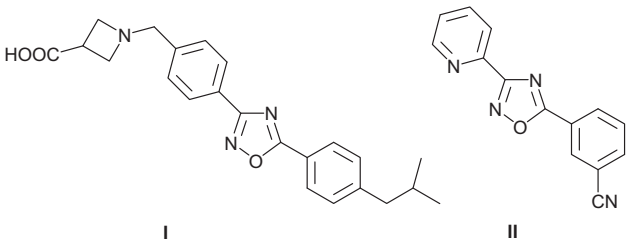

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Figure 1. Biologically active 1,2,4-oxadiazoles.

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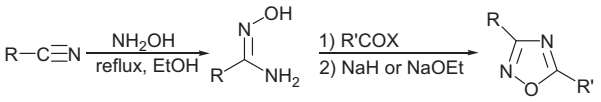


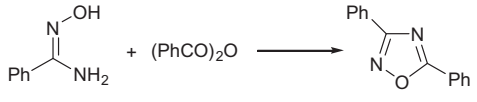
Scheme 1. Preparation of 1,2,4-oxadiazoles.

from that of conventional organic solvents. Thus, the development of novel reactivity and selectivity is one of the challenges of aqueous chemistry. As part of our efforts to explore the utility of novel methods for the synthesis of heterocyclic compounds,[23] we report here a new method for the synthesis of 1,2,4-oxadiazoles via reaction of amidoximes with anhydrides under mild, catalyst-free conditions in water.

Initially, we carried out the reaction of benzamidoxime (**1a**) with benzoic anhydride (**2a**), as a model reaction, in various solvents under catalyst-free conditions. The progress of the reaction was monitored by TLC and the experimental data for the screening conditions are listed in Table 1.

Among the solvents studied (EtOH, EtOAc, dichloromethane, chloroform, toluene, and water), water was found to be the most suitable (Table 1). Treatment of **1a** with **2a** failed to give the corresponding 1,2,4-oxadiazole adduct **3a** in water after 24 h at ambient temperature (entry 11). When the reaction was carried out at reflux, compound **3a** was obtained in 93% isolated yield after 12 h (entry 12). Benzoyl chloride (PhCOCl) was not as effective as benzoic anhydride and gave a very low yield of the product. These results prompted us to extend this process to other amidoximes and anhydrides. Interestingly, amidoximes reacted smoothly with anhydrides under catalyst-free conditions in water to produce the corresponding 1,2,4-oxadiazoles in good yields (Table 2 and Scheme 2). As shown in Table 2, various substituted benzamidoximes **1a–1e** in the presence of benzoic anhydride (**2a**) afforded 1,2,4-oxadiazoles **3a–3e** in 52–93% isolated yields. Treatment of benzoic anhydride with aliphatic amidoximes **1f,g** gave the desired compounds **3f,g** in good yields (entries 6 and 7). The reaction of *p*-methylbenzoic anhydride with amidoximes in water under catalyst-free conditions gave the desired compounds **3h–3j** in moderate to good yields (entries 8–10). The reaction of hexanoic anhydride, an aliphatic anhydride, with various amidoximes gave the corresponding adducts **3k–3n** in lower 35–53% yields, which is possibly due to the electronic effect (entries 11–14). Thus, the cyclization reaction reported herein tolerates a wide variety of

Table 1
Reaction of benamidoxime (**1a**) with benzoic anhydride (**2a**) in various solvents



1a **2a** **3a**

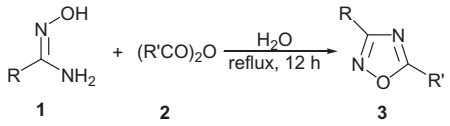
Entry	Solvent	Temperature (°C)	Time (h)	Yield[a] (%)
1	EtOH	rt	24	10
2	EtOAc	rt	24	<5
3	CH_2Cl_2	rt	24	—
4	$CHCl_3$	rt	24	<5
5	Toluene	rt	24	<5
6	EtOH	Reflux	12	86
7	EtOAc	Reflux	12	69
8	CH_2Cl_2	Reflux	12	—
9	$CHCl_3$	Reflux	12	<5
10	Toluene	Reflux	12	84
11	H_2O	rt	24	—
12	H_2O	Reflux	12	93

[a] Isolated yield.

Table 2
Reaction of amidoximes with anhydrides in water under catalyst-free conditions

Entry	R	R′	Product	Yield %[a]
1	C_6H_5–	C_6H_5–	**3a**	93
2	*p*-ClC_6H_4–	C_6H_5–	**3b**	60
3	*p*-BrC_6H_4–	C_6H_5–	**3c**	81
4	2,4-$Cl_2C_6H_3$–	C_6H_5–	**3d**	52
5	*m*-ClC_6H_4–	C_6H_5–	**3e**	85
6	*p*-$MeOC_6H_4CH_2$	C_6H_5–	**3f**	69
7	Cyclohexyl	C_6H_5–	**3g**	86
8	C_6H_5–	*p*-$CH_3C_6H_4$–	**3h**	81
9	2,4-$Cl_2C_6H_3$–	*p*-$CH_3C_6H_4$–	**3i**	72
10	*p*-BrC_6H_4–	*p*-$CH_3C_6H_4$–	**3j**	76
11	C_6H_5–	*n*-C_5H_{11}–	**3k**	53
12	2,4-$Cl_2C_6H_3$–	*n*-C_5H_{11}–	**3l**	40
13	*m*-ClC_6H_4–	*n*-C_5H_{11}–	**3m**	35
14	*p*-BrC_6H_4–	*n*-C_5H_{11}–	**3n**	48

[a] Yield refers to isolated yield following column chromatography.



1 **2** **3**

Scheme 2. Reaction of amidoximes with anhydrides in water.

amidoximes and anhydrides for the synthesis of 1,2,4-oxadiazoles.[24]

In summary, we have developed a simple and practical method for the synthesis of 1,2,4-oxadiazoles via the reaction of readily available amidoximes with anhydrides in water under catalyst-free conditions. The simple work-up, mild reaction conditions, moderate to good yields, and clean reactions are the advantages of this method.

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Supplementary data

Supplementary data (experimental procedures and spectroscopic characterization for compounds **3b–3n)** associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.081.

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24. The amidoxime (10 mmol, amidoxime was obtained according to the method of our previously published article)[23d] and anhydride (11 mmol) were added to H_2O (20 mL) and the solution was stirred for 12 h at reflux. After cooling, the reaction mixture was washed with Et_2O (3 × 50 mL). Organic layers were dried over $MgSO_4$ and evaporated. The residue was subjected to column chromatography on silica gel with EtOAc/*n*-hexane (1:9) and evaporation of the solvent under reduced pressure gave pure products in 35–93% yields. All products gave satisfactory spectral data in accord with the assigned structures. Spectral data for the representative examples: *3,5-diphenyl-1,2,4-oxadiazole* (**3a**): mp: 108–109 °C [Lit.[18b] 109–110 °C]; ^{1}H NMR, δ_H ($CDCl_3$, 400 MHz): 7.52–7.67 (m, 6H), 8.20–8.28 (m, 4H); ^{13}C NMR, δ_c ($CDCl_3$, 100 MHz): 124.34, 127.00, 127.56, 128.20, 128.88, 129.13, 131.22, 132.76, 169.00, 175.74. *3-(2,4-Dichlorophenyl)-5-phenyl-1,2,4-oxadiazole* (**3d**): mp: 138–140 °C[Lit.[23d] 140–142 °C]; ^{1}H NMR, δ_H ($CDCl_3$, 400 MHz): 7.44 (dd, 1H, J = 8.4 and J = 2.0 Hz), 7.57–7.66 (m, 4H), 8.04–8.24 (m, 3H); ^{13}C NMR, δ_c ($CDCl_3$, 100 MHz): 123.95, 124.86, 127.38, 128.26, 129.20, 130.89, 132.60, 133.02, 134.55, 137.29, 167.08, 175.39.