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One-Pot Synthesis of 3,5-Disubstituted 1,2,4-Oxadiazoles Directly from Nitrile and Hydroxylamine Hydrochloride Under Solvent-Free Conditions Using Potassium Fluoride as Catalyst and Solid Support

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ONE-POT SYNTHESIS OF 3,5-DISUBSTITUTED 1,2,4-OXADIAZOLES DIRECTLY FROM NITRILE AND HYDROXYLAMINE HYDROCHLORIDE UNDER SOLVENT-FREE CONDITIONS USING POTASSIUM FLUORIDE AS CATALYST AND SOLID SUPPORT

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A one-pot synthesis of 3,5-disubstituted 1,2,4-oxadiazoles with two identical substituents directly from the reaction of nitriles and hydroxylamine hydrochloride in the presence of potassium fluoride as catalyst and solid support under solvent-free condition is described. Moreover, the formation of products has been discussed, and a plausible mechanism has been presented. Simplicity of the process, workup in aqueous media, and excellent yields are some advantages of this method.

Keywords: Amidoximes; nitriles; one-pot reaction; 1,2,4-oxadiazole; potassium fluoride; solvent-free condition

For reasons of economy and pollution prevention, solvent-free methods are of fundamental and growing interest and are used to modernize classical procedures by making them cleaner, safer, and easier to perform. The demand for clean and efficient chemical syntheses is becoming more urgent. The so-called green technologies are alternative ways to reduce drastic requirements for reactions. Among proposed solutions, solvent-free conditions are popular. Now, it is often claimed that "the best solvent is no solvent."[1]

Among oxadiazoles, 1,2,4-oxadiazole derivatives have received increased importance in medicinal chemistry. These compounds, when selectively functionalized, have shown affinities for serotonin, norepinephrine transporters,[2] and urea bioisostere in β_3-adrenergic receptor agonists.[3]

Several methods have been reported in the literature for the synthesis of these useful heterocycles.[4–10] Most commonly, they have been prepared by a two-step process involving *O*-acylation of an amidoxime with an activated carboxylic acid

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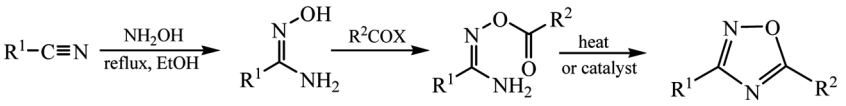


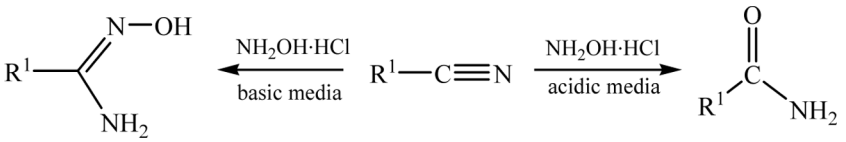
Scheme 1. Main reaction pathway for the formation of 1,2,4-oxadiazoles.

derivative, typically an active acyl chloride, followed by cyclodehydration (Scheme 1).

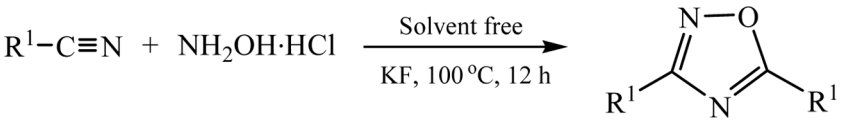
These methods, however, suffer from several drawbacks. Toxicity, high reactivity of acid chlorides, difficult storage and handling, as well as limited commercial availability of acid chlorides are major disadvantages of using these chemicals for synthetic purposes. In addition, carboxylic acids need a coupling reagent such as DCC, EDC, CDI, TBTU, HOBt, or HBTU to react with amidoximes. In these cases, the reaction time is relatively long. Application of organic solvents during the main process of synthesis and/or workup is also another deficiency of these methods from the green chemistry point of view.[11]

Very recently, different methods have been reported for the synthesis of 1,2,4-oxadiazoles. Some of them include formation of these compounds under microwave irradiation in the presence of solvent or under solvent-free conditions in which amidoximes are required as starting materials.[12] Also, 3,5-disubstituted 1,2,4-oxadiazoles with two identical substituents were synthesized in ethylene glycol with sodium carbonate under heating at 195 °C for 30 h, in which a higher temperature and longer reaction time were required, but the proposed mechanism was not completely described.[13] As shown in Scheme 2, for conversion of nitrile to amidoxime, we need basic (not acidic) media, because in acidic media the nitrile would convert to an amide.[14]

Bases such as NaH or NaOEt at room temperature as well as pyridine with heating[10] and tetrabutylammonium fluoride[15] in dichloromethane have been reported for the cyclization and cyclodehydration of formed intermediates. Therefore, it seems that strong bases can promote this reaction. To improve the method used for the synthesis of 3,5-disubstituted 1,2,4-oxadiazoles with two identical substituents, we chose potassium fluoride as a strong base and solid support under solvent-free conditions. Potassium fluoride has proven to be a versatile reagent in many organic reactions such as decarboxylation,[16] Michael addition,[17] and various Knoevenagel reactions.[18] The main advantage of using potassium fluoride is in the ease of the workup process. An aqueous potassium fluoride solution can dissolve by-products, such as amidoxime, and we are able to separate the pure 1,2,4-oxadiazole from the reaction mixture by simple filtration. Almost all of the reported methods for the conversion of nitriles to amidoximes require high temperatures under reflux



Scheme 2. Conversion of nitriles to amides and amidoximes in acidic and basic media.

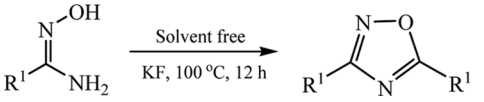


Scheme 3. Potassium fluoride–catalyzed synthesis of 3,5-disubstituted 1,2,4-oxadiazoles with two identical substituents.

conditions and long reaction times. Because of this and the safety profile of hydroxylamine hydrochloride,[19] we adjusted the reaction temperature to 100 °C. Thus, 1,2,4-oxadiazoles were obtained in excellent yields and a good state of purity (under this condition) using a strong base such as potassium fluoride (Scheme 3).

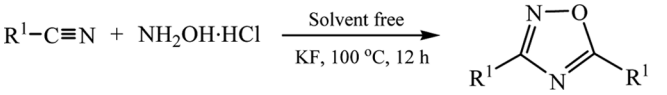
In the formation of 3,5-disubstituted 1,2,4-oxadiazoles with two identical substituents, three possibilities can be imagined:

1. Thermal decommission of amidoxime [Eq. (1)].



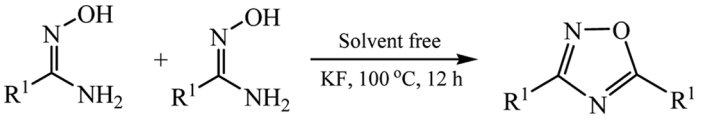
(1)

2. Reaction between nitrile and amidoxime [Eq. (2)].



(2)

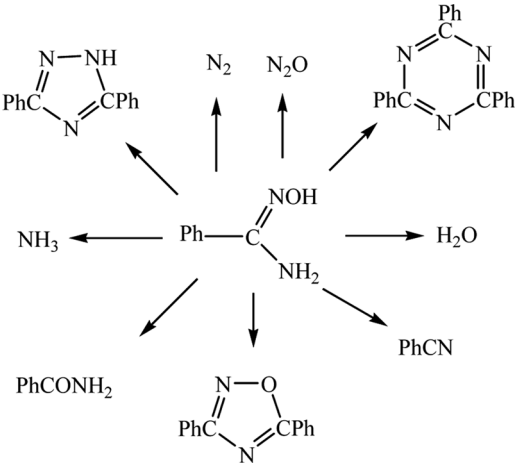
3. Reaction of two amidoximes with each other [Eq. (3)].



(3)

Regarding the first equation, we found out that benzamidoxime melts at 80 °C and that it is stable up to 170 °C. At this temperature, it decomposes, yielding several products identified as nitrogen, nitrous oxide, ammonia, water, benzonitrile, benzamide, 3,5-diphenyl-1,2,4-oxadiazole, 3,5-diphenyl-l,2,4-triazole, and triphenyl-1,3,5-triazine[10d] (Scheme 4). However, in our process, only 1,2,4-oxadiazole and a minor amount of amidoxime were formed. Consequently, the hypothesis of the thermal decomposition of amidoxime during the synthesis of 1,2,4-oxadiazole could be ruled out this way.

To find out whether the formation of 1,2,4-oxadiazoles could result from the reaction of an amidoxime and nitrile [Eq. (2)], we studied the effect of the amount of hydroxylamine hydrochloride on the formation and the yield of 1,2,4-oxadiazoles. Results are shown in Table 1.



Scheme 4. Thermal decomposition of benzamidoximes.

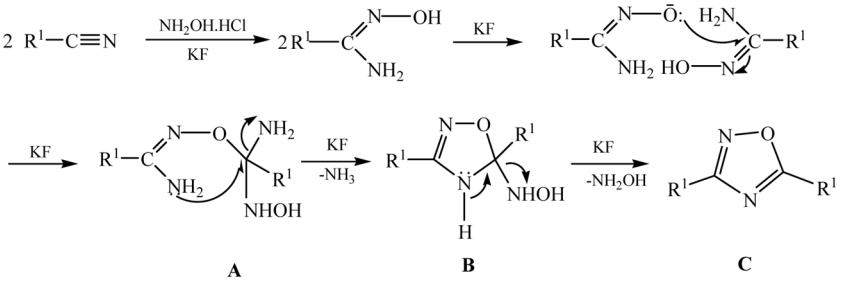
At the beginning of the reaction (after 1 h), all of the nitriles were converted to amidoxime, and there was no nitriles left to react with amidoxime (Table 1, entry 1). When the heating continued for 12 h, 1,2,4-oxadiazole was obtained in 88% yield (Table 1, entry 2). In the presence of excess amounts of nitrile (2 mmol), the excess nitriles did not enter the reaction and remained untouched until the end of the reaction (Table 1, entry 3). Thus, the only possibility remaining is the reaction of two amidoxime molecules with each other to give 3,5-disubstituted 1,2,4-oxadiazoles with two identical groups [Eq. (3)].[20]

We also performed the reaction in the presence of different amounts of KF, and application of 1 g potassium fluoride gave the best result. Any further increase in the amount of potassium fluoride did not have much effect on the yield of the reaction (Table 1, entry 4). It is reasonable to assume that at first the in situ formation of amidoximes happened and then two molecules of amidoximes condensed with each other to form the intermediate **A**. Then, this intermediate, under the reaction conditions, was cyclized to disubstituted 4,5-dihydro-1,2,4-oxadiazoline intermediate **B**, which was next aromatized to the final product **C** (Scheme 5). In fact, ammonia released in the reaction mixture was observed as another proof for the proposed mechanism.

Table 1. Screening the effect of amount of $NH_2OH \cdot HCl$ on the yield of 1,2,4-oxadiazoles[a]

Entry	KF (mmol)	$NH_2OH \cdot HCl$ (mmol)	4-ClC_6H_5CN[b] (mmol)	Amidoxime[b] (%)	1,2,4-Oxadiazole[b] (%)
1	2	2	2	98[c]	—
2	2	2	2	8	88
3	2	1	2	7	40
4	1 (g)	2	2	8	90

[a]All reactions were performed at 100 °C for 12 h.
[b]Isolated yields.
[c]1 h after the reaction.

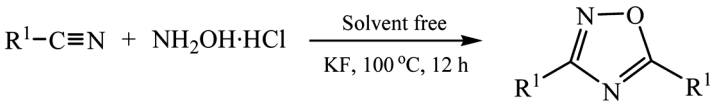


Scheme 5. Proposed mechanism for the synthesis of 3,5-disubstituted 1,2,4-oxadiazoles with two identical substituents directly from nitrile.

To obtain further information and understand the effect of the nitrile on the yield of 1,2,4-oxadiazoles, we chose a variety of structurally divergent benzonitriles possessing a wide range of functional groups, the results of which are summarized in Table 2. Among the various nitriles tested, the haloaromatics gave good yields (Table 2, entries 2–5). The interesting point about haloaromatics is that nitriles with substituents on position 4 of the ring relative to the cyano moiety react more efficiently than those with substituents on positions 2 and 3.

It is worth mentioning that electron-donating groups (Table 2, entries 6–8) reduced the rate of the formation of 1,2,4-oxadiazole. So, it seems that electronic effects play a major role in this process. The reaction was also performed with aliphatic nitriles where the reaction yield was low (Table 2, entry 9). Also, the reaction did not give good results with *o*-hydroxy and *o*-amino benzonitriles (Table 2, entries 10 and 11).

Table 2. Effect of substituents on the yield of formation of disubstituted 1,2,4-oxadiazole[a]



Entry	R^1	Yields[b] (%)	Melting point (°C)	
			Found	Reported
1	C_6H_5-	75	106–108	109–110[21]
2	4-ClC_6H_4-	90	183–184	183[13]
3	4-BrC_6H_4-	92	189–190	189–190[22]
4	2-ClC_6H_4-	85	93–94	93–93[21]
5	3-ClC_6H_4-	89	141–142	141–142[21]
6	4-$CH_3C_6H_4-$	65	104–105	104–105[21]
7	4-$CH_3OC_6H_4-$	60	127–128	128–129[13]
8	4-FC_6H_4-	75	126–127	—
9	$C_6H_5CH_2-$	Low	—	—
10	2-OHC_6H_4-	—	—	—
11	2-$NH_2C_6H_4-$	—	—	—

[a]All reactions were performed with 2 mmol nitrile, 2 mmol hydroxylamine hydrochloride, and 1 g potassium fluoride at 100 °C for 12 h.
[b]Isolated yields.

Additionally, the reaction was performed with weaker bases such as potassium carbonate and sodium bicarbonate, with a yield lower than that of potassium fluoride.

In conclusion, we have developed a solvent-free one-pot reaction for the preparation of 3,5-disubstituted 1,2,4-oxadiazoles with two identical substituents. Excellent yields, a simple purification process, short reaction times, and no use of carboxylic acid derivatives are the main advantages of this method.

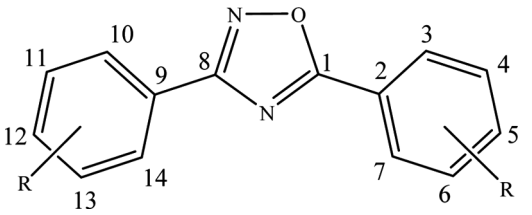
EXPERIMENTAL

General Procedure for the Synthesis of 3,5-Disubstituted 1,2,4-Oxadiazoles with Two Identical Substituents

Aramatic nitrile (2 mmol, 0.275 g), hydroxylamine hydrochloride (2 mmol, 0.138 g, finely ground), and potassium fluoride (1 g) were mixed thoroughly in a mortar and pestle by grinding to form a homogeneous mixture. This mixture was then heated at 100 °C while being stirred for 12 h. Then, the mixture was cooled, and water (10 ml) was added. The mixture was filtered with a Buchi funnel, washed with water (30 ml), and dried at 60 °C. The residues were further recrystallized from EtOH 96%. The product was obtained as colorless crystals.

Yields and melting points are shown in Table 2.

Spectral Data



3,5-Bis(phenyl)-1,2,4-oxadiazole (Table 2, entry 1). IR (KBr, cm^{-1}): 2921, 1606, 1560; ^1H NMR (300 MHz, DMSO-d_6) δ 7.56–7.76 (6H, m, 6CH), 8.07–8.19 (4H, m, 4CH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 175.43 (C_1), 126.13 (C_2), 129.58 (C_3), 129.29 (C_4), 133.38 (C_5), 129.29 (C_6), 129.58 (C_7), 168.26 (C_8), 123.35 (C_9), 127.92 (C_{10}), 127.10 (C_{11}), 131.69 (C_{12}), 127.10 (C_{13}), 127.92 (C_{14}).

3,5-Bis(4-chlorophenyl)-1,2,4-oxadiazole (Table 2, entry 2). IR (KBr, cm^{-1}): 2921, 1606, 1555, 1488; ^1H NMR (300 MHz, DMSO-d_6) δ 7.67 (d, 2H, $J = 8.3$ Hz, 2CH), 7.74 (d, 2H, $J = 8.3$ Hz, 2CH), δ 8.08 (d, 2H, $J = 8.2$ Hz, 2CH), δ 8.18 (d, 2H, $J = 8.2$ Hz, 2CH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 174.82 (C_1), 124.89 (C_2), 129.79 (C_3), 129.82 (C_4), 138.34 (C_5), 129.82 (C_6), 129.79 (C_7), 167.56 (C_8), 122.14 (C_9), 129.53 (C_{10}), 128.94 (C_{11}), 136.50 (C_{12}), 128.94 (C_{13}), 129.53 (C_{14}).

3,5-Bis(4-bromophenyl)-1,2,4-oxadiazole (Table 2, entry 3). IR (KBr, cm^{-1}): 2922, 1599, 1552, 1480; ^1H NMR (300 MHz, DMSO-d_6) δ 7.80 (d, 2H,

$J = 8.5$ Hz, 2CH), 7.87 (d, 2H, $J = 8.5$ Hz, 2CH), δ 8.01 (d, 2H, $J = 8.5$ Hz, 2CH), δ 8.10 (d, 2H, $J = 8.5$ Hz, 2CH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 174.94 (C_1), 125.20 (C_2), 132.71 (C_3), 132.45 (C_4), 127.38 (C_5), 132.45 (C_6), 132.71 (C_7), 167.66 (C_8), 122.43 (C_9), 129.86 (C_{10}), 129.07 (C_{11}), 125.35 (C_{12}), 129.07 (C_{13}), 129.86 (C_{14}).

3,5-Bis(2-chlorophenyl)-1,2,4-oxadiazole (Table 2, entry 4). IR (KBr, cm^{-1}): 2921, 1606, 1555; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.55–7.65 (m, 3H, 3CH), 7.67–7.99 (m, 3H, 3CH), 8.01 (dd, 1H, $J_1 = 7.5$ Hz, $J_2 = 1.9$ Hz, 1CH), 8.18 (dd, 1H, $J_1 = 7.7$ Hz, $J_2 = 1.65$ Hz, 1CH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 174.25 (C_1), 125.21 (C_2), 132.43 (C_3), 134.43 (C_4), 132.83 (C_5), 132.23 (C_6), 131.89 (C_7), 166.89 (C_8), 122.46 (C_9), 125.21 (C_{10}), 127.79 (C_{11}), 128.09 (C_{12}), 130.92 (C_{13}), 132.51 (C_{14}).

3,5-Bis(3-chlorophenyl)-1,2,4-oxadiazole (Table 2, entry 5). IR (KBr, cm^{-1}): 2921, 1608, 1555, 1478; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.62–7.73 (m, 3H, 3CH), 7.80–7.84 (m, 1H, 1CH), 8.04–8.08 (m, 2H, 2CH), 8.14– 8.21 (m, 2H, 2CH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 174.53 (C_1), 133.31 (C_2), 134.20 (C_3), 125.09 (C_4), 134.00 (C_5), 131.70 (C_6), 131.44 (C_7), 167.32 (C_8), 131.65 (C_9), 127.93 (C_{10}), 127.79 (C_{11}), 126.70 (C_{12}), 126.73 (C_{13}), 127.51 (C_{14}).

3,5-Bis(4-metylphenyl)-1,2,4-oxadiazole (Table 2, entry 6). IR (KBr, cm^{-1}): 3028, 2955, 1608, 1558, 1490; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.37 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 7.37 (d, 2H, $J = 8.0$ Hz, 2CH), 7.43 (d, 2H, $J = 8.0$ Hz, 2CH), δ 7.95 (d, 2H, $J = 8.1$ Hz, 2CH), δ 8.03 (d, 2H, $J = 8.1$ Hz, 2CH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 175.29 (C_1), 123.41 (C_2), 130.07 (C_3), 129.76 (C_4), 143.71 (C_5), 129.76 (C_6), 130.07 (C_7), 168.11 (C_8), 120.68 (C_9), 127.82 (C_{10}), 127.00 (C_{11}), 141.52 (C_{12}), 127.00 (C_{13}), 127.82 (C_{14}).

3,5-Bis(4-flourophenyl)-1,2,4-oxadiazole (Table 2, entry 8). Milky crystal; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.43–7.46 (2H, m, 2CH), 7.50–7.53 (2H, m, 2CH), 8.13–8.16 (2H, m, 2CH), 8.25–8.28 (2H, m, 2CH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 176.37 (C_1), 124.16 (C_2), 134.28 (C_3), 130.44 (C_4), 165.89 (C_5), 130.44 (C_6), 134.28 (C_7), 168.34 (C_8), 123.61 (C_9), 128.79 (C_{10}), 117.23 (C_{11}), 161.20 (C_{12}), 117.23 (C_{13}), 128.79 (C_{14}); MS (70 ev) m/z (%): 258 (M^+, 94%), 137 (100%), 109 (43%), 95 (29%).

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