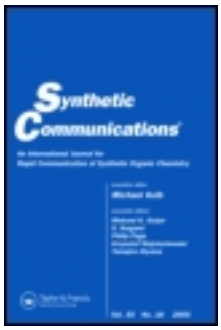

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

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http://www.tandfonline.com/loi/lsyc20

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Accepted author version posted online: 27 Aug 2013.

To cite this article: Synthetic Communications (2013): A Mild and Efficient One-Pot Synthesis of 3,5-disubstituted 1,2,4-oxadiazoles From Nitriles Mediated by K_3PO_4 , Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, DOI: 10.1080/00397911.2013.797997

To link to this article: http://dx.doi.org/10.1080/00397911.2013.797997

A Mild and Efficient One-pot Synthesis of 3,5-disubstituted 1,2,4-Oxadiazoles from Nitriles Mediated by K_3PO_4

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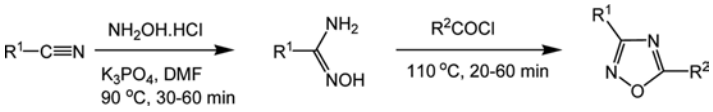
Abstract

Potassium phosphate, K_3PO_4, has been proved to be a cheap, strong, and efficient reagent for the one-pot synthesis of 3,5-disubstituted-1,2,4-oxadiazoles from nitriles and acid chlorides under mild conditions.

[Supplementary materials are available for this article. Go to the publisher's online edition of *Synthetic Communications*® for the following free supplemental resource(s): Full experimental and spectral details.]



KEYWORDS: 1,2,4-Oxadiazoles; potassium phosphate; nitriles; amidoximes; acid chlorides

INTRODUCTION

Recently, the compounds containing the 1,2,4-oxadiazole scaffold have received considerable attention because of their unique chemical structure and broad spectrum of biological properties including histamine H3 antagonism,[1] muscarinic agonism,[2] tyrosine kinase inhibition,[3] antitumor,[4] anti-inflammation,[5] and monoamine oxidase

inhibition.[6] In addition, anticancer activity of some 3,5-disubstituted-1,2,4-oxadiazoles has recently been reported.[7] The 1,2,4-oxadiazoles are also widely used as heterocyclic amide or ester bioisosters[8] and in the design of dipeptidomimetics as peptide building blocks,[9] and are found in several drugs and drug leads[4] including the metabotropic glutamate subtype 5 (mGlu 5) receptor (Fig. 1, **1**),[10] the muscarinic receptor for the treatment of Alzheimer's disease (Fig. 1, **2**),[11] and the potent S1P1 agonist (Fig.1, **3**).[12]

Generally, five synthetic methods are used for the preparation of 1,2,4-oxadiazole scaffold: (i) cyclization of *O*-acylamidoxime formed from reaction of the amidoxime with a carboxylic acid or its activated derivative,[13] (ii) condensation of *N*-acylamidoximes,[14] (iii) 1,3-dipolar cycloaddition of nitriles to nitrile oxides,[15] (iv) oxidation of 4,5-dihydro-1,2,4-oxadiazoles [16] and (v) electrocyclic ring closure of nitrenoides.[17] More commonly, 1,2,4-oxadiazoles are prepared from amidoximes and carboxylic acid derivatives in two steps. In the first step, the amidoxime, prepared by the addition of hydroxylamine to a nitrile compound, is *O*-acylated by a carboxylic acid or its activated derivative; the heterocycle is subsequently formed by intramolecular cyclodehydration.[18–20] However, to react with amidoximes, carboxylic acid needs a coupling reagent, such as diisopropylcarbodiimide (DIC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), *O*-benzotriazol-1-yl-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate (HBTU), and dicyclohexylcarbodiimide (DCC).[13] In these cases, the reaction time is relatively long. Moreover, many methods are not one-pot procedures and instead of readily available nitriles, they require amidoximes, as their starting materials;[13a,c,d,16b] also, some of the reported procedures

suffer from long reaction times and harsh reaction conditions which exclude additional functionality on the oxadiazole.[13a,c,d,18] Very recently, a one-pot synthesis of 1,2,4-oxadiazoles directly from nitriles and hydroxylamine hydrochloride using potassium fluoride has been introduced;[21] this method, however, has the following drawbacks: (a) synthesizing oxadiazoles with only two identical substituents on the 3- and 5-positions, (b) having a long reaction time (12 h), and (c) being inapplicable to aliphatic nitriles. In fact, to improve these procedures several microwave-[18,22] and ultrasound-assisted[23] methods have been introduced.

RESULTS AND DISCUSSION

Tripotassium phosphate, K_3PO_4, continues to attract the attention of organic chemists due to its versatile applications in synthetic chemistry; it is a cheap, non-toxic, and strong inorganic base (p*Ka* 12.32 for the conjugate acid), used as an alternative non-nucleophilic base in several reactions.[24] In the framework of our ongoing research on the synthetic utility of potassium phosphate in different reactions,[25] we have examined its application in the one-pot synthesis of 1,2,4-oxadiazoles from readily available starting materials.

Owing to the pharmacological importance of the compounds containing the 1,2,4-oxadiazole scaffold, in this communication, we report a very simple, convenient, and high yielding one-pot method mediated by K_3PO_4, as a strong base, for the synthesis of these compounds from nitriles and hydroxylamine hydrochloride.

In initial studies, benzonitrile (1 equiv) and hydroxylamine hydrochloride (1.25 equiv)

were first mixed and monitored, by TLC, with various amounts of K_3PO_4, solvents, and temperatures to test the feasibility of the reagent to produce the corresponding amidoxime (Scheme 1, Table 1). Different solvents such as toluene, 1,2-dichloroethane, and *N,N*-dimethylformamide (DMF) were screened for this reaction; the best result was obtained in

DMF with 2 equiv of K_3PO_4 at 90 °C (Table 1, entry 3). Then, various amounts of K_3PO_4, and temperatures were studied in this solvent, DMF; complete conversion to the corresponding benzamidoxime intermediate was observed after 45 min when 1.5 equiv of K_3PO_4 in DMF at 90 °C was used (Table 1, entry 4). Utilizing this reaction conditions in a one-pot manner, starting from benzonitrile and hydroxylamine hydrochloride (90 °C) followed by reaction with acetyl chloride at 110 °C, without the separation of benzamidoxime, gave 3-phenyl-5-methyl-1,2,4-oxadiazole in 85% overall yield (based on benzonitrile).

In order to probe into the scope of the K_3PO_4-mediated synthesis of a wide range of 3,5-disubstituted-1,2,4-oxadiazoles, a variety of nitriles reacted with hydroxylamine hydrochloride followed by reaction with different acid chlorides (Scheme 2). The results are shown in Table 2. All products were fully characterized by physical and spectroscopic methods and compared with the authentic samples. The methodology appears to be quite common with respect to substitution at the oxadiazole 3-and 5-positions, with a range of aliphatic and aromatic substituents.

In order to investigate the possibility of observing the *N*-acylated adduct alongside the *O*-acylated derivative, an experiment was conducted with pure benzamidoxime (mp 70-71 °C) as starting material; treatment of benazamidoxime **5a** (2 mmol) with acetyl chloride (2 mmol) in the presence of K_3PO_4 (2 mmol) in DMF (4 mL) at 110 °C, after 7 min, gave *O*-acylamidoxime **8a** (28%; mp 89-91 °C; υ (cm^{-1}): 1756 (C=O), 3404 and 3348 (NH_2)), along with the *N*-acylated adduct **9a** (17%; υ (cm^{-1}): 3430 (OH), 1648 (C=O)), and the condensation product **7a** (34%) as indicated from their IR spectra after separation (Scheme 3).

In conclusion, K_3PO_4-mediated preparation of various 3,5-disubstituted-1,2,4-oxadiazoles from nitriles and acid chlorides under mild conditions is unveiled. This protocol offers high to excellent yields of the corresponding 1,2,4-oxadiazoles. The one-pot character of the process, short reaction times, and ready availability of the reagent can be considered as advantages of this method.

EXPERIMENTAL

General Procedure: Nitrile (2 mmol) was added to a suspension of hydroxylamine hydrochloride (2.5 mmol) and K_3PO_4 (3 mmol) in DMF (4 mL). Then, the reaction mixture was heated at 90 °C for 30-60 min. After nearly complete conversion to the corresponding amidoxime, as indicated by TLC monitoring, acid chloride (2 mmol) was added dropwise, and the mixture was heated at 110 °C for another 20-60 min. On completion of the reaction (TLC), the hot mixture was poured into ice-water (50 mL). In the case of the products **7a**, **7b-7f** and **7h-7m**, the obtained crude solids were purified by

recrystallization from 95% ethanol, and the oxadiazoles **7b** and **7g** were purified, after extraction with $CHCl_3$ (2 × 10 mL) and drying (Na_2SO_4), by preparative TLC (silica gel, cyclohexane-EtOAc, 1:3 as eluent).

ACKNOWLEDGEMENT

This work was supported by the Research Council of the K. N. Toosi University of Technology. The authors express their gratitude to Dr. Sogand Noroozizadeh for editing the English content of this manuscript.

Supporting Information: This material can be found via the "Supplementary Content" section of this article's webpage.

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Table 1. Optimization of the K_3PO_4-mediated preparation of benzamidoxime

Entry	Solvent	K_3PO_4 (equiv)	Temp (°C)	Time (h)	Yield (%)[a]
1	Toluene	2	90	7	43
2	1,2-Dichloroethane	2	83	6	21
3	DMF	2	90	0.75	87
4	DMF	1.5	90	0.75	89
5	DMF	1	90	1.7	77
6	DMF	1.5	70	1.7	78
7	DMF	1.5	110	0.75	65

[a]Isolated yields.

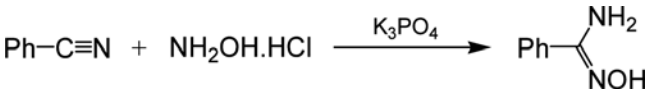
Table 2. Synthesis of 3,5-disubstituted-1,2,4-oxadiazoles

Entry	R^1	R^2	Product[a]	Time(h)	Yield (%)[b]
1	C_6H_5	CH_3	**7a**[26]	1	85
2	C_6H_5	$(CH_3)_2CH$	**7b**[26]	1.75	76
3	C_6H_5	C_6H_5	**7c**[22a]	1.5	83
4	C_6H_5	*p*-$CH_3OC_6H_4$	**7d**[18]	1.75	82
5	C_6H_5	*p*-ClC_6H_4	**7e**[22a]	1.5	87
6	*p*-ClC_6H_4	CH_3	**7f**[26]	0.83	88
7	*p*-ClC_6H_4	$(CH_3)_2CH$	**7g**[25]	1.25	88
8	*p*-ClC_6H_4	C_6H_5	**7h**[18]	1.5	87
9	*p*-ClC_6H_4	*p*-$CH_3OC_6H_4$	**7i**[18]	1.5	86
10	*p*-ClC_6H_4	*p*-ClC_6H_4	**7j**[22b]	1.25	90
11	2,4-$Cl_2C_6H_3$	C_6H_5	**7k**[18]	1.25	96
12	2,4-$Cl_2C_6H_3$	*p*-$CH_3OC_6H_4$	**7l** [18]	1.25	92
13	CH_3	C_6H_5	**7m**[20d]	2	62

[a]References provided for known compounds.

[b]Isolated yields.

Scheme 1.



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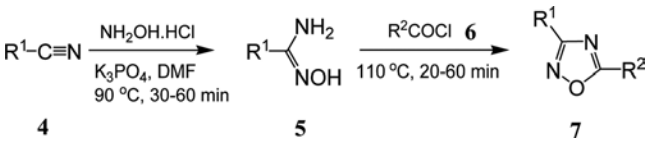
Scheme 2.



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Scheme 3.

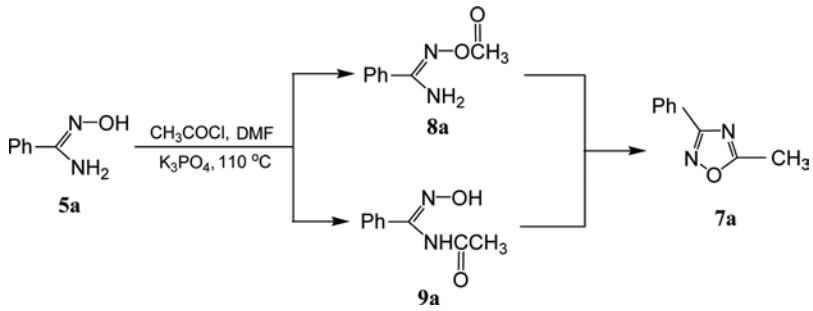

Figure 1. Examples of some biologically active oxadiazoles.