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Microwave assisted synthesis of 3,5-disubstituted 1,2,4-oxadiazoles from substituted amidoximes and benzoyl cyanides

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ABSTRACT

We report herein the synthesis of 3,5-disubstituted 1,2,4-oxadiazoles from amidoximes and substituted or unsubstituted benzoyl cyanides under microwave irradiation. Substituted or unsubstituted *O*-carboxyphenyl amidoxime is a key intermediate of this alternative method developed for the synthesis of these heterocycles. These reactions employ simple synthetic protocols devoid of lengthy purification procedures and proceed with good yield.

The heterocycle, 1,2,4-oxadiazole is frequently observed in a number of biologically relevant molecules.[1a–e] The importance of a 1,2,4-oxadiazole motif in medicinal chemistry has increased due to its application as a stable bioisostere in place of an amide, ester, or urea functionality.[2a–c] Within literature, the 1,2,4-oxadiazole ring system appears as a part of several compounds that may potentially act as serotonergic (5-HT3) antagonists,[3] tyrosine kinase inhibitors,[4] monoamine oxidase inhibitors,[5] aldose reductase inhibitors,[6] metabotropic glutamate subtype 5 (mGlu5) receptor antagonists,[7] muscarinic agonists,[8] and S1P1 agonists.[9] The application of 5-benzyloxy-1,2,4-oxadiazole as a precursor and protecting group for amidines has also been documented.[10] As a result of such a wide spread application of the 1,2,4-oxadiazole ring system, there has been an immense interest in developing convenient methodologies for the synthesis of this heterocycle.

An approach commonly reported for 1,2,4-oxadiazole synthesis undertakes O-acylation of an amidoxime by an activated carboxylic acid derivative in the first step followed by a second step of cyclodehydration.[11] Activated carboxylic acid derivatives used for the O-acylation step include esters,[12] orthoesters,[13] acid chlorides,[14] and anhydrides.[15] The use of carbodiimides such as EDC,[16a–c] CDI,[17] and DCC[18a,b] for in situ activation of carboxylic acids has been previously published. Cyclization of the *O*-acyl amidoxime intermediate can be subsequently achieved following the use of bases such as sodium hydride or sodium ethoxide at room temperature, or in pyridine on heating. Effective cyclization of the *O*-acyl amidoxime intermediate generally warrants the use of elevated temperature coupled with varying reaction times.[19] Another commonly used method for the synthesis of 1,2,4-oxadiazoles involves a 1,3-dipolar cycloaddition of nitriles to nitrile oxides.[20] Microwave assisted organic synthesis of 1,2,4-oxadiazoles involving a one pot three-component reaction between organic nitriles, hydroxylamine, and aldehydes has also been reported.[21] This reaction requires conditions that involve heating under microwave irradiation at 150 °C with an organic nitrile and exhibits excellent yields of 3,5-disubstituted 1,2,4-oxadiazoles. The use of PTSA-$ZnCl_2$ provides a milder alternative for the synthesis of 3,5-disubstituted 1,2,4-oxadiazoles from amidoximes and organic nitriles.[22] Tetrabutylammonium fluoride (TBAF) has also been developed as a mild catalyst for the synthesis of 1,2,4-oxadiazoles from amidoximes.[23] A one pot palladium mediated coupling of amidoximes with aryliodides under one atmosphere carbon monoxide for the synthesis of 1,2,4-oxadiazoles has also been published.[24] A simple catalyst-free synthesis of 1,2,4-oxadiazoles from amidoximes and anhydrides in water with moderate yields is also possible.[25]

With a variety of challenges involved in organic synthesis and the advent of newer technologies, methodologies providing for ease of synthesis from readily available chemical reagents, purification, and convenient isolation of the products prove valuable additions to existing scientific literature. The use of microwave irradiation for shortening reaction time and improving yield has increased dramatically in recent years. In this letter, we have evaluated the feasibility of synthesizing 1,2,4-oxadiazoles from amidoximes and commercially available benzoyl cyanides. Our

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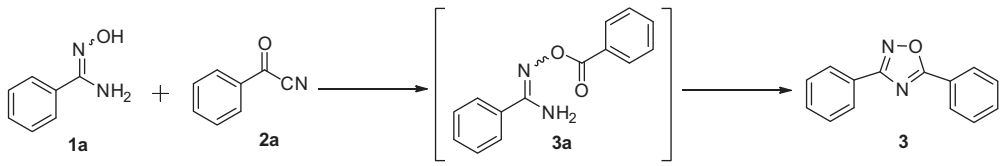
Table 1
Reaction of benzamidoxime (**1a**) with benzoyl cyanide (**2a**) in various conditions



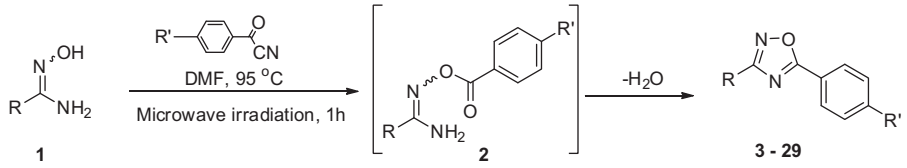
Entry	Solvent	Yield of 3[a] (reaction time) at varying conditions			
		Reflux	MW at 80 °C	MW at 95 °C	MW at 130 °C
1	Water	20% (8 h)	74% (4 h)	63% (1 h)	57% (40 min)
2	1,4-Dioxane	51% (8 h)	80% (4 h)	77% (1 h)	67% (40 min)
3	Toluene	62% (8 h)	74% (4 h)	83% (1 h)	80% (20 min)
4	DMF	70% (8 h)	84% (1 h)	88% (1 h)	69% (20 min)
5	Acetonitrile	49% (16 h)	42% (4 h)	66% (1 h)	81% (20 min)

[a] Isolated yield.

results demonstrate the applicability of benzoyl cyanides for such microwave assisted synthesis of 1,2,4-oxadiazoles. We have further exemplified the applicability of this methodology for the synthesis of methyl 3-(4-((4-(5-phenyl-1,2,4-oxadiazol-3-yl)benzyl)amino)phenyl)propanoate (**31**) and compared the yield with that from another microwave assisted methodology reported in the literature.[21] Our efforts, described herein, identify an effective alternative, demonstrate the applicability, and identify limitations of this microwave mediated synthesis of 1,2,4-oxadiazoles.

Initially, this reaction was standardized by reacting benzamidoxime (**1a**) with benzoyl cyanide (**2a**) in a variety of solvents at different temperatures under both conventional as well as microwave heating conditions. The experimental yields of these standardization efforts are listed in Table 1. The use of microwave heating greatly reduced reaction time as well as improved product yields over conventional heating. It was highlighted that the use of higher temperature aids in the cyclization of the *O*-carboxyphenyl amidoxime intermediate (**3a**) formed during this reaction. The solvents studied included water, dioxane, toluene, DMF, and acetonitrile of which DMF was found to be more suitable for conducting these reactions. The selection of DMF over toluene as a solvent was driven by the observation of marginally improved product

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



Entry	R	R′	Compound	Yield (%)
1	Phenyl	–H	**3**	88
2	Phenyl	–F	**4**	92
3	Phenyl	$-CH_3$	**5**	80
4	2-Methoxyphenyl	–H	**6**	88
5	3-Methoxyphenyl	–H	**7**	79
6	4-Methoxyphenyl	–H	**8**	86
7	2-Methoxyphenyl	–F	**9**	93
8	3-Methoxyphenyl	–F	**10**	89
9	4-Methoxyphenyl	–F	**11**	92
10	2-Methoxyphenyl	$-CH_3$	**12**	77
11	3-Methoxyphenyl	$-CH_3$	**13**	65
12	4-Methoxyphenyl	$-CH_3$	**14**	73
13	2-Nitrophenyl	–H	**15**	58
14	3-Nitrophenyl	–H	**16**	75
15	4-Nitrophenyl	–H	**17**	76
16	2-Nitrophenyl	–F	**18**	61
17	3-Nitrophenyl	–F	**19**	72
18	4-Nitrophenyl	–F	**20**	70
19	2-Nitrophenyl	$-CH_3$	**21**	56
20	3-Nitrophenyl	$-CH_3$	**22**	64
21	4-Nitrophenyl	$-CH_3$	**23**	53
22	Cyclohexyl	–H	**24**	87
23	Cyclohexyl	–F	**25**	93
24	Cyclohexyl	$-CH_3$	**26**	65
25	Adamantyl	–H	**27**	89
26	Adamantyl	–F	**28**	92
27	Adamantyl	$-CH_3$	**29**	77

yields and the ease of product isolation observed in DMF. Microwave heating in DMF at 95 °C for 1 h was found optimum due to shorter reaction times and increased product purities and yields. Although increasing the reaction temperature to 130 °C in DMF lowered the time required for reaction completion to 20 min, it was also observed that the product yields reduced to 69% as a result of increased side-products seen at this elevated temperature.

Following optimization of reaction conditions, the scope of this simplistic method was studied by reacting several amidoximes and substituted or unsubstituted benzoyl cyanides in DMF using microwave heating at 95 °C for 1 h (Table 2).[26] The reaction proceeds via a *O*-carbophenyl amidoxime intermediate (**2**) that subsequently dehydrates and undergoes cyclization to yield the appropriately substituted 3,5-disubstituted 1,2,4-oxadiazoles. After completion of the reaction, the desired product precipitates as a solid on addition of water to DMF and is thus isolated using simple filtration thereby avoiding the need for column chromatographic purification techniques. The 3-position substituent is obtained from the amidoxime whereas the 5-position substituent is obtained from the corresponding benzoyl cyanide used in this reaction. The aromatic and aliphatic amidoximes used to develop this methodology were synthesized using a reported procedure.[23] Although the benzoyl cyanides used in this study are commercially available, they can also be readily synthesized from appropriate acyl chlorides as reported in the literature.[27a,b]

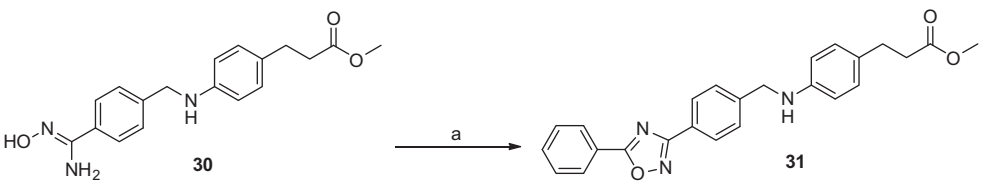
In this study, the reactivities of an unsubstituted phenyl amidoxime (Table 2, entries 1–3) were compared with *ortho*-, *meta*-, or *para*-methoxy substituted phenyl amidoximes (Table 2, entries 4–12) and *ortho*-, *meta*-, or *para*-nitro substituted phenyl amidoximes (Table 2, entries 13–21). The reactivities of aliphatic amidoximes such as cyclohexyl amidoxime (Table 2, entries 22–24) and an adamantly amidoxime (Table 2, entries 25–27) were also evaluated. We have thus attempted to understand the effects exerted by electron withdrawing and electron donating amidoxime substituents on the yields of corresponding 3,5-disubstituted 1,2,4-oxadiazoles. The corresponding benzoyl cyanides that have been evaluated for their reactivity include either an unsubstituted benzoyl cyanide yielding a phenyl substituent, an electron withdrawing *para*-fluoro benzoyl cyanide yielding a *para*-fluorophenyl substituent, and an electron donating *para*-methyl benzoyl cyanide yielding a *para*-methylphenyl substituent at the 5-position.

The reactivity trend can be discussed from the benzoyl cyanide perspective as well as from the amidoxime perspective. From the benzoyl cyanide perspective, the general reactivity trend observed is *para*-fluorophenyl substituent > phenyl substituent > *para*-methylphenyl substituent indicating that the presence of an electron withdrawing substituent on the phenyl favors reactivity as compared to the presence of an electron donating substituent. However this reactivity trend appears reversed in the case of amidoximes, wherein the yields with methoxy phenyl substituents ⩾ phenyl substituent > nitrophenyl substituent indicate that the presence of an electron donating substituent on phenyl amidoxime favors reactivity as compared to the presence of an electron withdrawing substituent. The order of reactivity of phenyl amidoximes substituted with an electron donating methoxy group appears to be *ortho* substituent ⩾ *para* substituent > *meta* substituent. A similar comparison with an electron withdrawing nitro phenyl amidoxime identifies the order of reactivity to be *meta* ⩾ *para* > *ortho*. The aliphatic cyclohexyl and adamantyl amidoximes exhibit similar reactivity as seen with aromatic phenyl amidoxime thereby exemplifying the utility of this reaction. All the studied examples (Table 2, entries 1–27) proceeded with moderate to high yields and in each case the desired product was isolated using simple filtration. This methodology thus provides an attractive alternative to existing literature methodologies.

To demonstrate the utility of our developed methodology, we compared the synthesis of methyl 3-(4-((4-(5-phenyl-1,2,4-oxadiazol-3-yl)benzyl)amino)phenyl)propanoate (**31**) with another reported microwave reaction condition[21] and compared the yields obtained from each methodology (Table 3). The reported microwave procedure for the synthesis of 1,2,4-oxadiazoles reports yields in excess of 90% on reacting an aldehyde with an amidoxime for 3 min at 150 °C. However the reaction of methyl 3-(4-((4-(N′-hydroxycarbamimidoyl)benzyl)amino)phenyl)propanoate (**30**) with benzaldehyde under microwave conditions at 150 °C for 15 min yielded only 24% of **31** (Table 3, entry 1). The reaction time was extended from the originally reported 3–15 min in an attempt to ensure complete consumption of the starting material and maximize the product yield. Although the yield obtained with the reported methodology was much lower than that anticipated, our alternative microwave methodology (Table 3, entry 2) that involves reacting amidoxime **30** with benzoyl cyanide at 95 °C for 1 h yielded 63% of compound **31**. Moreover, we were able to isolate compound **31** using simple filtration techniques as opposed to the column chromatographic purification warranted when the reported methodology[21] was implemented.

In summary, an alternate intermolecular synthesis of 3,5-disubstituted 1,2,4-oxadiazoles has been achieved. This reaction proceeds via an *O*-carbophenyl amidoxime intermediate synthesized in situ. Both aliphatic and aromatic amidoximes can undergo a reaction with substituted or unsubstituted benzoyl cyanides to yield 3,5-disubstituted 1,2,4-oxadiazoles in moderate to high yields. In general, electron donating substituents on the aromatic phenyl amidoxime are observed to favor the reactivity over electron withdrawing substituents. In the case of substituted *para*-substituted benzoyl cyanides, electron withdrawing substituents are favored over electron donating substituents. The synthetic methodology described herein allows for ease of purification as the desired product precipitates out as a solid and can thus be isolated using simple filtration as opposed to lengthy column chromatographic purification techniques. This synthetic protocol thus

Table 3
Effect of varying reaction conditions on product yield



Entry	Reaction conditions (a)	Yield of 31 (%)
1	Benzaldehyde/150 °C/MW/15 min	24
2	Benzoyl cyanide/DMF/95 °C/MW/1 h	63

provides a simple yet effective alternative for the synthesis of certain 3,5-disubstituted 1,2,4-oxadiazoles in moderate to high yields.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.04.101.

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26. *General procedure for synthesis of 1,2,4-oxadiazoles*: To a solution of the amidoxime (1.0 equiv) in DMF (1 mL) was added the appropriate benzoyl cyanide (1.05 equiv) and the reaction mixture was stirred at 95 °C for 1 h under microwave irradiation. Following reaction completion a solid precipitated on addition of water. The slurry was subsequently filtered, washed with water, and dried to yield 56–93% 3,5-disubstituted 1,2,4-oxadiazoles as solid. Spectral data for the representative examples: *3,5-Diphenyl-1,2,4-oxadiazole* (**3**) ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20–8.25 (m, 4H), 7.54–7.59 (m, 6H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 177.1, 169.0, 132.7, 131.2, 129.1 (2C), 128.8 (2C), 128.2 (2C), 127.5 (2C), 126.9, 124.3; MS: *m*/*z* 223.0 $[M+H]^+$; HRMS (ESI+) calcd for $C_{14}H_{11}N_2O$ $[M+H]^+$ 223.0866, found 223.0849; Melting point: 108–110 °C (lit.[28] 109–110 °C); HPLC: Retention time—13.56 min, Purity—99.90%. *3-Phenyl-5-(p-tolyl)-1,2,4-oxadiazole* (**5**) ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19–8.20 (m, 2H), 8.12 (d, *J* = 7.8 Hz, 2H), 7.52–7.54 (m, 3H), 7.38 (d, *J* = 8.1 Hz, 2H), 2.47 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.8, 168.9, 143.5, 131.1, 129.8 (2C), 128.8 (2C), 128.1 (2C), 127.5 (2C), 127.1, 121.6, 21.8; MS: *m*/*z* 237.1 $[M+H]^+$; HRMS (ESI^+) calcd for $C_{15}H_{13}N_2O$ $[M+H]^+$ 237.1022, found 237.1029; Melting point: 118–119 °C (lit.[29] 117–118 °C); HPLC: Retention time—14.21 min, Purity—99.82%. *3-(4-Methoxyphenyl)-5-phenyl-1,2,4-oxadiazole* (**8**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (d, *J* = 6.6 Hz, 2H), 8.14 (d, *J* = 8.1 Hz, 2H), 7.58–7.56 (m, 3H), 7.03 (d, *J* = 8.1 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 176.0, 168.2, 162.1, 132.6, 129.1 (2C), 129.1 (2C), 128.1 (2C), 124.5, 119.5, 114.2 (2C), 55.4; MS: *m*/*z* 253.0 $[M+H]^+$; HRMS (ESI^+) calcd for $C_{15}H_{13}N_2O_2$ $[M+H]^+$ 253.0972, found 253.0986; Melting point: 98–100 °C (lit.[28] 98–99 °C); HPLC: Retention time—8.14 min, Purity—99.65%.
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