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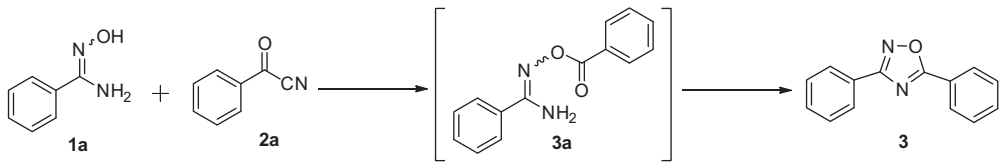
Table 1
Reaction of benzamidoxime (**1a**) with benzoyl cyanide (**2a**) in various conditions



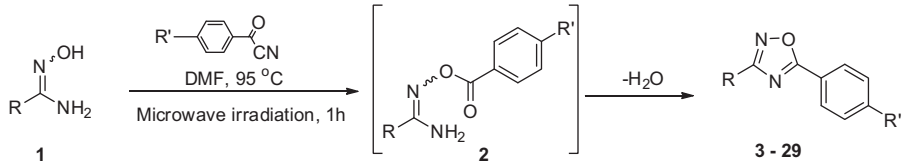
Entry	Solvent	Yield of 3[a] (reaction time) at varying conditions			
		Reflux	MW at 80 °C	MW at 95 °C	MW at 130 °C
1	Water	20% (8 h)	74% (4 h)	63% (1 h)	57% (40 min)
2	1,4-Dioxane	51% (8 h)	80% (4 h)	77% (1 h)	67% (40 min)
3	Toluene	62% (8 h)	74% (4 h)	83% (1 h)	80% (20 min)
4	DMF	70% (8 h)	84% (1 h)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