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A Simple and Straightforward Protocol to 3,5-Disubstituted 1,2,4-Oxadiazoles from Carboxylic Acids

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A convenient one-pot synthesis of 1,2,4-oxadiazoles is described. The condensation of carboxylic acids and amidoximes in the presence of 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) and *N*-methylmorpholine (NMM) has been employed to synthesize a variety of 3,5-disubstituted 1,2,4-oxadiazoles in good to excellent yields. The methodology has been applied for the synthesis of a metabotropic glutamate subtype 5 (mGlu5) receptor antagonist.

Heterocycles containing 1,2,4-oxadiazole moiety exhibit a wide range of biological activities such as anti-inflammatory,[1,2] antiviral,[3] antirhinoviral,[4] and antitumor agents.[5] 1,2,4-Oxadiazoles have often been used as bioisosteres of esters and amides,[4] and as dipeptide mimetics[6] in a number of pharmacologically important molecules. They can also be found in a number of biologically important molecules, such as muscarinic agonists,[7] serotoninergic (5-HT_3) antagonists,[8] benzodiazepine receptor antagonists,[9] and dopamine ligands.[10] Moreover, 1,2,4-oxadiazole scaffolds are found in several drugs and drug leads[10] including the potent S1P1 agonist **A**[11a] (Figure 1) and the metabotropic glutamate subtype 5 (mGlu5) receptor antagonist **B**,[11b] and muscarinic receptor[11c] for the treatment of Alzheimer's disease. Owing to their important applications various methodologies have been developed for the synthesis of 1,2,4-oxadiazoles.[12a] Generally, 1,2,4-oxadiazoles are synthesized by cyclodehydration of *O*-acylamidoximes, promoted by either heat or by bases, such as NaH, NaOEt, or pyridine.[12b] A recent report has described the use of tetrabutylammonium fluoride (TBAF) as an activator to promote the cyclization of *O*-acylamidoximes.[13] Usually, *O*-acylamidoximes are prepared by the reaction of amidoximes with activated carboxylic acid derivatives or with carboxylic acids. The majority of the reported methods use expensive coupling reagents such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), *N*,*N*′-diisopropylcarbodiimide (DIC), or 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) for the formation of *O*-acylamidoximes. Moreover, cyclization of the *O*-acylamidoximes is also a most difficult and time-consuming step, and often requires sealed tube conditions and long reaction times, and gives unsatisfactory yields. Therefore, developing a mild and more general procedure to access 1,2,4-oxadiazoles is still highly desirable.

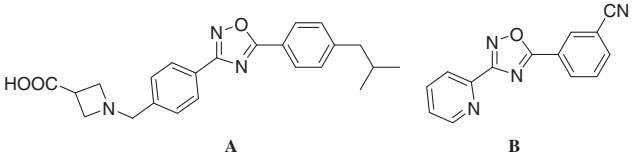
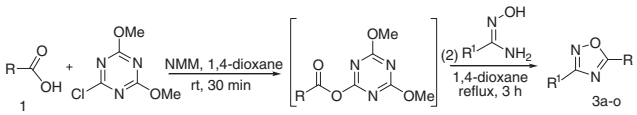


Figure 1. Biologically active 3,5-disubstituted 1,2,4-oxadiazoles.

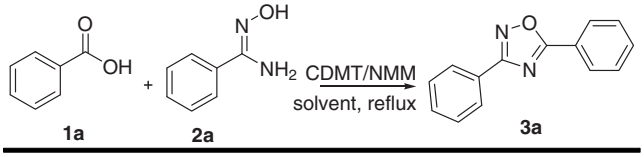
Over the last few years, there has been considerable application of cyanuric chloride or its derivatives in organic synthesis.[14] 2-Chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) was recently found to have applications as a condensing reagent in peptide chemistry[15] and used for the in situ activation of the carboxylic group in many transformations, such as the synthesis of *N*-methoxy-*N*-methyl amides,[16] aldehydes, ketones or α-amino ketones,[17] 2-oxazolines,[18] and monoacylated piperazines.[19] It is commercially available, stable and can also be prepared from commercially available and inexpensive cyanuric chloride. Thus, in continuation of our work[20] on the development of efficient new synthetic methodologies for heterocyclic compounds, herein, we describe an efficient one flask method for the synthesis of 3,5-disubstituted 1,2,4-oxadiazoles from carboxylic acids and amidoximes using CDMT and NMM in 1,4-dioxane at reflux conditions (Scheme 1).

In the standard procedures, first the CDMT reacts with *N*-methylmorpholine (NMM) to form 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM), and then the carboxylic acid is added to generate an active ester. This activated ester is further treated with an amidoxime to afford the 3,5-disubstituted 1,2,4-oxadiazoles. In a model study, benzoic acid (**1a**) was treated with CDMT and NMM in dichloromethane at room temperature. The corresponding activated ester was quantitatively formed after 30 min (monitored by TLC). This white suspension containing the activated ester was subsequently treated with *N*-hydroxybenzamidine (**2a**) at reflux conditions to get desired 3,5-diphenyl-1,2,4-oxadiazole. It was found that the reaction led to 10% yield after 8 h (Table 1, Entry 1). Then we optimized the reaction conditions to increase the yield of the product and to reduce the reaction time. Thus, we investigated the effect of various solvents such as $CHCl_3$, THF, CH_3CN, 1,4-dioxane, and toluene on the model reaction (Table 1, Entries 2–6). Among the tested solvents 1,4-dioxane and toluene gave the best result. However, 1,4-dioxane was preferred over toluene because it provided better solubility for polar reactants. But, other solvents were not as sufficient for this purpose. Furthermore, the by-products formed were removed by a simple aqueous workup, and the desired 1,2,4-oxadiazole product was purified by silica gel column chromatography.



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

Table 1. Effect of various solvents in the synthesis of **3a**



Entry	Solvent	Time/h	Yield[a]/%
1	CH_2Cl_2	8	10
2	$CHCl_3$	8	15
3	THF	5	45
4	CH_3CN	5	52
5	1,4-dioxane	3	92
6	Toluene	3	90

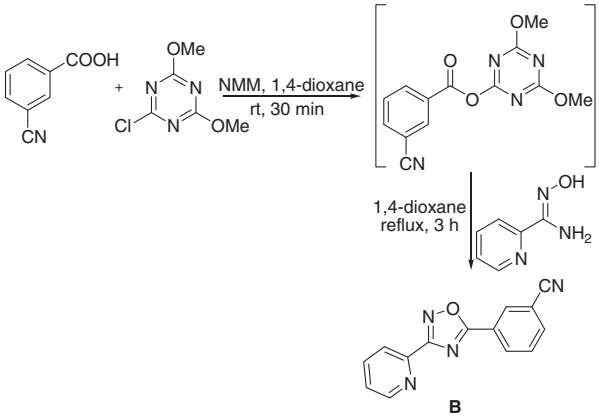
[a]Isolated yield.

Table 2. Synthesis of 3,5-disubstituted 1,2,4-oxadiazoles using CDMT/NMM in 1,4-dioxane at reflux conditions[21]

S.No	R^1	R	Compound	Yield/%[a]
1	Ph	Ph	**3a**	92
2	Ph	Me	**3b**	93
3	Ph	4-MeOPh	**3c**	93
4	Ph	4-ClPh	**3d**	92
5	Ph	4-NO_2Ph	**3e**	89
6	Ph	cyclohexyl	**3f**	94
7	Ph	3-CNPh	**3g**	92
8	Ph	CH_2NHBoc	**3h**	91
9	2-py	Me	**3i**	90
10	2-py	Ph	**3j**	91
11	2-py	Cyclohexyl	**3k**	90
12	2-py	2-py	**3l**	87
13	2-py	CH_2NHBoc	**3m**	92
14	2-Py	2-ClPh	**3n**	89
15	Ph	2-ClPh	**3o**	91

[a]Isolated yield of pure product after purification of crude reaction mixture using column chromatography.

With the optimized conditions in hand, the scope of the reaction substrates was investigated. First, we examined the reaction with different *N*-hydroxybenzamidines, and the results are listed in Table 2. It was found that various substrates were converted into the corresponding products with excellent yields under the conditions. Next, different carboxylic acids and amino acids were investigated as the reaction substrates (Table 2). Aromatic carboxylic acids with different substitutions (both electron donating and electron withdrawing) provide the corresponding products in excellent yields regardless of the difference of the substituent. This meant that steric and electronic effects had no influence on the reaction. Aliphatic and alicyclic carboxylic acids also gave excellent yields. Then nitrogen-containing heterocyclic carboxylic acids (Table 2, compound **3l**) and *N*-protected amino acids (Table 2, compounds **3h** and **3m**) were employed as the reaction substrates and the corresponding reactions afforded the 3,5-disubstituted 1,2,4-oxadiazoles with excellent yields. All the compounds were characterized by advanced spectroscopic analysis (^{1}H NMR, ^{13}C NMR, and MS).



Scheme 2. Synthesis of mGlu5 receptor antagonist **B**.

The methodology has been applied to the preparation of 3-[3-(pyridine-2-yl)-1,2,4-oxadiazol-5-yl]benzonitrile, **B** (Scheme 2), a metabotropic glutamate subtype 5 (mGlu5) receptor antagonist. 3-Cyanobenzoic acid was treated with CDMT and NMM in 1,4-dioxane. The corresponding activated ester was quantitatively formed after 30 min. It was then treated with *N*-hydroxypicolinamidine at reflux temperature for 3 h to get **B** with an yield of 88%.

The superiority of the method over the previous methods can be established by comparing the results obtained with 3-cyanobenzoic acid. Thus, 3-cyanobenzoyl chloride was condensed with *N*-hydroxypilcolinamidine in pyridine under sealed tube conditions to afford 3-[3-(pyridine-2-yl)-1,2,4-oxadiazol-5-yl]benzonitrile (**B**) in 72 h with an yield of 45%,[22] whereas the corresponding product could be obtained in 88% yield within 3 h in the present method.

In summary, we have developed a mild and one-pot synthetic method for the preparation of 3,5-disubstituted 1,2,4-oxadiazoles from various carboxylic acids and amidoximes using CDMT/NMM. This method provided structurally diverse 1,2,4-oxadiazoles in excellent yields. Furthermore, the by-products formed can be removed from the reaction mixture using an aqueous workup. The method has been applied to the preparation of compound 3-[3-(pyridine-2-yl)-1,2,4-oxadiazol-5-yl]benzonitrile (**B**), a metabotropic glutamate subtype 5 (mGlu5) receptor antagonist.[23]

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21 **General procedure for synthesis of 1,2,4-oxadiazoles**: To a stirred solution of CDMT (1.3 mmol) in 1,4-dioxane, NMM (3.9 mmol) was added dropwise and allowed to stir for 5 min. To the white suspension containing DMTMM salt, a solution of carboxylic acid (1.3 mmol) in 1,4-dioxane was added and stirred at rt for 30 min. Then a solution of amidoxime (1.18 mmol) in 1,4-dioxane was added to the above reaction mixture and stirred at reflux conditions for 3 h. After the completion of the reaction (as monitored by TLC), the reaction mixture was cooled to room temperature, 5% aq. Na_2CO_3 solution was added and extracted with ethyl acetate. The organic layer was separated and dried over anhydrous sodium sulfate and concentrated under vacuum to afford the crude compound. The crude compound was purified with silica gel column chromatography using hexane/EtOAc as eluents to afford the pure product.
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23 Supporting Information is available electronically on the CSJ-Journal web site, http://www.csj.jp/journals/chem-lett/index.html.

