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Facile room-temperature assembly of the 1,2,4-oxadiazole core from readily available amidoximes and carboxylic acids

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ABSTRACT

A one-pot ambient-temperature procedure for the synthesis of 3,5-disubstituted-1,2,4-oxadiazoles from amidoximes and carboxylic acids under superbase-promoted conditions is reported.

Introduction

1,2,4-Oxadiazoles constitute an important class of heterocyclic compounds, which continues to attract the growing attention of medicinal chemists [1] due to a broad spectrum of exhibited bioactivity, such as antimicrobial [2], antiviral [3], anticancer [4], antifungal [5], anti-inflammatory [6], antidiabetic [7], antitubercular [8], neuroprotective [9], and antiglaucoma properties [10]. Moreover, the 1,2,4-oxadiazole motif has an acceptable ADME profile, giving rise to its use in the "hit-to-lead" optimization of drug candidates [11]. A representative example of the above mentioned optimization tactic is the bioisosteric replacement of amide and ester functional groups [12].

From a drug discovery point of view, the most attractive procedure to assemble the 3,5-disubstituted 1,2,4-oxadiazole ring is the reaction of amidoximes with carboxylic acids (Scheme 1) [13]. In comparison to other known approaches, i.e. 1,3-dipolar cycloaddition of nitriles to nitrile oxides [14], oxidative coupling reactions [15], oxidation of *N*-substituted amidoximes [16], and the rearrangement of other heterocycles [17], this method has a number of advantages. In particular, easy handling and commercially/synthetically [18] available starting materials are complemented by the possibility of process "parallelization"[13a,d,f]. However, the prolonged heating required for the conversion of *O*-acylamidoxime intermediate **3** into the 1,2,4-oxadiazole is limiting for the reaction scope, resulting in decreased yields and product purity. In order to solve this problem, some basic catalysts were proposed [19]. The latter allow the cyclodehydration of *O*-acylamidoxime **3** to be performed at ambient temperature, nevertheless this intermediate requires a separate step and isolation. In our previous work [20] we reported the MOH/DMSO system to be more effective than other known catalysts in terms of yield, cost, and reaction time. Furthermore, it was successfully applied to the synthesis of different 1,2,4-oxadiazoles [21], including a series of selective and potent carbonic anhydrase isoform II (CAII) inhibitors [10]. Simultaneously, our efforts were focused on the development of one-pot protocols and expanding reagent diversity [22]. Herein, we report an one-pot room temperature protocol for CDI-promoted amidoxime carboxylic acid coupling as a powerful tool for the synthesis of 1,2,4-oxadiazoles.

Results and discussion

Initially, we evaluated several activating agents commonly applied in the pharmaceutical industry for amide synthesis: *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC), 1,1′-carbonyldiimidazole (CDI), isobutyl chloroformate (IBCF), and ethyl chloroformate (ECF) [23], using the coupling between benzoic acid **1a** and 4-tolylamidoxime **2a** in DMSO as a model reaction. NaOH was chosen for catalysis of the cyclodehydration step since it provided the best yield in our previous studies

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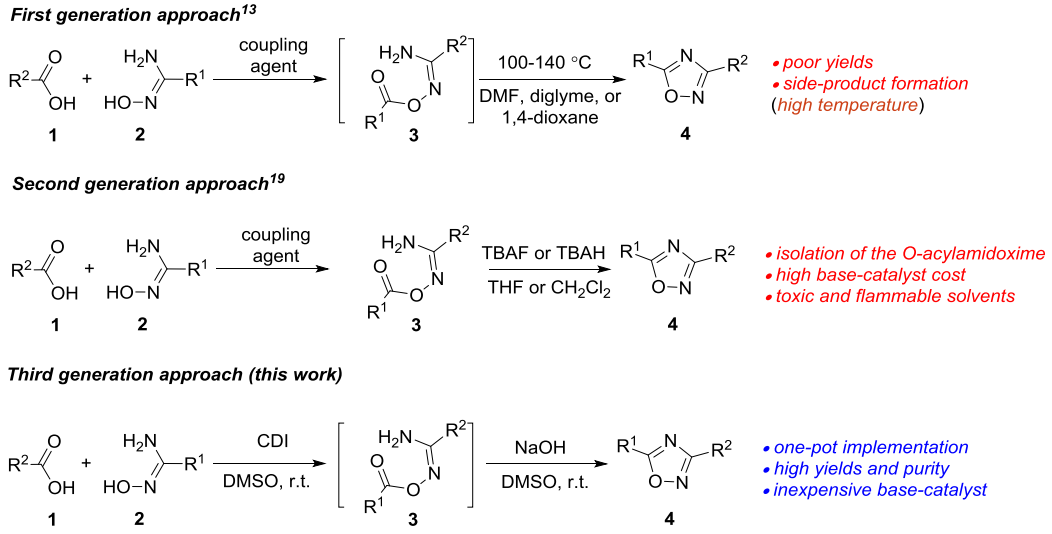


Scheme 1. The evolution of 1,2,4-oxadiazole synthesis from carboxylic acids and amidoximes.

[22]. In the case of IBCF and ECF, additional base was required for the acylation step due to the release of HCl. As shown in Table 1 CDI (Entry 2) is the most suitable coupling agent for this reaction, while EDC demonstrated the worst result, which could be explained by the interaction of the carbodiimide with DMSO [24]. Subsequent optimization of the reagents ratio and reaction time (Table 1, entries 8–11) resulted in the one-pot protocol providing 1,2,4-oxadiazole **4a** in excellent (95%) yield.

Since the amidoxime scope was exhaustively investigated in our previous work [20–22], in the present study we predominantly varied the carboxylic acids in combination with representative amidoximes (Table 2, entries 1–4). Carboxylic acids were divided into 4 groups: 1) aromatic acids bearing strong electron-donating or electron-withdrawing moieties (Table 2, entries 5 and 6); 2) acids with different functionalities (Table 2, entries 7–10); 3) heterocyclic acids (Table 2, entries 11–19); and 4) substituted acetic acids (Table 2, entries 20–26).

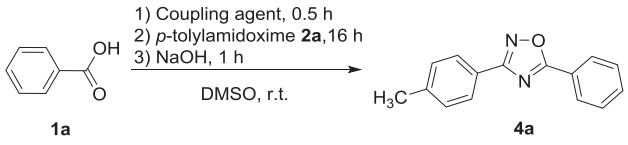
The first group of acids (**1b** and **1c**) demonstrated comparable reactivity regardless of the substituent electronic effect. In contrast, the reactivity levels of the esters previously reported by our group varied significantly [22a]. In particular, full conversion of methyl 4-methoxybenzoate into 1,2,4-oxadiazole required 16 h, while methyl 4-(trifluoromethyl)benzoate and methyl 4-methylbenzoate completely react after 4 h.

In the second group of acids, primary sulfonylamide (**1g**), *N*-Boc protected amine (**1e**), double bond (**1d**), and cyano group (**1f**) functionalities were all well-tolerated. It is worth noting that an earlier reported [20] *O*-acylamidoxime cyclodehydration reaction under the same conditions was accompanied by hydrolysis of the nitrile functionality to the amide. In our opinion, the reason for this distinction is the use of dry DMSO in conjunction with an excess of CDI.

The third group acids, furan (**1j**), thiophene (**1i**), pyridine (**1h**), indole (**1k**, **1l**), and quinolone (**1n**) derivatives, generally provided the desired 1,2,4-oxadiazoles at good to excellent yields. The only exception was the reaction of pyrazinecarboxylic acid **1m** with amidoxime **2f** which resulted in a relatively low product yield (<60%).

Finally, a set of substituted acetic acids **1o-s** was examined as representative compounds containing acidic CH_2 protons. Previously [22a], we found that methyl 2-(4-methyltolyl)acetate and ethyl acetoacetate do not react with amidoximes in NaOH/DMSO, which is likely caused by the presence of the acidic CH_2 group. Similar difficulties were observed in the present study for 2-arylacetic acids **1o–q** (Table 2, entries 20–22). However, the reaction did proceed where the aromatic ring was separated from the methylene group by a heteroatom: O (**1r**), N (**1s, 1t**), S (**1u**) (Table 2, entries 23–26).

Table 1
Reaction conditions optimization.[a]



Entry	Coupling agent (equiv.)	Base (equiv.)	Yield **4a** (%)
1	EDC (1.0)	–	0
2	CDI (1.0)	–	65
3	ECF (1.0)	TEA (1.0)	23
4	IBCF (1.0)	TEA (1.0)	56
5	ECF (1.0)	Py (1.0)	22
6	IBCF (1.0)	Py (1.0)	41
7	ECF (1.5)	TEA (1.5)	76
8	CDI (1.5)	–	89
9	CDI (1.2)	–	87
10	**CDI (1.2)**	**–**	**95**[b]
11	CDI (1.2)	–	95[c]

[a] Reagents and conditions: benzoic acid **1a** (1.1 mmol), *p*-tolylamidoxime **2a** (1.0 mmol), NaOH (1.2 mmol), DMSO (1 mL).
[b] Cyclodehydration step 2 h.
[c] Cyclodehydration step 3 h.

Conclusion

A novel one-pot ambient-temperature protocol was developed for the synthesis of disubstituted 1,2,4-oxadiazoles from readily available starting materials. For many reasons i.e. simple work-up and excellent functional group compatibility, this methodology appears to be more practical than those reported earlier, and