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Room-temperature synthesis of pharmaceutically important carboxylic acids bearing the 1,2,4-oxadiazole moiety

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ABSTRACT

An efficient and mild one-pot protocol has been developed for the synthesis of 1,2,4-oxadiazoles *via* the reaction of amidoximes with dicarboxylic acid anhydrides in a NaOH/DMSO medium. The method allows the synthesis of diversely substituted carboxylic acids bearing the 1,2,4-oxadiazole motif, – a popular building block for pharmaceutical research, in moderate to excellent yields. The reaction scope includes aromatic and heteroaromatic amidoximes as well as five-, six- and seven-membered anhydrides. The advantages of this procedure are proven gram-scalability and the use of inexpensive starting materials, which from a process chemistry point of view are essential for future industrial applications.

Introduction

3-(Substituted-1,2,4-oxadiazol-5-yl)propanoic and butanoic acids are valuable tools in drug discovery and in the parallel synthesis of candidates for high throughput screening or "hit to lead" optimization of bioactive compounds. The pharmaceutical applications of small molecules based on these motifs include nonpeptidic procollagen C-proteinase inhibition,[1] cannabinoid receptor 2 (CB_2) agonist,[2] nonsteroidal anti-inflammatory,[3] lung and larynx carcinoma cell growth inhibition,[4] $\alpha_v\beta_3$ receptor antagonist,[5] analgesic,[6] niacin receptor (GPR109A) agonist,[7] dipeptidyl peptidase IV inhibition,[8] larvicide[9] and antibiotic[10] properties (Fig. 1). Furthermore, some acids are of interest as peptidomimetic building blocks[11] or starting materials for the synthesis heterocyclic compounds, as exemplified by benzimidazoles with antimicrobial activities.[12]

A condensation of amidoximes with dicarboxylic acid anhydrides represents a general route to 1,2,4-oxadiazole-based acids.[13] Typically this reaction is carried out in "two-step, one-pot" fashion *via* *O*-acylamidoxime intermediate generation and subsequent thermal cyclodehydration to the corresponding 1,2,4-oxadiazole (Scheme 1). Unfortunately, the cyclodehydration process requires high temperatures (~100–140 °C), which often results in poor product yields and the formation of undesired by-products.[13,14] For this reason, a number of reagents have been developed for the room-temperature synthesis of 1,2,4-oxadiazoles: TBAF (Gangloff in 2001),[15a] TBAH (Otaka in 2014),[15b] and MOH/DMSO (our group, in 2016).[15c] These systems provided good yields of the desired heterocycles at ambient temperature with short reaction times. Nevertheless, examples of the room-temperature synthesis of 1,2,4-oxadiazoles with the carboxyl functionality have not been described at the present time. Additionally, only *O*-acylamidoximes can be utilized as starting materials for this approach. Thereby an extra stage for their isolation and purification is necessary, which significantly increases the work-up complexity of the procedure and reduces the final yield of the 1,2,4-oxadiazoles. Thus, a mild and efficient protocol for the synthesis of 1,2,4-oxadiazoles containing a carboxyl functionality from readily available starting materials such as amidoximes and dicarboxylic acid anhydrides is highly desirable.

Previously, we proposed a one-pot route to 1,2,4-oxadiazoles based on the reaction between amidoximes and esters in a NaOH/DMSO medium at ambient-temperature.[16] This achievement encouraged us to continue our research, and herein we report a mild and gram-scalable procedure for the preparation of 1,2,4-oxadiazoles from amidoximes and dicarboxylic acid anhydrides.

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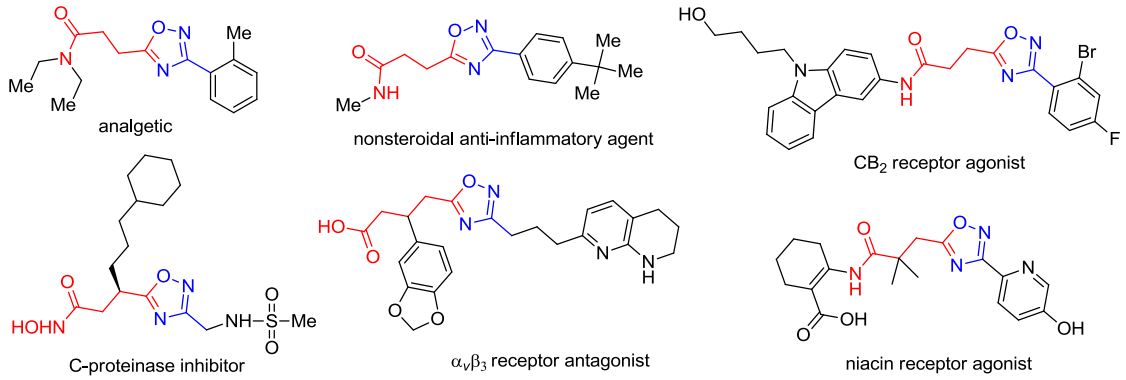
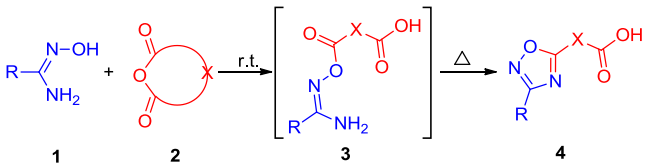
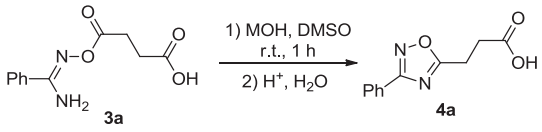


Fig. 1. Representative examples of bioactive alkyl carboxylic acid derivatives containing the 1,2,4-oxadiazole motif.



Scheme 1. Direct reaction of amidoximes and dicarboxylic acid anhydrides.

Table 1
Cyclodehydration of *O*-acylamidoxime **3a**.[a]



Entry	MOH (equiv.)	Yield **4a** (%)
1	KOH (1.1)	30
2	KOH (1.5)	49
3	KOH (2.0)	76
4	KOH (2.5)	71
5	KOH (3.0)	63
6	NaOH (2.0)	90
7	LiOH (2.0)	85

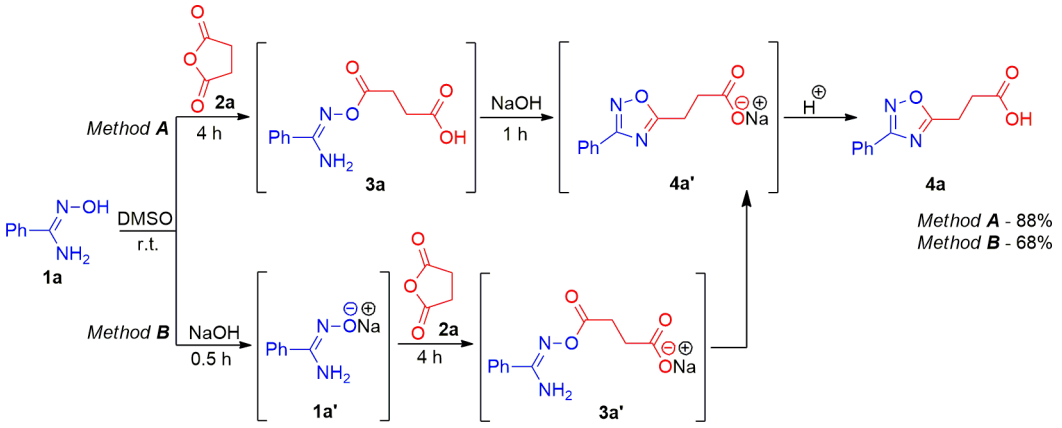
[a] Reagents and conditions: *O*-acylamidoxime **3a** (2 mmol), DMSO (2 mL).

Results and discussion

In the literature, only one unsuccessful example of the base-catalyzed (TBAF in MeCN), room-temperature cyclodehydration of *O*-acylamidoximes containing a carboxylic functionality has been described.[17] Initially, we investigated conversion of *O*-acylamidoxime **3a**, which was previously synthesized from benzamidoxime **1a** and succinic anhydride **2a**,[18] into 1,2,4-oxadiazole **4a** in the MOH/DMSO medium at ambient temperature (Table 1). Alkali metal hydroxides in different amounts were screened as the MOH-component, and NaOH (2.0 equiv.) was found to be the most effective.

Having developed optimal conditions for the cyclodehydration process, we transferred this to the reaction between benzamidoxime **1a** and succinic anhydride **2a**. Initially, two sequences of manipulations (***A*** and ***B***) were compared (Scheme 2).[19] In the case of method ***A***, anhydride **2a** was treated with amidoxime **1a** in DMSO followed by the addition of NaOH (2 equiv.) after 4 h. The alternative procedure ***B*** consisted of the addition of anhydride **2a** to a suspension of the amidoxime **1a** sodium salt, prepared previously by the treatment **1a** with NaOH (2 equiv.) in DMSO. The best result was obtained when the reaction was carried out under the first sequence of manipulations (***A***): 88% versus 68% yield of **4a** (Scheme 2). Thus, all further experiments were pursued according to method ***A***.

Next, we examined the effect of reaction time for both steps (anhydride-amidoxime and cyclodehydration reactions) of this one-pot process (Table 2). This showed that 2 h for the *O*-acylation step and 1 h for the cyclodehydration step were the most suitable



Scheme 2. Reaction pathways for methods ***A*** and ***B***. Reagents and conditions: amidoxime **1a** (2.5 mmol), succinic anhydride **2a** (2.5 mmol), NaOH (5 mmol), DMSO (2 mL).

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