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The first one-pot ambient-temperature synthesis of 1,2,4-oxadiazoles from amidoximes and carboxylic acid esters

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ABSTRACT

The first one-pot room-temperature protocol for the synthesis of 3,5-disubstituted-1,2,4-oxadiazoles via the condensation between amidoximes and carboxylic acid esters in superbase medium MOH/DMSO is reported. A broad spectrum of alkyl, aryl and hetaryl amidoximes and esters was examined. This reaction route provides convenient access to 1,2,4-oxadiazoles, which is highly desirable because in the light of this privileged scaffold is recognized as an important core in the design of novel therapeutic agents and high-tech materials.

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1. Introduction

Since 1,2,4-oxadiazoles first gained the attention of medicinal chemists in 1940's, these five-membered heterocycles have demonstrated themselves as privileged scaffolds in various therapeutic areas.[1] Firstly, several new classes of 1,2,4-oxadiazole-based antibiotics were recently identified.[2] Secondly, the development of anticancer agents turned out to be an important area of the medicinal application of 1,2,4-oxadiazoles.[3] Furthermore, 1,2,4-oxadiazole containing immune modulators, antidiabetic and neuroprotective agents were described in the last few years.[4]

In addition, 1,2,4-oxadiazoles were actively used in material science in recent decades.[1] In this sphere they are utilized as liquid crystals (LCs), functional salts or ionic liquids (ILs), sensors, oxygen friendly media, materials for light-emitting devices, and high-energetic materials (HEMs).[5]

At the present time, lots of methods for the construction of 1,2,4-oxadiazole system are known. These comprise 1,3-dipolar cycloaddition of nitriles to nitrile oxides[4,6]; condensation of amidoximes with carboxylic acids and their derivatives[7]; oxidation of aldoximes[8] and *N*-substituted amidoximes[9]; copper-catalyzed oxidative coupling[10] as well as rearrangements of other heterocycles.[11] Disappointingly, these methods require harsh conditions and are usually associated with low yields and formation of a number of unwanted byproducts. These facts constitute one of the main challenges to the development of novel 1,2,4-oxadiazole-based pharmaceuticals and materials. The use of tetrabutylammonium fluoride (TBAF) as a basic catalyst for the synthesis of 1,2,4-oxadiazoles initiated a breakthrough in this field (Scheme 1, a).[12] Furthermore, this approach was modified by Otaka and co-workers by replacing TBAF with the somewhat more efficient and less corrosive tetrabutylammonium hydroxide TBAH (Scheme 1, b).[13] Finally, it was recently demonstrated by our group that a superbase medium (MOH/DMSO) can represent an excellent alternative to TBAF and TBAH (Scheme 1, c).[14]

It should be noted, however, that *O*-acylamidoximes are employed as starting materials in the abovementioned room-temperature methods. Involving an extra stage for preparation and isolation of the former increases the difficulty of the procedure (in work-up) and reduces 1,2,4-oxadiazole yield. Moreover, it makes this approach inapplicable for combinatorial synthesis,

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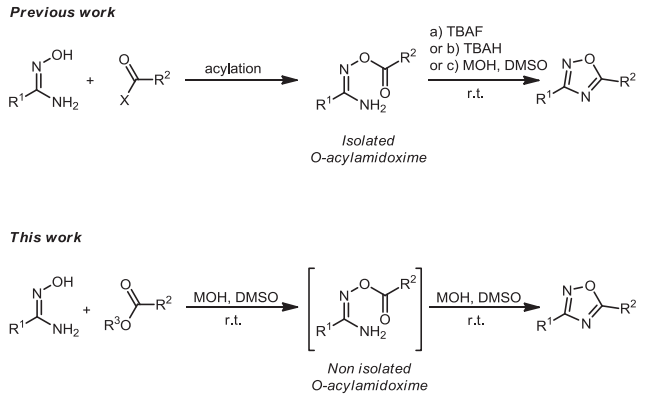


Scheme 1. Content of this work.

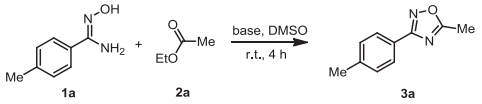
which is a key instrument of drug discovery.[15] It was our goal to overcome this limitation, mainly because our current investigations are focused on development of 1,2,4-oxadiazole based drug candidates. Herein, detailed efforts to improve the room temperature superbase medium methodology are described.

2. Results and discussion

We initiated studies on the investigation of the synthesis of 1,2,4-oxadiazoles synthesis starting from amidoximes and carboxylic acid derivatives at ambient temperature. We preferred to use esters as starting materials since the latter are more tolerant of the superbase medium (Scheme 1).

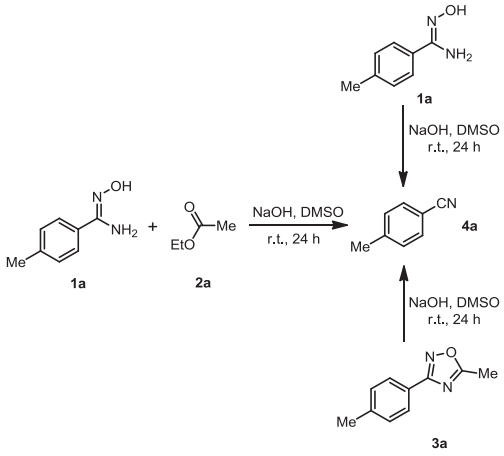
We were elated to find that condensation of 4-methylphenyl amidoxime **1a** and ethyl acetate (EA) **2a** provided 1,2,4-oxadiazole **3a** is 55% yield after stirring for 4 h at room temperature in our initial experiments using KOH/DMSO superbase system (Table 1, entry 1). By comparison, similar yield was achieved only after 8 h in case of the NaOEt/EtOH system at 80 °C.[16]

Table 1
Optimization of reaction conditions.



Entry	Base (equiv.)	2a equiv.	Yield 3a, %
1	KOH (1.0)	2.0	55
2	NaOH (1.0)	2.0	59
3	LiOH (1.0)	2.0	50
4	MeONa (1.0)	2.0	48
5	*t*-BuOK (1.0)	2.0	67
6	KOH (1.5)	2.0	56
7	NaOH(1.5)	2.0	79
8	LiOH (1.5)	2.0	53
9	MeONa (1.5)	2.0	66
10	*t*-BuOK (1.5)	2.0	74
11	NaOH (2.0)	2.0	84
12	NaOH (2.5)	2.0	25
13	NaOH (1.0)	1.0	81
14	NaOH (1.0)	1.5	83
15	NaOH (1.5)	1.0	79
16	NaOH (1.5)	1.5	86
17	NaOH (2.0)	1.0	80
18	NaOH (2.0)	1.5	84
19	NaOH (0.1)	2.0	42[a]
20	NaOH (0.5)	2.0	72[a]

[a] Reaction time was 24 h.



Scheme 2. Routes of nitrile **4a** formation.

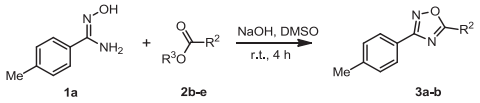
Encouraged by this success, we used the condensation of **1a** and **2a** as model reaction for base screening in order to increase the yield of the desired product (Table 1, entries 2–10). Though, the results achieved in the presence of both NaOH and *t*-BuOK were equally good, only the cheaper NaOH found further application in our subsequent investigations.

Next we examined the influence of base/EA ratio on the yield of corresponding 1,2,4-oxadiazole **3a** (Table 1, entries 11–18). The equimolar ratio of the base and the ester was recognized as optimal conditions.

We also carried out the condensation of **1a** and **2a** in the presence of catalytic amounts (0.1/0.5 eq.) of NaOH (Table 1, entries 19, 20). In the case of 0.1 equivalents, the yield of **3a** was found to be 42% after 24 h of stirring at room temperature. Additionally, small amounts (about 5%) of nitrile **4a** were detected in the reaction mixture. The mechanism of nitrile formation remains uncertain, however stability studies demonstrated that **4a** can be formed from both amidoxime **1a** and the resulting 1,2,4-oxadiazole **3a** (Scheme 2). There is no available data about the conversion of *O*-acylamidoxime into nitrile **4a**. Nevertheless, these possible side reactions would require a significantly longer time, than the condensation process, thus possessing negligible effect on the yield of 1,2,4-oxadiazole **3a**.

The reactivity of acetic acid methyl **2b** and *tert*-butyl **2c** esters was compared to the previously obtained data for ethyl ester **2a** (Table 2, entries 1, 2). The yields of **3a** for all the esters were good after the same reaction time. The methyl and ethyl esters of benzoic acid **2d** and **2e** demonstrated comparable reactivity as well (Table 2, entries 3, 4). Moreover, in the course of our investigation, we did not observe any principal difference between methyl and ethyl ester reactivity.

Table 2
Condensation amidoxime **1a** with different esters.



Entry	Ester 2	R^2	R^3	3 (yield, %)
1	**2b**	Me	Me	**3a**, (85)
2	**2c**	Me	*t*-Bu	**3a**, (84)
3	**2d**	Ph	Me	**3b**, (87)
4	**2e**	Ph	Et	**3b**, (85)

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