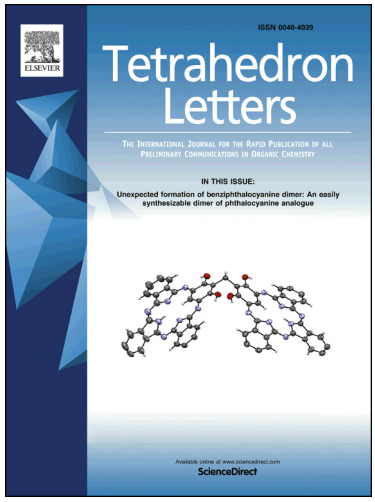


# Room-temperature synthesis of pharmaceutically important carboxylic acids bearing the 1,2,4-oxadiazole moiety

Marina Tarasenko, Nikolay Duderin, Tatyana Sharonova, Sergey Baykov, Anton Shetnev, Alexey V. Smirnov

PII: S0040-4039(17)31009-2
DOI: http://dx.doi.org/10.1016/j.tetlet.2017.08.020
Reference: TETL 49210

To appear in: *Tetrahedron Letters*

Received Date: 18 July 2017
Revised Date: 2 August 2017
Accepted Date: 7 August 2017

Please cite this article as: Tarasenko, M., Duderin, N., Sharonova, T., Baykov, S., Shetnev, A., Smirnov, A.V., Room-temperature synthesis of pharmaceutically important carboxylic acids bearing the 1,2,4-oxadiazole moiety, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.08.020

## Graphical Abstract

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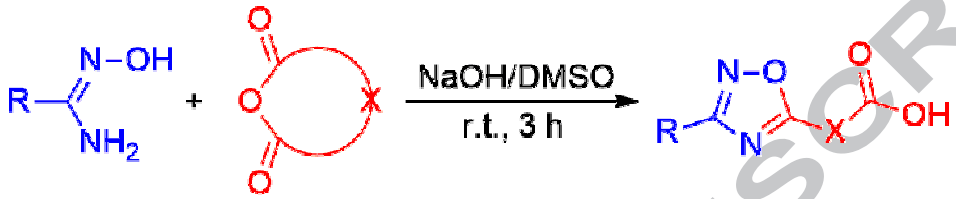


*20 examples*
*43-95% yield*

*R = aromatic or heteroaromatic*
*X = linear chain (heteroatoms tolerated) or aromatic carbocycle(s)*

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

**Marina Tarasenko[a], Nikolay Duderin[b], Tatyana Sharonova[b], Sergey Baykov[b,*], Anton Shetnev[c] and Alexey V. Smirnov[b]**

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ARTICLE INFO

*Article history:*
Received
Received in revised form
Accepted
Available online

*Keywords:*
Heterocycles
Anhydride
Carboxylic acid
Superbase catalysis
Room temperature synthesis

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. 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]

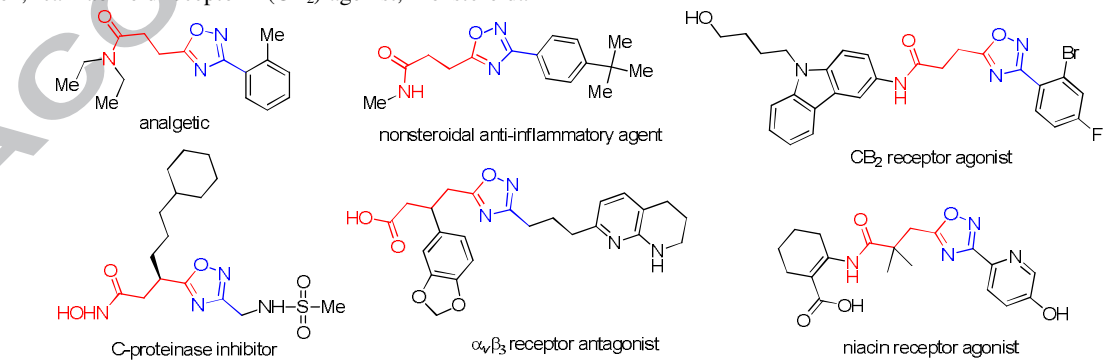


**Figure 1.** Representative examples of bioactive alkyl carboxylic acid derivatives containing the 1,2,4-oxadiazole motif.

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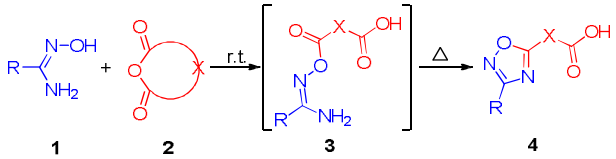
A condensation of amidoximes with dicarboxylic acid anhydrides represents a general route to 1,2,4-oxadiazole-based acids.[13] Typically this reaction is carried out in "two-step, one-pot" fashion *via* *O*-acylamidoxime intermediate generation and subsequent thermal cyclodehydration to the corresponding 1,2,4-oxadiazole. 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.



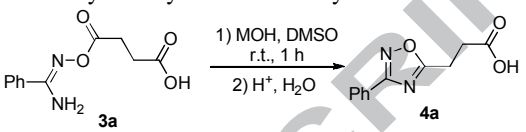

**Scheme 1.** Direct reaction of amidoximes and dicarboxylic acid anhydrides.

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.

**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.

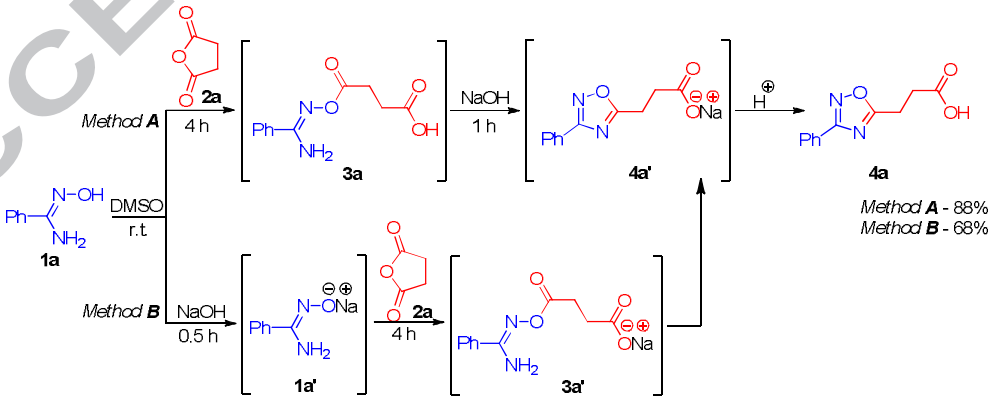
**Table 1.** Cyclodehydration of *O*-acylamidoxime **3a.**[a]




| 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).

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). 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 hours. 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***.

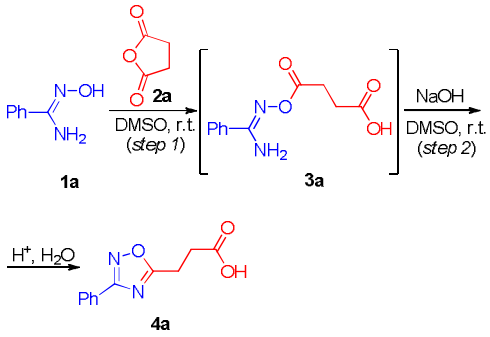



**Scheme 2.** Reaction pathways for methods ***A*** and ***B***. Reagents and conditions: amidoxime **1a** (2.5 mmol), succinic anhydride **2a** (2.5 mmol), NaOH (5 mmol), DMSO (2 mL).

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 reaction times. Further increases in the reaction time had no significant effect on the yield of 1,2,4-oxadiazole **4a**.

**Table 2.** Cyclodehydration of *O*-acylamidoxime **3a**[a].




| Entry | Reaction time (h) | | Yield **4a** (%) |
|---|---|---|---|
| | *Step 1* | *Step 2* | |
| 1 | 1 | 1 | 61 |
| 2 | 2 | 1 | 88 |
| 3 | 3 | 1 | 88 |
| 5 | 2 | 0.5 | 76 |
| 6 | 2 | 2 | 88 |

[a] Reagents and conditions: amidoxime **1a** (2.5 mmol), succinic anhydride **2a** (2.5 mmol), NaOH (5 mmol), DMSO (2 mL).

The reaction scope and limitations were then examined using different amidoximes as well as several anhydrides. Firstly, aliphatic, aromatic (containing both electron donating and withdrawing substituents), and heteroaromatic amidoximes **1b-k** were reacted with succinic anhydride **2a** (Table 3, entries 1-10), only indole-derivative **1f** provided at unfavourable result (Table 3, entry 5). In the case of other amidoximes, 1,2,4-oxadiazole-5-ylpropanoic acids were obtained in good yields. All substituents, including primary sulfonamide (**1h**) and protected amino groups (**1i** and **1j**), were tolerated under these conditions. Moreover, NaOH/DMSO was demonstrated as a convenient medium for the synthesis of 1,2,4-oxadiazoles with an unprotected amino functional group **4k** (Table 3, entry 11). In comparison, the synthesis of compound **4k** in 1,4-dioxane at reflux for 6 h gave the target acid **4k** in only 11% yield after purification by column chromatography (Table 3, entry 11).

Furthermore, the reactivity of cyclic anhydrides **2b-k** was explored (Table 3, entries 12-21). Most of the studied anhydrides reacted with the amidoximes in moderate to excellent yields (> 50%). However, 1,8-naphthalic anhydride **2i** demonstrated poor reactivity, and the corresponding 1,2,4-oxadiazole derivative **4s** was only obtained in 43% yield (Table 3, entry 19).

Satisfactory selectivity was observed for homophthalic anhydride **2k** (Table 3, entry 21), which can react *via* the two non-equivalent acyl carbons, leading to two different 1,2,4-oxadiazoles. Although both compounds were formed, isomer **4u** was the major product ($^1$H NMR analysis). This was isolated by recrystallization from toluene in 62% yield, and its structure determined by single-crystal X-ray analysis (Fig. 2).

The reaction of anhydrides **2e-k** with amidoximes **1** followed by 1,2,4-oxadiazole ring formation was hitherto unreported, and 1,2,4-oxadiazoles **4o-q**, **4s,** and **4u** were not previously synthesized *via* the anhydride route.[19] Moreover, compound **4t** represents the novel backbone of carboxylic acids containing a 1,2,4-oxadiazole core.[20]

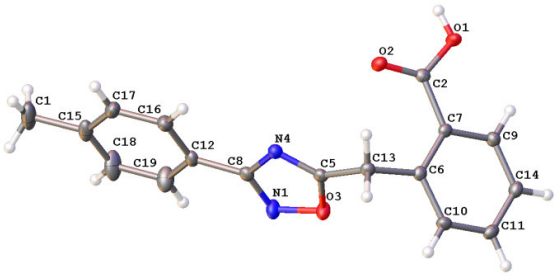
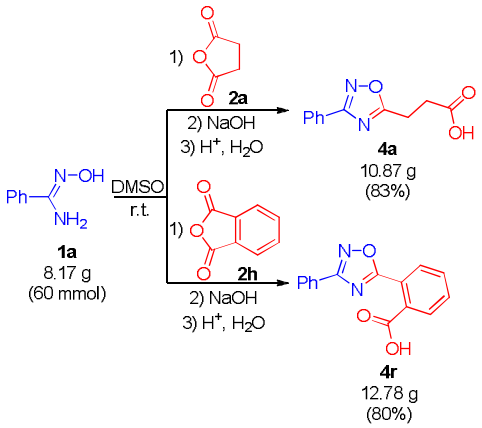


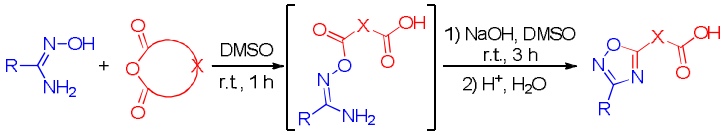

**Figure 2**. Single-crystal X-ray structure of acid **4u** (CCDC 1557057).

Finally, we decided to check the scalability of our method. To this end, two selected 1,2,4-oxadiazoles **4a** and **4r** were synthesized according to the general procedure on a 60 mmol scale (Scheme 3). Both heterocycles were obtained in good isolated yields (83% and 80%, respectively) and sufficient purity. Another advantage of our approach in industrial applications is the utilisation of a low-toxicity solvent (DMSO).[21]



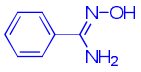
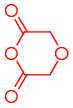
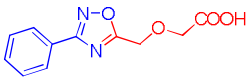
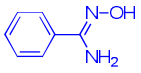
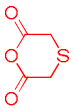
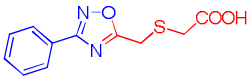
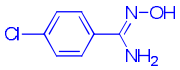
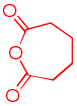
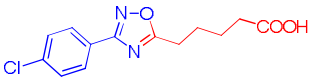
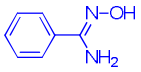
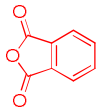
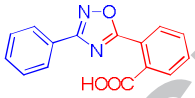
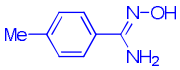
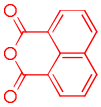
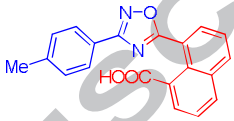
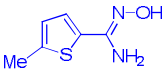
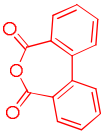
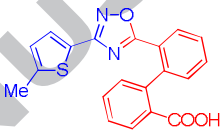
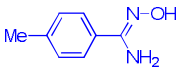
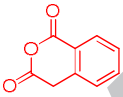

**Scheme 3.** Gram-scale synthesis of **4a** and **4r**.

**Table 3.** Investigation of the reaction scope[a].




**1a-l** **2a-j** **3a-u** **4a-u**

| Entry | Amidoxime **1** | Anhydride **2** | 1,2,4-oxadiazole **4** | Yield (%) |
|---|---|---|---|---|
| 1 | **1b** | **2a** | **4b** | 81 |
| 2 | **1c** | **2a** -//- | **4c** | 71 |
| 3 | **1d** | **2a** -//- | **4d** | 94 |
| 4 | **1e** | **2a** -//- | **4e** | 89 |
| 5 | **1f** | **2a** -//- | - | 0 |
| 6 | **1g** | **2a** -//- | **4f** | 70 |
| 7 | **1h** | **2a** -//- | **4g** | 61 |
| 8 | **1i** | **2a** -//- | **4h** | 80 |
| 9 | **1j** | **2a** -//- | **4i** | 74 |
| 10 | **1k** | **2a** -//- | **4j** | 87 |
| 11 | **1l** | **2a** -//- | **4k** | 77, (11[b]) |
| 12 | **1a** | **2b** | **4l** | 78 |
| 13 | **1a** | **2c** | **4m** | 86 |
| 14 | **1a** | **2d** | **4n** | 81 |

| Entry | Amidoxime **1** | Anhydride **2** | 1,2,4-oxadiazole **4** | Yield (%) |
|---|---|---|---|---|
| 15 | **1a**  | **2e**  | **4o**  | 95 |
| 16 | **1a**  | **2f**  | **4p**  | 52 |
| 17 | **1m**  | **2g**  | **4q**  | 78 |
| 18 | **1a**  | **2h**  | **4r**  | 91 |
| 19 | **1n**  | **2i**  | **4s**  | 43 |
| 20 | **1o**  | **2j**  | **4t**  | 85 |
| 21 | **1n**  | **2k**  | **4u**  | 62 |

[a] Reagents and conditions: amidoxime **1** (2.5 mmol), anhydride **2** (2.5 mmol), NaOH (5.0 mmol), DMSO (2-3 mL).

[b] Reaction was carried out in 1,4-dioxane at 100 °C for 6 h.

## Conclusion

In conclusion, an effective, convenient and scalable one-pot protocol for the synthesis of 1,2,4-oxadizoles bearing carboxyl group from dicarboxylic acid anhydrides and amidoximes has been developed. The present method could be applied to various five-, six-, and seven-membered anhydrides, as well as aliphatic, aromatic and heteroaromatic amidoximes. We hope that the simple work-up procedure, mild condition (particularly, the ambient temperature), inexpensive and readily available starting materials, and a low-toxicity solvent, will make this method a useful tool in medicinal and process chemistry.

## Acknowledgments

This paper was financially supported by the Ministry of Education and Science of the Russian Federation as part of the program to improve the competitiveness of the People's Friendship University (RUDN University) among the world's leading research and education centers in 2016-2020 (Agreement number 02.a03.21.0008). The authors also express their gratitude to Dr. Alexander Sapegin (St. Petersburg State University) for his strong support of this research.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/

## References and notes

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18. **Preparation of (*E*)-4-(((amino(phenyl)methylene)amino)oxy)-4-oxobutanoic acid 3a.** To a solution of amidoxime **1a** (7.48 g, 55 mmol) in acetone (50 mL) succinic anhydride **2a** (5.50 g, 55 mmol) was added. The reaction mixture was stirred at room temperature for 2 h. Upon reaction completion, acetone was evaporated under reduced pressure and water (50 mL) was added to the residue. The resulting precipitate was filtered off, washed with cold water (25 mL) and dried in air (room temperature). White powder, 11.82 g (91%) yield, mp 133-134 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.54-2.58 (m, 2H), 2.64-2.77 (m, 2H), 6.78 (br. s, 2H), 7.39-7.58 (m, 3H), 7.68-7.77 (m, 2H), 12.28 (br. s, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 28.4, 29.3, 127.2, 128.8, 130.9, 132.1, 157.1, 170.8, 174.1. HRMS (ESI) calcd for $C_{11}H_{13}N_2O_4$ $[M+H]^+$ 237.0870, found 237.0879.
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22. Starting amidoximes **1a-o** were prepared by heating commercially available nitriles (1 equiv.) with hydroxylamine hydrochloride (1.5 equiv.) and $NaHCO_3$ (1.5 equiv.) in EtOH (50 mL) at reflux for 6 h. This procedure was described in Srivastava, R.; Pereira, M.; Faustino, W.; Coutinho, K.; dos Anjos, J.; de Melo, S. *Monatsh Chem.* **2009**, *140*, 1319-1324.
23. **General procedure for the synthesis of 1,2,4-oxadiazoles 4a-u from amidoximes 1 and cyclic anhydrides 2 in DMSO.**
***Method A***. To a solution of amidoxime **1** (2.5 mmol) in DMSO (2-3 mL) cyclic anhydride **2** (2.5 mmol) was added. The reaction mixture was stirred at room temperature for 2 h. Next, powdered NaOH (5 mmol) was rapidly added and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was then diluted with cold water (30 mL) followed by the addition of hydrochloric acid to pH ~ 1. The resulting precipitate was filtered off, washed with cold water (25 mL) and dried in air at 50 °C.
***Method B***. To a solution of amidoxime **1** (2.5 mmol) in DMSO (2-3 mL) was rapidly added powdered NaOH (5 mmol). The reaction mixture was stirred at room temperature for 20 min, then to the mixture was added cyclic anhydride **2** (2.5 mmol). The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with of cold water (30 mL) followed by the addition of hydrochloric acid to pH ~ 1. The resulting precipitate was filtered off, washed with cold water (25 mL) and dried in air at 50 °C.
**Note 1**: In the case of compounds **4d** and **4k** acetic acid was used instead hydrochloric acid and the pH was ~ 5.
**Note 2**: The gram-scale synthesis of acids **4a** and **4r** was carried out according to method ***A***: using amidoxime **1a** (8.17 g, 60 mmol), anhydride **2** (60 mmol), NaOH (120 mmol) and DMSO (45 mL).

Highlights for

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

- An efficient protocol for the 1,2,4-oxadiazoles preparation were developed.
- Amidoximes and dicarboxylic acid anhydrides were used as starting materials.
- The reaction carries out at room temperature due to the strong base effect.
- The method can be scaled.