A convenient and mild method for 1,2,4-oxadiazole preparation: cyclodehydration of *O*-acylamidoximes in the superbase system MOH/DMSO

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PII: S0040-4039(16)30604-9
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.05.071
Reference: TETL 47690

To appear in: *Tetrahedron Letters*

Received Date: 12 April 2016
Revised Date: 12 May 2016
Accepted Date: 18 May 2016

Please cite this article as: Baykov, S., Sharonova, T., Osipyan, A., Rozhkov, S., Shetnev, A., Smirnov, A., A convenient and mild method for 1,2,4-oxadiazole preparation: cyclodehydration of *O*-acylamidoximes in the superbase system MOH/DMSO, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.05.071

Graphical Abstract

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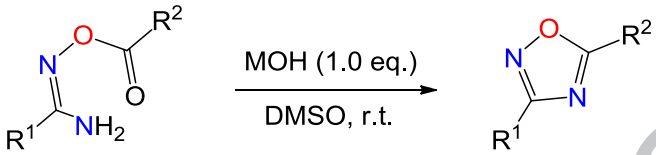

R^1, R^2 = alkyl, cycloalkyl, aryl, heteroaryl
M = Li, Na, K

23 examples
81-98% yield

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A convenient and mild method for 1,2,4-oxadiazole preparation: cyclodehydration of *O*-acylamidoximes in the superbase system MOH/DMSO

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
1,2,4-Oxadiazoles,
Cyclodehydration
Superbase system
O-acylamidoximes
DMSO

ABSTRACT

Herein,we reported a general, convenient and efficient synthesis of 3,5-disubstituted-1,2,4-oxadiazoles *via* cyclodehydration of *O*-acylamidoximes in the superbase system MOH/DMSO (M = Li, Na, K). Excellent isolated yields (up to 98%) were attained within short reaction times (10-20 minutes). In addition, mild reaction conditions and a simple work-up procedure allow the synthesis of a wide range of heat-labile 1,2,4-oxadiazole-containing substances.

1,2,4-Oxadiazoles are one of the most popular objects in medical chemistry and material science.[1] For example, translarna (ataluren or PTC124) is a drug for the treatment of cystic fibrosis and Duchenne disease, caused by nonsense mutation, which has successfully passed three phases of clinical trials.[2] Also, 1,2,4-oxadiazoles possessing antimicrobial, antibacterial, antitumor, antiinflammatory and antiviral properties are described.[3] 1,2,4-Oxadiazoles are also actively used in the development of new materials with useful properties: solar cells, fluorogenic chemosensory polymers, liquid crystals, organic light emitting diodes (OLEDs) and high energy materials (HEDM).[4] Considering the many applications of 3,5-disubstituted-1,2,4-oxadiazoles, our goal was to provide a more efficient and convenient method by which they could be prepared.

The cyclodehydration of *O*-acylamidoximes is the most important method for 1,2,4-oxadiazole ring construction.[5] The reaction has been known for over a hundred years[6] and has been extensively studied.[7] Traditionally, it is carried out with prolonged heating at high temperature.[8] In some cases such harsh conditions are the reason for the low yield of the desired products or their total absence. Consequently, approaches have been proposed for improvement of the cyclodehydration: the use of a microwave irradiation[9] or ultrasound.[10] Gangloff and co-workers showed that in the presence of tetrabutylammonium fluoride (TBAF) *O*-acylamidoximes closed to give 1,2,4-oxadiazoles even at room temperature and with a short reaction times.[11] This effect is explained by the basic catalytic action of the fluoride anion (pKa = 15 in DMSO). In subsequent years TBAF was used in the laboratory synthesis of various 3,5-disubstituted-1,2,4-oxadiazoles.[12] However, the corrosive effects of fluoride anion makes this method unsuitable for industrial application.[5] Therefore, in recent years several alternative basic reagents have been suggested. Lukin and co-workers reported the synthesis of 1,2,4-oxadiazoles in the presence of DBU (pKa = 12 in DMSO[14]) where heterocycle formation was occurred at 60 °C within 1 h.[13] Furthermore, tetrabutylammonium hydroxide (TBAH, pKa = 32 in DMSO) as proposed by Otaka was more effective.[5] Reactions were complete within 10 minutes at room temperature with reported product yields in excess of 90%.

The capacity of these reagents to catalyze cyclodehydration is determined by their basicity. It is known that in DMSO the strength of many bases are significantly higher than in other solvents.[14] Additionally, the formation of the 1,2,4-oxadiazole ring from *O*-acylamidoximes in DMSO at room temperature was previously reported.[15] The reaction proceeded in the absence of additional base, however complete conversion required 10 days. We have suggested that the addition of a base can significantly reduce the reaction time without increasing of the temperature. Primarily potassium hydroxide was proposed a base, since the superbase system KOH/DMSO is widely used in organic chemistry, including in the synthesis of heterocyclic compounds.[16] Furthermore, we have examined the

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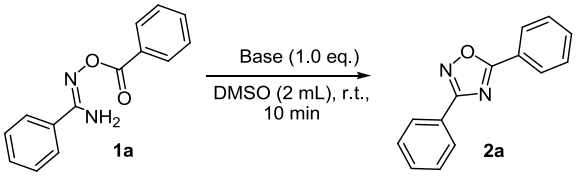
hydroxides of other alkali metals (LiOH, NaOH), a series of carbonates and bicarbonates (Na_2CO_3, K_2CO_3, Cs_2CO_3, $NaHCO_3$, $KHCO_3$), and also several organic bases (TEA, AcONa).

Table 1. Influence of bases on cyclodehydratation of O-benzoylbenzamidoxime **1a** to 3,5-diphenyl-1,2,4-oxadiazole **2a**



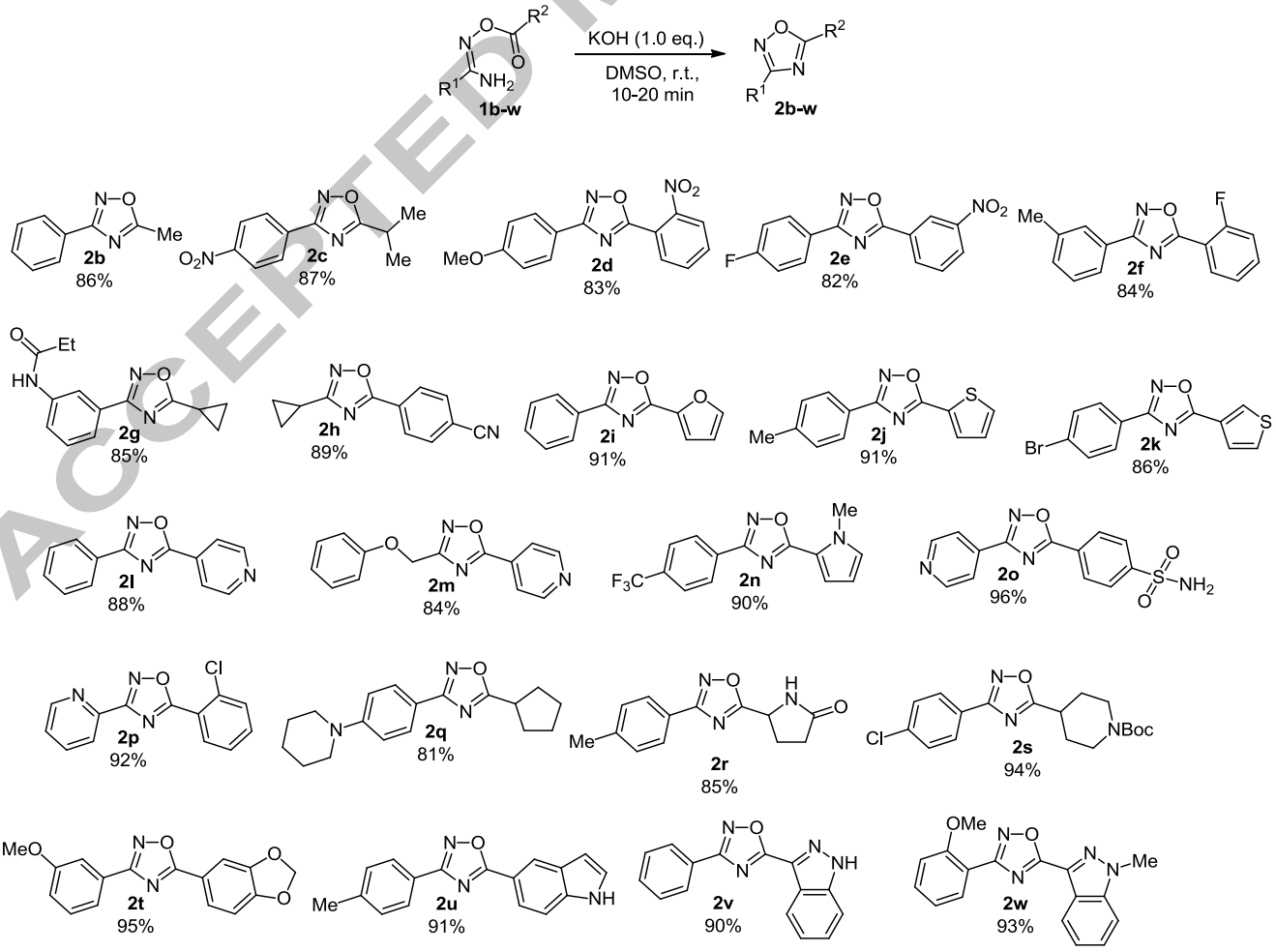
Entry	Base	Yield, %
1	KOH	98
2	LiOH	98
3	NaOH	98
4	Na_2CO_3	trace
5	K_2CO_3	71
6	Cs_2CO_3	86
7	$NaHCO_3$	trace
8	$KHCO_3$	trace
9	TEA	trace
10	AcONa	trace
11	KOH	96[a]

[a] 0.1 eq. KOH, reaction time 15 min

The cyclization of *O*-benzoylbenzamidoxime **1a** to 3,5-diphenyl-1,2,4-oxadiazol **2a** was used as a model reaction to study the effect of varrious bases (Table 1). The synthesis was carried out for 10 minutes at room temperature. Addition of powdered potassium hydroxide (1 equivalent) to a solution of compound **1a** in DMSO led to precipitation of the product **2a** after 1.5 minutes. Similar results were obtained with NaOH and LiOH (entries 2 and 3). Cs_2CO_3 and K_2CO_3 gave lower yields of **2a** (entries 5 and 6). Using other bases (entries 7-10) gave a trace amounts of the desired product **2a**. Thus, alkali metal hydroxides are the most suitable reagents for cyclodehydration under mild conditions. Moreover, hydrolysis of **1a** to the corresponding benzamidoxime was not observed when alkali metal hydroxides in DMSO were employed. In contrast, Itaka noted the hydrolysis of **1a** when a 25% aqueous NaOH solution in THF was used.[5]

We also studied the reaction with the catalytic amount of base (0.1 equivalent, entry 11). In this case, complete conversion of compound **1a** into 1,2,4-oxadiazol **2a** has required 15 minutes.

The cyclization of *O*-benzoylbenzamidoxime with alkali work well both in an open flask with aged DMSO without protection from CO_2 and under a blanket of inert gas with an initially anhydrous solvent.

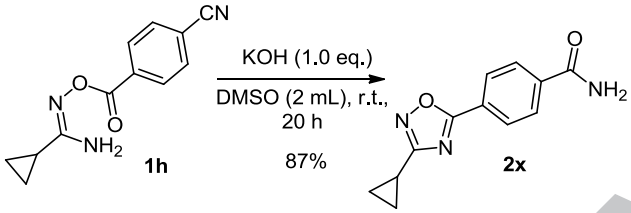


Scheme 1. Cyclization of various *O*-acylamidoximes **1b-w** into 3,5-disubstituted-1,2,4-oxadiazoles **2b-w.**

Leveling the harmful effects of carbon dioxide is achieved by using the equimolar ratio of alkali and *O*-acylamidoxime.

Furthermore, we examined the KOH/DMSO system for the synthesis of 3,5-disubstituted-1,2,4-oxadiazoles containing different functional groups (Scheme 1).

Most of the substituents considered were stable to the super basic medium and the corresponding 3,5-disubstituted-1,2,4-oxadiazoles were prepared in good yield. Nevertheless, in some cases side reactions were observed. For example, compound **1h** was successfully cyclized, although the nitrile was also partially hydrolyzed to form amide **2x** when the reaction was allowed to proceed for 2 hours. However, due to significant differences in the relative rates of the cyclodehydration and the nitrile hydrolysis reactions, we were able to prepare nitrile **2h** in 89% yield by halting the reaction after 10 min. The 1,2,4-oxadiazole amide **2x** also could be obtained as a single product simply by increasing the reaction time to 20 hours (Scheme 2).



Scheme 2. Cyclization of *O*-acylamidoxime **1h** into 1,2,4-oxadiazole **2x.**

In general, no significant effect of electron withdrawing and electron donating groups on the reaction on rate was detected. Also, the position of the group in the aromatic ring showed no effect, even thought it was earlier reported that the presence of a substituent in the *ortho*- position significantly reduces the reactivity of *O*-acylamidoximes.[5]

In conclusion, we have described an efficient and convenient method for 1,2,4-oxadiazole ring construction by the cyclodehydratation of *O*-acylamidoximes in the superbase system MOH/DMSO (M = Na, K, Li). This method uses the use of widely available and inexpensive reagents (DMSO, hydroxides of alkali metals) and provides good yields of the desired compounds. The reaction scope includes a wide range of aliphatic, aromatic, and heterocyclic substituents with both electron donating and electron withdrawing groups.

Acknowledgments

The authors would like to thank all reviewers who have contributed to the manuscript. The authors gratefully acknowledge financial support of this research from the Russian Scientific Fund (Project Grant 16-13-10243).

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General procedures for the synthesis of *O*-acylamidoximes 1a-w a) To a mixture of the carboxylic acid (5 mmol) in acetone (20 mL) was added EDC (5.5 mmol). The reaction mixture was stirred at room temperature for 30 min, then the amidoxime (5 mmol) was added. The resulting mixture was stirred at room temperature for 12 h. Acetone was evaporated at reduced pressure and to the residue was added water (100 mL). The resulting precipitate was filtered off, washed with water (50 ml) and dried and dried in air at RT.

b) To a cooled to 0 °C mixture of amidoxime (5 mmol) and TEA (5.5 mmol) in acetone (20 mL) was added acyl chloride (5.5 mmol). Reaction mixture was stirred at room temperature for 12 h. Acetone was evaporated at reduced pressure and to the residue was added water (100 mL). The resulting precipitate was filtered off, washed with water (50 ml) and dried in air at RT.

Spectral Data of 1a White powder, 91 % yield, mp 124-125 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.99 (br. s, 2H), 7.47-7.52 (m, 3H), 7.56 (t, *J* = 7.8 Hz, 2H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.78 (d, *J* = 7.3 Hz, 2H), 8.20 (d, *J* = 7.5 Гц, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 127.0, 128.4, 128.6, 128.7, 129.6, 130.6, 131.9, 133.1, 157.1, 163.7. MS (ESI$^+$): *m/z* 241 $[M+H]^+$.

General procedure for the synthesis of 3,5-diphenyl-1,2,4-oxadiazoles 2a-w. To a solution of *O*-acylamidoxime 1 (2 mmol) in DMSO (2-3 mL) was added KOH (2 mmol). The reaction mixture was stirred at room temperature for 10-20 min (TLC or precipitation of the product). The reaction mixture was diluted with 30 ml of cold water. The resulting precipitate was filtered off, washed with water (30 mL) and dried in air at 50°C.

Spectral Data of 2a White powder, 96 % yield, mp 107-109 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.59-7.64 (m, 3H), 7.68 (m, 2H), 7.75 (m, 1H), 8.11 (m, 2H), 8.20 (m, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 123.5, 126.3, 127.2, 128.0, 129.3, 129.6, 131.7, 133.4, 168.4, 175.5. MS (ESI$^+$): *m/z* 223 $[M+H]^+$. Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found: C, 75.43; H, 4.54; N, 12.54.

Supplementary Material

Supplementary data associated with this article can be found, in the online version.