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Acid-promoted reaction of *N*-(cyanomethyl) amide with nitrosation reagent: Facile synthesis of 1,2,4-oxadiazole-3-carboxamide

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ABSTRACT

1,2,4-Oxadiazole-3-carboxamide has been extensively used in the pharmaceutical chemistry. In this study, 1,2,4-oxadiazole-3-carboxamide is accomplished through an acid-promoted reaction of *N*-(cyanomethyl)amide with nitrosation reagent. This novel preparation of 1,2,4-oxadiazole-3-carboxamide was carried out at 25 °C, and the yield of target compounds was as high as 92%. At the same time, the amount of acid used is reduced. A mechanism speculation for the formation of 1,2,4-oxadiazole-3-carboxamide has been provided. The new synthetic method provides great convenience for the synthesis of compounds containing 1,2,4-oxadiazole-3-carboxamide.

Introduction

1,2,4-Oxadiazole was first synthesized by Tiemann and Kruger, and it was originally named furan[*ab*1]diazole [1]. The oxadiazole derivatives have a wide range of biological activities, such as insecticidal [2], antimicrobial [3,4], genotoxic activity [5], immunosuppressive [6], anticancer [7–9], antitrypanosomal [3], Alzheimer's disease [10], and antitumor activity [11,12]. When 1,2,4-oxadiazole is substituted with alkyl, aryl or carboxamide groups at the 3,5 positions, it can also be used as an antagonist [13–17] and antibacterial [18]. Due to its wide application in medicinal chemistry, agriculture and new materials, 1,2,4-oxadiazole-3-amide has attracted more attention [19,20].

One of synthesis method of 1,2,4-oxadiazole-3-amide is using acetic acid as a solvent, and the substituted formaldehyde and diaminoglyoxime are reacted at 100 °C for 120 min [21,22]. However, the reaction environment is not very friendly due to the use of acetic acid. And the reaction requires heating conditions, which the reaction conditions are not mild enough. Thus, more environmentally friendly synthesis methods need to be found.

Another synthesis method of 1,2,4-oxadiazole-3-amide is using acetic acid and ether as a solvent, and *N*-(cyanomethyl)benzamide can be nitrosated and dehydrated into a 1,2,4-oxadiazole-3-amide [23]. However, the research on the reaction mechanism is not thorough enough, and further exploration is needed.

In this study, we provided a new convenient synthetic method for 1,2,4-oxadiazole derivatives. *N*-(cyanomethyl)amide, nitrite reagent and acid were used as substrates to synthesize 1,2,4-oxadiazole-3-amide at 25 °C (Scheme 1). Initially, it was expected that the nitrososubstitution would occur on the amino group, leading to iminosydnones product. However, no desired product was observed for **1a** when the reaction was performed in tetrahydrofuran (THF) at 25 °C. The presence of a carbonyl group is thought to cause the change in charge distribution on aminoacetonitrile, and then, the intermediate **2a** was obtained instead of **2a–D**. Finally, 1,2,4-oxadiazole was obtained by completing the ring closure.

Results and discussion

N-(Cyanomethyl)benzamide (**1a**) was prepared according to the literature [24]. It was assumed that 5-phenyl-1,2,4-oxadiazole-3-carboxamide **3a** was produced from the reaction of *N*-(cyanomethyl)benzamide (**1a**), isoamyl nitrite and hydrogen chloride, which can perform nucleophilic substituted (intermediates **2a**) and then intramolecular cyclocondensation reactions to get **3a**. To perform such multi-component reactions (MCRs), the reaction will only take about 1 h at 25 °C. Upon completing the reaction, the final products were isolated and identified. The structural determination was performed by analyzing the ^{1}H NMR and ^{13}C NMR of the products. The ^{1}H NMR spectrum presented the

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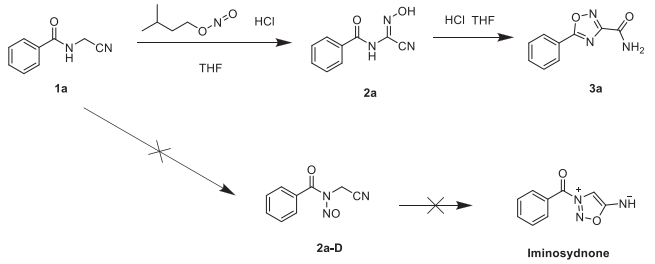


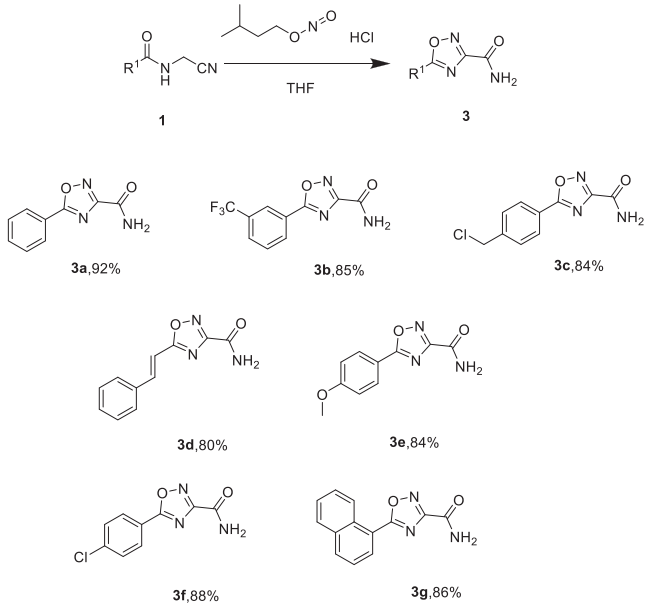
Scheme 1. An unexpected reaction of *N*-(cyanomethyl)benzamide (**1a**).

expected resonance signatures including one NH amide group signal at 8.41 ppm, another NH amide group signal at 8.20 ppm and five signals for benzene ring. In the ^{13}C NMR spectrum, the observed signals were all consistent with the structure of product **3a**.

At the beginning, the compound **3a** was obtained from entry 13, and the yield is only 67%. Because the reaction requires anhydrous reagents and hydrogen chloride in methanol, so the reaction conditions are strict. In order to optimize the reaction, the reaction conditions have been screened, which were shown in Table 1, at last, the yield of the reaction can reach 92%. After entry 13, ordinary THF was used instead of anhydrous THF, different acids were used for reaction. The yield of hydrochloric acid (92%) was higher than that of sulfuric acid (42%), nitric acid (63%) and trifluoroacetic acid (none). And the yield of THF (92%) as solvent is better than that of water (51%), acetonitrile (80%), acetic acid (75%) and dioxane (78%). Then the temperature and reaction time were screened, and the best reaction condition was one hour at 25 °C, namely entry 2.

To explore the scope and limitations of this reaction, the same procedure was applied to the various *N*-(cyanomethyl)amide **1**. As it can be found from Scheme 2, the reaction proceeded very efficiently and led to the formation of the 1,2,4-oxadiazole-3-carboxamide **3a–g** in good yields. However, if R^1 is not a benzene ring, such as pyridine, furan, cyclohexane, or cyclopropane, this reaction will not happen.

In order to confirm the reaction process, dry HCl in ethyl acetate (EA) without the presence of water was selected as an acid reagent. Through similar conditions, the intermediate state structure (**2a**) was obtained. This step demonstrates that a key step in the synthesis of 1,2,4-oxadiazole is a substitution reaction on the methylene of aminoacetonitrile to produce a nitrososubstitution, which is helpful for us to understand the mechanism of reactions.



Scheme 2. Reaction of Various Primary *N*-(cyanomethyl)amide.

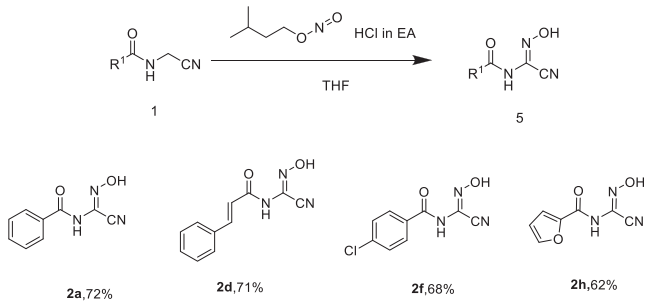
Various *N*-(cyanoethyl)amides (R^1 = pH, cinnamyl, 4-Cl-pH, furan-2-) were used as raw materials to study the range and limitation of the reaction. It was found that this reaction can be applied in a wider range and provides a new method to obtain *N*-(cyano (nitroso)methyl)amide (Scheme 3).

In order to determine whether a compound with a planar structure is conducive to this reaction, single crystal culture was carried out in **2d** (CCDC 2067456). From the crystal structure of **2d** (Fig. 1), it is true that the cinnamyl group is partly coplanar with the *N*-(-cyanomethyl)amide, which also proves the previous speculation. In addition, by calculating the 3D structure of other R^1 substitutions (pyridine, furan, cyclohexane, or cyclopropane), it is found that the reaction cannot occur when the molecules are not coplanar.

Table 1
Optimization of reaction conditions **3a**.

Entry	Solvent	Temp. (℃)	Time (h)	Nitrosation reagent	Acid [a]	Yield (%)[b]
1	THF	25	0.5	Isoamyl nitrite	HCl	65
2	THF	25	1	Isoamyl nitrite	HCl	92
3	THF	25	3	Isoamyl nitrite	HCl	92
4	Dioxane	25	1	Isoamyl nitrite	HCl	78
5	MeCN	25	1	Isoamyl nitrite	HCl	80
6	H_2O	25	22	Isoamyl nitrite	HCl	51
7	THF	60	0.5	Isoamyl nitrite	HCl	70
8	THF	60	1	Isoamyl nitrite	HCl	92
9	THF	25	1	Isoamyl nitrite	HNO_3	63
10	THF	25	1	Isoamyl nitrite	H_2SO_4	42
11	THF	25	1	*Tert*-butyl nitrite	HCl	86
12	THF	25	1	$NaNO_2$	HCl	–
13	THF (redistilled)	25	1	Isoamyl nitrite	HCl in MeOH	67
14	Acetic acid	25	1	Isoamyl nitrite	HCl	75
15	THF	25	1	Isoamyl nitrite	CF_3COOH	–

Reaction conditions: *N*-(cyanomethyl)amide (1 mmol),nitrosation reagent (1.2 eq.), acid (2 eq.).
[a] Acid concentration: HCl 36%; HNO_3 98%; H_2SO_4 98%; CF_3COOH 99%; HCl in MeOH 1 mol L^{-1}.
[b] Isolated yields.



Scheme 3. Reaction of Various Primary *N*-(cyanomethyl)amide.

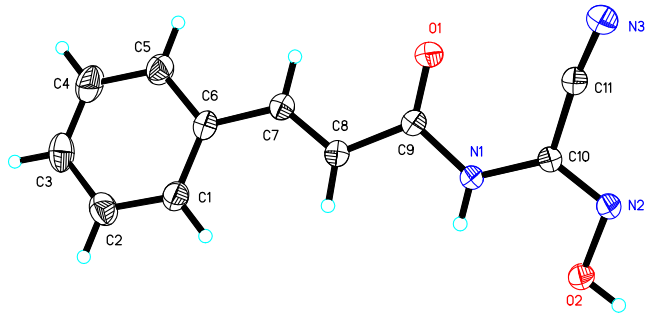
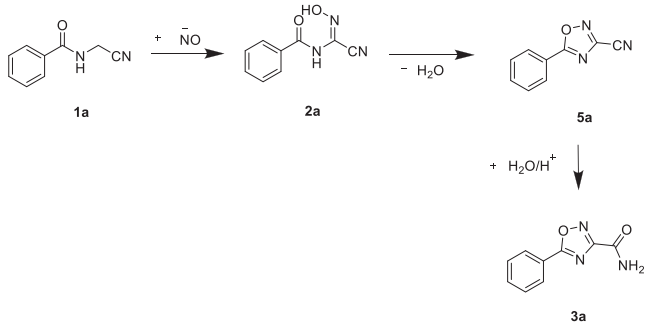


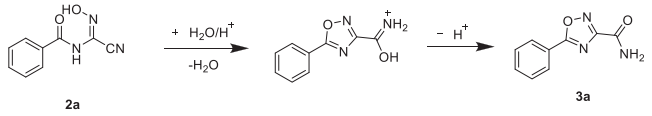
Fig. 1. General view of **2d** in a crystal.



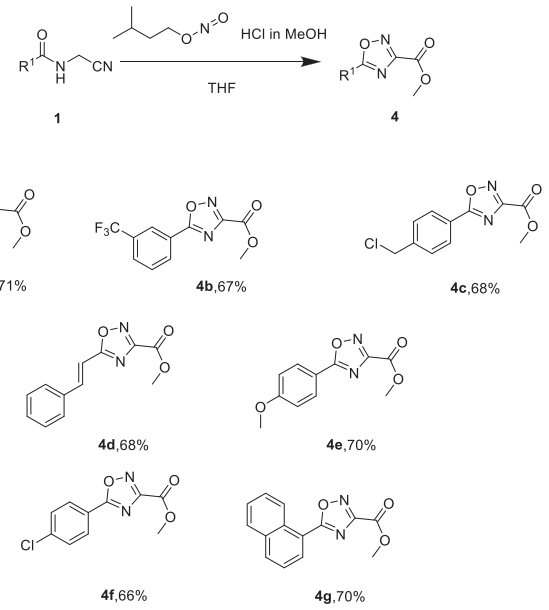
Scheme 4a. Reported mechanism for the formation of **3a**.

In Bracrmtz's article [23], the reaction mechanism is that the compound **1a** first undergoes a nitrosation reaction, then a ring-closure reaction, and finally completes the hydrolysis of the cyano group to obtain the target compound **3a** (Scheme 4a).

After experimental verification, a new reaction mechanism is proposed in Scheme 4b. Compound **2a** completes the cyano group hydrolysis and ring closure reaction at the same time under the action of acid, without producing other intermediate products (such as **5a**). Finally, the target product was obtained by dehydrogenation (Scheme 4b). The cyano group is important in this reaction. When the cyano group of the compound **2a** becomes a carboxyl group, the reaction cannot take place.



Scheme 4b. Proposed mechanism for the formation of **3a**.



Scheme 5. Reaction of Various Primary *N*-(cyanomethyl)amide.

In experiments, it was found that when the solvent contained alcohol, the product is no longer an amide, but the corresponding ester (Scheme 5). Similar to Scheme 2, the applicability of this reaction is limited. This reaction can only occur if the *N*-(cyanomethyl) amide and R^1 are planar. This reaction produces a by-product of compound **3** (yield 15%), so the target compound **4** is obtained at a medium yield.

In summary, we described an acid promoted reaction of *N*-(-cyanomethyl)amide with nitrosation reagent and water, by adjusting the type of acid to obtain products with different structures, such as 1,2,4-oxadiazole-3-carboxamide, methyl 1,2,4-oxadiazole-3-carboxylate and *N*′-hydroxycarbamimidoyl cyanide.

Compared with the traditional synthetic method, the advantages of current reaction include high yield, simple reaction conditions, short reaction time, and easy post-processing. And an acid-promoted reaction pathway is proposed. This provides great convenience for the synthesis of compounds containing such structures. Apart from this, the limitations of the reaction were explored, and the reaction mechanism proposed by the predecessors was revised to deepen the research on this reaction.

In addition, when designing active compounds containing benzamide, 1,2,4-oxadiazole-3-amide can be used to replace the relative benzamide, which can increase the diversity of the compound structure. At the same time, it can reduce the risk of resistance. This also provides an easy structure construction method for drug design.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix. Supplementary material

Supplementary material related to this chapter can be found on the accompanying CD or online at doi:10.1016/j.tetlet.2021.153209.

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