Tetrahedron Letters xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A new strategy for the synthesis of dioxime ether derivatives with nitromethylene imidazolidine

Hui Zeng, Zhengjie Dong, Xinfei Chen, Xusheng Shao, Xiaoyong Xu, Zhong Li *

Shanghai Key Laboratory of Chemical Biology, School of Pharmacy, East China University of Science and Technology, Shanghai 200237, China

ARTICLE INFO

Article history:
Received 30 November 2014
Revised 2 February 2015
Accepted 12 February 2015
Available online xxxx

Keywords:
One-pot
Oxime ether
Dioxime ether
Ring-opening

ABSTRACT

In the studies on oxime ether derivative synthesis, a serendipitous reactivity of dihydropyrroloimidazol-6-ones has been observed. Instead of expected oxime ethers, a new class of 1,2-dioxime ether derivatives with nitromethylene imidazolidine subunit were prepared in moderate to good yields. In this reaction, the adjacent carbon of carbonyl, but not the carbonyl, was preferentially attacked by oxyamine. The methodology has been applied on a wide range of oxyamine hydrochlorides, such as alkoxyamine hydrochlorides and benzyloxyamine hydrochlorides.

Introduction

Oxime ether moiety is an important motif in pharmaceutical and agricultural chemistry.[1,2] Oxime ether derivatives are well-known for their insecticidal,[3] acaricidal,[4] fungicidal,[5,6] and antiviral activities.[7] Various preparative methods for the construction of the oxime ether skeleton have been developed, including the direct oximation of ketones by oxyamine hydrochlorides (Scheme 1, Eq. 1),[8–10] the reaction of nitrites with the active methylene groups (Scheme 1, Eq. 2),[11] and the coupling of arylboronic acid.[12] However, the practical methods for the preparation of 1,2-dioxime ethers remain limited.

Dioxime ether derivatives also possess a wide range of biological activities, which are shown to act as insecticides, fungicides, acaricides, and nematicides (Fig. 1).[13] With growing applications of their synthesis and bioactivity, much attention has been paid to the development of efficient methods for the access of dioxime ether compounds. The commonly-used method was cascade reaction consisting of nitrosation, oximation, and alkylation from appropriate carbonyl compounds. However, the long reaction steps and low yields limit their broad application. As a result, there is a need to develop an efficient and convenient procedure for the synthesis of dioxime ethers. Here, we presented a novel one-pot approach to prepare dioxime ethers with nitromethylene imidazolidine subunit.

Results and discussion

Recently, we found that dihydropyrroloimidazol-6-one **1a** exhibited pronounced insecticidal activity.[14] During optimizing physicochemical properties to enhance biological activities, the reaction between **1a** and methoxyamine hydrochloride was carried out to introduce oxime ether moiety to **1a**. Interestingly, instead of the desired product **4a**, the *O*,*O*-dimethyl dioxime **3a** was obtained (Scheme 2), whose structure was further confirmed by X-ray crystal diffraction[15] (Fig. 2).

Initially, the reaction between **1a** and methoxyamine hydrochloride (**2a**) was explored as a model to optimize the reaction conditions. And the reaction was optimized in terms of solvent, base, the amount of base and the ratio of the reactants (Table 1). Among the solvents screened (entries 3–8), ethanol was found to be the solvent of choice. Pyridine gave a superior result compared to other bases such as piperidine, DABCO, DBU, C_2H_5ONa, and NaOH (entries 9–13). With 1 equiv of **1a** and 4 equiv of **2a**, the effect of the amount of pyridine on this reaction was examined, a 51% yield of **3a** with incomplete conversion of **1a** was obtained using 6 equiv of pyridine. A higher equiv of pyridine did not benefit this reaction (entry 15). A complete disappearance of the substrate **1a** was observed with an isolated 83% yield of **3a**, when the amounts of **2a** and pyridine were increased to 6 equiv and 8 equiv, respectively (entry 17). In addition, prolonging or reducing the reaction time did not provide a better result (entries 20 and 21). Based upon the above detailed investigations, we were pleased to observe that the reaction proceeded efficiently to afford the target dioxime ether **3a** in 83% yield when 1 equiv of **1a** was

* Corresponding author. Tel.: +86 21 64253540; fax: +86 21 64252603.
E-mail address: lizhong@ecust.edu.cn (Z. Li).

http://dx.doi.org/10.1016/j.tetlet.2015.02.041
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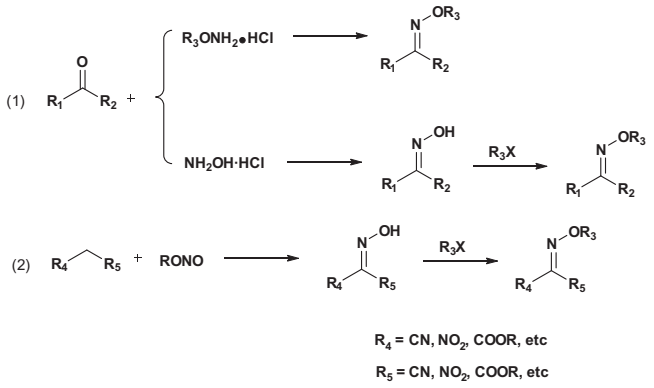
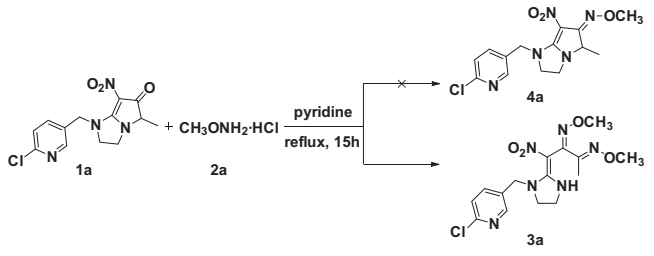


Scheme 1. Traditional methods for the synthesis of oxime ethers.

Figure 1. Biologically active compounds with dioxime ether moieties.

stirred with 6 equiv of **2a** and 8 equiv of pyridine in ethanol for 24 h under reflux conditions.

Under the optimized conditions, the scope of the oxyamine hydrochlorides was examined, and the results are summarized in Table 2 (entries 1–14). A series of alkoxyamine hydrochlorides and substituted benzyloxyamine hydrochlorides were employed for this one-pot reaction, and the corresponding dioxime ether derivatives **3a**–**3n**[16,17] were obtained in moderate to good yields (52–86%). For example, the reaction of the ketone **1a** with various alkoxyamine hydrochlorides (**2a**–**2c**) was explored, and the corresponding alkyl dioxime ether derivatives **3a**–**3c** were obtained in 74–86% yields. Using substituted benzyloxyamine hydrochlorides, including electron-withdrawing and electron-donating functional groups on the aromatic moieties, such as methoxy (**2e**), nitro (**2f**), methyl (**2g**–**2i**), and halo (**2j**–**2l**), the reaction also proceeded smoothly to afford the desired products. These results indicate that both electron-donating and electron-withdrawing groups were well-tolerated. An electron-donating group at the *ortho*-, *meta*-, and *para*-position on the aromatic ring of R_2 was also tolerated with a 75–78% yield (**3g**–**3i**). The reaction of **1a** with sterically hindered 2,6-dichlorobenzyloxyamine hydrochloride (**2l**) or 3,5-dimethylbenzyloxy amine hydrochloride (**2m**) provided the desired products **3l**–**3m** in 72–78% yields. The reaction of **1a** with **2n** led to the product **3n** in 52% yield. Unfortunately, running the reaction of **1a** with hydroxylamine hydrochloride (**2o**) under the optimized reaction conditions did not afford the desired product, which might be due to the weaker nucleophilicity of **2o**. Moreover, the ketones (**1b**–**1f**) with different *N*-substituted functional groups



Scheme 2. Unexpected formation of the *O*,*O*-dimethyl dioxime (**3a**).

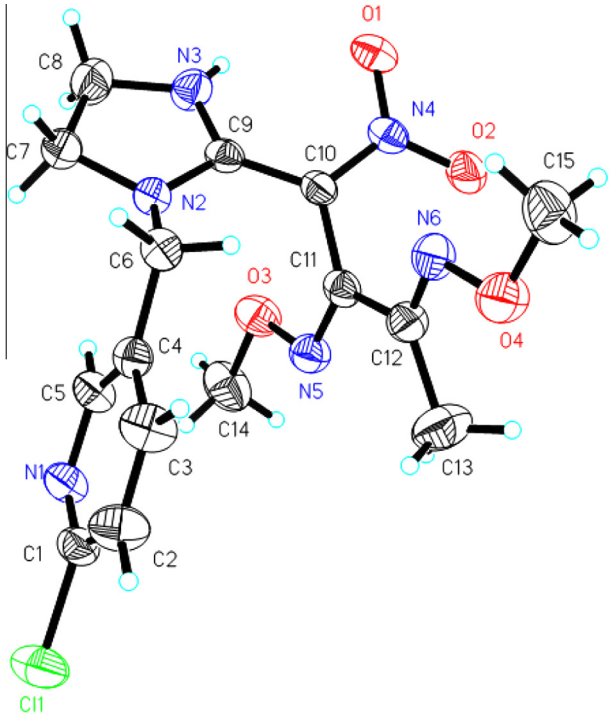
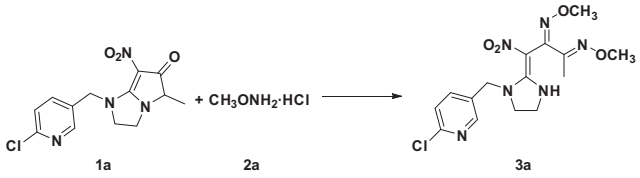


Figure 2. X-ray crystal structure of **3a**.

were also attempted. The reactions of the ketone **1b**[18] with various oxyamine hydrochlorides (**2a**, **2c**, **2g**, and **2f**) were carried out under the same conditions, and the desired products **3p**–**3s** were

Table 1
Reaction optimization



Entry	Molar ratio (**1a**:**2a**)	Base (equiv)	Solvent	*T* (°C)	*t* (h)	Yield[a]
1	1:2	Pyridine	Pyridine	90	15	Trace
2	1:3	Pyridine	Pyridine	90	15	Trace
3	1:4	Pyridine	Pyridine	90	15	31%
4	1:4	Pyridine (5)	*i*-PrOH	Reflux	15	28%
5	1:4	Pyridine (5)	*i*-BuOH	Reflux	15	18%
6	1:4	Pyridine (5)	CH_3OH	Reflux	15	44%
7	1:4	Pyridine (5)	EtOH	Reflux	15	47%
8	1:4	Pyridine (5)	*n*-BuOH	Reflux	15	25%
9	1:4	Pyridine (5)	EtOH	Reflux	24	48%
10	1:4	NaOH (5)	EtOH	Reflux	24	0
11	1:4	Piperidine (5)	EtOH	Reflux	24	0
12	1:4	DABCO (5)	EtOH	Reflux	24	Trace
13	1:4	CH_3COONa (5)	EtOH	Reflux	24	Trace
14	1:4	Pyridine (6)	EtOH	Reflux	24	51%
15	1:4	Pyridine (7)	EtOH	Reflux	24	45%
16	1:5	Pyridine (7)	EtOH	Reflux	24	76%
17	1:6	Pyridine (8)	EtOH	Reflux	24	83%
18	1:7	Pyridine (9)	EtOH	Reflux	24	80%
19	1:8	Pyridine (10)	EtOH	Reflux	24	78%
20	1:6	Pyridine (8)	EtOH	Reflux	15	65%
21	1:6	Pyridine (8)	EtOH	Reflux	36	82%

[a] UPLC yield.