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Triflic Acid Catalyzed Formal [3 + 2] Cycloaddition of Donor–Acceptor Oxiranes and Nitriles: A Facile Access to 3-Oxazolines

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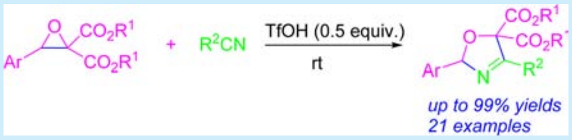
Ⓢ *Supporting Information*

ABSTRACT: A TfOH-catalyzed chemoselective [3 + 2] cycloaddition of donor–acceptor oxiranes and nitriles is described. This reaction provides an efficient and practical method for the preparation of useful 3-oxazolines in good to excellent yields (up to 99%).



Compared with 2-oxazolines, 3-oxazolines (or 2,5-dihydrooxazoles) as isomers are a rare class of compounds and have been relatively neglected. However, 3-oxazolines are very useful. Their derivatives such as 2,4,5-trimethyl-3-oxazoline have been isolated and characterized as volatile flavor compounds in various foods.[1] Some of them have presented important organoleptic properties.[2] Various substituted 3-oxazolines have also been used as artificial food flavors.[1,3] There are few methods known for their syntheses. Reported synthetic methods of 3-oxazolines include oxidative elimination of 1,3-oxazolidines,[4] photochemically induced or base-catalyzed ring opening of substituted 2*H*-azirines,[5] and Boyer reaction of aliphatic aldehyde with 2-aryl-2-azidoethanol.[6] Therefore, a new synthetic approach to this class of useful molecules is still highly desirable.

The formal [3 + 2] cycloaddition[7] of donor–acceptor oxiranes with dipolarophiles has emerged as a versatile tool for the construction of various five-membered heterocycles.[8] The reactions involve *in situ* generation of 1,3-dipoles through Lewis acid promoted C–C bond or C–O bond cleavage of oxiranes, which are then trapped by dipolarophiles bearing C–X (X = O, C) multiple bonds. The special features of the reactions include high efficiency, stereoselectivity, and atom economy.

Although nitriles have proved to be good dipolarophiles in the Lewis acid[9] or Brønsted acid[10] promoted formal [3 + 2] cycloaddition of donor–acceptor cyclopropanes, they still remain unexplored in the cycloaddition reaction with oxiranes. Thus, we envisioned that nitriles would easily undergo the intermolecular cycloaddition with donor–acceptor oxiranes via selective C–C bond breakage, producing the corresponding highly functionalized 3-oxazolines.

Oxiranes are usually prone to ring opening through the C–O bond cleavage in the presence of a Brønsted acid. Interestingly, oxiranes underwent intermolecular [3 + 2] cycloaddition with nitriles via Brønsted acid catalyzed chemoselective C–C bond cleavage of oxiranes in this work (Scheme 1).

To test our hypothesis, we initially started the study of the [3 + 2] cycloaddition reaction by using dimethyl-3-*p*-tolyloxiranyl-2,2-dicarboxylate (**1a**) and benzonitrile (**2a**) as the model substrates in the presence of a Brønsted acid (Table 1). Due to possible protonation of nitriles by Brønsted acids, an excess of **2a** was needed for completing the reaction.[9] Among several Brønsted acids screened, only triflic acid could efficiently promote the reaction to provide the desired 3-oxazoline **3aa** in 87% yield (entries 1–7). The yield was reduced slightly to 86%

Scheme 1. Proposed Selective Ring Opening of Oxiranes in the [3 + 2] Cycloadditions with Nitriles

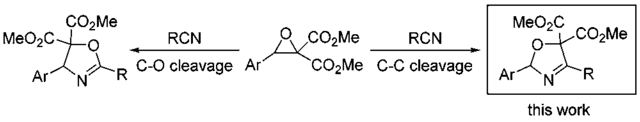
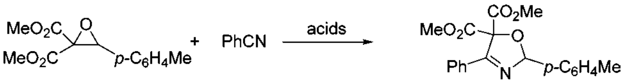


Table 1. Optimization of the Reaction Conditions[a]



1a **2a** **3aa**

entry[a]	acid (equiv)	solvent	temp[b]	yield (%)[c]
1	TfOH (1.0)	free	rt	87
2	TFA (1.0)	free	rt	0
3	CSA (1.0)	free	rt	0
4	HCl (1.0)	free	rt	0
5	PTSA (1.0)	free	rt	0
6	H_3PO_4 (1.0)	free	rt	0
7	H_2SO_4 (1.0)	free	rt	0
8	TfOH (0.5)	free	rt	86
9	TfOH (0.2)	free	rt	29
10	TfOH (1.0)	1,2-DCE	rt	85
11	TfOH (1.0)	DCM	rt	86
12	TfOH (1.0)	DCM	0 °C	53
13	TfOH (1.0)	DCM	−40 °C	41

[a]Reactions were performed by the addition of an acid to a mixture of 1.0 mmol of **1a** and 5.0 mmol of **2a** (with or without solvent). [b]Reaction temperature. [c]Isolated yields.

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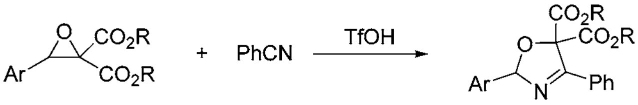
when the amount of TfOH was decreased to 50 mol % (entry 8). Further reduction of TfOH to 20 mol % led to a sharp decrease in yield to 29% (entry 9). The reaction also performed well when dichloromethane or 1,2-dichloroethane was used as solvent (entries 10 and 11). The cycloaddition could not work well at lower temperature (entries 12 and 13). By comparison, the optimal reaction conditions were selected as 0.5 equiv of triflic acid, **1a**/**2a** = 1:5, solvent-free, and room temperature.

With the optimized reaction conditions in hand, we continued to explore the scope of this TfOH-catalyzed formal [3 + 2] cycloaddition process. Different donor−acceptor oxiranes were investigated with benzonitrile (Table 2). This reaction was amenable to different ester groups of aryl oxiranyl dicarboxylates (entries 1−3). The results indicate that the electron-rich aryl substituted oxiranyl dicacarboxylates performed better than the electron-deficient aryl substituted ones (entries 1 and 4−10). This might be due to the destabilization of the incipient positive charge on the adjacent carbon of the dipole by the electron-deficient aryl moiety during the course of the reaction (see the proposed mechanism in Scheme 2). In addition, the 1-naphthyl substituted one could also furnish the corresponding product in an excellent yield of 91% (entry 11).

Table 2. TfOH-Catalyzed [3 + 2] Cycloaddition of Various Oxiranes 1 with Benzonitrile 2a[a]



1a-1k **2a** **3aa-3ak**

entry	Ar	R	yield (%)[b]
1	4-MeC_6H_4	Me	86 (**3aa**)
2	4-MeC_6H_4	Et	97 (**3ba**)
3	4-MeC_6H_4	Bn	78 (**3ca**)
4	3-MeC_6H_4	Me	89 (**3da**)
5	4-$MeOC_6H_4$	Me	86 (**3ea**)
6	4-BrC_6H_4	Me	99 (**3fa**)
7	4-ClC_6H_4	Me	91 (**3ga**)
8	4-$NO_2C_6H_4$	Me	70 (**3ha**)
9	3,4,5-$(MeO)_3C_6H_4$	Me	92 (**3ia**)
10	Ph	Me	99 (**3ja**)
11	1-naphthyl	Me	91 (**3ka**)

[a] Reaction conditions: 1.0 mmol of **1**, 5.0 mmol of **2a**, 0.5 mmol of triflic acid, rt. [b] Isolated yields.

We next examined the scope of this cycloaddition by varying the nitrile components under the optimized conditions, and the results are summarized in Table 3. This formal [3 + 2] cycloaddition was amenable to various aromatic nitriles possessing electron-donating or electron-withdrawing groups, giving the products in good to excellent yields (entries 1−7, up to 99%). An electron-withdrawing group, such as the nitro group, on the phenyl ring of the aryl nitirles usually decreased the yield (entry 7). The electron-withdrawing inductive effect of the nitro group will obviously decrease the reactivity of **3g** in this reaction. Various alkyl nitriles worked well (entires 8−10), and an *α*,*β*-unsaturated nitrile also gave an excellent yield of 92% (entry 11).

Scheme 2. Proposed Mechanism of [3 + 2] Cycloaddition of Donor−Acceptor Oxiranes with Nitriles

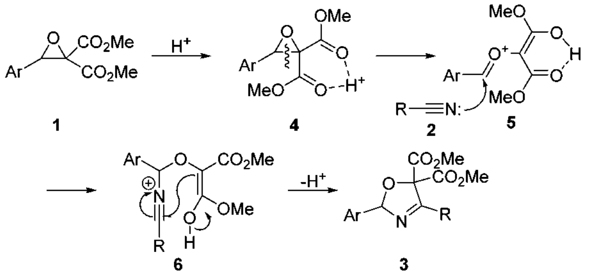
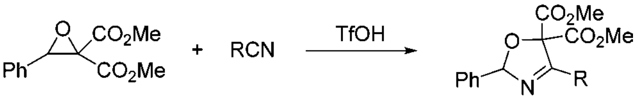


Table 3. TfOH-Catalyzed [3 + 2] Cycloaddition of Various Nitriles 2 with Oxirane 1j[a]



1j **2a-2k** **3ja-3jk**

entry	R	yield (%)[c]
1	Ph	99 (**3ja**)
2[b]	4-$MeOC_6H_4$	92 (**3jb**)
3	4-MeC_6H_4	87 (**3jc**)
4[b]	4-ClC_6H_4	76 (**3jd**)
5[b]	2-ClC_6H_4	82 (**3je**)
6[b]	3-ClC_6H_4	88 (**3jf**)
7[b]	4-$NO_2C_6H_4$	57 (**3jg**)
8	Me	79 (**3jh**)
9	*i*Pr	80 (**3ji**)
10	Bn	70 (**3jj**)
11	*E*-cinnamyl	92 (**3jk**)

[a] Reaction conditions: 1.0 mmol of **1j**, 5.0 mmol of **2**, 0.5 mmol of triflic acid, rt. [b] 2 mL of 1,2-DCE used as solvent. [c] Isolated yields.

The mechanism of this TfOH-catalyzed formal [3 + 2] cycloaddition reaction is proposed as shown in Scheme 2. A proton is coordinated to the two carbonyl groups of oxirane **1** to form an energetically favorable six-membered ring structure **4** which then gives oxocarbenium intermediate **5** (the zwitterionic intermediate) via C−C bond cleavage. The lone pair on the nitrogen atom of the nitriles attacks oxocarbenium to generate the 1,5-dipole **6**. The following nucleophilic attack of the malonate carbanion on the nitrile carbenium affords cycloadduct **3**. This mechanism is supposed to be similar to that of the [3 + 2] cycloaddition of donor−acceptor oxiranes with aldehydes[8b] or alkynes.[8d]

In summary, we developed an efficient triflic acid catalyzed formal [3 + 2] cycloaddition of donor−acceptor oxiranes with nitriles, leading to the formation of useful 3-oxazolines in good to excellent yields (up to 99%). To the best of our knowledge, this is the first report of [3 + 2] cycloadditions of donor−acceptor oxiranes and nitriles. This provides an efficient and practical method for the synthesis of structurally diverse 3-oxazolines under very mild conditions. Further investigation to expand the synthetic application of the reaction, to understand the mechanism of this formal [3 + 2] cycloaddition reaction, and to study the asymmetric version of the reaction is in progress.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and full spectroscopic data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00911.

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Notes

The authors declare no competing financial interest.

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