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TfOH-Catalyzed Formal [3+2] Cycloaddition of *N*-tosylaziridine dicarboxylates and Nitriles: Synthesis of Tetrafunctionalized 2-imidazolines

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1. Introduction

The synthesis of tetrafunctionalized 2-imidazolines has received considerable attention due to their common use as bioactive molecules,1-7 organocatalysts8 and ligands for asymmetric synthesis^{9,10} (Figure 1). For example, Nutlin-3, which is based on a tetrasubstituted 2-imidazoline scaffold, efficiently disrupted the interaction between p53-MDM2 for cancer treatment.5,6 Several approaches are known to synthesize 2-imidazolines, tetrafunctionalized involving multistep cyclization of 1,2-diamines¹¹⁻¹⁵ or β -amino alcohols,¹⁶ the metalcatalyzed or metal-free protocols for multicomponent reactions¹⁷⁻ ²⁵ or formal [3+2] annulation,²⁶⁻³⁰ and the transformations of the protected α , β -diamino esters³¹, unsymmetrical imidazolines^{32,33} or imidoyl chlorides with aziridines.34



Figure 1. Representative products containing 2-imidazoline cores in different areas.

ABSTRACT

We developed an efficient method for synthesis of tetrafunctionalized 2-imidazolines using TfOHcatalyzed formal [3+2] cycloaddition of *N*-tosylaziridine dicarboxylates and nitriles. This is the first report of C-N bond cleavage of *N*-tosylaziridine dicarboxylates catalyzed by Brønsted acid and the reaction worked well over wide scope of substrates in good to excellent yields under mild conditions. The method has the potential to be applied to pharmaceutical design and synthesis of tetrafunctionalized 2-imidazolines.

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However, there still remain challenges in this field such as difficult availability of precursors and the use of complex reagents including transition metal salts. Hence, a novel and efficient synthesis approach to the potentially bioactive heterocycles is still valuable.

A. Previous work: Lewis acids-catalyzed functionalization of *N*-tosyl aziridines dicarboxylates with diverse nucleophiles(**C-C bond cleavage**)



Nu: imines, aldehydes, indoles, alkynes, alkenes, ketenimines, isocyanides, cyclopropanes et al. except nitriles

B. Previous work: Brønsted acid-catalyzed [3+2] cycloaddition of cyclopropane 1,1-diesters or oxiranyldicarboxylates with **nitriles** (**C-C bond cleavage**)



C. This work: Brønsted acid-catalyzed [3+2] cycloaddition of N-tosylaziridines dicarboxylates with nitriles (C-N bond cleavage)



Tetrafunctionalized 2-imidazoline

Scheme 1. Different cleavage ways of aziridines.

(donor-acceptor aziridines) with diverse nucleophiles has emerged as a potentially powerful approach for convenient access to structurally complex five-membered azaheterocycles *via* Lewis acid-catalyzed/mediated C-C bond cleavage of donoracceptor (DA) aziridines (Scheme 1A).³⁵⁻⁴⁸ Although most nitriles are known to be poor dipolarophiles for [3+2] cycloaddition reactions, the groups of Zhong & Zeng⁴⁹ and Wang⁵⁰ have independently demonstrated that TfOH-catalyzed cycloaddition of oxiranes dicarboxylates or donor-acceptor cyclopropane and nitriles successfully *via* C-C bond cleavage of oxiranes or cyclopropanes (Scheme 1B).

Inspired by the above achievements and based on our interest in developing antitumor heterocycles and potentially bioactive azaheterocycles, we envisioned that the formal [3+2] cycloaddition of N-tosylaziridine dicarboxylates and nitriles to provide tetrafunctionalized 2-imidazolines. Herein, we describe the first example of the development of remarkably mild TfOH-catalyzed formal [3+2] а cycloaddition of N-tosylaziridine dicarboxylates and nitriles, providing a facile and step-economical access to tetrafunctionalized 2-imidazolines bearing ester functional groups, which serve as key building blocks in the potent NFκB inhibitor TCH-013 (Scheme 1C).^{51,52} Of particular note is the fact that Brønsted acid have been not exploited in annulation reaction of DA aziridines with diverse nucleophiles or electron-rich reaction groups, though the similar catalytic process has been reported to prepare trifunctionalized 1H-imidazoles using nitriles and common aziridines in the presence of TfOH via Ritter reaction,53 where the electronic nature of common aziridines were different from DA aziridines. In this light, DA aziridines inherently favour C-C bond cleavage, which was supported by density functional theory (DFT) studies⁵⁴ and the experimental results showed that Lewis acids catalyzed C-C bond heterolysis of DA aziridines.

2. Results and Discussion

We started to test our hypothesis by reacting 3-phenyl-1-tosylaziridine dicarboxylates **1a** and benzonitrile **2a** as model substrates in DCM using $Sc(OTf)_3$ as a conventional Lewis acid (Table 1, entry 1).⁵⁵⁻⁵⁷ Unfortunately, we found **1a** was decomposed and no identifiable products could be isolated.⁵⁸ And the same result was observed when excess nitrile was served as the solvent without DCM (entry 2) and in the presence of Cu(OTf)₂ with or without DCM as solvent (entries 3-4).

Inspired by the above achievement,^{49,50} we next turned our attention to Brønsted acids. On account of possible protonation of nitriles by Brønsted acid, excess **2a** was needed to complete the reaction. Several Brønsted acids and acid anhydrides were screened (entries 5-13), and only Tf₂O and TfOH could promote the reaction to give the [3+2] cycloaddition product **3a** in more than 85% yield when excess nitrile was served as the solvent due to their strong proton-donating properties. When the amount of TfOH was decreased to 10%, the yield decreased to 70% (entries 12, 14-16). The reaction performed not well at higher or lower temperature (entries 17-18). As suggested above, the optimal reaction condition was selected as 0.5 equiv of TfOH, 30 °C and excess nitriles as solvent.

With the optimal reactions established, we next investigated the substrate scope on *N*-tosylaziridine dicarboxylates 1 (Table 2A). We first examined the effect of the ester moieties on reaction outcome. The ethyl (3a, 3c) and methyl ester (3b, 3d)were also compatible but increasing the steric hinderance of the

Ĉ	Ts COOEt + Pho 1a	Catalys ────────────────────────────────────	t. Et000	Ja Ja
Entry	Catalyst (equiv)	Solvent	T (°C)	yield $(\%)^b$
1°	Sc(OTf) ₃	DCM	30	decompose
2^{c}	Sc(OTf) ₃		30	decompose
3 ^c	Cu(OTf) ₂	DCM	30	decompose
4 ^{<i>c</i>}	Cu(OTf) ₂		30	decompose
5	TFA (1.0)		30	N. R.
6	PTSA (1.0)		30	N. R.
7	HCl (1.0)		30	N. R.
8	HNO ₃ (1.0)		30	N. R.
9	TFAH (1.0)		30	N. R.
10	Ac ₂ O (1.0)		30	N. R.
11^d	Tf ₂ O (1.0)		30	89
12	TfOH (1.0)		30	94
13	TfOH (1.0)	DCM	30	trace
14	TfOH (0.5)		30	95
15	TfOH (0.2)		30	80
16	TfOH (0.1)		30	70
17	TfOH (0.5)		50	64
18	TfOH (0.5)		0	45

^{*a*}Reaction conditions: *N*-tosylaziridinedicarboxylate **1a** (0.025 mmol), benzonitrile **2a** (0.2 mL, analytical-reagent grade), and the nitrile also served as the solvent. ^{*b*}Isolated yields based on **1a** were given. N.R. stands for no reaction, decompose means **1a** was decomposed and the product **3a** was not detected. ^{*c*}The reaction was conducted at 0.05 mmol scale and 20% catalyst was added. ^{*d*}The transformation could be also catalyzed by TfOH which generated from Tf₂O in benzonitrile with trace amounts of water after strictly controlling the absence of water.

ester groups resulted in a decrease in yields, such as, the reaction did not progress in the presence of the *tert*-butyl ester. (see Table S1 in ESI for more details). We also explored various aryl groups with electron-withdrawing (Cl, I, NO₂) or electron-donating groups (Me) of aziridines (**3f-3i**) and found that *p*-methylphenyl substitution on aziridine **1i** performed better and gave the product **3i** in 72% yield. The *N*-substitution on aziridine dicarboxylates had little influence on the reactivity generally (**3a**, **3c**, **3j-3e**) and *N*-trifluoromethyl phenyl sulfonyl aziridines **1I** reacted with **2a** to provide the desired 2-imidazolines **3l** in 80% yield. The configuration of **3e** was determined by X-ray crystallographic analysis (see Figure S1 in ESI).

We next turned to investigate the scope of substituents on nitriles 2 (Table 2B). Results of the cycloaddition of 1a with various nitriles were delightful. Various alkyl nitriles, including acetonitrile, isobutyronitrile, and butyronitrile gave the corresponding product 3m-30 in 77-95% yields while trimethylacetonitrile didn't reacted with aziridines. The numbers of α -H to these nitriles varies from each other, and we proposed that these protons could affect the process. Those nitriles with vinyl groups also gave an excellent result to obtain the product 3p-3q in 72-75% yields. It is worth mentioning that the terminal C=C bond of but-3-enenitrile has been transferred to the internal place during the cycloaddition process and it gave the product 3p in 75% yield. We also explored that when changing the number of carbons between the imidazoline skeleton and the aryl group,





Tabl

^aReaction conditions: *N*-tosylaziridine dicarboxylate 1 (0.2 mmol), nitrile 2 (0.3 mL), and TfOH (8.8 mL, 0.1 mmol) at 30 °C, the excess nitrile also served as the solvent. ^bIsolated yields based on 1 were given. ^cThe reaction was conducted at 35 °C. ^dThe reaction was conducted at 0 °C. ^eUsing ethyl 3-phenyl-1-tosylaziridine-2-carboxylate 10 as the aziridine substrate.

the cycloaddition still performed well to give the product **3r-3s** in 77-88% yields. Electron-donating group (Me) and different positions of electron-withdrawing group (F) on the aryl moiety of the aromatic nitriles are amenable, affording the desired product 3t-3w in 66-80% yields. Unfortunately, electron-rich nitrile with p-methoxyphenyl group didn't reacted with N-tosylaziridine 1a with or without solvent (see Table S2 in ESI for more details). It is noteworthy that thiophene-substituted nitrile was well-tolerated in the presence of strong acid TfOH to furnish 3x in 54% yield. Furthermore, the 2,2'-diester N-tosyl-aziridine bearing 4-Cl substituent at aryl moiety could react with acetonitrile to give the corresponding cycloaddition product 3y (confirmed by X-ray study, Figure S2 in ESI). Additionally, it is noteworthy that the similar transformation observed with N-tosylaziridine bearing only one ester, afforded the corresponding product 3z in 20% vield with 6:1 dr.

To gain some insight into the reaction mechanism, we have explored the cycloaddition of the chiral aziridine⁵⁹ (*R*)-1a with benzonitrile 2a. The reaction proceeded smoothly to afford the corresponding chiral product 3a in 90% yield with 50% ee under the otherwise identical reaction conditions (Scheme 2). The

decomposition⁶⁰ or racemization⁶¹ of the chiral aziridine (*R*)-1a, which indicated that nucleophilic attack of the nucleophilic nitrile 2 could proceed through a $S_N 2$ model.



Scheme 2. The formal [3+2] cycloaddition of (R)-1a with benzonitrile 2a

On the basis of the above observations and previous studies.⁵³ The reaction pathway for this cycloaddition reaction is proposed (Scheme 3). Initially, a proton from TfOH is coordinated to the nitrogen of the aziridine and one of the carbonyl groups to enhance the electrophilicity of the adjacent carbon of DA aziridines, followed by the nucleophilic attack of the nitrile **2** to the aryl-substituted C2 atom of the activated DA aziridines in a S_N2 -type fashion to form a Ritter process intermediate **5** *via* C-N bond cleavage. Finally, the following nucleophilic attack of the TsNH on the nitrile carbenium affords tetrafunctionalized 2-imidazolines **3**. This proposed mechanism is similar to that of [3+2] cycloaddition of oxiranes dicarboxylates with aldehydes *via* C-O bond cleavage.⁶²



Scheme 3. Proposed mechanism

The further synthetic application of tetrafunctionalized 2imidazolines has been showcased by the transformation of 3n, which gave NH free 2-imidazoline **6** in 83% yield easily in the presence of LiCl at 160 °C in DMSO by the remove of Ts group and one ester group (Scheme 4).⁶³



Scheme 4. Synthetic application

3. Conclusions

To sum up, we developed a novel and efficient route to synthesize tetrafunctionalized 2-imidazolines using TfOHcatalyzed formal [3+2] cycloaddition of *N*-tosylaziridine dicarboxylates and nitriles. This is the first report of C-N bond cleavage of *N*-tosylaziridine dicarboxylates catalyzed by Brønsted acid and the method has the potential to be applied to pharmaceutical design and synthesis of tetrafunctionalized 2-imidazolines. Further study on biological activity is under investigation in our laboratory.

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Supplementary Material

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Graphical Abstract

4 Re Journal Pre-proofs

TfOH-Catalyzed Formal [3+2] Cycloaddition of *N*-tosylaziridine dicarboxylates and Nitriles: Synthesis of Tetrafunctionalized 2imidazolines

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Highlights

- TfOH-catalyzed cycloaddition of *N*tosylaziridine dicarboxylates and nitriles gave tetrafunctionalized 2-imidazolines.
- The method features mild conditions and wide scope of substrates.
- First example of C-N bond cleavage of Ntosylaziridine dicarboxylates catalyzed by Brønsted acid.
- A $S_N 2$ process.