FULL PAPER DOI: 10.1002/adsc.202001569

Advanced Synthesis & Catalysis

Synthesis of Diversely Substituted Imidazolidines *via* [3+2] Cycloaddition of 1,3,5-Triazinanes with Donor-Acceptor Aziridines and Their Anti-Tumor Activity

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Manuscript received: December 17, 2020; Revised manuscript received: February 25, 2021;
Version of record online: ■■, ■■

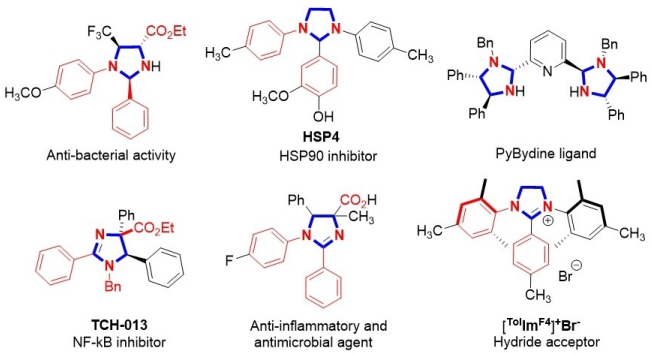
Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202001569

Abstract: A $Y(OTf)_3$-catalyzed [3+2] cycloaddition of 1,3,5-triazinanes with donor-acceptor aziridines has been developed, accessing diversely substituted imidazolidines high efficiency. Mechanistic investigations support the formation of imidazolidines through an S_N1-like pathway. Furthermore, these imidazolidines exhibit promising anti-tumor activity against a series of human cancer cell lines.

Keywords: Imidazolidines; Cycloaddition; Donor-acceptor aziridines; 1,3,5-Triazinanes; Anti-tumor activity

Introduction

Imidazolidine and imidazoline frameworks are characteristic and essential motifs embedded in an array of agrochemical fungicides,[1] pharmaceuticals[2] and ligands[3] (Scheme 1). Consequently, direct construction of diversely substituted imidazolidines has long been recognized as a preeminent goal for organic synthesis. Several approaches are known to synthesize imidazolidines,[4] involving mannich cyclization,[5] intramolecular amination and the metal-catalyzed or metal-free protocols for multicomponent reactions[6] or formal cycloaddition.[7] Among them, intermolecular [3+2] cycloaddition[8] is a viable strategy for synthesis of these valuable functionalized imidazolidines in an atom-economical fashion.

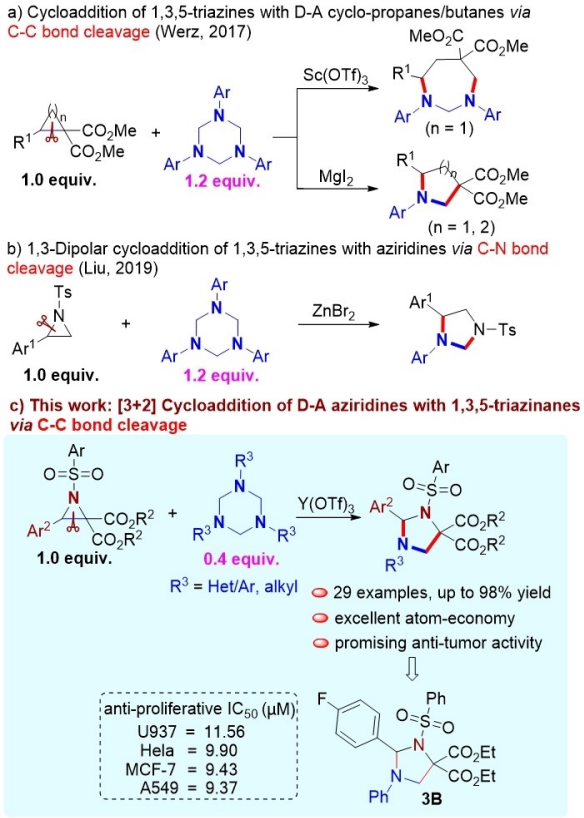


Scheme 1. Representative biologically active compounds and ligands.

Donor-acceptor (D–A) aziridine, a versatile synthetic building block in organic synthesis, is applicable to the construction of five-membered nitrogen heterocycles *via* [3+2] cycloaddition with diverse nucleophiles,[9] which prefers C–C bond cleavage in the presence of Lewis acids.[10] In this field, Feng X and co-workers have developed the chiral *N*, *N*′-dioxide/Lewis acid-catalyzed enantioselective [3+2] annulation of donor-acceptor aziridines with aldehydes,[11a] 3-methylindoles,[11b] 3,4-dihydropyran

derivatives or acyclic enol ethers[11c] respectively for the construction of enantioenriched nitrogen heterocycles. Additionally, Zhang and co-workers have reported a formal [3+2] cycloaddition of donor-acceptor aziridines with stable Bn-/Ph-substituted imines to afford the multisubstituted imidazolidines.[12] Recently, we have achieved the first [3+2] cycloaddition of donor-acceptor aziridines and nitriles mediated by Brønsted acid *via* C–N cleavage to afford tetrafunctionalized 2-imidazolines.[13] Furthermore, as part of our continuous efforts to construct the five-membered azaheterocycles,[14] we become interested in developing the reactions of the donor-acceptor aziridines and other nucleophiles to construct the potential bioactive five-membered azaheterocycles.

1,3,5-Triazinanes, as stable and readily available surrogates of formaldimines, were utilized in various nitrogen-containing heterocycle construction with various nucleophiles.[15] Most of the reactions of 1,3,5-triazinanes reported so far are involved in aminomethylations[16] and cycloaddition reactions.[17] Seminal work catalyzed by Lewis acid was performed by Werz and co-workers, who reported the cycloadditions of 1,3,5-triazinanes and donor-acceptor cyclopropanes/cyclobutanes (Scheme 2a).[18] Recently, Liu group presented the elegant Lewis acid catalyzed [3+2] cycloadditions of aziridines and 1,3,5-triazinanes to access to functionalized imidazolidines (Scheme 2b).[19] *Despite these achievements, to the best of knowledge, the cycloaddition of donor-acceptor aziridines and 1,3,5-triazinanes has not been demonstrated so far.* Herein, we disclose the first $Y(OTf)_3$ catalyzed [3+2] cycloaddition of donor-acceptor aziridines and 1,3,5-triazinanes *via* C–C bond cleavage to provide a range of diversely substituted imidazolidines, which show promising anti-proliferative activity against a number of human cancer cell lines (Scheme 2c).



Scheme 2. The cycloaddition of 1,3,5-triazinanes.

Results and Discussion

Inspired by Liu's earlier work on $ZnBr_2$-catalyzed 1,3-dipolar cycloadditions of 1,3,5-triazinanes with aziridines,[19] donor-acceptor aziridine **1a** and triazine **2a** were utilized as model substrates to optimize reaction conditions (Table 1). However, the reaction in the presence of $ZnBr_2$ with toluene as the solvent provided the desired product **3A** in poor yield (entry 1), and the reaction yield was increased to 72% by using 4 Å MS as an additive, thus indicating the

Table 1. Optimization of the reaction conditions.[a]

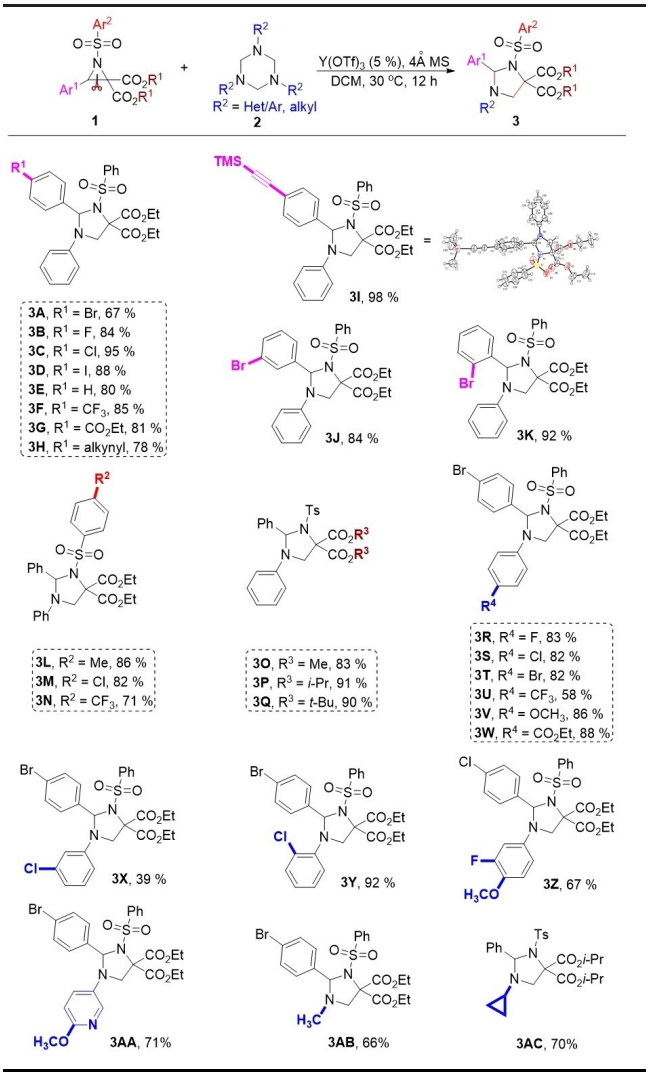
Entry	Catalyst	Solvent	Yield[b] (%)
1[c]	$ZnBr_2$	Toluene	42
2[d]	$ZnBr_2$	Toluene	72
3[e]	TfOH	DCM	nd
4[e]	$BF_3 \cdot Et_2O$	DCM	nd
5	$Cu(OTf)_2$	DCM	8
6	$Fe(OTf)_3$	DCM	42
7	$Zn(OTf)_2$	DCM	16
8	$Mg(OTf)_2$	DCM	72
9	$Ni(OTf)_2$	DCM	42
10	$Y(OTf)_3$	DCM	98
11	$Yb(OTf)_3$	DCM	36
12	$AgSbF_6$	DCM	4
13[f]	$Y(OTf)_3$	DCM	94
14[g]	$Y(OTf)_3$	DCM	96
15[h]	$Y(OTf)_3$	DCM	92

[a] Reaction conditions: **1a** (0.05 mmol), **2a** (0.06 mmol), catalyst (10 mol%), 4 Å MS (25 mg), solvent (0.5 mL); for more optimizated reaction conditions, see the SI.
[b] Yields were determined *via* ^1H NMR by using CH_2Br_2 as the internal standard.
[c] 80 °C, no 4 Å MS.
[d] 80 °C.
[e] Complex mixture. nd: not determined.
[f] Solvent (1 mL).
[g] Catalyst (5 mol%).
[h] **2a** (0.02 mmol), catalyst (5 mol%).

deleterious effect of water in the process. Inspired by our previous work,[13] TfOH and $BF_3 \cdot Et_2O$ were chose as the catalysts, unfortunately, they were completely ineffective in the present reaction (entries 3–4). Then we screened other commercially available Lewis acids, and found $Y(OTf)_3$ was most beneficial for the reaction, resulting in 98% yield (entry 10). Next, a solvent screen revealed DCM to be optimal, and decreasing the concentration of the reaction resulted in a yield of 94% (entry 13) (See Table S1 in SI for more details). We next studied this reaction with different loadings of $Y(OTf)_3$ under the optimal reaction conditions and found that the load could be reduced to 5 mol% without any remarkable effect on the yield of **3A** (entry 14). To our surprise, when **2a** was reduced to 0.4 equiv., the desired product **3A** was also obtained in 92% yield (entry 15), which indicated that our approach featured excellent atom-economy compared with the previous Werz's[18] and Liu's[19] work. After the investigation of other reaction parameters, we established the optimized reaction conditions as **1a** (0.05 mmol), **2a** (0.02 mmol), $Y(OTf)_3$ (5 mol%), 4 Å MS (25 mg), DCM (0.5 mL), at 30 °C for 12 h.

We explored the scope and limitations of the reaction by using various donor-acceptor aziridines and 1,3,5-triazinanes under the optimized reaction conditions, and the results are summarized in Table 2. All the donor-acceptor aziridines and 1,3,5-triazinanes underwent the cycloaddition smoothly to give the corresponding products in excellent yields. Imidazolidines **3A**–**3K** bearing electronically neutral or electron-rich groups at the *ortho*, *meta* or *para* position of the aryl ring were obtained in good yields. Particularly noteworthy is that alkynyl substituents **1h** and **1i** were well-tolerated, which is significant since aryl alkynyl groups are usually incompatible with Lewis acid-catalyzed cycloaddition of donor-acceptor aziridine systems.[9] The structure of **3I** was unambiguously confirmed by X-ray crystallographic analysis (Figure S1 in SI).[20] Meanwhile, variation on the substitution of the arylsulfonyl group also furnished the corresponding products in moderate yields. **1l**–**1n** bearing electron-withdrawing groups and electron-donating groups of the aryl ring participated in the reaction well to provide **3L**–**3N** respectively. Additionally, for the ester moieties, the reactions of aziridines **1o**–**1q** also worked very well under standard conditions to give the corresponding products in moderate yields, indicating the ester group does not affect the reaction. Furthermore, various 1,3,5-triazinanes also engaged in efficient cycloaddition, and high yields were observed for substrates bearing electron-withdrawing/donating groups at the *para*, *ortho* or *meta* position of the phenyl ring to afford products **3R**–**3Z**. Additionally, it is noteworthy that this transformation was also applicable to the substituted 1,3,5-triazinanes bearing pyridinyl, methyl and cyclopropyl group,

Table 2. Substrate scope of [3+2] cycloaddition of donor-acceptor aziridines with 1,3,5-triazinanes.[a,b]

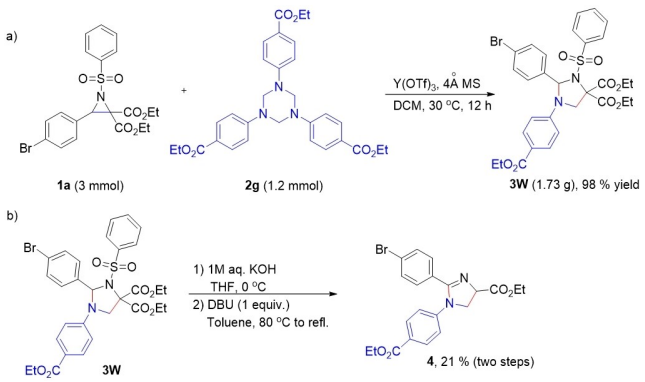


[a] Reactions were conducted on 0.2 mmol scale.
[b] Isolated yield based on **1** is given.

providing the corresponding products **3AA**–**3AC** in 66%–71% yield.

To further demonstrate the utility and practicality of this protocol, this [3+2] cycloaddition was conducted on gram-scale. The reaction of **1a** with **2g** could be easily run on the gram scale in a good yield of 98% (Scheme 3a). On the other hand, the removal of the benzenesulfonyl group and elimination of the acetoxy group of **3W** were carried out to afford the imidazoline derivative **4** (Scheme 3b),[21] which is a scaffold of biologically active compound[2b–d] (Scheme 1).

To obtain some insights into the reaction mechanism, we explored the stereospecificity of the reaction using enantioenriched D–A aziridine (*R*)-**1a** (97% ee).[18] Indeed, the corresponding racemic product **3A** was obtained with 3% ee, which indicated that the

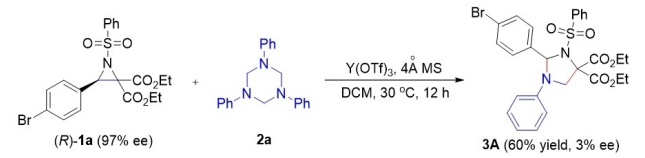


Scheme 3. Synthetic application.

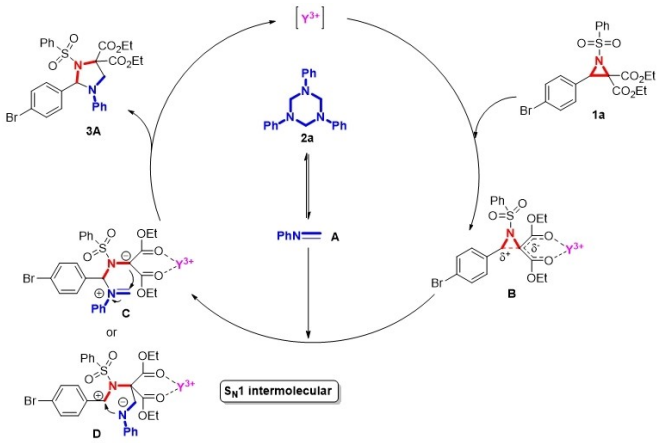
cycloaddition could proceed through a S_N1 model (Scheme 4).

Here, a general mechanism for the formal [3+2] cycloaddition was proposed. As depicted in Scheme 5, in the presence of $Y(OTf)_3$, the formaldimine **A** was first generated[22] and the 1,3-dipole **B** was produced *in situ* from the ring-opening reaction of the donor-acceptor aziridine **1a**, followed by a [3+2] cycloaddition between the formaldimine **A** and 1,3-dipole **B**, furnishing the desired product **3A** through an S_N1-like pathway.[23]

After completing the racemic version, as part of our continuous efforts in catalytic asymmetric transformations for the construction of potentially bioactive aza-



Scheme 4. Stereochemistry and mechanistic investigation.



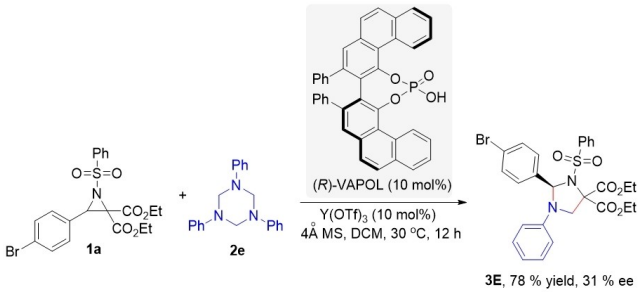
Scheme 5. Plausible reaction mechanism.

heterocycles,[14,24] we next proceeded to investigate the catalytic asymmetric [3+2]-cycloaddition of 1,3,5-triazinanes with racemic donor-acceptor aziridines by using our recently developed copper salts and CPA (chiral phosphoric acids) cooperative catalysis system.[24] To our delight, after screening of some commercial available chiral phosphoric acids, the (*R*)-VAPOL was turned out to be the most effective catalyst, providing 78% yield and 31% ee (Scheme 6). The preliminary positive result demonstrated that this catalytic asymmetric reaction was feasible *via* a cationic intermediate.

Finally, considering the importance of the constructed imidazolidine scaffold in pharmaceutical chemistry, we randomly selected a number of imidazolidines for the evaluation of anti-proliferative activity in different human cancer cell lines (Table 3, Table S2). In human histiocytic lymphoma cell line (U937), most of the tested compounds exhibited anti-proliferative activity with moderate inhibitory concentration (IC_{50}) values. Compounds **3B** and **3O** also effectively inhibited the proliferation of human cervical carcinoma (Hela), breast cancer (MCF-7), lung cancer (A549) and epidermoid carcinoma (A431) cell lines (Table S4). Besides, compound **3B** also displayed median inhibitory effect in human chronic myeloid leukemia cell line (K562) and human breast cancer cell line (MDA-MB-231). Notably, compound **3B** showed impressive anti-proliferative activity in these cancer cell lines with IC_{50} values. Furthermore, the cytotoxicity of compound **3B** against human normal colonic epithelial cell line (FHC) and human normal hepatic cell line (HL-7702) were also evaluated, interestingly, compound **3B** was found to be less toxic in comparison to Combretastatin A4 (CA-4) and Paclitaxel in human normal cell lines (Table S3, SI). Therefore, compound **3B** might be a promising compound for discovering more applications in medicinal chemistry.

Conclusion

In summary, we have reported a formal [3+2] cycloaddition of donor-acceptor aziridines with 1,3,5-triazinanes catalyzed by $Y(OTf)_3$, providing diversely



Scheme 6. Catalytic asymetric [3+2] cycloaddition reaction.

Table 3. Anti-proliferative activity in human cancer cell lines.

Compound	IC_{50} (μM)[a] U937	Hela	MCF-7	A549	K562	MDA-MB-231
3A	10.8 ± 3.4	> 25	> 25	20.1 ± 2.5	> 25	10.1 ± 3.3
3B	11.6 ± 2.1	9.9 ± 3.3	9.4 ± 2.9	9.4 ± 4.2	21.7 ± 6.6	20.2 ± 7.3
3C	11.8 ± 1.7	> 25	16.2 ± 10.4	13.5 ± 3.4	> 25	9.6 ± 3.0
3I	8.2 ± 3.9	> 25	> 25	> 25	10.6 ± 1.9	8.9 ± 2.9
3K	23.0 ± 14.4	> 25	> 25	> 25	> 25	18.0 ± 2.2
3L	> 25	> 25	9.5 ± 2.7	9.3 ± 5.4	> 25	22.4 ± 7.9
3N	14.2 ± 10.1	> 25	> 25	> 25	> 25	13.2 ± 4.2
3O	22.7 ± 13.1	12.6 ± 9.8	9.0 ± 6.1	17.5 ± 2.7	> 25	> 25
3Y	15.8 ± 16.1	> 25	> 25	4.2 ± 1.4	> 25	9.2 ± 1.2
CA-4[b]	0.8 ± 0.2[c]	2.2 ± 1.7[c]	8.2 ± 1.8[c]	60.9 ± 39.4[c]	7.2 ± 6.5[c]	13.5 ± 4.6[c]
Paclitaxel[b]	1.0 ± 0.4[c]	2.9 ± 0.8[c]	13.8 ± 2.9[c]	3.0 ± 2.8[c]	7.6 ± 6.0[c]	21.5 ± 7.1[c]

[a] IC_{50} values were measured by the MTT assay upon 72 h compounds treatment. Data are expressed as the mean ± SD (standard error) from the dose response curves of three independent experiments. The IC_{50} value is the concentration of a compound that was able to cause 50% cell death with respect to the control culture.
[b] Used as the positive control.
[c] The unit of IC_{50} for CA-4 and Paclitaxel is nM.

substituted imidazolidines in high yields under mild conditions. More importantly, the compound **3B** exhibited promising anti-proliferative activity against a number of human cancer cell lines, which could serve as a hit compound for the anti-tumor research. Further catalytic asymmetric transformation and more studies on biological activity are ongoing in our laboratory.

Experimental Section

General Procedure for the Synthesis of Products 3 A-3Z

Under argon, an oven-dried resealable Schlenk tube equipped with a magnetic stir bar was charged with substrate **1** (0.2 mmol, 1.0 equiv.), substrate **2** (0.08 mmol, 0.4 equiv.), $Y(OTf)_3$ (5.2 mg, 0.01 mmol, 5 mol%), 4 Å MS (100 mg), and DCM (2.0 mL) at 25 °C. Then, the sealed tube was then stirred at 30 °C. Upon completion (monitored by TLC), the reaction mixture was directly purified by a silica gel chromatography (eluent: *n*-hexane/EtOAc = 100/0–5/1, using *n*-hexane (100%) to remove the solvent (DCM) at first) to afford the desired product **3**.

Cytotoxicity Assay

The cytotoxic activity of selected compounds was evaluated by the standard MTT assay *in vitro*. Each type of cells (approximately $0.4–1 \times 10^4$) were suspended in the corresponding culture media and moved to 96-well plate. After incubated at 37 °C for 12 h, a series of compounds dissolved in DMSO at different concentrations were added to each well and continued for 72 h with a final concentration of 0.5% DMSO. After that, a terminal concentration of 0.5 mg/mL MTT was added and incubated at 37 °C for 4 h. The formazan crystals were dissolved in 100 μL DMSO after the media were removed. The absorbance was measured by a microplate reader (Tecan infinite M1000 Pro) at 490 nm.

Acknowledgements

This work was supported by Shenzhen Development and Reform Committee (No. 2019156), Shenzhen Science, Technology and Innovation Commission (JCYJ20180306174248782), Department of Science and Technology of Guangdong Province (No. 2017B030314083) and Shenzhen Bay Laboratory Open Funding (SZBL2019062801009).

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FULL PAPER

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