

NaOH-Promoted Chemoselective Cascade Cyclization of Cyclopropyl Esters with Unsaturated Imines: Access to Bioactive Cyclopenta[c]pyridine Derivatives

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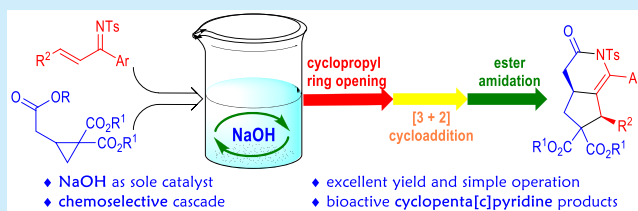
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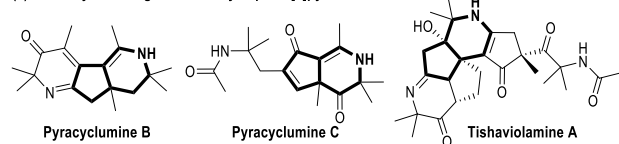
Supporting Information

ABSTRACT: A chemoselective cascade cycloaddition reaction is developed for green and efficient access to cyclopenta[c]pyridine derivatives. Simple and inexpensive NaOH is used as the sole catalyst for this process. The δ -carbon of cyclopropyl ester is activated as a nucleophilic carbon to initiate highly chemoselective cascade reactions. Cyclopenta[c]pyridines bearing various substituents are afforded in excellent yields. Preliminary studies on the bioactivities of the afforded products show promising antibacterial activities for potential applications in plant protections.

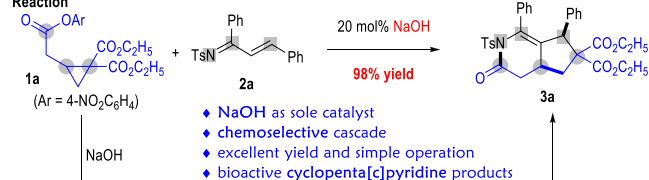


Cyclopenta[c]pyridines are frequently found as core structures in natural products and bioactive synthetic molecules (Figure 1a).¹ For instance, pyracyclumines B and C are key alkali fragments isolated from the roots of *Anacyclus pyrethrum*, a traditional medicine for treatment of epilepsy.^{1c} Tishaviolamine A is one of the important components in the extract of *Viola tianshanica*, a plant that has long been used as a

(a) Naturally Occurring Bioactive Cyclopenta[c]pyridines



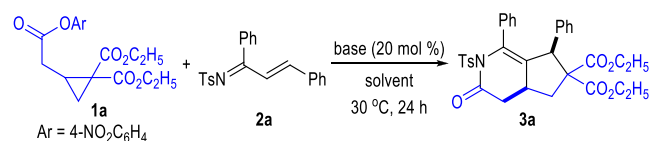
(b) One-Step Access to Cyclopenta[c]pyridines via NaOH-Promoted Chemo-Selective Cascade Reaction



multiple other possible reactions did not occur, our reactions are highly chemo-selective (see SI)

Figure 1. Cyclopenta[c]pyridines and our method for their quick and green access.

Table 1. Condition Optimization^a

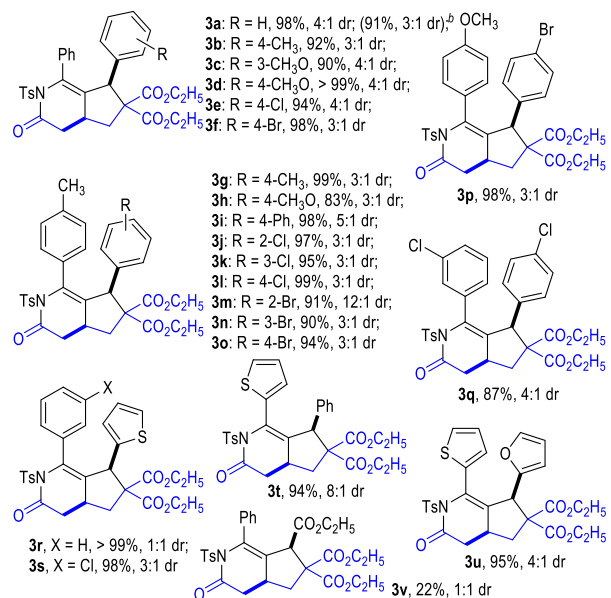
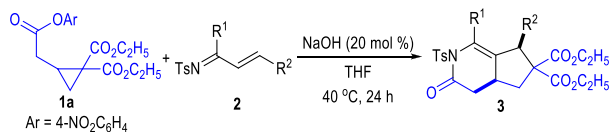


entry	base	solvent	yield (%) ^b	dr ^c
1	NaOH	THF	84	4:1
2	NaOCH ₃	THF	83	3:1
3	KOtBu	THF	52	4:1
4	CS ₂ CO ₃	THF	37	4:1
5	DBU	THF	<5	-
6	NaOH	EtOAc	54	3:1
7	NaOH	H ₂ O	<5	-
8	NaOH	toluene	<5	-
9 ^d	NaOH	THF	98	4:1

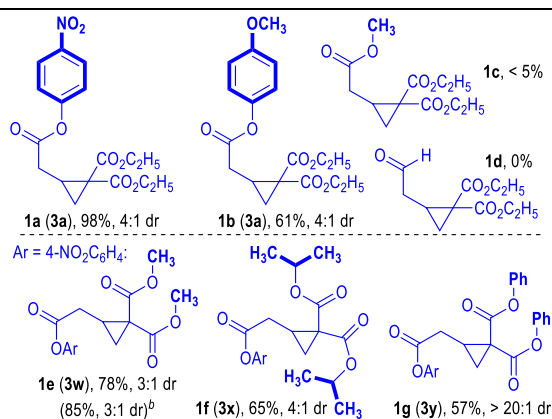
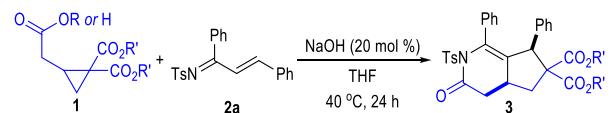
^aReaction conditions: **1a** (0.10 mmol), **2a** (0.05 mmol), base (0.01 mmol), solvent (1.0 mL), 30 °C, 24 h. ^bIsolated yields of **3a**. ^cdr values were determined by ¹H NMR on the crude product mixture. ^d**1a** (0.075 mmol), **2a** (0.05 mmol), NaOH (0.01 mmol), THF (1.0 mL), 40 °C, 24 h.

traditional Uyghur medicine to treat pharyngalgia, headache, fever, and acute pyogenic infection.^{1b} These functional molecules contain substituted cyclopenta[c]pyridine cores in

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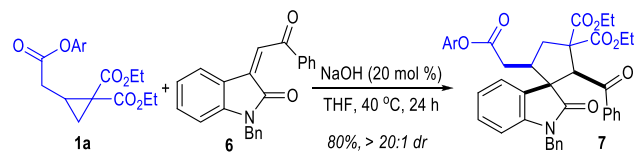
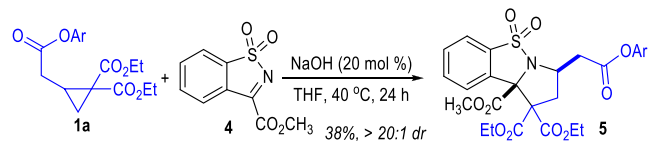
Scheme 1. Scope of α,β -Unsaturated Imines 2^{a,b}

^aReactions were carried out under condition as in Table 1, entry 9. Yield was isolated yield. dr value was determined by ¹H NMR on the crude product mixture. ^bData in parentheses indicate the results from the reaction carried out at 1.0 mmol scale based on 2a.

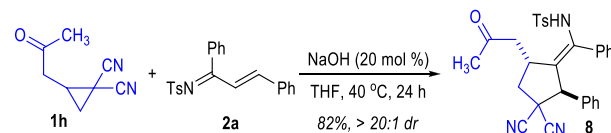
Scheme 2. Scope of Ester Substrates 1^a

^aReactions were carried out under conditions as in Table 1, entry 9. Yields were isolated yields. dr values were determined by ¹H NMR on the crude product mixture. ^bData in parentheses indicate the results from the reaction carried out at 1.0 mmol scale based on 2a.

either racemic or enantiomerically pure forms. Therefore, the rapid construction and bioactivity evaluation of substituted cyclopenta[c]pyridine derivatives are of considerable interests. However, despite of their importance, the preparation of this class of cyclopenta[c]pyridine derivatives remains challenging,

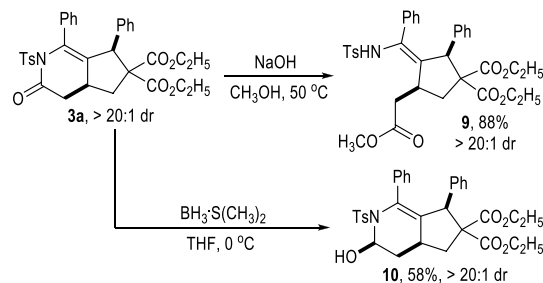
Scheme 3. Reactions of 1a with Imine 4 and Enone 6^a

^aReactions were carried out under conditions as in Table 1, entry 9. Yields were isolated yields. dr values were determined by ¹H NMR on the crude product mixture.

Scheme 4. Reaction of 2-Cyclopropyl Ketone 1h with 2a^a

^aReactions were carried out under conditions as in Table 1, entry 9. Yields were isolated yields. dr values were determined by ¹H NMR on the crude product mixture.

Scheme 5. Synthetic Transformation of 3a



and long synthetic steps have been required.² Cascade cyclization reactions promoted by simple and inexpensive small molecules are promising strategies for the synthesis of these complex structures.³

Here, we report a one-step method for highly efficient access to bicyclic cyclopenta[c]pyridine derivatives bearing multiple substituents (Figure 1b). Our reactions use NaOH as the only catalyst, and most of the reactions give desired products with over 90% yields. The key reaction processes include a NaOH-promoted activation of a 2-cyclopropyl ester (e.g., 1a) to form intermediate I bearing multiple reactive carbons. Although multiple different reactions from intermediate I are possible (see SI), we are delighted to see that with α,β -unsaturated imines as the other substrate the reaction cascades are highly chemoselective. Briefly, formal [3 + 2] reaction initiated from addition of the δ -carbon of intermediate I to unsaturated imine 2a forms intermediate II.⁴ Related [3 + 2] process was observed before by Jørgensen and co-workers in which 2-cyclopropyl ketones were activated by amine/thiourea catalysts to react with nitroalkenes.⁵ Proton transfer of II gives intermediate III, which subsequently undergoes lactam formation to afford cyclopenta[c]pyridine product 3a with excellent yield. Several of the cyclopenta[c]pyridine products from our approach exhibit

Table 2. Inhibition Rate of Compounds 3 against Bacteria^a

Compound	<i>X. oryzae</i> pv. <i>oryzae</i> (%) ^a		<i>X. axonopodis</i> pv. <i>citri</i> (%) ^a		<i>P. syringae</i> pv. <i>actinidiae</i> (%) ^a	
	100 μ g/mL	50 μ g/mL	100 μ g/mL	50 μ g/mL	100 μ g/mL	50 μ g/mL
3a	29.6 \pm 4.7	18.9 \pm 1.2	37.8 \pm 2.1	16.1 \pm 1.8	22.6 \pm 3.3	0
3c	13.2 \pm 3.5	0	38.8 \pm 2.7	11.4 \pm 1.9	54.1 \pm 2.0	22.6 \pm 0.7
3e	63.1 \pm 2.4	23.9 \pm 6.2	23.1 \pm 1.1	0	24.3 \pm 3.5	0
3f	22.6 \pm 2.2	5.2 \pm 3.0	14.9 \pm 4.0	0	48.9 \pm 4.9	12.5 \pm 2.0
3g	25.7 \pm 3.9	16.6 \pm 1.9	6.9 \pm 2.7	0	45.4 \pm 3.7	12.4 \pm 2.5
3m	9.7 \pm 1.9	0	33.5 \pm 2.5	8.8 \pm 2.9	33.4 \pm 4.3	9.4 \pm 1.3
3q	4.0 \pm 2.4	0	19.6 \pm 4.1	8.8 \pm 0.5	50.2 \pm 3.6	17.2 \pm 2.2
3r	42.2 \pm 1.3	15.2 \pm 2.3	30.6 \pm 3.8	13.9 \pm 1.5	28.7 \pm 3.2	5.1 \pm 3.0
3s	21.3 \pm 1.9	7.7 \pm 1.4	17.8 \pm 2.8	0	31.2 \pm 5.9	9.9 \pm 3.0
Bismertiazol ^b	48.1 \pm 0.5	11.2 \pm 1.7	- ^c	- ^c	- ^c	- ^c
Thiodiazole-Cu ^b	- ^c	- ^c	23.7 \pm 4.5	13.5 \pm 2.8	27.2 \pm 3.5	8.7 \pm 1.0
DMSO ^d	0	0	0	0	0	0

^aAll data were average data of three replicates. ^bCommercial bactericide, used as the positive control. ^cNot tested. ^dDMSO was used as the negative control.

encouraging antibacterial activities against *X. oryzae* pv. *oryzae*,⁶ *X. axonopodis* pv. *citri*,⁷ and *P. syringae* pv. *actinidiae*.⁸

We chose 2-cyclopropyl ester **1a** and α,β -unsaturated imine **2a** as the model substrates to search for suitable reaction conditions (Table 1). We initially intended to use *N*-heterocyclic carbene (NHC) organic catalysts to activate the ester substrates⁹ for cascade reactions. We found that NHC did not participate in the reaction, and the reaction proceeded smoothly with the presence of a simple base alone. For example, a variety of common inorganic bases could efficiently promote the cascade process and give the desired cyclopenta[c]pyridine products in moderate to good yields with moderate diastereoselectivities (Table 1, entries 1–4). Organic bases tested for this transformation were generally ineffective (e.g., entry 5). Organic solvents with high polarities could serve as suitable medium for this NaOH-catalyzed process (e.g., entry 6), while the reactions could not proceed well in either aqueous system or nonpolar organic solvents (entries 7–8). The product yield could be dramatically improved by slightly increasing the reaction temperature to 40 °C. Under this temperature, the loading of **1a** could be decreased and the desired product **3a** could be obtained in almost quantitative yield without erosion of the diastereoselectivity (entry 9). Further decreasing the amount of either NaOH or ester **1a** led to some drops on the product yields (see SI for details).

Having established optimized reaction conditions (Table 1, entry 9), we next examined the scope of α,β -unsaturated imines (**2**) bearing various substituents (Scheme 1). Both substituents R¹ and R² of the imine substrate **2** could be phenyl rings with different substitution patterns. The fused cyclopenta[c]pyridine products **3** were afforded in generally excellent yields with moderate to excellent diastereoselectivities (**3a** to **3q**). Heteroaromatic groups were also well tolerated on both sides of the imine substrates **2**, with the corresponding products afforded in excellent yields (**3r** to **3u**). It is worth noting that the aromatic R² group could be replaced with an ester substituent, although the corresponding product **3v** was only afforded in a low yield with a poor diastereoselectivity under current reaction conditions.

We then examined the scope of the 2-cyclopropyl ester substrates (**1**) (Scheme 2). The electron deficient 4-nitrophenol group on **1a** could be switched to an electron-rich aromatic group (**1b**), although the product yield decreased to 61%. Replacing the R group on ester substrate **1** with a simple methyl

group (**1c**) resulted in only trace formation of the final product. It is worth noting that the cyclopropyl aldehyde **1d** cannot be used as a reaction partner for this NaOH-promoted cycloaddition reaction with the imine **2a**. Both substrates decomposed without any cycloaddition products formed. Both aliphatic and aromatic substituents were well tolerated as the R' groups on the ester substrates **1**, with the corresponding products afforded in moderate yields (**1e** to **1g**). Notably, excellent diastereoselectivity (>20:1) could be observed when using ester substrate **1g** bearing phenyls as the R' groups.

Electron deficient cyclic imine **4** and enone **6** can also be used as suitable electrophiles in the NaOH-promoted reactions with the 2-cyclopropyl ester **1a** (Scheme 3). However, in these cases, pyrrole **5** and cyclopentane **7** from formal [3 + 2] cycloaddition reactions were afforded as the final products in moderate to good yields.

2-Cyclopropyl ketone substrate **1h** could also serve as an effective substrate in the cycloaddition reaction with α,β -unsaturated imine **2a** (Scheme 4). The [3 + 2] cyclization product **8** could be isolated in 82% yield as a single diastereomer under the current optimized reaction conditions.

The multifunctionalized cyclopenta[c]pyridine product (**3a**) is amenable for further transformations (Scheme 5). For example, addition of methanol to the lactam moiety of **3a** under a basic condition could produce ester **9** in 88% yield. The lactam group in **3a** could be selectively reduced by BH₃ (without affecting the ester groups) to afford *N,O*-hemiaminal adduct **10** with 58% yield.

The cyclopenta[c]pyridine products (**3**) obtained from our reactions were evaluated for their bioactivities with potential uses in plant protections (Table 2). *X. oryzae* pv. *oryzae* is a harmful bacterium that causes leaf blast in rice and seriously damages rice production.⁶ Bismertiazol is widely used an agrochemical in controlling the rice leaf blast via inhibition of *X. oryzae* pv. *oryzae*.¹⁰ To our delight, several of our cyclopenta[c]pyridine products showed excellent inhibition rate against *X. oryzae* pv. *oryzae*. For example, products **3a** and **3r** showed similar antibacterial activities as the bismertiazol, and product **3e** provided a better effect in the inhibition of *X. oryzae* pv. *oryzae*.

X. axonopodis pv. *citri*⁷ and *P. syringae* pv. *actinidiae*⁸ are widespread bacteria that cause decay in various kinds of fruits. Our cyclopenta[c]pyridine products showed encouraging antibacterial activities against both *X. axonopodis* pv. *citri* and

P. syringae pv *actinidiae* (Table 2). For example, compounds **3a**, **3c**, **3m**, and **3r** exhibited superior antibacterial activities against *X. axonopodis* pv *citri*, compared to the commercially used thiodiazole-copper.¹¹ Our products **3c**, **3f**, **3g**, **3m**, **3q**, and **3s** all showed better results than thiodiazole-copper in the inhibition of *P. syringae* pv *actinidiae*.

In summary, we have developed a chemoselective cascade cycloaddition reaction promoted by simple and inexpensive NaOH. Cyclopenta[*c*]pyridine derivatives are afforded as the final products in up to quantitative yields. The δ -carbon of the in situ generated α,β -unsaturated carboxylic ester is activated as the nucleophile to react with α,β -unsaturated imines in highly chemoselective manners. The multifunctional cyclopenta[*c*]pyridine products obtained from our method exhibit encouraging antibacterial activities with potential applications in the development of new green pesticides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02088.

Experimental procedures and spectral data for all new compounds (PDF)

Accession Codes

CCDC 1911186–1911188 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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