α,β-Epoxy Esters in Multiple C–O/C–N Bond-Breaking/Formation with 2-Aminopyridines; Synthesis of Biologically Relevant (*Z*)-2-Methylene-imidazo[1,2-*a*]pyridin-3-ones

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Abstract: A new reaction of aryl 2,3-epoxy esters with 2-aminopyridines has been developed that involves multiple C–O/C–N bond-breaking/formation reactions in one chemical step. Compared with known reactions of α,β-epoxy esters, which take place through oxiranyl C–O or C–C bond cleavage, the present reaction exploits the tendency of the oxirane ring to act as a bi-electrophile. Thus, the reaction follows a unique cascade pathway of epoxide C–O bond cleavage, formation of an α-enamine ester, and intramolecular transamidation with chemo-, regio- and diastereoselectivity. The reaction allows access to biologically relevant (*Z*)-2-methyleneimidazo[1,2-*a*]pyridin-3-ones. Water and ethanol are the only by-products. The reaction is flexible, and aryl 2,3-epoxy esters as well as 2-aminopyridines possessing either electron-donating or -withdrawing functionalities, can be used. In contrast to various Brønsted and Lewis acid catalysts, polyphosphoric acid plays a multifunctional role in this intermolecular cascade reaction.

Key words: domino reactions, amino alcohols, epoxides, heterocycles, fused-ring systems

Oxiranes are important building blocks in organic synthesis because of their easy accessibility, their propensity for opening of the strained ring, and because of their use in the preparation of versatile organic motifs. Most ring-opening reactions of oxiranes involve C–O bond cleavage, although C–C bond cleavage is also known. The cascade reaction[1] involving epoxide C–O bond cleavage in the synthesis of polycyclic natural products is well known.[2] In the context of exploring the use of the oxirane class of compounds for various reactions, the 2,3-epoxy esters/ketones have attracted significant attention because of their use as multifunctional substrates[3] and because of their ease of preparation.[4] A remarkable example is the reaction of glycidic ester with 2-aminothiophenol, which provides 1,4-benzothiazepinone, a synthetic precursor of calcium channel blocker drug diltiazem.[5] Aryl oxiranyl-carboxylates/ketones undergo interesting C–C bond heterolysis of the oxirane ring, generating carbonyl ylides[6] that undergo dipolar cycloaddition with various π-systems. For example, the [3+2] cycloaddition of aryl oxiranyl-dicarboxylate/diketone/cyanoketone with indole,[7] alkyne,[8] or [60]fullerene[9] furnishes furo[3,4-*b*]indole, 2,5-dihydrofuran, or C60-fused tetrahydrofuran, respectively. Other significant applications of 2,3-epoxy esters/ketones include [3+2] heterocyclization for the construction of quaternary imidazole skeletons,[10] palladium(0)-catalyzed transformation into β-diketone,[11] and SmI_2-mediated deoxygenation to produce the α,β-unsaturated ester.[12] Herein, we report a new reaction of aryl α,β-epoxy esters with 2-aminopyridines that exploits the tendency of the oxirane ring to act as a bi-electrophile. The reaction involves a cascade pathway of epoxide C–O bond cleavage, formation of α-enamine ester, and intramolecular transamidation with chemo-, regio- and diastereoselectivity. The approach allows access to biologically relevant (*Z*)-2-methyleneimidazo[1,2-*a*]pyridin-3-one.

(*Z*)-2-Methyleneimidazo[1,2-*a*]pyridin-3-ones represent a scaffold-hopped[13] skeleton of aurones, which are a flavonoid class of natural products that exhibit various bioactivities[14] including antitumor, antimicrobial, anti-inflammatory, antidiabetic and anti-Alzheimer's activities, and modulation of drug efflux.[15] In addition, (*Z*)-2-methylene- and 3-keto-substituted imidazo[1,2-*a*]heterocycles are important chromophore-substrates for bioluminescence in marine organisms.[16] Consequently, the development of efficient syntheses of these molecules is considered valuable.

To develop reactions that can be used for the preparation of bioactive natural flavonoid compounds, we considered a new reaction of easily accessible α,β-epoxy esters and 2-aminopyridine. Initial experiments with a model reaction of ethyl 3-(4′-methoxyphenyl)oxirane-2-carboxylate and 2-aminopyridine were performed by using several Lewis acid catalysts and conditions known for oxirane C–O opening with amines.[17] All of these conditions led to the formation of inseparable mixtures of products, which indicated multiple competing reactions.[18] Catalysis by *p*-TsOH produced a less complex mixture of products from which one major product was isolated (Table 1, entry 1). Spectroscopic studies revealed that the product was (*Z*)-2-(4′-methoxybenzylidene)imidazo[1,2-*a*]-pyridin-3-one. To check for consistency, the reaction of a different epoxy ester 3-(4′-chlorophenyl)oxirane-2-carboxylate with 2-aminopyridine was performed to give **3a**; the reaction provided the same class of scaffold. The structure was confirmed by X-ray diffraction study (Figure 1 and the Supporting Information).[19]

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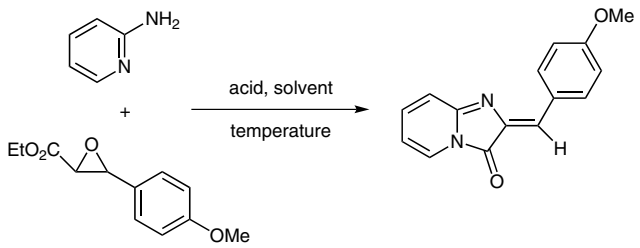
Table 1 Optimization of the Reaction[a]



Entry	Acid (equiv)	Solvent	Temp (°C)	Time (h)[b]	Yield (%)[c]
1	*p*-TsOH (0.2)	toluene	110	18	12
2	*p*-TsOH (0.2)	DMF	110	18	9
3	*p*-TsOH (0.2)	DMSO	110	18	16
4	*p*-TsOH (1)	DMSO	110	18	23
5	TfOH (1)	DMSO	110	3	20
6	MsOH (1)	DMSO	110	14	25
7	$HClO_4$ (1)	DMA	110	14	NR[d]
8[e]	MsOH	–	110	1	22
9[e]	AcOH	–	110	1	NR[d]
10[e]	MsOH–AcOH (1:1)	–	110	1	43
11[e]	MsOH–AcOH (1:2)	–	110	1	35
12[e]	Eaton's Reagent	–	110	1	42
13[e]	$ZrCl_4$ (0.05) + Eaton's Reagent	–	110	1	46
14[f]	PPA	–	110	1	62
15[f]	$ZrCl_4$ (0.05) + PPA	–	110	1.5	45
16	PPA (1)	MeCN	78	14	10

[a] Substrates: 0.5 mmol each.
[b] Optimum time.
[c] Isolated yield.
[d] Poor conversion, and no desired product formed.
[e] 1 mL acid was used.
[f] 1.5 g PPA was used.

The results of the optimization study of the reaction are summarized in Table 1. Various Brønsted acids (entries 1–7) with a range of concentrations and solvents did not improve the yield of the product beyond 25%. The use of $HClO_4$ (entry 7) or AcOH (entry 9) resulted in the generation of more side reactions without formation of the desired product. The use of MsOH–AcOH, Eaton's reagent, $ZrCl_4$–Eaton's reagent, poly(phosphoric acid) (PPA), or $ZrCl_4$–PPA under neat conditions, enhanced the product yield substantially and PPA was found to be most effective (entry 14). Conducting the reaction with 1 equiv PPA in MeCN resulted in reduced yield.

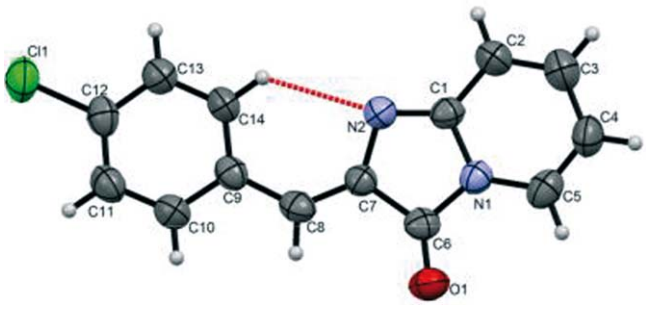


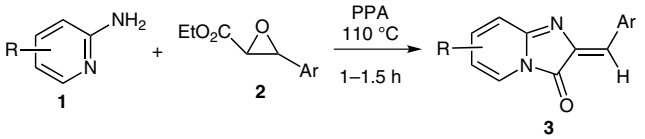
Figure 1 ORTEP structure of **3a**[19]

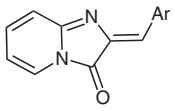
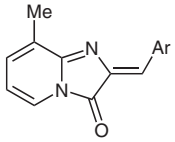
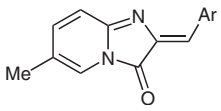
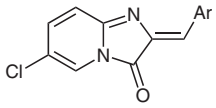
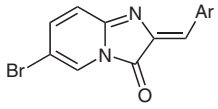
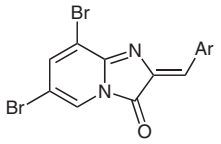
We next examined on the generality of the developed reaction with regard to both cascade partners. To our delight, various ethyl 3-aryloxirane-2-carboxylates and 2-aminopyridines underwent the reaction (Table 2). Both electron-withdrawing and electron-donating functionalities on the aryl of the epoxy ester as well as on the 2-aminopyridines were compatible, although 3-(4′-nitrophenyl)oxirane-2-carboxylate provided less yield of product **3j** because of a lack of chemoselectivity. Unfortunately, conducting the reaction with the alkyl 2,3-epoxy ester, ethyl 3-methyloxirane-2-carboxylate, gave a complex product mixture that could not be separated. The tolerance of the reaction towards functionalities such as chloro, bromo, nitro, and methoxy groups provides the opportunity for further chemical manipulations of the products.

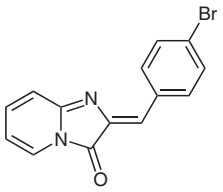
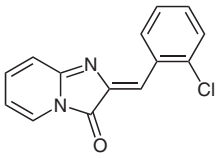
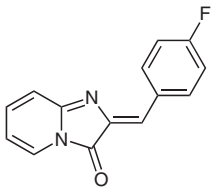
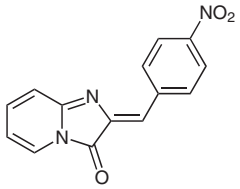
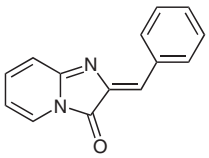
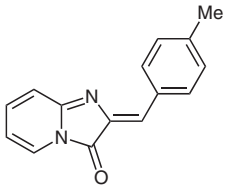
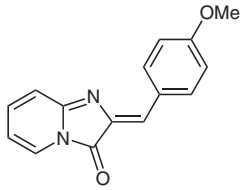
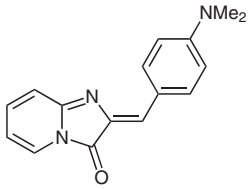
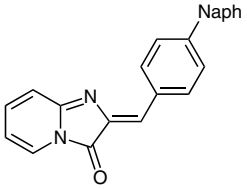
We were then curious to probe the transformations involved in this reaction. Under the optimized conditions, a few products other than imidazo[1,2-*a*]pyridinone **3** were found to form in trace amounts. When the reaction of ethyl 3-(4′-chlorophenyl)oxirane-2-carboxylate with 2-aminopyridine was carried out at lower temperature (60 °C), an additional product was obtained, which was found to be enamine ester (**IV**; Scheme 1). Upon treatment of this isolated intermediate with PPA, imidazopyridinone **3** was obtained in similar yield. In a different study, authentic β-amino alcohol (**I**) was treated with PPA to also produce imidazopyridinone **3** in similar yield. These results imply that the reaction follows a cascade pathway involving β-amino alcohol (**I**) and enamine ester (**IV**; path A, Scheme 1). The 1,2-migration of the pyridinylamine moiety in conversion of β-amino alcohol (**I**) into enamine (**IV**) indicates the formation of a N-bridging ring, i.e., aziridine (**II**). In next step, rearrangement through C–N opening of aziridine (**II**) and elimination, assisted by PPA as nucleophilic catalyst[20] and dual activator, for the formation of enamine (**IV**) is quite possible (for diastereoselectivity in the pathway, see Scheme 2).

In normal acid-catalyzed epoxide C–O bond cleavage with amine, the product β-amino alcohol does not undergo further aziridination.[17] Interestingly, in the PPA-promoted reaction, β-amino alcohol (**I**) underwent aziridination (path **A**) chemoselectively over *trans*-amidation of carboxyethyl with the ring NH of pyridin-2(1*H*)-imine (path **B**). This signifies that aziridination of β-amino alcohol (**I**) occurred through dual activation of OH and NH by PPA, which is not observed in usual methods, and, ultimately, the oxirane of the epoxy ester served as a bi-electrophile. The results of the optimization study together with the physical properties of the acids, and the ineffec-

Table 2 Scope of the Reaction



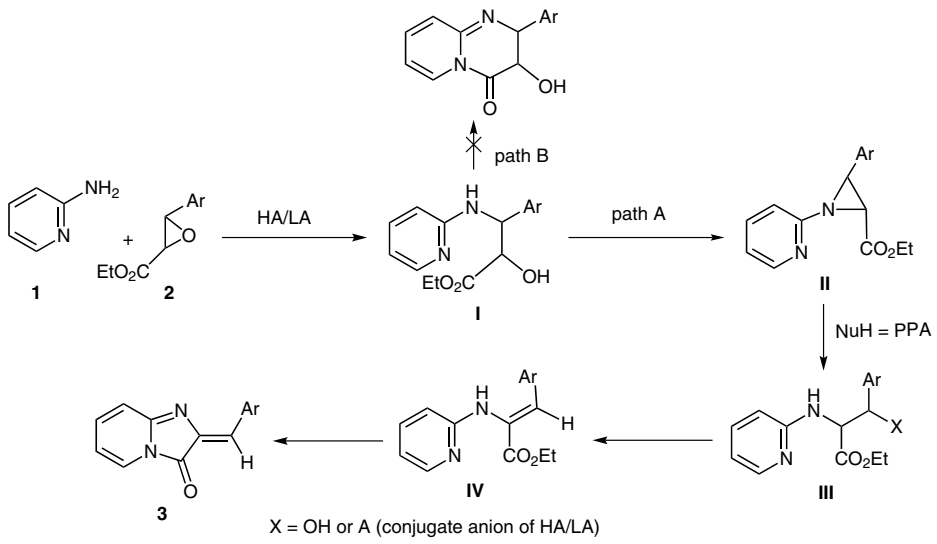
Variation in azine for reaction with β-(4-chlorophenyl)epoxy ester		
		
3a, 83%	**3b**, 77%	**3c**, 65%
		
3d, 82%	**3e**, 70%	**3f**, 38%

Variation in epoxy ester for reaction with 2-aminopyridine		
		
3g, 73%	**3h**, 76%	**3i**, 66%
		
3j, 40%	**3k**, 53%	**3l**, 58%
		
3m, 62%	**3n**, 60%	**3o**, 68%

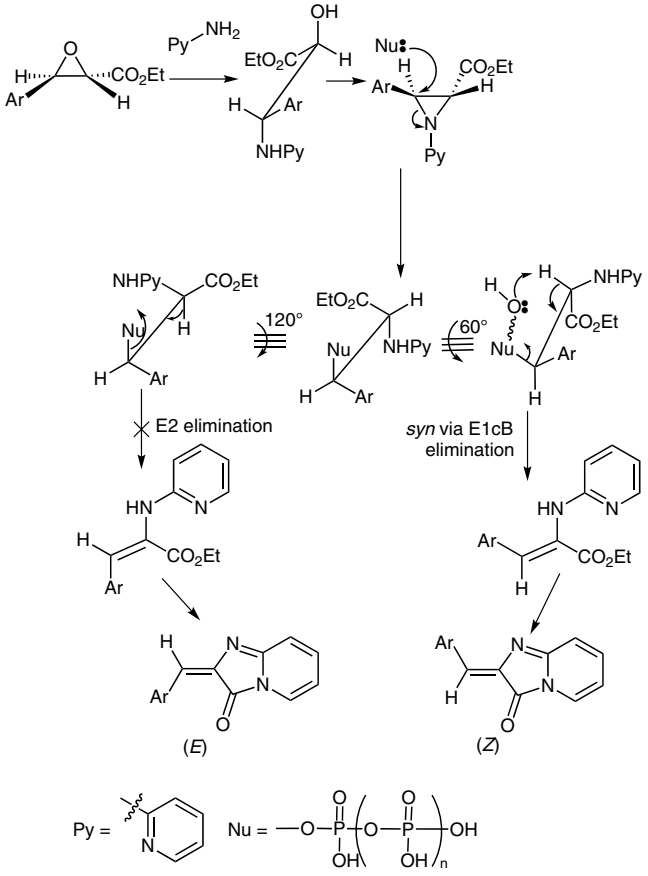
tiveness of acids possessing non-nucleophilic counter-anion ($HClO_4$) or low acidity (AcOH) signify that PPA plays a crucial role in the present cascade reaction. The multifunctional behavior, Brønsted acidity, nucleophilic catalysis, dual activation, and polar protic solvent characteristics of PPA are critical features of this reagent.

Interestingly, the reaction involves several C–O/C–N bond-breaking/making events in one chemical step and proceeds with chemo-, regio-, and diastereoselectivity. By-products were water and ethanol only. Considering that five transformations take place, the yields of the products are very good to excellent.

In conclusion, a new reaction of aryl α,β-epoxy esters with 2-aminopyridine derivatives mediated by poly(phosphoric acid) as a multifunctional activator, leads to biologically relevant (*Z*)-2-methyleneimidazo[1,2-*a*]pyridin-3-one derivatives.[21] In contrast to known reactions of α,β-epoxy esters, which take place through oxiranyl C–O or C–C bond cleavage, the present reaction involves the oxirane ring acting as a bi-electrophile in a cascade pathway of epoxide C–O bond-cleavage, formation of α-enamine ester, and intramolecular transamidation. The process takes place with chemo-, regio- and diastereoselectivity. This work is expected to prompt further strategic use of α,β-ep-



Scheme 1 Cascade pathway of the reaction



Scheme 2 Diastereoselectivity in the cascade reaction

oxy ester derivatives in the discovery of new organic compounds and reactions. The convenient preparation of imidazopyridinone derivatives by the developed method will facilitate the use of this important class of compound in organic synthesis and medicinal chemistry research.

Acknowledgment

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Supporting Information, with experimental details, characterization data (^{1}H and ^{13}C NMR spectra, xIR, HRMS, and melting points) for products and intermediates, and X-ray crystallographic data for product **3a** (CCDC 959103), for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/ 10.1055/s-00000083.

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(18) This selectivity problem also arises because of constraints commonly associated with epoxide ring opening by amines, such as the formation of regioisomeric and undesired products, incompatibility with less nucleophilic amines, and the required use of an excess of amine.
(19) CCDC 959103 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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(21) **Synthesis of (Z)-2-(4′-Chlorobenzylidene)-2*H*-imidazo-[1,2-*a*]pyridin-3-one; Typical Procedure (Table 2):** To a mixture of 2-aminopyridine (47 mg, 0.5 mmol) and ethyl 3-(4′-chlorophenyl)oxirane-2-carboxylate (113 mg, 0.5 mmol) in a round-bottom flask, was added PPA (1.5 g), and the mixture was magnetically stirred at 110 °C under open air. Upon completion of the reaction as indicated by TLC (1–1.5 h), the resultant mixture was poured into crushed ice (2 g) and neutralized with 5% aq NaOH. The mixture was extracted with CH_2Cl_2 (2 × 25 mL) and the organic layer was washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Column chromatographic purification of the crude mass on silica gel (EtOAc–hexane, 1:6) gave (*Z*)-2-(4-chlorobenzylidene)-2*H*-imidazo[1,2-*a*]pyridin-3-one (**3a**; 106 mg, 83%) as a red solid. Mp 182–184 °C; R_f = 0.33 (EtOAc–hexane, 10%). Compounds **3a**–**o** were prepared by following a similar procedure.

Data for 3a: See Figure 2 for numbering. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 8.3 Hz, 2 H, H_j), 7.62 (d, *J* = 6.8 Hz, 1 H, H_a), 7.40 (d, *J* = 8.3 Hz, 2 H, H_k), 7.23 (s, 1 H, H_h), 7.17 (dd, *J* = 6.6, 9.2 Hz, 1 H, H_c), 6.93 (d, *J* = 9.4 Hz, 1 H, H_d), 6.25 (dd, *J* = 6.6, 6.6 Hz, 1 H, H_b); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4 (C_g), 156.7 (C_e), 138.6 (C_f), 137.9 (C_c), 136.4 (C_i), 133.7 (C_j), 133.2 (C_l), 129.1 (C_k), 127.2 (C_a), 126.0 (C_d), 119.3 (C_b), 109.3 (C_h); IR (neat): 2879, 1707, 1650, 1601 cm^{-1}; HRMS (ESI): *m*/*z* [M(^{35}Cl) + H]$^+$ calcd. for $C_{14}H_9ClN_2O$: 257.0481; found: 257.0477.

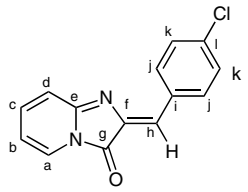

Figure 2

