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Reversal of Nucleophilicity of Enamides in Water: Control of Cyclization Pathways by Reaction Media for the Orthogonal Synthesis of Dihydropyridinone and Pyrrolidinone *Clausena* Alkaloids

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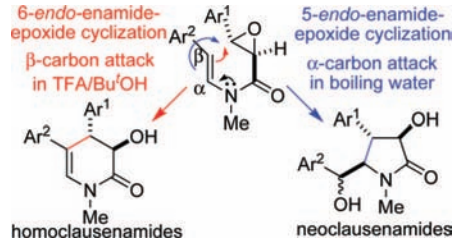
ABSTRACT



A highly efficient, metal-free, and divergent method for the synthesis of 3,4-dihydropyridin-2-one and pyrrolidin-2-one *Clausena* alkaloids and their analogs is reported. While the oxirane-containing enamides underwent the TFA-mediated 6-*endo*-enamide-epoxide cyclization reaction in Bu^{t}OH to produce homoclausenamides, an unprecedented nucleophilic reaction occurred at the α-carbon of enamides in water to yield 5-*endo*-enamide-epoxide cyclization products in excellent yields. The reversal of nucleophilicity of enamides in intramolecular cyclization is discussed in terms of steric and electronic effects of the oxirane-containing enamides.

Homoclausenamide[1] and neoclausenamide[2] are 3,4-dihydropyridin-2-one and pyrrolidin-2-one alkaloids, respectively, isolated from the leaf extract of Rutaceae *Clausena lansium* (Lour.) Skeels, a fruit tree widely distributed in southern China. In folk medicine, the fruits and leaves of the tree are used for the treatment of influenza, gastrointestinal disorder, viral hepatitis, and dermatological diseases.[3] Despite the interesting structures and potential pharmacological activities, surprisingly, synthesis of these *Clausena* alkaloids and their analogs has remained largely unexplored.[4]

Although enamide compounds have been known for a long time, the enaminic reactivity of enamides has not attracted attention until very recently.[5–13] Kobayashi demonstrated in

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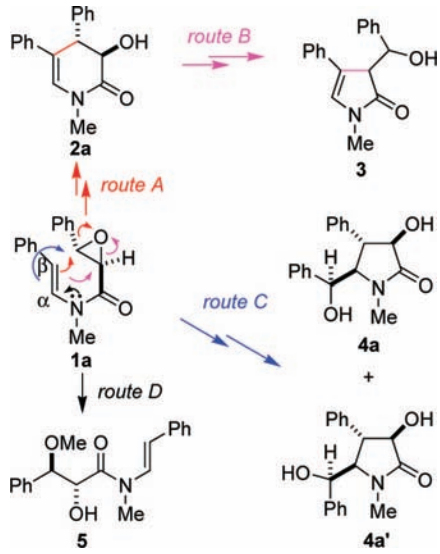
recent years that enamides can act as nucleophiles to react enantioselectively with imines,[5,9] aldehydes and ketones,[6,9] azodicarboxylates,[7,9] and Michael receptors[8] in the presence of a chiral catalyst. Herein, we report a Brønsted acid mediated stereospecific intramolecular enaminic reaction (β-carbon attack) of enamide with the epoxide ring (6-*endo*-enamide-epoxide cyclization) to synthesize homoclausenamide and its analogs (route A, Scheme 1). Astoundingly,

Scheme 1. Reaction Pathways of Oxirane-Containing Enamide **1a**



enamide **1** was found to reverse its nucleophilicity (α-carbon attack versus β-carbon attack) in pure water, undergoing a highly efficient 5-*endo*-enamide-epoxide cyclization reaction to produce a mixture of neoclausenamide **4** and its 6-epimer **4′** (route C, Scheme 1).

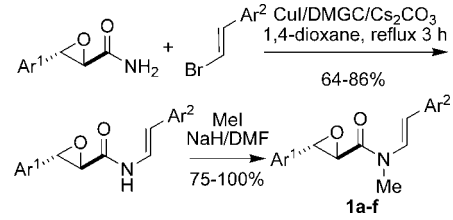
Table 1. Reactions of **1a** under Various Conditions[a]

entry	conditions	**2a** (%)	**4a** + **4a′** (%)	**5** (%)
1	MeOH, 48 h			
2	CH_3CO_2H (2 equiv), MeOH, 24 h			23
3	TFA (2 equiv), MeOH, 5 h			66
4	Bu^{t}OH, 24 h			
5	TFA (2 equiv), Bu^{t}OH, 24 h	36		
6	TFA (2 equiv), Bu^{t}OH, MS (4Å), 12 h	72		
7	TFA (2 equiv), Bu^{t}OH/H_2O (9/1), 24 h	47	49	
8	TFA (2 equiv), Bu^{t}OH/H_2O (1/1), 5 h	30	67	
9	TFA (2 equiv), H_2O, 5 h	31	68	
10	H_2O, 5 h		91	

[a] Reaction was performed by refluxing **1a** in the media and the yield was isolated yield.

As indicated in Table 1, the oxirane-containing enamide **1a**, which was obtained from the cross-coupling reaction of oxiranecarboxamide with (*E*)-(2-bromovinyl)benzene followed by *N*-methylation[14] (Scheme 2 and Supporting Information), was stable and remained intact after heating 2 days in methanol (entry 1). In the presence of acetic acid or trifluoroacetic acid (TFA) (2 equiv), **1a** underwent epoxide ring-opening reaction with methanol (route D, Scheme 1) to form product **5** (entries 2 and 3). To eliminate the epoxide ring-opening reaction by methanol, sterically bulky and less nucleophilic *tert*-butanol was used as the solvent. While **1a** did not react in refluxing *tert*-butanol (entry 4), TFA did promote the 6-*endo*-enamide-epoxide cyclization reaction (route A, Scheme 1) of **1a** to produce the desired homoclausenamide **2a** in 36% yield (entry 5). The use of molecular sieve (4 Å) improved the chemical yield of the six-membered lactam alkaloid **2a** to 72% (entry 6). Surprisingly, addition of water to the reaction mixture led to the formation of neoclausenamide **4a**and its 6-epimer **4a′** (route C, Scheme 1) in addition to **2a**. The five-membered lactam alkaloids became the major products with the increase of water in the reaction media (entries 7−9). Remarkably, heating of **1a** in pure water[15,16] without using TFA led to the exclusive formation of the pyrrolidin-2-one alkaloids **4a** and **4a′** in excellent yield (entry 10).

Scheme 2. Preparation of Oxirane-Containing Enamides **1a**−**f**



The structures of all products were established on the basis of spectroscopic data and microanalysis (see Supporting Information). To assign the stereochemistry of products beyond doubt, the structures of homoclausenamide **2a**, neoclausenamide **4a**, and its 6-epimer **4a′** were determined unambiguously by X-ray crystallography[17] (Figures 1 and 2). It is noteworthy that the vicinal substituents on both the six- and the five-membered rings are all *trans*-configured,

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(15) For recent references for organic reactions using water as the media, see:(a) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275. (b) Jung, Y.; Marcus, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 5492, and references therein.
(16) An excellent example of water-promoted epoxide-opening cascade reactions was reported very recently. Vilotijevic, I.; Jamison, T. F. *Science* **2007**, *317*, 1189.

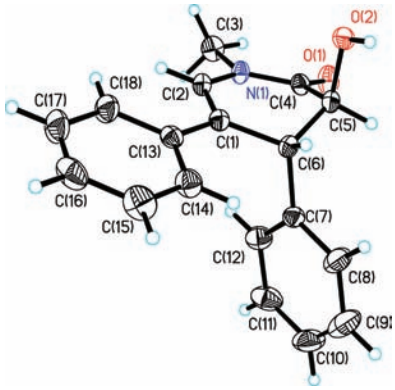


Figure 1. X-ray structure of **2a**.

indicating stereospecific intramolecular epoxide ring-opening reactions by the β- and the α-carbon of the enamide **1a**,

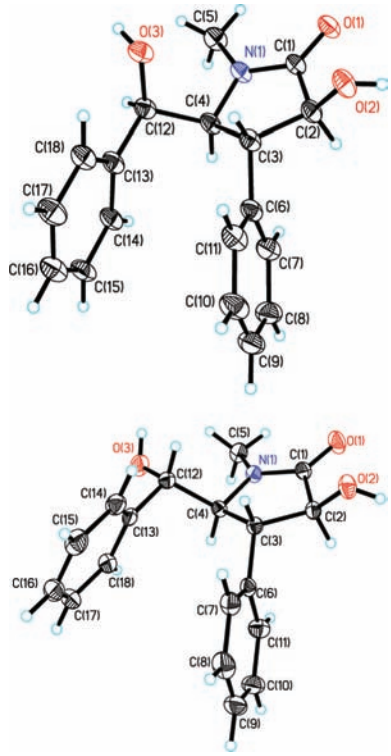
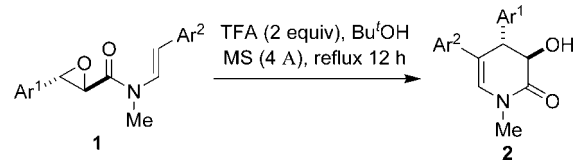


Figure 2. X-ray structure of **4a**′ (bottom) and **4a**′ (bottom).

respectively (Scheme 1). It should also be noted that, under all reaction conditions investigated, no 5-exoenamide-epoxide cyclization reaction product (route B, Scheme 1) was observed.

Both the TFA-mediated 6-*endo*-enamide-epoxide cyclization reaction and the 5-*endo*-enamide-epoxide cyclization reaction appeared general and thus allowed orthogonal synthesis of homoclausenamide and neoclausenamide analogs very efficiently. As tabulated in Table 2, enamides **1b**−**f**

Table 2. Synthesis of Homoclausenamide and Its Analogs from TFA-Mediated 6-*endo*-Enamide-Epoxide Cyclization of **1**



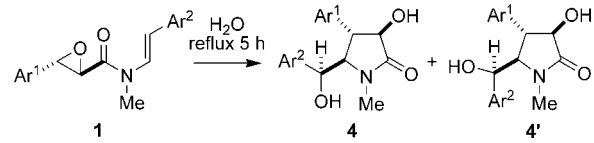
1 **2**

entry	**1**	Ar^1	Ar^2	**2**	yield (%)[a]
1	**1a**	C_6H_5	C_6H_5	**2a**	72
2	**1b**	4-Cl-C_6H_4	C_6H_5	**2b**	67
3	**1c**	4-Me-C_6H_4	C_6H_5	**2c**	58
4	**1d**	C_6H_5	4-Cl-C_6H_4	**2d**	50
5	**1e**	C_6H_5	4-Me-C_6H_4	**2e**	86
6	**1f**	C_6H_5	4-MeO-C_6H_4	**2f**	81

[a] Isolated yield.

(Scheme 2 and Supporting Information), in which both benzene rings were substituted by either an electron-withdrawing or an electron-donating group, underwent the identical TFA-mediated cyclization reaction smoothly in refluxing *tert*-butanol to produce homoclausenamide analogs **2b**−**f** in 50% to 86% yields. When the reaction was performed in pure water under refluxing, all oxirane-containing enamides **1b**−**e**, irrespective of the nature of the substituents on both benzene rings, were transformed efficiently into the five-membered lactam products **4** and **4**′ in good to excellent yields (Table 3). The ratio of homoclause-

Table 3. Synthesis of Neoclausenamide and Its Analogs from 5-*endo*-Enamide-Epoxide Cyclization of **1** in Water



1 **4** **4′**

entry	**1**	Ar^1	Ar^2	**4** + **4**′	yield (%)[a]	**4**:**4**′[b]
1	**1a**	C_6H_5	C_6H_5	**a**+**a**′	91	30:70
2	**1b**	4-Cl-C_6H_4	C_6H_5	**b**+**b**′	89	9:91
3	**1c**	4-Me-C_6H_4	C_6H_5	**c**+**c**′	91	50:50
4	**1d**	C_6H_5	4-Cl-C_6H_4	**d**+**d**′	75	44:56
5	**1e**	C_6H_5	4-Me-C_6H_4	**e**+**e**′	93	45:55
6	**1f**	C_6H_5	4-MeO-C_6H_4	**f**+ **f**′	68	61:39

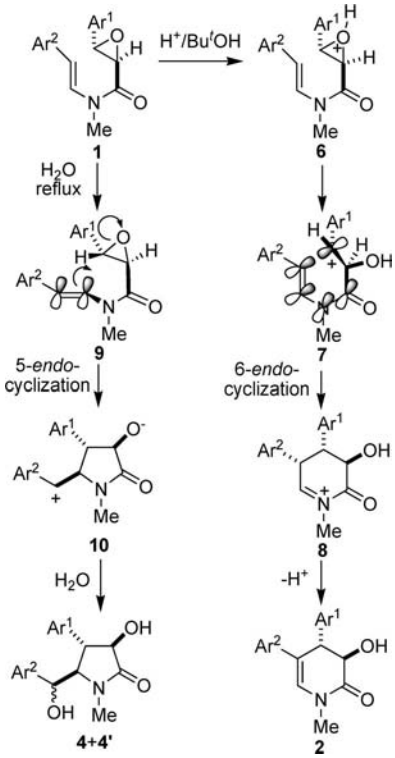
[a] Isolated yield. [b] Determined by ^{1}H NMR spectra.

namide analogs **4** over their corresponding 6-epimers **4**′, which was determined roughly by ^{1}H NMR spectra, were governed by the electronic effect of the substituents on both aromatic rings. While an electron-withdrawing group on Ar^1 was in favor of the formation of 6-epimer **4**′, the presence of an electron-donating group on Ar^2 seemed beneficial for neoclausenamide analogs **4**. This has been exemplified by

the observation of 9:91 for **4b**:**4b′** (entry 2, Table 3) and 61:39 for **4f**:**4f′** (entry 6, Table 3).

The mechanism for the formation of the six-membered homoclausenamide products **2** from oxirane-containing enamides **1** was proposed in Scheme 3. In the presence of TFA,

Scheme 3. Plausible Mechanism for 6-*endo*- and 5-*endo*-Enamide-Epoxide Cyclizations of **1**



the epoxide ring might be protonated and opened to form carbonium intermediate **7**. Intramolecular enaminic cyclization (β-carbon attack) gives iminium **8**, which undergoes deprotonation to afford **2**. The formation of the five-membered neoclausenamides **4** and their 6-epimers **4′** in boiling water was intriguing.[15,16] While the detailed mechanism awaits further study, the plausible reaction pathway might involve the attack of α-carbon of the enamide moiety of **1** to the benzylic carbon of the epoxide. The resulting zwitterion intermediate **10** reacts with water to yield a mixture of epimers **4** and **4′**.

The function of the α-carbon rather than the β-carbon (enaminic carbon) of the enamide as the nucleophilic site to attack epoxide ring would suggest that the lone pair electrons on the nitrogen do not form conjugation with the carbon−carbon double bond. In other words, under the reaction conditions such as in pure water, the oxirane-enamide molecule **1** might adopt the conformation **9** in which the amido plane might be perpendicular to the plane of carbon−carbon double bond. This conformation inhibits delocalization of the lone pair electrons of nitrogen into the carbon−carbon double bond, alleviating therefore the nucleophilicity of the "enaminic β-carbon". The conformation **9** brings the proximity of p-orbital of the α-carbon with benzylic carbon of the epoxide ring, facilitating the 5-*endo*-enamide-epoxide cyclization reaction. In addition, the stabilization gained from the formation of benzylic cation intermediate **10** might also pay contribution to the 5-*endo*-enamide-epoxide cyclization reaction (Scheme 3).

In summary, we have developed a highly efficient, metal-free, and divergent method for the synthesis of 3,4-dihydropyridin-2-one and pyrrolidin-2-one *Clausena* alkaloids and their analogs by stereospecific intramolecular cyclization reaction of oxirane-containing enamides. The orthogonal reactivity of enamides, especially the unprecedented nucleophilicity of the α-carbon of enamides, has been exploited under different conditions. The mechanism and application of intriguing nucleophilic reactions of enamides in water are currently investigated in our laboratory and will be reported in due course.

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Supporting Information Available: Experimental details, ^{1}H and ^{13}C NMR spectra of products, and X-ray structure of **2a**, **4a**, and **4a′** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) A single crystal of **2a** was obtained from slow evaporation of the solvent from **2a** solution in a mixture of ethyl acetate and hexane (1:1). To obtain single crystals of **4a** and **4a′**, recrystalization of a mixture of reaction products **4a** and **4a′** (**4a**:**4a′** = 3:7) in ethyl acetate gave pure **4a′** as solid. Slow evaporation of the solvent from **4a′** solution in a mixture of ethyl acetate and THF (1:1) gave single crystal of **4a′**. The filtrate, which contains a mixture of **4a** and **4a′** (**4a**:**4a′** = 1:1) after recrystalization of **4a′**, was subjected to the preparative HPLC with a C-18 column to give a fraction in which the ratio of **4a** over **4a′** was 6:1. Slow evaporation of the solvent from its solution in a mixture of ethyl acetate and THF (1:1) gave single crystal of **4a.**