Unprecedented carbon–carbon bond cleavage in nucleophilic aziridine ring opening reaction, efficient ring transformation of aziridines to imidazolidin-4-ones†

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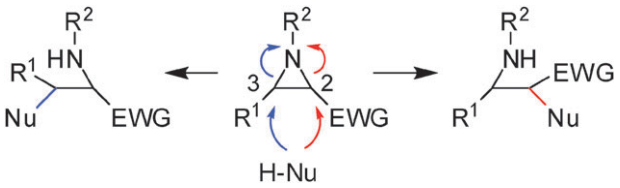
***N*-Styryl-3-aryl-1-methylaziridine-2-carboxamides, which were readily obtained from the cross coupling reaction between 3-aryl-1-methylaziridine-2-carboxamides and 1-aryl-2-bromoethenes catalyzed by CuI/*N*,*N*-dimethylglycine in the presence of Cs_2CO_3, underwent a base-mediated intramolecular nucleophilic aziridine ring opening reaction effectively *via* the carbon–carbon bond cleavage of aziridine to afford the ring expanded imidazolidin-4-one products in good yields.**

Owning to the ring strain and the electronegativity of nitrogen, aziridines, the smallest *N*-heterocyclic compounds, exhibit intriguing and diverse reactivity, and have thus become unique and versatile synthons in organic synthesis.[1–4] The ring opening reactions of aziridines, widely investigated reactions, for example, have been used to generate a large number of functionalized organic molecules that are not easily accessible by other means. Noticeably, however, the regioselectivity and the efficiency of the ring opening reactions of aziridines are heavily dependent upon the nature of the substituents on the three-membered heterocyclic ring, the nucleophiles, and the reaction conditions employed.[1–4] To the best of our knowledge, all nucleophilic ring opening reactions of aziridines reported to date occur on the C-2 and C-3 positions of the aziridine ring with the cleavage of the carbon–nitrogen bond[1–4] (Scheme 1). Only under pyrolysis conditions such as at 280 °C does the carbon–carbon bond cleavage proceed to form azomethine ylide 1,3-dipolar intermediates that can be trapped by alkenes, yielding five-membered pyrrolidine products.[5–9] We report herein an unprecedented example of carbon–carbon bond cleavage in the nucleophilic ring opening reaction of aziridine under mild conditions. Mediated by a base, intramolecular nucleophilic ring opening reaction of *N*-styryl-3-aryl-1-methylaziridine-2-carboxamides led to the formation of the ring expansion imidazolidin-4-one products.

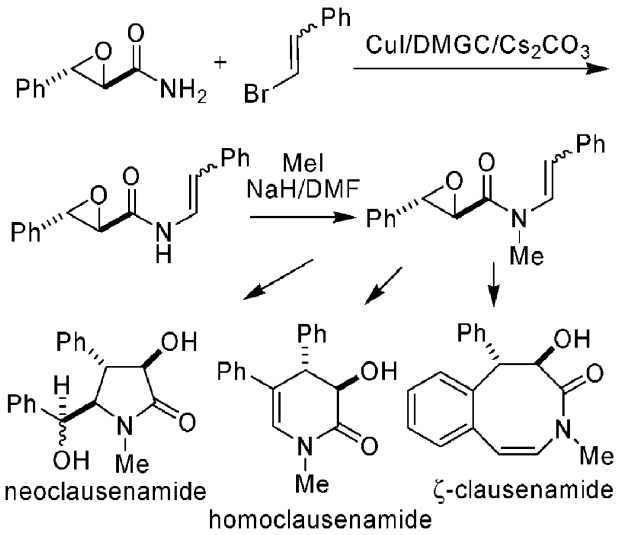
We[6,7] have recently reported the cross coupling reaction of 3-aryloxirane-2-carboxamides with 1-bromovinyl benzene. The resulting oxirane-containing enamides were found to undergo divergent intramolecular nucleophilic oxirane ring opening reactions under different conditions to produce ζ-clausenamide,[10] homoclausenamide and neoclausenamide,[11]



Scheme 1 Carbon–nitrogen bond cleavages in nucleophilic aziridine ring opening reactions.

8-, 6- and 5-membered lactam-containing alkaloids that were isolated from the leaf extract of Rutaceae *Clausena lansium* (Lour.) Skeels (Scheme 2). It was envisaged that if the oxirane ring is replaced by an aziridine ring, the analogous intramolecular aziridine ring opening reactions would give rise to amino substituted natural product-like lactam derivatives.

We initially examined the cross coupling reaction between *trans*-1-methyl-3-phenylaziridine-2-carboxamide **1a** with (*Z*)-(2-bromovinyl)benzene **2a**. Catalyzed by CuI/*N*,*N*-dimethylglycine (DMGC) in the presence of Cs_2CO_3, the reaction conditions successfully used for the cross coupling reaction between 3-aryloxirane-2-carboxamides with (*Z*)-(2-bromovinyl) benzene **2a**,[10,11] we found the reaction of **1a** with **2a** proceeded smoothly in refluxing 1,4-dioxane. After 3.5 h, the expected *N*-(*Z*)-styryl-1-methyl-3-phenylaziridine-2-carboxamide **3** was obtained in 60% yield. Surprisingly, in addition to enamide



Scheme 2 Diverse intramolecular oxirane ring opening reactions of oxirane-containing enamides for the synthesis of *Clausena* alkaloids.

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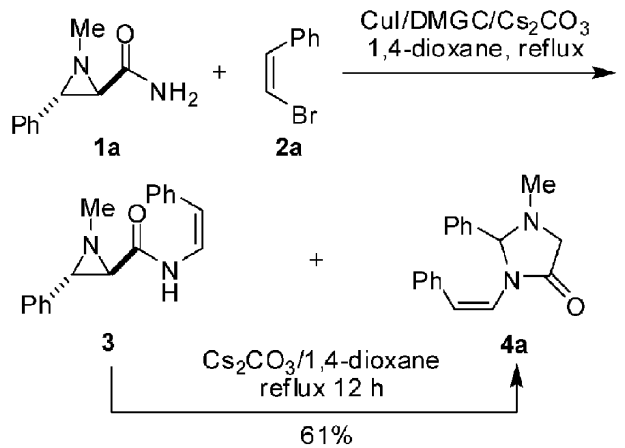
product **3**, a five-membered heterocyclic product 1-methyl-2-phenyl-3-(*Z*)-styrylimidazolidin-4-one **4a** was also isolated in 15% yield. The ring expansion product **4a** was obtained as the sole isolable product in 65% when the reaction mixture was refluxed for an elongated period of time (12 h), implying the conversion of aziridine-bearing enamide **3** into the five-membered heterocycle **4a** under the reaction conditions. To shed light on the formation of imidazolidin-4-one **4a**, the reaction of the isolated aziridine intermediate **3** was tested. *N*-(*Z*)-styryl-1-methyl-3-phenylaziridine-2-carboxamide **3** was found to undergo efficiently a Cs_2CO_3-mediated intramolecular nucleophilic aziridine ring opening reaction with the cleavage of the carbon–carbon bond to furnish the ring expanded product **4a** in 61% yield (Scheme 3).

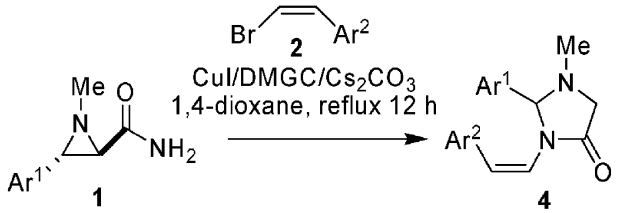
The tandem CuI/DMGC-catalyzed cross coupling reaction and the base-mediated intramolecular nucleophilic aziridine ring opening reaction appeared general. Summarized in Table 1 are the results of the reaction between *trans*-3-aryl-1-methyl-aziridine-2-carboxamides **1** and (*Z*)-1-aryl-2-bromoethenes **2**. In all cases, imidazolidin-4-one products **4** were obtained in good yield after 12 h regardless of the substituent on the benzene rings of both reactants. When (*E*)-(2-bromovinyl)benzene **5** was used instead of its *Z*-isomer **2a**, the same tandem CuI/DMGC-catalyzed cross coupling reaction and the base-mediated intramolecular nucleophilic aziridine ring opening reaction proceeded equally well. As exemplified in Scheme 4, 2-aryl-1-methyl-3-(*E*)-styrylimidazolidin-4-ones **6a–c**, were produced in 71–84% yield from the corresponding substrates.

We finally studied the reaction of *cis*-1-methyl-3-phenyl-aziridine-2-carboxamide **7** with (*Z*)-(2-bromovinyl)benzene **2a** and (*E*)-(2-bromovinyl)benzene **5** (Scheme 5). Under the identical CuI/DMGC catalytic conditions for the reaction of **1**, *cis*-1-methyl-3-phenylaziridine-2-carboxamide **7** was converted efficiently into enamide products **8** and **9** in 78% and 70%, respectively. No further ring transformation was evidenced under the reaction conditions, however. Treatment of **8** with Cs_2CO_3 in DMSO solution at 70 °C led to the isomerization of carbon–carbon double bond, affording enamide product **9** in 77% yield. Among the bases such as NaOH, K_2CO_3, Cs_2CO_3 and NaH examined, only the combination of NaH in DMF at 70 °C effected the efficient intramolecular nucleophilic



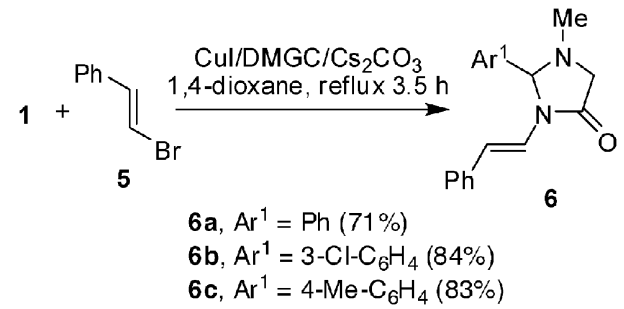
Scheme 3 Cross coupling reaction of **1a** with **2a** and the conversion of **3** into **4a**.

Table 1 Ring transformation of aziridine to imidazolin-4-one

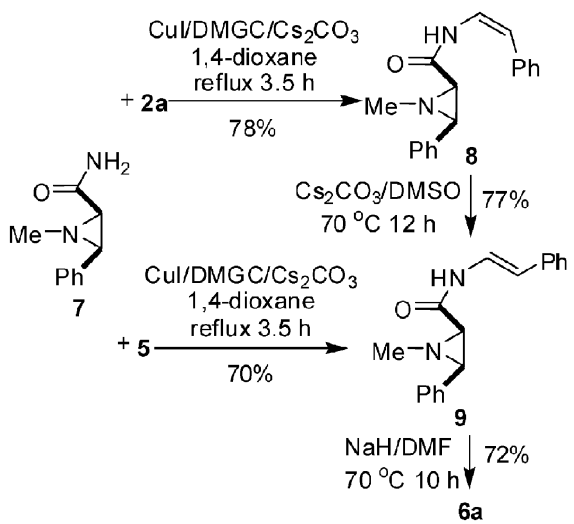


Entry	1	Ar^1	2	Ar^2	4 (%)[a]
1	**1a**	C_6H_5	**2a**	C_6H_5	**4a** (65)
2	**1a**	C_6H_5	**2b**	4-Cl-C_6H_4	**4b** (85)
3	**1a**	C_6H_5	**2c**	4-Me-C_6H_4	**4c** (74)
4	**1b**	4-F-C_6H_4	**2a**	C_6H_5	**4d** (71)
5	**1c**	4-Cl-C_6H_4	**2a**	C_6H_5	**4e** (80)

[a] Isolated yield.



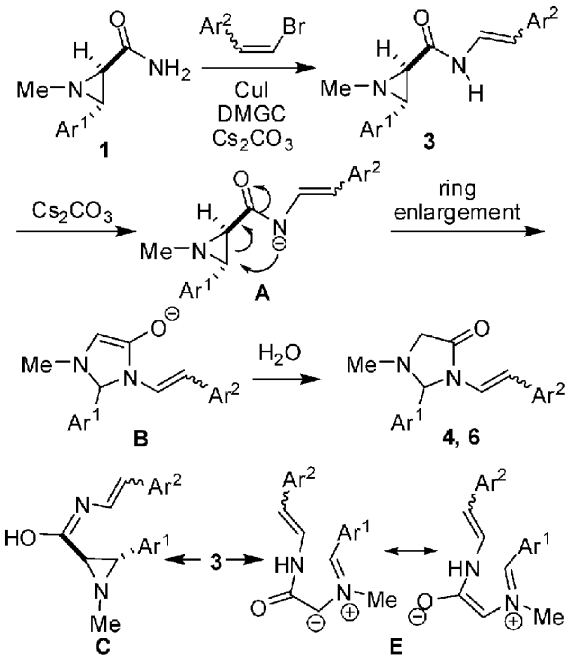
Scheme 4 Reaction of *trans*-3-aryl-1-methylaziridine-2-carboxamides **1** with (*E*)-(2-bromovinyl)benzene **5**.



Scheme 5 Reaction of *cis*-1-methyl-3-phenylaziridine-2-carboxamide **7** with **2** and **5**.

aziridine ring opening reaction of **9** to give imidazolidin-4-one **6a** (Scheme 5).

The unusual nucleophilic ring opening reaction of aziridine with the cleavage of carbon–carbon bond is intriguing. To account for the ring transformation of *N*-styryl-3-aryl-1-methylaziridine-2-carboxamides, a plausible reaction mechanism



Scheme 6 Plausible pathway for the tandem cross coupling reaction and ring transformation.

was proposed. As depicted in Scheme 6, CuI/DMGC-catalyzed cross coupling reaction of amides and 1-aryl-2-bromoethenes results in the formation of aziridine-containing enamides. Under the basic conditions, deprotonation of enamides occurs to form amide anion intermediate **A**, which can be stabilized by the styryl group. Intramolecular nucleophilic attack of the amide nitrogen at the C-3 of the aziridine ring leads to carbon–carbon bond cleavage to form intermediate **B**. Subsequent *O*-protonation and tautomerization furnish the imidazolidin-4-one products. It is worth addressing the regiospecific nucleophilic attack of amide nitrogen on the C-3 of aziridine ring, which might be regarded as a disfavored process according to Baldwin's rules,[12] is probably due to its close proximity to the C-3 position. More likely, it is the electrophilic nature of the benzylic C-3 that determines the regiospecific nucleophilic aziridine ring opening reaction. The cleavage of the carbon–carbon bond rather than carbon–nitrogen bond of the aziridine ring is most probably attributed to the release of the ring strain by forming a more stable five-membered imidazoline intermediate **B**. The stabilization energy gained from the formation of conjugation in **B** may also contribute to the ring transformation pathway. It should also be noted that, due to the weaker electrophilicity of the aziridine ring in comparison to the oxirane ring, and because of the weaker reactivity of enamide than enamine, neither intramolecular aryl–aziridine cyclization nor enamine–aziridine cyclization took place. A similar intramolecular aryl–epoxide cyclization[10] and intramolecular enamine–epoxide cyclization[11] in the analogous oxirane-containing enamide derivatives were reported (Scheme 2). Alternatively, imidazolin-4-one products **4** and **6** might also be formed from electrocyclization of **C**,[13,14] a tautomer of **3**, and from spontaneous ring opening of aziridine to form azomethine ylide **E**[5–9,14] followed by ring closure reaction (Scheme 6). Both reaction pathways would also give oxazoline products. However, no oxazoline products were observed experimentally in our study.

In conclusion, we have shown the first example of carbon–carbon bond cleavage of the aziridine ring in a nucleophilic aziridine ring opening reaction. *N*-Styryl-3-aryl-1-methylazaridine-2-carboxamides, which are readily obtained from the CuI/DMGC-catalyzed cross coupling reaction of 3-aryl-1-methyl-aziridine-2-carboxamides with 1-aryl-2-bromoethenes, are able to undergo efficiently a base-mediated intramolecular aziridine ring opening reaction *via* carbon–carbon bond cleavage to afford the ring expanded imidazolidin-4-one products. The carbon–carbon bond cleavage of the aziridine ring should open a new avenue for the exploration of new applications of aziridine compounds in organic synthesis.

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Notes and references

1 For a recent monograph about aziridine chemistry, see: *Aziridines and Epoxides in Organic Synthesis*, ed. A. K. Yudin, Wiley-VCH, 2006.

2 For recent reviews on aziridine chemistry, see: (*a*) H. M. Osborn and J. Sweeney, *Tetrahedron: Asymmetry*, 1997, **8**, 1693; (*b*) X. E. Xu, *Tetrahedron*, 2004, **60**, 2701; (*c*) W. McCoull and F. A. Davis, *Synthesis*, 2000, 1347; (*d*) J. B. Sweeney, *Chem. Soc. Rev.*, 2002, **31**, 247.

3 For recent examples, see: (*a*) C. S. Park, H. G. Choi, H. Lee, W. K. Lee and H.-J. Ha, *Tetrahedron: Asymmetry*, 2000, **11**, 3283; (*b*) T. B. Sim, S. H. Kang, K. S. Lee and W. K. Lee, *J. Org. Chem.*, 2003, **68**, 104; (*c*) J. M. Yun, T. B. Sim, H. S. Hahm and W. K. Lee, *J. Org. Chem.*, 2003, **68**, 7675; (*d*) Y. Kim, H.-J. Ha, K. Han, S. W. Ko, H. Yun, H. J. Yoon, M. S. Kim and W. K. Lee, *Tetrahedron Lett.*, 2005, **46**, 4407; (*e*) B. K. Lee, M. S. Kim, H. S. Hahm, D. S. Kim, W. K. Lee and H.-J. Ha, *Tetrahedron*, 2006, **62**, 8393; (*f*) B. Denolf, S. Mangelinkx, K. W. Törnroos and N. De Kimpe, *Org. Lett.*, 2006, **8**, 3129; (*g*) T. Manaka, S.-I. Nagayama, W. Desadee, N. Yajima, T. Kumamoto, T. Watanabe, T. Ishikawa, M. Kawahata and K. Yamaguchi, *Helv. Chim. Acta*, 2007, **90**, 128; (*h*) F. Crestey, M. Witt, K. Frydenvang, D. Staerk, J. W. Jaroszewski and H. Franzyk, *J. Org. Chem.*, 2008, **73**, 3566.

4 (*a*) J.-Y. Wang, D.-X. Wang, Q.-Y. Zheng, Z.-T. Huang and M.-X. Wang, *J. Org. Chem.*, 2007, **72**, 2040; (*b*) J.-Y. Wang, D.-X. Wang, J. Pan, Z.-T. Huang and M.-X. Wang, *J. Org. Chem.*, 2007, **72**, 9391; (*c*) J.-Y. Wang, X.-F. Guo, D.-X. Wang, Z.-T. Huang and M.-X. Wang, *J. Org. Chem.*, 2008, **73**, 1979.

5 Y. Gelas-Mialhe, T. Touraud et Roger and R. Yessiere, *Can. J. Chem.*, 1982, **60**, 2830.

6 S. Takano, T. Iwabuchi and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1988, 1204.

7 J. Vebrel, D. Gree and R. Carrie, *Can. J. Chem.*, 1984, **62**, 939.

8 A. Derdour and F. Texier, *Can. J. Chem.*, 1985, **63**, 2245.

9 S. Takano, M. Moriya and K. Ogasawara, *Tetrahedron: Asymmetry*, 1992, **3**, 681.

10 L. Yang, G. Deng, D.-X. Wang, Z.-T. Huang, J. Zhu and M.-X. Wang, *Org. Lett.*, 2007, **9**, 1387.

11 L. Yang, Q.-Y. Zheng, D.-X. Wang, Z.-T. Huang and M.-X. Wang, *Org. Lett.*, 2008, **10**, 2461.

12 J. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734.

13 J. March, *AdvancedOrganic Chemistry*, John Wiley & Sons Inc., 1992, 4th edn., pp. 1128–1129 and references cited therein.

14 The authors are grateful to a referee for have their attention to alternative mechanisms describing the observed conversion.

