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Synthesis of Aminocyclobutanes through Ring Expansion of *N*-Vinyl-β-Lactams

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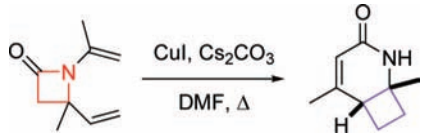
ABSTRACT



Both eight-membered enamide rings and fused [4.2.0]aminocyclobutane-containing δ-lactams can be accessed from *N*-vinyl-β-lactams. The eight-membered rings are made through a [3,3] sigmatropic rearrangement. At elevated temperature, the eight-membered lactam undergoes electrocyclization to furnish fused cyclobutane δ-lactams in a diastereoselective manner.

As part of a program aimed at synthesis of stereochemically complex cyclobutanes, we evaluated the possibility of their construction from β-lactams. The latter are structural constituents in a number of biologically active molecules and are valuable intermediates in chemical synthesis.[1] The ring strain embedded in the four-membered ring of a β-lactam is an attractive structural feature that has been exploited in numerous ring-opening and ring-expansion reactions.[1] Compared to cyclobutanes, β-lactams have received more attention and are generally easier to make. We sought a method that transposes the strain of a β-lactam into that of a cyclobutane. There are many ways to prepare β-lactams, including ester−enolate imine cycloaddition,[2] olefin−isocyanate cycloaddition,[3] Kinugasa reaction,[4] and the Staudinger reaction.[5] In comparison, there are not many general methods to make cyclobutanes, the most popular process being the photochemical [2 + 2] cycloaddition. However, the latter reaction has inherent drawbacks such as dimerization of starting materials and formation of product mixtures resulting from lack of regio- and stereoselectivity.[6] In this paper, we report that ring scission of β-lactams can give rise to diversely substituted aminocyclobutanes[7] via sigmatropic ring opening/electrocyclic ring closure sequence.

The β-lactam starting materials can be prepared on a multigram scale in three steps that include a single purification (Scheme 1). The synthesis begins with a cycloaddition between isoprene and chlorosulfonyl isocyanate[8] to afford the *N*-chlorosulfonyl β-lactam that is cleanly reduced to the corresponding *N*-H β-lactam with aqueous sodium sulfite.[9] The β-lactam is then cross coupled with an appropriate vinyl[10] iodide under copper catalysis[11] to give the corresponding *N*-vinyl-β-lactam.

(1) (a) Alcaide, B.; Almendros, P. *Synlett* **2002**, *3*, 381. (b) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, *107*, 4437. (c) Alcaide, B.; Almendros, P. *Curr. Med. Chem.* **2004**, *29*, 1921.

(2) (a) Gilman, H.; Speeter, H. *J. Am. Chem. Soc.* **1943**, *65*, 2255. (b) Hart, D. J.; Ha, D. C. *Chem. Rev.* **1989**, *89*, 1447.

(3) (a) Grai, R. *Justus Liebigs Ann. Chem.* **1963**, *661*, 111. (b) Hoffmann, H.; Diehr, H. J. *Tetrahedron Lett.* **1963**, *4*, 1875. (c) Friedrich, H. J. *Tetrahedron Lett.* **1971**, *12*, 2981.

(4) (a) Kinugasa, M.; Hashimoto, S. *J. Chem. Soc., Chem. Commun.* **1972**, 466. (b) Pal, R.; Ghosh, S. C.; Chandra, K.; Basak, A. *Synlett* **2007**, 2321.

(5) (a) Staudinger, H *Justus Liebigs Ann. Chem.* **1907**, *356*, 51. (b) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223. (c) France, S.; Taggi, A. E.; Lectka, T. *Acc. Chem. Res.* **2004**, *37*, 592.

(6) Rappoport, Z.; Liebman, J. F. *The chemistry of cyclobutanes*; John Wiley & Sons: Chichester, 2005.

(7) For utility of aminocyclobutane derivatives in drug discovery, see: Allan, R. D.; Hanrahan, J. R.; Hambley, T. W.; Johnston, G. A. R.; Mewett, K. N.; Mitrovic, A. D. *J. Med. Chem.* **1990**, *33*, 2905.

(8) Moriconi, E. J.; Meyer, W. C. *Tetrahedron Lett.* **1968**, *35*, 3823.

(9) Durst, T.; O'Sullivan, M. J. *J. Org. Chem.* **1970**, *35*, 2043.

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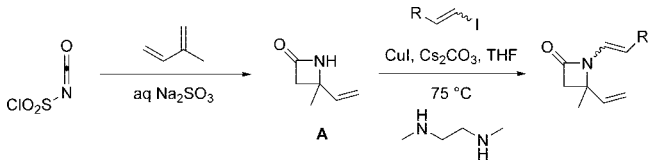
Scheme 1. Synthesis of β-Lactam Starting Materials

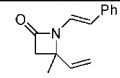
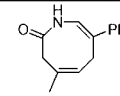
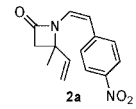
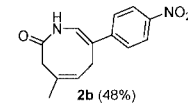
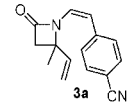
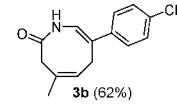
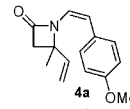
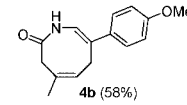
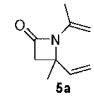
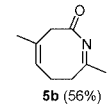
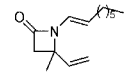
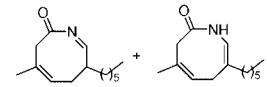
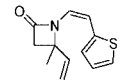
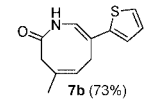
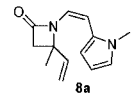
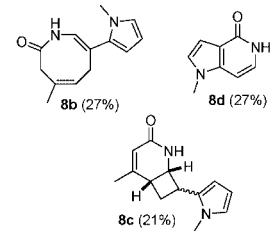
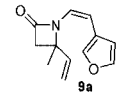
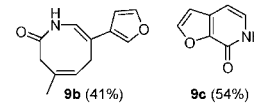
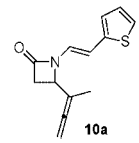
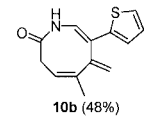


Upon thermal activation, we observed the formation of eight-membered enamide rings via a [3,3] sigmatropic rearrangement. As shown in Table 1, electron-rich, -poor, and -neutral enamide substituents are tolerated (entries 1−4). Various aromatic heterocycles such as furan, thiophene and pyrrole also participate in this chemistry (entries 7−9). The β-lactam component can be modified to contain an allene, instead of an olefin, to participate in the formal [3,3] sigmatropic rearrangement leading to a conjugated triene ring system (entry 10). When the R group is an alkyl substituent (entries 5 and 6), the initial product is an imine that tautomerizes to the enamide product.

Entry 8 of Table 1 indicates that a fused cyclobutane δ-lactam product **8c** has been formed as a byproduct. Despite the low yield, **8c** sparked our interest. The reaction was initially studied through a cascade sequence involving coupling 2-bromoprop-1-ene and β-lactam **A** (Scheme 2) under thermal cooper-catalyzed cross-coupling conditions. The product of *N*-vinylation was found to undergo a formal [3,3] sigmatropic rearrangement without concomitant tautomerization to the enamide form. This behavior is particularly noticeable when R and R^1 = alkyl, rather than aryl, groups (entries 5 and 6, Table 1). In this case, the imine lifetime is long enough that deprotonation α to the carbonyl can occur to produce a 6π electron system that can undergo the electrocyclization to produce the fused cyclobutane δ-lactam. The reaction yields are highest when *N*-vinyl-β-lactam is used as the starting material without isolation of the intermediate product of the [3,3] sigmatropic rearrangement. Cs_2CO_3 and a copper source, such as CuI or CuCl, were found to be essential for the reaction. This sequence represents a rare thermal method to produce fused cyclobutane δ-lactams as most methods employ photochemistry to make the fused cyclobutane δ-lactams.[12]

Table 2 shows the scope of the reaction. The substrates initially tested were those of entries 1−3. The reaction worked well in each case with moderate levels of diastereoselectivity. The reaction with the geminally disubstituted enamides worked particularly effectively (entries 4 through 6). The crude material did not require any purification. In entry 7, a trisubstituted olefin was employed to afford a

Table 1. Substrate Scope of the [3,3] Sigmatropic Rearrangement

entry	starting material	product
1	 **1a**	 **1b** (86%)
2	 **2a**	 **2b** (48%)
3	 **3a**	 **3b** (62%)
4	 **4a**	 **4b** (58%)
5	 **5a**	 **5b** (56%)
6	 **6a**	 **6b** (25%) **6c** (8%)
7	 **7a**	 **7b** (73%)
8	 **8a**	 **8b** (27%) **8d** (27%) **8c** (21%)
9	 **9a**	 **9b** (41%) **9c** (54%)
10	 **10a**	 **10b** (48%)

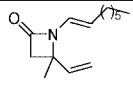
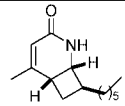
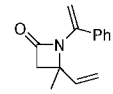
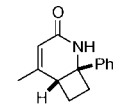
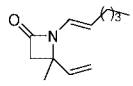
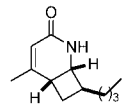
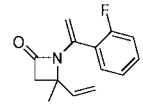
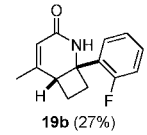
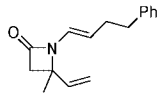
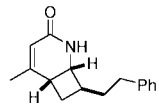
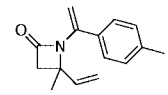
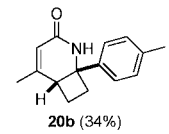
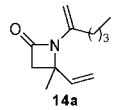
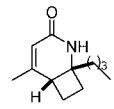
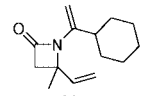
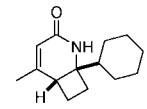
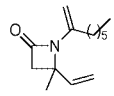
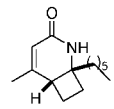
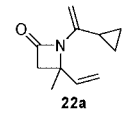
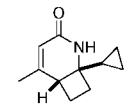
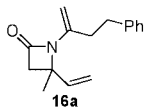
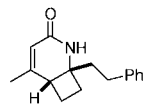
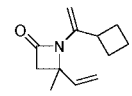
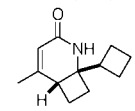
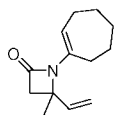
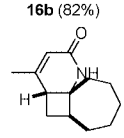
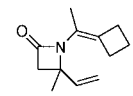
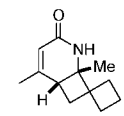
[a] Yields of isolated products obtained under microwave heat (160−200 °C).

(10) (a) Harried, S. S; Lee, C. P.; Yang, G.; Lee, T. I. H.; Myles, D. C. *J. Org. Chem.* **2003**, *68*, 6646. (b) Trost, B. M.; Rudd, M. T. *Org. Lett.* **2003**, *5*, 4599. (c) Barton, D. H. R.; Bashiardes, G.; Pourrey, J. L. *Tetrahedron Lett.* **1983**, *24*, 1605. (d) Blaskovicova, M.; Gaplovsky, A.; Blasko, J. *Molecules* **2007**, *11*, 188. (e) Kamiya, N.; Chikami, Y.; Ishii, Y. *Synlett* **1990**, 675.

(11) Jiang, L.; Job, G. E.; Klapers, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667.

(12) (a) Chen, P.; Chen, Y.; Carroll, P. J.; Sieburth, S. M. *Org. Lett.* **2006**, *8*, 3367. (b) Commins, D. L.; Zheng, X.; Goehring, R. R. *Org. Lett.* **2002**, *4*, 1611. (c) Chiba, T.; Takada, Y.; Kaneko, C.; Kiuchi, F.; Tsuda, Y. *Chem. Pharm. Bull.* **1990**, *38*, 3317. (d) Chiba, T.; Takada, Y.; Naito, T.; Kaneko, C. *Chem. Pharm. Bull.* **1990**, *38*, 2335. (e) Kaneko, C.; Ychiyama, K.; Sato, M.; Katagiri, N. *Chem. Pharm. Bull.* **1986**, *34*, 3658. (f) Naito, T.; Kaneko, C. *Chem. Pharm. Bull.* **1985**, *33*, 5328. (g) Kaneko, C.; Katagiri, N.; Uchiyama, K.; Yamada, T. *Chem. Pharm. Bull.* **1985**, *33*, 4160.

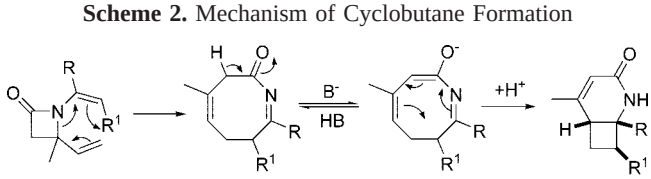
Table 2. Cyclobutane Formation: The Substrate Scope

entry	starting material	product	entry	starting material	product
1[b]	 **6a**	 **11b** (95%) (dr = 86:14)	8[b]	 **18a**	 **18b** (42%)
2[b]	 **12a**	 **12b** (98%) (dr = 83:17)	9[b]	 **19a**	 **19b** (27%)
3[b]	 **13a**	 **13b** (93%) (dr = 83:17)	10[b]	 **20a**	 **20b** (34%)
4	 **14a**	 **14b** (83%)	11	 **21a**	 **21b** (84%)
5	 **15a**	 **15b** (89%)	12	 **22a**	 **22b** (89%)
6	 **16a**	 **16b** (82%)	13	 **23a**	 **23b** (95%)
7	 **17a**	 **17b** (83%)	14	 **24a**	 **24b** (93%)

[a] Yields of isolated products obtained under microwave heat (160−200 °C). [b] See the Supporting Information.

tricyclic system with three contiguous stereocenters. When aryl groups were used at the geminal position the reaction selectivity was not as high as with geminal alkyl substituents: both the fused cyclobutane δ-lactam product and the eight-membered ring product of the sigmatropic rearrangement were isolated. The cyclopropyl, cyclobutyl, and cyclohexyl carbocycles at the geminal position can also be used. Lastly, spirocyclic compounds can be made from tetrasubstituted olefins that are exocyclic to the carbocycle (entry 14).

Scheme 2. Mechanism of Cyclobutane Formation



R = Me, R^1 = H **25** (4%)

R = H, R^1 =  **8c** (27%)

In summary, we have developed a versatile class of stable β-lactam intermediates that can undergo ring expansion to afford 8-membered enamide rings. The [3,3] sigmatropic rearrangement of these β-lactams proceeds without any relative stereochemical requirement imposed on the starting material unlike the ring-strain releasing [3,3] sigmatropic rearrangements that require a syn relative stereochemistry between the reacting olefins.[13] Most importantly, we have also demonstrated that β-lactams can undergo ring expansion/ring closure in a domino fashion to produce highly substituted fused cyclobutane δ-lactams with high levels of diastereoselectivity. Catalytic asymmetric synthesis of fused cyclobutane δ-lactams is currently underway.

(13) (a) Brown, J. M.; Golding, B. T.; Stofko, J. J. *J. Chem. Soc., Chem. Commun.* **1973**, 319b. (b) Vogel, E. *Ann.* **1958**, *615*, 1. (c) Alcaide, B.; Rodríguez-Ranera, C.; Rodríguez-Vicente, A. *Tetrahedron Lett.* **2001**, *42*, 3081.

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Supporting Information Available: Crystallographic data, NMR spectra, and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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