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Stereospecific ring expansion of β-lactams to γ–lactams with trimethylsilyldiazomethane

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Abstract

Ring opening of *N*-carboxylated β-lactams with trimethylsilyldiazomethane anion followed by photolytic Wolff rearrangement provided γ-lactams in a stereospecific manner. © 1998 Elsevier Science Ltd. All rights reserved.

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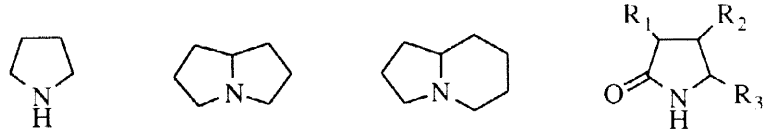
Alkaloids with pyrrolidine(**1**), pyrrolizidine(**2**), and indolizidine(**3**) ring skeletons have long been the targets of many synthetic efforts due to their diverse and interesting biological activities [1-3]. Many of the synthetic approaches to these alkaloids involve 2-pyrrolidinone intermediates(**4**), and it is highly desirable to develop a method for the efficient conversion of routinely available materials to 2-pyrrolidinones in a stereoselective manner. β-Lactams are probably the most intensively studied molecules due to their potent antibacterial activities. As a result of such interest, diverse methods for the ring formation have been developed, including ketene-imine cycloadditions [4] and ester enolate-imine condensations [5]. With the practical and stereoselective synthetic methods available, β-lactam rings have also been recognized as useful synthetic building blocks for the other classes of molecules [6-10]. For example, opening of β-lactam ring by internal or external nucleophiles exploiting the ring strain provided β-aminocarbonyl derivatives. Though a few examples for the insertion of oxygen or nitrogen between the C(2) and C(3) of β-lactam ring are known [11-13], no study for the insertion of carbon to expand the ring has been reported. In this communication, we report our preliminary study on the ring expansion of β-lactam and this process will provide an easy access to the pyrrolidines having stereochemistry preadjusted at the β-lactam stage.



1 **2** **3** **4**

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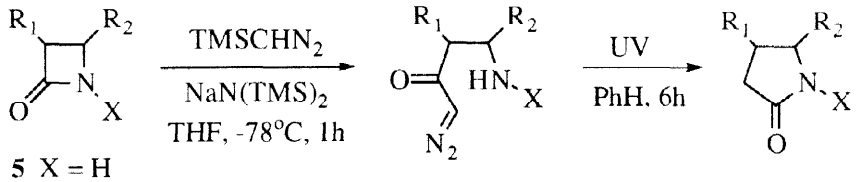
Trimethylsilyldiazomethane($TMSCHN_2$) is a stable substitute for diazomethane and has been used for Lewis acid-catalyzed homologation of aldehydes and ketones [14,15]. And the ring expansions of cyclic ketones with $TMSCHN_2$ and diazoalkane in the presence of Lewis acid were reported [16,17]. Our initial study for the expansion of *N*-protected β-lactams under the similar conditions provided only the ring-opened diazoketones with very low yield, and ring-homologated product was not detected. Thus, we turned our attention to develop a two-step process for the ring expansion, opening of β-lactam ring with the anion of $TMSCHN_2$ and photolytic Wolff rearrangement of the resulting α-diazoketone to provide γ-lactam after cyclization.

The *cis*-β-lactams **5a** and **5c** were prepared by the condensation of Li-enolate of the corresponding ester with benzylidene-*N*-(trimethylsilyl)imine in THF [18]. β-Lactam **5d** was obtained by catalytic hydrogenation after the condensation with cinnamylidene-*N*-(trimethylsilyl)imine. *trans*-β-Lactam **5b** was prepared by condensation with benzylidene-*p*-anisidine in THF-HMPA followed by oxidative removal of *N*-(*p*-methoxyphenyl) group with CAN [18,19]. β-Lactam **5e** was prepared by [2+2]-cycloaddition between benzyloxyacetyl chloride and *p*-anisilidene-*p*-anisidine followed by *N*-dearylation [4]. Epimerization with *t*-BuOK before the CAN dearylation provided the *trans* **5f** [20]. These *cis*- and *trans*-β-lactams **5** were carboxylated on ring nitrogen to give **6** with CbzCl, EtOCOCl or $(t\text{-Boc})_2O$, which increase the reactivity of the ring toward the anion of $TMSCHN_2$.



5 X = H
6 X = CO_2R

7 **8**

The ring cleavage of the β-lactams to the diazoketone **7** was accomplished by addition of $NaN(TMS)_2$ to the mixture of the carboxylated β-lactam **6a-6g** and $TMSCHN_2$ in THF at -78°C and stirring for 1h of the resulting solution before the aqueous work-up. The stereochemistry of *cis* and *trans* β-lactams was preserved during the ring cleavage and no epimerized product, even with **6g** having relatively acidic C(3)-H, was observed probably due to the formation of stable enolate of the α-diazoketone **7**.[1] Diazoketone **7** was irradiated at rt for 6h in benzene with xenon UV-lamp for the photolysis and rearrangement to the ketene intermediate which spontaneously cyclized to the γ-lactam **8** (Table 1).[2]

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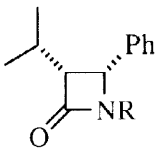
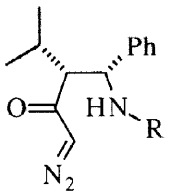
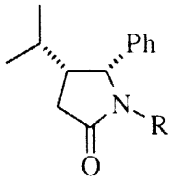
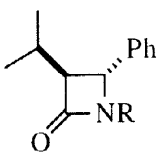
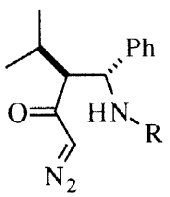
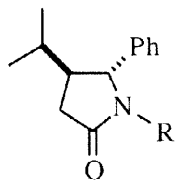
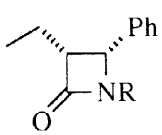
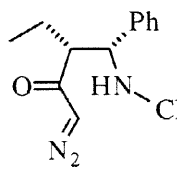
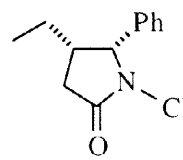
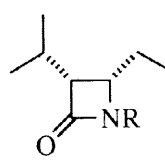
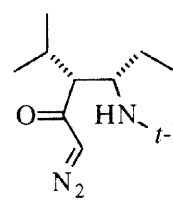
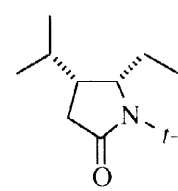
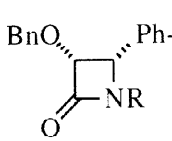
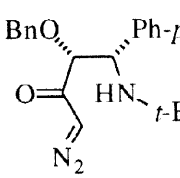
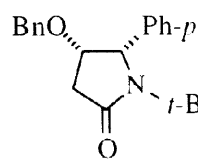
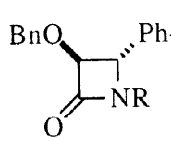
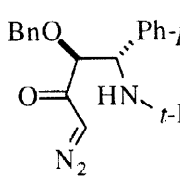
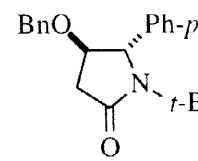
[1] data for **7a**: mp=123-128°C; R_f=0.37 (EtoAc: hexane = 1:2); IR (KBr, cm^{-1}) 2961, 2105, 1712, 1623, 1251; ^{1}H-NMR (300MHz, $CDCl_3$) δ 1.12 (2d, 6H), 2.16(m, 1H), 2.73 (m, 1H), 4.95 (s, 1H), 5.09-5.19 (m, 4H), 7.32-7.38 (m, 10H); ^{13}C-NMR (75MHz, $CDCl_3$) δ 18.5, 21.8, 28.0, 54.7, 56.9, 61.2, 66.9, 127.2, 127.7, 128.1, 128.4, 128.5, 136.1, 140.3, 155.4, 194.0; Anal. Calcd: C, 69.02; N, 11.50; H, 6.34. Found: C, 69.03; N, 11.42; H, 6.21.

[2] data for **8a**: mp=165-167°C; R_f = 0.44 (EtoAc: hexane = 1:2); IR (KBr, cm^{-1}) 2949, 1787, 1723, 1279; ^{1}H-NMR (300MHz, $CDCl_3$) δ 0.78 (d, 3H), 0.87 (d, 3H), 1.08 (m, 1H), 2.30 (m, 1H), 2.60 (m, 2H), 5.06 (d, 1H), 5.16 (d, 1H), 5.24 (d, 1H), 7.12-7.34 (m, 10H); ^{13}C-NMR (75MHz, $CDCl_3$) δ 20.1, 21.0, 27.9, 36.4, 37.6, 45.1, 64.5, 67.8, 127.5, 127.8, 128.0, 128.1, 128.3, 128.5, 135.0, 137.5, 150.7, 173.8; Anal. Calcd: C, 74.75; N, 4.15; H, 6.87. Found: C, 74.75; N, 4.18; H, 6.78.

Table 1. β-Lactam ring expansion to γ-lactams *via* diazoketones

β-Lactam (yield)[a,b]	Diazoketone (yield)[a,b]	γ-Lactam (yield)[a,b]
		
5a R = H **6a** R = Cbz (99%) **6b** R = CO_2Et (99%)	**7a** R = Cbz (81%) **7b** R = CO_2Et (82%)	**8a** R = Cbz (81%) **8b** R = CO_2Et (80%)
		
5b R = H **6c** R = Cbz (99%) **6d** R = CO_2Et (98%)	**7c** R = Cbz (44%) **7d** R = CO_2Et (77%)	**8c** R = Cbz (82%) **8d** R = CO_2Et (75%)
		
5c R = H **6e** R = Cbz (98%)	**7e** (60%)	**8e** (81%)
		
5d R = H **6f** R = *t*-Boc (98%)	**7f** (65%)	**8f** (75%)
		
5e R = H **6g** R = *t*-Boc (99%)	**7g** (61%)	**8g** (62%)
		
5f R = H **6h** R = *t*-Boc (98%)	**7h** (70%)	**8h** (72%)

a: Isolated yields (not optimized) after chromatography on silica gel.
b: All products exhibited spectral (NMR, IR, Mass) data in accord with the assigned structure

In conclusion, we developed a stereospecific method for the ring expansion of β-lactam to γ-lactam through ring opening with the anion of $TMSCHN_2$ followed by photolytic Wolff rearrangement and cyclization. Introduction of substituents and stereochemistry can be preadjusted at the β-lactam stage to prepare the useful pyrrolidines for the synthesis of the alkaloids having nitrogen-containing five-membered rings.

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