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New Fragmentation and Rearrangement Reactions of the Azetidine Ring Promoted by $AlEt_2Cl$

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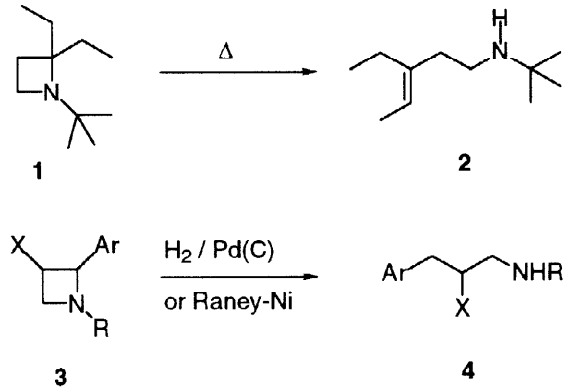
Abstract: Azetidines **6** prepared by AlH_2Cl reduction of easily available β-lactams **5** react with $AlEt_2Cl$ in CH_2Cl_2 solution at room temperature to yield, through new fragmentation or rearrangement reactions of the azetidine ring, either, olefins **7** or bicyclic fused pyrrolidines **8**,depending on the nature of the group bonded to C2 of the four membered ring.

Since the discovery of the β-lactam ring as the essential feature of the β-lactam antibiotics,[1] much has been learned about the chemical reactivity of this four membered heterocycle. Thus, processes of ring opening, fragmentation and rearrangement involving either of the four bonds of the 2-azetidinone ring have been reported,[2] and developed to a synthetically useful level, to prepare different kind of compounds.[3] However, the chemistry of azetidines has been much less investigated. While much of the effort involving the azetidine nucleus have been directed to its synthesis,[4] as it is a component of many biologically active drugs and natural products,[5] few examples of rearrangements or fragmentations of the azetidine ring are known. It has been shown that azetidine **1** forms olefin **2** when heated through a Hoffmann type elimination.[6] Amino alcohols **4** have been obtained by hydrogenolysis of 4-arylazetidines **3**, as well as from bis-azetidines (Scheme 1).[7] Different Pd and Pt complexes are known to promote the azetidine ring breakage to yield diamine complexes,[8] and aliphatic polyamines.[9] Finally, the parent azetidine is broken by heating at 400°C,[10] or by continuos-wave CO_2 laser irradiation,[11] to form *N*-aminomethyl azetidine, and polymethanimine, respectively. We report now two



Scheme 1

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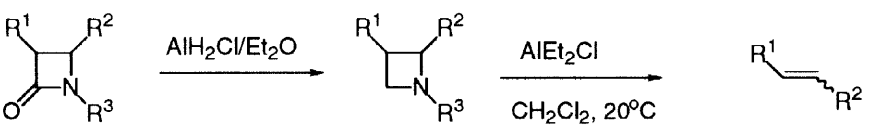
new, hitherto unknown, reactions of the azetidine nucleus, namely its fragmentation to form olefins and its rearrangement to form bicyclic pyrrolidines, promoted by $AlEt_2Cl$.

Azetidines **6** were prepared from easily available[12] β-lactams **5**, following the reduction procedure developed by Ojima.[7] Reaction of compounds **5** with *in situ* generated AlH_2Cl (from $LiAlH_4/AlCl_3$) formed the desired azetidines **6** in fair to good yields (Table 1). Azetidines **6** were reacted with $AlEt_2Cl$ (1M solution in hexanes) in Cl_2CH_2 at RT. Depending on the structure of the starting azetidine, olefins **7** (Table 1) or bicyclic fused pyrrolidines **8** (Scheme 2) were formed as the sole reaction products. Pure compounds were isolated by flash chromatography.[13] Due to extensive decomposition during purification, sensitive vinyl ethers **7a-b** were obtained in fair yields. The stereochemistry of the azetidine was transferred unaltered to the olefin in the cases tested, except for *trans*-azetidine **6d** which gave an *E/Z*-mixture of olefins.[14] The presence of an acetal or thioacetal attached to the position 2 of the four membered ring, produced exclusively fused pyrrolidines **8a-b** as single diastereomers, instead of the expected olefins. Compounds **8a-b** were isolated in fair yields by flash chromatography, extensive decomposition during the isolation process being observed. The bicyclic structure of compounds **8** was established by standard NMR mono- and two-dimensional techniques, and the relative stereochemistry depicted in Scheme 3 was established by NOE measurements. It should be noted that the fragmentation process depicted in Scheme 3, is analogous to the thermal fragmentation of azetidine[12,13] but, in this case, the reaction occurs at room temperature.

Table 1. Synthesis of Azetidines 6 and Products 7



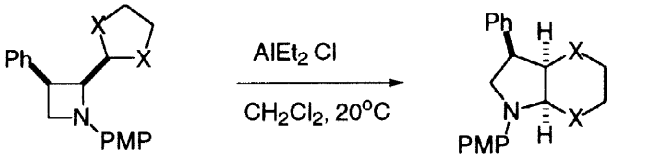
5 **6** **7**

	R^1	R^2	R^3	**Azetidine**	Yield[a]	**Product**	E/Z	Yield[a]
***cis*-5a**	PhO	*p*-$MeOC_6H_4$	Bn	***cis*-6a**	91	**7a**	0:100	57
***cis*-5b**	PhO	Ph	Bn	***cis*-6b**	91	NR[d]	—	—
***cis*-5c**	PhO	*p*-$NO_2C_6H_4$	Bn	***cis*-6c**	91	NR[d]	—	—
***cis*-5d**	PhO	2-Furyl	Allyl	***cis*-6d**	97	**7b**	0:100	58
***trans*-5d**	PhO	2-Furyl	Allyl	***trans*-6d**	85	**7b**	67:33	61
***cis*-5e**	PhO	2-Furyl	Bn	***cis*-6e**	85	**7b**	0:100	53
***cis*-5f**	PhO	2-Furyl	*p*-$MeOC_6H_4$	***cis*-6f**	57	NR[d]	—	—
***trans*-5g**	Ph	*p*-$MeOC_6H_4$	Bn	***trans*-6g**	54	**7c**	100:0	68
***cis*-5h**	Ph	Diox[b]	*p*-$MeOC_6H_4$	***cis*-6h**	55	e		
***cis*-5i**	Ph	Dith[c]	*p*-$MeOC_6H_4$	***cis*-6i**	81	e		

[a] In pure, isolated, material. [b] Diox = 1,3-dioxolan-2-yl. [c] Dith = 1,3-dithiolan-2-yl. [d] NR = No reaction was observed. Unreacted starting azetidine **6** was recovered. [e]In these cases bicycles **8a** and **8b** were obtained. See Text.

To test the requisites to promote the fragmentation reaction, a preliminary study was carried out with azetidines having R^2 groups with different electronic characteristics. Thus, azetidines having *p*-anisyl, **6a**, phenyl, **6b**, and *p*-nitrophenyl, **6c**, groups at the ring C2, and a benzyl group at the nitrogen, were reacted with $AlEt_2Cl$ under the conditions above. While azetidines **6b** and **6c** were unreactive, starting azetidine being recovered unchanged, vinyl ether **7a** was obtained smoothly from azetidine **6a**. These results together with the

successful examples listed in Table 1, which always have an electron donor group R^2, strongly suggest that the ability of the moiety at this position to stabilize a positive charge, is needed for the fragmentation to occur. The influence of the nature of the R^1 group bonded to the azetidine nitrogen was studied next. Azetidine **6f** having a *p*-anisyl group at the nitrogen was unreactive, in spite of the furyl group at C2. The analogous compounds **6d** and **6e**, having an aliphatic substituent attached to the nitrogen, gave the desired olefins in all cases. We can conclude that both an electron donor substituent at C2 and a basic azetidine nitrogen are needed for the fragmentation. The

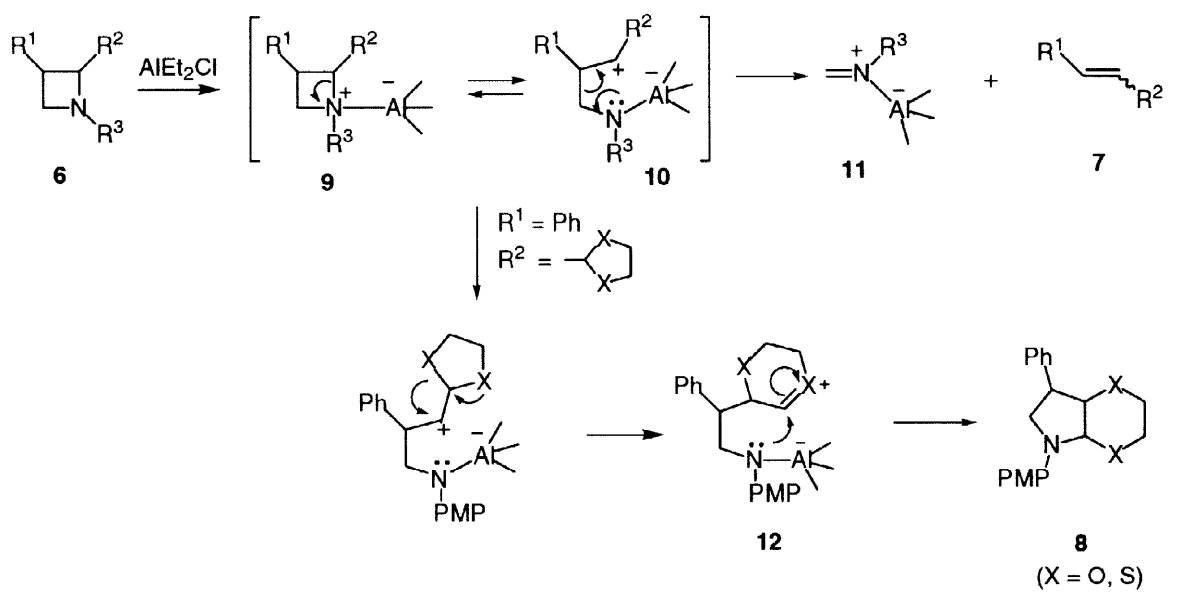


6h X = O PMP = *p*-$MeOC_6H_4$ **8a** X = O (57 %)
6i X = S **8b** X = S (50 %)

Scheme 2

presence of an aliphatic substituent at the nitrogen is not essential for the rearrangement process of azetidines **6h-i**. Both compounds bear a *p*-anisyl group at the azetidine nitrogen, but rearranged smoothly to fused pyrrolidines **8a-b**.

Formation of olefins **7** and fused pyrrolidines **8** may occur by the initial coordination of the lone electron pair of the azetidine nucleus to the $AlEt_2Cl$ to give intermediate **9**. This coordination should promote the C2-N1 bond breakage to form zwitterion **10**.[15] Intermediate **10** may react through two different pathways depending on the nature of the group attached to C2. For electron-donor aryl groups (R^2 = furyl, *p*-anisyl), the C3-C4 bond would break to yield the observed olefin **7**, together with the iminium salt **11**. The presence of an acetal or thioacetal group on C2, promotes the conversion of intermediate **10** to a new carbocation **12**, which is, in turn, trapped intramolecularly by the nitrogen atom, to yield the double rearranged product **8** (Scheme 3). Alternatively, the high selectivity observed in the reactions of azetidines **6** may point to a concerted fragmentation of the aluminium coordinated azetidine **9** to form the reaction products without involvement of chelated or not open-chain zwitterions. According to the proposed reaction pathway, the presence of electron donating groups attached at C2 should promote the formation of the carbon-carbon double bond to give compounds **7**. The strong preference for the rearrangement of the five membered ring in compounds **6h** and **6i** may be due to the increased stability of the new carbocation **12** formed.



Scheme 3

In conclusion, two new fragmentation and rearrangement, highly stereoselective processes, of the azetidine ring have been discovered. Preliminary studies on the electronic requisites for these processes pointed to carbocationic intermediates in the fragmentation process. Research to determine the scope of these new ways of reactivity of the azetidine ring, as well as their potential synthetic applications are now in progress.

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12. β-Lactams **5** were prepared in multigram quantities by standard acid chloride-imine cyclization, and were used as single *cis*- or *trans*-diastereomers through this work.
13. The following experimental procedure for the reaction of azetidine **6a** with $AlEt_2Cl$ is representative: To a solution of 0.08 g (0.2 mmol) of azetidine **6a** in CH_2Cl_2 (6 mL) was added via syringe 0.2 mL (0.2 mmol) of a solution of $AlEtCl_2$ 1M in hexanes. The mixture was stirred under argon at RT for 48 hours. The crude mixture was quenched with cold (0 °C) $NaHCO_3$ (10 mL), and diluted with CH_2Cl_2 (15 mL). The organic layer was dried ($MgSO_4$) and the solvent removed under vacuo. Residues were purified by flash chromatography (AcOEt/hexanes 1/20)) to yield 0.02 g (57%) of olefine **7a**.
14. In all cases the isomer ratio was determined on the ^1H NMR spectra of the crude reaction mixtures *prior to* purification. The *E/Z* stereochemistry of the olefin was assigned from the coupling constants of the vinyl protons (J = 6.6-6.9 Hz for the *Z*-isomer, and J = 12,3-14.3 Hz for the *E*-isomer).
15. 2-Alkoxy azetidines, putative intermediates in the transformation of β-chloroimines to β-(alkylamino)-carbonyl compounds, have been postulated to experiment a related N1-C2 bond breakage, in basic alkoxide media. Sulmon, P.; De Kimpe, N.; Schamp, N. *Tetrahedron* **1989**, *45*, 2937.