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New reactions of functionalized β-lactams*

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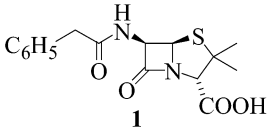
Abstract: An easy synthesis of 4-(1- and 2-haloalkyl)azetidin-2-ones by a [2+2] cycloaddition protocol is described. Starting from these functionalized β-lactams, new pathways toward bicyclic β-lactams were developed via intramolecular nucleophilic substitutions and radical cyclizations. 4-(1- and 2-Haloalkyl)azetidin-2-ones also proved to be very useful starting products in the synthesis of various highly substituted aziridines, azetidines, and alkenoates.

Keywords: β-lactams; aziridines; azetidines; alkenoates; azetines; bicyclic β-lactams.

INTRODUCTION

The chemistry of β-lactams has taken an important place in organic chemistry since the discovery of penicillin **1** by Sir Alexander Fleming in 1928 and shortly thereafter cephalosporin **2**, compounds which were both used as successful antibiotics. Even now, the research in this area is still stimulated by the development of bacterial resistance to widely used antibiotics of this type. There is a continuous need for functionalized β-lactams or for new active principles in the β-lactam series [1]. However, the importance of this specific class of azaheterocycles lies not only in their antibiotic activity. β-Lactams also possess cholesterol absorption inhibitory activities, as well as antithrombotic, antiviral, and antifungal activities [2–5].



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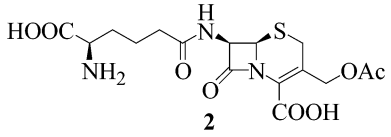

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In the present research, the potential of new halogenated β-lactams as synthons in the synthesis of bicyclic azetidin-2-ones was investigated. Moreover, the incorporation of a halogen in the side chain of different substituted β-lactams gave the potential for ring transformations and specific ring-opening reactions.

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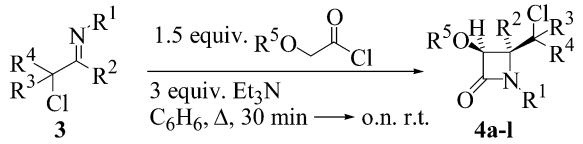
RESULTS AND DISCUSSION

The cycloaddition of ketenes, mostly prepared in situ from acid chlorides and bases, to imines is an established method for the generation of the β-lactam nucleus [6]. Although this reaction has been well developed because of the straightforward approach and wide scope, little is known about the application of halogenated imines in this strategy. α-Haloimines **3** and β-haloimines **5** reacted with different types of acid chlorides in benzene in the presence of triethylamine to generate the intermediate ketenes. [2+2]-Cycloaddition of the in situ generated ketenes with the appropriate imines yielded the corresponding new β-lactams **4** and **6**, respectively. The general usefulness has been demonstrated by application of this methodology to numerous α-haloimines **3** (Table 1) and β-haloimines **5** (Table 2).

Table 1 Reaction of α-haloimines **3** with acetyl chlorides toward 4-(1-haloalkyl)-azetidin-2-ones **4**.

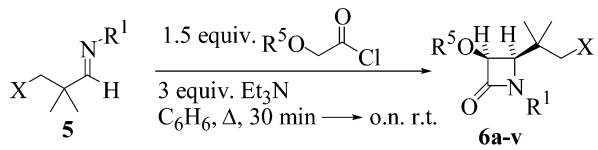


3 **4a-l**

Compound	R^1	R^2	R^3	R^4	R^5	Yield (%)[a]
4a	iPr	H	Me	Me	Bn[c]	82
4b	cHex	H	Me	Me	Bn	79
4c	allyl	H	Me	Me	Bn	97
4d	Et	H	Me	Me	Bn	85
4e	PMP[b]	H	Me	Me	Bn	65
4f	iPr	H	Me	Me	C_6H_5	60
4g	allyl	H	Me	Me	C_6H_5	85
4h	iPr	H	Me	Me	OMe	72
4i	cHex	H	Me	Me	OMe	82
4j	allyl	H	Me	Me	OMe	65
4k	iPr	Me	Me	Me	Bn	50
4l	iPr	Me	Cl	H	Bn	84

[a]Yield after purification by flash chromatography or recrystallization.
[b]PMP = 4-methoxyphenyl.
[c]Bn = $CH_2C_6H_5$.

Table 2 Reaction of β-haloimines **5** with acetyl chlorides toward 4-(2-haloalkyl)-azetidin-2-ones **6**.

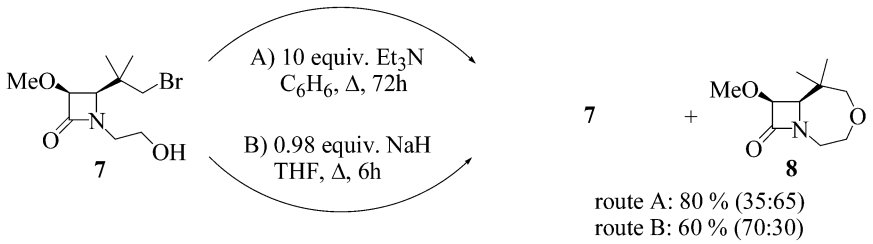


5 **6a-v**

Compound	R^1	X	R^2	Yield (%)[a]
6a	iPr	Cl	Bn[c]	70
6b	cHex	Cl	Bn	65
6c	allyl	Cl	Bn	97
6d	allyl	Cl	C_6H_5	45
6e	iPr	Cl	Me	73
6f	allyl	Cl	Me	68
6g	iPr	Br	Bn	75
6h	cHex	Br	Bn	99
6i	allyl	Br	Bn	90
6j	Et	Br	Bn	75
6k	*n*-Pr	Br	Bn	67
6l	$CH_2CHCHC_6H_5$	Br	Bn	78
6m	iPr	Br	Me	76
6n	allyl	Br	Me	90
6o	Et	Br	Me	61
6p	CH_2CH_2Br	Br	Me	77
6q	CH_2CH_2OBn	Br	Me	85
6r	$CH_2CHCHC_6H_5$	Br	Me	63
6s	$CH_2C(CH_3)CH_2$	Br	Me	90
6t	$C(CH_2CH_2)CHCH_2$	Br	Me	77
6u	$CH(C_6H_5)CHCH_2$	Br	Me	90
6v	iPr	Br	Phth[b]	76

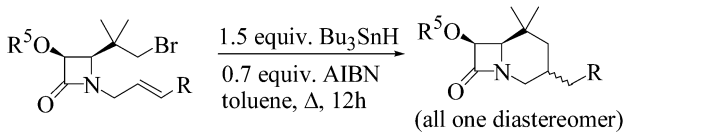
[a]Yield after purification by flash chromatography or recrystallization.
[b]Phth = phtalimidoyl.
[c]Bn = $CH_2C_6H_5$.

The first approach toward the synthesis of bicyclic β-lactams started from *N*-(2-hydroxyethyl)azetidin-2-on **7**, which was synthesized by hydrogenolysis of the corresponding *N*-(2-benzyloxyethyl)azetidin-2-on. β-Lactam **7** was treated with triethylamine in benzene or with sodium hydride in tetrahydrofuran, leading in both cases to a reaction mixture of the starting material **7** and the bicyclic compound **8** (Scheme 1). Separation of both compounds by means of flash chromatography proved to be difficult. More forced reaction conditions did not lead toward complete conversion of the starting material. In the case of triethylamine, the same results as before were obtained, while a longer reflux period in the presence of sodium hydride led to decomposition. This may result from the difficult substitution of the bromine at a neopentylic position.



Scheme 1

In a second approach, bicyclic β-lactams were synthesized via radical cyclizations of 4-(2-bromo-1,1-dimethylethyl)azetidin-2-ones **9**. This method led to the formation of carbacephams **10** as the sole isolated products, besides the recovery of approximately 20–30 % of starting material **9** (Scheme 2). Although both 6-*exo-trig* and 7-*endo-trig* are favored processes according to Baldwin's rules [7], the only product formed in this reaction results from 6-*exo-trig* cyclization. Moreover, compounds **10** were obtained as single diastereomers. The exact stereochemistry at the C3 carbon atom of 1-azabicyclo[4.2.0]octan-8-ones **10** was not established yet. Attempts to perform nuclear Overhauser effect (NOE) experiments on the latter compounds did not reveal the exact configuration of the C3-epimer since most of the necessary proton signals were overlapping and selective irradiation proved to be impossible.

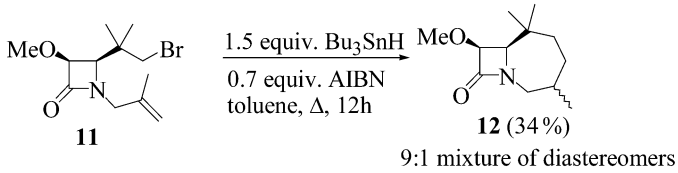


9a R^5= Bn, R= H
9b R^5= Bn, R= C_6H_5
9c R^5= Me, R= H
9d R^5= Me, R= C_6H_5

10a R^5= Bn, R= H (35 %)
10b R^5= Bn, R= C_6H_5 (38 %)
10c R^5= Me, R= H (35 %)
10d R^5= Me, R= C_6H_5 (30 %)

Scheme 2

Application of the same reaction conditions to *N*-(2-methylallyl)-azetidin-2-one **11** led unexpectedly to the formation of the 7-*endo-trig* product, i.e., 8-methoxy-3,6,6-trimethyl-1-azabicyclo[5.2.0]nonan-9-one **12** (Scheme 3). This product was obtained as a 9 to 1 mixture of diastereomers. Apparently, incorporation of an additional substituent at the 2-position of the *N*-substituent can provide a directing effect between 6-*exo-trig* and 7-*endo-trig* cyclization.

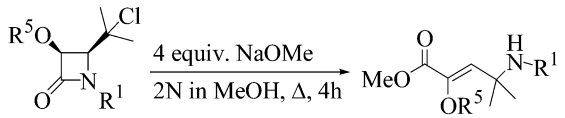


Scheme 3

β-Lactams have been widely applied in the synthesis of various classes of compounds, since ring opening of 2-azetidinones gave immediate access to nonproteogenic β-amino acids and further on to peptides [8]. The ring opening of β-lactams by nucleophiles is well studied [9], and the application of this methodology to 4-(1-haloalkyl)-2-azetidinones **4** and 4-(2-haloalkyl)-2-azetidinones **6** may lead to

ring transformation. Functionalized aziridines should be accessible from 4-(1-chloro-1-methylethyl)-2-azetidinones **4**, while functionalized azetidines should be accessible from 4-(2-chloro-1,1-dimethylethyl)-2-azetidinones and 4-(2-bromo-1,1-dimethylethyl)-2-azetidinones **6**. The results obtained in this area are summarized hereafter [10].

4-(1-Chloro-1-methylethyl)-2-azetidinones **4** were treated with an excess of a 2N sodium methoxide in methanol at reflux temperature for 4 h (Scheme 4). In the reaction mixtures, no cyclized products, i.e., aziridines, could be detected, but only ring-opened products (*Z*)-**13** were isolated and purified by flash chromatography. Intermediate workup of the reaction (e.g., after 1 h) resulted in the isolation of a mixture of 4-(1-chloro-1-methylethyl)-2-azetidinones **4** and reaction products **13**, pointing to a straightforward conversion.



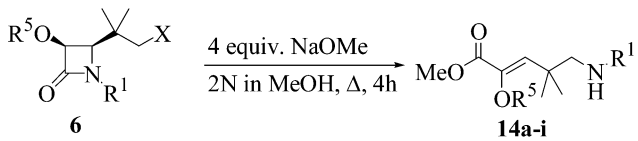
4a R^1= iPr, R^5= Bn
4b R^1= allyl, R^5= Bn
4c R^1= iPr, R^5= Me

13a R^1= iPr, R^5= Bn (65 %)
13b R^1= allyl, R^5= Bn (60 %)
13c R^1= iPr, R^5= Me (55 %)

Scheme 4

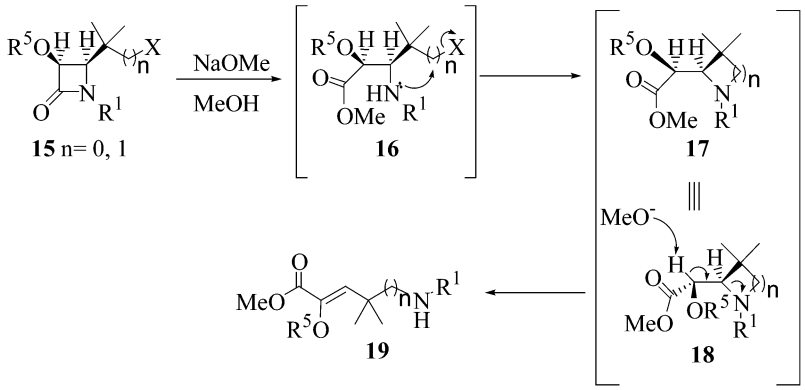
Similar observations as for 4-(1-chloro-1-methylethyl)-2-azetidinones **4** were obtained for 4-(2-halo-1,1-dimethylethyl)-2-azetidinones **6**. Also in this case, the only products obtained were the ring-opened (*Z*)-methyl-2-alkoxy-4,4-dimethyl-5-(alkylamino)-pent-2-enoates **14** (Table 3). The proposed reaction mechanism starts with nucleophilic attack of sodium methoxide at the amide functionality of β-lactam **15**, resulting in ring opening (Scheme 5). The secondary amine thus formed attacks then the halogenated carbon leading to ring closure by intramolecular nucleophilic substitution. The ring-closed products **17** are the originally expected aziridine (n = 0) and azetidine (n = 1) derivatives. However, in the presence of excess sodium methoxide, deprotonation at the α-position of the ester **17** occurs and *anti* elimination leads unexpectedly to the stereospecific formation of alkenoates **19**. The ring opening by this mechanism is quite understandable for the more strained aziridines **17** (n = 0), while this result is surprising for the more stable azetidines **17** (n = 1). To the best of the authors' knowledge, no similar ring opening of *N*-alkyl functionalized azetidines has been reported.

Table 3 Synthesis of (*Z*)-methyl-2-alkoxy-4,4-dimethyl-5-(alkylamino)-pent-2-enoates **14**.



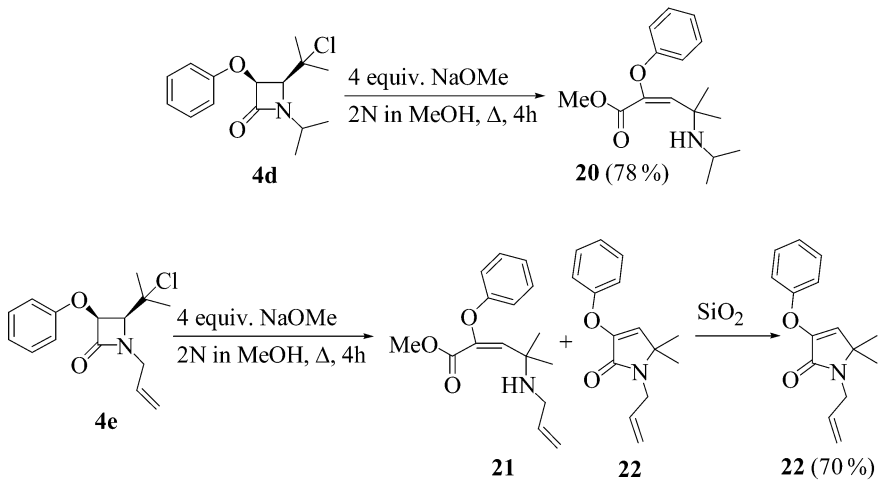
Compound	R^1	R^5	X	Yield (%)[a]
14a	iPr	Bn	Cl or Br	65
14b	Et	Bn	Br	66
14c	allyl	Bn	Cl or Br	60
14d	*n*-Pr	Bn	Cl or Br	75
14e	iPr	Me	Cl or Br	68
14f	allyl	Me	Cl or Br	70
14g	Et	Me	Br	50
14h	$CH_2CHCHC_6H_5$	Me	Br	68
14i	$CH_2(CH_3)CCH_2$	Me	Br	45

[a]Yields after purification by flash chromatography.



Scheme 5

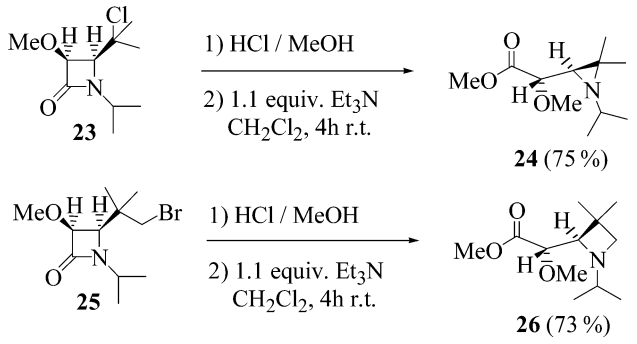
According to the reaction mechanism, the products obtained should be the *Z*-alkenoates **19**, if no isomerization of the carbanionic center occurs during the reaction. Experimentally obtained products consisted of one isomer exclusively, and the geometry was firmly established by the performance of NOE experiments on derivatives **14**. These experiments clearly showed the proximity between the benzylic CH_2 (cf. **14**, R^5 = Bn) and methoxy protons (cf. **14**, R^5 = Me) and the geminal dimethyl group (3.0 and 2.0 %, respectively). The olefinic protons of the 4-(alkylamino)- and 5-(alkylamino)pentenoates **13** and **14** all appear in the range of 6.13–6.25 ppm in ^{1}H NMR ($CDCl_3$, 270 MHz). Because of all these facts, also alkenoates **13** were assumed to possess the *Z*-geometry. However, additional evidence for this geometry was found in the reaction of 3-phenoxy-β-lactams **4d** and **4e** with sodium methoxide in methanol (Scheme 6).



Scheme 6

Reacting azetidin-2-one **4d** with excess 2N sodium methoxide in methanol for 4 h under reflux led to the formation of a ring-opened product, similar to the previously isolated compounds **13**. However, the chemical shift of the double-bond proton of this product was higher than for compounds **13**, i.e., 6.60 ppm ($CDCl_3$, 270 MHz). When the same reaction was performed with 1-allyl-2-azetidinone **4e**, a mixture of two compounds was obtained. One compound was also believed to be the ring-opened product **21** because of the appearance of the double-bond proton at 6.55 ppm ($CDCl_3$, 270 MHz). The main product, however, was pyrrolidinone **22**, derived from the *E*-isomer **21** after ring closure. The ratio **21**:**22** in the reaction mixture was 1:3, based on signal integration of the double-bond protons in the ^{1}H NMR spectrum. Although (*E*)-methyl 4-(allylamino)-4-methyl-2-phenoxypent-2-enoate **21** was clearly present in the reaction mixture, after flash chromatography only the cyclized 1-allyl-5,5-dimethyl-3-phenoxy-pyrrolinone **22** could be isolated in 70 % yield. Apparently, in the case of the 3-phenoxy substitution at the β-lactams **4**, isomerization took place during the reaction, which led to the formation of the corresponding *E*-alkenoates. Stopping the reaction before completion gave no clear indication of this epimerization. Previously, ring opening of 3-azido-4-chloroazetidin-2-ones with sodium methoxide gave rise to the formation of the corresponding α,β-unsaturated β-aminoesters as a mixture of *E*- and *Z*-isomers [11]. However, it is not clear from these data which stereochemistry was involved in the starting materials.

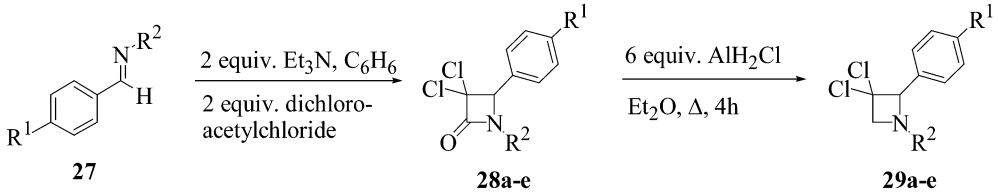
Attempts were made to block the rearrangement of 4-(1-haloalkyl) and 4-(2-haloalkyl)-2-azetidinones at an intermediate stage using acidic methanolysis. Gaseous hydrogen chloride was bubbled through a solution of 2-azetidinones **23** and **25** in methanol. This reaction mixture was kept in a closed vessel during 24 h and methanol was subsequently evaporated. The intermediate salt was not characterized, but was taken up in dichloromethane and stirred in the presence of triethylamine for 4 h at room temperature. The resulting aziridine **24** and azetidine **26** were isolated in 75 and 73 % yield, respectively (Scheme 7).



Scheme 7

In a last part of this research, 3,3-dichloroazetidin-2-ones were evaluated as starting products toward 3,3-dichloroazetidines. These compounds form interesting synthetic targets since remarkably little is known about the synthesis and reactivity of these compounds. Azetidines in general constitute an important class of azaheterocycles, exhibiting a wide range of biological activities [12]. 2-Aryl-3,3-dichloroazetidin-2-ones were prepared by cycloaddition of different arylaldimines with dichloroketene, derived from dichloroacetyl chloride and triethylamine, in good yields. Reduction of β-lactams has been performed with a variety of reducing agents, including diisobutyl aluminum hydride [13], monochloroalane, dichloroalane [14], and lithium aluminum hydride [15]. The reduction with chloroalanes has already proven to be a powerful method, and also in the case of 3,3-dichloroazetidin-2-ones **28**, this became the method of choice. The latter compounds were very cleanly converted to 3,3-dichloroazetidines **29** by reaction with monochloroalane in ether for 4 h at reflux temperature, affording the latter compounds pure after aqueous workup of the reaction mixture (Table 4).

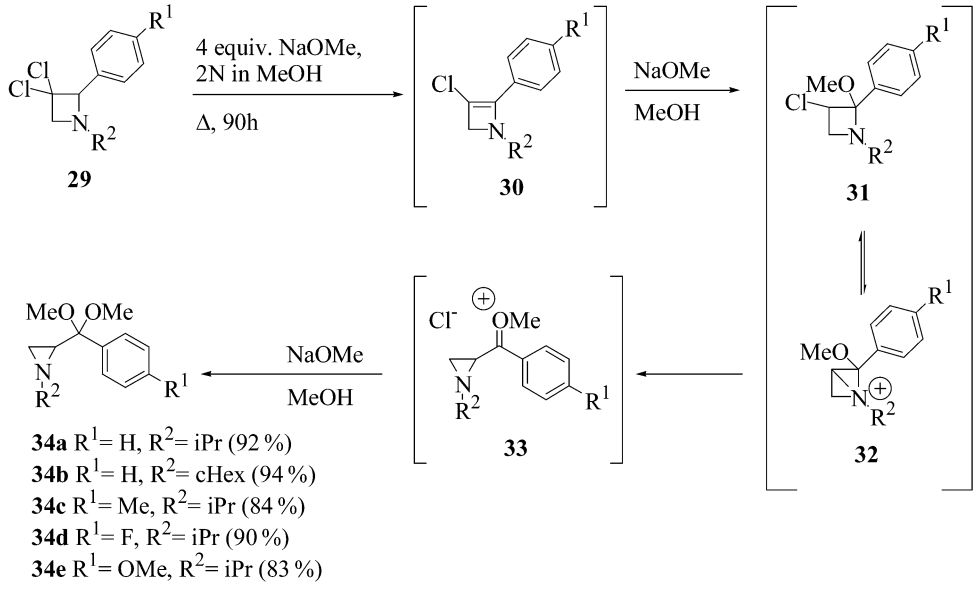
Table 4 Synthesis of 4-aryl-3,3-dichloroazetidin-2-ones **28** and 2-aryl-3,3-dichloroazetidin-2-ones **29**.



Compound	R^1	R^2	Yield of **28** (%)[a]	Yield of **29** (%)[a]
a	H	iPr	71	97
b	H	cHex	84	98
c	Me	iPr	70	82
d	F	iPr	86	95
e	OMe	iPr	77	90

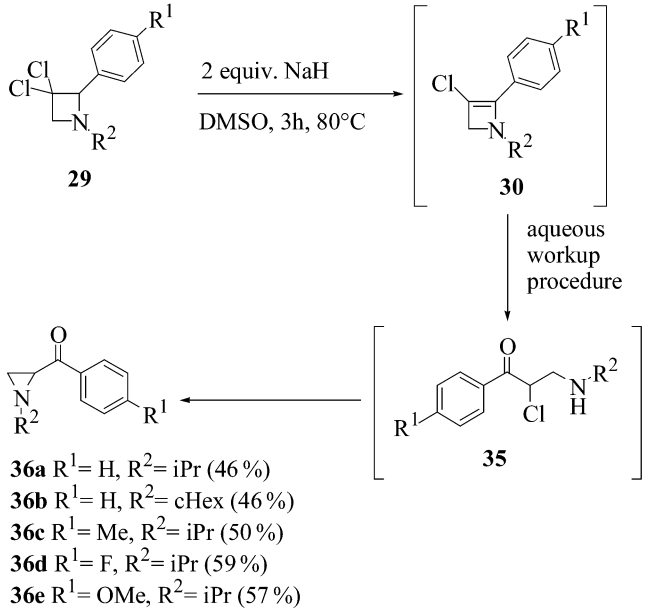
[a]Yield after purification by flash chromatography.

For investigation of the reactivity of the resulting 3,3-dichloroazetidines, these compounds were treated with 4 equiv of 2N NaOMe in MeOH at reflux. The 3,3-dichloroazetidines converted rather slowly to 2-[dimethoxy(phenyl)methyl]-aziridines **34**. The reaction mixture is believed to occur via the intermediate 2-azetines **30** (Scheme 8). The conversion of 3,3-dichloroazetidines **29** into aziridines **34** proceeds via elimination of hydrogen chloride, generating the strained heterocyclic enamine **30**. Addition of methanol and expulsion of a chloride anion by the nitrogen lone pair generates the bicyclic aziridinium intermediate **32**, which opens to give the aziridine derivative **34**.



Scheme 8

To explore further the reactivity of 2-aryl-3,3-dichloroazetidines **29**, reactions with sodium hydride in dimethyl sulfoxide were performed, and aziridines **36** were obtained (Scheme 9). These reactions gave another indication of the intermediacy of the strained 2-azetines **30**, because the formation of the reaction products **36** can be rationalized by an elimination reaction toward 2-azetines **30**, followed by hydrolysis of this intermediate by the aqueous workup procedure. The 2-chloro-3-(alkylamino)-1-aryl-1-propanone derivatives **35** thus formed cyclized spontaneously to the aziridines **36**. The lower yields of the aziridines **36** are due to the unstability of these azaheterocycles during the purification by flash chromatography over silica gel.



Scheme 9

In summary, 4-(2-haloalkyl)azetidin-2-ones have been proven to be useful starting products in the synthesis of bicyclic β-lactams via different intramolecular nucleophilic substitutions and radical cyclizations. Reaction of 4-(1- and 2-haloalkyl)azetidin-2-ones with sodium methoxide resulted in ring opening of the azetidinone and subsequent ring closure to intermediate aziridines and azetidines which suffered further ring opening, leading to the corresponding alkenoates. The rearrangement of the 4-(haloalkyl)azetidin-2-ones can be blocked by performing the methanolysis in acidic medium, affording the corresponding aziridines and azetidines. Furthermore, 3,3-dichloroazetidin-2-ones could be converted into 3,3-dichloroazetidines by reduction with monochloroalane. Treatment of the latter compounds with sodium methoxide in methanol or sodium hydride in dimethyl sulfoxide gave rise to the formation of intermediate 2-azetines, which ring opened toward aziridines.

ACKNOWLEDGMENTS

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