Pure Appl. Chem., Vol. 82, No. 9, pp. 1749–1759, 2010.
doi:10.1351/PAC-CON-09-09-39

Use of functionalized β-lactams as building blocks in heterocyclic chemistry*

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Abstract: β-Lactams represent flexible building blocks suitable for the preparation of a large variety of nitrogen-containing target compounds. In the present study, the formerly neglected synthetic potential of 4-haloalkyl-β-lactams has been elaborated in detail with a focus on the preparation of different mono- and bicyclic heterocycles. A first approach involved ring transformations of these halogenated building blocks toward stereodefined aziridines, azetidines, pyrrolidines, and piperidines via intermediate aziridinium or azetidinium ions. In a second part, novel and stereoselective entries into 1,4- and 3,4-fused bicyclic β-lactams were developed through either a radical or an ionic cyclization protocol. Furthermore, the ring enlargement of halogenated β-lactams into functionalized mono- and bicyclic pyrrolidin-2-ones was established as the aza-analog of the cyclobutylmethylcarbenium ion to cyclopentylcarbenium ion rearrangement. Finally, chiral versions toward azetidin-2-ones and ring transformation products were elaborated, involving the synthesis of 3(*S*)-alkoxy-4(*S*)-[1(*S*)-chloroethyl]azetidin-2-ones and the preparation of bicyclic β-lactams annelated to piperazines, morpholines, and diazepanes.

Keywords: azetidines; aziridines; β-lactams; γ-lactams; piperidines; pyrrolidines; stereoselectivity.

INTRODUCTION

The class of β-lactam antibiotics is generally recognized as a cornerstone of human health care due to the unparalleled clinical efficacy and safety of this type of antibacterials [1]. For example, the world antibiotics market is dominated by Augmentin, a combination of amoxicillin **1** and potassium clavulanate **2**, produced by GlaxoSmithKline. Nevertheless, the recent appearance of highly resistant bacteria profoundly challenges the way medicinal chemists contemplate innovation of the β-lactam structure and corroborates the need for continuous efforts within this field of research.

Besides their biological relevance as potential antibiotics, β-lactams have also acquired a prominent place in organic chemistry as synthons for further elaboration [2,3]. In this way, the azetidin-2-one framework has already demonstrated its utility for the construction of a wide variety of novel (aza)heterocyles, which can serve as lead compounds for the development of new biologically relevant targets.

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*Paper based on a presentation at the 22nd International Congress on Heterocyclic Chemistry (ICHC-22), 2–7 August 2009, St. John's, Newfoundland and Labrador, Canada. Other presentations are published in this issue, pp. 1735–1853.

†Aspirant of the Fund for Scientific Research Flanders (FWO-Vlaanderen).

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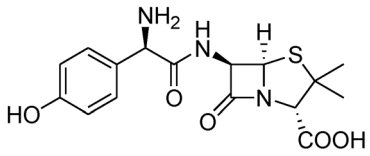
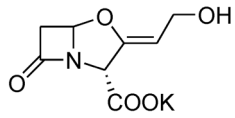


1
Amoxicillin



2
Potassium Clavulanate

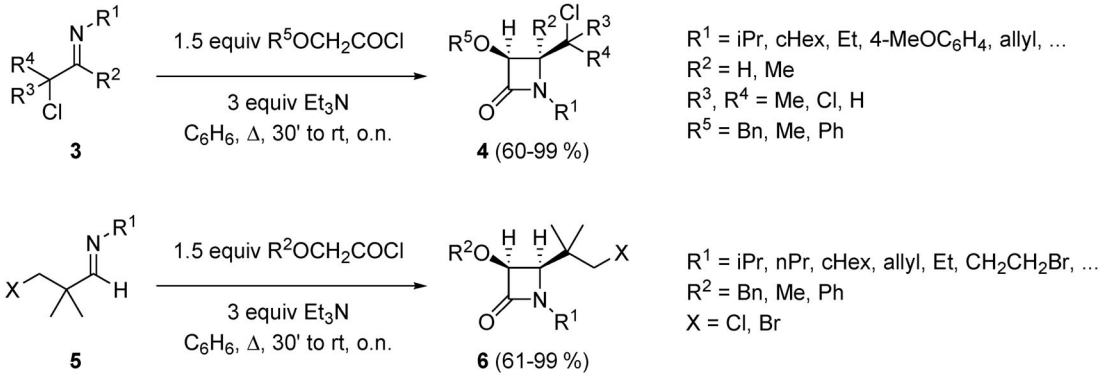
Within drug discovery and medicinal chemistry, the introduction of structural diversity and novelty is of primordial importance in order to cope with the emerging bacterial resistance. In that context, a suitable synthetic strategy toward novel organic compounds comprises a non-target direct approach starting from well-designed, easily accessible, and versatile building blocks. Indeed, the elaboration of such substrates incontestably results in a rich chemistry, giving access to multiple classes of new compounds with great diversity of functionalities.

In the present paper, the applicability of the mainly unexplored class of 4-(haloalkyl)azetidin-2-ones is surveyed based on different synthetic protocols leading to the preparation of a large variety of novel heterocyclic compounds and β-amino acid derivatives.

SYNTHESIS OF 4-(HALOALKYL)AZETIDIN-2-ONES

In continuation of our efforts regarding the synthesis and transformation of novel β-lactam scaffolds, the evaluation of a new class of functionalized azetidin-2-ones bearing halogenated side chains was contemplated. The interest in these types of substrates is due to the potential elaboration of their high intrinsic reactivity, which is based on the combination of a strained four-membered ring system, a nucleophilic nitrogen (or obtained after further elaboration), and an electrophilic center in the side chain.

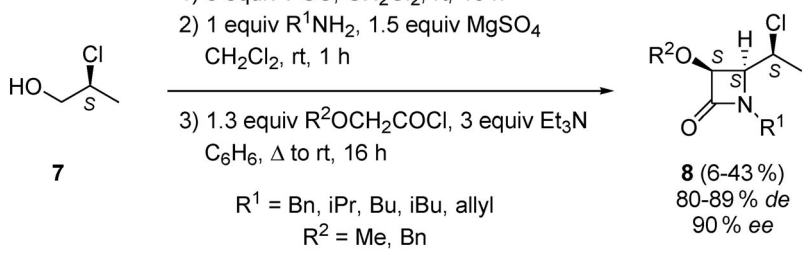
In particular, the synthesis of 4-haloalkyl-β-lactams was devised, in which the halogen atom resides in β- or γ-position with respect to the nitrogen atom [4]. Thus, cyclocondensation of Bose–Evans ketenes generated from phenoxy-, methoxy- or benzyloxyacetyl chloride in the presence of a base, and α-chloroimines **3**, prepared through α-chlorination of the corresponding imines using *N*-chlorosuccinimide in CCl_4 [5] or via imination of α-chloroketones or α-chloroaldehydes with primary amines in the presence of titanium(IV) chloride as water scavenger [6], afforded the corresponding *cis*-4-(1-chloroalkyl)azetidin-2-ones **4** in high yields (Scheme 1). Accordingly, β-haloimines **5** were synthesized via condensation of 3-halo-2,2-dimethylpropanal with the corresponding amine [7], and treated with appropriate ketenes to furnish *cis*-4-(2-halo-1,1-dimethylethyl)-β-lactams **6** (Scheme 1). It should be



Scheme 1 Synthesis of β-lactams **4** and **6**.

noted that the Staudinger synthesis of β-lactams **4** and **6** proceeded in a highly diastereoselective way, which can be attributed to the electron-donating alkoxy- or phenoxy group present in Bose–Evans ketenes, favoring direct conrotatory ring closure of the Zwitterionic intermediates toward the corresponding kinetic products [8].

In recent years, the introduction of chirality has become a key issue and challenge in medicinal chemistry. Consequently, the development of chiral approaches (often catalytic methodologies) toward β-lactams has gained much interest and has become the topic of intensive research. The Staudinger reaction, using either a chiral ketene or a chiral imine, is generally acknowledged as the method of choice for the asymmetric synthesis of β-lactams [9]. In light of the successful use of chiral α-oxy and α-amino substituted aldehydes for the stereoselective synthesis of β-lactams, the application of chiral α-chloroimines was evaluated as a potential tool useful for the synthesis of chiral 4-(1-chloroalkyl)-β-lactams in a convenient way. The attainability of the concept was first evaluated using racemic substrates, resulting in a racemic mixture of (*S*,*S*,*S*)- and (*R*,*R*,*R*)-4-(1-chloroethyl)-4-methyl-β-lactams **4** (R^2 = Me, R^3 = Me, R^4 = H) in excellent diastereomeric excess starting from the appropriate α-chloroketimines **3** (Scheme 1). The relative configuration of these 4-methylazetidin-2-ones **4** was confirmed by X-ray analysis of one derivative. Based on these encouraging results, an asymmetric version using chiral α-haloimines was developed. To obtain 4-(1-chloroethyl)azetidin-2-ones **8**, 2(*S*)-chloro-1-propanol **7** was chosen as substrate for oxidation with pyridinium chlorochromate (PCC) to 2(*S*)-chloropropanal, further imination with primary amines and Staudinger reaction. In this way, chiral 4-(1-chloroethyl)azetidin-2-ones **8** were prepared for the first time in a one-pot synthesis in high diastereomeric excess (80–89 %) and overall yields of 19–43 % (except for the 3-methoxy derivative in 6 %) (Scheme 2) [10]. The enantiomeric excess was shown to be 90 % through coupling of β-lactam **8** (R^1 = Bu, R^2 = Bn) with (*R*)-α-methoxy-α-trifluoromethyl phenylacetic acid and subsequent GC analysis.



Scheme 2 Synthesis of β-lactams **8**.

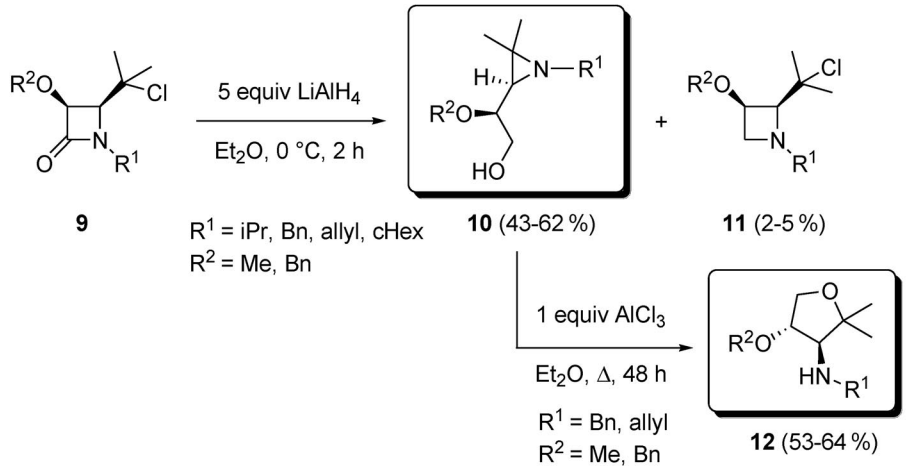
SYNTHETIC APPLICATIONS OF 4-(HALOALKYL)AZETIDIN-2-ONES

4-Haloalkyl-β-lactams are ideally suited for the synthesis of stereodefined aziridines, azetidines, pyrrolidines, and piperidines due to the reactive combination of a constrained ring system, a halogenated carbon atom, and a nucleophilic nitrogen, either present or to be generated.

Upon choice of the substrate and through variation of the reactions conditions, the inherent reactivity can be tuned at will in order to prepare different azaheterocyclic compounds.

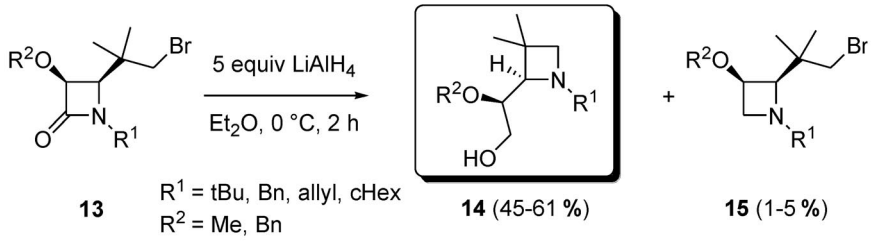
A first example involved the diastereoselective synthesis of functionalized aziridines and azetidines via reduction of 4-(1- or 2-haloalkyl)azetidin-2-ones. Treatment of the latter compounds with $LiAlH_4$ gave 1,2-fission of the β-lactam nucleus resulting in a lithium amide, followed by intramolecular substitution of the halogen atom giving rise to the formation of 2-(1-alkoxy-2-hydroxyethyl)aziridines or -azetidines, respectively [11]. Thus, treatment of 4-(1-chloro-1-methylethyl)azetidin-2-ones **9** with $LiAlH_4$ in diethyl ether at 0 °C for 2 h afforded 2-(1-alkoxy-2-hydroxy-

ethyl)aziridines **10** in 43–62 % yield, next to a small fraction of azetidines **11** in 2–5 % yield (Scheme 3). This transformation proceeded with retention of stereochemistry, as defined during the Staudinger synthesis of β-lactams **9**. The synthetic relevance of 2-(1-alkoxy-2-hydroxyethyl)aziridines **10** was demonstrated by means of their transformation into the corresponding *trans*-3,4-disubstituted oxolanes **12** via an intramolecular nucleophilic ring opening, triggered by the addition of $AlCl_3$ in diethyl ether under reflux for 48 h (Scheme 3).



Scheme 3 Synthesis of aziridines **10** and oxolanes **12**.

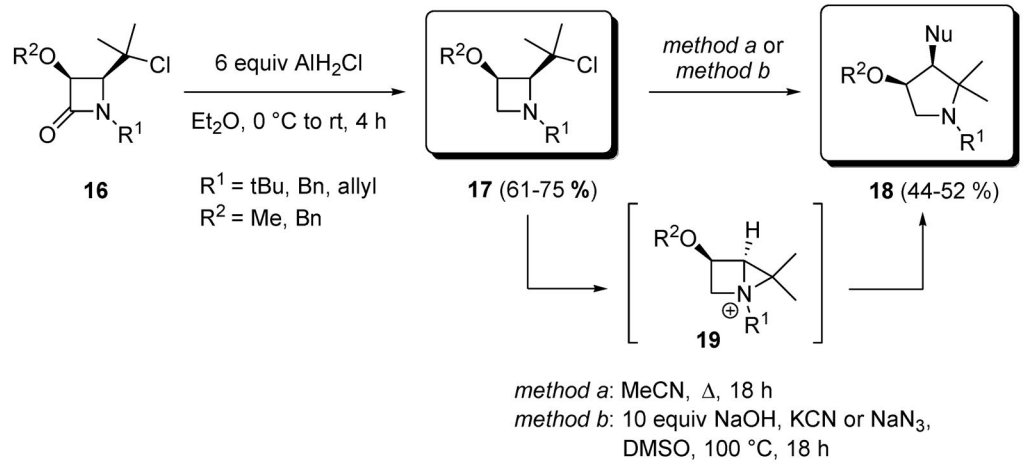
In analogy, treatment of 4-(2-bromo-1,1-dimethylethyl)azetidin-2-ones **13** with $LiAlH_4$ in diethyl ether at 0 °C for 2 h resulted in 2-(1-alkoxy-2-hydroxyethyl)azetidines **14** in 45–61 % yield, next to small amounts of *cis*-4-(2-bromoalkyl)azetidines **15** (1–5 %) (Scheme 4) [11]. Again, the relative stereochemistry of azetidin-2-ones **13** was transferred through the reaction sequence, affording azetidines **14** in a stereoselective way.



Scheme 4 Synthesis of azetidines **14**.

In a second approach, the nucleophilicity of the ring nitrogen atom was exploited prior to ring opening of the four-membered scaffold. This methodology is based on the reduction of the β-lactam carbonyl moiety without cleavage of the amide bond in order to enhance the nucleophilicity of the ring nitrogen, followed by displacement of the halide by the nucleophilic nitrogen lone pair toward a reactive bicyclic azetidinium intermediate.

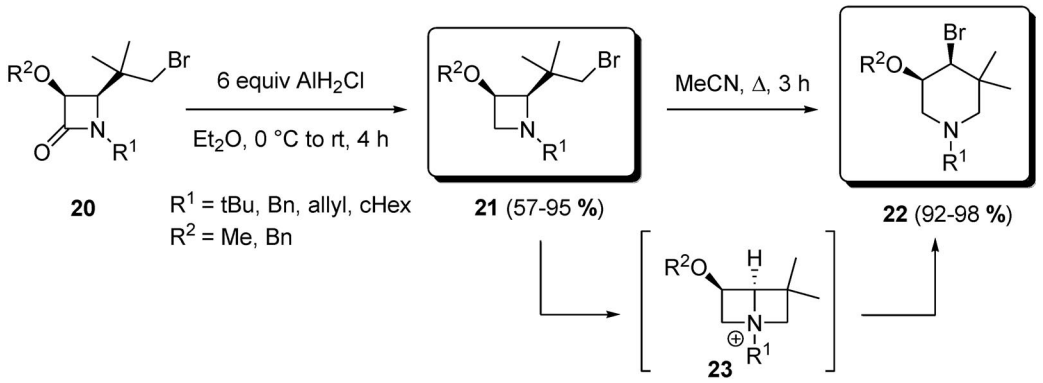
Treatment of 4-(1-chloro-1-methylethyl)azetidin-2-ones **16** with monochloroalane (AlH_2Cl), prepared in situ from $LiAlH_4$ and $AlCl_3$, in diethyl ether at 0 °C furnished the corresponding 2-(1-chloro-1-methylethyl)azetidines **17** in good yields (Scheme 5). Furthermore, the latter azetidines **17** proved to



Scheme 5 Synthesis of azetidines **17** and pyrrolidines **18**.

be very useful starting materials for rearrangements toward stereospecifically defined 3,4-*cis*-disubstituted pyrrolidines. Indeed, when 2-(1-chloro-1-methylethyl)azetidines **17** were heated in acetonitrile under reflux, 3-chloropyrrolidines **18** were obtained in 44–46 % yield (method a, Nu = Cl, Scheme 5) [12]. Alternatively, several other nucleophiles were used successfully, affording 3-hydroxy-, 3-cyano-, or 3-azidopyrrolidines **18** in 44–52 % yield upon treatment of azetidines **17** with NaOH, KCN, or NaN_3 in DMSO at 100 °C for 18 h (method b, Nu = OH, CN, N_3, Scheme 5). The *cis*-stereochemistry of the pyrrolidines **18** was confirmed through nuclear Overhauser effect (nOe) experiments and analysis of vicinal coupling constants, and was consistent with a reaction mechanism involving the formation and consecutive ring opening of bicyclic azetidinium salts **19** (Scheme 5).

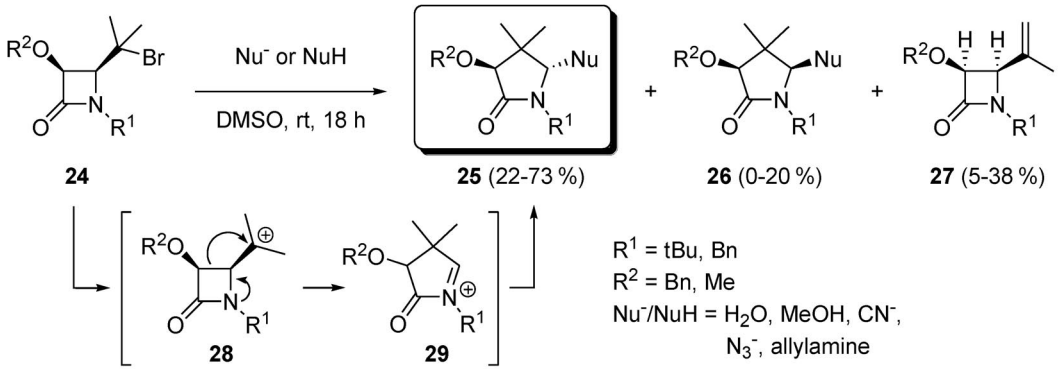
The same methodology, i.e., carbonyl to methylene reduction followed by ring transformation, was applied on 4-(2-bromo-1,1-dimethylethyl)azetidin-2-ones **20**. Treatment of the latter β-lactams **20** with monochloroalane in diethyl ether afforded 2-(2-bromo-1,1-dimethylethyl)azetidines **21**, which were subsequently transformed into *cis*-3-alkoxy-4-bromopiperidines **22** in excellent yields through reflux in acetonitrile for 3 h (Scheme 6) [12]. The observed *cis*-stereochemistry was rationalized considering the in situ formation of a bicyclic azetidinium intermediate **23**, which is prone to ring opening by the nucleophilic counter-ion, i.e., bromide, at the bridgehead carbon atom in a S_N2 fashion. It should be



Scheme 6 Synthesis of azetidines **21** and piperidines **22**.

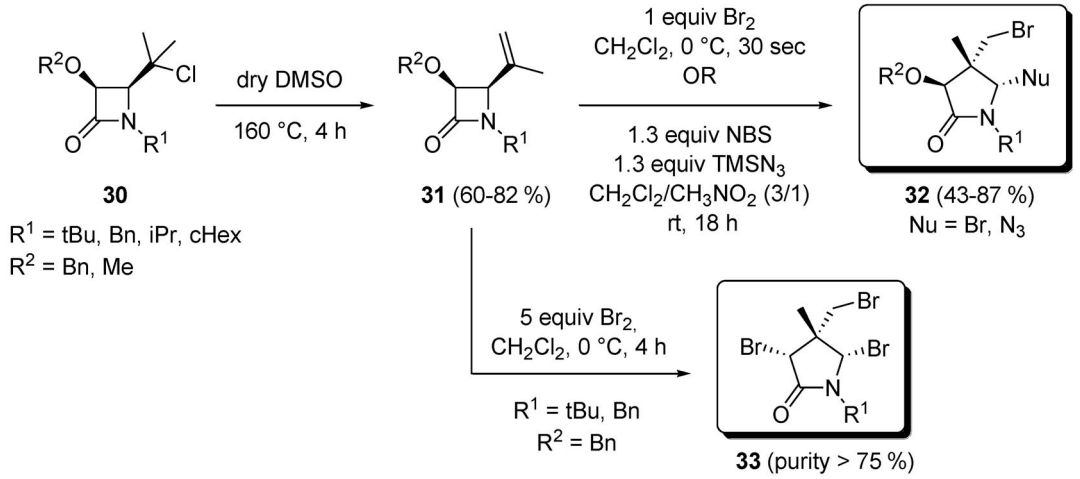
noted that the occurrence of 1-azoniabicyclo[2.2.0]hexanes such as **23** was unprecedented in the chemical literature.

Besides ring transformations of β-lactams based on the reductive removal of the carbonyl group, other approaches have also been worked out. A synthetically versatile method in that respect comprises the ring expansion of 4-(1-halo-1-methylethyl)azetidin-2-ones into functionalized γ-lactams via *N*-acyliminium intermediates. For example, dissociation of the bromide in 4-(1-bromo-1-methylethyl)azetidin-2-ones **24** gave rise to carbenium ions **28**, which in their turn were converted into stable *N*-acyliminium intermediates **29** via an intramolecular rearrangement upon stirring in dimethylsulfoxide (DMSO). In principle, this ring expansion can be considered as the aza-analog of the cyclobutylmethylcarbenium ion rearrangement toward cyclopentanes or cyclopentenes. Subsequent attack of different nucleophiles onto iminium salts **29** led to the formation of functionalized *trans*-γ-lactams **25** as the major reaction products, besides the corresponding *cis*-γ-lactams **26** and 4-isoprenylazetidin-2-ones **27** (obtained via dehydrobromination) as minor constituents (Scheme 7) [13]. The degree of diastereocontrol appeared to be dependent on both the type of nucleophile and the substituents present at the starting azetidin-2-ones **24**. When the same ring expansion was performed in tetrahydrofuran (THF) as a solvent and in the presence of potassium *tert*-butoxide, *trans*-5-hydroxy-, and *trans*-5-methoxypyrrolidin-2-ones **25** (Nu = OH, OMe) were obtained in a highly diastereoselective way (64–71 %). Furthermore, no dehydrobromination was observed when using THF as a solvent instead of DMSO. Attempts with sodium azide, allylamine, and potassium cyanide, however, failed.



Scheme 7 Synthesis of pyrrolidin-2-ones **25**.

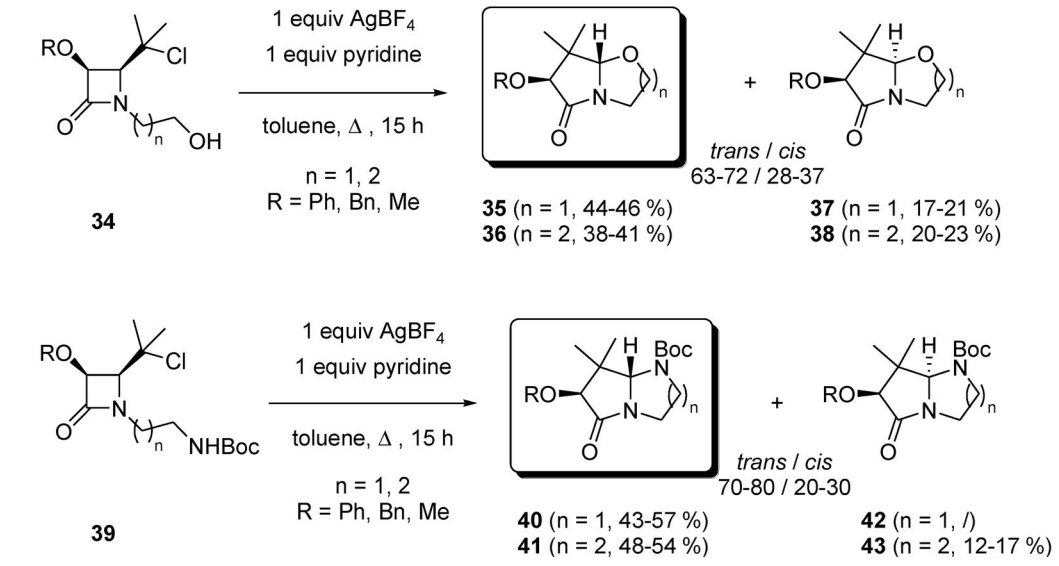
Alternatively, the ring enlargement of β-lactams into γ-lactams was accomplished starting from 4-(1-methylethenyl)azetidin-2-ones **31** through the creation of an electrophilic center by the addition of a suitable electrophile across the olefin [14]. The required 4-isoprenyl-β-lactams **31** were efficiently synthesized starting from 4-(1-chloroalkyl)azetidin-2-ones **30** through dehydrochlorination in dry DMSO at 160 °C for 4 h [14]. 4-(1-Alkenyl)-β-lactams can also be prepared via Staudinger reaction of ketenes with α,β-unsaturated imines, which are accessible by 1,2-dehydrohalogenation of α-haloimines or by condensation of enals with primary amines [15]. Subsequent treatment of β-lactams **31** with 1 equiv of bromine in dichloromethane resulted in a diastereoselective, electrophile-induced ring expansion toward 5-bromopyrrolidin-2-ones **32** via intermediate *N*-acyliminium salts. Remarkably, when 3-benzyloxy-4-isoprenylazetidin-2-ones **31** (R^2 = Bn) were treated with 5 equiv of bromine for 4 h at 0 °C, oxidative cleavage of the benzyloxy moiety occurred, resulting in 3,5-dibromopyrrolidin-2-ones **33** in a diastereoselective fashion (Scheme 8). Besides bromine, the use of *N*-bromosuccinimide (NBS) in the presence of azidotrimethylsilane ($TMSN_3$) was shown to be successful, leading to the formation



Scheme 8 Synthesis of pyrrolidin-2-ones **32** and **33**.

of 5-azidopyrrolidin-2-ones **32** (Nu = N_3) in moderate to high yields in a dichloro-/nitromethane (3/1) solvent system at room temperature (Scheme 8).

Finally, the broad synthetic applicability of this β-lactam to γ-lactam ring expansion reaction was demonstrated through the development of a full intramolecular version leading to functionalized bicyclic γ-lactams [16]. In this context, 4-(1-chloro-1-methylethyl)-1-(ω-hydroxyalkyl)azetidin-2-ones **34** were treated with $AgBF_4$ and pyridine in toluene under reflux, resulting in the diastereoselective formation of novel *trans*-1-aza-4-oxabicyclo[3.3.0]octan-8-ones **35** and *trans*-1-aza-5-oxabicyclo[4.3.0]nonan-9-ones **36**, besides minor amounts of the corresponding *cis*-isomers **37** and **38** (Scheme 9). These observations could be explained considering the intramolecular nucleophilic trapping of *N*-acyliminium intermediates, formed through $AgBF_4$-mediated chloride dissociation, by the hydroxyl moiety, in analogy with the above described reaction pathway (cf. Scheme 7). Furthermore,

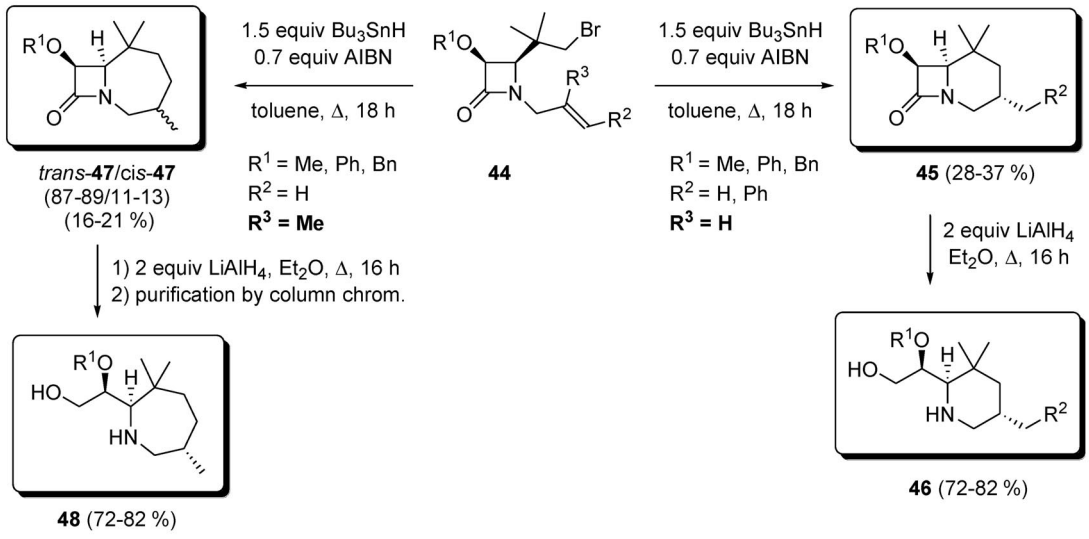


Scheme 9 Synthesis of bicyclic γ-lactams **35**, **36**, **40**, and **41**.

the corresponding aza-analogs of bicyclic γ-lactams **35–38** were prepared accordingly, starting from *cis*-4-(1-chloroalkyl)-1-{ω-[(*tert*-butoxycarbonyl)amino]alkyl}azetidin-2-ones **39**. Thus, treatment with $AgBF_4$ and pyridine in toluene under reflux for 15 h furnished *trans*-1,4-diazabicyclo[3.3.0]octan-8-ones **40** and *trans*-1,5-diazabicyclo[4.3.0]nonan-9-ones **41**, next to minor amounts of the corresponding *cis*-isomers **42** and **43** (Scheme 9). This approach involved the first general transformation of monocyclic β-lactams into bicyclic γ-lactams via *N*-acyliminium intermediates.

A major incentive in β-lactam chemistry comprises the synthesis of novel bicyclic β-lactam systems as potential new analogs of the potent class of bicyclic β-lactam antibiotics. Within this framework, different methodologies have been elaborated toward a variety of carbo- and heterocyclic 1,4- and 3,4-fused bicyclic azetidin-2-ones.

In a first approach, novel carbacepham derivatives **45** were prepared diastereoselectively through radical cyclization of 4-(2-bromo-1,1-dimethylethyl)azetidin-2-ones **44** (Scheme 10) [17,18]. Treatment of 1-(2-propenyl)azetidin-2-ones **44** (R^3 = H) with tributyltin hydride and azoisobutyronitrile (AIBN) in toluene at reflux temperature for 18 h afforded 7-alkoxy-5,5-dimethyl-1-azabicylo[4.2.0]octane-8-ones **45** as single diastereomers through 6-*exo-trig* cyclization of intermediate methyl radicals, besides a small amount (6–11 %) of the corresponding monocyclic 4-*tert*-butyl-β-lactams. The relative stereochemistry of bicyclic β-lactams **45** was unequivocally established by means of X-ray analysis, pointing to a *cis*-disposition between the bridgehead hydrogen atom and the methyl or benzyl substituent at the six-membered ring. 1-Azabicylo[4.2.0]octane-8-ones **45** are not only of interest from a biological but also from a synthetical point of view, as was demonstrated by reductive ring opening by means of $LiAlH_4$ in diethyl ether at reflux temperature for 16 h. This approach enabled the preparation of stereodefined 2-(1-alkoxy-2-hydroxyethyl)piperidines **46** as valuable members of the biologically important class of functionalized piperidines (Scheme 10).

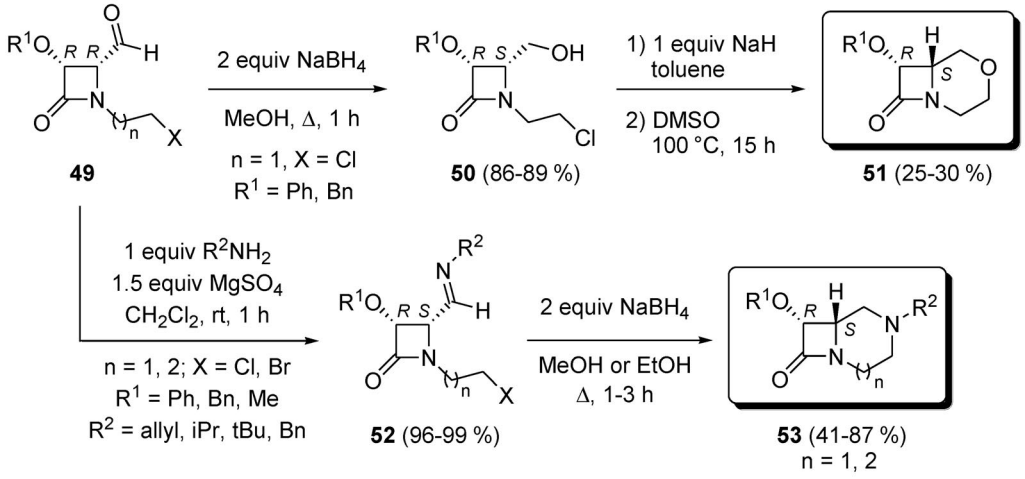


Scheme 10 Synthesis of piperidines **46** and azepanes **48**.

Interestingly, the use of β-lactams **44** bearing a 2-methyl-2-propenyl group at nitrogen allowed a convenient entry into the higher homologues of azaheterocycles **45** through a 7-*endo-trig* cyclization protocol via stable intermediate tertiary radicals. Thus, treatment of azetidin-2-ones **44** (R^2 = H, R^3 = Me) with tributyltin hydride and azoisobutyronitrile in toluene afforded 3,6,6-trimethyl-1-azabicyclo[5.2.0]nonan-9-ones **47** in a 87–89/11–13 diastereomeric ratio (*trans*-**47**/*cis*-**47**) (Scheme 10), be-

sides a small amount (7–11 %) of the corresponding 4-*tert*-butyl-β-lactams [17,18]. Steric hindrance is probably the main factor orienting the cyclization to a 7-*endo-trig* selectivity in the case of bicyclic β-lactams **47**. Furthermore, the reduction of 1-azabicyclo[5.2.0]nonan-9-ones **47** with $LiAlH_4$ in diethyl ether at reflux temperature for 16 h afforded the corresponding diastereomeric mixture of 2-(1-alkoxy-2-hydroxyethyl)azepanes, after which the major isomers *trans*-2-(1-alkoxy-2-hydroxyethyl)azepanes **48** were isolated in pure form upon column chromatography (Scheme 10).

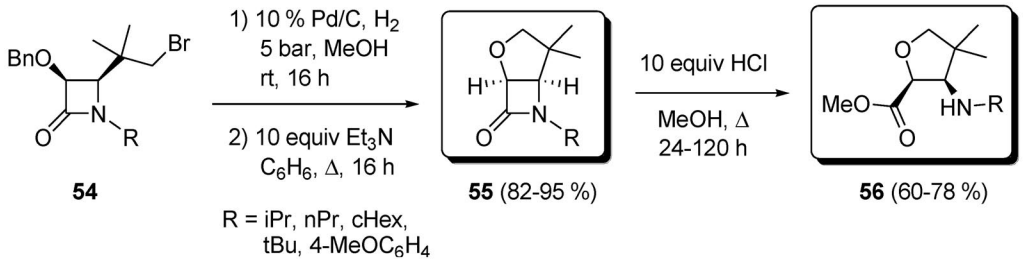
In another approach, bicyclic β-lactams in which the second ring contains a heteroatom have been prepared, although in this case optically active 4-formyl-1-(2- and 3-haloalkyl)azetidin-2-ones **49** [19] were used as substrates. Treatment of the latter β-lactams **49** with $NaBH_4$ in methanol under reflux for 1 h afforded the corresponding chiral 4-hydroxymethyl-β-lactams **50**, which, upon reaction with NaH in toluene and subsequent heating in DMSO, were transformed into bicyclic morpholine derivatives **51** (Scheme 11) [20]. To broaden the scope of this methodology, the synthesis of the corresponding nitrogen counterparts was devised. After condensation of 4-formylazetidin-2-ones **49** with different primary amines, 4-imidoyl-β-lactams **52** were obtained in high yields. Reduction of these imines **52** with $NaBH_4$ in methanol or ethanol afforded optically active piperazine and 1,4-diazepane annelated β-lactams **53** in good to high yields in a one-step procedure (Scheme 11).



Scheme 11 Synthesis of bicyclic β-lactams **51** and **53**.

The construction of bicyclic azetidin-2-ones in which the second ring is attached to the β-lactam unit at the 3,4-position ("C-fused" bicyclic β-lactams) comprises an interesting challenge as an alternative for the conventional 1,4-fused bicyclic β-lactams. A suitable entry into this class of heterocycles was provided through internal nucleophilic displacement of a leaving group present in the side chain at the 4-position by a nucleophile attached to the C3 of the β-lactam ring. At first, hydrogenolysis of the benzyl ether substituent in 3-benzyloxy-4-(2-bromo-1,1-dimethylethyl)azetidin-2-ones **54** using palladium on activated carbon in methanol afforded the corresponding *cis*-3-hydroxy-β-lactams after 16 h at room temperature. Formation of the premised *cis*-6-aza-2-oxabicyclo[3.2.0]heptan-7-ones required the addition of Et_3N to these *cis*-3-hydroxy-β-lactams, resulting in bicyclic β-lactams **55** in 82–95 % yield after reflux for 16 h in benzene (Scheme 12) [21]. At present, little information regarding this type of oxygen-containing 3,4-fused β-lactam systems can be found in the literature [22].

Due to the presence of a propiolactam moiety, azetidin-2-ones are ideally suited for the synthesis of biologically interesting β-amino acids through hydrolysis of the amide bond [23–25]. Accordingly, the synthesis of the 3-aminotetrahydrofuran-2-carboxylates **56** was accomplished through ring opening



Scheme 12 Synthesis of oxolanes **56**.

of bicyclic *cis*-β-lactams **55** by means of HCl in methanol in 60–78 % yield (Scheme 12). X-ray analysis of 3-aminotetrahydrofuran-2-carboxylate **56** (R = 4-$MeOC_6H_4$) acknowledged the *cis*-relationship between the amino group and the ester moiety. Cyclic β-amino acids in which the amino group and the acid functionality are vicinally attached to an aliphatic ring represent an important challenge due to their biological utility, as, for example, the antifungal agent Cispentacin [26,27]. Moreover, the synthesis of the corresponding oxolane derivatives, which are known for their antimycotic activity [28], has become a relevant challenge in organic chemistry.

In conclusion, 4-haloalkyl-β-lactams can be considered as suitable, flexible, and versatile building blocks in heterocyclic chemistry. Their applicability toward the synthesis of a whole variety of functionalized heterocycles has been demonstrated, including the preparation of aziridines, azetidines, pyrrolidines, piperidines, azepanes, pyrrolidin-2-ones, oxolanes, bicyclic β-lactams, and bicyclic γ-lactams. These methodologies are characterized by a high degree of efficiency and stereoselectivity, thus providing useful entries into different classes of heterocyclic compounds.

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