ChemComm

1,3-Dipolar cycloaddition of 2-azetidinone-tethered azomethine ylides. Application to the rapid, stereocontrolled synthesis of optically pure highly functionalised pyrrolizidine systems

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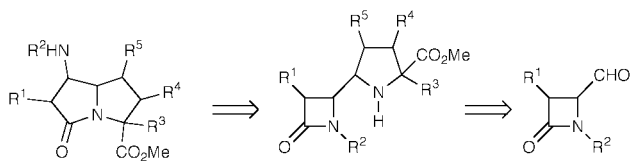
Received (in Liverpool, UK) 4th January 2000, Accepted 14th February 2000

A new straightforward methodology to prepare polyfunctionalised enantiopure pyrrolizidine systems, based on the 1,3-dipolar cycloaddition of 2-azetidinone-tethered azomethine ylides as the key reaction, is presented.

1,3-Dipolar cycloaddition employing azomethine ylides is an important process in organic synthesis, acquiring a prominent place of synthetic strategy for a variety of targets, including natural products such as azasugars and alkaloids.[1] Pyrrolizidine alkaloids occur in many natural products of potential use in medicine and agriculture.[2] In view of their potent and various biological activities, pyrrolizidine alkaloids as well as structurally related unnatural compounds are continuosly stimulating new synthetic approaches.[3] On the other hand, the importance of 2-azetidinones as synthetic intermediates has been widely recognized in organic synthesis. This usefulness is based on the impressive variety of transformations which can be derived from this system.[4] The application of β-lactams in stereoselective synthesis may be divided into two groups, namely, those processes based on transformation of the 2-azetidinone by external reagents and those based on rearrangements of the four-membered ring. The first type of reactivity is exemplified by the β-lactam synthon method.[5] The second group of reactions is based on the building of a conveniently functionalised 2-azetidinone to produce different types of, usually cyclic, compounds by selective bond breakage and rearrangement.[6] Despite the versatility of the 2-azetidinone ring, there is little information available on the use of β-lactams as chiral synthons for the synthesis of pyrrolizidine alkaloids, just the groups of Reuschling[7] and Palomo[8] have reported β-lactam routes to simple pyrrolizidines. Our interest in the use of 4-oxoazetidine-2-carbaldehydes as substrates for addition reactions and cyclization processes,[9] prompted us to evaluate the combination of the 1,3-dipolar cycloaddition of alanine (glycine) derived iminoester ylides with rearrangement reactions on the 2-azetidinone ring as a route to complex pyrrolizidine alkaloids (Scheme 1). We report here, a straightforward asymmetric synthesis of different kinds of highly fuctionalised bi- and tri-cyclic pyrrolizidine systems using β-lactams as chiral building blocks.

Cyclization precursors, 4-oxoazetidine-2-carbaldehydes **1**, were prepared both in the racemic form and in optically pure form using standard methodology.[9–12] Treatment of aldehydes **1** with various α-aminoesters in the presence of molecular sieves provided the corresponding aliphatic aldimines **2**. Imines **2** were obtained in quantitative yields and were used for next step without further purification



Scheme 1

We sought to explore the reactivity of 2-azetidinone-tethered azomethine ylides with cyclic and acyclic dienophiles such as *N*-phenyl maleimide and methyl acrylate.‡ The 1,3-dipolar cycloaddition was achieved *via* metal ion catalysis at room temperature. Treatment of aldimines **2** with the appropriate dienophile in the presence of $AgOAc–Et_3N$ in toluene at room temp. for 40 h gave with reasonable diastereoselectivity mixtures of cycloadducts **3** and **4** (Table 1) in moderate to excellent yields (45–90%).§ Fortunately, in all cases the diastereomeric cycloadducts were easily separated by flash chromatography. Furthermore, the reaction with an unsymmetric monoactivated alkene, methyl acrylate, proceeded with total regioselectivity. The steric properties of the C3 substituent on the 2-azetidinone ring influence the stereoselectivity of the cycloaddition, sterically less demanding groups increasing the diastereoisomeric ratio (Table 1). Next, our aim was to find an expedient transformation of the cycloadducts into pyrrolizidine systems. First we tested sodium methoxide as reagent for the conversion of adducts **3** or **4** into the framework of pyrrolizidine alkaloids. In the event, the pyrrolizidine skeleton was obtained. Sodium methoxide works well in maleimide derived cycloadducts, however epimerization was observed in adducts coming from methyl acrylate. This preliminary result encouraged us to find a more convenient reagent for this transformation. To our delight, when the reaction was conducted in a saturated solution of HCl(g) in isopropanol at room temperature for 36 h, optically pure pyrrolizidine systems **5** and **6** were obtained in moderate to good yields and without by-products (Scheme 2).¶ However, bicycle (−)-**6b** was more efficiently obtained in a saturated methanolic solution of HCl(g), with some isopropyl transesterification being observed when adduct (+)-**4d** was treated with HCl(g) in isopropanol. The reaction of (+)-**3d** in a saturated solution of HCl(g) in methanol for 36 h gave a quantitative yield of the monocyclic pyrrolidine (+)-**7**, which requires 2 h of heating in toluene under PTSA catalysis to give the expected tricyclic system (+)-**5b**.‖ The formation of pyrrolizidinones **5** and **6** involves a selective C–N bond cleavage of the four-membered ring, followed by a rearrangement under the reaction conditions. The relative *anti*-disposition of the ester and amine moieties in bicycles **6** must be responsible for the failure of the third cyclization to occur, preventing the formation of a highly strained tricyclic system. The polycyclic structures (by DEPT, HETCOR and COSY) and the stereochemistry (by vicinal proton couplings and NOE experiments) of compounds **5** and **6** were established by one- and two-dimensional NMR techniques.** Taking into account that separated diastereomeric cycloadducts **3** and **4** could be obtained and cyclized, the stereochemistry for compounds **3** and **4** was inmediately deduced by comparison with the NOE results of the polycyclic systems. Also, the *cis*-stereochemistry of the four-membered ring is set during the cyclization step to form the 2-azetidinone ring and it is transferred unaltered during the further synthetic steps.

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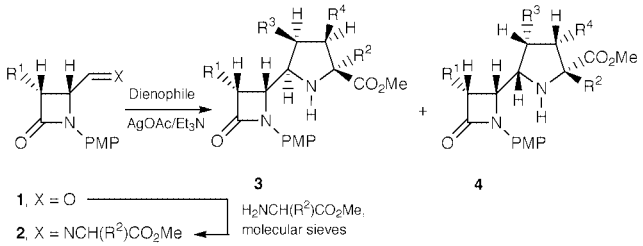
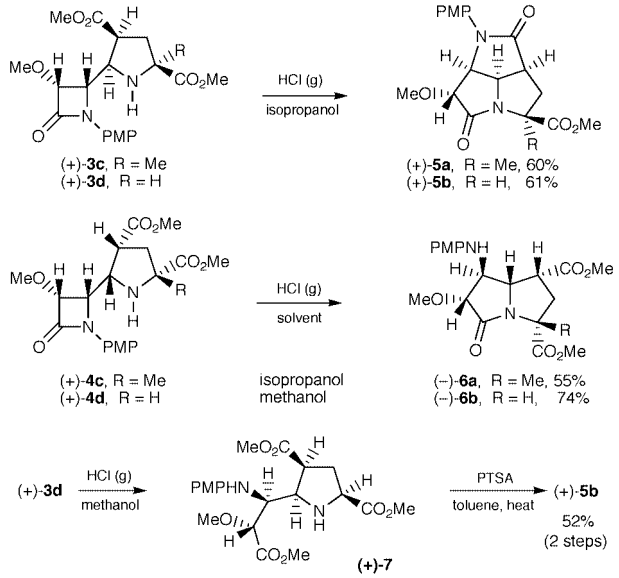
DOI: 10.1039/b000249f

Table 1 1,3-Dipolar cycloaddition of 2-azetidinone-tethered azomethine ylides



Entry	Aldehyde	R^1	R^2	R^3	R^4	Products	**3**:**4** ratio[a]	**3**:**4** yield[b]
1	**1a**	H	Me	CO_2Me	H	**3a**[c]	—[c]	48[d]
2	**1b**	Vinyl	H	CO_2Me	H	**3b**/**4b**	95:5	43/2
3	(+)-**1c**	MeO	Me	CO_2Me	H	(+)-**3c**/(+)-**4c**	65:35	39/21
4	(+)-**1c**	MeO	H	CO_2Me	H	(+)-**3d**/(+)-**4d**	70:30[e]	46/20

[a] The ratio was determined by integration of well resolved signals in the ^{1}H NMR spectra of the crude reaction mixtures before purification. PMP = 4-$MeOC_6H_4$. [b] Yield of pure, isolated product with correct analytical and spectral data. [c] The ^{1}H NMR spectrum of the crude mixture showed mainly **3a** togheter with unmeasurable traces of two other isomers. [d] Additional fractions containing the major cycloadduct together with traces of the minor isomers were isolated after column chromatography, accounting for an overall 80% yield. [e] Two additional diastereoisomeric cycloadducts were detected in the ^{1}H NMR spectra of the crude reaction mixture accounting, respectively, for 7 and 4% of the products formed.



Scheme 2

In summary, we have demonstrated that the combination of 1,3-dipolar cycloaddition of 2-azetidinone-tethered azomethine ylides with rearrangement reactions on the 2-azetidinone ring is a powerful, hitherto unknown, strategy for the asymmetric synthesis of different types of highly functionalised pyrrolizidine systems. In addition, this methodology is very versatile offering the possibility of obtaining a variety of complex pyrrolizidine derivatives just by changing the substituents in readily available 4-oxoazetidine-2-carbaldehydes, α-amino-esters or dipholarophiles.

We thank the DGES (MEC-Spain, grant PB96-0565) for financial support. P. A. thanks the DGES (MEC, Spain) for a 'Contrato de Incorporación'. J. M. A. thanks the UCM for a predoctoral grant.

Notes and references

‡ During the evaluation of this manuscript a report appeared describing the 1,3-dipolar cycloaddition of closely related β-lactam azomethine ylides: R. Grigg, M. Thornton-Pett and L.-H. Xu, *Tetrahedron*, 1999, **55**, 13 841.

§ When DBU was used instead of Et_3N, complex mixtures of unidentified products were obtained, whereas pyridine gave erratic results. Perfoming the reaction in acetonitrile afforded poor yields of cycloadducts.

¶ *Representative experimental procedure* for the synthesis of pyrrolizidine systems: HCl(g) was bubbled, during 1 h, through an unstirred solution of the appropriate cycloadduct **3** or **4** (0.4 mmol) in isopropyl alcohol (6 ml) and the reaction solution left to stand in a sealed vessel for 36 h. The reaction mixture was concentrated under reduced pressure, diluted with dichloromethane (10 ml), washed with saturated aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$) and concentrated under reduced pressure. After purification by flash chromatography, pyrrolizidinones **5** and **6** were obtained in analytically pure form.

‖ Tricycle (+)-**5b** was alternatively obtained *via* heating overnight the adduct (+)-**3d** in methanol using 37% aqueous hydrochloric acid as a catalyst.

** All new compounds were fully characterised by spectroscopic methods and microanalysis and/or HRMS.

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Communication b000249f