Diastereoselective Baylis–Hillman reaction of 4-oxoazetidine-2-carbaldehydes: rapid, stereocontrolled and divergent radical synthesis of highly functionalised β-lactams fused to medium rings

Benito Alcaide,* Pedro Almendros and Cristina Aragoncillo

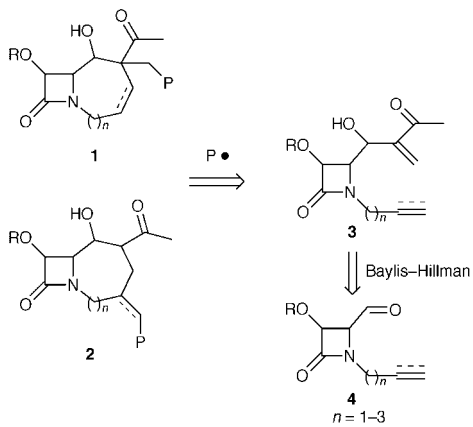
Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense, 28040-Madrid, Spain. E-mail: alcaideb@eucmax.sim.ucm.es

Received (in Liverpool, UK) 21st June 1999, Accepted 30th July 1999

Baylis–Hillman adducts derived from enantiopure 1-alkenyl- or alkynyl-4-oxoazetidine-2-carbaldehydes are used for the stereoselective and divergent preparation of highly functionalised β-lactams fused to medium rings through novel, chemocontrolled tandem radical addition–cyclization sequences.

The Baylis–Hillman reaction is an emerging carbon–carbon bond forming reaction for the preparation of densely functionalysed products involving an activated alkene, a carbon electrophile and a suitable catalyst (particularly a tertiary amine).[1] On the other hand, synthetic methodologies based on free radical cyclization reactions have experienced an impressive growth and are the focus of extensive studies. This wide research has been fostered by its operational simplicity, its tolerance to substrate functionalization, and the fact that it proceeds usually with high degrees of regio- and stereo-control.[2]

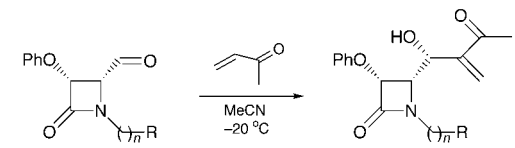
The increased resistance of bacteria to the commonly used β-lactam antibiotics[3] and the ever-growing new applications of these products in fields ranging from enzyme inhibition to the use of azetidin-2-ones as starting materials to develop new synthetic methodologies, has triggered a renewed interest in the construction of new systems having the azetidin-2-one ring as a common feature.[4] Our interest in the use of 4-oxoazetidine-2-carbaldehydes as substrates for intramolecular cyclization processes[5] prompted us to evaluate the combination of the Baylis–Hillman reaction with free-radical methodology as a route to unusual, chiral non-racemic bicyclic β-lactams. We report here novel, simple strategies for the stereoselective and divergent preparation of medium sized ring-fused highly functionalized bicyclic β-lactams **1** and **2** based on chemocontrolled tandem radical addition–cyclization sequences (Scheme 1). The useful and expedient approach described herein presents the opportunity to merge the rapidly expanding fields of Baylis–Hillman reaction and radical chemistry. The problems associated with the formation of medium sized rings are widely appreciated. Even the formation of seven-membered rings in the 7-*exo-trig* mode is likely to be unsuccessful in most cases (at 25 °C, $k_{7\text{-}exo} < 7 \times 10^{-1}\ s^{-1}$). Nevertheless, several authors were able to prepare seven-membered rings by radical cyclization on substrates bearing only a limited degree of freedom, including β-lactam-tethered haloalkenes or alkynes[6,7] and aryl-bridged compounds.[8]



Scheme 1

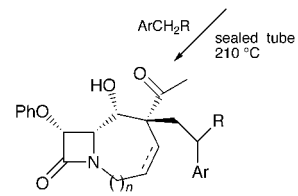
Baylis–Hillman adducts **3** were easily prepared by DABCO-mediated reaction of enantiopure 4-oxoazetidine-2-carbaldehydes **4** with methyl vinyl ketone in excellent yields and stereoselectivities (Scheme 2). Alkenyl or alkynyl aldehydes **4** were easily prepared as single *cis*-enantiomers from imines of (*R*)-2,3-*O*-isopropylidenepropanal, through Staüdinger reactions with the corresponding acid chlorides in the presence of Et_3N,[9] followed by standard transformations of the acetal moiety.[5] The Baylis–Hillman reaction using protected α-amino aldehydes has been attempted with limited success, due to partial racemisation of the chiral aldehyde by DABCO after prolongate exposure times.[10] We were pleased to find that the Baylis–Hillman reaction proceeds faster than racemization (our typical reaction time ranging from 18 h for **4a** to 72 h for **4b**) using an equimolar amount of DABCO and 10 equiv. of methyl vinyl ketone and performing the experiment in MeCN at low temperature (−20 °C).†

Subjection of any organic molecule to a high enough temperature in the gas phase results in the formation of free radicals. When the molecule contains bonds with dissociation energies from 20 to 40 kcal mol^{-1}, cleavage can be caused in the liquid phase. The dissociation energy of the $PhCH_2$–H bond is 88 kcal mol^{-1}, so the generation of the benzylic radical is an unexpected process *via* heating at usual temperatures.[11] To our



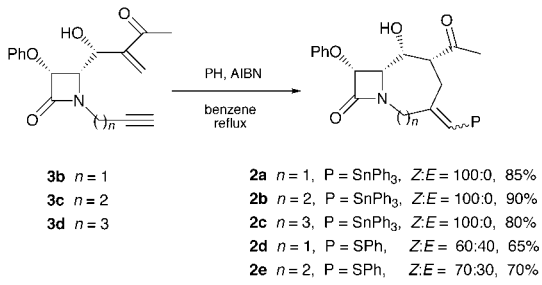
4a *n* = 1, R = vinyl
4b *n* = 1, R = ethynyl
4c *n* = 2, R = ethynyl
4d *n* = 3, R = ethynyl

3a *n* = 1, R = vinyl, de > 97%, 80%
3b *n* = 1, R = ethynyl, de = 92%, 78%
3c *n* = 2, R = ethynyl, de > 97%, 67%
3d *n* = 3, R = ethynyl, de > 97%, 60%



1a *n* = 1, R = H, Ar = Ph, 37%
1b *n* = 1, R = H, Ar = 4-MeC_6H_4, 45%
1c *n* = 1, R = H, Ar = 4-MeC_6H_4, 60%
1d *n* = 1, R = OH, Ar = Ph, 20%
1e *n* = 2, R = H, Ar = 4-MeC_6H_4, 53%

Scheme 2



3b $n = 1$
3c $n = 2$
3d $n = 3$

2a $n = 1$, P = $SnPh_3$, $Z:E$ = 100:0, 85%
2b $n = 2$, P = $SnPh_3$, $Z:E$ = 100:0, 90%
2c $n = 3$, P = $SnPh_3$, $Z:E$ = 100:0, 80%
2d $n = 1$, P = SPh, $Z:E$ = 60:40, 65%
2e $n = 2$, P = SPh, $Z:E$ = 70:30, 70%

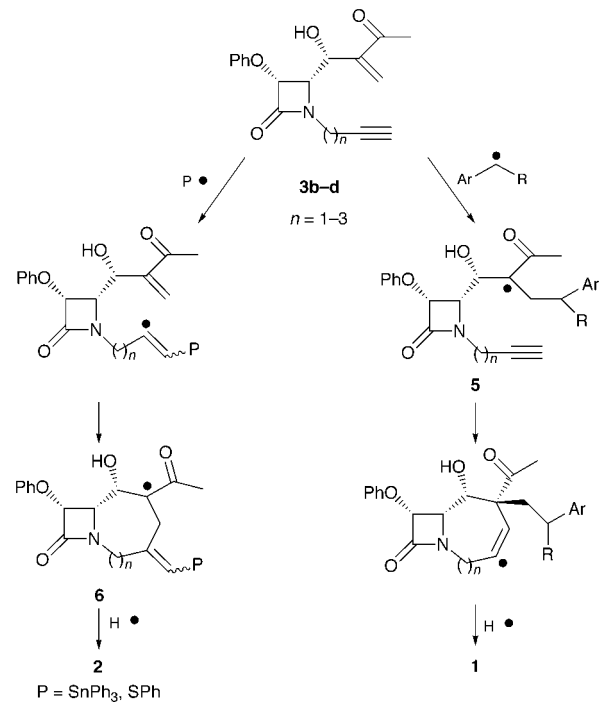
Scheme 3

surprise, Baylis–Hillman adduct (+)-**3a**, on heating in toluene or *p*-xylene in a sealed tube at 210 °C, formed the bicyclic products **1a**, **b**, which were isolated in modest yields (37–45%).‡ Use of chlorobenzene or anisole as solvents gave unaltered starting material (+)-**3a**. When enyne (+)-**3b** was used instead of diene (+)-**3a** the reaction proceeded in the same manner, giving product (+)-**1c** in good yield (60%). Furthermore, thermal treatment of enyne (+)-**3c** with *p*-xylene gave the bicycle (+)-**1e** in reasonable yield (Scheme 2). Interestingly, the use of benzyl alcohol allowed us to obtain the hemiacetal derivative of compound **1d**. Although this latter compound was isolated in low yield (20%) this is an interesting case because three new chiral centers are generated in a highly stereoselective manner.§ All compounds **1** were obtained as single diastereomers. When a catalytic amount of hydroquinone was added, the reaction rate was considerably reduced and the product yield fell dramatically. This fact confirms that a radical reaction is involved. Also, together with compounds **1**, 1,2-diarylethanes were isolated as byproducts in all cases. These products may be formed by recombination of the initially generated benzylic radicals.

In view of the particular disposition of the 1,5- and 1,6-enyne azetidin-2-ones to undergo 5-*exo* and 6-*exo* tin promoted radical cyclization,[12] we examined the applicability of this methodology to our novel Baylis–Hillman 1,ω-enyne substrates **3b**–**3d** for the synthesis of less common bicyclic β-lactams. This approach in the synthesis of seven-membered or higher sized rings has not been hitherto applied.[13] A dramatic change in the chemoselectivity was observed when the bicyclic β-lactam (+)-**2a** was formed as the exclusive product from (+)-**3b**, in nearly quantitative yield as crude product. The tin-promoted radical reaction was also useful in the conversion of the homologous 1,4-tethered enynes (+)-**3c** and (+)-**3d** into the corresponding bicyclic systems with similar efficiency and selectivity. Compounds **2** were exclusively obtained as *Z*-isomers. In addition, PhSH reacted smoothly with β-lactams (+)-**3b** and (+)-**3c** in the presence of AIBN, in boiling benzene, to give in good yields the corresponding phenylthiovinyl derivatives as mixtures of easily separable *Z* and *E* isomers (Scheme 3). The bicyclic structure (by DEPT, HETCOR, and COSY) and the stereochemistry (by vicinal proton couplings and NOE experiments) of compounds **1** and **2** were established by NMR one- and two-dimensional techniques.

Formation of bicyclic β-lactams **1** and **2** can be explained in terms of a competition between a tandem radical Michael addition–*endo*-cyclization and a tandem radical addition–Michael addition, depending on the electronic nature of the radical promoter (Scheme 4). The more nucleophilic benzylic radical would favour formation of compounds **1**, while the more electrophilic radicals, such as PhS· and Ph_3Sn·, should promote formation of compounds **2**. The high stereoselectivity of the processes can be tentatively interpreted in terms of the allylic strain model of Giese, showing for planar substituents such as Ac good levels of 1,2-stereoinduction on α-substituted β-oxy radicals (types **5** and **6** in Scheme 4).[14]

We would like to thank the DGES (MEC-Spain, grant PB96-0565) for financial support. P. A. thanks the DGES (MEC, Spain) for a 'Contrato de Incorporación'. C. A. thanks the DGI (CEC-Comunidad de Madrid-Spain) for a fellowship.



Scheme 4

Notes and references

† When the reaction was performed at room temperature maintaining the molar ratio of reagents (aldehyde:DABCO:methyl vinyl ketone = 1:1:10), partial epimerisation together with some unreacted aldehyde were observed.

‡ *Representative experimental procedure* for thermal promoted tandem radical reaction: A solution of Baylis–Hillman adduct **3** (0.2 mmol) in the corresponding benzylic solvent (10 ml) was heated in a sealed tube at 210 °C for 3 h. The reaction mixture was allowed to cool to room temperature, the solvent was removed under reduced pressure and, after purification by flash chromatography, bicycles **1** were obtained in analytically pure form.

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

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Communication 9/05017E