Pergamon

Tetrahedron Letters 40 (1999) 7537–7540

TETRAHEDRON LETTERS

Asymmetric synthesis of densely functionalized 3-substituted 3-hydroxy-β-lactams via novel, highly stereoselective Baylis–Hillman and allylation reactions of enantiopure 3-oxo-2-azetidinones

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Received 13 July 1999; accepted 10 August 1999

Abstract

New asymmetric routes based on both Baylis–Hillman and allylation reactions of enantiopure 3-oxo-2-azetidinones are used for the highly stereoselective, efficient preparation of densely functionalized 3-substituted 3-hydroxy-β-lactams. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Keywords: allylation; asymmetric synthesis; azetidinones; Baylis–Hillman reactions.

The Baylis–Hillman reaction is an emerging carbon–carbon bond forming reaction for the preparation of β-hydroxy-α-methylene ketones, nitriles, esters, etc. involving an activated alkene, a carbon electrophile and a suitable catalyst (particularly a tertiary amine).[1] This fascinating reaction has many of the basic properties that an efficient synthetic method should have, e.g. it is selective, economical in atom count and requires mild conditions, providing densely funtionalized products.[2] However, the reaction suffers from poor reaction rates as it takes several days and even weeks for completion. On the other hand, the reactions of propenylmetal reagents with chiral carbonyl compounds are widely employed in organic synthesis, due to the versatility of homoallylic alcohols as synthetic intermediates.[3] Although many investigations have been made in these fields into various types of carbonyl compounds, the Baylis–Hillman reaction of 3-oxo-2-azetidinones has not been reported yet. Furthermore, there is little information available on the use of β-lactams as chiral synthons for the allylation reaction, just Bose[4a] and Paquette[4b] having recently reported the allylindation of 3-oxo-2-azetidinones in aqueous tetrahydrofuran.[5] However, the asymmetric version was achieved with poor diastereoselectivity on 3-oxo-2-azetidinones bearing a chiral auxiliary at nitrogen.[4b] In addition, the 3-substituted 3-hydroxy-2-azetidinone moiety[6] is present in several monobactams such as sulphazecin,[7] tabtoxin and related microbial products,[8] representing an efficient carboxylate mimic.[9]

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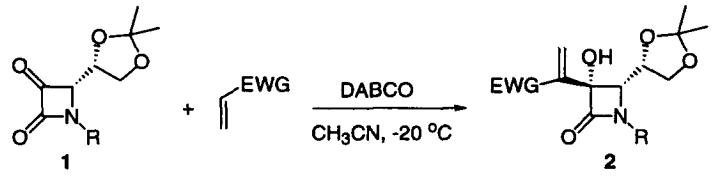
PII: S0040-4039(99)01527-0

Table 1
Stereoselective Baylis–Hillman reaction of 3-oxo-2-azetidinones 1[a]



Product	R	EWG	DABCO (mol %)	t (h)	d.r.[b]	Yield (%)[c]	$[\alpha]_D$[d]
(+)-**2a**	PMP	$COCH_3$	10	72	100:0	80	+120.1
(+)-**2a**	PMP	$COCH_3$	20	16	100:0	80	
(+)-**2a**	PMP	$COCH_3$	50	2	100:0	80	
(+)-**2a**	PMP	$COCH_3$	100	1	100:0	80	
(+)-**2b**	PMP	$COOCH_3$	50	3	100:0	87	+96.0
(−)-**2c**	PMP	CN	50	24	97:3	90	−4.2
(−)-**2d**	Allyl	$COCH_3$	50	2	100:0	69	−62.1
(+)-**2e**	Propargyl	$COCH_3$	50	5	100:0	68	+30.3

[a] All reactions were carried out on 1 mmol scale. PMP = 4-$MeOC_6H_4$. [b] The ratio was determined by integration of well-resolved signals in the ^1H NMR spectra of the crude reaction mixtures before purification. [c] Yield of pure, isolated product with correct analytical and spectral data. [d] Specific rotation is given in deg per dm at 20 °C (*c* 1, $HCCl_3$).

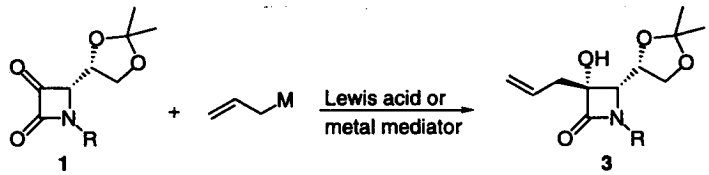
In our ongoing project on the asymmetric synthesis and synthetic applications of functionalized 2-azetidinones,[10] we have recently described both the chelation controlled allylation[11] and the stereoselective Baylis–Hillman reaction[12] of 4-azetidinone-2-carbaldehydes. In connection with this work we wish to report here the manner in which 3-oxo-2-azetidinones and a variety of activated alkenes or allylmetal reagents undergo coupling. We reasoned that by placing a chiral substituent at C-4 we might be able to control the stereochemistry of the addition. First at all we needed an efficient synthesis of homochiral 3-oxo-2-azetidinones bearing a chiral group at C-4. The starting 3-oxo-2-azetidinones **1** were available in high yield by Swern oxidation of 3-hydroxy-β-lactams.[13]

The Baylis–Hillman reaction using protected α-amino aldehydes has been attempted with limited success, due to partial racemization of the chiral aldehyde by the tertiary amine after prolongate times of exposure.[14] To our delight, Baylis–Hillman adducts **2a–e** can be prepared, in a few hours, almost as single diastereoisomers by the DABCO promoted reaction of activated vinyl systems with the appropriate 3-oxo-2-azetidinone **1**. We carried out a study in order to see the effect of the amount of catalyst on the conversion rate, finding that the process can be significantly accelerated on increasing the amount of catalyst (DABCO) (Table 1).

Once we had established the best reaction conditions to carry out the Baylis–Hillman reaction, the diastereoselectivities of Lewis acid or metal-mediated allylation of 3-oxo-2-azetidinones **1** were investigated under anhydrous conditions and in aqueous media. The tin(IV) chloride promoted addition of allyltrimethylsilane to the 3-oxo-compounds **1** gave homoallylic alcohols **3a–c** as single diastereoisomers. Different Lewis acid or metal mediators showed total diastereoselectivity on product formation during allylation reactions of 3-oxo-2-azetidinone **1a** with allyltrimethylsilane, allytributylstannane or allyl bromide, in anhydrous and aqueous environments (Table 2).

The stereochemistry at C-3 was established for compound **2a** by the absence of any NOE enhancement for the signal corresponding to the hydroxylic hydrogen when the C-4 hydrogen was irradiated. NOE irradiation of the methylenic hydrogens of compound **3a** resulted in a 6% enhancement on the signal at δ

Table 2
Stereoselective allylation of 3-oxo-2-azetidinones 1[a]



1 3

Compound	R	M	Lewis acid or metal	T (°C) / t (h)	Solvent	Yield (%)[b]	$[\alpha]_D$[c]
(+)-3a	PMP	$SiMe_3$	$SnCl_4$	-78 / 0.75	CH_2Cl_2	75	+53.4
(+)-3a	PMP	$SnCl_3$	–	-78 / 1	CH_2Cl_2	70	
(+)-3a	PMP	$SnBu_3$	$BF_3.Et_2O$	-78 / 1	CH_2Cl_2	55	
(+)-3a	PMP	Br	$Mg/BiCl_3$	20 / 18	THF/H_2O	72	
(+)-3a	PMP	Br	In	20 / 18	THF/H_2O	73	
(−)-3b	Allyl	$SiMe_3$	$SnCl_4$	-78 / 0.75	CH_2Cl_2	66	−99.0
(−)-3c	Propargyl	$SiMe_3$	$SnCl_4$	-78 / 0.75	CH_2Cl_2	64	−33.6

[a] All reactions were carried out on 1 mmol scale. PMP = 4-$MeOC_6H_4$. The d.r. was determined by integration of well-resolved signals in the ^1H NMR spectra of the crude reaction mixtures before purification. [b] Yield of pure, isolated product with correct analytical and spectral data. [c] Specific rotation is given in deg per dm at 20 °C (*c* 1, $HCCl_3$).

3.95 for H-4, which is in agreement with an *anti* H-4/OH stereochemistry. The facial selectivity of these two addition reactions may be controlled by the bulky chiral auxiliary at C-4 in which one face of the ketone is blocked, the carbon nucleophile being delivered preferentially to the less hindered face.

In conclusion, the present results provide the first insight into the stereoselective manner in which 3-oxo-2-azetidinones undergo Baylis–Hillman reactions, together with their first efficient stereoselective allylation.

Acknowledgements

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

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