ORGANIC LETTERS

2000
Vol. 2, No. 10
1411−1414

Regio- and Stereocontrolled Metal-Mediated Carbonyl Propargylation or Allenylation of Enantiomerically Pure Azetidine-2,3-diones: Synthesis of Highly Functionalized 3-Substituted 3-Hydroxy-β-lactams

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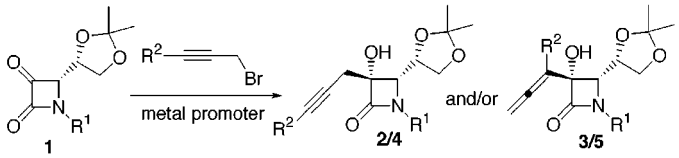
Received February 29, 2000

ABSTRACT



Regio- and stereocontrolled metal-mediated Barbier-type reactions of azetidine-2,3-diones with differently substituted propargyl bromides offer an efficient asymmetric entry to densely functionalized 3-propargyl- (or allenyl-) substituted 3-hydroxy-β-lactams.

Metal-mediated carbon−carbon bond formation between a carbonyl compound and a propargyl halide has been the subject of a number of investigations over the past two decades, by virtue of its synthetic usefulness and mechanistic intrigue.[1] The reaction of propargyl bromide with metals has been proposed to generate an equilibrium between the allenyl and propargyl organometallics.[2] This metallotropic rearrangement often results in poor regioselection in the final organic product, because both organometallic species can react with the carbonyl compounds. Hence, a pertinent synthetic challenge is to tune the regioselectivity toward either acetylenic or allenic products.[3] In this context, the synthesis of homopropargyl alcohols from propargylpalladium reported by Tamaru, using the umpolung approach,[4] and the preparation of homopropargyl and homoallenyl alcohols from transient allenylindium reagents or propargylic stannanes respectively, described by Marshall,[5] are noteworthy. Although many efforts have been made in these fields into various types of carbonylic compounds, the allenylation

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(3) For recent examples of the propargylation/allenylation reaction, see: (a) Sakamoto, T.; Takahashi, K.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **1999**, *64*, 9467. (b) Kundu, A.; Prabhakar, S.; Vairamani, M.; Roy, S. *Organometallics* **1999**, *18*, 2782. (c) Masuyama, Y.; Ito, A.; Fukuzawa, M.; Terada, K.; Kurusu, Y. *Chem. Commun.* **1998**, 2025. (d) Yi, X.-H.; Meng, Y.; Hua, X.-G.; Li, C.-J. *J. Org. Chem.* **1998**, *63*, 7472. (e) McCluskey, A.; Muderawan, W.; Young, D. J. *Synlett* **1998**, 909.

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10.1021/ol005736f CCC: $19.00
Published on Web 04/28/2000

of azetidine-2,3-diones has not been reported yet. Furthermore, the information available on the use of β-lactams as chiral building blocks on the propargylation reaction is still very scarce; just Cho has recently reported the propargylzincation of 6-oxopenicillanates in anhydrous tetrahydrofuran.[6] On the other hand, the 3-substituted 3-hydroxy-2-azetidinone moiety, representing an efficient carboxylate mimic,[7] is present in several pharmacologically active monobactams such as sulphazecin and related products,[8] and in enzyme inhibitors such as tabtoxin and its analogues.[9] Moreover, these compounds with correct absolute configurations serve as precursors to the corresponding α-hydroxy-β-amino acids (isoserines), which are key components of a large number of therapeutically important compounds.[10] However, little attention has been paid to develop methods for the construction of β-lactams with quaternary stereogenic centers at the C3 position.[11]

In our ongoing project directed toward the asymmetric synthesis and synthetic applications of functionalized 2-azetidinones,[12] in a previous paper we reported a detailed study of both the allylation and the stereoselective Baylis−Hillman reaction of azetidine-2,3-diones.[13] In connection with this work we report here the manner in which enantiomerically pure azetidine-2,3-diones and a variety of allenyl organometallics or propargylmetal reagents undergo coupling. The starting azetidine-2,3-diones **1** were available in high yield by Swern oxidation of 3-hydroxy-β-lactams, by following a previously reported procedure.[13]

Our aim was to evaluate the feasibility of the metal-mediated Barbier-type reactions in enantiomerically pure azetidine-2,3-diones, studying the regiochemistry of the connection (e.g., allenylation vs propargylation) and the diastereochemistry (syn vs anti). To achieve the goal of full control of stereochemistry at the C3-substituted C3-hydroxy quaternary center, we have devised a strategy by placing a chiral substituent at C-4. To develop full regiocontrol we have investigated a number of protocols in anhydrous and aqueous environments, being involved a variety of metal mediators and different prop-2-ynyl systems. Chemical yields were generally good, but the regioselectivity of the process was a function of the nature of both the metal reagent and the prop-2-ynyl bromide, and in many cases of the solvent system as well. The diastereoselectivity was complete in all cases.

Initially the regio- and diastereoselectivity of the carbon−carbon bond formation were investigated through the indium-mediated reaction between the 2,3-azetidinedione (+)-**1a** and propargyl bromide in aqueous tetrahydrofuran at room temperature. In the event, the 3-substituted 3-hydroxy-β-lactam moiety was obtained with total diastereoselection; however, the observed regioselectivity was very poor (42:58) in favor of the allenic product. Surprisingly, the regiochemical preference was reversed on the indium-promoted reaction just by changing the system solvent (a saturated aqueous solution of NH_4Cl in THF was used instead of aqueous tetrahydrofuran), with the expected alcohols (+)-**2a** and (+)-**3a** being obtained as a mixture of regioisomers in a ratio of **2a**:**3a** = 71:29. This preliminary result encouraged us to find a more convenient reagent for this transformation. To our delight, when the above reaction was mediated by zinc and was conducted in a saturated aqueous solution of NH_4Cl in THF at 0 °C, it gave rise to the optically pure homopropargyl alcohol (+)-**2a** as single regio- and diastereoisomer in a reasonable 70% yield. However, the yield fell dramatically when the zinc-mediated coupling of the 2,3-azetidinedione (+)-**1a** and propargyl bromide in anhydrous THF in the presence of solid NH_4Cl was performed. No reaction was observed in anhydrous THF when the NH_4Cl was supressed, and the change of the system solvent from tetrahydrofuran/NH_4Cl (aq. sat.) to methanol/NH_4Cl (aq. sat.) resulted in the absence of regioselection. When propargylmagnesium bromide was added to the dione (+)-**1a** the homopropargylic alcohol was afforded as a major product, containing 15% of the homoallenic alcohol. The tin-mediated reaction between ketone (+)-**1a** and propargyl bromide in aqueous tetrahydrofuran resulted in the absence of coupling. By contrast, when the same experiment was carried out in a saturated aqueous solution of NH_4Cl in THF, the homoallenyl alcohol was formed as major product, together with 25% of the homopropargylic alcohol. Allenylation with propargyl bromide in anhydrous THF using the bimetal system copper(II)/tin(II) as the mediator, further lowered the regioselectivity (34:66).[14] Efforts to promote the copper(II)/tin(II)-mediated propargylation in DMF were proven to be unsuccessful. Similar results were obtained in the metal-mediated Barbier-type reactions of different N-substituted azetidine-2,3-diones **1b**−**d** with propargyl bromide (Table 1).

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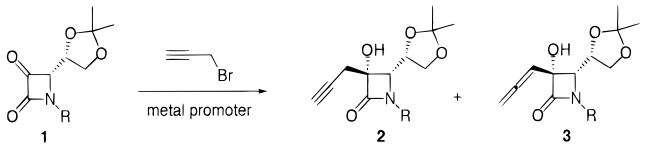
(14) For a reversal of the regiochemistry on the reaction of propargyl bromide with simple aldehydes using the systemt copper(II)/tin(II) as the mediator, see ref 3b.

Table 1. Regio- and Stereoselective Propargylation of Azetidine-2,3-diones **1**[a]



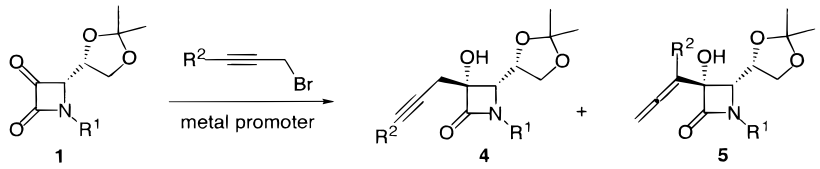
compound	R	M	system solvent	**2**:**3** ratio[b]	yield (%)[c]
2a/3a	PMP	Zn	THF/NH_4Cl (aq. sat.)	100:0	70
2a/3a	PMP	Zn	THF (dry)/NH_4Cl (solid)	100:0	34
2a/3a	PMP	Zn	THF (dry)		
2a/3a	PMP	Zn	MeOH/NH_4Cl (aq. sat.)	50:50	65
2a/3a	PMP	In	THF/NH_4Cl (aq. sat.)	71:29	67
2a/3a	PMP	In	THF/H_2O	42:58	50
2a/3a	PMP	Sn	THF/NH_4Cl (aq. sat.)	25:75	65
2a/3a	PMP	Sn	THF/H_2O		*d*
2a/3a	PMP	$SnCl_2/CuBr_2$	THF (dry)	34:66	50
2a/3a	PMP	$SnCl_2/CuBr_2$	DMF (dry)		*d*
2a/3a	PMP	Mg	THF (dry)	85:15	60
2b/3b	allyl	Zn	THF/NH_4Cl (aq. sat.)	100:0	53
2c/3c	propargyl	Zn	THF/NH_4Cl (aq. sat.)	100:0	56
2d/3d	4-pentynyl	Zn	THF/NH_4Cl (aq. sat.)	100:0	58

[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] Acetonide cleavage and further internal acetal formation was observed.

Our next aim was to find an allenylation method that proceeds in a highly regio- and diastereoselective fashion. Metal-mediated reactions of 2,3-azetidinediones **1** with propargyl bromides bearing an aliphatic or an aromatic substituent at the terminal position, afforded the homoallenyl alcohols **5** as essentially regio- and diastereoisomerically pure products (Table 2). This result is in sharp contrast to the metal-promoted reaction of propargyl bromide itself.[15]

This difference in behavior of the organometallic reagents, derived from various metals and differently substituted propargyl bromides in a variety of solvents, may be due to structural differences in the organometallic species involved

Table 2. Regio- and Stereoselective Allenylation of Azetidine-2,3-diones **1**[a]

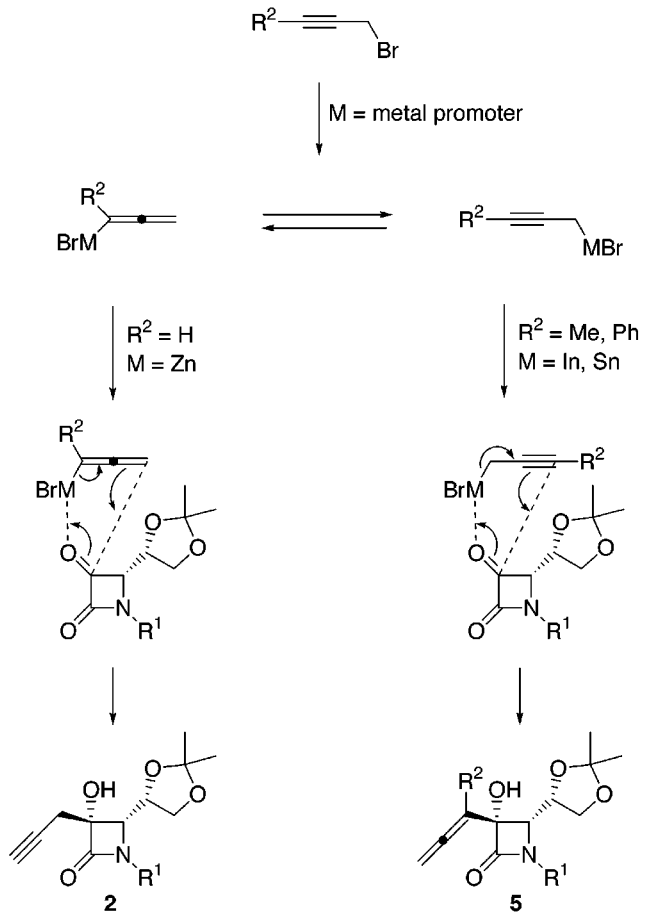


compound	R^1	R^2	M	system solvent	**4**:**5** ratio[b]	yield (%)[c]
4a/5a	PMP	Me	Zn	THF/NH_4Cl (aq. sat.)	0:100	59
4a/5a	PMP	Me	In	THF/NH_4Cl (aq. sat.)	0:100	74
4a/5a	PMP	Me	Sn	THF/NH_4Cl (aq. sat.)	0:100	16
4b/5b	Allyl	Me	In	THF/NH_4Cl (aq. sat.)	0:100	63
4c/5c	PMP	Ph	Zn	THF/NH_4Cl (aq. sat.)	20:80	71
4c/5c	PMP	Ph	Zn	THF/H_2O	0:100	16
4c/5c	PMP	Ph	In	THF/NH_4Cl (aq. sat.)	0:100	76
4c/5c	PMP	Ph	In	THF/H_2O	0:100	75
4c/5c	PMP	Ph	Sn	THF/NH_4Cl (aq. sat.)	0:100	75
4c/5c	PMP	Ph	Sn	THF/H_2O		*d*
4c/5c	PMP	Ph	$SnCl_2/CuBr_2$	THF (dry)		*d*
4d/5d	Allyl	Ph	In	THF/NH_4Cl (aq. sat.)	0:100	62
4e/5e	Propargyl	Ph	In	THF/NH_4Cl (aq. sat.)	0:100	48

[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] Acetonide cleavage and further internal acetal formation was observed.

in the reaction. It may be reasonable to postulate a metallotropic rearrangement between the propargylmetal and allenylmetal species. Both intermediates from this equilibrium are able to react with the 2,3-azetidinediones **1** through a six-membered transition state, leading to the homoallenyl or homopropargylic alcohols (Scheme 1).[16] The different

Scheme 1



regioselectivities observed in various system solvents should be attributed perhaps to the extent of coordination of the solvent molecules to the reactive organometallic species, stabilizing one of the intermediates involved in the metallotropic equilibrium rather than the other. These suggestions are presently made to try explain the regioselectivity of the reactions.

The stereochemistry at the C3-heterosubstituted quaternary center in compounds **2** and **5** was established by a study of their ^{1}H NMR spectra and comparing them with our previously reported azetidine-2,3-dione Baylis−Hillman adducts.[13] Qualitative homonuclear NOE difference spectra performed on the β-lactams (−)-**2b** and (+)-**5a** further confirmed these assignments. 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, thus the organometallic reagent being delivered preferentially to the less hindered face.

In conclusion, the present results provide the first insight into the manner in which 3-oxo-2-azetidinones undergo regio- and stereoselective metal-mediated carbonyl propargylation or allenylation of enantiomerically pure azetidine-2,3-diones, giving rise to the 3-substituted 3-hydroxy-β-lactam moiety, that should be useful in the elaboration of potentially bioactive compounds. Other aspects of this chemistry, together with a study involving the coupling between 4-oxoazetidine-2-carbaldehydes and a variety of propynyl/allenylmetal reagents both in anhydrous and aqueous environments are currently under investigation in our laboratory.

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

Supporting Information Available: Compound characterization data and experimental procedures for products (+)-**1d**, (+)-**2a**, (+)-**2b**, (+)-**4a**, and (+)-**4c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For a similar regiochemical preference on the indium-mediated allenylation of substituted propargyl bromides with aldehydes, see refs 2b and 3d.

(16) For related indium-mediated reactions, the regioselectivity has been proposed to be controlled by both steric and electronic effects. See refs 2b and 3d. For a comprehensive information on indium reagents, see: Cintas, P. *Synlett* **1995**, 1087.