

Environ-friendly Approaches to Densely Functionalized β -Lactams¹

M. Jayaraman, Maghar S. Manhas and Ajay K. Bose*

Department of Chemistry and Chemical Biology
 Stevens Institute of Technology, Hoboken, NJ 07030, USA

Dedicated to Prof. Ernest W. Robb on the occasion of his sixty-fifth birthday

Abstract: A convenient approach to densely functionalized α -allyl- β -lactams has been developed using organometallic reagents and α -keto- β -lactams. Indium mediated Barbier reaction in aqueous media proceeded with a higher level of diastereoselectivity and chemical yield than zinc mediated Barbier reaction in anhydrous organic solvents. © 1997, Elsevier Science Ltd. All rights reserved.

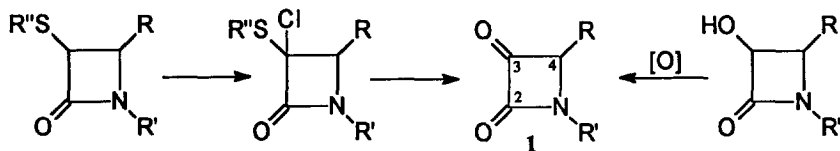
Publications from our research group² and other laboratories³ record many instances of β -lactams being used as synthons. A variety of natural products⁴ and biologically active compounds⁵ have been prepared from appropriately substituted β -lactams. In recent years we have reported stereocontrolled synthetic approaches to diverse types of 1,3,4-substituted azetidin-2-ones. However, alternative strategies that are more eco-friendly than traditional synthetic steps are being sought now, because of the increasing concern about the impact of chemical processes on the environment. We wish to report here preliminary results from our studies on environmentally benign reactions suitable for some β -lactam synthons with multiple functional groups.

Of special interest to us was the possibility of utilizing the recently described technique for conducting organometallic reactions in aqueous media.⁶ We planned to study reactions leading to α -allyl- β -lactams which are convenient intermediates for a variety of heterocyclic compounds including pyrrolidine and piperidine alkaloids.⁷

The 3-keto group in azetidin-2,3-diones (**1**) is known to be very active. Sheehan and Lo⁸ had conducted an aza-Wittig reaction on 6-oxo-penamams for generating the cephamycin type side chain. Palomo *et al.*⁹ have used the Reformatsky type reaction on azetidin-2,3-diones. In light of this we selected compounds of type **1** to be our starting material for model reactions.

In an earlier publication¹⁰ we had described a convenient access to 3-oxo-2-azetidinones (**1**) via 3-mercapto-2-azetidinones. The 3-oxo-2-azetidinones **1** are also available in high yield by the oxidation of 3-hydroxy-2-azetidinones (Scheme 1).¹¹

Scheme 1



α -Allylation of β -Lactams

Encouraged by the recent results¹² on Barbier type allylation of carbonyl compounds using zinc we tested a similar approach to the synthesis of α -allyl- β -lactams. At first we examined the reaction of allyl bromide with azetidin-2,3-diones **1** (Scheme 2).

Scheme 2

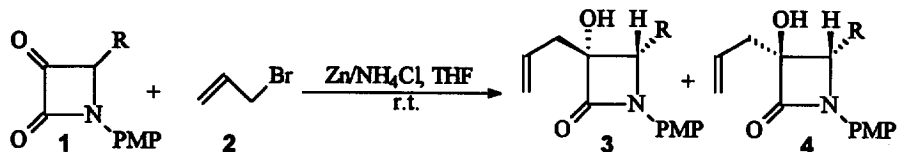


Table 1

Compound	R	Time	Yield (%) ^a	Ratio (3:4) ^b
1a	Ph	30 min	93	1:1
1b	PMP	3 h	94	4:1
1c	<i>o</i> -Br Ph	12 h	10	1:1

PMP = *p*-methoxyphenyl; *o*-Br Ph = *o*-bromophenyl;

a : isolated yields of pure products after column purification;

b : ratios were determined from the ¹H NMR spectra of crude reaction products.

We observed that allyl bromide (2,1 mmol) reacted at room temperature with azetidin-2,3-diones **1** (1 mmol) in THF (10 mL) as solvent, in the presence of zinc dust (1 mmol) and ammonium chloride (1 mmol) to afford the expected 3-allyl-3-hydroxy-2-azetidinones **3** and **4** as a mixture of diastereomers in varying ratios. The reaction proceeded in high chemical yield with **1a** and **1b**. However, in the case of **1c** (R = *o*-Br Ph), a complex mixture of products was formed from which the desired products were isolated in only 10% yield (Table 1).

The stereochemistry of the major product (80%) from the reaction of **1b** (R = PMP) was deduced to be **3b** from a study of the ¹H NMR spectrum of the mixture of **3** and **4** obtained as the crude reaction product. The methylene protons in **4** are in the shielding cone of the aryl group at C-4; their signal (multiplet) is therefore more upfield (2.83 - 2.66 ppm) than the corresponding signal in **3** which has the hydroxy group in the shielding cone of the aryl group (2.95 - 2.86 ppm). The methyl signal of the acetate of **3** is expected to be and was indeed observed at a higher field (1.50 - 1.60 ppm) than the corresponding signal (2.10 - 2.20 ppm) of **4**. The chemical shifts for the methylene signal observed in the ¹H NMR spectra of **3** and **4** thus provide a dependable clue to the stereochemistry of the other allylated β -lactams under study here (Table 2).

Indium Mediated Reactions in Aqueous Media

Organometallic reactions of indium can be conducted in aqueous media because of the high reactivity of this metal and its exceptional stability to air and water.¹³ Recent publications¹⁴ have shown that indium mediated coupling of carbonyl compounds with allyl halides can proceed with a high level of regio- and diastereo- selectivity. We have conducted the reactions of allyl bromide and indium with azetidin-2,3-diones

(Scheme 3) in water/tetrahydrofuran mixtures.¹⁵ The reaction proceeded in high yield (89%) even for 1c (R = *o*-Br Ph) which had given a poor yield when zinc was used as the metal.

In every case only a single diastereomer was obtained when indium was used. On the basis of ¹H NMR data, the stereochemistry in each case was deduced to be "Z" (i. e., the OH and the aryl group are *cis* to each other).²⁰

Scheme 3

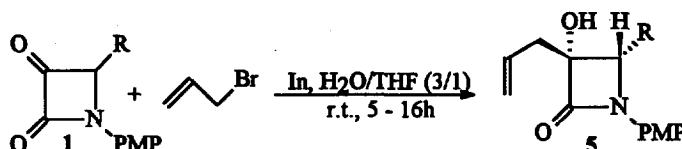


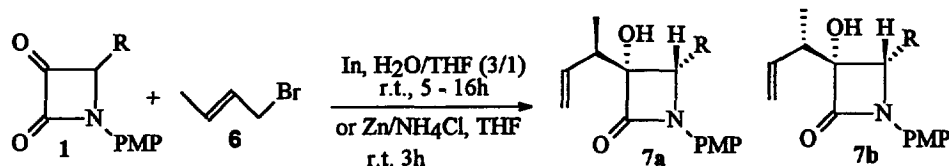
Table 2

Compd.	R	Time	Yield (%)
5a	Ph	8 h	89
5b	PMP	12 h	98
5c	Styryl	5 h	77
5d	<i>o</i> -Br Ph	16 h	83

Homoallylation with Crotyl Bromide

When crotyl bromide (6) was used in the organometallic reaction with 1, products were likely to be more diverse than in the case of allyl bromide because of the possibility of allylic shift which would create a new chiral center. In the zinc mediated reaction in THF, the major products were 7a and 7b formed via allylic rearrangement. ¹H NMR spectra indicated the presence of a vinyl group which disappeared on catalytic transfer hydrogenation to provide an ethyl group. These compounds (7a and 7b) were formed in equal proportion (1:1). Their stereochemistry was assigned on the basis of the chemical shifts in their ¹H NMR spectra (see above).

Scheme 4



Reaction between 6 and 1 mediated by indium in water-THF mixture led to 7a and 7b with a higher level of diastereoselectivity. The two isomers were obtained in the ratio 1:2. It would appear that the organoindium reagent favored the approach of the allyl group to the C-3 carbonyl from the less hindered face (i.e., the face opposite the aryl group at C-4). Such steric effect of a bulky group at C-4 in 2-azetidinones has been reported before for other reactions involving the C-3 site.¹⁶

The diastereospecific nature and the very high yield of the allyl bromide/indium reaction with 1 result in "atom economy"¹⁷; also the purification of the desired product becomes easier and organic waste is reduced. The use of an aqueous medium also reduces "pollution at the source". Further studies are in

progress on indium mediated eco-friendly reactions for the synthesis of α -alkylidene- β -lactams and spiro β -lactams.

Acknowledgment. Support of this research by Stevens Institute of Technology and the National Science Foundation (Grant No. HRD - 9450388) is gratefully acknowledged. We thank Ruby Cruz¹⁸ and Maria Batista^{18,19} for technical help.

References and Notes

1. Studies on Lactams Part 102. For Part 101, see: Bose, A. K.; Jayaraman, M.; Okawa, A.; Bari, S. S.; Robb, E. W.; Manhas, M. S. *Tetrahedron Lett.* **1996**, *39*, 6989.
2. (a) Manhas, M. S.; Amin, S. G.; Bose, A. K. *Heterocycles* **1976**, *5*, 699. (b) Manhas, M. S.; Wagle, D. R.; Chiang, J. *Heterocycles* **1988**, *27*, 1755.
3. Ojima I. In *The Organic Chemistry of β -Lactams*; Georg, G. I., Ed.; VCH: New York, **1992**; pp 197- and references cited therein.
4. Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383.
5. Georg, G.I.; Ravikumar, V. T. In *The Organic Chemistry of β -Lactams*; Georg, G. I., Ed.; VCH: New York, **1992**; pp 299-303 and references cited therein.
6. Li, C. J. *Tetrahedron* **1996**, *52*, 5643.
7. Bose, A. K.; Krishnan, L.; Wagle, D. R.; Manhas, M. S. *Tetrahedron Lett.* **1986**, *27*, 5955.
8. Sheehan, J. C.; Lo, Y. S. *J. Org. Chem.* **1973**, *38*, 3227.
9. Palomo, C.; Aizpurua, J. M.; Lopez, M. C.; Aurrekoetxea, N.; Oiarbide, M. *Tetrahedron Lett.* **1990**, *31*, 6425.
10. van der Veen, J. M.; Bari, S. S.; Krishnan, L.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1989**, *54*, 5758.
11. Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Carreaux, F.; Cuevas, C.; Maneiro, E.; Ontoria, J. M. *J. Org. Chem.* **1994**, *59*, 3123.
12. Ranu, B. C.; Majee, A.; Das, A. R. *Tetrahedron Lett.* **1995**, *36*, 4885 and references cited therein.
13. For recent reviews see: (a) Li, C. J.; *Chem. Rev.* **1993**, *93*, 2023. (b) Cintas, P. *Synlett* **1995**, 1087.
14. Isaac, M. B.; Chan, T. H. *Tetrahedron Lett.* **1995**, *36*, 8957.
15. In a typical procedure, azetidin-2,3-diones (1, 1 mmol) were dissolved in minimum amounts of THF (about 5 mL). Water (15 mL) was added to this solution followed by indium powder (1 mmol) and the reaction mixture was then stirred at room temperature. After the completion of the reaction (TLC monitoring), the reaction mixture was filtered through a pad of neutral alumina which was then washed with methylene chloride. The combined filtrates were taken in a separatory funnel and washed successively with water and brine and dried (Na_2SO_4). Removal of the solvent provided the crude product which was purified by column chromatography or crystallization.
16. (a) Kant, J.; Schwartz, W. S.; Vyas, D. *Tetrahedron Lett.* **1996**, *37*, 6495. (b) Palomo, C.; Cossio, F. P.; Ontoria, J. M.; Odriozola, J. M. *Tetrahedron Lett.* **1991**, *32*, 3105. Also see: ref. 9.
17. Trost, B. M. *Science* **1991**, *254*, 1471.
18. Undergraduate participants in our RISE (Research Initiation for Science Excellence) Project supported by the National Science Foundation (Research Careers for Minority Scholars Initiative).
19. American Chemical Society Minority Scholar.
20. All new compounds described in this paper provided satisfactory analytical and spectral data.

(Received in USA 23 October 1996; accepted 26 November 1996)