ORGANIC REACTIONS IN WATER: INDIUM MEDIATED SYNTHESIS OF α-ALKYLIDENE-β-LACTAMS[1]

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(Dedicated to Dr. Bernhard Witkop)

Abstract - Indium mediated Barbier type addition of allyl bromides to azetidine-2,3-diones (1) in aqueous media provided two homoallylic alcohols (for example, 2 and 3) which on mesylation followed by elimination in the presence of DBU gave a mixture of E and Z isomers of α-alkylidene-β-lactams (4 and 5) in excellent yield. These highly substituted β-lactams are versatile synthons for a variety of structures.

The need for designing environmentally benign organic synthesis[2] has directed attention to reactions in aqueous media. Some recent publications[3] have demonstrated that indium mediated Barbier type reactions are suitable for this approach. In this context, we[4] studied the reaction of an azetidine-2,3-dione (**1**) with allyl bromide and crotyl bromide in the presence of indium in aqueous tetrahydrofuran and reported stereoselective formation of homoallylic alcohols. Similar findings have been described more recently by Paquette and Isaac.[5]

Homoallylic Alcohols from Cinnamyl and Propargyl Bromides

We have now extended our studies to cinnamyl bromide and propargyl bromide which have the potential for producing a diversity of products because of the possible creation of a new chiral center. We have also examined the course of reaction with variously substituted azetidine-2,3-diones including an optically active member of the family, **1d**. The reaction conditions were the same as reported before.[4]

In our earlier study with crotyl bromide we had observed only the products of S_N2' reaction. The same mechanism appeared to be involved in the reaction with cinnamyl bromide (Scheme 1). Only two homoallylic alcohols (**2** and **3**) were obtained in very unequal amounts. The structure and stereochemistry of these alcohols were established mainly from ^{1}H NMR studies.

The hydroxyl group formed at C-3 and the aryl substituent at C-4 were found to be *cis* to each other. This preferred geometry could be accounted for by assuming that the allyl group favored approach to the C-3 carbonyl from the less hindered side (i.e., *trans* to the C-4 substituent). Such steric effect has been observed before.[6] Thus, the sodium borohydride reduction of 4-substituted azetidine-2,3-diones leads exclusively to the *cis* -α-hydroxy-β-lactam. This effect of steric hindrance is also compatible with the finding that isomer (**2**) with the side chain phenyl group and the 3-hydroxy group *threo* to each other is favored over **3**, the *erythro* isomer (Scheme 1). An examination of Table 1 shows that the styryl group at C-4 provides more steric hindrance than an aryl group. On the other hand, a glycol acetonide (Acet) group at C-4 shows limited

stereoselectivity. The azetidine-2,3-dione (**1d**) directs entry of the allyl group exclusively *trans* to Acet (i.e., from the less hindered face of the β-lactam ring) but it discriminates only slightly between *threo* and *erythro* isomers (**2d** and **3d**). The diastereoselectivities observed in similar reactions were recently explained by Paquette[5] *et al.* in terms of chelated transition states and our resutls are in line with their observations.

Scheme 1

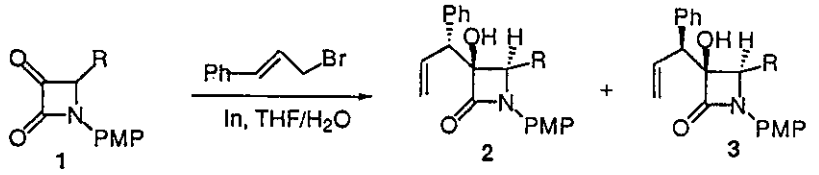


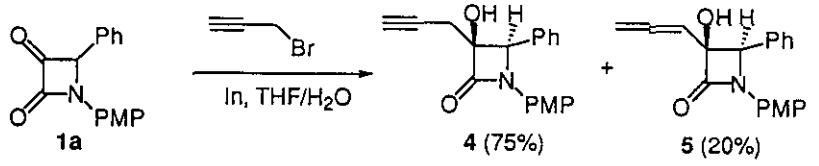
Table 1 : Synthesis of Homoallylic Alcohols (2) and (3)

Compound	R	Time	Yield (%)[a]	Ratio (2:3)[b]
a	Ph	20 min	94	80:20
b	PMP	2 h	87	81:19
c	Styryl	30 min	89	90:10
d	Acet	4 h	62	55:45

PMP = *p*-methoxyphenyl; Acet =  ; a: Total yield of both isomers after column purification;
b: Ratios were determined from the ^{1}H NMR spectra of crude reaction products.

Indium mediated addition of propargyl bromide to the azetidine-2,3-dione (**1a**) also proceeded with high level of diastereoselectivity. Only a single diastereomer (**4**) was isolated in 75% yield along with a 20% yield of the isomerized allene (**5**) (Scheme 2). The C-3 hydroxy group in both **4** and **5** was *cis* to the C-4 phenyl substituent. Such isomerization of the alkyne to an allene has been reported by Issac[7] *et al.* and our results are in line with their reported observation that simple prop-2-yn-1-yl bromide produced the homopropargyl alcohol (**4**) as the major product.

Scheme 2



Densely Functionalized β-Lactam Synthons

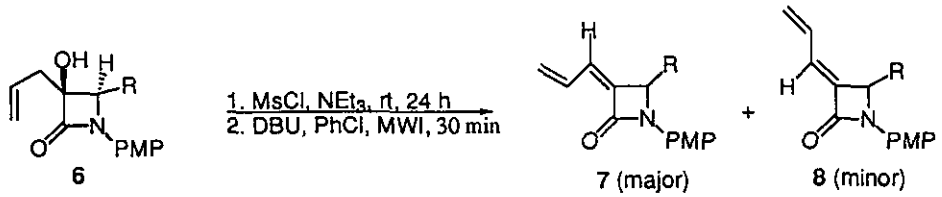
The indium mediated reaction described here is an eco-friendly pathway to diverse allyl groups with an additional homoallylic hydroxy function at C-3. These allyl groups provide access to variously substituted β-lactams and other structures. For example, in an earlier publication we[8] ozonized an allyl group in the C-3 side chain of an optically active β-lactam related to **2d**; we obtained an aldehyde which led in a few steps to an optically active morpholine derivative *via* a facile rearrangement of the β-lactam ring. The PMP group on the nitrogen in **2** and **3** can be removed by ceric (IV) ammonium nitrate oxidation[9] and alkyl or acyl groups

can be introduced in its place. The C-4 aryl group can be oxidized to a carboxy group which can be transformed into many other useful functional groups.

α-Alkylidene-β-lactams

Treatment of the homoallylic alcohols (**6**) (previously prepared in our laboratory[4]) with mesyl chloride and triethylamine led to the mesylate in near quantitative yield. Base catalyzed elimination of the mesylate was conducted using Microwave induced Organic Reaction Enhancement (**MORE**) chemistry techniques developed in our laboratory.[10] Treatment of the mesylates with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in chlorobenzene under microwave irradiation provided the α-alkylidene-β-lactams (**7**) and (**8**) in good yield in 20-30 min (Scheme 3). The products were a mixture of *E* and *Z* isomers (Table 2).

Scheme 3



MWI = Irradiation in a domestic microwave

Table 2 Synthesis of α-Alkylidene-β-lactams 7 and 8

Compound	R	Yield (%)[a]	Ratio (7:8)[b]
a	Ph	95	79:21
b	PMP	82	82:18
c	*m*-Br Ph	79	75:25
d	Styryl	96	>98:<2
e	Acet	93	>98:<2

PMP = *p*-methoxyphenyl; Acet =  ; a: Total yield of both isomers after column purification; b: Ratios were determined from the ^{1}H NMR spectra of crude reaction products.

The stereochemistry of the products was determined from the chemical shift of the olefin doublet of the γ-proton.[11] The γ-proton doublet was more downfield (6.70 - 6.90 ppm) for the *E* isomer because of the deshielding effect of the β-lactam carbonyl. In the case of the *Z* isomer a doublet appeared upfield (6.00 - 6.20 ppm). In all the cases, the *Z* isomer was found to be the major product[12] and this could be attributed to the steric hindrance from the bulky R group which strongly disfavors the formation of **8**.

On the basis of our earlier work[13] we expect that catalytic transfer hydrogenation of **7** and **8** using MORE chemistry techniques will stereospecifically generate a *cis*-alkyl group at C-3. The Staudinger reaction for α-alkyl-β-lactams is known to produce only the *trans*-isomer in most cases.

In conclusion, we have developed an efficient and stereoselective method for the introduction of various side chains at the C-3 position of 2-azetidinones. The conjugated diene in the side chain so obtained is under study as an intermediate for the Diels-Alder reaction.

ACKNOWLEDGMENT

Support of this research by Stevens Institute of Technology and the National Science Foundation (HRD - 9450388) is gratefully acknowledged. Ms. Maria Batista, an undergraduate participant in the summer research program UPTAM (Undergraduate Projects in Technology and Medicine) at Stevens Institute, is thankful to the 'Minority Scholars Program' of the American Chemical Society and the 'Research Careers for Minority Scholars' program of the National Science Foundation for financial aid.

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12. All new compounds described in this paper provided satisfactory analytical and spectral data: Representative data for **7a**: mp 124-126 °C ; IR (KBr) 1720, 1612 and 1510 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30 - 7.20 (m, 5 H), 7.15 (d, *J* = 9 Hz, 2 H), 7.12 - 7.03 (m, 1 H), 6.66 (d, *J* = 9 Hz, 2 H), 5.88 (d, *J* = 11.3 Hz, 1 H), 5.25 (s, 1 H), 5.20 (d, *J* = 7.8 Hz, 1 H), 3.61 (s, 3 H); Anal. Calcd for $C_{19}H_{17}NO_2$ C, 78.33; H, 5.88; N, 4.81. Found: C, 78.27; H, 6.15; N, 4.92. **8a**: mp 110-112 °C; IR (KBr) 1726 and 1512 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40 - 7.10 (m, 7 H), 6.62 (d, *J* = 9 Hz, 2 H), 6.51 (d, *J* = 11.4 Hz, 2 H), 6.06 - 5.93 (m, 1 H), 5.38 - 5.25 (m, 2 H), 5.17 (d, *J* = 10 Hz, 1 H), 3.55 (s, 3 H); Anal. Calcd for $C_{19}H_{17}NO_2$ C, 78.33; H, 5.88; N, 4.81. Found: C, 78.47; H, 6.01; N, 4.89.
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Received, 1st June, 1998