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Indium and Zinc Mediated Barbier Type Reactions: Allylation and Propargylation Reactions of 6-Oxopenicillanate and 7-Oxocephalosporanate

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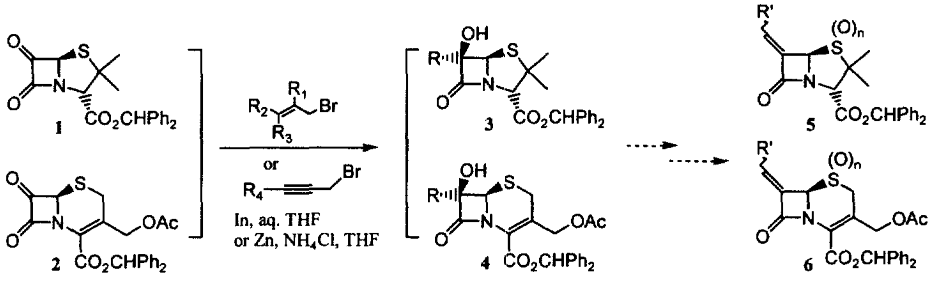
Abstract: Allylation and propargylation of compounds, 6-oxopenicillanate **1** and 7-oxocephalosporanate **2**, were accomplished by reacting the corresponding bromides in the presence of indium or zinc. Both indium and zinc gave alkylated products in moderate yields under mild conditions. Indium mediated Barbier reactions in aqueous THF exhibited slightly higher stereoselectivity than zinc mediated reactions in anhydrous THF.

Allylation and propargylation at 6- and 7-carbonyl of **1** and **2** respectively can be a key step in preparing new β-lactam antibiotics. The 6-exomethylenepenam compound **5** has been known as a potent β-lactamase inhibitor.[1] This compound was prepared by the Wittig reaction of the corresponding ylide with **1**, or by a coupling reaction of an aldehyde and a metallated compound generated from mono or dihalopenams at low temperature followed by dehydration.[2,3] Recently Bose *et al.* reported that azetidine-2,3-diones could be alkylated with allyl bromides by the mediation of indium or zinc to give the corresponding α–allyl–β–hydroxy-2-azetidinones, in which indium mediated reaction afforded a higher level of diastereoselectivity and chemical yield than zinc mediated one.[4]



R = allyl, propargyl, allenyl

n = 0, 2

In this paper we report the results of indium and zinc mediated allylation and propargylation of 6-oxopenicillanate **1** and 7-oxocephalosporanate **2**. Starting compounds **1** and **2** were prepared by a known

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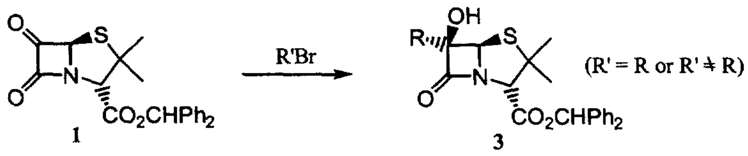
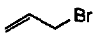
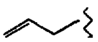
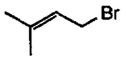
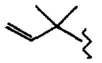
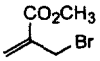
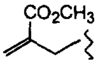
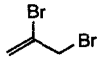
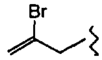
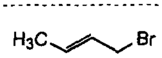
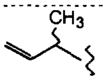
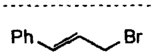
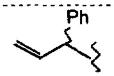
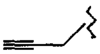
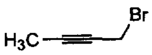
method[5] and purified by a short column chromatography due to their instability. Barbier type reactions of compounds **1** and **2** were achieved with two methods; method A, indium mediated reaction in aqueous THF and method B, zinc mediated reaction with NH$_4$Cl in anhydrous THF. The stereochemical assignments of **3** and **4** were based on the result of Buynak *et al.* that the reaction between **1** or **2** and a Grignard reagent (ethynylmagnesium bromide) gave the corresponding 6β-hydroxylactam owing to their convex structure.[6] The proton and carbon NMR data of the products **3** and **4** obtained from the reaction of allyl bromide mediated by indium and zinc were correctly matched to the NMR data of the products obtained from the reaction of allylmagnesium bromide, respectively.[7] Thus the hydroxy groups of **3** and **4** were assigned to be located at the β-position.

Table 1. Indium and zinc mediated Barbier type reactions of 6-oxopenicillanate **1**[a]

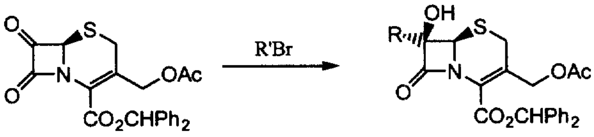


Entry	Bromide (R'Br)	Method	Time(h) (r.t.)	Isolated yield	R
1		A B	1.5 2	68 56	
2		A B	2 2	69 75	
3		A B	3 4	70 74	
4		A B	12 9	35 21	
5		A B	3 4	78(1.5:1)[b] 55(1.3:1)[b]	
6		A B	3 4	71(9:1)[b] 70(4:1)[b]	
7		A B	3 2	44(5:1)[c] 71(40:1)[c]	 
8		A B	3 4	72 65	

a; All reactions were carried out 0.2 – 0.5 mmol scale. b; diastereomeric ratio (determined by ^{1}H or ^{13}C NMR). c; propargyl : allenyl

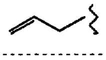
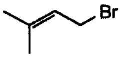
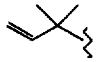
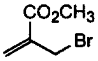
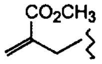
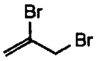
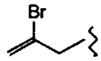
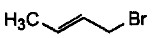
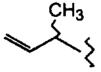
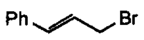
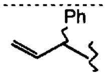
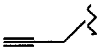
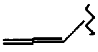
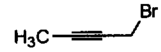
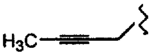
Typical reaction procedures are as follows; Method A: α-Oxo-lactam (0.39 mmol, **1** or **2**) was dissolved in water (3 mL) and THF (1mL), followed by the addition of indium powder (0.47 mmol) and bromide (0.58 mmol) at room temperature. The reaction mixture was stirred for the appropriate time (see Table 1, 2), filtered through a pad of alumina and washed with CH$_2$Cl$_2$. After a usual workup, the crude product was purified by column chromatography. Method B: α-Oxo-lactam (0.28 mmol, **1** or **2**) and NH_4Cl (0.34 mmol) were added in THF (3mL), followed by adding zinc dust (0.34 mmol) and bromide (0.42 mmol) at room temperature. The reaction mixture was stirred for the appropriate time (see Table 1, 2) and extracted with ethyl acetate. After a usual workup, the crude product was purified by column chromatography. Table 1 represents the results obtained from indium and zinc mediated Barbier reactions of compound **1** according to method A and B. Except entry 4, the yields were largely improved compared to the corresponding Grignard reactions. It took a long reaction time for the entry 4 (2,3-dibromopropene) and extensive decomposition of **1** was observed. Regarding stereoselectivity, indium was slightly more effective than zinc (entry 5, 6). The higher selectivity for cinnamyl bromide (entry 6) than crotyl bromide (entry 5) could be explained by the conventional six-membered transition state (Figure 1).[8] In entry 7, the reaction of propargyl bromide gave both propargyl and allenyl compounds, and zinc provided higher chemical yield and more propargyl compound than indium. Substituted propargyl alcohol, 1-bromo-2-butyne (entry 8) yielded only 2-butynyl compound.

Table 2. Indium and zinc mediated Barbier type reactions of 7-oxocephalospranate **2**[a]



2 **4**

(R' = R or R' ≠ R)

Entry	Bromide (R'Br)	Method	Time (r.t.)	Isolated yield	R
1		A	1.5	59	
		B	4	55	
2		A	4	47	
		B	2	61	
3		A	4	73	
		B	4	80	
4		A	12	19	
		B	12	16	
5		A	3	68(1.5:1)[b]	
		B	4	51(1.3:1)[b]	
6		A	3	57(30:1)[b]	
		B	4	61(12:1)[b]	
7		A	3	42(6:1)[c]	 
		B	2	55(40:1)[c]	
8		A	3	69	
		B	4	55	

a; All reactions were carried out 0.2 – 0.5 mmol scale. b; diastereomeric ratio (determined by ^{1}H or ^{13}C NMR). c; acetylene : allene

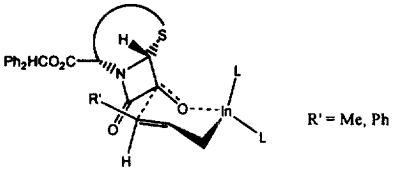


Figure 1

Indium and zinc mediated reactions were also applied to 7-oxocephalosporanate **2** under the same conditions. The results were similar to those observed in the reaction of 6-oxopenicillanate **1**. Generally the yields were relatively lower than 6-oxopenicillanate **1**, but the stereoselectivity in entry 6 was much increased.

In summary, allylation and propargylation of compounds, **1** and **2**, using both indium and zinc gave reasonable yields under mild conditions. Indium mediated allylation of compounds, **1** and **2**, afforded relatively higher stereoselectivity than zinc.

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7. Entry 1 in table 1: ^{1}H NMR (CDCl$_3$, δ): 7.35(m, 10H), 6.96(s, 1H), 5.88(m, 1H), 5.42(s, 1H), 5.25(m, 2H), 4.57(s, 1H), 2.72 (m, 2H), 1.61(s, 3H), 1.29(s, 3H); ^{13}C NMR(CDCl$_3$, δ): 175, 166, 139, 130, 128.5, 128.4, 127.5, 126.9, 119.9, 99.9, 86.2, 78.4, 74.3, 69.5, 65.2, 38.4, 26.1. Entry 1 in table 2: ^{1}H NMR(CDCl$_3$, δ): 7.35(m, 10H), 6.92(s, 1H), 5.87(m, 1H), 5.24(d, J = 20 Hz, 1H), 5.20(d, J = 6 Hz), 5.10(d, A of ABq, J = 18 Hz, 1H), 4.81(d, B of ABq, J = 18 Hz, 1H), 4.24 (s, 1H), 3.51(d, A of ABq, J = 15 Hz, 1H), 3.32(d, B of ABq, J = 15 Hz), 2.75(d, J = 9 Hz), 2.01(s, 3H); ^{13}C NMR((CDCl$_3$, δ): 171.0, 168.2, 161.1, 139.8, 139.6, 130.9, 129.2, 129.1, 129.0, 128.9, 128.7, 128.6, 128.5, 128.2, 127.9, 127.7, 127.4, 126.0, 121.0, 87.3, 80.2, 63.4, 62.4, 39.7, 26.8, 21.1.
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