

Studies Towards Total Synthesis of Antillatoxin: Investigation of the Indium-mediated Allylation Reactions of Carbonyl Compounds with β -Bromocrotylbromide in Water

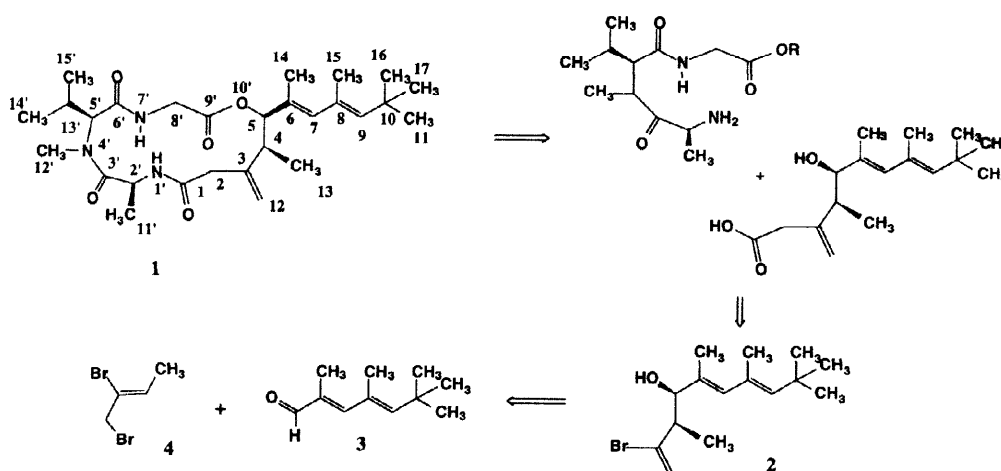
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Abstract: Indium mediates the coupling of β -bromocrotylbromide with carbonyl compounds in saturated ammonium chloride in the presence of lanthanide triflate under sonication to give the corresponding compounds in good yield and moderate to high *syn* diastereoselectivity.
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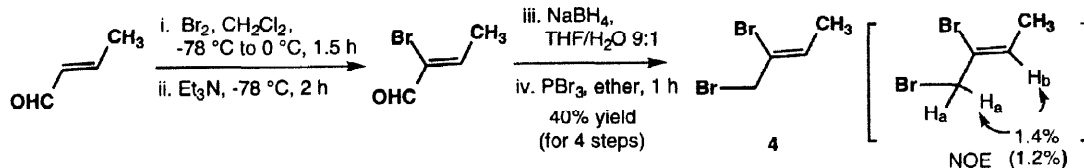
As part of our studies towards the total synthesis of antillatoxin (**1**),¹ we are interested in the synthesis of the advanced intermediate, homoallylic alcohol (**2**) (Scheme 1). We envisage that the homoallylic alcohol (**2**) can be obtained from the metal-mediated allylation of aldehyde (**3**) and β -bromocrotylbromide in water.^{2,3} We attempted the indium-mediated reactions of β -bromocrotylbromide with various aldehydes in water using procedures described in the literature.^{3,4} Unfortunately, the desired coupling product was not observed or obtained in low yield under various conditions even with the use of water-stable Lewis acids.⁵ These results have prompted us to find new conditions for the metal mediated coupling of this unreactive bromide with carbonyl compounds in water. In this paper, we describe a new procedure for the coupling of unreactive bromide (**3**) with carbonyl compounds to give the corresponding product in good yields. In certain cases, high *syn* selectivity was observed. The conditions are sonication carried out in saturated ammonium chloride with indium in the presence of an external Lewis acid affording the homoallylic alcohol in good yield.



Scheme 1

The *Z*-2-bromo crotyl bromide (**4**) was prepared in four steps from commercially available crotonaldehyde (Scheme 2). Bromination of crotonaldehyde with bromine followed by base treatment (Et_3N) afforded the 2-bromoaldehyde. Reduction of the aldehyde to alcohol was accomplished using NaBH_4 in $\text{THF}/\text{H}_2\text{O}$ at 0°C for 1 h. Treatment of the alcohol with PBr_3 in Et_2O at 0°C afforded the

desired product **4** in 40% overall yield (4 steps). The *Z*-configuration of olefin **4** was confirmed by NOE studies. Irradiation of H_a causes an NOE enhancement of H_b (1.4%) but not of the methyl group.



Scheme 2

As model studies, we first investigated the reaction of cinnamaldehyde with 2-bromocrotylbromide (**4**) using indium in various reaction conditions. Especially noteworthy is the fact that the reactions using

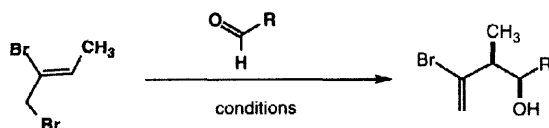


Table 1. Indium-Mediated Allylation reaction ^a

Entry	Aldehyde	Allylic bromide	Conditions	% Yield (<i>anti:syn</i>)
1			In, H ₂ O, 23 °C	no reaction
2		4	In, La(OTf) ₃ , H ₂ O, 23 °C	15%
3		4	In, Yb(OTf) ₃ , H ₂ O, 23 °C	38% (76:24)
4		4	In, EtOH/0.1N HCl 9:1, 40 °C, 2 days	55% (76:24)
5		4	In, sat. NH ₄ Cl, 48 h	55% (67:33)
6		4	In, La(OTf) ₃ , sat. NH ₄ Cl, 36 h	80% (75:25)
7		4	In, La(OTf) ₃ , sat. NH ₄ Cl, 16 h	80% (78:22)

a. the reaction scale: 0.3 mmol In, 0.1 mmol La(OTf)₃, 0.3 mmol bromide **4**, 0.1 mmol aldehyde in 5 ml sat. NH₄Cl.

classical procedures proceeded to afford the product in either no reaction or low yield (Table 1, entries 1, 2 and 3). The reaction in the presence of lanthanide triflate or ytterbium triflate yielded the product in very low yield. Using Whiteside's procedure the reaction afforded the product in moderate yield after 2 days. The best condition is when the reaction was carried out in sat. ammonium chloride in the presence of lanthanum triflate under sonication. The reaction was completed after 16 h affording the product in good

yield. The reaction was clean. Only the 1,2-addition product and γ -product was obtained. Especially noteworthy is the fact that the reaction proceeded to yield the *syn* isomer as the major product.

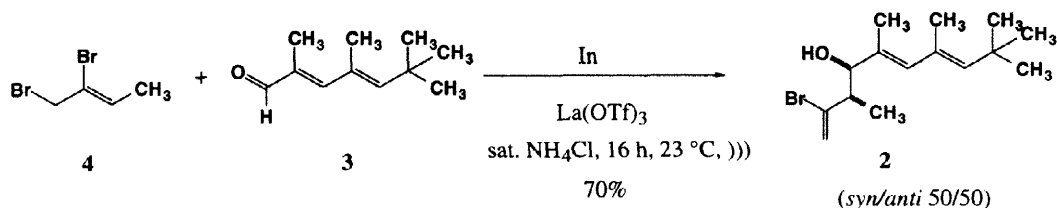
Once the reaction conditions were optimized, the reactions of 2-bromocrotylbromide (**4**) with a variety of aldehydes were investigated. The results are summarized in Table 2. In all cases, the reactions proceeded smoothly to afford the corresponding products in good yields. As indicated in Table 2, the major isomer in all cases was found to have *syn* configuration except for 2-pyridine carboxaldehyde. Only 1,2-addition product was observed for α,β -unsaturated aldehydes (entries 1, 8 & 9). Especially noteworthy is the reaction of bromide **4** with benzaldehyde which afforded the *syn* product as the sole isomer. The high *syn* selectivity observed can be explained using the reported proposed mechanism.^{5b,6}

Table 2. Indium-Mediated Allylation reaction using 2-bromocrotylbromide (**4**)^a

Entry	Aldehyde	Allylic bromide	Conditions	% Yield ^b (<i>anti</i> : <i>syn</i>) ^c
1			In, La(OTf) ₃ , sat. NH ₄ Cl,)), 16 h	80% (78:22)
2		4	In, La(OTf) ₃ , sat. NH ₄ Cl,)), 16 h	100% (50:50)
3		4	In, La(OTf) ₃ , sat. NH ₄ Cl,)), 16 h	88% (81:19)
4		4	In, La(OTf) ₃ , sat. NH ₄ Cl,)), 16 h	50% (42:58)
5		4	In, La(OTf) ₃ , sat. NH ₄ Cl,)), 16 h	70% (73:27)
6		4	In, La(OTf) ₃ , sat. NH ₄ Cl,)), 16 h	95% (76:24)
7		4	In, La(OTf) ₃ , sat. NH ₄ Cl,)), 16 h	70% (100:0)
8		4	In, La(OTf) ₃ , sat. NH ₄ Cl,)), 16 h	80% (50:50)
9		4	In, La(OTf) ₃ , sat. NH ₄ Cl,)), 16 h	93% (77:23)

a. All reactions were done on 0.1-0.5 mmol scales; Reactions were carried out with aldehyde (1 eq.), Indium (3 eq.), allylic bromide (3 eq.), La(OTf)₃ (1 eq) in sat. NH₄Cl with sonication ; b. the yield was based on separated product by flash column chromatography; c. the *syn/anti* ratio was determined by ¹H NMR and the relative stereochemistry was determined by comparing the ¹H NMR with that of literature. ²

The indium mediated allylation of bromide **4** with aldehyde **3** was carried out using the conditions as described above, that is in sat. NH₄Cl in the presence of lanthanide triflate under sonication. The reaction proceeded smoothly to give the desired homoallylic alcohol (**2**) in 70% yield. Although, no selectivity was observed, the two diastereomers can be easily separated by flash column chromatography.



In conclusion, we have found a new procedure for the indium-mediated coupling of unreactive halide (**4**) with aldehydes. The reaction proceeded smoothly with a wide variety of aldehydes which afforded the corresponding homoallylic alcohols in high yields. In certain cases, high *syn* selectivities were observed. Furthermore, it has provided an easy entry to the advanced intermediate for the total synthesis of antillatoxin.⁷

References and Notes

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