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An In-Mediated Tandem Reaction of Aldehydes with 3-Bromo-1-propyne To Produce 1-Substituted-3-methylene-5-yn-1-ol Compounds

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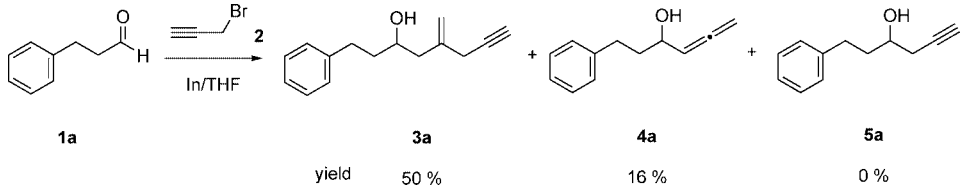
A one-pot reaction for the synthesis of 1-substituted-3-methylene-5-yn-1-ol compounds from In-mediated propargylation of aldehydes with 3-bromo-1-propyne was reported. Our studies showed that the propargylic alcohol formed in the reaction was selectively subjected to further propargylation of the triple bond to afford the Markovnikov addition products in a regiospecific fashion.

Introduction

Organoindium chemistry has attracted considerable interest.[1] In particular, the reaction of carbonyl compounds with propargylic halides and indium has been extensively studied because they provide an efficient method to the syntheses of propargylic and allenic alcohols.[2] Usually the use of propargyl– and allenyl–metal derivatives resulted in the formation of product mixtures[3] because of the potential for metallotropic rearrangement between these two species.[4] Moreover, accessibility of these propargyl and allenyl nucleophiles is highly substrate dependent.[3–5] Experimental and theoretical studies[2f] have showed that substitution on the propargyl bromide affects the equilibrium between propargyl– and allenyl–metal derivatives, and the nature of the organoindium species [In^{I} or In^{III}] formed depends on the solvent used. Highly regioselective syntheses of allenic and homopropargylic alcohols has been achieved by In-mediated reactions of silicon-substituted propargyl bromide with aldehydes in THF.[2d] Here we present a chemo- and regioselective method for the synthesis of 1-substituted-3-methylene-5-yn-1-ols by the In-mediated tandem reaction of aldehydes with 3-bromo-1-propyne.

Results and Discussion

Recently, while investigating the In-mediated (In powder, 2.5 mmol) reaction of hydrocinnamyl aldehyde (1 mmol) with 3-bromo-1-propyne (**2**, 2.5 mmol) in THF (1 mL), we



Scheme 1. Products of propargylation of hydrocinnamyl aldehyde mediated by In in THF.

consistently detected the formation of product **3a** in addition to allenic alcohol **4a** (Scheme 1). No trace of homopropargylic alcohol **5a** was detected. The structure of **3a** was determined and confirmed by high-resolution mass spectrometry and 1D NMR (^{1}H and ^{13}C) and 2D NMR (COSY and HMQC) spectroscopy.

This interesting result prompted us to monitor the progress of the reaction by using NMR spectroscopy.[6]It was observed that after 10 min of stirring, all the aldehyde was consumed with the appearance of a mixture of allenic alcohol **4a**, homopropargylic alcohol **5a** and **3a**. As the re-

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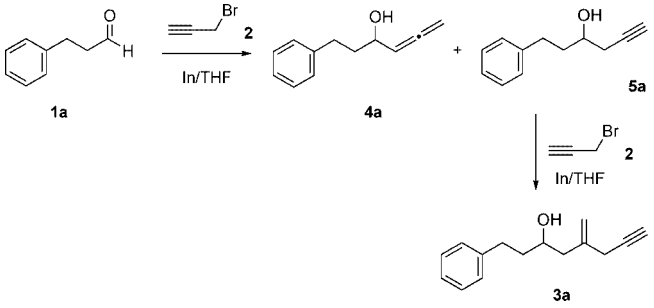
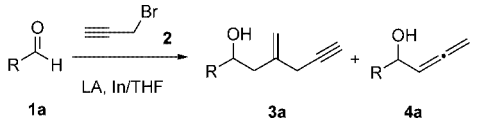
action progressed, the amount of **5a** decreased as the amount of **3a** increased, whereas the amount of allenic alcohol remained unchanged. These results showed that the initially formed homopropargylic alcohol was slowly converted into **3a** in the presence of an excess amount of propargylic bromide and indium (Scheme 2).



Scheme 2. The reaction pathway for the formation of **3a**.

Because of the potential usefulness of 1-substituted-3-methylene-5-yn-1-ol compounds (**3a**) in organic synthesis, our studies were further directed to improve the yield of **3a**. A variety of solvents were screened, and the reaction done in THF was found to afford the product with the highest yield of 50%. In contrast, **3a** was obtained in only 15% yield when toluene was used as the solvent. All other solvents screened (ether, methanol, DMF, dichloromethane and water) suppressed the formation of **3a** completely. Several Lewis acids were also screened with THF as the solvent to investigate the impact on the reaction (Table 1), and it was found that with the $InBr_3$ catalyst, the yield of **3a** increased to 65%. Further optimization by carrying out the reaction at lower temperature (0 °C) increased the product yield to 70%.

Table 1. Impact of Lewis acids on the tandem propargylation of aldehyde.[a]

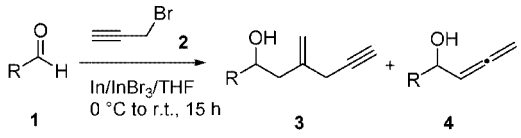


Entry	Lewis Acid	Yield of **3a+4a** [%] (ratio of **3a/4a**)[b]
1	–	66 (76:24)
2	$La(OTf)_3$	66 (76:24)
3	$Yb(OTf)_3$	34 (70:30)
4	$In(OTf)_3$	37 (71:29)
5	$InCl_3$	77 (76:24)
6	$InBr_3$	84 (77:23)
7	InI_3	71 (76:24)
8	$InBr_3$[c]	85 (82:18)

[a] Reaction conditions (unless otherwise stated): aldehyde (1 mmol), propargyl bromide (2.5 mmol), In (powder, 2.5 mmol), Lewis acid (0.1 mmol), THF (1 mL), r.t., 15 h. [b] Isolated yield. [c] Mixing was initially carried out at 0 °C.

The optimized reaction conditions with propargyl bromide **2** were extended to other aldehydes. The results are summarized in Table 2. In most cases, the reaction proceeded smoothly to afford desired products **3** in moderate-to-good yields.

Table 2. $InBr_3$-catalyzed tandem reaction of different aldehydes with 3-bromo-1-propyne.



Entry	Aldehyde **1**, R=	Product **3+4**[a]	Yield of **3+4** [%] (ratio of **3**:**4**)[b]
1	**1a**	**3a+4a**	85 (82:18)
2	**1b**	**3b+4b**	74 (92:8)
3	**1c**	**3c+4c**	84 (83:17)
4	**1d**	**3d+4d**	76 (86:14)
5	**1e**	**3e+4e**	93 (86:14)
6	**1f**	**3f+4f**	91 (86:14)
7	**1g**	**3g+4g**	78 (91:09)

[a] Reaction conditions: aldehyde (1 mmol), propargyl bromide (2.5 mmol), In (powder, 2.5 mmol), $InBr_3$ (0.1 mmol), THF (1 mL), 0 °C to r.t., 15 h. [b] Isolated yield.

With both the aliphatic and aromatic aldehydes, further propargylation was selective on the triple bonds and produced Markovnikov addition products **3**. One can rationalize that the reaction is similar to the reported allylindation of alkynes with allylindium,[7] and it was demonstrated that Markovnikov addition products were selectively produced by allylindation of alkynes with allylindium. The authors suggested the reaction occurred by initial indium acetylide formation followed by the addition of one equivalent of allylindium across the triple bond. Our results also suggested a similar pathway.

The propargylation of **3** did not proceed further even with an excess amount of propargylic indium. This result was consistent with a previous report by Chan et al.[2b] Our result also implied that the hydroxy group facilitated the propargylation of triple bonds.

Attention is drawn to the fact that the subsequent propargylation to form **3** occurred preferentially with **5** that bears the alkyne moiety rather than **4** that bears the allenic group. This result was different from the recently reported observation by Chan.[2b] They found that when methyl-substituted propargyl bromide (1-bromo-2-butyne) was used, further allenation on the allenic alcohol was observed. To demonstrate that further propargylation was not favoured on allenic alcohol in our reaction system, we carried out a reaction by using a preformed mixture of allenic alcohol

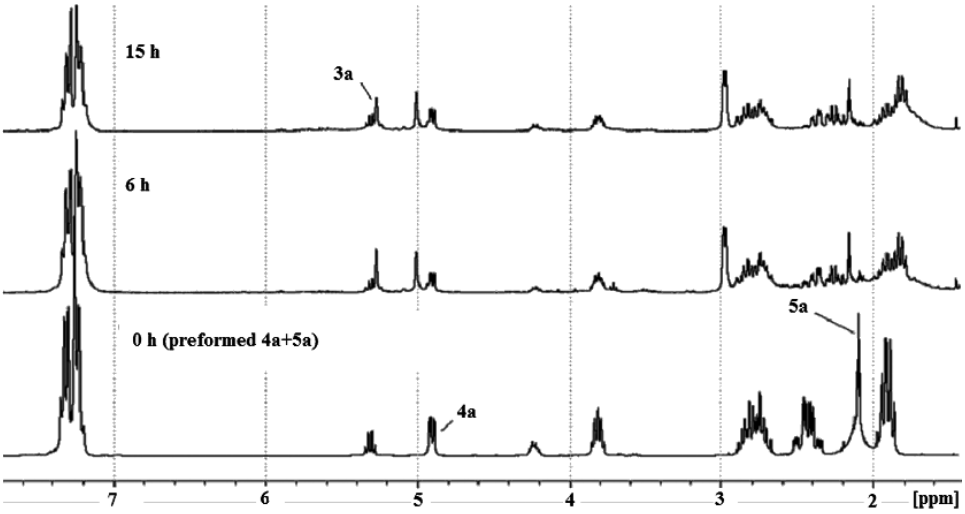


Figure 1. NMR study on the chemoselectivity of subsequent propargylation.

(**4a**) and propargylic alcohol **5a**[8] for further propargylation, which was mediated by indium in THF, with an excess amount of propargylic bromide **2** (2.5 equiv.).[9] The result was consistent with our initial observation on the direct propargylation on aldehydes; the propargylation of **5a** occurred smoothly to produce **3a** and the reaction was complete in 15 h (Figure 1). Most importantly, **4a** remained unchanged in the reaction, thus confirming our initial proposal. However, the reason for the different selectivity is still, at present, not fully understood.

Our results also showed that further reaction on the triple bond was highly regioselective; only the propargylation product was produced and no allenylation product was collected. This can be best interpreted by the equilibrium between propargyl and allenyl metal intermediates. Studies by Chan et al.[2f] showed that in the parent propargyl/allenyl indium system, the equilibrium is in favour of the allenylindium species. Hence, in our reaction, when the parent bromide (3-bromo-1-propyne) was used, further propargylation occurred and a product with a terminal triple bond was collected. Studies also showed that with methyl substitution on the propargyl bromide, the equilibrium is in favour of the propargyl species. Thus, as reported by Chan's group, further reaction on the triple bond producing a terminal allenic product (allenylation product) was observed when methyl-substituted propargyl bromide was used.[2b]

It is worthy to note that under the current reaction conditions, the obtained products were different than the ones obtained in the presence of the chiral promoter cinchonidine, as previously reported by our group.[2c] Further reaction at the triple bond to produce 1-substituted-3-methylene-5-yn-1-ol was not observed in the presence of cinchonidine, and we suggested that this was due to the deactivation of the allenylindium species through the formation of allenyl indium–cinchonidine complexes.

Conclusions

A chemo- and regioselective method was developed for the synthesis of 1-substituted-3-methylene-5-yn-1-ols by the In-mediated tandem reaction of aldehydes with 3-bromo-1-propyne. Further studies to expand the scope of this reaction and its application to the synthesis of complex molecules are in progress.

Experimental Section

Illustrative Experimental Procedure

Synthesis of 3a: Propargyl bromide (**2**; 0.22 mL. 2.5 mmol) was added to a mixture of In (powder, 285 mg, 2.5 mmol), hydrocinnamyl aldehyde (**1a**; 0.12 mL, 1 mmol) and $InBr_3$ (35 mg, 0.1 mmol) in THF (1 mL) at 0 °C. The resulting mixture was warmed to room temperature and stirred for 15 h. The reaction was quenched by the addition of water (0.5 mL), and the mixture was extracted with diethyl ether (3 × 10 mL). The organic layer was combined and washed with brine and dried with anhydrous $MgSO_4$. Evaporation of the solvent followed by purification by silica gel chromatography gave a mixture of **3a** and **4a** as an oil (**3a**, 150 mg, 70%). FTIR (KBr, neat): $\tilde{\nu}$ = 3310, 2117, 1680, 1602, 1494, 1454 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.34–7.21 (m, 5 H, Ph), 5.28 (d, J = 1.5 Hz, 1 H, =C*H*H), 5.01 (s, 1 H, =CH*H*), 3.84–3.79 (m, 1 H, C*H*OH), 2.97 (br. s, 2 H, HCCCH_2), 2.89–2.81 (m, 1 H, PhC*H*H), 2.79–2.70 (m, 1 H, PhCH*H*), 2.37 (dd, J = 3.7, 14.1 Hz, 1 H, CHOHC*HH*C=C), 2.25 (dd, J = 6.0, 14.1 Hz, 1 H, CHOHCH*H*C=C), 2.19 (t, J = 2.5 Hz, 1 H, CC*H*), 1.83–1.80 (m, 2 H, $PhCH_2CH_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 142.0, 140.8, 128.5, 128.4, 125.9, 114.6, 81.2, 71.2, 68.6, 44.0, 38.8, 32.1, 26.0 ppm. HRMS (EI): calcd. for $C_{15}H_{18}O$ $[M]^+$ 214.1352; found 214.1344.

Supporting Information (see footnote on the first page of this article): Experimental procedures and spectroscopic data for **3a**–**g**.

Acknowledgments

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[3] For selected examples, see: a) U. Schneider, M. Sugiura, S. Kobayashi, *Tetrahedron* **2006**, *62*, 496; b) Y. Masuyama, A. Watabe, Y. Kurusu, *Synlett* **2003**, 1713; c) S. Konishi, H. Hanawa, K. Maruoka, *Tetrahedron: Asymmetry* **2003**, *14*, 1603; d) D. A. Evans, Z. K. Sweeney, T. Rovis, J. S. Tedrow, *J. Am. Chem. Soc.* **2001**, *123*, 12095; e) A. McCluskey, I. W. Muderawan, Muntari, D. J. Young, *J. Org. Chem.* **2001**, *66*, 7811; f) M. Hojo, R. Sakuragi, S. Okabe, A. Hosomi, *Chem. Commun.* **2001**, 357; g) Y. Masuyama, A. Watabe, A. Ito, Y. Kurusu, *Chem. Commun.* **2000**, 2009; h) C.-M. Yu, S.-K. Yoon, K. Baek, J.-Y. Lee, *Angew. Chem. Int. Ed.* **1998**, *37*, 2392.

[4] See ref.[2f] and references cited therein.

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[6] Experimental procedure for the NMR study: Propargyl bromide (**2**; 0.44 mL, 5 mmol) was added to the mixture of In (powder, 570 mg, 5 mmol), hydrocinnamyl aldehyde (**1a**; 0.24 mL, 2 mmol) in THF (2 mL) at room temperature. The resulting mixture was stirred at this temperature and an aliquot (0.1 mL) of the reaction mixture was taken out by syringe at each time when the reaction was run for 10 min, 30 min, 1 h, 2.5 h and 15 h. Each portion of reaction mixture was quenched by adding water (0.1 mL), and the mixture was extracted with diethyl ether (5 mL). The organic layer was washed with brine and dried with anhydrous $MgSO_4$. The solvent was evaporated, and the residue was subjected to NMR analysis.

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[8] The ratio of **5a**/**4a** was 1:2, and the mixture was obtained from the In-mediated coupling of hydrocinnamyl aldehyde with propargylic bromide in water. See ref.[2a]

[9] The experimental procedure for the NMR study was similar to that in ref.[6] An aliquot (0.1 mL) of the reaction mixture was taken out by syringe at each time when the reaction was run for 6 h and 15 h. Each portion of the reaction mixture was quenched by adding water (0.1 mL), and the mixture was extracted with diethyl ether (5 mL). The organic layer was washed with brine and dried with anhydrous $MgSO_4$. The solvent was evaporated, and the residue was subjected to NMR analysis.

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