

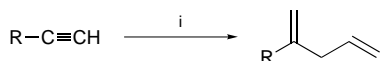
Indium-mediated regioselective Markovnikov allylation of unactivated terminal alkynes

Brindaban C. Ranu* and Adinath Majee

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta-700 032, India

Allylation of unactivated terminal alkynes by a simple treatment with allyl bromide and indium metal in THF at room temperature produces 1,4-dienes via regioselective Markovnikov addition.

Metal-mediated reactions play a significant role in organic synthesis. Of all the metals, indium has emerged in recent years as the one with most potential because of its advantages with regard to handling, toxicity, reactivity and selectivity.¹ Although indium-mediated carbonyl addition reactions have experienced tremendous growth in recent times,² its other interesting domains, including carboidation, still remain less well-explored.³ Recently, a procedure for allylation of carbon-carbon triple bonds, using indium powder and allylic bromides in DMF at elevated temperature to produce allylalkenols predominantly *via* anti-Markovnikov addition, has been demonstrated.^{3a} One serious limitation of this procedure is that the presence of a hydroxyl functionality near the triple bond is essential, and thus nonfunctionalised† or hydroxy-protected alkynes are not susceptible to allylation.^{3a} We have observed a very significant effect on the course of the indium-mediated allylation reaction with a change of solvent and modification of the experimental conditions. Thus, unactivated (nonfunctionalised and hydroxy-protected) alkynes underwent efficient allylation *via* Markovnikov addition by simple treatment with allyl bromide and indium metal in THF at room temperature (Scheme 1).



Scheme 1 Reagents and conditions: i, In, THF, room temp.

The experimental procedure is very simple. A mixture of alkyne (1 mmol), allyl bromide (8 mmol)‡ and indium metal (1 mmol, cut into small pieces) in THF (2 cm³) was stirred at room temperature until completion of the reaction (TLC). The reaction mixture was quenched with a few drops of dilute HCl and extracted with diethyl ether. Evaporation of the solvent followed by purification *via* silica gel chromatography furnished the pure product.§

Several structurally varied terminal alkynes underwent allylation by this procedure to provide the corresponding 1,4-dienes. The results are summarised in Table 1. Nonfunctionalised alkynes such as hex-1-yne, oct-1-yne and phenylacetylene (entries 1–3) produced Markovnikov addition products as the sole isolable compounds in high yields. Very interestingly, although the alkynols (entries 4, 9 and 11) furnished almost exclusively or predominantly the anti-Markovnikov addition products, the corresponding ethers (entries 5–8, 10 and 12) underwent Markovnikov coupling exclusively. This reversal of regioselectivity with protection of the hydroxy group is very significant from a mechanistic as well as a synthetic point of view.

In general, the reactions are very clean, and no side products were found. No reaction occurred with internal alkynes. THF is found to be the best choice as solvent. Reactions in water and in

aqueous THF are not successful. At lower temperature (0–5 °C), no efficient coupling is also observed.

In conclusion, the present procedure provides an efficient and general methodology for indium-mediated allylation of unactivated terminal alkynes. The notable advantages are the mild conditions (room temperature), operational simplicity (one-pot reaction), high yield (75–90%) and excellent regioselectivity (Markovnikov addition). To the best of our knowledge, this is the first report of indium-mediated Markovnikov allylation of unactivated alkynes. We believe this procedure will find useful application in organic synthesis. Further investigations to gain a better understanding of the criteria for selectivity and to broaden the scope of this reaction are in progress.

Table 1 Allylation of alkynes with allyl bromide and indium metal in THF

Entry	Alkyne	t/h	Product	Yield (%) ^a
1	Bu-C≡CH	3	Bu-CH=CH-CH=CH ₂	86
2	C ₆ H ₁₃ -C≡CH	3	C ₆ H ₁₃ -CH=CH-CH=CH ₂	85
3	Ph-C≡CH	3	Ph-CH=CH-CH=CH ₂	90
4	≡CH ₂ OH	3	CH ₂ =CH-CH=CH-CH ₂ OH	80 ^b
5	≡CH ₂ OC ₅ H ₁₁	5	CH ₂ =CH-CH=CH-CH ₂ OC ₅ H ₁₁	85
6	≡CH ₂ OPh	6	CH ₂ =CH-CH=CH-CH ₂ OPh	86
7	≡CH ₂ OCH ₂ CH=CHPh	6	CH ₂ =CH-CH=CH-CH ₂ OCH ₂ CH=CHPh	85
8	≡CH ₂ OBn	24	CH ₂ =CH-CH=CH-CH ₂ OBn	75
9	4-MeOC ₆ H ₄ -CH(OH)-C≡CH	8	4-MeOC ₆ H ₄ -CH(OH)-CH=CH-CH=CH ₂	83 ^b
10	4-MeOC ₆ H ₄ -CH(OMe)-C≡CH	8	4-MeOC ₆ H ₄ -CH(OMe)-CH=CH-CH=CH ₂	90
11	Ph-CH(OH)-C≡CH	6	Ph-CH(OH)-CH=CH-CH=CH ₂ + Ph-CH(OH)-CH ₂ -CH=CH ₂	85 (55:45)
12	Ph-CH(OCH ₂ CH ₂ CH ₂)-C≡CH	7	Ph-CH(OCH ₂ CH ₂ CH ₂)-CH=CH-CH=CH ₂	86

^a Yields refer to pure isolated products fully characterised by ¹H and ¹³C NMR spectroscopy. ^b The corresponding Markovnikov product is formed in less than 5%.

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Footnotes

* E-mail: ocbcr@iacs.ernet.in

† At higher reaction temperature (150–180 °C) oct-1-yne and phenylacetylene underwent coupling with cinnamylindium in only 12–28% yield [ref. 3(a)].

‡ Excess allyl bromide is found to accelerate the reactions considerably; stoichiometric or a slightly larger amount (2–3 mmol) of allyl bromide makes the reactions slow.

§ The alkynes and allyl bromide were freshly distilled before use. A few alkynes, namely hex-1-yne, oct-1-yne, phenylacetylene and prop-2-ynyl alcohol, are commercial materials (E. Merck, Germany) and others were prepared *via* standard procedures. Allyl bromide was also purchased from E. Merck. Indium metal was obtained from SRL, India, as ingots and cut

into small pieces whenever required. THF was procured from SD, India, and freshly distilled over sodium–benzophenone.

References

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