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# Indium-mediated *vic*-diallylation/propargylation of phenacyl bromides: a facile synthesis of 4-arylocta-1,7-dien-4-ol derivatives

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**Abstract**

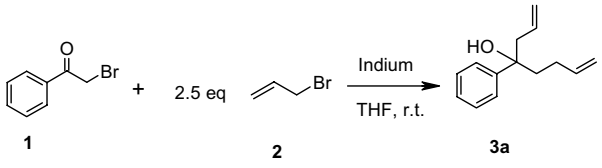
Phenacyl bromides undergo smooth *vic*-diallylation and dipropargylation with allyl and propargyl indium reagents generated in situ from metallic indium and allyl or propargyl bromide to produce 4-arylocta-1,7-dien-4-ol derivatives in good yields. Phenacyl chloride and azide also participated effectively in bis-allylation. Similar results are also obtained from in situ generated allyl or propargyl zinc bromide.


*Keywords:* Indium metal; Phenacyl bromide; *vic*-diallylation/propargylation; C–C bond formation

The allylation/propargylation of carbonyl compounds is of great interest in organic synthesis[1–4] because the resultant homoallylic and propargylic alcohols are versatile precursors for various transformations.[5–9] In particular, bis-allylated products are important intermediates for Grubbs' ring closing metathesis.[10,11] Since the successful introduction of magnesium metal in Grignard reactions for carbon–carbon bond formation, the utilization of other metals of the Periodic System for organic synthesis has received widespread attention and one of the latest additions is indium. During the last decade, indium has emerged as a metal of high potential in organic synthesis because it possesses certain unique properties. Indium metal is unaffected by air or oxygen at ambient temperatures and can be handled safely without any apparent toxicity. In addition, indium exhibits low heterophilicity in organic reactions and thus oxygen- and nitrogen-containing functional groups are usually well tolerated by organoindium reagents.[12,13] Moreover, indium-assisted reactions display low nucleophilicity thus permitting chemoselective transformations of groups of similar reactivity.[14–18] However, there have been no reports on the *vic*-diallylation/propargylation of phenacyl bromides using allyl/propargyl indium bromide.

In this Letter, we describe an efficient protocol for the *vic*-diallylation/propargylation of phenacyl bromides using allyl/propargyl bromide and indium metal. Initially, we attempted the allylation of phenacyl bromide (**1**) with 2.5 equiv of allyl bromide (**2**) in the presence of indium metal. The reaction proceeded smoothly in THF at room temperature to produce 4-phenylocta-1,7-dien-4-ol **3a** in 74% yield (Scheme 1).

This result provided the incentive for further study of reactions with various other phenacyl bromides such as *p*-methoxy-, *p*-methyl-, *p*-chloro-, 2,4-dichloro-, and *o*-methoxy derivatives to furnish the corresponding 4-arylocta-1,7-dienol derivatives (Table 1, entries c, e, g, i, and j).




Scheme 1. Allylation of phenacyl bromide.

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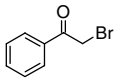
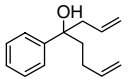
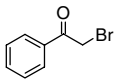
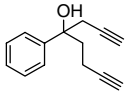
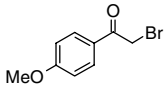
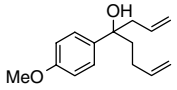
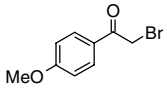
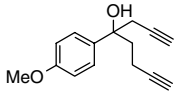
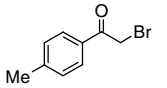
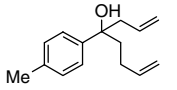
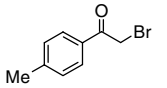
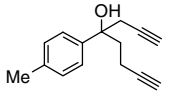
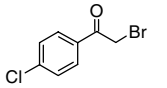
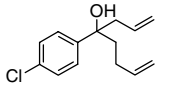
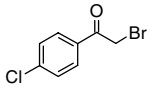
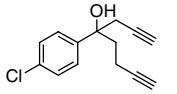
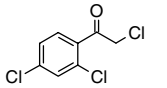
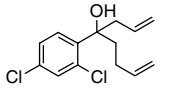
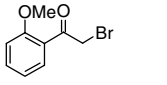
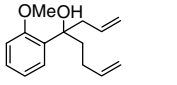
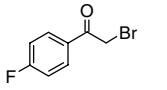
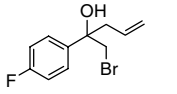
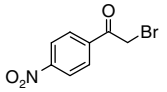
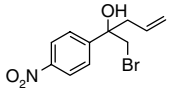
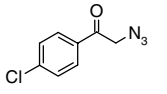
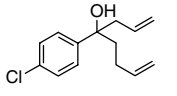
Table 1
Indium-mediated bis-allylation/ propargylation of phenacyl bromides

| Entry | Phenacyl bromide | Allyl bromide/ Propargyl bromide | Product[a] | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|
| a |  |  |  | 26 | 74 |
| b |  |  |  | 21 | 72 |
| c |  |  |  | 16 | 78 |
| d |  |  |  | 17 | 65 |
| e |  |  |  | 16 | 72 |
| f |  |  |  | 18 | 62 |
| g |  |  |  | 15 | 69 |
| h |  |  |  | 17 | 67 |
| i |  |  |  | 15 | 64 |
| j |  |  |  | 16 | 61 |
| k |  |  |  | 35 | 55 |
| l |  |  |  | 38 | 58 |
| m |  |  |  | 15 | 70 |

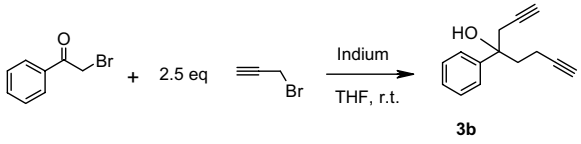
[a] Products were characterized by NMR, IR, and mass spectrometry.
[b] Yield refers to pure products after column chromatography.

In the cases of *p*-nitro- and *p*-fluorophenacyl bromides, mono-allylated products were isolated as the major products even after an extended reaction time (48 h). This method is well tolerated with substrates bearing nitro and halide functionalities (Table 1, entries g–i and k–m). Interestingly, the allylation of phenacyl azide gave the bis-allylated product with concomitant loss of nitrogen and was comparatively faster than with phenacyl halides (Table 1, entry m). Similarly, phenacyl bromides underwent propargylation with propargyl bromide under identical conditions (Table 1, entries b, d, f, and h). For example, treatment of propargyl indium bromide, generated in situ from metallic indium and propargyl bromide, with phenacyl bromide in THF gave the bis-propargylated product in 72% yield (Table 1, entry b, Scheme 2).

The method is clean and the products were obtained in good yields with high selectivity. As solvent, THF gave the best results over acetonitrile and dichloromethane. Activated zinc was also equally effective for this conversion. In situ generated allyl/propargyl indium bromide from 2.5 equiv of indium and 2.5 equiv of allyl/propargyl bromide was effective for the allylation/propargylation of phenacyl bromides. The scope of this method is illustrated in Table 1.[19]

Mechanistically, it would appear that addition occurs initially on the carbonyl group followed by reaction with another equivalent of allyl/propargyl indium leading to bis-allylation/propargylation. A tentative reaction sequence is depicted in Scheme 3.

In conclusion, we have developed an efficient protocol for the *vic*-diallylation/propargylation of phenacyl bromides using allyl/propargyl bromide and indium or zinc metal. The use of indium makes this procedure simple and convenient for scale-up. The products are potentially useful precursors for the preparation of aryl substituted cyclohexadiene derivatives (via Grubbs' ring closing




Scheme 2. Propargylation of phenacyl bromide.




Scheme 3. A plausible reaction mechanism.

metathesis and dehydration), which are important building blocks in organic synthesis.

## Acknowledgment

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19. *General procedure*: A mixture of allylbromide/propargyl bromide (2.5 mmol) and indium metal (2.6 mmol) was stirred in THF at room temperature for 15–20 min to dissolve the metal then phenacyl bromide (1 mmol) was added and the reaction stirred for the appropriate time (Table 1). After complete conversion as indicated by TLC, the reaction mixture was quenched with aqueous saturated ammonium chloride (10 mL) and extracted with ethyl acetate ($3 \times 10$ mL). The combined organic extracts were dried over anhydrous $Na_2SO_4$ and concentrated in vacuo. The resulting product was purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:7) to afford the pure product. Product **3k** has been reported in the literature.[20] *Spectral data for selected products*: 4-Phenyl-1,7-octadien-4-ol (**3a**): Liquid, IR (KBr): $\nu$ 3449, 3063, 2926, 2852, 2365, 1719, 1631, 1461, 1281, 907, 811, 739 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 8.08–7.81 (m, 2H), 7.33–7.11 (m, 3H), 5.92–5.72 (m, 2H), 5.17–5.09 (m, 4H), 2.39 (dd, 2H, $J = 6.3$, 13.9 Hz), 2.02–1.64 (m, 4H); $^{13}C$ NMR (75 MHz, Proton decoupled $CDCl_3$): $\delta$ 30.1, 39.4, 51.3, 74.4, 116.1, 118.3, 128.2, 129.4, 135.1, 137.2, 138.8, 149.1; LC-MSD-Trap-SL: *m*/*z*: 225 (M+23); HRMS calcd for $C_{14}H_{18}O$: 202.1357; found, 202.1367. 4-(4-Methoxyphenyl)-1,7-octadiene-4-ol (**3c**): Liquid, IR (KBr): $\nu$ 3448, 2924, 2855, 2365, 1732, 1642, 1513, 1458, 1364, 1249, 1177, 1037, 916, 826 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.07 (dd, $J = 8.0$, 15.4 Hz, 2H), 6.75 (d, $J = 8.8$ Hz, 2H), 5.98–5.77 (m, 2H), 5.16–4.97 (m, 4H), 3.78 (s, 3H), 2.86 (s, 2H), 2.17 (d, $J = 7.3$ Hz, 4H); $^{13}C$ NMR (75 MHz, Proton decoupled, $CDCl_3$): $\delta$ 36.1, 39.4, 43.3, 55.1, 73.9, 113.5, 113.8, 118.6, 129.2, 131.5, 134.9, 137.1, 158.2; LC-MSD-Trap-SL: *m*/*z*: 255 (M+23). HRMS calcd for [M+Na] $C_{15}H_{20}O_2Na$: 255.1360; found, 255.1363. 4-(4-Methylphenyl)-1,7-octadiene-4-ol (**3e**): Liquid, IR (KBr): $\nu$ 3444, 3067, 2925, 2855, 2364, 1724, 1638, 1457, 1283, 912, 813, 759, 539 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.07–6.97 (m, 4H), 5.80–5.50 (m, 2H), 5.09–4.82 (m, 4H), 2.76–2.37 (m, 3H), 2.31 (s, 3H), 2.18–1.85 (m, 3H); $^{13}C$ NMR (75 MHz, Proton decoupled, $CDCl_3$): $\delta$ 21.0, 29.6, 36.0, 39.5, 51.4, 74.1, 115.8, 118.2, 128.3, 129.1, 134.9, 137.0, 138.6; LC-MSD-Trap-SL: *m*/*z*: 239 (M+23); HRMS calcd for $C_{15}H_{20}O$: 216.1514; found, 216.1521. 4-(4-Methylphenyl)-1,7-octadiyn-4-ol (**3f**): Liquid, IR (KBr): $\nu$ 3485, 2961, 2892, 1371, 791 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.36 (d, 2H, $J = 8.3$ Hz), 7.14 (d, 2H, $J = 8.3$ Hz), 2.88 (d, 2H, $J = 2.3$ Hz), 2.63 (br, 1H), 2.36 (s, 3 H), 2.23 (d, 1H, $J = 2.3$ Hz), 2.09 (m, 2H), 2.01 (d, 1H, $J = 2.3$ Hz), 1.92 (m, 2H); $^{13}C$ NMR (75 MHz, Proton decoupled $CDCl_3$): $\delta$ 15.1, 21.2, 32.9, 39.8, 68.6, 78.5, 80.2, 84.7, 84.9, 128.3, 129.2, 137.0, 141.2. LC-MSD-Trap-SL: *m*/*z* (%): 235 (M+23), 174, 141, 129, 102, 74; HRMS calcd for [M+Na] $C_{15}H_{16}ONa$: 235.1098; found, 235.1107. 1-Bromo-2-(4-nitrophenyl)-4-penten-2-ol (**3l**): Liquid, IR (KBr): $\nu$ 3549, 2868, 1521, 1350, 1495, 1445, 1329, 1261, 956, 712 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 8.23 (d, $J = 8.7$ Hz, 2H), 8.09 (d, $J = 8.7$ Hz, 2H), 5.76–5.65 (m, 1H), 5.08 (m, 2H), 3.96 (dd, 2H, $J = 3.2$, 10.9 Hz), 2.56 (s, 2H), 2.26 (br, 1H); $^{13}C$ NMR (75 MHz, Proton decoupled, $CDCl_3$): $\delta$ 43.2, 49.7, 74.5, 115.8, 119.8, 129.3, 135.9, 145.3, 158.1 HRMS calcd for [M+Na] $C_{11}H_{12}BrNO_3Na$: 307.9898; found, 307.9905.
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