## **Granular Indium Barbier Allylation of Carbonyl Compounds: A More Economical Protocol**

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We wish to dedicate this paper to Prof. Jaime Valderrama on the occasion of his retirement.

**Abstract:** A new protocol, amenable to be used in large-scale preparations, using a cheaper form of indium metal and mild warming is reported for the Barbier allylation of aldehydes and ketones with allyl bromide in *N*,*N*-dimethylformamide.

**Key words:** indium, carbonyl complexes, allylation, homoallylic alcohols, addition reactions

The indium-mediated allylation of aldehydes and ketones is a well established method for C-C bond formation and its chemistry has recently been extensively reviewed.<sup>1</sup> Indium chemistry has received considerable attention from the organic chemists, especially after the discovery that the indium-mediated Barbier addition reactions of allylic bromides (or iodides) on aldehydes and ketones can be performed in aqueous media (Scheme 1).<sup>2</sup> Despite the relative abundance of references on the subject almost all experimental data involve simple unfunctionalized carbonyl compounds containing only one reactive aldehyde or ketone, and perhaps an aromatic ring. For our research on the general applicability of a new reaction of lead tetraacetate<sup>3</sup> we needed an easy access to functionalized homoallylic alcohols and, after trying several conditions and reagents, we decided to try several indium allylations of aldehydes and ketones containing diverse chemical functions.



Scheme 1 Indium-mediated allylation of aldehydes and ketones

Indium powder, the customary form of metal used in such reaction, was too expensive for our preparative needs. Nevertheless, we found that other forms of commercial indium metal were priced up to ten times less than the powder. We used the most affordable commercial form that we could locate: metal shot, 99.9% pure.<sup>4</sup> The solvent was a small amount (1 mL/mmol) of technical grade *N*,*N*-dimethylformamide, used as purchased. After trying

SYNLETT 2006, No. 19, pp 3337–3339 Advanced online publication: 23.11.2006 DOI: 10.1055/s-2006-951529; Art ID: S15206ST © Georg Thieme Verlag Stuttgart · New York several different conditions, we learned that indium metal in granular form works exactly as well as the powder, in terms both of yield and product purity (Table 1).<sup>5</sup> The carbonyl compounds tested were both aldehydes (Table 1, entries 1–10; Figure 1) and ketones (Table 1, entries 11– 20; Figure 1), either aliphatic and aromatic, including several bifunctional compounds and two dicarbonyl compounds (entries 9 and 13). In all cases good to excellent isolated yields were obtained, ranging from 42% to 100%, as long as a small excess of indium was used. In a couple of cases (entries 3 and 4) a rather low yield was observed, which we attributed mainly to decomposition and problems during the workup and chromatographic purification. In one case (entry 9) dialdehyde 1i gave a cyclic hemiacetal instead of the usual homoallylic alcohol, product of intramolecular attack of the homoallylic alcohol oxygen on the remaining carbonyl group, and also a rather low (56%) yield was obtained in that case.

At room temperature the Barbier allylations using granular indium turned out to be sluggish, taking several days to complete. Fortunately, we found that a slight warming to 40–50 °C, together with vigorous magnetic stirring significantly shortened our reaction times to less than two hours, giving better yields and purer products. The use of indium in small pieces had an extra bonus, as it allowed us to observe obvious color changes on the metal surface that would have gone unnoticed when using the powdered metal.

We observed that for the reaction to start the originally clean and shiny metal surface had to lose its sheen first and it acquired a grayness, which sometimes turned to a deep-purple or dark-brown color. Simultaneously, the initially clear or slightly colored *N*,*N*-dimethylformamide solution became somewhat cloudy and moss-green in color.<sup>6</sup> Both changes occurred between five minutes and 30 minutes at 40–50 °C, and sometimes even earlier. Next, the reaction mixture remained in the same state until the limiting reactant, whichever it was, got exhausted, and the metal surface turned shiny and clean again, as it had been initially.

If the green reaction mixture was centrifuged, a reddishbrown solution and a gray solid were obtained. The solution contained no identifiable organic materials but the insoluble solid on treatment with water followed by solvent extraction gave the product, homoallylic alcohol **2**. When left overnight after the reaction completion, the mossgreen mixture also turned reddish-brown and sometimes a heavy and dark-gray precipitate was observed. Once water or any other proton source was added to quench the reaction and extract the organics, the mixture turned to a clear pale-yellow solution.<sup>7</sup>



Figure 1 Carbonyl compounds tested

We tried to correlate the disappearance of signals belonging to the starting materials to the appearance of colored products by performing a series of <sup>1</sup>H NMR experiments. Unfortunately, we could not observe the advent of any new signals corresponding to a reaction intermediate or product, but instead we observed that the moss-green color intensified as the signals corresponding to the starting allyl bromide and carbonyl compound disappeared. No precipitate was evident, but rather an apparent increase in the sample viscosity (and the consequent loss in field homogeneity) occurred. When an aliquot of that reaction mixture was allowed to react with water the green color disappeared and the signals corresponding to alcohol 2 were detected in the spectra. As indium is a main group metal, the green color should arise due to electronic transitions within ligands orbitals.<sup>8</sup> So we reasoned that the metal Lewis acid could act as an anchor allowing a ligand coupling of the carbonyl and allyl ligands to occur, with one or various radical species involved, as previously reported.<sup>9–11</sup> These observations imply that in the absence of a proton source the allylation is heterogeneous, giving a highly insoluble indium alcoholate as the final product that, upon protonation, finally yields alcohol 2.

 Table 1
 Indium-Mediated Reaction of Allyl Bromide with Several Carbonyl Compounds 1

Entry	Substrate	Product	Yield (%) <sup>a</sup>
1	1a	2a	75
2	1b	2b	100
3	1c	2c	57
4	1d	2d	42
5	1e	2e	87
6	1f	2f	79
7	1g	2g	90
8	1h	2h	97
9	1i	2i	56 <sup>b</sup>
10	1j	2j	86
11	1k	2k	91
12	11	21	89
13	1m	2m	89 <sup>b</sup>
14	1n	2n	88
15	10	20	94
16	1p	2p	94
17	1q	2q	73
18	1r	2r	86
19	1s	2s	78
20	1t	2t	100

<sup>a</sup> All yields correspond to products isolated after column chromatography.

<sup>b</sup> Corresponds to attack on a single carbonyl group.

We also reacted allyl bromide and indium metal in *N*,*N*-dimethylformamide (Grignard conditions) and in this case no green color was observed. The appearance of two sets of signals in the <sup>1</sup>H NMR spectrum, at  $\delta = 2.02$  ppm and  $\delta = 1.75$  ppm, was assigned to the methylene group directly bonded to indium metal, in obvious agreement with those previously reported for the *N*,*N*-dimethylformamide and tetrahydrofuran solutions of allylindium organometallics.<sup>12,13</sup> Previously,<sup>12</sup> both signals were assigned to a triallyldiindium trihalide (In<sub>2</sub>Br<sub>3</sub>R<sub>3</sub>), formed by reaction between indium and allyl bromide, on the basis of their relative intensities. However, we believe that they belong to two different organometallic compounds as signal at  $\delta = 2.02$  ppm quenches immediately on addition of water to leave the one at  $\delta = 1.75$  ppm alone, which disappears at a much slower rate, and a N,N-dimethylformamide solution left standing overnight shows a reduction in the intensity of the signal at  $\delta=1.75\ ppm$  and an enhancement of the signal at  $\delta = 2.02$  ppm.<sup>13,14</sup> Chan et al.,<sup>13</sup> previously postulated that the signal at  $\delta = 1.75$  ppm belongs to an allylindium(I) species. We believe that the other signal at  $\delta = 2.02$  ppm, corresponds to another, less reactive organometallic species, in slow dynamic equilibrium with the former (Grignard conditions). Under Barbier conditions like those used in the present syntheses, the actual concentration of the active organoindium species tends to be zero at all times, as it would react with the carbonyl species immediately after its formation, which explains the complete absence of signals at  $\delta = 2.02$  ppm and  $\delta =$ 1.75 ppm in the NMR spectra.<sup>14–16</sup>

Details of the reaction mechanism and new applications of the above-described protocol aiming to develop a method usable at a larger scale are currently under investigation in our laboratories.

## **Typical Procedure**

The carbonyl compound **1** (1 mmol) and allyl bromide (484 mg, 4 mmol) were dissolved in DMF (1 mL), contained in a thick-walled reaction tube with threaded Teflon cap. Granular indium (230 mg, 2 mmol) was added at once, the reaction tube was tightly closed and magnetically stirred into a hot oil bath with the temperature carefully set at 40–50 °C, and controlled by an immersion thermometer. The progress of the reaction was followed by TLC, until total consumption of **1** (usually 2 h) was observed. The resulting mixture was diluted with EtOAc, poured into water, and washed thrice with water. The organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated in vacuo to yield crude homoallylic alcohol **2**, which was purified by flash chromatography. Compounds **2a**,<sup>17</sup> **2b**,<sup>18</sup> **2c**,<sup>19</sup> **2d**,<sup>20</sup> **2g**,<sup>19</sup> **2j**,<sup>19</sup> **2k**<sup>19</sup> and **2n**<sup>19</sup> have been previously described and characterized in detail.

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- (5) Indium is so soft that an ingot of metal can be easily flattened by pressing with a spatula (or even strong fingernails) between two pieces of clean filter paper, and then cut into small pieces of a few square millimeters with scissors.
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