



## Indium-mediated one-pot, three-component synthesis of homoallyl alcohol esters without catalysts and dehydrants

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### ABSTRACT

Indium-mediated one-pot esterification reaction of acyl chlorides or anhydride by using in situ-prepared homoallyl alcohols from aromatic aldehydes and allyl bromide proceeded smoothly to afford the corresponding homoallyl alcohol esters in high yields within about 1 h, which provided a simple and efficient protocol for the simultaneous allylation and esterification of aldehydes without other catalysts and dehydrants.

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The allylation reaction of carbonyl compounds is very important due to the formation of new carbon–carbon bond between different hybrid orbitals to give synthetically useful homoallyl alcohol derivatives.<sup>1</sup> As a type of homoallyl alcohol derivatives, the synthesis of homoallyl ethers and esters has attracted considerable attention. Several catalysts have been used to perform this transformation. However, most of them involve the use of corrosive, expensive, and toxic catalysts, such as CF<sub>3</sub>COOH,<sup>2</sup> BiBr<sub>3</sub>,<sup>3</sup> Sc(OTf)<sub>3</sub>,<sup>4</sup> Bi(OTf)<sub>3</sub>·x-H<sub>2</sub>O,<sup>5</sup> LiBF<sub>4</sub>,<sup>6</sup> Mn metal,<sup>7</sup> and strictly anhydrous and inconveniently low temperatures conditions. Furthermore, the original substrates of these reactions are almost acetals which are not commercially available and must be synthesized from the corresponding aldehydes.

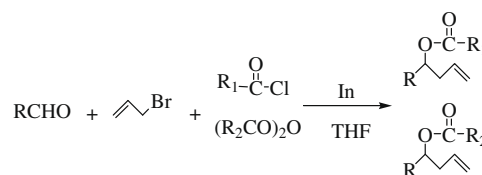
Recently, indium-mediated transformations have attracted the attention of synthetic organic chemists because of certain unique properties inherent to indium, such as low ionization potential, high reactivity, and high stability in water, alkali aqueous and air.<sup>8</sup> The allylation of carbonyl compounds giving homoallyl compounds,<sup>9</sup> the synthesis of acetals and ketals,<sup>10</sup> the Knoevenagel condensation of aldehydes with methyl acetoacetate<sup>11</sup> mediated by indium metal and indium salts have been reported. The indium-mediated allylation of *gem*-diacetates to homoallylic acetates was also achieved by Yadav et al.<sup>12</sup>

However, up to now, no literature is reported for the synthesis of homoallyl alcohol esters with three component reaction of aldehydes, allyl bromide, and acylation reagents, which are a type of important homoallyl alcohol derivatives with versatile functional groups amenable to further synthetic manipulations and are mediated by indium.

Herein we report a convenient and simple one-pot three-component synthesis of homoallyl alcohol esters by esterification of

in situ-prepared homoallyl alcohols from aldehydes and allyl bromide mediated by indium,<sup>13</sup> as shown in Scheme 1.

The one-pot synthesis of the homoallyl ester from *p*-cyanobenzaldehyde, propionyl chloride and allyl bromide as a model reaction was first carried out in the presence of indium in THF at room temperature. However, we found that this reaction was very sensitive to temperature. The reaction time was shortened and high yield (90%) was simultaneously obtained when the reaction was conducted at invariable 40 °C in water bath. The molar ratios of indium, *p*-cyanobenzaldehyde, allyl bromide and propionyl chloride were also optimized and showed that 1.0/1.0/1.5/1.2 was ideal for this three component tandem reaction. Under these optimized conditions, the allylation and esterification of various aldehydes with different substituents using acyl chlorides as acylation reagents were investigated. The results are shown in Table 1. From Table 1, it is found that all reactions of aromatic aldehydes can proceed smoothly to yield corresponding homoallyl alcohol esters and the effect of substituents of aromatic aldehydes are not significant. When aliphatic acyl chloride was replaced by benzoyl chloride, the allylation–esterification of aromatic aldehydes needed more reaction times but to obtain moderate yields (Table 1, entry 9), which might be due to larger steric hindrance and electronic and resonance effect of benzoyl chloride. As for aliphatic aldehydes and heterocyclic aromatic aldehydes with electron-rich



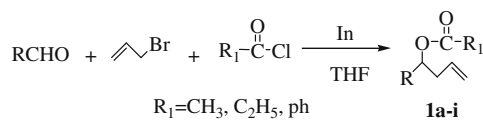
**Scheme 1.** Indium-mediated one-pot, three-component tandem synthesis of homoallyl alcohol esters.



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**Table 1**

Indium-mediated one-pot synthesis of homoallyl esters from aldehydes, acyl chlorides, and allyl bromide<sup>a</sup>



Entry	R	R <sub>1</sub>	Time (min)	Yield <sup>b</sup> (%)
1	Ph	CH <sub>3</sub>	40	<b>1a</b> , 87
2	4-ClC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	50	<b>1b</b> , 89
3	2-ClC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	50	<b>1c</b> , 87
4	4-CNC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	45	<b>1d</b> , 90
5	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>5</sub>	40	<b>1e</b> , 90
6	3-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>5</sub>	35	<b>1f</b> , 92
7	4-CNC <sub>6</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>5</sub>	50	<b>1g</b> , 91
8	2-ClC <sub>6</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>5</sub>	50	<b>1h</b> , 92
9	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	Ph	80	<b>1i</b> , 51
10	C <sub>6</sub> H <sub>11</sub>	C <sub>2</sub> H <sub>5</sub>	120	NP <sup>c</sup>
11	C <sub>6</sub> H <sub>11</sub>	Ph	180	NP <sup>c</sup>
12		CH <sub>3</sub>	60	NP <sup>c</sup>
13		Ph	100	NP <sup>c</sup>

<sup>a</sup> Reaction conditions: indium 1.0 mmol, ArCHO 1.0 mmol, allyl bromide 1.5 mmol, R<sub>1</sub>COCl 1.2 mmol, THF 2 ml, 40 °C water bath. The reaction was monitored by TLC.

<sup>b</sup> Isolated yield.

<sup>c</sup> NP: no pure product was isolated.

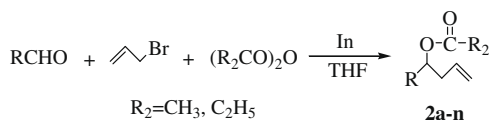
systems, however, although they reacted and disappeared in longer time monitored by TLC, the homoallyl alcohol esters could not be isolated because the products were very complex and included several byproducts, such as long chain alkanes, alkyl bromide, and homoallyl ether (Table 1, entries 10–13). The details are under investigation.





Similarly, the reactions of indium-mediated one-pot synthesis of homoallyl esters were also conducted by using acid anhydride as acylation reagents. The results are summarized in Table 2. As depicted in Table 2, aliphatic acid anhydrides, such as acetic anhydride and propionic anhydride, can react well with various aromatic aldehydes and allyl bromide to form the corresponding homoallyl alcohol esters in excellent yields (91–96%) within about 1 h under the above optimized conditions (Table 2, entries 1–11). With the same to the reaction of acyl chloride, aromatic aldehydes carrying either electron-withdrawing or electron-donating groups could be efficiently converted into the aimed products, and different substituents have almost no effect on the result of the reaction. It is surprising that heterocyclic aromatic aldehydes can also be converted into the desired products by using aliphatic anhydrides in excellent yields (Table 2, entries 12–14). In comparison with aliphatic acid anhydride, benzoic anhydride almost couldn't react even if the reaction time was elongated to 10 h, which might be due to large steric hindrance (Table 2, entries 15 and 16).

In summary, a new and efficient method for the synthesis of homoallyl alcohol esters through indium-mediated one-pot three component tandem reaction of aromatic aldehydes, acylation reagents, and allyl bromide in short reaction time in excellent yields is described. The primary investigation on this reaction shows that the allylation of aldehydes and the esterification of the aforementioned in situ-formed homoallyl alcohols are completed simultaneously. It is noted that aliphatic aldehydes and heterocyclic aromatic aldehydes have a lower reactivity than aromatic aldehydes, and aromatic acylation reagents have larger steric hindrance than that of aliphatic ones. The advantages of this method include the use of easy to handle, stable nontoxic metal indium,

**Table 2**

Indium-mediated one-pot synthesis of homoallyl esters from aldehydes, acid anhydrides, and allyl bromide<sup>a</sup>



Entry	R	R <sub>2</sub>	Time (min)	Yield <sup>b</sup> (%)
1	3-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	50	<b>2a</b> , 94
2	2-ClC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	50	<b>2b</b> , 94
3	4-ClC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	50	<b>2c</b> , 93
4	2-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	50	<b>2d</b> , 96
5	4-CNC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	45	<b>2e</b> , 92
6	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	CH <sub>3</sub>	50	<b>2f</b> , 92
7	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	65	<b>2g</b> , 91
8	2-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>5</sub>	40	<b>2h</b> , 94
9	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>5</sub>	45	<b>2i</b> , 92
10	4-CNC <sub>6</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>5</sub>	50	<b>2j</b> , 91
11	4-BrC <sub>6</sub> H <sub>4</sub>	C <sub>2</sub> H <sub>5</sub>	50	<b>2k</b> , 93
12		CH <sub>3</sub>	55	<b>2l</b> , 92
13		C <sub>2</sub> H <sub>5</sub>	55	<b>2m</b> , 93
14		C <sub>2</sub> H <sub>5</sub>	55	<b>2n</b> , 91
15		Ph	60	NR <sup>c</sup>
16	2-ClC <sub>6</sub> H <sub>4</sub>	Ph	10 h	NR <sup>c</sup>

<sup>a</sup> Reaction conditions: indium 1.0 mmol, ArCHO 1.0 mmol, allyl bromide 1.5 mmol, (R<sub>2</sub>CO)<sub>2</sub>O 1.2 mmol, THF 2 ml, 40 °C water bath. The reaction was monitored by TLC.

<sup>b</sup> Isolated yield.

<sup>c</sup> NR: almost no reaction was proceeded.

excellent yields, short reaction times, no use of catalysts and dehydrants, and no separation of intermediates, which might be used in the scale-up production of homoallyl alcohol esters in related medical synthesis.

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Financial support by Natural Science Foundation of China (No. 20702042), Key Laboratory of Polymer Materials of Gansu Province (No. zd-06-18) and Yong Teachers Research Foundation of NWNNU (No. NWNNU-QN-06-27) is acknowledged.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.092.

## References and notes

- Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31–48.
- McCluskey, A.; Mayer, D. M.; Young, D. J. *Tetrahedron Lett.* **1997**, *38*, 5217–5218.
- Komatsu, N.; Uda, M.; Suzuki, H.; Takahashi, T.; Domae, T.; Wada, M. *Tetrahedron Lett.* **1997**, *38*, 7215–7218.
- Yadav, J. S.; Subba Reddy, B. V.; Srihari, P. *Synlett* **2001**, 673–675.
- (a) Wieland, L. C.; Zerth, H. M.; Mohan, R. S. *Tetrahedron Lett.* **2002**, *43*, 4597–4600; (b) Anzalone, P. W.; Baru, A. R.; Danielson, E. M.; Hayes, P. D.; Nguyen, M. P.; Panico, A. F.; Smith, R. C.; Mohan, R. S. *J. Org. Chem.* **2005**, *70*, 2091–2096.
- Yadav, J. S.; Subba Reddy, B. V.; Vishnumurthy, P.; Chary, Ch. J. *Tetrahedron Lett.* **2007**, *48*, 5915–5918.
- Cahiez, G.; Chavant, P. Y. *Tetrahedron Lett.* **1989**, *30*, 7373–7376.
- (a) Rieke, R. D.; Hanson, M. V. *Tetrahedron* **1997**, *53*, 1925–1956; (b) Li, C. J.; Chan, T. H. *Tetrahedron Lett.* **1999**, *55*, 11149–11176; (c) Nair, V.; Ros, S.; Jayan, C. N.; Pillai, B. S. *Tetrahedron* **2004**, *60*, 1959–1982.
- (a) Li, C. J.; Chan, T. H. *Tetrahedron Lett.* **1991**, *32*, 7017–7020; (b) Hu, L. H.; Ji, S. J. *Chin. J. Org. Chem.* **2008**, *28*, 1107–1110.
- Gregg, B. T.; Golden, K. C.; Quinn, J. F. *Tetrahedron* **2008**, *64*, 3287–3295.

11. Paquette, L. A.; Kern, B. E.; Méndez-Andino, J. *Tetrahedron Lett.* **1999**, *40*, 4129–4132.
12. (a) Yadav, J. S.; Subba Reddy, B. V.; Kiran Kumar Reddy, G. S. *Tetrahedron Lett.* **2000**, *41*, 2695–2697; (b) Yadav, J. S.; Subba Reddy, B. V.; Madhuri, Ch.; Sabitha, G. *Chem. Lett.* **2001**, *30*, 18–19.
13. *General operation for the synthesis of homoallyl alcohol ester:* All reagents were used as obtained from commercial sources except specially mentioned. Tetrahydrofuran was dealt with sodium and benzophenone to show blue. Allyl bromide was redistilled prior to use. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker MERCURY-PLUS 400 MHz NMR spectrometer. Chemical shifts were reported in parts per million (ppm,  $\delta$ ). IR was measured on an Alpha Centauri FT-IR spectrometer and MS was analyzed by a QP-1000A GC-MS with EI sources. *Typical procedures for the synthesis of 1-(4-cyanophenyl)-3-butenyl propionate (1g):* indium powder (114 mg, 1.0 mmol) was placed into a 50 ml flask under argon, followed by the addition of THF (2 ml), *p*-cyanobenzaldehyde (132 mg, 1.0 mmol), allyl bromide (181 mg, 1.5 mmol), and propionyl chloride (111 mg, 1.2 mmol). The mixture was stirred at 40 °C water bath for 50 min until *p*-cyanobenzaldehyde disappeared as detected by TLC. The reaction was then quenched by saturated 3 ml of  $\text{NH}_4\text{Cl}$  aqueous solution. The product was extracted with ethyl acetate ( $3 \times 5$  ml), dried with anhydrous  $\text{Mg}_2\text{SO}_4$  and concentrated under reduced pressure, then purified by column chromatography using a mixture of petroleum ether and ethyl acetate as the eluent, affording the pure homoallyl ester in 91% of yield, a colourless viscous liquid. *Spectra data of compound 1g:*  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.65–7.64 (m, 2H, ArH), 7.43–7.41 (m, 2H, ArH), 5.82–5.79 (m, 1H, CH), 5.70–5.63 (m, 1H, CH), 5.08–5.03 (m, 2H,  $\text{CH}_2$ ), 2.63–2.52 (m, 2H,  $\text{CH}_2$ ), 2.41–2.34 (m, 2H,  $\text{CH}_2$ ), 1.16–1.11 (t, 3H,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 9.0 ( $\text{CH}_3$ ), 27.6 ( $\text{CH}_2$ ), 40.5 ( $\text{CH}_2$ ), 74.0 (C–O), 118.6 (CN), 118.8, 111.6., 127.0, 132.2, 145.5 (all unsaturated  $\text{CH}_2$  and CH), 173.4 (C=O); IR ( $\nu/\text{cm}^{-1}$ ): 3079, 2982, 2924, 2853, 2230, 1740, 1643, 1177; EI-MS ( $m/z$ ): 188 [ $\text{M}^+$ ], 129, 102, 57, 41.