

# Indium-mediated Barbier-type allylation reaction in PEG400 and PEG400/H<sub>2</sub>O

Zhengyin Du\*, Fen Wang, Wanwei Zhou and Jin-Xian Wang

Key Laboratory of Eco-Environment Related Polymer Materials of Ministry of Education; Key Laboratory of Polymer Materials of Gansu Province & College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou 730070, P. R. China

A green method for the allylation of aldehydes with allyl bromide mediated by indium in polyethylene glycol 400 (PEG400) and PEG400/H<sub>2</sub>O is described. Aldehydes with different substituents afforded the corresponding homoallylic alcohols in good to excellent yields. Comparative studies show that water promoted this reaction in PEG 400.

**Keywords:** indium, allylation, homoallylic alcohols, PEG400, aqueous reaction, green synthesis

Recently there has been interest in developing organometallic reactions in water amongst which allylation of aldehydes to give homoallylic alcohols has received the most attention.<sup>1</sup> This reaction has been carried out by using metals such as Mn,<sup>2</sup> Fe,<sup>3</sup> Sb,<sup>4</sup> Ga,<sup>5</sup> Sn,<sup>6</sup> Mg.<sup>7</sup> Most reactions required an activator such as ammonium chloride, hydrobromic acid and trimethyl chlorosilane (TMSCl), and used a volatile organic compound (VOC) as a cosolvent. In comparison with those metals, indium offers a number of advantages, including its low toxicity, tolerance towards air and moisture and low ionisation potential.<sup>8,9</sup> For these reasons, indium metal-mediated carbon-carbon bond formation reactions, including the Barbier-type allylation of carbonyl compounds, have become a major topic in organic synthesis. The previous reports of indium-mediated allylation reaction used the volatile organic solvent tetrahydrofuran (THF),<sup>10,11</sup> an aqueous organic media (THF/H<sub>2</sub>O),<sup>12,13</sup> and water,<sup>14,15</sup> which caused environmental contamination and health problems.

Polyethylene glycol 400 (PEG400) has the advantages of low vapour pressure and nonflammability. The workup is easy and it is a non-toxic, good reaction medium that is inexpensive and eco-friendly.<sup>16,17</sup> However, there are no examples of the allylation of carbonyl compounds in PEG400 which have been reported. We report here a simple and convenient method for the preparation of homoallylic alcohol from aldehydes and allyl bromide by using PEG400 and PEG400/H<sub>2</sub>O as green reaction medium and indium as the promoting metal reagent (Scheme 1).

## Results and discussion

The reaction of 4-bromobenzaldehyde with allyl bromide was chosen as the model to define the optimum reaction conditions for this indium-mediated allylation reaction. The results are shown in Table 1. From Table 1, it could be seen that only 53% of yield was obtained when the reaction was conducted in pure water for 12 hours (entry 1). This indicates that pure water is not the ideal medium for the reaction. When PEG400 was used as the reaction medium, however, a good yield of 84% was obtained (entry 6). This comparison shows that PEG400 as a reaction medium is better than pure water. In order to clarify the effect of water in this reaction, mixtures of PEG400 and water with different volume ratios were examined as the reaction media under the same conditions (entries 2–5). The yields

**Table 1** Optimisation of allylation reaction conditions<sup>a</sup>

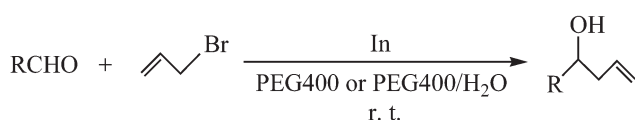
Entry	Reaction media (V/V)	Time/h	Yield/% <sup>b</sup>
1	H <sub>2</sub> O	12	53
2	PEG/H <sub>2</sub> O (1/1)	12	57
3	PEG/H <sub>2</sub> O (2/1)	12	75
4	PEG/H <sub>2</sub> O (3/1)	12	88
5	PEG/H <sub>2</sub> O (4/1)	12	97
6	PEG	12	84

<sup>a</sup>Reaction conditions: 2-bromobenzaldehyde 1 mmol, allyl bromide 2 mmol, r.t., TLC tracking.

<sup>b</sup>Isolated yield after flash column chromatography.

of the product demonstrate that PEG/H<sub>2</sub>O (V/V=4/1) is the best choice for the reaction media affording the homoallylic alcohol in a high yield of 97% (entry 5). It is clear that water can promote the allylation of 4-bromobenzaldehyde with allyl bromide in PEG400 whereas large amount of water is disadvantageous to this reaction. This might be ascribed to the acceleration of electron transfer from indium metal to organic substrates when a small quantity of water is added and a decrease of solubility of substrates when large amount of water is used in PEG400 although PEG400 and water can be miscibility with random ratios.

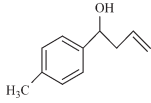
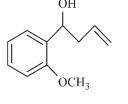
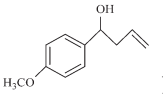
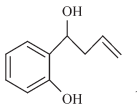
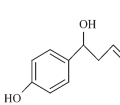
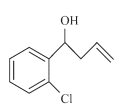
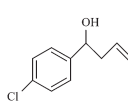
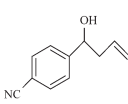
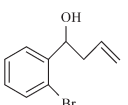
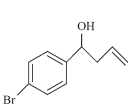
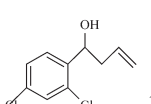
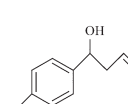
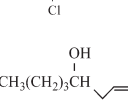
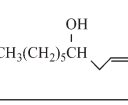
In order to explore the scope of this reaction, a variety of aldehydes with different substituents were investigated in both PEG and PEG/H<sub>2</sub>O (V/V=4/1) at room temperature based on the optimised conditions. The reactions were followed with thin layer chromatography until aldehydes disappeared. The results shown in Table 2 reveal that all the aldehydes that were used were converted smoothly to give the corresponding homoallylic alcohols in good to excellent yields either in PEG400 or in PEG400/H<sub>2</sub>O (V/V=4/1). Overall, the reactions in PEG400/H<sub>2</sub>O gave similar or higher yields in shorter reaction times than in pure PEG400. Among the substituted aromatic aldehydes, those with a 2-bromo and 4-bromo substituent gave higher yields of 88% and 97%, respectively (entries 9 and 10). Other substituents, including electron-donating groups and electron-withdrawing groups, have no demonstrable effect on the yield of products (entries 1–8, 11 and 12). It is noteworthy that for the same substituent, 2-substituted aromatic aldehydes gave lower yields of products than 4-substituted ones. This may be attributable to the larger steric hindrance of the 2-substituent. For example, 2-methoxy- and 4-methoxybenzaldehyde gave yields of 81 and 84%, respectively (entries 2 and 3). Two aliphatic aldehydes were also explored in this reaction. Fortunately, they gave the corresponding homoallylic alcohols in good yields (entries 13 and 14). These indicate that indium-mediated allylation of aldehydes has a wide range of substrates, which can be used for large-scale synthesis of homoallylic alcohols. These are important organic synthesis and as medicinal intermediates.



**Scheme 1** Indium-mediated synthesis of homoallylic alcohols in PEG400.

\* Correspondent. E-mail: Zhengyin Du - clinton\_du@126.com

**Table 2** Synthesis of homoallylic alcohols from various aldehydes<sup>a</sup>

Entry	R	PEG400		PEG400/H <sub>2</sub> O		Product <sup>b</sup>
		Time/h	Yield/%	Time/h	Yield/%	
1	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	14	79	16	84	 <b>1a</b> <sup>3-6,18</sup>
2	2-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	15	73	13	81	 <b>1b</b> <sup>18</sup>
3	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	14	79	16	84	 <b>1c</b> <sup>3-7,18,19</sup>
4	2-HOC <sub>6</sub> H <sub>4</sub>	16	76	14	73	 <b>1d</b> <sup>18,19</sup>
5	4-HOC <sub>6</sub> H <sub>4</sub>	18	79	15	81	 <b>1e</b> <sup>7</sup>
6	2-ClC <sub>6</sub> H <sub>4</sub>	13	82	13	83	 <b>1f</b> <sup>7</sup>
7	4-ClC <sub>6</sub> H <sub>4</sub>	14	82	14	83	 <b>1g</b> <sup>19</sup>
8	4-CNC <sub>6</sub> H <sub>4</sub>	13	75	14	80	 <b>1h</b> <sup>3,7</sup>
9	2-BrC <sub>6</sub> H <sub>4</sub>	14	83	12	88	 <b>1i</b> <sup>7,18</sup>
10	4-BrC <sub>6</sub> H <sub>4</sub>	12	84	12	97	 <b>1j</b> <sup>3,19</sup>
11 <sup>c</sup>	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	16	73	15	83	 <b>1k</b> <sup>3,19,20</sup>
12	3,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	15	69	14	78	 <b>1l</b> <sup>21</sup>
13	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub>	14	78	14	78	 <b>1m</b> <sup>22</sup>
14	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub>	15	77	13	83	 <b>1n</b> <sup>4,19</sup>

<sup>a</sup>Reactions conditions: indium 1 mmol, aldehyde 1 mmol, allyl bromide 2 mmol, PEG400 4mL or PEG400 3.2 mL and water 0.8 mL, r. t., TLC tracked.<sup>b</sup>Isolated yield after flash column chromatography; all products are known compounds and characterised thoroughly by <sup>1</sup>H and <sup>13</sup>C NMR, which were consistent with the literature data.<sup>c</sup>The melting point of this product is 59–60°C (lit.<sup>21</sup>, 59.5 °C).

## Conclusion

In summary, a simple and green protocol for the synthesis of homoallylic alcohols by the allylation of aldehydes with allyl bromide mediated by indium in PEG400 and PEG400/H<sub>2</sub>O has been developed. In comparison with previous reports, this method has some notable advantages, such as using a green medium, which is more environmentally acceptable. It has a wide application, simple reaction conditions giving good to excellent yields, which can be applied for the scale-up synthesis of these compounds.

## Experimental

All reagents were used as obtained from commercial sources except where mentioned. PEG400 was AR grade and used directly. Indium granules with a purity of 99.999% were pressed into flakes and then cut into small pieces prior to use. Allyl bromide was redistilled for use. Melting points were determined on an XT-4 electrothermal micromelting-point apparatus. The <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker MERCURY-PLUS 400 MHz NMR spectrometer. Chemical shifts were reported in parts per million (ppm,  $\delta$ ).

### Synthesis of homoallylic alcohols

A mixture of indium (1 mmol), allyl bromide (2 mmol), aldehyde (1 mmol), and PEG400 (or PEG400/H<sub>2</sub>O) was placed in a 50 mL round-bottomed flask and stirred at room temperature. The progress of reaction was monitored by TLC. The resultant mixture was extracted with ether (4×5 mL) and the combined organic layers were dried over anhydrous MgSO<sub>4</sub>. After removal of the solvent under reduced pressure, purification of the residue by silica column chromatography using petroleum ether/ethyl acetate as the eluent gives the pure homoallylic alcohols. Physical spectroscopic data of product 1-(4-Methylphenyl)-3-buten-1-ol (**1a**): a colourless viscous liquid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) ( $\delta$ , ppm):  $\delta$  = 7.18 (dd,  $J$  = 8.0 Hz,  $J$  = 4.8 Hz, 4H, ArH), 5.81–5.75 (m, 1H, =CH), 5.15–5.09 (m, 2H, =CH<sub>2</sub>), 4.69–4.65 (m, 1H, CH), 2.49–2.46 (m, 2H, CH<sub>2</sub>), 2.35 (s, 3H, CH<sub>3</sub>), 2.15–2.13 (m, 1H, OH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 140.9, 137.1, 134.6, 129.1, 125.7, 118.1 (all unsaturated CH<sub>2</sub> and CH), 73.2 (C-O), 43.7 (CH<sub>3</sub>), 21.5 (CH<sub>3</sub>).

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.

## Electron Supplementary Information

Electron supplementary information includes the experimental, spectroscopic data and spectra of the products and is available via <http://www.ingentaconnect.com/content/stl/jcr>

Received 29 May 2010; accepted 16 July 2010

Paper 1000162 doi: 10.3184/030823410X12813608471242

Published online: 30 August 2010

## References

- 1 P. Anastas and T.C. Williamson, *Green chemistry: frontiers in benign chemical synthesis and processing*, Oxford University Press, New York, 1988.
- 2 J. Augé, N. Lubin-Germain, S. Marque and L. Seghrouchni, *J. Organometal. Chem.*, 2003, **679**, 79.
- 3 T.C. Chan, C.P. Lau and T.H. Chan, *Tetrahedron Lett.*, 2004, **45**, 4189.
- 4 T.C. Chan, C.P. Lau and T.H. Chan, *Tetrahedron Lett.*, 2000, **41**, 5009.
- 5 Z.Y. Wang, S.Z. Yuan and C.J. Li, *Tetrahedron Lett.*, 2002, **43**, 5097.
- 6 Z.Y. Wang, Z.G. Zha and C.L. Zhou, *Org. Lett.*, 2002, **4**, 1683.
- 7 W.C. Zhang and C.J. Li, *J. Org. Chem.*, 1999, **64**, 3230.
- 8 J. Podlech and T.C. Maier, *Synthesis*, 2003, 633.
- 9 Z. Du and Y. Li, *Prog. Chem.*, 2010, **22**, 71.
- 10 T.D. Haddad, L.C. Hirayama, P. Taynton and B. Singaram, *Tetrahedron Lett.*, 2008, **49**, 508.
- 11 J. Augé, N. Lubin-Germain and A. Thiaw-Woaye, *Tetrahedron Lett.*, 1999, **40**, 9245.
- 12 J.S. Kwon, A.N. Pae, K.I. Choi, H.Y. Koh, Y. Kim and Y.S. Cho, *Tetrahedron Lett.*, 2001, **42**, 1957.
- 13 K.-T. Tan, S.-S. Chng, H.-S. Cheng and T.-P. Loh, *J. Am. Chem. Soc.*, 2003, **125**, 2958.
- 14 T.H. Chan and Y. Yang, *J. Am. Chem. Soc.*, 1999, **121**, 3228.
- 15 C.J. Li and T.H. Chan, *Tetrahedron Lett.*, 1991, **32**, 7017.
- 16 D.J. Heldebrant and P.G. Jessop, *J. Am. Chem. Soc.*, 2003, **125**, 5600.
- 17 J. Chen, S.K. Spear, J.G. Huddleston and R.D. Rogers, *Green Chem.*, 2005, **7**, 64.
- 18 S.E. Denmark and S.T. Nguyen, *Org. Lett.*, 2009, **11**, 781.
- 19 Y. Zhang, X. Jia and J.-X. Wang, *Eur. J. Org. Chem.*, 2009, 2983.
- 20 G.-L. Li and G. Zhao, *Org. Lett.*, 2006, **8**, 633.
- 21 R.A. Batey, A.N. Thadani and D.V. Smil, *Tetrahedron Lett.*, 1999, **40**, 4289.
- 22 K.-H. Shen and C.-F. Yao, *J. Org. Chem.*, 2006, **71**, 3980.

Copyright of Journal of Chemical Research is the property of Science Reviews 2000 Ltd. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.