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Regioselective Propargylation of Aldehydes with Propargyl Bromide Mediated by Sn-In in Aqueous Media under Microwave Irradiation

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Abstract: Tin-indium were employed in the propargylations of various aldehydes with propargyl bromide in the presence of $SnCl_2$ and $C_6H_5(CH_3)_3NBr$ under microwave irradiation to afford the corresponding homopropargyl alcohols exclusively in high yields. All the reactions were completed smoothly in predominantly aqueous media in 200 seconds only.

Keywords: Propargylation, aldehydes, tin-indium, regioselectivity, microwave.

Propargylation of carbonyl compounds is one of the important methods in organic synthesis because the propargyl group is a useful three-carbon building block and the propargylation products, homopropargyl alcohols, can be versatile intermediates for various synthetic targets, and as the structural moiety in a variety of biologically active compounds[1-4]. In last two decades, metal mediated Barbier-type propargylation as well as allylation of carbonyl compounds in organic media have been studied extensively. Examples include indium[5], antimony[6], lead[7], titanium[8], zinc[9], chromium[10], galium[11] and tin[12]. In recent decade, reactions in water are of great interest with the development of green chemistry. So far many metals have been reported to be effective in mediating the coupling between carbonyl compounds and propargyl halides to give the corresponding homopropargyl alcohols in aqueous media, including indium[2,13], zinc[2,14], tin[2,15], *etc.*. However, the long reaction times that are frequently required for full conversion, moderate yields of homopropargyl alcohols with the considerable contamination of homoallenyl alcohols have limited the application of propargylation in aqueous media. Herewith, we wish to report a rapid and regioselective propargylation method starting from a series of aldehydes **1a-k** for the synthesis of homopropargyl alcohols **3a-k** as the only or major products by a microwave-chemical Barbier-type reaction in predominantly aqueous media (**Scheme 1**). It is well known that a mixture of homopropargyl alcohol **3** and homoallenyl alcohol **4** was generally produced by reactions involving propargylic or allenic anion equivalents[13a,14,15].

We have carried out an extensive study of reaction conditions, and most importantly have paid considerable attention to the regioselectivity in the introduction of propargyl function by using a binary metal system Sn-In (10:1) instead of a single metal Sn or In,

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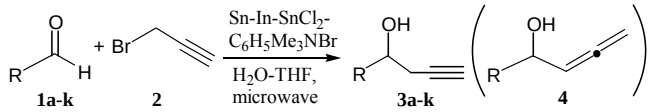
Scheme 1



1a-k **2** **3a-k** **4**

which was historically used[2,5,12]. In addition, we have also found that Lewis acid and phase-transfer catalyst (PTC) are essential and considerably affect the yields of the reactions. To our knowledge, this is the first report on regioselective propargylation of aldehydes in aqueous media under microwave irradiation.

Our first effort was the determination of the optimal conditions on microwave power setting and irradiation time periods for this reaction. Initially, benzaldehyde **1a** was taken as the carbonyl substrate and a single metal tin (Sn) was used for mediation of the reactions. The reaction was performed in a predominantly aqueous media, H_2O / THF = 3:1, which has been successfully used in Barbier-type reaction[13b]. The results indicated that the propargylation of aldehyde was obviously promoted by microwave irradiation on a certain condition and the yield of homopropargyl alcohol **3a** was influenced by both macrowave power setting and irradiation time period in considerable degree. The yields of the homopropargyl alcohol **3** decreased drastically, when the microwave power or irradiation time was set on an over degree. In our experiments the propargylation of aldehydes could complete smoothly with a power setting at 20% P_{max} (P_{max}= 800 W), namely 160 W, and a pulsed irradiation time of 200 seconds (20 s $\times$10).

The effects of Lewis acid catalyst and PTC were next examined. Four kinds of Lewis acids were tested, including NH_4Cl, $ZnCl_2$, $ZnBr_2$ and $SnCl_2$. Of these, $SnCl_2$ was clearly superior. This result is agreement with the Barbier-type reaction in aqueous media studied[16]. Hence, $SnCl_2$ was chosen as an additive to improve the reaction and 0.2 equiv. of $SnCl_2$ was found to be sufficient for the reaction. It is well known that activation of the metal by PTC is needed for Barbier-type reaction to proceed. To examine PTC, three kinds of catalysts were tested, including Et_4NBr, Bu_4NBr and $C_6H_5(CH_3)_3NBr$. Among them, $C_6H_5(CH_3)_3NBr$ was found to be more effective than the others, being used as PTC to give more higher yields of the homopropargyl alcohols **3** and accelerates the propargylation procedure efficiently. Approximately 0.1 equiv. of $C_6H_5(CH_3)_3NBr$ was found to be sufficient for the reaction. Moreover, a binary metal system of Sn-In (10:1) was found to be more efficient than the single metal to the regioselectivity of the reaction.

With the optimized conditions, a general procedure for the propargylation of aldehydes was established. A 50 mL teflon vessel was charged with solid materials $C_6H_5(CH_3)_3NBr$ (0.1 mmol), $SnCl_2$ (0.2 mmol), tin powder (3 mmol), and indium powder (0.3 mmol) in 1 mL of THF. To this resulting mixture, liquid materials benzaldehyde (1 mmol), propargyl bromide (2 mmol) and 3 mL of distilled water were successively added. The vessel was placed in a commercial unmodified microwave oven (Galanz WD800B) for pulsed irradiations (20 s $\times$ 10) at 160 W. After aqueous work-up, the crude products were separated by column chromatography on silica gel. All the isolated products were characterized by ^1H, ^{13}C NMR, IR and mass spectral analysis[17].

Table 1 Sn-In mediated the propargylation reaction of aldehydes with propargyl bromide in the presence of $SnCl_2$ and $C_6H_5(CH_3)_3NBr$ under microwave irradiation[a]

Entry	R	Substrate	Product	Yield[b]
1	C_6H_5	**1a**	**3a**	93
2	*p*-FC_6H_4	**1b**	**3b**	95
3	*p*-MeC_6H_4	**1c**	**3c**	92
4	*p*-ClC_6H_4	**1d**	**3d**	94
5	*p*-$O_2NC_6H_4$	**1e**	**3e**	93
6	3,4-$OCH_2OC_6H_3$	**1f**	**3f**	91
7	*m*-$MeOC_6H_4$	**1g**	**3g**	89
8	*m*-$O_2NC_6H_4$	**1h**	**3h**	87
9	$C_6H_5CH_2$	**1i**	**3i**	94
10	$C_6H_5CH_2CH_2$	**1j**	**3j**	94
11	C_6H_5CH=CH	**1k**	**3k**	93

[a] All reactions were carried out on 1 mmol scale in H_2O/THF (3:1) with aldehyde/bromide/Sn/In = 1:2:3:0.3; $SnCl_2$: 0.2 equiv; $C_6H_5(CH_3)_3NBr$: 0.1 equiv. Microwave conditions: 2.45 GHz, pulsed irradiations (20 s × 10 = 200 s) at 160 W; [b] Isolated yields (%).

A series of 11 homopropargyl alcohols **3a-k** were synthesized from various aldehydes **1a-k** with propargyl bromide **2** by this microwave assisted propargylation reaction. The results are summerized in **Table 1**. Homopropargyl alcohols **3a-k** were produced as the only products in high yields and without the formation of allenyl alcohols **4** in all the reactions listed in the **Table**.

Besides benzaldehyde **1a** (entry 1), the examples involved the *para* substituted benzaldehydes **1b-f** have given satisfactory results in yields of 91-95% (entry 2-6). It is noted that electron-attracting groups, such as fluoro and nitro, in the *para* position would be favorable to the reactions as the carbonyl groups were highly activated by conjugated electron-attracting effects. In the case of *meta* substituted benzaldehydes **1g** and **1h**, (entry 7 and 8), similar results were obtained with somewhat lower yields of 89% and 87%, respectively. Note that the strongly electron-attracting substituent NO_2 (entry 8) in the *meta* position, which is not directly conjugated with the reaction center, could not enhance its reactivity, resulting in its yield below 90%. Furthermore, three aldehydes **1i, 1j** and **1k** (entry 9-11), in which the carbonyl groups are not connected directly to the benzene rings, also gave homopropargyl alcohols **3i, 3j** and **3k** as the only products in high yields (94, 94 and 93%). In all the eleven examples, the region- selectivity of the coupling was much higher than in the cases of the aqueous reactions mediated by single metal tin or indium[15,13].

In conclusion, we have developed an efficient microwave assisted method for the synthesis of homopropargyl alcohols mediated by tin-indium in the presence of $SnCl_2$ and $C_6H_5(CH_3)_3NBr$. The short reaction time, high yield and excellent regioselectivity were obtained. It has significant advantages over existing methods for the homopropargyl alcohols formation from various aldehydes.

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17. Selected spectral data (**3g** and **3i** are new compounds). **3a**[11,18] IR (neat, *v*): 3396, 3294, 3063, 2119, 1603 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, δ ppm, J Hz): 7.30-7.39 (m, 5 H), 4.87 (t, 1H, *J* = 6.1), 2.63-2.66 (m, 2H), 2.50 (s, 1H), 2.08 (t, 1H, *J* = 2.6); HRMS: Calcd. for $C_{10}H_{10}O$ *m/z* 146.0732, found *m/z* 146.0720. **3b**[11] IR (neat, *v*): 3396, 3302, 2119, 1604, 1510 cm^{-1}; ^1H NMR (300 MHz , $CDCl_3$, δ ppm, J Hz): 7.30 (ddd, 2H, *J* = 11.8, 5.3, 3.0), 7.00 (ddd, 2H, *J* = 11.8, 6.3, 3.0), 4.80 (dt, 1H, *J* = 6.3, 2.2), 2.55 (dd, 2H, *J* = 6.3, 2.4), 2.33 (d, 1H, *J* = 2.2), 2.01 (t, 1H, *J* = 2.4); HRMS: Calcd. for $C_{10}H_9OF$ *m/z* 164.0637, found *m/z* 164.0646. **3c**[11] IR (neat, *v*): 3423, 3295, 2120, 1609, 1514 cm^{-1}; ^1H NMR (300 MHz , $CDCl_3$, δ ppm, J Hz): 7.28 (d, 2H, *J* = 8.1), 7.17 (d, 2H, J= 8.1), 4.84 (t, 1H, *J* = 6.4), 2.63 (dd, 2H, *J* = 6.4, 2.6), 2.34 (s, 3H), 2.06 (t, 1H, *J* = 2.6), 2.04 (s, 1H); HRMS Calcd. for $C_{11}H_{12}O$ *m/z* 160.0896, found *m/z* 160.0888. **3d**[11,18] IR (neat, *v*): 3403, 3300, 2120, 1598, 1492 cm^{-1}; ^1H NMR (300 MHz , $CDCl_3$, δ ppm, J Hz): 7.27-7.33 (m, 4H), 4.81 (t, 1H, *J* = 6.3), 2.72 (s, 1H), 2.58 (dd, 2H, *J* = 6.3, 2.6), 2.06 (t, 1H, *J* = 2.6); HRMS: Calcd. for $C_{10}H_9OCl$ *m/z* 180.0342, found *m/z* 180.0349. **3e**[15] IR (neat, *v*): 3459, 3250, 2118, 1607, 1516 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm, J Hz): 8.21-8.24 (m, 2H), 7.57-7.61 (m, 2H), 4.99 (t, 1H, *J* = 6.3), 2.70 (ddd, 1H, *J* = 16.5, 6.3, 2.6), 2.64 (ddd, 1H, *J* = 16.5, 6.3, 2.6), 2.53 (s, 1H), 2.10 (t, 1H, *J* = 2.6); HRMS: Calcd. for $C_{10}H_9O_3N$ *m/z* 191.0582, found *m/z* 191.0594. **3f**[18] IR (neat, *v*): 3404, 3292, 2118, 1609, 1504 cm^{-1}; ^1H NMR (400 MHz , $CDCl_3$, δ ppm, J Hz): 6.91 (d, 1H, *J* = 1.6), 6.84 (dd, 1H, *J* = 7.8, 1.6), 6.78 (d, 1H, *J* = 7.8), 5.95 (s, 2H), 4.79 (t, 1H, *J* = 6.4), 2.61 (dd, 2H, *J* = 6.4, 2.6), 2.31 (s, 1H), 2.07 (t, 1H, *J* = 2.6); HRMS: Calcd. for $C_{11}H_{10}O_3$ *m/z* 190.0630, found *m/z* 190.0632. **3g** IR (neat, *v*): 3442, 3292, 3003, 2118, 1602 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm, J Hz): 7.22-7.27 (m, 1H), 6.92-6.94 (m, 2H), 6.80-6.83 (m, 1H), 4.80 (t, 1H, *J* = 6.2), 3.78 (s, 3H), 2.71 (s, 1H), 2.60 (dd, 2H, *J* = 6.2, 2.6), 2.06 (t, 1H, *J* = 2.6); HRMS: Calcd. for $C_{11}H_{12}O_2$ *m/z* 176.0837, found *m/z* 176.0838. **3h**[15] IR (neat, *v*): 3400, 3296, 3081, 2127, 1531 cm^{-1}; ^1H NMR (400 MHz , $CDCl_3$, δ ppm, J Hz): 8.30 (dd, 1H, *J* = 2.2, 1.8), 8.17 (ddd, 1H, *J* = 8.2, 1.1, 2.2), 7.73-7.76 (m, 1H), 7.52-7.57 (m, 1H), 5.00 (dd, 1H, *J* = 6.9, 5.4), 2.72 (ddd, 2H, *J* = 16.7, 5.4, 2.6), 2.11 (t, 1H, *J* = 2.6); HRMS: Calcd. for $C_{10}H_9O_3N$ *m/z* 191.0582, found *m/z* 191.0577. **3i** IR (neat, *v*): 3404, 3296, 3028, 2118 cm^{-1}; ^1H NMR (300 MHz , $CDCl_3$, δ ppm, J Hz): 7.28-7.44 (m, 5H), 4.02-4.07 (m, 1H), 2.85-3.01 (m, 2H), 2.49 (ddd, 1H, *J* = 16.6, 5.5, 2.7), 2.41 (ddd, 1H, *J* = 16.7, 6.0, 2.7), 2.19 (s, 1H), 2.16 (t, 1H, *J* = 2.7); HRMS: Calcd. for $C_{11}H_{12}O$ *m/z* 160.0888, found *m/z* 160.0876. **3j**[19] IR (neat, *v*): 3389, 3295, 3027, 2932, 2118, 1603 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ ppm, J Hz): 7.19-7.29 (m, 5H), 3.75-3.81 (m, 1H), 2.66-2.85 (m, 2H), 2.45 (ddd, 1H, *J* = 16.8, 4.8, 2.7), 2.35 (ddd, 1H, *J* = 16.8, 6.7, 2.7), 2.06 (t, 1H, *J* = 2.7), 1.84-1.90 (m, 2H); HRMS Calcd. for $C_{12}H_{14}O$ *m/z* 174.1045, found *m/z* 174.1048. **3k**[11] IR (neat, *v*): 3404, 3296, 3082, 2119, 1655, 1599, 1578 cm^{-1}; ^1H NMR (300 MHz , $CDCl_3$, δ ppm, J Hz): 7.25-7.41 (m, 5H), 6.66 (d, 1H, *J* = 15.9), 6.28 (dd, 1H, *J* = 15.9, 6.3), 4.44-4.50 (m, 1H), 2.59 (ddd, 1H, *J* = 15.7, 5.5, 2.6), 2.53 (ddd, 1H, *J* = 15.7, 6.4, 2.6), 2.25 (s, 1H), 2.09 (t, 1H, *J* = 2.6); HRMS: Calcd. for $C_{12}H_{12}O$ *m/z* 172.0888, found *m/z* 172.0887.
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