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Catalyst and Solvent Free Allylation of aldehyde with allyltributylstannane under microwave irradiation

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ABSTRACT

In contrast to widely reported Lewis acid catalyzed allylation of aldehydes with allyltributylstannane, it is observed that aldehydes can generate homoallylic alcohols in excellent yields with allyltributylstannane upon irradiation with microwave without any acid catalyst or solvent.

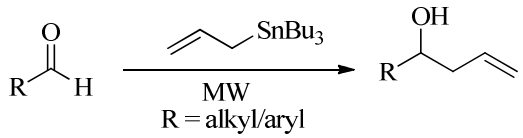
Keywords: Aldehyde, allyltributylstannane, homoallylic alcohol, microwave, solvent-free, catalyst-free.

INTRODUCTION

Homoallylic alcohols are considered as one of the most ubiquitous building blocks in organic synthesis as evident from their applications in the field of organic total synthesis and pharmaceutical research [1]. In recent years, with the advent of ring closing metathesis (RCM) approach [2], homoallylic alcohols and amines are finding new impetus in the synthesis of bioactive natural products [3]. Henceforth, many methods are reported in the literature to achieve the homoallylic alcohols through diverse routes. Major efforts in this line can be credited to metal-mediated allylations and Berbier-type allylations in aqueous media [4]. Metals, such as indium, tin, gallium, iron, zinc, etc. that are used with allyl halides always require more than stoichiometric amount even in the presence of inorganic salts [5] and organic co-solvents [6]. But major drawback of metal mediated allylation of aldehyde lies with the generation of undesired Pinacol and Wurtz products. That is one of the most important reasons, for which allytributyltins came into prominence for allylation of aldehydes to generate homoallylic alcohols. Among the Lewis acids [7] that are used to catalyze this transformation, such as

$BF_3.Et_2O$, $SnCl_4$, $TiCl_4$, etc. are highly moisture sensitive and hence require strictly anhydrous conditions, while transition metal complexes, such as AgOTf, $ReBr(CO)_5$, and $Sc(OTf)_3$ are very expensive, albeit being water-tolerant. Although palladium and platinum complexes were also used as catalysts [8], they were found to be inconsistant in terms of reaction yields and require either high temperature or long reaction time besides being highly expensive. It is worthwhile to mention that for all the reactions of carbonyl compounds with allylstannane, various Lewis acid are used to bind with the oxygen atom of the carbonyl group to render enhanced electrophilicity of the carbonyl carbon for nucleophilic addition of the allyl group. Since operational simplicity, environmental benignness and cost effectiveness are some of the most cardinal criteria that drive the synthetic chemists to develop newer synthetic methodology, we wanted carry out synthesis of homoallylic alcohols from aldehyde and allylstannanes in the absence of any Lewis caid, for that matter any catalyst.

In recent years, microwave-accelerated organic reactions under solvent free condition [9] have increasingly become popular from the viewpoint of green chemistry. As microwave aided reactions are getting huge impact both on industrial and academic fronts, we present herein the efficacy of microwave irradiation towards the said transformation in a bid to generalize allylation of aldehyde on diverse range of substrates (Scheme 1) with sensitive functional groups in the absence of any solvent and catalyst.



Scheme 1. Synthesis of homoallylic alcohols

EXPERIMENTAL SECTION

All reagents were commercially available and used without further purification. Most of the aldehydes were purchased from Sigma Aldrich. The IR spectra were recorded on a Perkin Elmer 983 spectrophotometer. For column chromatography, we employed Merck silica gel 60-120 mesh. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on an AMX-400 MHz spectrometer using $CDCl_3$ as solvent and TMS as internal standard, unless otherwise stated. Mass spectra were obtained from Waters ZQ 4000 mass spectrometer by the ESI method, while the elemental analyses of the complexes were performed on a Perkin–Elmer-2400 CHN/S analyzer.

General Procedure for preparation of Homoallylic alcohols: A microwave tube charged with the aldehyde (1 mmol) and allyl tributyl tin (333 mg, 1 mmol) was irradiated in CEM microwave digester (CEM DISCOVERY BENCHMATE) at 120 ^oC for the specified time (See Table III). After complete conversion of the starting material, as evident from TLC monitoring, the reaction mixture was partitioned between ethyl acetate (3 x 20 mL) and water. The combined organic layer was dried over Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel 60-120 mesh with petroleum ether/ethyl acetate as eluent to obtain the pure product.

Spectral data of selected compounds

1-(benzo[d][1,3]dioxol-5-yl)but-3-en-1-ol (P10): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (s, 1H), 2.39 (t, *J* = 6.8 Hz, 2H), 4.57 (t, *J* = 6.4 Hz, 1H), 5.05-5.06 (d, *J*= 4.4 Hz, 1H), 5.07-5.10 (d, *J*= 11.2 Hz, 1H), 5.60 (m, 1H), 5.87 (s, 2H), 6.65-6.80 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 43.84, 73.19, 100.99, 106.38, 108.05, 118.42, 119.22, 134.42, 137.95, 146.90, 147.72 ppm. ESI MS (m/z): 215 (M^++ 23). Elemental analysis: Calculated for $C_{11}H_{12}O_3$ C 68.74, H 6.29; Observed C 68.67, H 6.20.

1-(4-*tert*-Butyldimethylsilyloxyphenyl)but-3-en-1-ol (P13): ^{1}H NMR (400 MHz, $CDCl_3$): δ -0.00 (s, 6H), 0.78 (s, 9H), 1.42 (s, 1H), 2.30 (t, *J* = 6.8 Hz, 2H), 4.48 (t, *J* = 6.8 Hz, 1H), 4.93 (d, *J* = 5.2 Hz, 1H), 4.93 (d, *J* = 5.2 Hz, 1H), 4.97 (d, J = 14.0 Hz, 1H), 5.60 (m, 1H), 6.62 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ -4.42, 18.20, 25.67, 43.79, 73.03, 118.27, 119.97, 126.98, 134.65, 136.59, 115.08 ppm. ESI MS (m/z): 215 (M^++ 23). Elemental analysis: Calculated for $C_{16}H_{26}O_2Si$ C 69.01, H 9.41; Observed C 68.95, H 9.39.

12-(Tetrahydro-2H-pyran-2-yloxy)dodec-1-en-4-ol (P14) : ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25- 1.30 (m, 10H), 1.45-1.84 (m, 10H), 2.09-2.33 (m, 2H), 3.34-3.4 (m, 2H), 3.47-3.52 (m, 1H), 3.63 (s, 1H), 3.69-3.75 (m, 2H), 3.84-3.89 (m, 1H), 4.57 (d, J = 4 Hz, 1H), 5.11-5.15 (m, 1H), 5.77-5.88 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.7, 25.5, 25.6, 26.2, 29.4, 29.5, 29.6, 29.7, 30.7, 36.8, 41.3, 62.3, 67.6, 70.6, 98.8, 118, 134.9 ppm. ESI MS (m/z): 307.1 (M^+ + 23). Elemental analysis: Calculated for $C_{17}H_{32}O_3$ C 71.79, H 11.34; Observed C 70.56, H 11.43.

Non-1-en-4-ol (P15): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.62 (t, *J*= 6.8 Hz, 3H), 1.02-1.10 (m, 4H), 1.13-1.20 (m, 4H), 1.74 (s, 1H), 1-79-1.91 (m, 1H), 2.01-2.06 (m, 1H), 3.36 (m, 1H), 4.86 (m, 2H) 5.57 (m, 1H), ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.99, 22.59, 25.31, 31.83, 36.71, 41.88, 70.68, 117.83, 134.95 ppm. ESI MS (m/z): 151.1 (M^++ 23). Elemental analysis: Calculated for $C_9H_{18}O$ C 76.00, H 12.76; Observed C 75.76, H 12.61.

1-phenylhexa-1,5-dien-3-ol (P17): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.86 (s, 1H), 2.26-2.39 (m, 2H), 4.27 (q, *J*= 6.4 Hz, 1H), 5.07 (d, *J*= 4.4 Hz, 1H), 5.10 (d, *J*= 10.8 Hz, 1H), 5.77 (m, 1H), 6.16 (dd, *J*= 16.0, 6.4 Hz, 1H), 6.52 (d, *J*=16 Hz, 1H), 7.11-7.30 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 42.0, 71.73, 118.51, 126.50, 127.68, 128.59, 130.36, 131.56, 134.07, 136.65 ppm. ESI MS (m/z): 173 (M^+-1), 172 (100). Elemental analysis: Calculated for $C_{12}H_{14}O$ C 82.72, H 8.10; Observed C 82.55, H 8.01.

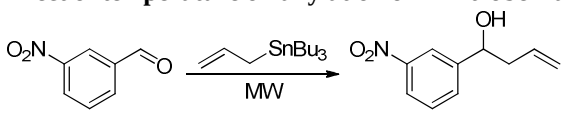
***tert*-Butyl 2-(1-hydroxybut-3-enyl)pyrrolidine-1-carboxylate (P18):** ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (s, 9H), 1.68 (m, 2H), 1.81 (m, 2H), 2.09 (m, 2H), 3.18 (m, 3H), 3.45 (m, 1H), 3.82 (s, 1H), 5.01 (d, *J* = 9.2 Hz, 1H), 5.04 (d, *J* = 15.6 Hz, 1H), 5.83 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.2, 27.4, 28.4, 37.1, 48.0, 62.6, 72.7, 79.9, 116.7, 135.6 ppm. ESI MS (m/z): 264 (M^++ 23). Elemental analysis: Calculated for $C_{13}H_{23}NO_3$ C 64.70, H 9.61, N 5.80; Observed C 64.52, H 9.52, N 6.02.

RESULTS AND DISCUSSION

Initially, a mixture of *m*-nitrobenzaldehyde and allyltributylstannane (1 equiv.) was stirred at RT for 24 h to find that no reaction was taking place. Then the reaction mixture was irradiated with microwave at 110 ^{o}C for 10 min to find that a polar product was formed, which was later

confirmed to be the desired homoallylic alcohol. Keeping the reaction temperature constant, we extended the reaction time to observe that complete conversion was not achieved even after an hour (Table 1). The optimum temperature to accomplish the reaction of *m*-nitrobenzaldehyde with allyltributylstannane under solvent free conditions was studied (Table I) and was found that reaction gives best result when heated at 120 ^{o}C for 20 min.

Table 1. Effect of temperature on allylation of *m*-nitrobenzaldehyde[a]



Entry	Temp (^{o}C)	Time (min)	% yield
1	23	24 h[b]	-
2	110	10	50
3		30	53
4		60	57
5	120	10	55
6		20	92
7		40	66

[a]Aldehyde : allyltributylstannane = 1 : 1; [b]Without microwave irradiation.

To study the effect of solvent, we carried out the reaction in diethyl ether, dichloromethane, chloroform, actonitrile and DMF at different temperature range (Table 2) to find that the reaction does not work in the first three solvents, even after irradiation at their boiling temperature, while reaction undergoes completion when irradiated at 80 ^{o}C for two hours in both acetonitrile and DMF. In an attempt to see whether the reaction works in water, we mixed *m*-nitrobenzaldehyde and allyltributylstannane in water and irradiated at 100 ^{o}C for an hour to get back only the unreacted starting materials. When n-tetrabutylammonium bromide (TBAB), a phase transfer catalyst was added to the aforesaid mixture to facilitate the reaction in water, we found that the reaction does take place and undergoes complete conversion. This observation lead us to conclude that because of the inhomogeneity of the reaction medium, reaction does not work in water.

Table 2. Effect of solvent on the reaction of *m*-nitrobenzalde-hyde with allytributylstannane[a]

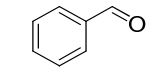
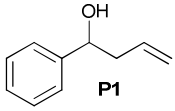
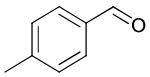
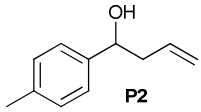
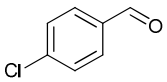
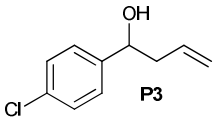
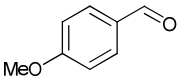
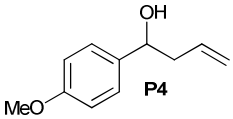
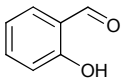
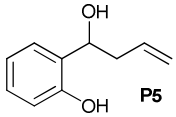
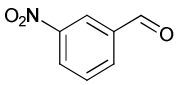
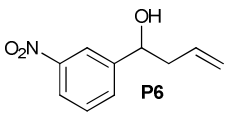
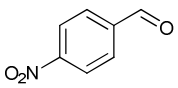
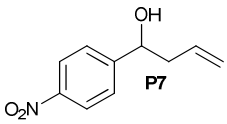
Entry	Solvent	Temp (^{o}C)	Time (min)	% yield
1	Et_2O	RT	120	NR
2		Reflux	120	NR
3	CH_2Cl_2	RT	120	NR
4		Reflux	120	NR
5	$CHCl_3$	59	120	NR
6	CH_3CN	RT	120	NR
7		80	120	65
8	DMF	RT	120	NR
9		80	120	60
10	H_2O	100	60	NR
11	TBAB	120	30	93

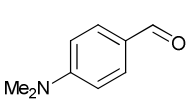
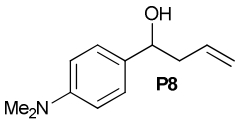
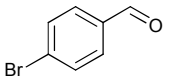
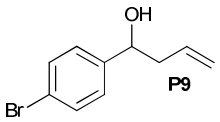
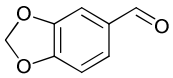
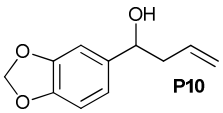
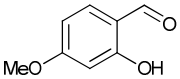
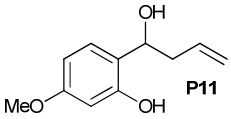
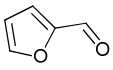
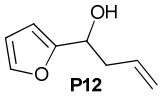
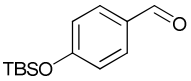
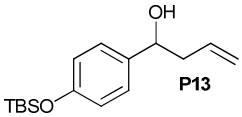
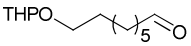
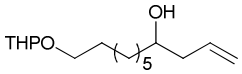
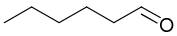
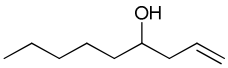
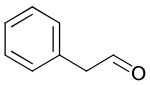
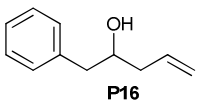
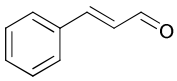
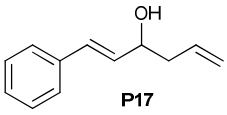
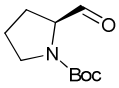
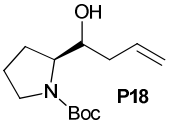
[a]Aldehyde : allyltributylstannane = 1 : 1

After standerdization of the reaction conditions, we turned our attention to its application in the synthesis of homoallylic alcohols from various aromatic and aliphatic aldehydes as shown in

Table 3. It is observed that reaction works exceedingly well for aromatic aldehydes having either +M or –M effect on the phenyl rings. The presence of phenolic –OMe (entry 5) group in the *p*-position of the aldehyde group seems to interfere the yield of the product which is evident from comparatively moderate yield of the products (entry 4, Table 3). Ironically, the product carrying both *p*-methoxy and *o*-hydroxy derived from vanillin (entry 11, Table 3) gives many unidentified products under the reaction conditions. Several functional groups such as OTHP, methylenedioxy, etc. are hardly affected by the reaction conditions, as reflected by their excellent yields. The protection as OTBS (entry 13) seems to be very stable under our reaction conditions, as reflected by its excellent yields. We did not observe any significant differences in reactivity for *m*- and *p*-nitrobenzaldehyde (entry 6 and 7), where they almost took similar reaction time for complete conversion. Ironically, *p*-*N*,*N*-dimethylaminobenzaldehyde did not give the desired product, although we could isolate an unknown solid mass instead of the unreacted starting material. It is interesting to note that the aliphatic aldehydes (entry 14, 15 and 16) take lesser reaction time as compared to the aromatic aldehydes to obviate their corresponding homoallylic alcohols. Excellent yield of homoallylic alcohol derived from cinnamaldehyde (entry 17) shows 1,2-addition is prefered one in α,β-unsaturated aldehydes. *N*-Boc pyrrolidine-2-carbaldehyde also generates its corresponding homoallylic alcohol (entry 18) in good yield to verify the fact that amide group α-to the aldehyde functionality hardly has any negative impact on the efficiency of the reaction system.

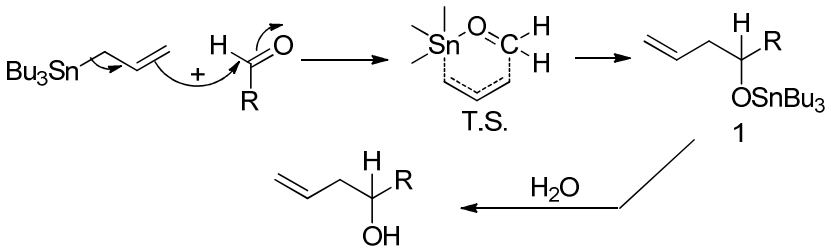
Table 3. Syntheis of homoallylic alcohols *via* Scheme 1[a,b]

Entry	Substrate	Product	Temp (^oC)	Time (min)	% yield[c]
1		 **P1**	120	10	92
2		 **P2**	120	10	85
3		 **P3**	120	18	85
4		 **P4**	120	20	50
5		 **P5**	120	15	75
6		 **P6**	120	20	92
7		 **P7**	120	9	82

8		 **P8**	120	30	NR
9		 **P9**	120	20	85
10		 **P10**	120	15	85
11		 **P11**	120	15	DP
12		 **P12**	110	20	87
13		 **P13**	110	5	85
14		 **P14**	120	15	70
15		 **P15**	110	12	85
16		 **P16**	120	20	81
17		 **P17**	120	15	95
18		 **P18**	120	30	76

[a]The reaction were carried out mixing the aldehydes with n-tributyl stannane in 1:1 ratio, followed by microwave irradiation at normal pressure for the specified times. [b]CEM Discover Benchmate open vessel was used for microwave irradiation. [c]Yield of the pure product. NR= No reaction. DP= Decomposed product.

The pathway might involve a plausible six-membered transition state (Scheme 2), which initially forms the tributyltin alkoxide, **1** to obviate the homoallylic alcohol upon hydrolysis.



Scheme 2. Possible reaction pathway

In conclusion, this report demonstrates a simple, yet efficient method for environmentally benign synthesis of homoallylic alcohols from aldehyde just by heating with microwave. Use of no catalyst and solvent besides having no aqueous work-up, are some of the most intersting features of this conversion. The reaction conditions are compatible to various sensitive functional groups that may provide better dividend to the corresponding Lewis acid catalyzed reactions.

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