ORGANIC LETTERS
2011
Vol. 13, No. 2
332−335

Tin Mediated Allylation Reactions of Enol Ethers in Water

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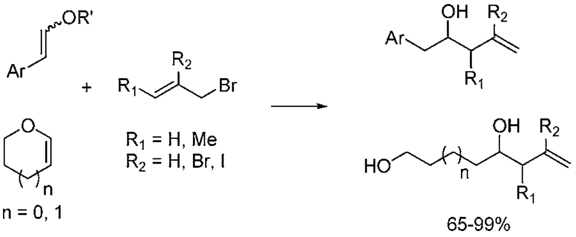
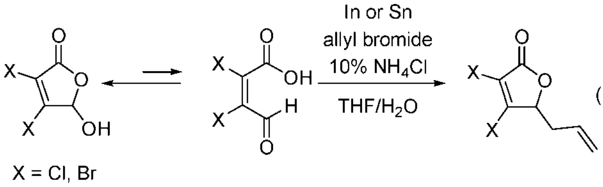
Received November 21, 2010

ABSTRACT



Under tin-mediated Barbier-type reaction conditions, hydration of enol ethers takes place to form aldehydes that undergo allylation reactions. By using this process, various homoallylic alcohols and 2-halohomoallylic alcohols are produced in good to excellent yields.

Water is a readily available, environmentally benign solvent. Recently, the use of water as a solvent in chemical reactions has received considerable attention owing to cost, safety, and environmental concerns.[1] In this regard, metal-mediated C−C bond forming reactions occurring in aqueous media have been intensively investigated.[2] Metal-mediated Barbier allylation reactions in water have several advantages over those carried out in organic solvents. Typically, allylation reactions of hemiacetals, catalyzed by $InCl_3$ and Me_3SiBr, are performed in organic solvents and lead to direct substitution of the hydroxyl group.[3] Whitesides[4] reported that addition of tin, indium, or zinc complexed allyl anions to the glycosidic carbons of unprotected carbohydrates, which exist in water predominantly as cyclic hemiacetals, takes place smoothly in aqueous/organic solvent mixtures. Thus, the carbonyl group of ring-opened hydroxyaldehydes is the actual reactant in these allylation reactions. Likewise, mucohalic acids exist predominantly as a mixture of lactol and aldehyde forms, the latter of which is favored in aqueous media (eq 1). Zhang[5] has demonstrated that γ-allylic α,β-unsaturated γ-butyrolactones can be produced via indium or tin mediated allylation reactions of mucohalic acids (eq 1). Later, Loh[6] described a one-pot indium trichloride-catalyzed allylation process in aqueous solution that transforms dihydropyrans and dihydrofurans to lactols. Apparently, water plays an important role in the formation of aldehydes from the corresponding hemiacetals, which then undergo allylation in the presence of allyl anion equivalents.



(1)

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[1] (a) Li, C. J. *Chem. Rev.* **2005**, *105*, 3095. (b) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751. (c) Chan, T. H.; Issac, B. M. *Pure Appl. Chem.* **1996**, *68*, 919. (d) Li, C. J. *Tetrahedron* **1996**, *52*, 5643. (e) Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; John Wiley & Sons, Inc.: New York, 1997. (f) Paquette, L. A. In *Green Chemistry: Frontiers in Benign Chemical Synthesis and Processing*; Anastas, P., Williamson, T., Eds.; Oxford University Press: New York, 1998.

[2] Li, C. J. Metal-Mediated C-C Bond Formations in Aqueous Media. In *Organic Reactions in Water Principles, Strategies and Applications*; Lindström, U. M., Ed.; Blackwell: Ames, IA, 2007.

[3] Saito, T.; Nishimo, Y.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2006**, *71*, 8516.

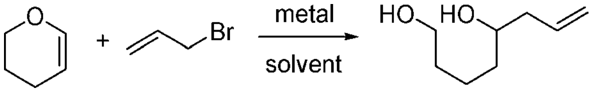
[4] Kim, E.; Gordon, D. M.; Schmid, W.; Whitesides, G. W. *J. Org. Chem.* **1993**, *58*, 5500.

10.1021/ol102825t © 2011 American Chemical Society
Published on Web 12/13/2010

Enol ethers are electron-rich alkenes that participate in certain organic processes, such as the Diels−Alder and the Claisen rearrangement reactions.[7] In general, they do not serve as good substrates in allylation reactions with metal-allyl reagents. However, the outcome could be different if these processes were carried out in aqueous solution. In water, hydration of enol ethers can occur via oxocarbonium ion intermediates, which then react with water to form hemiacetals and finally aldehydes and alcohols.[8] Tin and tin-containing Lewis acids have been extensively used in organic chemistry owing to their low cost, commercial availability, and modestly low toxicity.[9] Several examples of methods that use tin metal and stannic chloride to promote allylation reactions of aldehydes in aqueous media have been described.[10] When taking into account both of these features, we envisioned that enol ethers would serve as substrates in organotin mediated allylation reactions in aqueous solutions. Below, we describe the results of a study which demonstrate that enol ethers serve as starting materials for tin mediated reactions with various allylating reagents, including allyl bromide and 2-bromo- and 2-iodo-3-bromopropene.

This effort began with an investigation of tin mediated allylation reactions of 5,6-dihydropyran with allyl bromide, in which various in situ generated allylstannane sources were screened for their reactivity in aqueous solution. The conditions employed and the results of the reactions are presented in Table 1. The allylation reaction promoted by tin metal proceeded smoothly when water was used as the solvent (Table 1, entry 1). In contrast, no allylation product formed when the process was carried out in organic solvents, such as ether or THF (Table 1, entry 2), and the reaction occurred only slowly and inefficiently even when aqueous HBr was added to these solvents (Table 1, entry 4). The results show that water is required in order to facilitate the hydration step that initiates the process. In addition, formation of the allylstannane intermediate by reaction of allyl bromide with tin appears to create a sufficiently acidic solution to enable hydration of the enol ether moiety so that addition of hydrobromic acid does not play a dramatic role in enhancing the overall rate of allylation (Table 1, entry 1 versus 3). Use of a combination of $SnCl_2$ with Al or Zn led to successful operation of the allylation process, but the reaction does not take place when Al or Zn was used alone (Table 1, entries 5−8). None of the desired product was produced when tin chloride, accompanied by other metals such as copper, copper(II) chloride, and titanium(III) chloride, was utilized (entries 9−11). The allylation product was generated efficiently when $SnCl_2$ and KI were used as promoters (entry 12). It should be noted that the $SnCl_2$ and KI combination has not only been used in allylation reactions of aldehydes[10c] but also in those of acetals.[11]

Table 1. Metal-Mediated Allylation of Dihydropyran in Water[a]

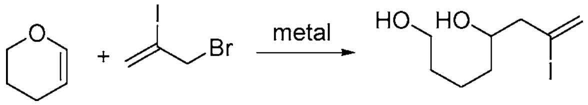


entry	metal/additive	solvent	yield (%)
1	Sn	H_2O	85
2	Sn	THF or Et_2O	0
3[b]	Sn/HBr	H_2O	91
4[b]	Sn/HBr	THF or Et_2O	36
5	Al	H_2O	0
6	Zn	H_2O	0
7	$SnCl_2$/Al	H_2O	76
8	$SnCl_2$/Zn	H_2O	85
9	$SnCl_2$/Cu	H_2O	0
10	$SnCl_2$/$CuCl_2$	H_2O	0
11	$SnCl_2$/$TiCl_3$	H_2O	0
12[c]	$SnCl_2$/KI	H_2O	90

[a] Conditions: Dihydropyran (DHP, 1.0 mmol), allyl bromide (1.5 mmol), and indicated metal (1.0 mmol) in 2.0 mL of solvent at rt. [b] HBr (0.1 mL) was used as an additive, and 1.9 mL of the solvent was added. [c] $SnCl_2$ (1.5 mmol)/KI (1.5 mmol).

Transition metal-catalyzed cross-coupling reactions of vinyl halides have proven to be a powerful method for C−C bond formation.[12] We believe that 2-haloallylation reactions of enol ethers could have similarly wide applications in organic synthesis. Therefore, our attention turned to an exploration of the 2-iodoallylation reaction of dihydropyran. As can be seen by viewing the results summarized in Table 2, dihydropyran is

Table 2. Metal-Mediated 2-Iodoallylation of Dihydropyran



entry	metal/additive	solvent	yield (%)[a]
1	In/$InCl_3$	H_2O	0
2	Sn	H_2O	0
3	Sn/HBr	H_2O	<5
4	$SnCl_2$/Zn	H_2O	0
5	Sn/HBr	H_2O/THF	70
6	$SnCl_2$/KI	H_2O	87

[a] The product was isolated as the corresponding acetate derivative after the diol was treated with Ac_2O, DIEA, and DMAP in ether.

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(5) Zhang, J.; Blazecka, P. G.; Berven, H.; Belmont, D. *Tetrahedron Lett.* **2003**, *44*, 5579.

(6) Juan, S.; Hua, Z.-H.; Qi, S.; Ji, S.-J.; Loh, T.-P. *Synlett* **2004**, *5*, 829.

(7) (a) Pindur, U.; Gundula, L.; Otto, C. *Chem. Rev.* **1993**, *93*, 741. (b) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, Part 4.1, p 315. (c) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, Part 7.2, p 827. (d) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423.

(8) Kresge, A. J. *Acc. Chem. Res.* **1987**, *20*, 364.

(9) (a) Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworth: London, 1987. (b) Smith, P. J. *Toxicological Data on Organotin Compounds*; International Tin Research Inst.: London, 1978.

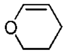
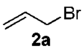
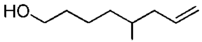
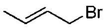
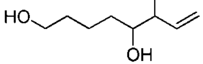
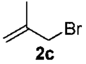
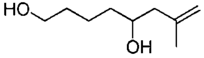
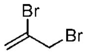
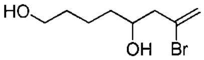
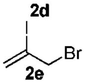
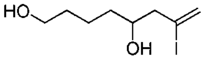
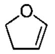
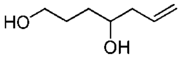
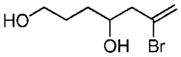
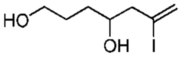
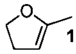
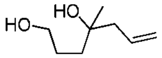
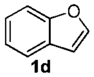
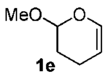
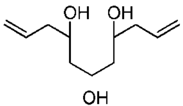
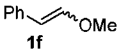
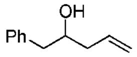
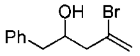
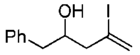
(10) (a) Nokami, J.; Otera, J.; Sudo, T.; Okawara, R. *Organometallics* **1983**, *2*, 191. (b) Einhorn, C.; Luche, J.-L. *J. Organomet. Chem.* **1987**, *322*, 177. (c) Houllemare, D.; Outurquin, F.; Paulmier, C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1629. (d) Chan, T. H.; Yang, Y.; Li, C. J. *J. Org. Chem.* **1999**, *64*, 4452. (e) Tan, X.-H.; Shen, B.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* **2002**, *43*, 9373. (f) Tan, X.-H.; Shen, B.; Deng, W.; Zhao, H.; Liu, L.; Guo, Q.-X. *Org. Lett.* **2003**, *5*, 1833. (g) Zhou, C.; Zhou, Y.; Jiang, J.; Xie, Z.; Wang, Z.; Zhang, J.; Wu, J.; Yin, H. *Tetrahedron Lett.* **2004**, *45*, 5537. (h) Tan, X.-H.; Hou, Y.-Q.; Huang, C.; Liu, L.; Guo, Q.-X. *Tetrahedron* **2004**, *60*, 6129.

transformed to the corresponding lactol when reacted with 2-iodo-3-bromopropene in water using the In/$InCl_3$ conditions described by Loh[5] (entry 1), tin metal (entry 2), or $SnCl_2$/Zn (entry 4). However, in each case none of the iodoallylation product was produced. The results show that 2-iodoallylation is a much more sluggish process than the closely related allylation reaction (Table 2, entries 2, 3, and 4 versus Table 1, entries 1, 3, and 8).

Reactions of 2,3-dibromopropene with acetals to form bromo-homoallylic alcohols that occur via allyltin intermediates have been reported to take place under acid catalyzed conditions.[13] Yet, reaction of dihydropyran with 2-iodo-3-bromopropene in an aqueous solution containing Sn and HBr failed to produce the corresponding allylation product (Table 2, entry 3). By way of contrast, iodoallylation of dihydropyran occurs with relatively high efficiency when the reaction is carried out in a mixed THF/H_2O solvent system (Table 2, entry 3 versus 5). Moreover, this process is highly efficient when promoted by $SnCl_2$/KI in water (Table 2, entry 6). It is important to note that the iodoallylation product is not stable when stored at room temperature. Therefore, reaction yields were determined by transformation of the alcohol group in the product to its acetate derivative.

The substrate scope of allylation reactions of enol ethers with allylic bromides was probed (Table 3).[14] The γ-addition product was formed predominantly in the reaction of dihydropyran with crotyl bromide, but a low level of diastereoselectivity accompanies this process (Table 3, entry 2). In addition, high yields were obtained for allylation reactions of dihydropyran and dihydrofuran using a variety of substituted allylic bromides (Table 3, entries 1−8). However, the efficiency of the process was slightly lower for the reaction of the sterically hindered cyclic enol ether, 2,3-dihydro-5-methylfuran, with allyl bromide (Table 3, entry 6 versus 9), and only starting materials are recovered when this enol ether is reacted with 2-iodo-3-bromopropene (Table 3, entry 10). Allylation of benzofuran does not take place under these conditions, presumably a consequence of the fact that it would be attended by partial loss of aromatic stabilization of the substrate (Table 3, entry 11). In addition, a bis-homoallylic alcohol is formed in a high yielding allylation reaction of 6-methoxy-5,6-dihydropyran with allyl bromide (Table 3, entry 12). In allylation reactions of β-methoxystyrene with allylic bromides, including 2-bromo- and 2-iodo-3-bromopropene, addition of hydrobromic acid to the aqueous solutions was required to promote high yielding conversions to product (Table 3, entries 13−15).

Table 3. Tin-Mediated Allylation of Enol Ethers

entry	substrate	allyl bromide	product		yield (%)
1	 **1a**	 **2a**		**3a**	85
2	**1a**	 **2b**		**3b**	90[a]
3	**1a**	 **2c**		**3c**	88
4	**1a**	 **2d**		**3d**	83[b]
5	**1a**	 **2e**		**3e**	87[b]
6	 **1b**	**2a**		**3f**	90
7	**1b**	**2d**		**3g**	87[b]
8	**1b**	**2e**		**3h**	90[b]
9	 **1c**	**2a**		**3i**	72
10	**1c**	**2e**	—		0
11	 **1d**	**2a**	—		0
12[c]	 **1e**	**2a**		**3j**	89
13[d]	 **1f**	**2a**		**3k**	99
14[d]	**1f**	**2d**		**3l**	99
15[d]	**1f**	**2e**		**3m**	74

[a] Anti/syn = 1:1.27. [b] The product was isolated as the corresponding acetate derivative. [c] Conditions: enol ether (1.0 mmol), allyl bromide (3.0 mmol), and tin powder (2.0 mmol) in water (2.0 mL) at rt. [d] Conditions: enol ether (1.0 mmol), allyl bromide (2.0 mmol), tin powder (1.0 mmol) and HBr (0.2 mL) in THF (1.0 mL)/water (0.8 mL) at rt.

The success of these bromo-homoallylic alcohol forming processes should be contrasted with the results of earlier studies, which show that the reaction of 2,3-dibromopropene with phenylacetaldehyde takes place in a very low yield (33%)[15] when the procedure developed by Otera is employed.[13] The

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(11) (a) Gremyachinskiy, D. E.; Smith, L. L.; Gross, P. H.; Samoshin, V. V. *Green Chem.* **2002**, *4*, 317. (b) Samoshin, V. V.; Gremyachinskiy, D. E.; Smith, L. L.; Bliznets, I. V.; Gross, P. H. *Tetrahedron Lett.* **2002**, *43*, 6329.

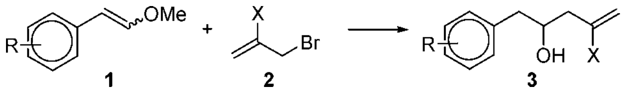
(12) de Meijere, A., Diederich, F., Eds. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2004.

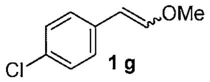
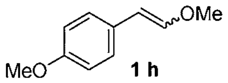
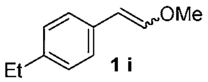
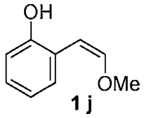
(13) Mandai, T.; Nokami, J.; Yano, T.; Yoshinaga, Y.; Otera, J. *J. Org. Chem.* **1984**, *49*, 172.

(14) **General procedure for tin-mediated allylation of enol ethers (Table 3, entries 1, 2, 3, 6, 9, 11, 12):** A mixture of an enol ether (1.0 mmol), an allylating agent (1.5 mmol), and tin powder (1.0 mmol) in water (2.0 mL) was stirred at rt. Reaction was monitored by TLC until no starting material was observed, and normally the reaction was stirred at rt overnight. Et_2O (5 mL) was then added to the reaction, and the mixture was transferred to a separatory funnel. The organic layer was back extracted with Et_2O (5 mL). The combined organic layers were washed with brine (3 mL × 2), dried over Na_2SO_4, and concentrated in a rotary evaporator. The residue was purified by silica-gel chromatography to give the product. **Table 3, entries 4, 5, 7, 8, 10:** A mixture of an enol ether (1.0 mmol), an allylating agent (1.5 mmol), and $SnCl_2$ (1.5 mmol)/KI (1.5 mmol) in water (2.0 mL) was stirred at rt overnight. Work-up and purification procedures were similar to those described above. **Table 3, entries 13−15:** A mixture of an enol ether (1.0 mmol), an allylating agent (2.0 mmol), tin powder (1.0 mmol), and HBr (47−49% aqueous, 0.2 mL) in THF (1.0 mL)/water (0.8 mL) was stirred at rt overnight. Work-up and purification procedures were similar to those described above. Structures of the products and yields are indicated in Table 3. Conditions presented in Table 3are through optimization.

(15) (a) Lei, M.-Y.; Fukamizu, K.; Xiao, Y.-J.; Liu, W.-M.; Twiddy, S.; Chiba, S.; Ando, K.; Narasaka, K. *Tetrahedron Lett.* **2008**, *49*, 4125. (b) Lei, M.-Y.; Xiao, Y.-J.; Liu, W.-M.; Fukamizu, K.; Chiba, S.; Ando, K.; Narasaka, K. *Tetrahedron* **2009**, *65*, 6888.

Table 4. Tin-Mediated Allylation of β-Methoxystyrenes



entry	substrate	allyl bromide	yield[a] (%)
1	 1 g	**2a**; X = H	**3n**; 78
2		**2d**; X = Br	**3o**; 78
3		**2e**; X = I	**3p**; 65
4	 1 h	**2a**; X = H	**3q**; 98
5		**2d**; X = Br	**3r**; 90
6		**2e**; X = I	**3s**; 82
7	 1 i	**2a**; X = H	**3t**; 92
8		**2d**; X = Br	**3u**; 91
9		**2e**; X = I	**3v**; 72
10	 1 j	**2a**; X = H	**3w**; 99
11		**2d**; X = Br	**3x**; 91
12		**2e**; X = I	**3y**; 89

[a] Conditions: enol ether (1.0 mmol), allyl bromide (2.0 mmol), tin powder (1.0 mmol), and HBr (0.2 mL) in THF (1.0 mL)/water (0.8 mL) at rt.

exceptional lability of phenylacetaldehyde might be the reason behind the poor yield of its 2-bromoallylation reaction. This problem is further complicated by the fact that 2-arylacetaldehydes are relatively difficult to prepare. Consequently, the results of our studies show that by replacing 2-arylacetaldehydes with β-methoxystyrene derivatives it is possible to efficiently generate the corresponding bromo-homoallylic alcohols starting with substrates that are readily prepared by straightforward Wittig olefination of the corresponding benzaldehydes.[16] To explore this process further, β-methoxystyrenes, prepared in this manner, were subjected to allylation reaction conditions. In each case, the corresponding arylmethyl-homoallylic alcohols were produced in excellent yield (Table 4). Some of the products of these reactions have been synthesized earlier by using more complicated routes.[17] Consequently, the results of this effort have led to the development of a simple method for the preparation of homoallylic alcohols from β-methoxystyrenes by using a method that is superior to the more difficult allylation reactions of 2-arylacetaldehydes.

In summary, in the observations made in this effort demonstrate that tin mediated allylation and 2-haloallylation reactions of enol ethers take place efficiently in aqueous media. In addition the results show that the process serves as an alternative and perhaps superior method for the synthesis of highly functionalized homoallylic alcohols from readily available enol ethers under simple, inexpensive, and environmentally friendly conditions.

Acknowledgment. Financial support from the National Science Council of the Republic of China, Taiwan (NSC98-2119-M-018-001 and NSC99-2119-M-018-001) and National Changhua University of Education is gratefully acknowledged. We also thank Professor T. V. RajanBabu at The Ohio State University for his suggestions during manuscript preparation.

Supporting Information Available: Complete characterization data (^{1}H and ^{13}C NMR and mass spectral data) for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL102825T

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