Water Accelerated Allylation of Aldehydes by Using Water Tolerant Grignard-Type Allylating Agents from Allylmagnesium Chloride and Various Metallic Salts

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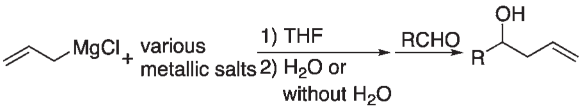
(Received October 25, 2001; CL-011052)

Some water-tolerant allylating agents prepared *in situ* from allylmagnesium chloride and bismuth trichloride, tin tetrachloride, tin dichloride, antimony trichloride, indium trichloride, or nickel dichloride reacted with aldehydes in THF–H_2O to afford the desired homoallylic alcohols in good yields. The present reaction proceeded more smoothly than that under non-aqueous media.

The allylation reaction of carbonyl compounds is one of the most fundamental carbon-carbon bond forming reactions in organic synthesis, and efficient methods using allylmetallic compounds have been reported in anhydrous solvents.[1] In general, organometallic compounds usually have to be prepared and treated in anhydrous solvents, owing to rapid protonolysis. In the last decade there has been increasing recognition that organic reactions carried out in aqueous media or protic solvents may offer advantages over those occurring in organic solvents.[2] For example, protection and deprotection processes of the functional groups such as hydroxyl groups and carboxyl groups can sometimes be simplified.

The Grignard reagent is one of the most useful and convenient reagents for performing allylation reactions. However, there are few reports on the allylation using allylmagnesium-type reagents in aqueous media.[3] On the other hand, although a lot of Barbier-type allylations in aqueous media have been reported by using various metals such as zinc (Zn), indium (In), and tin (Sn),[2] a Grignard-type allylation in aqueous media by using allylating agents generated *in situ* from allylmagnesium reagents and metallic salt ($SnCl_4$ or $InCl_3$), to our knowledge, was only reported by Whitesides and co-workers.[4] However, they have not reported the character and reactivity of their agents under aqueous or non-aqueous conditions. Therefore, it is desirable to develop a new stable allylating agent in aqueous media or protic solvents and to devise an efficient method using those solvents. Herein, we wish to report water accelerated allylation of aldehydes by using water-tolerant Grignard-type allylating agents from allylmagnesium chloride ($CH_2 = CHCH_2MgCl$) and various metallic salts (eq 1).

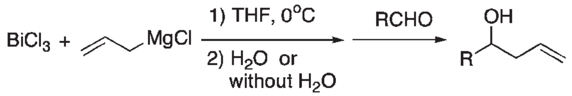


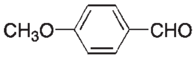
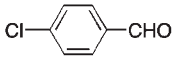
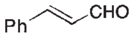
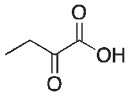
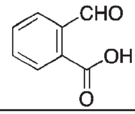
(1)

We have already reported allylation reactions of aldehydes by the use of Bi or bismuth trichloride ($BiCl_3$)—Zn, —metallic iron (Fe), or —metallic aluminium (Al).[5] We have also reported a novel aqueous Barbier-type allylation of aldehydes by using allyl bromide in the presence of Mg and $BiCl_3$.[6] Therefore, we speculated $CH_2 = CHCH_2MgCl$ might react with $BiCl_3$ to produce some water-tolerant allylating agent.

So, we investigated the reaction of the allylbismuth reagent prepared *in situ* in THF from $CH_2 = CHCH_2MgCl$ and $BiCl_3$ with aldehydes in non-aqueous or aqueous conditions. It was found that the present reaction proceeded more smoothly than that under non-aqueous media, and the yields of the corresponding homoallylic alcohols increased under aqueous conditions rather than that under non-aqueous conditions as shown in Table 1.[7] Not only various aldehydes (both aromatic and aliphatic aldehydes; Entries 1–3 and Entries 4–8) but also carbonyl compounds containing a carboxyl group (Entries 10 and 11) reacted smoothly to afford the corresponding homoallylic alcohols or the allylated lactone in good yields. It is noteworthy that nearly equimolar amount of allylbismuth reagent was used and the reaction took place smoothly without the protection of the carboxyl group.

Table 1. Allylation of carbonyl compounds by using allylbismuth reagent in aqueous media[a]

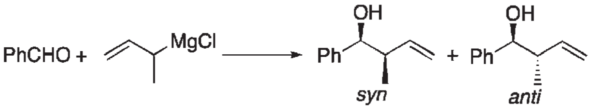


Entry	Aldehyde	Yield / %[b]	
		Solvent: THF	Solvent: THF-H_2O
1	PhCHO	80	85
2		85	90
3		—	82
4	$PhCH_2CHO$	—	76
5	$PhCH_2CH_2CHO$	81	93
6	$CH_3(CH_2)_7CHO$	79	89
7	*c*-Hex-CHO	73	80
8	$CH_2{=}CH(CH_2)_9CHO$	—	84
9[c]		—	78
10		61	79
11[d]		72	88

[a] The molar ratio of $CH_2{=}CHCH_2MgCl:BiCl_3$:aldehyde=1.5:1.5:1.0. All the products gave satisfactory IR and ^1H NMR spectra, and some products were also identified by elemental analyses or by comparison with authentic samples. [b] Isolated yields are given. [c] 1,2-Addition product was obtained. [d] Allylated lactone was obtained.

Furthermore, we next investigated the stereoselectivity of the reaction of benzaldehyde with crotylating agent prepared from 1-methyl-2-propenylmagnesium chloride (commercially available from Sigma-Aldrich Inc.) and $BiCl_3$, and the results are summarized in Table 2. Thus, the reaction in the presence of $BiCl_3$ gave predominant *syn* selectivity (85 : 15) although a mixture of *syn* and *anti* isomers (59 : 49) was obtained when Grignard reagent alone was used. It is particularly interesting that the addition of water is also effective in the present reaction, viz., both chemical yield and stereoselectivity increased (Entry 3). Our finding is comparable with *syn*-selective addition of crotyltrialkyltins (*cis* and *trans* mixture) to aldehydes.[8] However, it is noteworthy that bismuth compounds are less toxic than tin compounds.

Table 2. Stereoselectivity of crotylation of benzaldehyde

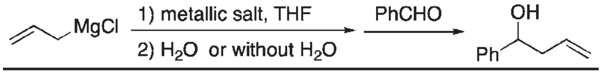


Entry	Reaction conditions	Yield / %[a]	*syn* : *anti*[b]
1	without $BiCl_3$ / THF	83	51 : 49
2[c]	$BiCl_3$ / THF	69	85 : 15
3[c]	$BiCl_3$ / THF-H_2O	87	90 : 10

[a]Isolated yields are given. [b]The ratio of diastereomer was determined by ^1H NMR spectra. See Ref. 5a. [c]The molar ratio of 1-methyl-2-propenyl magnesium chloride:$BiCl_3$:benzaldehyde=1.5:1.5:1.0.

These above results prompted us to try the allylation in aqueous environment using the allylating agents generated from Grignard reagent and various metallic salts except $BiCl_3$. Some of the results are summarized in Table 3, and the reactions using $NiCl_2$, $InCl_3$, $SnCl_4$, $SnCl_2$, and $SbCl_3$ proceeded more smoothly in aqueous media to afford the corresponding homollylic alcohols in good yields although $AlCl_3$, $ScCl_3$, and $ZnCl_2$ were not effective.

Table 3. Allylation of benzaldehyde by using allyl Grignard reagent and metallic salts[a]

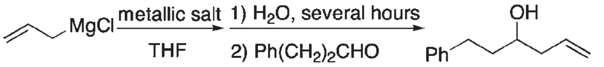


Entry	Metallic salt	Yield / %[b]	
		Solvent:THF	Solvent:THF-H_2O
1	$NiCl_2$	53	67[c]
2	$InCl_3$	73	98
3	$SnCl_4$	84	96
4	$SnCl_2$	59	85[d]
5	$SbCl_3$	78	86

[a]The molar ratio of metallic salt:CH_2=$CHCH_2MgCl$:benzaldehyde is 1.2:1.2:1.0 unless otherwise stated. [b]Isolated yield. [c]The molar ratio is 1.5:1.5:1.0. A quantitative yield was obtained when the molar ratio was 1.5:3.0:1.0. [d]The molar ratio is 1.0:1.0:2.0.

Based on the above results, we assumed that the allylating agents prepared *in situ* were stable in aqueous media. Therefore, we next investigated the stability of the allylating agent prepared *in situ*. After leaving the allylating agents prepared *in situ* from $CH_2 = CHCH_2MgCl$ and various metallic salts in THF for several hours by the addition of H_2O (THF : H_2O = 4 : 1), 3-phenylpropanal was added to the reaction mixture. As shown in Table 4, it is noteworthy that the reactivity of the allylating agent prepared *in situ* to 3-phenylpropanal did not disappear for several hours in aqueous media in the case of $SnCl_4$, $SnCl_2$, and $BiCl_3$. To our surprise, it was found that the allyating agent prepared *in situ* from $CH_2 = CHCH_2MgCl$ and $SnCl_4$ in THF had an enough reactivity in aqueous media even after 3 days. Furthermore, the reaction of the above allylating agent[9] with benzaldehyde occurred very rapidly (within 15 min) in water to give the homoallylic alcohol in 86% yield.

Table 4. Investigation of the stability of the allylating agents in aqueous environment



Entry	Delay period / h	Y ield / %					
		$BiCl_3$	$SnCl_4$	$SnCl_2$	$NiCl_2$	$InCl_3$	$SbCl_3$
1	Immediately	93	94	91	92	93	86
2	1	86	92	87	81	47	83
3	3	86	87	90	68	22	55
4	5	83	92	80	30	13	46
5	7	—	93	—	21	5	—
6	10	53	91	81	—	—	—
7	3 days	—	85	—	—	—	—

Finally, we found that the allylating agents prepared *in situ* from $CH_2 = CHCH_2MgCl$ and various metallic salts were water-tolerant and the reactions with these agents were accelerated by water.

References and Notes

1 Y. Yamamoto and N. Asao, *Chem. Rev.*, **93**, 2207 (1993), and references cited therein.

2 Reviews on organic reactions in aqueous media: a) C.-J. Li, *Chem. Rev.*, **93**, 2023 (1993). b) A. Lubineau, J. Auge, and Y. Queneau, *Synthesis*, **1994**, 741. c) T. H. Chan, C.-J. Li, M. C. Lee, and Z. Y. Wei, *Can. J. Chem.*, **72**, 1181 (1994). d) C.-J. Li, *Tetrahedron*, **52**, 5643 (1996). e) "Organic Synthesis in Water," ed. by P. A. Grieco, Blackie, London (1998), and references cited therein.

3 Unexpected Barbier-Grignard allylation of aldehydes with magnesium in THF—water has been reported. However, only aromatic aldehydes are usable as a substrate. a) C.-J. Li and W.-C. Zhang, *J. Am. Chem. Soc.*, **120**, 9102 (1998). b) W.-C. Zhang and C.-J. Li, *J. Org. Chem.*, **64**, 3230 (1999).

4 a) E. Kim, D. M. Gordon, W. Schmid, and G. M. Whitesides, *J. Org. Chem.*, **58**, 5500 (1993). b) Recently there has been a report of allylation of aldehydes by using commercially available tetraallyltin in water. A. McCluskey, *Green Chemistry*, **1999**, 167. We have also found that benzaldehyde—tetraallyltin reaction (the molar ratio = 1 : 1) in water at room temperature for 28 h gave the corresponding homoallylic alcohol in 66% yield, giving the quantitative yield in the presence of glucose.[4c] c) M. Wada, unpublished results. d) Carbonyl addition of allyl unit in water with a pre-prepared allyldibutyltin chloride has been reported. A. Boaretto, D. Marton, G. Tagliavini, and A. Gambaro, *J. Organomet. Chem.*, **286**, 9 (1985).

5 a) M. Wada, H. Ohki, and K. Akiba, *Bull. Chem. Soc. Jpn.*, **63**, 1738 (1990). b) M. Wada, M. Honna, Y. Kuramoto, and N. Miyoshi, *Bull. Chem. Soc. Jpn.*, **70**, 2265 (1997).

6 M. Wada, T. Fukuma, M. Morioka, T. Takahashi, and N. Miyoshi, *Tetrahedron Lett.*, **38**, 8045 (1997).

7 A typical procedure of the reaction of 3-phenylpropanal with $CH_2 = CHCH_2MgCl$ and $BiCl_3$ is described as follows: Under an argon atmosphere, ca. 2.0 M ($1\,M = 1\,mol\,dm^{-3}$) THF solution of $CH_2 = CHCH_2MgCl$ (0.6 ml, ca. 1.2 mmol) was added to THF (8 ml) solution of $BiCl_3$ (354 mg, 1.12 mmol) at 0 °C. After stirring for 15 min, H_2O (2 ml) was added to the reaction mixture. After stirring for 5 min at 0 °C and 5 min at room temperature, 3-phenylpropanal (104 mg, 0.77 mmol) was added. After stirring for 12 h, the reaction mixture was quenched with an aqueous 1 M hydrochloric acid (10 ml). The organic materials were extracted with diethyl ether (30 ml × 3), and the combined organic layer was washed successively with water and brine, and dried over Na_2SO_4. After evaporation of the solvents, the residue was purified by thin layer chromatography on silica gel (hexane : ether = 4 : 1) to give the corresponding homoallylic alcohol, 1-phenyl-5-hexen-3-ol (128 mg, 93% yield).

8 Y. Yamamoto, H. Yatagai, Y. Ishihara, N. Maeda, and K. Maruyama, *Terahedron*, **40**, 2239 (1984).

9 In this case, we used the allylating agent (yellow powder) obtained from evaporation of the solvent (THF).