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A Grignard-Type Addition of Allyl Unit to Carbonyl Compounds Containing a Carboxyl Group by Using $BiCl_3$–Zn(0)–Allyl Bromide

Makoto Wada,* Munekazu Honna, Yoshihiro Kuramoto, and Norikazu Miyoshi

Department of Chemistry, Faculty of Integrated Arts and Sciences, University of Tokushima,
1-1 Minamijosanjima, Tokushima 770

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In the presence of $BiCl_3$–Zn(0), nearly equimolar amounts of allyl bromide reacted with carbonyl compounds containing a carboxyl group to afford the corresponding homoallylic alcohols having a carboxyl group or the intramolecular dehydrated lactones in good yields.

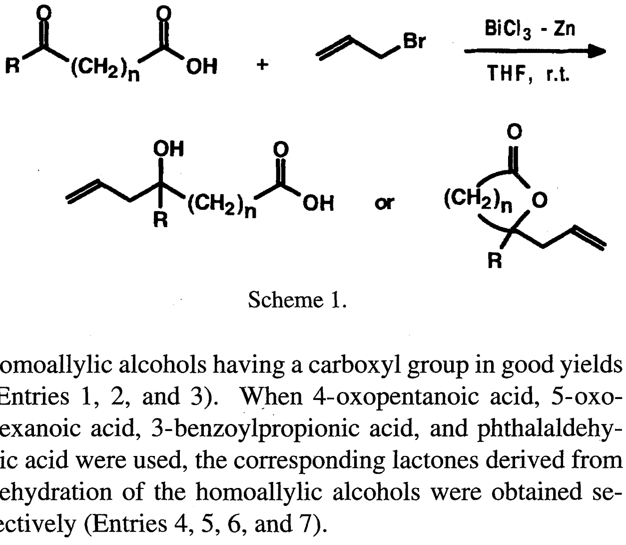
The addition of allylic organometallics to carbonyl compounds is an important synthetic reaction for the preparation of homoallylic alcohols. Numerous methods utilizing allylic organometallics derived from a number of metallic elements have been developed in anhydrous solvents.[1] In general, organometallic 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 in organic synthesis can sometimes be simplified. It is therefore important to investigate the reaction of organometallic reagents with substrates which possess unprotected hydroxy groups and carboxyl groups. For this purpose it is desirable to develop a new reagent which is stable in aqueous media or protic solvents and to devise an efficient method using those solvents. Among the many organometallic reagents that have been successfully employed, allylzinc, allyltin, and allylindium reagents comprise a unique group which undergo reactions with aldehydes in aqueous media.[3]

We have already found and reported the first example of chemoselective metallic bismuth and bismuth(III) chloride ($BiCl_3$)–metallic zinc–, iron–, or aluminum– mediated allylation of aldehydes with allylic halides to afford homoallylic alcohols.[4] Herewith we now wish to disclose in full the recent results of bismuth-mediated allylation of carbonyl compounds containing a carboxyl group at room temperature in aqueous media without protection of the carboxyl group to afford the corresponding homoallylic alcohols having a carboxyl group or the intramolecular dehydrated lactones in good yields.[5]

Results and Discussion

The overall reaction is shown in Scheme 1. Typical results are summarized in Table 1.

Pyruvic acid, 2-oxobutyric acid, and acetoacetic acid lithium salt reacted smoothly to afford the corresponding homoallylic alcohols having a carboxyl group in good yields (Entries 1, 2, and 3). When 4-oxopentanoic acid, 5-oxohexanoic acid, 3-benzoylpropionic acid, and phthalaldehydic acid were used, the corresponding lactones derived from dehydration of the homoallylic alcohols were obtained selectively (Entries 4, 5, 6, and 7).



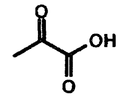
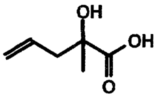
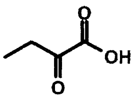
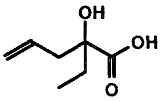
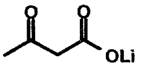
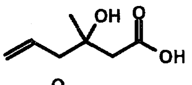
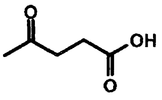
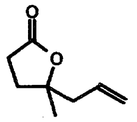
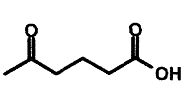
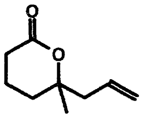
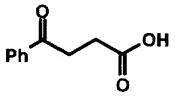
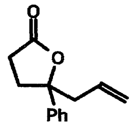
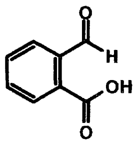
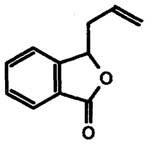
Scheme 1.

In a similar fashion, commercially available glyoxylic acid monohydrate and succinaldehydic acid (15% solution in water) could be used as starting materials, as shown in Scheme 2. It is remarkable that the present reaction takes place in aqueous media.

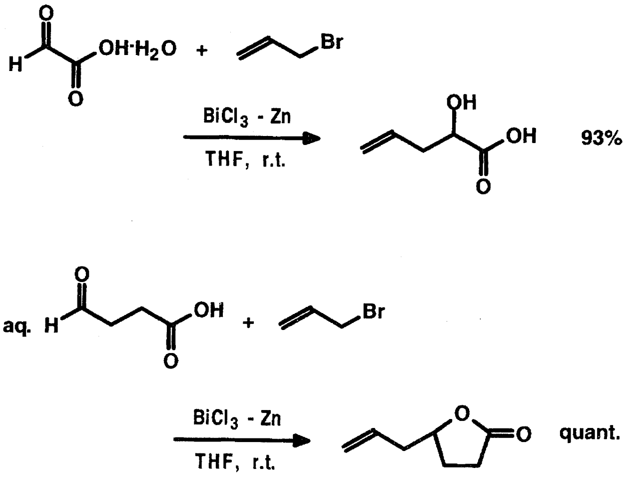
It is noteworthy that the use of $BiCl_3$ is essential in this reaction, viz., the yield of the expected product decreases by less than half using Zn(0) alone. For example, when 5-oxohexanoic acid was reacted with allyl bromide using Zn(0) alone, the corresponding product was obtained only in 34% yield. Noteworthy also is the fact that the corresponding desired products were obtained from the carbonyl compounds containing a carboxyl group using a nearly equimolar amount of allylation reagent, which may signify that some allylbismuth reagent prepared in situ[6] is stable in aqueous media and does not react with a carboxyl group.[7]

Based on the above results and some speculation, we next examined the reaction of 3-phenylpropanal with allyl bromide carried out under conditions similar to the typical procedure in acidic, neutral, or basic conditions. As shown in Table 2, the reaction proceeded smoothly not only in strongly

Table 1. $BiCl_3$–Zn(0) Mediated Allylation of Carbonyl Compounds Containing a Carboxyl Group without Protection of a Carboxyl Group

Entry	Substrate	Product[a)]	Yield/%[b)]
1			78
2			85
3			55
4			94
5			97
6			52
7			94

a) All the products gave satisfactory IR and ^{1}H NMR spectra, and correct elemental analyses. b) Isolated yield by Kugelrohr distillation.



Scheme 2.

acidic conditions using an acid such as TsOH or aq HCl, but also in strongly basic conditions using a base such as aq KOH.

We believe that the present reactions have potential utility in organic synthesis. Further application of allylbismuth reagent is now in progress and will be published elsewhere.

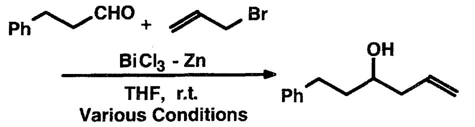


Table 2. Allylation of 3-Phenylpropanal under Various Reaction Conditions

Entry	Conditions[a)]	Yield/%
1	$TsOH\cdot H_2O$	87
2	HCl–water	85
3	KH_2PO_4–water	83
4	KOH–water	79

a) These reactions were carried out under conditions similar to the typical procedure using 1.5—2.0 equimolar amounts of an acid or a base to 3-phenylpropanal.

Experimental

General Methods. ^{1}H NMR spectra were recorded with JEOL PMX-60Si spectrometer and chemical shifts (δ) were reported in ppm using tetramethylsilane as an internal standard. IR spectra were taken on a Hitachi I-2000 spectrometer. Tetrahydrofuran was freshly distilled from sodium diphenylketyl. All other reagents are commercially available and were used without further purification.

General Procedure for the Preparation of 5-Methyl-7-octen-5-olide. Under a nitrogen atmosphere, 5-oxohexanoic acid (0.65 g, 5.0 mmol) and allyl bromide (0.85 g, 7.0 mmol) were added to a THF (15 ml) suspension of bismuth trichloride (2.2 g, 7.0 mmol) and metallic zinc (0.69 g, 10.6 mmol) at room temperature. After stirring for 16 h, the reaction mixture was quenched with aqueous 1 M hydrochloric acid (10 ml) (1 M = 1 mol dm^{-3}). Organic materials were extracted with diethyl ether (20 ml×3), and combined organic layers were dried over anhydrous $MgSO_4$. After evaporation of the solvents, the residue was distilled by Kugelrohr to give the corresponding lactone (0.75 g, 97%, bp 70—80 °C/0.9 mmHg, 1 mmHg = 133.322 Pa). ^{1}H NMR (60 MHz, $CDCl_3$) $\delta = 1.37$ (s, 3H), 1.50—2.10 (m, 4H), 2.23—2.67 (m, 4H), 4.83—5.30 (m, 2H), and 5.40—6.10 (m, 1H). IR (neat) 2976, 1730, 1642, 1138, and 1052 cm^{-1}. Found: C, 69.83; H, 9.03%. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15%.

2-Hydroxy-2-methyl-4-pentenoic Acid: ^{1}H NMR (60 MHz, $CDCl_3$) $\delta = 1.46$ (s, 3H), 2.48 (d, 2H, $J = 6.4$ Hz), 4.90—5.32 (m, 2H), 5.43—6.11 (m, 1H), and 7.02 (brs, 2H). IR (neat) 3400—3000, 1718, 1228, 1168, 1068, and 922 cm^{-1}. Found: C, 55.04; H, 7.64%. Calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.75%.

2-Hydroxy-2-ethyl-4-pentenoic Acid: ^{1}H NMR (60 MHz, $CDCl_3$) $\delta = 0.94$ (t, 3H, $J = 7.6$ Hz), 1.64—2.02 (m, 2H), 2.50 (d, 2H, $J = 6.8$ Hz), 4.88—5.30 (m, 2H), 5.43—6.11 (m, 1H), and 6.50—7.40 (brs, 2H). IR (neat) 3450—2900, 1728, 1644, 1158, 1070, 1028, and 918 cm^{-1}. Found: C, 58.11; H, 8.64%. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39%.

3-Hydroxy-3-methyl-5-hexenoic Acid: ^{1}H NMR (60 MHz, $CDCl_3$) $\delta = 1.30$ (s, 3H), 2.35 (d, 2H, $J = 6.7$ Hz), 2.54 (s, 2H), 4.90—5.25 (m, 2H), 5.45—6.20 (m, 1H), and 7.24 (brs, 2H). IR (neat) 3400—2900, 1702, 1642, 1200, 1140, 1064, and 918 cm^{-1}.

4-Methyl-6-hepten-4-olide: ^{1}H NMR (60 MHz, $CDCl_3$) $\delta = 1.39$ (s, 3H), 1.73—2.80 (m, 6H), 4.86—5.30 (m, 2H), and 5.37—6.13 (m, 1H). IR (neat) 3080, 2976, 2936, 1766, 1644, 1382, 1229, 1200, 1158, 1090, 1062, and 944 cm^{-1}. Found: C, 68.11; H, 8.43%. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63%.

4-Phenyl-6-hepten-4-olide: ^{1}H NMR (60 MHz, $CDCl_3$) δ = 2.46 (brs, 4H), 2.66 (d, 2H, J = 7.0 Hz), 4.88—5.23 (m, 2H), 5.27—6.00 (m, 1H), and 7.24 (s, 5H). IR (neat) 1778, 1596, 1544, 1448, 1254, 1208, 1170, 1058, 988, 946, 850, and 764 cm^{-1}.

3-Allylphthalide: ^{1}H NMR (60 MHz, $CDCl_3$) δ = 2.68 (t, 2H, J = 6.6 Hz), 5.86—6.07 (m, 4H), and 7.10—9.20 (m, 4H). IR (neat) 3080, 1764, 1644, 1616, 1600, 1468, 1286, 1192, 1156, 1070, 1014, and 984 cm^{-1}. Found: C, 75.67; H, 5.81%. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79%.

2-Hydroxy-4-pentenoic Acid: ^{1}H NMR (60 MHz, $CDCl_3$) δ = 2.37—2.77 (m, 2H), 4.33 (t, 1H, J = 6.6 Hz), 4.90—5.37 (m, 2H), 5.43—6.12 (m, 1H), and 6.92 (brs, 2H). IR (neat) 3408, 3072, 1714, 1644, 1244, 1190, 1130, 1082, and 918 cm^{-1}. Found: C, 51.89; H, 6.90%. Calcd for $C_5H_8O_3$: C, 51.72; H, 6.94%.

6-Hepten-4-olide: ^{1}H NMR (60 MHz, $CDCl_3$) δ = 1.68—2.86 (m, 6H), 4.52 (quint, 1H, J = 6.6 Hz), 4.89—5.34 (m, 2H), and 5.41—6.10 (m, 1H). IR (neat) 1776, 1644, 1216, 1182, 1112, 1020, 990, and 918 cm^{-1}. Found: C, 66.36; H, 7.76%. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99%.

1-Phenyl-5-hexen-3-ol: ^{1}H NMR (60 MHz, $CDCl_3$) δ = 1.53—2.00 (m, 3H), 2.03—2.40 (m, 2H), 2.57—2.93 (m, 2H), 3.63 (quint., 1H, J = 6.0 Hz), 4.83—5.26 (m, 2H), 5.43—6.23 (m, 1H), and 7.13 (s, 5H). IR (neat) 3373, 2929, 1641, 1602, 1496, 1454, 1049, 916, 748, and 700 cm^{-1}. Found: C, 81.49; H, 8.88%. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15%.

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5) a) Only one example of allylation of the carbonyl compound containing a carboxyl group by allyl bromide and metallic tin in the presence of water has been reported using 4-oxopentanoic acid in which the yield of allylation was low. See Ref. 3f. b) Without protection of a carboxyl group, the bromoacrylic acid–carbonyl compounds reaction with $SnCl_2$–AcOH, $SnCl_2$–Amberlyst 15, or In in aqueous media at refluxing temperature has been reported: (i) Using $SnCl_2$–AcOH: K. Uneyama, K. Ueda, and S. Torii, *Chem. Lett.*, **1986**, 1201; (ii) using $SnCl_2$–Amberlyst 15: P. Talaga, M. Schaeffer, C. Benezra, and J.-L. Stamp, *Synthesis*, **1990**, 530; (iii) using In: a) T.-H. Chan and M.-C. Lee, *J. Org. Chem.*, **60**, 4228 (1995); b) T.-P. Loh and X.-R. Li, *Chem. Commun.*, **1996**, 1929; c) T.-P. Loh, D. S.-C. Ho, K.-C. Xu, and K.-Y. Sim, *Tetrahedron Lett.*, **38**, 865 (1996); d) T.-P. Loh and X.-R. Li, *Tetrahedron Lett.*, **38**, 869 (1996).

6) In the previous paper, we assumed that some allylbismuth reagent was formed in the allylation reaction of an allylic bromide and an aldehyde in the presence of $BiCl_3$–Zn(0), $BiCl_3$–Fe(0), or $BiCl_3$–Al(0). See Ref. 4d.

7) Equimolar amount of allylation reagent reacted with benzaldehyde in the presence of $BiCl_3$–Zn(0) even if benzoic acid was present in the reaction mixture, and benzoic acid was recovered intact. See Ref. 4d.