



# Metal zinc-promoted *gem*-bisallylation of acid chlorides with allyl chlorides in the presence of chlorotrimethylsilane

Yoshio Ishino,\* Masatoshi Mihara and Manabu Kageyama

Osaka Municipal Technical Research Institute, 1-6-50, Morinomiya, Joto-ku, Osaka 536-8553, Japan

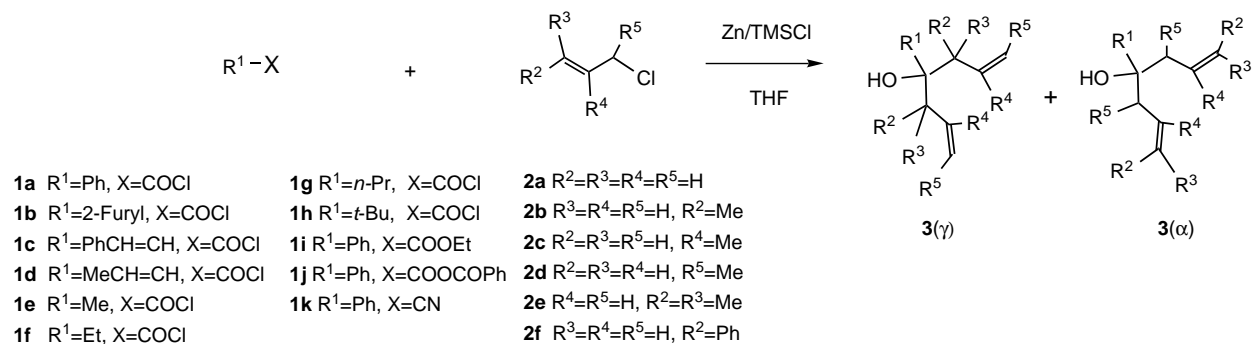
Received 7 June 2002; revised 1 July 2002; accepted 12 July 2002

**Abstract**—Treatment of acid chlorides (**2**) with allyl chlorides (**1**) in the presence of zinc dust and a catalytic amount of chlorotrimethylsilane (TMSCl) in THF brought about highly facile and effective coupling to give the corresponding *gem*-bisallylation products, 4-hydroxy-penta-1,6-dienes (**3**), in good to excellent yields. These reactions are assumed to proceed through allylzinc intermediates generated in situ. © 2002 Elsevier Science Ltd. All rights reserved.

The reaction of organometallics and carbonyl compounds provides a fundamental methodology in synthetic organic chemistry. Aldehydes, ketones, esters and acid halides are widely used as convenient starting materials for such transformations. Allylation and *gem*-bisallylation of these are most interesting processes since these are useful methods for the preparation of homoallylic alcohols,  $\beta,\gamma$ -unsaturated ketones, and so on.<sup>1</sup> Various metals such as In, Sm, Mg, sonoelectro produced Zn, Sn, Al, and so on have been used for this purpose.<sup>2</sup> Among these, however, the bisallylation reactions of carboxylic esters and acid chlorides has scarcely been investigated.<sup>3</sup> The synthetic utility of these methods may be considerably limited because special equipment, expensive reagents, and multi-step procedure are required. In addition, some of these procedures entail problems of corrosive and effluent pollution. Therefore, the development of new allylmetals was explored to

overcome these difficulties. Recently, we have reported that metallic zinc with chlorotrimethylsilane (TMSCl) markedly facilitates the olefination of aldehydes and ketones by reaction with *gem*-dihalides.<sup>4</sup>

In this letter, we report a mild, efficient, and convenient zinc metal-promoted *gem*-bisallylation reaction of acid chlorides (**1**) with allyl chlorides (**2**) in the presence of TMSCl to provide various 4-hydroxy-penta-1,6-dienes (**3**) in THF (Scheme 1). To our knowledge, *gem*-bisallylation of acid chlorides with allyl chlorides using zinc metal without any pre-treatment has not yet been reported.<sup>5</sup> The present method using these easily available reagents is also characterized by high operational simplicity, convenient one-pot, and inexpensive method. The 4-hydroxy-penta-1,6-dienes can be easily converted to many important building blocks for natural and bioactive product synthesis.<sup>6</sup>



Scheme 1.

\* Corresponding author. Tel.: +81-6-6963-8057; fax: +81-6-6963-8049; e-mail: [ishino@omtri.city.osaka.jp](mailto:ishino@omtri.city.osaka.jp)

The reactions were usually carried out at 60°C for 4 h in anhydrous THF containing powdered metallic zinc (60 mmol), a catalytic amount of TMSCl (3 mmol), acid chlorides (10 mmol), and allyl chlorides (30 mmol).<sup>7</sup> Commercially available zinc dust (purity; 95%) was used without any pre-treatment. Detailed studies on the reaction of benzoyl chloride (**1a**) with allyl chloride (**2a**) to 4-phenyl-4-hydroxy-hepta-1,6-diene (**3a**) showed that this catalytic cross-coupling is considerably influenced by the molar ratio of **2/1**, **Zn/1**, and the solvents used, as shown in Table 1.







Noteworthy is the fact that none of the products **3a** was obtained when the reaction was run in the ratio of **2a/1a**=1 (entry 1), while increasing the ratio let the bisallylation reaction proceed smoothly to give **3a** in excellent yields. Though 4-hydroxy-penta-1,6-diene (**3a**) was obtained in the absence of TMSCl, the reaction proceeded more smoothly and efficiently by the addition of TMSCl. Allyl chloride showed the same satisfactory reactivity compared with allyl bromide. As shown in Table 1, the best result for formation of product **3a** was obtained when the relative proportion of **1a:2a:Zn:TMSCl** was 1:2:6:0.3. Also, THF was found to be a much better solvent for this reaction than other aprotic solvents such as DMF and DCE.

A combination of zinc metal and a catalytic amount of TMSCl has been found to promote the transformation of various acid chlorides with allyl chlorides to the corresponding cross-coupling *gem*-bisallylation products under mild reaction conditions. To demonstrate the efficiency and scope of the present method, we applied this catalytic system to a variety of allyl chlorides. For the allyl chlorides as coupling partners, the presence of various alkyl and aryl substituents at the  $\alpha$ ,  $\beta$ , and  $\gamma$  positions did not exhibit any significant effect on the yield. The results are summarized in Tables 2 and 3.

Under the optimized conditions, **1a** was treated with allyl chloride (**2a**) and methallyl chloride (**2c**) to produce **3a** and **3c** in 92 and 97% yield, respectively. The

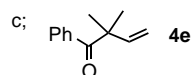
reaction of **1a** with crotyl chloride (*cis:trans*=1:6.2, **2b**) and 3-chloro-1-butene (**2d**) gave **3b** and **3d** in 84 and 71% yield, respectively, as a mixture of *Z* and *E* isomers of  $\alpha$  and  $\gamma$  products. The reaction of **1a** with prenyl chloride (**2e**) gave selectively a 1:1 monoallylation product, phenyl prenyl ketone (**4e**), as a  $\gamma$  product. In the case of cinnamyl chloride (**2f**), the desired product **3f** was obtained in 60% yield as a mixture of  $\alpha$  and  $\gamma$  products ( $\alpha:\gamma$ =4:1), but the product resulting from the  $\alpha$  attack predominates. For a large number of acid chlorides, e.g. aryl, alkyl,  $\alpha,\beta$ -unsaturated, and hetero-aromatic acid chlorides, the reaction with allyl chloride (**2a**) did not show any significant effect on the product yields.

**Table 2.** Reaction of benzoylchloride (**1a**) and allyl chlorides (**2**) in the presence of Zn/TMSCl

Entry	<b>2</b>	Products	Yield(%) <sup>a</sup>
1	 ( <b>2a</b> )	<b>3a</b>	92
2	 ( <b>2b</b> )	<b>3b<sup>b</sup></b>	84
3	 ( <b>2c</b> )	<b>3c</b>	97
4	 ( <b>2d</b> )	<b>3d<sup>b</sup></b>	71
5	 ( <b>2e</b> )	<b>4e<sup>c</sup></b>	86
6	 ( <b>2f</b> )	<b>3f<sup>b</sup></b>	60

a; Isolated yield.

b; Stereoisomeric mixture of  $\alpha$ - and  $\gamma$ -addition and *E*- and *Z*-isomers.



**Table 1.** Zinc-promoted reaction of benzoylchloride (**1a**) and allylchloride (**2a**) in the presence of TMSCl<sup>a</sup>

Entry	Solvent	Molar ratio of			Yield of <b>3a</b> (%) <sup>b</sup>
		<b>2a/1a</b>	<b>Zn/1a</b>	<b>TMSCl/1a</b>	
1	THF	1	6	0.3	0 <sup>c</sup>
2	THF	2	6	0.3	85
3	THF	3	6	0.3	92
4	THF	3	6	0.3	91 <sup>d</sup>
5	THF	3	3	0.3	63
6	THF	3	6	0	80
7	DMF	3	6	0.3	63
8	DCE <sup>e</sup>	3	6	0.3	0

<sup>a</sup> General reaction conditions: **1a** 10 mmol was used in THF 40 ml at 60°C for 4 h.

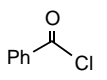
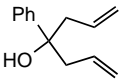
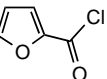
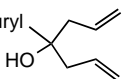
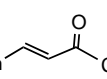
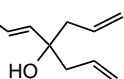
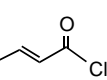
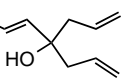
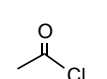
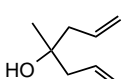
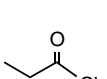
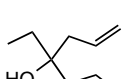
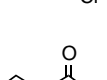
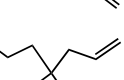
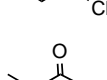
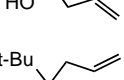
<sup>b</sup> Isolated yield.

<sup>c</sup> Adducts of THF and **1a**, such as 4-chlorobutylbenzoates, were obtained in 28% yield.

<sup>d</sup> Allyl bromide was used instead of allyl chloride.

<sup>e</sup> 1,2-Dichloroethane

**Table 3.** Reaction of allyl chlorides (**2a**) with various acylating agents in the presence of Zn/TMSCl

Entry	RCOX	Products <b>3</b>	Yield(%) <sup>a</sup>
1	 (1a)	 ( <b>3a</b> )	92
2	 (1b)	 ( <b>3b</b> )	43
3	 (1c)	 ( <b>3c</b> )	43
4	 (1d)	 ( <b>3d</b> )	66
5	 (1e)	 ( <b>3e</b> )	66
6	 (1f)	 ( <b>3f</b> )	66
7	 (1g)	 ( <b>3g</b> )	66
8	 (1h)	 ( <b>3h</b> )	77
9	PhCOOEt ( <b>5</b> )	<b>3a</b>	88
10	(PhCO) <sub>2</sub> O ( <b>6</b> )	<b>3a</b>	38
11	PhCN ( <b>7</b> )	<b>3a</b>	43

a; Isolated yield.

Further applications of the reaction were studied by using esters (**5**), acid anhydrides (**6**), and nitriles (**7**) instead of acid chlorides. The reaction of **5**, **6**, and **7** with allyl chloride lies to the formation of **3a** in the yield of 88, 38, and 43%, respectively. These results well demonstrated that the allylzinc reagent generated from the reaction of zinc with allyl chloride in the presence of a catalytic amount of TMSCl has sufficient reactivity for some of the unreactive carbonyl and nitrile compounds.

Although the mechanistic details still remain ambiguous, the reaction may proceed through in situ generated allylzinc as a reaction intermediate. This in situ generated allylzinc gave the 1:1 products (allylic ketones) by the reaction with acid chlorides, and then the 1:1 products react with additional allylzinc smoothly to obtain the 1:2 cross-coupling products **3**.<sup>8,9</sup> Elucidation of the detailed reaction mechanism must await further study.

In conclusion, we have demonstrated that in situ generated allylzinc reagents from the reaction of zinc with allyl chlorides in the presence of TMSCl could be effectively cross-coupled with acid chlorides to give the corresponding *gem*-bisallylation products, 4-hydroxy-penta-1,6-dienes (**3**), in good to excellent yields. The present method complements the existing synthetic method due to some advantageous properties of the allylzinc reagents such as availability and selectivity, operational simplicity, and low toxicity.

## References

- For example: Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207; Ranu, B. C.; Majee, A.; Das, A. R. *Tetrahedron Lett.* **1995**, *36*, 4885; Hamann-Gaudinet, B.; Namy, J.-L.; Kagan, H. B. *Tetrahedron Lett.* **1997**, *38*, 6585.
- For example: Durant, A.; Delplancke, J. L.; Libert, V.; Reisse, J. *Eur. J. Org. Chem.* **1999**, 2845; Machrouhi, F.; Parlea, E.; Namy, J.-L. *Eur. J. Org. Chem.* **1998**, 2431; Bubnov, Y. N.; Misharin, M. A.; Ingnatenko, A. V. *Tetrahedron Lett.* **1997**, *38*, 6259; Snowden, R. L.; Muller, B. L.; Schulte-Elte, K. H. *Tetrahedron Lett.* **1982**, *23*, 335; Tanaka, H.; Nakahata, S.; Watanabe, H.; Zhao, J.; Kuroboshi, M.; Torii, S. *Inorg. Chim. Acta* **1999**, *296*, 204.
- (a) Cardillo, G.; Simone, A. D.; Mingardi, A.; Tomasini, C. *Synlett* **1995**, 1131; (b) Yadav, J. S.; Srinivasa, D.; Reddy, G. S.; Bindu, K. H. *Tetrahedron Lett.* **1997**, *38*, 8745; (c) Inoue, K.; Shimizu, Y.; Shibata, I.; Baba, A. *Synlett* **2001**, 1659.
- Ishino, Y.; Mihara, M.; Nishihama, S.; Nishiguchi, I. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2669.
- A reaction of allylbromide with acid chlorides and Zn under sonication was reported to provide  $\beta,\gamma$ -unsaturated ketones: Ranu, B. C.; Majee, A.; Das, A. R. *Tetrahedron Lett.* **1996**, *37*, 1109.
- Sabitha, G.; Reddy, Ch. S.; Babu, R. S.; Yadav, J. S. *Synlett* **2001**, 1787.
- General procedure for the Zn-promoted cross-coupling of acyl chlorides with allyl chlorides in the presence of TMSCl: A dry THF suspension (10 mL) of Zn metal (60 mmol, 3.94 g) and TMSCl (3 mmol, 0.33 g) was stirred under a nitrogen atmosphere for about 15 min at 50°C. A mixture of benzoyl chloride (10 mmol, 1.40 g) and allyl chloride (30 mmol, 2.28 g) in 10 mL of THF was slowly added to the suspended solution, and the reaction mixture was then stirred for about 3 h at the same temperature. The reaction mixture was then poured into 200 mL of saturated aqueous ammonium chloride solution and the crude reaction products were extracted using three 100 mL portions of ether. The combined ethereal solution was washed with a 100 mL portion of water, and then dried over anhydrous magnesium sulfate. After removing the drying agent by filtration, the solvent was evaporated by distillation. Then, the products were isolated by silica-gel column chromatography of the resulting residue. All new compounds, **3** and **4** prepared in this study, were identified by <sup>1</sup>H and <sup>13</sup>C NMR, IR and mass spectroscopies. Typical spectra data is as follows: 4-hydroxy-4-phenyl-hepta-1,6-diene (**3a**) <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.26 (m, 5H), 5.53 (m, 2H), 5.06 (d, *J*=24.4 0 Hz, 2H), 5.05 (s, 1H), 2.53 (q/d, *J*=13.58/6.06 Hz, 4H), 2.17 (s, 1H); <sup>13</sup>C NMR (75

MHz, CDCl<sub>3</sub>)  $\delta$  135.97, 133.69, 124.07, 118.68, 73.22, 45.39, 30.90; IR (film) 3552, 3075, 2978, 1639, 1446, 999, 702 cm<sup>-1</sup>; HRMS (EI) calcd for C<sub>10</sub>H<sub>16</sub>O M<sup>+</sup> 188.1201, found 188.1197. 4-Hydroxy-4-(2-propenyl)-hepta-1,6-diene (**3j**) <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  5.65 (m, 2H), 5.14 (s, 2H), 5.10 (d, *J* = 10.46 Hz, 2H), 2.29 (s, 2H), 2.29 (d, *J* = 10.03 Hz, 4H), 2.17 (s, 1H), 1.72 (d, *J* = 6.24 Hz, 2H), 1.27 (s, 2H), 0.87 (m, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  135.97, 133.69, 124.07, 118.68, 73.22, 45.39, 30.90; IR (film) 3465, 2934, 2921, 1438, 1420, 1363, 1223, 998, 972, 915 cm<sup>-1</sup>; HRMS (EI) calcd for C<sub>13</sub>H<sub>16</sub>O M<sup>+</sup> 152.1201, found 152.1205.

8. (a) Knochel, P. In *Active Metals*; Fürstner, A., Ed.; VCH: Weinheim, New York, Basel, Cambridge, Tokyo, 1995; p. 191; (b) Fürstner, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 164; (c) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2671; (d) Stadtmüller, H.; Greve, B.; Lennick, K.; Chair, A.; Knochel, P. *Synthesis* **1995**, 69; (e) Picotin, G.; Miginiac, P. *J. Org. Chem.* **1987**, *52*, 4796.
9. In this reaction, the roles of TMSCl may be postulated mainly in two ways, that is, one is activation of zinc metal surface and the other one is activation of **1** and **2** by coordination of the Si atom to the carbonyl group and the chlorine atom.