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Triethylborane-induced radical allylation of α-halo carbonyl compounds with allylgallium reagent in aqueous media

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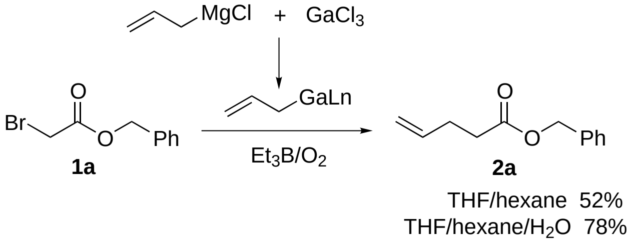
Abstract—An allylgallium reagent is found to be effective for radical allylation of α-iodo or α-bromo carbonyl compounds. Treatment of benzyl bromoacetate with allylgallium, prepared from allylmagnesium chloride and gallium trichloride, in the presence of triethylborane in THF provided benzyl 4-pentenoate in good yield. The addition of water as a cosolvent improved the yields of allylated products. It was revealed that the allylgallium species resists immediate decomposition on exposure to water.

Radical allylation reactions provide a mild and efficient method to introduce allyl groups into organic molecules bearing ionically labile functionalities.[1] Allylstannanes have played an important role in radical allylation because of their high reactivity.[2] However, allylation reactions based on allylstannanes have serious drawbacks in the synthesis of biologically active compounds, because the inherent toxicity of organotin derivatives and the difficulty of removal of residual tin compounds often prove fatal. The development of other allylating reagents is still in its infancy compared to the tin-free radical reduction.[3] Allylsilanes[4] and allylsulfones[5] are efficient alternatives and are being actively investigated. Here we wish to introduce an alternative allylating reagent. Radical allylation proceeded smoothly with allylgallium reagents[6] in the presence of triethylborane as a radical initiator.[7]

Allylmagnesium chloride (3.0 mmol) was added to a THF (2 mL)/hexane (1 mL) mixed solution of $GaCl_3$ (3.0 mmol) under argon to prepare an allylgallium reagent. Benzyl bromoacetate (**1a**, 1 mmol) and triethylborane (1.0 M hexane solution, 0.50 mL, 0.50 mmol) were added to the solution and air (10 mL) was introduced to the reaction flask by a syringe. After the mixture was stirred for 2 h, extractive workup followed by silica gel column purification afforded benzyl 4-pentenoate (**2a**) in 52% yield (Scheme 1). The reaction did not proceed at all in the absence of Et_3B. The azo initiator, V-70 [2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile)],[8] was also effective to afford **2a** in 48% yield after 14 h at 25°C. Additionally, radical scavengers such as galvinoxyl and 2,2,6,6-tetramethylpiperidine-*N*-oxyl, completely inhibited the reaction. Therefore, a radical reaction mechanism is suggested for the allylation with allylgallium. Although the yield was moderate, the result encouraged us to modify the reaction conditions. Consequently, we have found that addition of water as a cosolvent to the reaction mixture improved the yield of **2a**. Water (1 mL) was added to a THF (2 mL)/hexane (1 mL) solution of the allylgallium reagent prior to the addition of benzyl bromoacetate, Et_3B, and air. After 2 h at 25°C, **2a** was obtained in 78% yield.[9] Thus, the allylgallium species proved to be somewhat stable in aqueous media[10,11] and to act as a radical allylating reagent.

The origin of the favorable solvent effect is not clear at this stage. Similar phenomena were reported[12] on atom-transfer radical reaction of α-iodo carbonyl compounds in aqueous media, where the high cohesive energy



Scheme 1.

Keywords: allylation; radical reaction; solvents and solvent effects; gallium.

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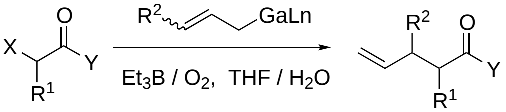
density of water causes reduction of the volume of an organic molecule. In the present case, the addition step could be accelerated because the addition necessarily accompanies the decrease of the total volume of the reactants. It is also probable that the structure of the allylgallium species would change and that the addition of water could increase the reactivity of allylgallium. Allylgallium dichloride is likely to be transformed into allylgallium hydroxide that is possibly more reactive for radical allylation.[13]

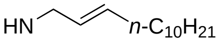
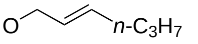
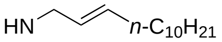
Various combinations of α-halo carbonyl compounds and allylic gallium reagents were examined (Table 1). More reactive α-iodo carbonyl compounds gave better results compared with their bromo analogs. 2-Halopropanoate or 2-halopropanamide also reacted with the allylgallium reagent to give 2-methyl-4-pentenoate or 2-methyl-4-pentenamide (entries 2, 3, and 5). In contrast, 2-bromo-2-methylpropanoate did not give the anticipated product, and the starting material was recovered unchanged, probably due to the steric hindrance around the carbon-centered radical. Interestingly, allylation was effective for the substrates having a terminal carbon–carbon double bond (entries 9 and 10). An electron-deficient (alkoxycarbonyl)methyl radical reacted faster with the highly electron-rich alkene moiety of the allylgallium species than with the olefinic parts of the substrate and of the product. Furthermore, **1k**, prepared from butyroin, was selectively allylated to give 4-pentenoate **2k** in excellent yield. Allylation of the ketone moiety was not observed.[14]

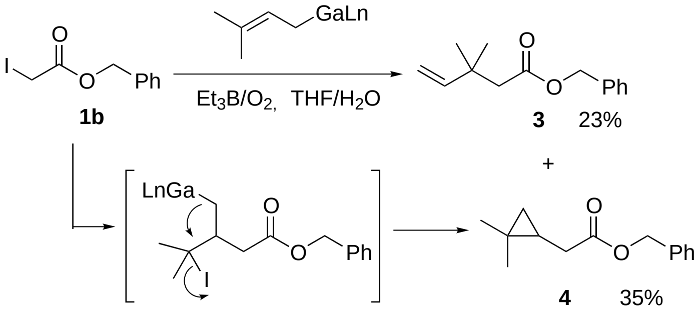
2-Butenylgallium, not 1-methyl-2-propenylgallium,[15] was also available by simply mixing $GaCl_3$ and a Grignard reagent prepared from 1-chloro-2-butene and magnesium, whereas synthesis of 2-butenylstannane is somewhat troublesome.[16] 3-Methyl-4-pentenoates were obtained in high yields without contamination by 4-hexenoates (entries 12–16).[17] However, methallylation of α-halo carbonyl compounds with 2-methyl-2-propenylgallium was disappointing (ca. 10% yield in the case of **1a**).[18] The starting materials were mostly recovered.

3-Methyl-2-butenylgallium reagent afforded 3,3-dimethyl-4-pentenoate **3** in spite of the steric effect of the dimethyl groups in the gallium reagent (Scheme 2). In this case, the allylation product was contaminated with cyclopropane **4**. Bond formation at the less substituted carbon would yield the γ-iodoalkylgallium via atom-transfer addition, which undergoes intramolecular cyclization to form the cyclopropane ring.

Table 1. Radical allylation of α-halo carbonyl compounds with allylgallium species



Entry		X	Y	R^1	R^2	Time /h	Yield /%
1	**1a**	Br	OCH_2Ph	H	H	2	**2a:** 78
2	**1b**	Br	OCH_2Ph	Me	H	2	**2b:** 63
3	**1c**	Br	NMe_2	Me	H	2	**2c:** 64
4	**1d**	I	OCH_2Ph	H	H	0.5	**2a:** 89
5	**1e**	I	OCH_2Ph	Me	H	0.5	**2b:** 81
6	**1f**	I		H	H	1	**2f:** 87
7	**1g**	I		H	H	0.5	**2g:** 95
8	**1h**	I	$O(CH_2)_6Cl$	H	H	1	**2h:** 85
9	**1i**	I	$O(CH_2)_2OCH_2CH{=}CH_2$	H	H	0.5	**2i:** 64
10	**1j**	I	$OCH(Ph)CH_2CH{=}CH_2$	H	H	2	**2j:** 71
11	**1k**	I	$OCH(n\text{-}C_3H_7)COn\text{-}C_3H_7$	H	H	1	**2k:** 84
12	**1d**	I	OCH_2Ph	H	Me	0.5	**2a':** 70
13	**1f**	I		H	Me	2	**2f':** 85
14	**1h**	I	$O(CH_2)_6Cl$	H	Me	1	**2h':** 46
15	**1a**	Br	OCH_2Ph	H	Me	2	**2a':** 50
16	**1c**	Br	NMe_2	Me	Me	7	**2c':** 65 (d.r.=2/1)



Scheme 2.

The reaction mechanism of allylation, especially the fate of the β-gallylalkyl radical intermediate, is not clear at this stage. Two plausible mechanisms involve (1) elimination of a gallyl radical from the β-gallylalkyl radical,[19] which is similar to the case of allylstannane, or (2) halogen atom abstraction of the β-gallylalkyl radical from an α-halo carbonyl compound like β-silylalkyl radical. Further investigation to establish the mechanism is necessary.[20]

In conclusion, the allylgallium reagent is found to be effective for radical allylation of α-iodo or α-bromo carbonyl compounds in place of allylstannane. The addition of water as a cosolvent improved the yields of allylated products. Allylic gallium reagents are easily prepared, and this allylation avoids the use of tin reagents that require prior preparation of the reagent and special treatment for its removal.

Typical procedure for allylation with allylgallium in aqueous THF

THF (2 mL) was mixed with a hexane solution of gallium trichloride (1.0 M, 1.5 mL, 1.5 mmol) under argon. Allylmagnesium chloride (1.0 M THF solution, 1.5 mL, 1.5 mmol) was added dropwise to the solution of gallium trichloride at 25°C to give a white suspension. The suspension was then stirred for 20 min at 25°C. Water (1 mL) was added to the suspension. The whole mixture turned clear although it was heterogeneous. A solution of benzyl iodoacetate (**1d**, 0.14 g, 0.50 mmol) in THF (2 mL), triethylborane (1.0 M hexane solution, 0.25 mL, 0.25 mmol), and air (10 mL) were then successively added. After being vigorously stirred for 2 h, the mixture was poured into a 1 M HCl solution, and the product was extracted with ethyl acetate (20 mL×3). The combined organic layer was dried over Na_2SO_4 and was concentrated in vacuo. Purification of the residual oil by silica gel column chromatography provided benzyl 4-pentenoate (**2a**, 85 mg, 0.45 mmol) in 89% yield.

Acknowledgements

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15. We confirmed that the reaction of GaCl$_3$ with crotylmagnesium chloride gives 2-butenylgallium as an (*E*) and (*Z*) isomeric mixture by the NMR experiments as follows. In ^{1}H NMR, the vinylic proton signals of 2-butenyltributylstannane appeared at 5.4–5.7 (1H) and 5.9–6.1 (1H) ppm in THF, whereas those of 1-methyl-2-propenyltributylstannane were detected at 5.0–5.2 (2H) and 6.4–6.6 (1H) ppm. In the ^{13}C NMR of 2-butenylstannane, we detected two sets of two singlets at 118, 130 (for major isomer) and 120, 131 ppm (for minor isomer). The ^{13}C NMR spectrum of 1-methyl-2-propenylstannane showed two singlets at 106 and 145 ppm. The NMR of the mixture of GaCl$_3$ and crotylmagnesium chloride in aqueous THF was then measured. The ^{1}H NMR chart shows vinylic proton signals at 5.2–5.4 (1H), 5.7–5.8 (1H) ppm (for minor isomer) and 5.5–5.7 (1H), 5.9–6.0 (1H) ppm (for major isomer). Furthermore, two sets of two singlets were observed at 121, 129 (for major isomer) and 119, 130 ppm (for minor isomer) in the ^{13}C NMR analysis. Based on the comparison of the signals of the gallium species with those of stannanes, the 2-butenyl form of the gallium reagent was concluded.
16. Treatment of chlorotributylstannane with crotylmagnesium chloride at 0°C in THF provided a mixture of 2-butenylstannane and 1-methyl-2-propenylstannane (69/31). For the selective synthesis of 2-butenylstannane, see: Seyferth, D.; Jula, T. F.; Dertouzos, H.; Pereyre, M. *J. Organomet. Chem.* **1968**, *11*, 63.
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