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Me_3Ga-mediated alkynylation of aldehydes

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Abstract

The trimethylgallium reagent was found to promote the addition of phenylacetylene to various aromatic and aliphatic aldehydes. This reaction was efficiently carried out in anhydrous CH_2Cl_2 at room temperature under mild conditions and the corresponding propargylic alcohols were obtained in good to excellent yields up to 98%.

Keywords: Trimethylgallium; Alkynylation; Propargylic alcohol; Benzaldehyde

The alkynylation of carbonyl compounds is one of the most useful carbon carbon bond-forming reactions.[1] The corresponding propargylic alcohols are important and versatile building blocks for many biologically active compounds and natural products such as adociacetylene B,[2a] longimicin D,[2b] leukotriene B_4,[2c] and steroids,[2d] and have gained considerable significance in recent years. The nucleophilic addition of alkynylmetals containing Ce,[3] B,[4] V[5] and Al[6] to carbonyl compounds represents a type of useful methods for producing these compounds. However, these methods are not straightforward, because most of these alkynylmetals must be generated by the transmetalation of Li, Na, or Mg acetylides,[7] and low temperature condition is required to stabilize the metal acetylides. On the other hand, the combined use of a Lewis acid, such as $Sn(OTf)_2$,[8] GaI_3,[9] $Zn(OTf)_2$,[10a] $ZnCl_2$,[10b] and $InBr_3$,[11] with a Lewis base, such as an amine, provides a practical method for the preparation of propargylic alcohols in stoichiometric or catalytic amounts. Apart from the methods mentioned above, stoichiometric amounts of dialkylzinc reagents are also widely used for synthesis of propargylic alcohols with or without Lewis acid.[12] Although many significant results have been achieved in this area, the importance of these compounds in academic research and industrial applications provides the constant driving force for the development of this reaction.

Recently, organogallium reagents have attracted considerable attention in synthetic organic chemistry. However, the synthetic potential of organogallium compounds has scarcely been explored because of their very low reactivity toward most organic electrophiles. Most of the studies on the utilization of organogallium are based on the Lewis acidity of gallium. Maruoka et al.[13a] and Utimoto et al.[13b] reported that trimethylgallium could be used as a catalyst in the reaction of alkynyllithium with epoxides. Our group presented the first example of enantioselective isocyanosilylation of meso-epoxides using TMSCN to form β-isocyanohydrins catalyzed by chiral organogallium and organoindium complexes with moderate to excellent enantioselectivities.[14] Very recently, Yamaguchi et al. reported that trialkylgalliums could serve as a base to generate enolates from ketones, the resulting gallium enolates underwent facile C-benzoylation,[15a] an aldol reaction[15a] and *a*-ethynylation reaction[15b] of ketones. The first example of the utilization of trialkylgallium as an alkylation reagent was reported by Huang et al. in the synthesis of ketones from acyl chlorides with the formation of lithium tetraorganogallates.[16] To the best of our knowledge, there

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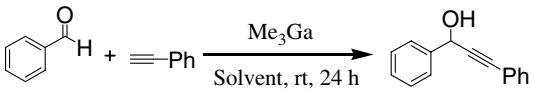
are few examples which apply organogallium reagent to the addition of phenylacetylene to aldehydes. Over the course of our continuing studies on organogallium reagents,[17] we herein wish to report the novel synthesis of propargylic alcohols by the alkynylation of aldehydes in the presence of trimethylgallium.

Initially, the commercially available 1 M solution of Me_3Ga in toluene was mixed with phenylacetylene (1.2 equiv each) in anhydrous CH_2Cl_2 at room temperature and an hour later benzaldehyde (1 equiv) was added, 1,3-diphenylprop-2-yn-1-ol was isolated in 40% yield after reacting for 24 h (entry 1).[18] When the amount of phenylacetylene (2 equiv) and trimethylgallium (2.2 equiv) was increased, the yield of the product was promoted to 65% (entry 2). To obtain the optimized reaction conditions, we changed the amount and ratio of phenylacetylene and trimethylgallium reagent, then carried out the reaction using several different solvents. The results are summarized in Table 1. Consequently, we found that the yield of the product was improved to 95% when the mixture of phenylacetylene (2.5 equiv) and Me_3Ga (3 equiv) was used (entry 5). Methane dichloride was the best solvent among all the ones examined. In contrast, in the cases of 1,2-dichloroethane and toluene, the yields decreased sharply (entries 7 and 8). When THF and hexane were used, no alkynylation product was observed (entries 9 and 10).

With above optimized conditions in hand, a variety of aromatic and aliphatic aldehydes were screened to evaluate the scope of this reaction. We were pleased to find that all substrates were smoothly converted to the corresponding propargylic alcohols in good to excellent yields. The results are listed in Table 2. The reactivity of different aromatic aldehydes was influenced by the nature and position of the substituents on the aromatic ring. The benzaldehyde derivatives having an electron-withdrawing substituent were highly reactive and gave the products in excellent yields (entries 2–8). Changing the substituent from nitro to trifluoromethyl, halogens groups, the yields of the products had a slight decrease. It was surprising that the addition of phenylacetylene to the sterically more hindered carbonyl group in 2-nitro- and 2-chlorobenzaldehyde proceeded easier than 4-substituted congeners. Especially 2-nitrobenzaldehyde gave the product in nearly quantitative yield (entry 4). This behavior could be explained by a strong inductive effect from 2-substituents. When the aromatic aldehydes containing electron-donating group (–Me, –OMe) were used, the yields of the products decreased slightly (entries 9–11). In the case of *m*-tolualdehyde, reaction time was prolonged to obtain a satisfactory yield (entry 10). It should be noted that the heterocyclic aromatic aldehydes and 2-naphthaldehyde were also good substrates for this reaction (entries 12–14). More importantly, our method was also suitable to both linear and branched aliphatic aldehydes (entries 15–17), for example, the alkynylation of isovaleraldehyde proceeded with 84% yield (entry 17). For the α,β-unsaturated cinnamaldehyde, good result was also observed when reaction time was increased to 36 h (entry 18).

We also checked the reaction of aliphatic-substituted acetylene such as 1-heptyne with several aldehydes under optimized conditions. Unfortunately, no products were detected. This behavior could result from the low reactivity of alkyl acetylene. Du et al. have also reported that alkyl-substituted acetylene did not work in their conditions.[12e] According to Dahmen's report, less acidic acetylene required a higher deprotonation temperature.[12j] We then

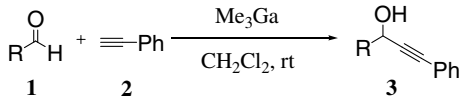
Table 1
Optimization of reaction conditions[a]



Entry	Phenylacetylene (equiv)	Me_3Ga (equiv)	Solvent	Yield[b] (%)
1	1.2	1.2	CH_2Cl_2	40
2	2	2.2	CH_2Cl_2	65
3	2	2.5	CH_2Cl_2	84
4	2	3	CH_2Cl_2	90
5	2.5	3	CH_2Cl_2	95
6	3	3	CH_2Cl_2	86
7	2.5	3	ClC_2H_4Cl	64
8	2.5	3	Toluene	54
9	2.5	3	THF	ND[c]
10	2.5	3	Hexane	ND[c]

[a] All reactions were carried out in anhydrous solvent at room temperature for 24 h.
[b] Isolated yields based on the benzaldehyde.
[c] ND = not detected.

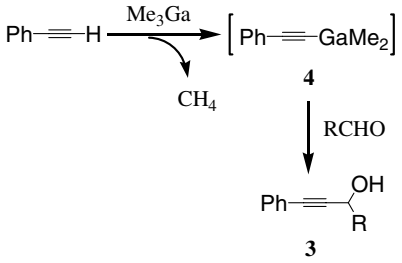
Table 2
Alkynylation of aldehydes with phenylacetylene mediated by Me_3Ga[a]



1 2 3

Entry	Aldehyde	Product	Time (h)	Yield[b] (%)
1	Benzaldehyde	**3a**	24	95
2	4-Nitrobenzaldehyde	**3b**	8	91
3	3-Nitrobenzaldehyde	**3c**	8	94
4	2-Nitrobenzaldehyde	**3d**	8	98
5	3-Bromobenzaldehyde	**3e**	8	90
6	2-Fluoromethylbenzaldehyde	**3f**	24	86
7	2-Chlorobenzaldehyde	**3g**	18	88
8	4-Chlorobenzaldehyde	**3h**	24	85
9	4-Methoxybenzaldehye	**3i**	24	84
10	*o*-Tolualdehyde	**3j**	18	84
11	*m*-Tolualdehyde	**3k**	36	79
12	2-Furaldehyde	**3l**	24	88
13	Thiophene-2-carboxaldehyde	**3m**	24	88
14	2-Naphthaldehyde	**3n**	24	75
15	Butyraldehyde	**3o**	24	72
16	Isobutyraldehyde	**3p**	24	74
17	Isovaleraldehyde	**3q**	24	84
18	Cinnamaldehyde	**3s**	36	67

[a] All reactions were performed on 0.5 mmol scale of substrates for indicated time, detail experiments see Ref. 18.
[b] Isolated yields.



Scheme 1. Proposed reaction course.

carried out the reaction of 1-heptyne with aldehydes mediated by Me_3Ga at higher temperature (60 °C), and the products were not obtained. This demonstrated that aliphatic terminal alkynes could not be applied to our reaction systems.

Although the mechanism of Me_3Ga-mediated alkynylation of aldehydes has not yet been clarified, we presume that the first step involves the formation of alkynylgallium species **4**, in situ generated from phenylacetylene and trimethylgallium, which is most likely as the reactive intermediate, and this intermediate further attack carbonyl of aldehydes to produce the corresponding propargylic alcohols **3** in the following step (Scheme 1).

In conclusion, we have described the efficient and facile addition of phenylacetylene to aldehydes using trimethylgallium as a promoter. The present method is complementary to the previously reported methods, and applicable to various aromatic and aliphatic aldehydes. This reaction did not require other Lewis acid catalyst and the use of Lewis base. The corresponding propargylic alcohols were obtained in high yields under the mild reaction conditions. Further work is underway in our group to achieve the catalytic asymmetric version of this reaction and other application of organogallium reagent.

Acknowledgments

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18. *General procedure for alkynylation of various aldehyde*: In a 20 mL Schlenk reaction tube, commercially available 1 M solution of Me_3Ga (1.5 mL, 1.5 mmol, 1 M in toluene) was mixed with phenylacetylene (0.125 mL, 1.25 mmol) in anhydrous CH_2Cl_2 (3 mL) at room temperature under an argon atmosphere. The solution was stirred for an hour followed by the addition of aldehyde (0.5 mmol). After the resulting mixture was stirred at this temperature for indicated time in Table 2, water (4 mL) was added to quench the reaction. The aqueous layer was separated and further extracted with dichloromethane; the organic layers were combined and dried. Evaporation of the solvent gave the crude product, which was further purified by preparative TLC (petroleum ether–ethyl acetate = 5:1) to give corresponding propargylic alcohols.