



CuI-catalyzed tandem carbomagnesiation/carbonyl addition of Grignard reagents with acetylenic ketones: Convenient access to tetrasubstituted allylic alcohols

Meihua Xie*, Chengyou Feng, Jitan Zhang, Changqing Liu, Kuang Fang, Guanying Shu, Wansheng Zuo

Key Laboratory of Functional Molecular Solids (Ministry of Education), Anhui Key Laboratory of Molecular Based Materials, College of Chemistry and Materials Science, Anhui Normal University, Wuhu 241000, China

ARTICLE INFO

Article history:

Received 17 June 2011

Received in revised form

20 July 2011

Accepted 22 July 2011

Keywords:

Allylic alcohol

Acetylenic ketone

Grignard reagent

CuI

Indene

ABSTRACT

Highly functionalized tetrasubstituted allylic alcohols were prepared conveniently by CuI-catalyzed tandem carbomagnesiation/carbonyl addition of Grignard reagents with acetylenic ketones. The obtained allylic alcohols can be further transformed to polysubstituted indenenes by intramolecular cyclization.

© 2011 Elsevier B.V. All rights reserved.

1. Introduction

Allylic alcohols are important structural motifs in many natural products and bioactive compounds [1–4]. Allylic alcohols are also valuable intermediates in many synthetic applications. For example, allylic alcohols are potential precursors to allylic amines [5–7], epoxy alcohols [8], cyclopropyl alcohols [9,10], and natural products [11–14]. Therefore, development of new methods to synthesize allylic alcohols is in high demand. Addition of alkenylmetal reagents to carbonyl compounds and the reductive coupling of alkynes and carbonyl compounds are the commonly used methods to synthesize allylic alcohols and substantial progress has been made in the synthesis of di- or trisubstituted allylic alcohols by these methods [15–20]. In sharp contrast, few general methods exist that allow the direct creation of tetrasubstituted allylic alcohols [21–23].

Multicomponent tandem reaction allows formation of several bonds in a single manipulation and it offers rapid and convergent construction of complex structures from readily available materials. Tandem reaction has become a powerful and useful tool in organic synthesis and has remained an active area of research for organic chemists [24–29]. Carbometalation of alkynes and its further

reaction with electrophiles is a typical and time-tested method for the formation of polysubstituted alkenes and has been extensively studied [30–35]. However, synthesis of tetrasubstituted allylic alcohols by tandem carbometalation of alkynes and coupling with carbonyl compounds are relatively scarce [21–23]. Furthermore, to the best of our knowledge, synthesis of allylic alcohols by carbomagnesiation reaction of Grignard reagents and α,β -acetylenic ketones has not been reported so far. In continuation of our research interest in exploring carbometalation of alkynes and its application in the synthesis of polysubstituted alkenes [23,36–38], we investigated the reaction of Grignard reagents with acetylenic ketones, hoping to synthesize carbonyl-contained polysubstituted alkenes. The results show that tandem carbomagnesiation/carbonyl addition was happened and highly functionalized tetrasubstituted allylic alcohols containing carbon–carbon triple bond and carbonyl group were obtained in good yields in a single operation. Herein, we wish to report the novel one-pot synthesis of highly functionalized tetrasubstituted allylic alcohols via the CuI-catalyzed tandem carbomagnesiation/carbonyl addition of Grignard reagents with acetylenic ketones.

2. Results and discussion

Initially, the reaction of phenylmagnesium bromide with 1,3-diphenyl-2-propyn-1-one (**1a**) was examined. It was found that a complex mixture of products was obtained when 1.2 equiv

* Corresponding author. Tel.: +86 553 3869310; fax: +86 0553 3883517.

E-mail address: xiemh@mail.ahnu.edu.cn (M. Xie).

PhMgBr react with **1a** in THF in the presence of 10 mol% CuI at -20°C . Fortunately, product **3a** was obtained in 61% yield when 0.5 equiv PhMgBr was used (Table 1, entry 1). Product **3a** was obtained in a similar yield when THF was replaced by Et₂O or toluene/THF (Table 1, entries 2 and 3). The yield of **3a** was improved to 90% when the reaction was carried out in THF/CH₂Cl₂ (v/v 1/1) (Table 1, entry 4). The amount of compound **3a** was greatly decreased in the elevated temperature (Table 1, entries 5 and 6). Other Cu-catalyst such as CuCN or Cu(OTf)₂ is less effective than CuI (Table 1, entries 7 and 8). An increase in the amount of CuI has no apparent effect on the reaction while the yield of **3a** was decreased when the amount of CuI reduced from 10 mol% to 5 mol% (Table 1, entries 10 and 11). Thus, we defined 10 mol% CuI, 0.5 equiv of Grignard reagent, 1.0 equiv acetylenic ketone and THF/CH₂Cl₂ as solvent at -20°C as the standard reaction conditions.

Under the optimized reaction conditions, we next examined the scope of the reaction. It was found that the tandem carbomagnesiation/carbonyl addition of Grignard reagents and acetylenic ketones proceeded smoothly and differently substituted allylic alcohols were obtained in good to excellent yields. The results are compiled in Table 2. Grignard reagents can be phenylmagnesium bromide or *n*-butylmagnesium bromide. R¹ in acetylenic ketones can be phenyl or *n*-butyl and R² in acetylenic ketones can be phenyl (Table 2, entries 1 and 8), electron-rich phenyl (Table 2, entries 2, 3 and 9), electron-deficient phenyl (Table 2, entries 4, 5 and 10), *n*-propyl (Table 2, entry 6) and 2-furyl (Table 2, entry 7). Unfortunately, a mixture of (*Z*)- and (*E*)-isomers was obtained when R¹ in acetylenic ketone is different from the R in RMgBr.

The molecular structure of compound **3a** was determined by X-ray diffraction analysis (Fig 1) [39].

Carbonyl, hydroxyl and carbon–carbon triple bond are useful functional groups in organic transformations, so it is predictable that the highly functionalized compounds **3** are potential intermediates in organic synthesis. Substituted indenenes are important building blocks for many functional materials, medicines and metallocene-based catalysts [40–44]. The utility of compound **3** as useful synthetic intermediates was investigated by FeCl₃·6H₂O-catalyzed intramolecular cyclization, which afforded functionalized indenenes in good to excellent yields (Scheme 1). The molecular structure of compound **4c** was affirmatively characterized by X-ray diffraction analysis (Fig. 2) [45].

In summary, highly functionalized tetrasubstituted allylic alcohols containing carbon–carbon triple bond and carbonyl group

Table 1
Optimization of reaction conditions

Entry	Catalyst (10 mol%)	Temperature (°C)	Solvent	Yield (%) ^a
1	CuI	-20	THF	61
2	CuI	-20	Et ₂ O	55
3	CuI	-20	Toluene/THF	68
4	CuI	-20	THF/CH ₂ Cl ₂	90
5	CuI	25	THF/CH ₂ Cl ₂	64
6	CuI	reflux	THF/CH ₂ Cl ₂	10
7	CuCN	-20	THF/CH ₂ Cl ₂	85
8	Cu(OTf) ₂	-20	THF/CH ₂ Cl ₂	80
10 ^b	CuI	-20	THF/CH ₂ Cl ₂	88
11 ^c	CuI	-20	THF/CH ₂ Cl ₂	60

^a Isolated yield based on **1a**.

^b 20 mol% CuI was used.

^c 5 mol% CuI was used.

Table 2

Tandem carbomagnesiation/carbonyl addition of Grignard reagents and acetylenic ketones.

Entry	R ¹	R ²	Yield (%) ^a
1	Ph	Ph	90 (3a)
2	Ph	4-CH ₃ OC ₆ H ₄	92 (3b)
3	Ph	2,4-(CH ₃ O) ₂ C ₆ H ₃	93 (3c)
4	Ph	4-ClC ₆ H ₄	65 (3d)
5	Ph	4-O ₂ NC ₆ H ₄	70 (3e)
6	Ph	<i>n</i> -C ₃ H ₇	60 (3f)
7	Ph	2-furyl	62 (3g)
8	<i>n</i> -C ₄ H ₉	Ph	60 (3h)
9	<i>n</i> -C ₄ H ₉	4-CH ₃ OC ₆ H ₄	61 (3i)
10	<i>n</i> -C ₄ H ₉	4-ClC ₆ H ₄	56 (3j)

^a Isolated yield based on **1**.

were synthesized conveniently by tandem carbomagnesiation/carbonyl addition of Grignard reagents and acetylenic ketones. The obtained tetrasubstituted allylic alcohols can be conveniently converted to polysubstituted indenenes. Further studies and applications of the tandem reaction are ongoing in our laboratory.

3. Experimental

All solid products were recrystallized from ethyl acetate and hexane, and the melting points are uncorrected. All reactions were carried out under an argon atmosphere. THF was distilled from sodium-benzophenone and CH₂Cl₂ was distilled from calcium hydride before use. ¹H NMR spectra were measured at 300 MHz and ¹³C NMR spectra were measured at 75 MHz in CDCl₃ with TMS as the internal standard. Acetylenic ketones were prepared according to the previously described procedures [46,47].

3.1. General procedure for the synthesis of allylic alcohols **3**

RMgBr (0.5 mmol) and CuI (20 mg, 0.1 mmol) in THF (2 mL) were added dropwise to the solution of acetylenic ketone (1.0 mmol) in CH₂Cl₂ (2 mL) at -20°C . The reaction mixture was stirred at -20°C for 5–10 min. After acetylenic ketone was completely consumed (monitored by TLC), the reaction was quenched with saturated NH₄Cl and extracted with ethyl acetate. The organic phase was combined and dried over anhydrous Na₂SO₄. After filtration and removal of solvent in vacuo, the crude product

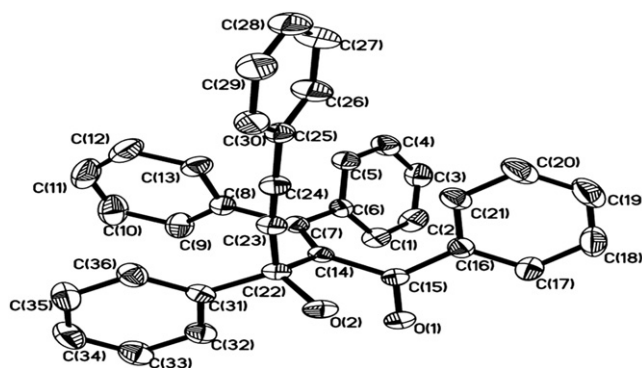


Fig. 1. The molecular structure of compound **3a**.

Download English Version:

<https://daneshyari.com/en/article/1323717>

Download Persian Version:

<https://daneshyari.com/article/1323717>

[Daneshyari.com](https://daneshyari.com)