



Base-catalyzed cross coupling of secondary alcohols and aryl-aldehydes with concomitant oxidation of alcohols to ketones: An alternative route for synthesis of the Claisen-Schmidt condensation products



Naveen Satrawala^{a,c}, Kamal N. Sharma^{a,c}, Leah C. Matsinha^b, Latisa Maqeda^b, Shepherd Siangwata^b, Gregory S. Smith^{b,*}, Raj K. Joshi^{a,*}

^a Department of Chemistry, Malaviya National Institute of Technology, Jaipur 302017, Rajasthan, India

^b Department of Chemistry, University of Cape Town, Rondebosch 7701, Cape Town, South Africa

ARTICLE INFO

Article history:

Received 5 May 2017

Revised 30 May 2017

Accepted 31 May 2017

Available online 1 June 2017

Keywords:

Cross coupling

Base catalyzed

One-pot synthesis

Bis-(Benzylidene) alkanones

Claisen-Schmidt condensation

ABSTRACT

Base-catalyzed C–C cross coupling of secondary alcohols and aryl-aldehydes was achieved, when an alcoholic solution of an aryl-aldehyde was stirred under reflux for 45 h in the presence of a catalytic (20 mol %) amount of K_2CO_3 . The consistent formation of α,α' -bis-(benzylidene) alkanones was obtained in moderate to good yields using various secondary alcohols and substituted aryl-aldehydes. Herein, α,α' -bis-(benzylidene) alkanones, which are the classical products of Claisen-Schmidt (cross aldol) condensation, have been synthesized via an alternative strategy using secondary alcohols. Bis-(benzylidene) alkanones are an integral part of various drug regimes and the production of bis-(benzylidene) alkanones without using any precious metal is a major outcome of the present reaction.

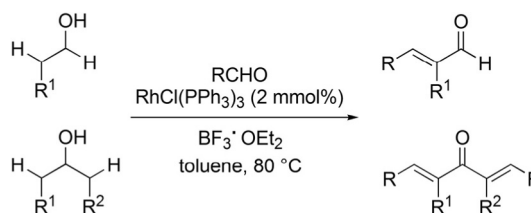
© 2017 Elsevier Ltd. All rights reserved.

Introduction

Diarylidene ketones are of special interest due to their intriguing biological activities such as HIV-1 integrase inhibitors,¹ antiangiogenics,² methyltransferase inhibitors,³ quinine reductase inducers,⁴ cholesterol-lowering activity,⁵ arginine cytotoxicity,⁶ and their use in various agrochemical, pharmaceutical and perfume industries.⁷ Moreover, these are important precursors in the synthesis of 2,7-disubstituted tropones,⁸ and natural products such as cystodytins.⁹ The Claisen-Schmidt condensation reaction is the classical method used for the synthesis of α,α' -bis-(benzylidene) alkanones. Through this method, alkanones are transformed to α,α' -bis-(benzylidene) alkanones in the presence of strong acids¹⁰ and bases with or without solvent and conventional heating.¹¹ Several protocols for Claisen-Schmidt condensation reaction have been reported using different catalysts such as basic or acidic alumina,¹² Na_2CO_3 -TBAB,¹³ bis(*p*-methoxyphenyl)telluroxide,¹⁴ expensive Lewis acids (e.g. amberlyst-15 and B_2O_3/ZrO_2),¹⁵ and hazardous or toxic solvents. The synthesis of α,α' -bis-(benzylidene) alkanones by direct C–C cross-coupling of alcohols at the β -

position with aldehydes has also been reported by Zhang and co-workers (Scheme 1).¹⁶

This is the only reported method which avoids the use of alkanones. However, a rhodium catalyst was used to promote this coupling. To the best of our knowledge, there is no method reported where a metal-free coupling of secondary alcohols and aryl-aldehydes through the β -position, with concomitant oxidation of the alcohol to the ketone, has been reported. Hence, to our mind, it seemed worthwhile to explore a metal-free C–C cross-coupling strategy between secondary alcohols and aryl aldehydes for the preparation of biologically important bis-(benzylidene) alkanones. Moreover, the vast expense of rhodium complexes and dwindling Rh resources, provides further motivation for pursuing this



Scheme 1. Cross coupling reaction of primary and secondary alcohols with aldehydes.

* Corresponding authors.

E-mail address: rkjoshi.chy@mnit.ac.in (R.K. Joshi).

^c N.S. and K.N.S. have contributed equally.

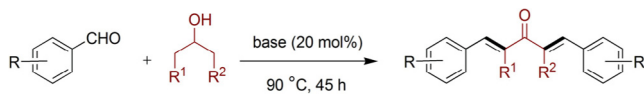
metal-free route for the synthesis of α,α' -bis-(benzylidene) alkanones.

Results and discussion

When a secondary alcohol (2-propanol) and benzaldehyde were heated at 90 °C for 45 h in the presence of catalytic K_2CO_3 , the formation of a new light yellow product, α,α' -bis-(benzylidene)alkanone was observed in a significant amount.

It was quite surprising to obtain the Claisen-Schmidt product without using any alkanone. It is probable that the alcohol transforms *in situ* to the alkanone and then initiates the Claisen-Schmidt reaction. However, there is no report available which indicates dehydrogenation of a secondary alcohol without using aluminium alkoxides.¹⁷ Since, the alcohol is working as a reagent as well as solvent for this reaction, the purity of alcohols has also been confirmed through gas chromatography (GC) analysis and refractive indexes. The optimization of the solvents was further investigated in different primary, secondary (Scheme 2), and tertiary alcohols. However, the exclusive formations of α,α' -bis-(benzylidene)alkanone was observed only with secondary alcohols (Table 1).

It was also observed, that cyclopentanol is a slightly better reactant and solvent compared to other secondary alcohols i.e., 2-propanol and cyclohexanol (Entry 8, Table 1). It was noted that the reaction does not proceed using 1° and 3°-alcohols (Entries 6–7, Table 1). This indicates that secondary alcohols containing a β -hydrogen is an elementary prerequisite for this transformation. The presence of an alkali base is an essential necessity for this transformation and it was observed that the reaction does not initiate in the absence of an alkali base (Entry 1, Table 1). The reaction was further explored using various alkali and alkaline earth metal bases, and it was found that K_2CO_3 is the most suitable base for this catalytic reaction, resulting in good yield of 60% (Entry 8, Table 1).



Scheme 2. Base catalyzed cross coupling of secondary alcohols with aldehydes.

Table 1
Optimization of base and alcohols for the C–C cross coupling of secondary alcohols with benzaldehyde.

Entry	Base	Alcohol	Base (mol%)	Time (h)	Yield ^a (%)
1	–	2-Propanol	–	65	–
2	K_2CO_3	2-Propanol	5	45	10
3	K_2CO_3	2-Propanol	10	45	25
4	K_2CO_3	2-Propanol	20	45	55
5	K_2CO_3	2-Propanol	30	45	35 ^b
6	K_2CO_3	Methanol	20	48	–
7	K_2CO_3	Ethanol	20	48	–
8	K_2CO_3	Cyclopentanol	20	60	60
9	K_2CO_3	Cyclohexanol	20	65	32
10	K_2CO_3	<i>tert</i> -Butanol	20	48	–
11	Cs_2CO_3	2-Propanol	20	48	45
12	NaOH	2-Propanol	20	45	23 ^b
13	KOH	2-Propanol	20	45	31 ^b
14	^t BuOK	2-Propanol	20	48	40
15	$Ca(OH)_2$	2-Propanol	20	60	–
16	$CaCO_3$	2-Propanol	20	60	–
17	$Mg(OH)_2$	2-Propanol	20	60	–
18	$MgCO_3$	2-Propanol	20	60	–

^a Reaction conditions: benzaldehyde (0.212 g, 2.0 mmol), alcohol (excess, 15 mL), base.

^b Starting material consumed; desired product as minor and Cannizzaro reaction product as major product is observed.

Other alkali bases *viz.* Cs_2CO_3 , NaOH, KOH, and KOt -Bu are also effective for the reaction but require longer times for the reaction to be completed in comparison with K_2CO_3 . Moreover, the yield of the products are significantly reduced (Entry 11–14, Table 1). It was also observed that the yield of the desired product decreases when strong alkali bases such as NaOH and KOH are used. Moreover, benzyl alcohol and benzoic acid (Cannizzaro reaction products) formed as the major products. The formation of the products was not observed with alkaline earth bases, i.e. $Ca(OH)_2$, $CaCO_3$, $Mg(OH)_2$, $MgCO_3$ (Entries 15–18, Table 1). Careful selection of the alkali base is therefore essential for the selective preparation of the desired products. In addition, the mol% of alkali base also influences the course of reaction and yields of product as well. After performing a series of reactions, it was established that 20 mol% is an ideal quantity of the base (K_2CO_3) required for the reaction (Entries 2–4, Table 1), while further increasing the mol% of the base drove the reaction towards the Cannizzaro reaction and results in the formation of the benzyl alcohol and benzoic acid, as the major products of the reaction (Entry 5, Table 1). Lowering the mol% of the base significantly reduced the yield of the products (Entries 2–4, Table 1).

The duration of reaction also influences the course of reaction. The initial formation of desired products was detected after 10–15 h of the reaction. However, a further 20–40 h of stirring is required to obtain the best yields. The reaction time profile of representative reactions of benzaldehyde with various secondary alcohols i.e. cyclopentanol, 2-propanol, and cyclohexanol under ambient reaction conditions was studied and is shown in Fig. 1.

This study reveals that maximum conversion can be achieved in 45–50 h, increasing the time of the reaction with keeping the amount of base constant does not bring significant changes to the product yield, even after 60 h. This reaction has also been investigated at high pressure using either Argon or N_2 at 20 bar and at 100 °C in an autoclave. A slight improvement in the yield of the desired product was observed while maintaining similar reaction parameters.

To examine the scope of the present coupling reaction, different combinations of secondary alcohols with benzaldehyde and various substituted benzaldehydes were explored. This is summarized in Table 2.

The transformations proceeded efficiently and give the desired bis-benzylidene ketones with various alcohols and aldehydes. However, the group bonded to the benzene ring influences the

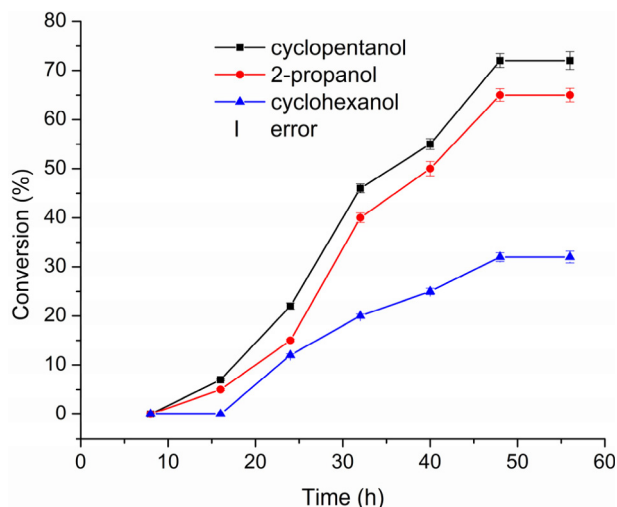


Fig. 1. Time profile of base promoted C–C coupling of benzaldehyde with cyclopentanol/2-propanol/cyclohexanol.

Download English Version:

<https://daneshyari.com/en/article/5259392>

Download Persian Version:

<https://daneshyari.com/article/5259392>

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