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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

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ABSTRACT

Base-catalysed 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 K₂CO₃. 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.

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1. Introduction

Diarylidene ketones are of special interest due to their intriguing biological activities such as HIV-1integrase inhibitors, 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 Na₂CO₃-TBAB,¹³ *bis(p*-methoxyphenyl)telluroxide,¹⁴ expensive Lewis acids (e.g. amberlyst-15 and B₂O₃/ZrO₂),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).¹



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

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

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2. Results and discussion

When a secondary alcohol (2-propanol) and benzaldehyde were heated at 90 °C for 45 h in the presence of catalytic K₂CO₃, the formation of a new light yellow product, α, α' -bis-(benzylidene)alkanone was observed in a significant amount.



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

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 $\alpha, \alpha'-bis$ -(benzylidene)alkanone was observed only with secondary alcohols (Table 1).

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

Entry	Base	Alcohol	Base	Time	Yield ^a
			(mol%)	(h)	(%)
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 ₂ CO ₃	Cyclopentanol	20	60	60
9	K_2CO_3	Cyclohexanol	20	65	32
10	K_2CO_3	tert-butanol	20	48	-
11	Cs_2CO_3	2-propanol	20	48	45
12	NaOH	2-propanol	20	45	23 ^b
13	КОН	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	-

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

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

It was also observed, that cyclopentanol is a slightly better reactant and solvent compared to other secondary alcohols i.e., 2propanol 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 K₂CO₃ is the most suitable base for this catalytic reaction, resulting in good yield of

60% (Entry 8, Table 1). Other alkali bases viz. Cs₂CO₃, NaOH, KOH, and KOt-Bu are also effective for the reaction but require longer times for the reaction to be completed in comparison with K₂CO₃. 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, CaCO₃ Mg(OH)₂, MgCO₃ (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 (K₂CO₃) 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 fomration 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 Figure 1



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

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 N₂ at 20 bar and at 100 °C in an autoclave. A slight improvement in the yield of the desired product was observed whilst 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.

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 Table 2. Base promoted C-C cross coupling of secondary alcohols with aryl-aldehydes for synthesis of diarylidene ketones

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 yield of the desired products. An electron-donating group bonded to the benzene ring favours high conversions (in the range 68-82%) for 3b, 3f, 3g, 3k, 3i, 3j, 3m, and 3n. In contrast, the yield of products remarkebly reduced (up to 35% for 3s) when an electron-withdrawing group is attached to benzene ring. For the ferrocene-based substrates, the yield of products range between moderate to average, i.e. for 3u and 3t 58% and 35%, The reaction of ferrocene-aldehyde respectively. and cyclohexanol yielded only a trace amount (1-2%) of the desired product. This may be due to the bulkier nature of ferrocene, which can sterically hinder the formation of the desired product.

All coupling products were structurally characterized using FT-IR, $^1\!H$ NMR and $^{13}\!C$ NMR spectroscopy and mass

spectrometry. FT-IR spectra of the product show the stretching frequencies between 3100-3000 cm⁻¹, 1711-1640 cm⁻¹ and 1640-1606 cm⁻¹ for the C-H (alkene), C=O (carbonyl) and C=C (alkene) functional entities, respectively. This confirmed the basic skeleton of *bis*-benzylidene alkanones. In the ¹H NMR spectra, doublets for the α and β C-H protons of α,β -unsaturated ketones appear in the range δ 6.58-7.33 ppm and δ 7.37–8.04 ppm, respectively. The vicinal coupling constants (${}^{3}J_{H-H}$) in the range 12-18 Hz, confirm the *trans* configuration of the alkene hydrogens in the product.¹⁸ Mass spectral analysis of the compounds further support the formation of the desired products and also confirm the exact composition of the compounds. Details of the spectral analysis have been provided separately in the Supplementary Material.

For the afore-mentioned C–C coupling reactions, we have proposed a mechanistic pathway, depicted in Scheme 3.

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Scheme 3. Plausible mechanism for base catalyzed C-C cross coupling of secondary alcohol and aldehydes

It has been assumed that a combinatory mechanism involving well-understood Meerwein-Ponndorf-Verley (MPV)¹ the reduction, reverse Oppenauer oxidation²⁰ and Claisen-Schmidt condensation²¹ is responsible for the final outcome of this reaction. Most probably, the secondary alcohol is first converted into an alkoxide in the presence of a base e.g., K2CO3 or potassium iso-propoxide. It transfers a hydride to the carbonyl of benzaldehyde through MPV reduction type six-membered concerted mechanism resulting in acetone and this immediately initiates the Claisen-Schmidt condensation reaction with benzaldehyde and providing the diarylidene ketones. Moreover, the MPV reduction is reversible and has the ability to undergo the reverse Oppenauer oxidation. Thus, the reaction runs under a thermodynamic equilibrium with the ratio of the products related to their relative thermodynamic stabilities.

3. Conclusion

A base-catalyzed, mild and very feasible methodology for the catalytic synthesis of biological important his-(benzylidene)alkanones from readily available secondary alcohols and aryl/ferrocenyl-aldehydes, has been developed. The presented method can be considered as one of the favored and conventional methods, since the ultimate goal of the current research was to develop economically viable and metal-free reactions using simple and easily available reagents for bulk synthesis of organic products. Moreover, the use of secondary alcohols in place of alkanones can serve as alternatives for the Claisen-Schmidt condensation reactions.

General procedure for the catalytic reaction. In an ovendried 100 mL two neck flask, mixture of aryl-aldehyde (2.0 mmol), K_2CO_3 (20.0 mol%) and secondary alcohol (15 mL) was heated at 90 °C with continuously stirring for 45-60 h under aerobic reaction conditions. Progress of the reaction was continuously monitored on TLC until the maximum conversion of aldehyde to the desired product observed. After completion, the reaction mixture was cooled to room temperature and a yellow/orange compound was extracted with ethyl acetate (2 × 25 mL). This extract was further washed with water and dried over anhydrous Na₂SO₄. Finally, the solvent was reduced through rotary evaporator. Obtained crude product was further purified by column chromatography on silica gel using ethyl acetate/hexane as eluent. A dark orange band (for ferrocene derivatives) and a light yellow oily band (for benzaldehyde derivatives) was isolated, and characterized through FT-IR, NMR and mass spectral analyses.

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Supplementary Material

Supplementary material has been provided separately.

Highlights

- Base-catalyzed formation of α, α' -bis-• (benzylidene) alkanones using sec-alcohols.
- Claisen-Schmidt Alternative for route • condensation products without using alkanones.
- J C-C cross coupling of sec-alcohols and • aryl-aldehydes with no use of transition metal catalyst or additives.