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Arabian Journal of Chemistry (2016) xxx, xxx–xxx

King Saud University

Arabian Journal of Chemistry

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ORIGINAL ARTICLE

Optimized one-pot synthesis of monoarylidene and unsymmetrical diarylidene cycloalkanones

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Received 1 June 2016; accepted 15 September 2016

KEYWORDS

Monoarylidene;
Diarylidene cycloalkanone;
Ionic liquid;
DIMCARB;
Curcuminoids

Abstract Ionic liquid dimethylammonium dimethylcarbamate (DIMCARB) catalyzed reaction for the synthesis of monoarylidene and unsymmetrical diarylidene cycloalkanones has been developed. Catalytic amount of DIMCARB was used in green solvent (water and ethanol) for different reaction of cyclic and acyclic ketones with different electron donating and withdrawing substituted aldehydes. Yields were recorded from low to excellent. This synthetic methodology provides mild, efficient, and environmentally friendly access to unsymmetrical curcuminoid analogs, avoiding the use of excess catalysts, chlorinated organic solvent, and high temperature reaction. It is green and environmentally sound alternative to the existing protocols for the synthesis of pharmaceutically important unsymmetrical natural product analogs.
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1. Introduction

The reaction of aldehydes with ketones in conventional acidic or basic condition yields symmetrical diaryl alkanones (Fig. 1). Several methodologies have been reported for the synthesis of symmetrical diaryl alkanone (Shetty et al., 2015). By the use of existing methodology we got compound **1–4** by the reaction of cyclohexanone with *p*-substituted different benzaldehyde (benzaldehyde, *p*-methoxy benzaldehyde, *p*-chloro benzaldehyde, *p*-bromo benzaldehyde). The challenge is to control the reaction to obtain monoarylidene product, which can further be utilized as an intermediate for the design of unsymmetrical diaryl cycloalkanone.

Unsymmetrical diaryl alkanones are promising building blocks for pronounced pharmacological chemistry (Zia et al., 2014). But they cannot be synthesized by aldol or Claisen–Schmidt condensation when symmetrical ketones are used for reaction. Unfortunately different inorganic acid and base catalysts produce symmetrical bisarylidene alkanones even when using adjusted stoichiometric ratio of aldehydes and ketones (Braga et al., 2014; Cai et al., 2006; Jonathan et al., 2003; Weber et al., 2005). Microwave method with Al_2O_3 and $NaNO_3$ also yields symmetrical bisarylalkanones products (Esmaeili et al., 2005; Solhy et al., 2011).

There was a need of controlling the reaction in monoarylidene step, for the formation of unsymmetrical diaryl alkanone (Fig. 2). Amine based catalyst is the best option to deal with this challenge. There is limited literature which shows the synthesis of monoarylidene alkanone using the amine based catalyst DIMCARB (Kreher et al., 2003; Rosamilia et al., 2007). Preparation of the monoarylidene adducts usually requires two steps, i.e. aldol addition followed by a separate elimination (Light and Hauser, 1961). The challenge to

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Peer review under responsibility of King Saud University.

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http://dx.doi.org/10.1016/j.arabjc.2016.09.014
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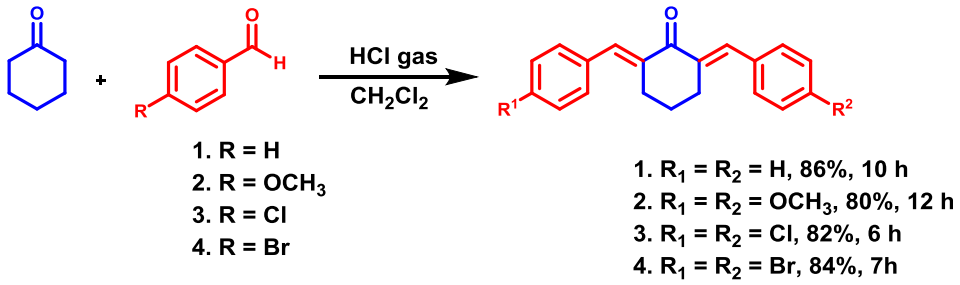

Figure 1 Synthesis of symmetrical diaryl alkanone.

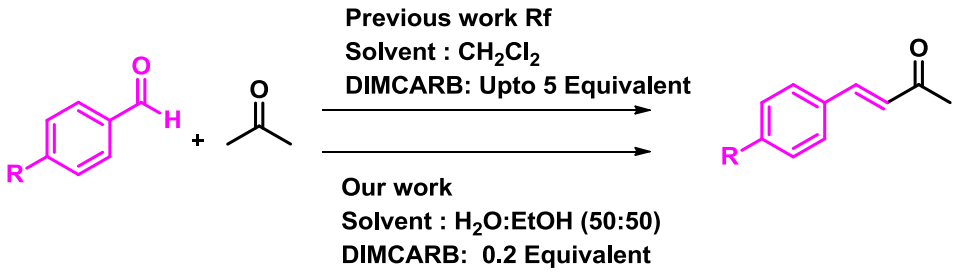

Figure 2 Synthesis of monoarylidene alkanone.

synthesize monoarylidene cyclic and acyclic alkanones required different methods of investigation. Previously Strauss et al. used ionic liquid successfully for the synthesis of monoarylidene cyclic and acyclic alkanones (Kreher et al., 2003), but DIMCARB was used as a solvent and as a reaction medium. The other drawback was the use of chlorinated solvent (CH_2Cl_2), and limited application toward the use of different ketones. We focused to optimize the reaction, which was performed successfully by catalytic amount of DIMCARB, in green solvent (H_2O and EtOH). The modification avoids the use of chlorinated solvent, and reduces the quantity of DIMCARB and also the chance of side products. DIMCARB is an adduct of CO_2 and Me_2NH (dimethylamine). Both components are gaseous under ambient conditions and are relatively stable liquid up to 50 °C. The important achievement is the replacement of chlorinated solvent previously used by Strauss and his colleagues by ethanol and water (50:50) (Table 2). It was observed that the reaction is more efficient in green solvent than in dichloromethane. The conversion of reactants to products in model reactions in ethanol water mixture was 100 percent, while the reaction in dichloromethane showed 92 percent conversion. Different bases were screened for this reaction. DIMCARB and DBU (1,8-Diazabicycloundec-7-ene) were found excellent for this type of conversion. Other bases did not give any products or gave very less yield.

The targeted unsymmetrical diarylalkanones were focused to synthesis due to their carbon-chain containing a dienone system that works as an inter aromatic-rings spacer moiety, which look like those of the curcuminoids (1,7-diarylheptanes) and the chalcones (1,3-diarylpropanes). Curcuminoids are very important bioactive natural products found in some plant species. The promising structures of unsymmetrical biarylalkanone analogs exhibit important biological activity (Maydt et al., 2013), such as antitumor (Cabrera et al., 2007; Jin et al., 2013), anti-nematodal (Attar et al., 2011), anti-cancer (Anto et al., 1995), antioxidant (Acche et al., 2008), antifungal (Lahtchev et al., 2008), antimitotic (Ducki et al., 1998), anti-viral (Lv et al., 2012), anti-HIV (Marambaud et al., 2005), chemoprotective (Forejtníková et al., 2005), anti-inflammatory (Araico et al., 2007), antimicrobial (De et al., 2009), antibacterial (Batovska et al., 2009), antimalarial (Franco et al., 2012), anti-tubercular (Mascarello et al., 2010), anti-tubulin (Ruan et al., 2011; Zhang et al., 2012),

Table 1 Efficiency of bases used for synthesis of monoarylidenes.

Entry	Base	Conversion (%)
1	Pyridine	No reaction
2	DMF	No reaction
3	Diisopropylethylamine	No reaction
4	DIMCARB (0.2 equivalent)	100 %
6	DBU (0.2 equivalent)	100 %
8	*N*,*N*-dimethylamine (0.2 equivalent)	100 %

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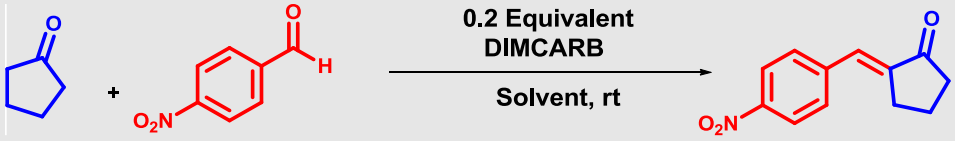
Table 2 Table of selected solvents for the synthesis of mono arylidene alkanone.



Entry	Solvent	Conversion (%)[a]
1	CH_2Cl_2	91
2	H_2O	ND
3	CH_3OH	96
4	CH_3CH_2OH	92
5	CH_3CH_2OH/H_2O (1:1)	100
6	CH_3CN	100

[a] Calculated from HPLC analysis.

anti-fertility (Hall et al., 1974), anti-parasitic (Zia et al., 2014), neuro-protective (Leong et al., 2014) and anti-metastatic (Menon et al., 1999).

2. Experimental

2.1. General

All chemicals were purchased from Organics, Sigma-Aldrich, Acros Chemicals and Fisher Scientific Ltd., and used without further purification. The deuterated solvents of Apolo were used for the NMR analysis. Thin layer chromatography was performed with precoated silica gel G-25-UV254 plates and detection was carried out at 254 nm under UV, and by vanillin in H_2SO_4 solution. ^1H NMR and ^{13}C NMR were performed on a Brüker AVANCE 400 operating at 400.15 MHz and 100.62 MHz, respectively; $CDCl_3$ was used as solvent and tetramethylsilane (TMS) as internal reference. All compounds were dissolved in organic solvents at about 5–10 mg mL^{-1} each and shifted into a 5-mm NMR tube. Chemical shifts (δ in ppm) were measured with accuracy of 0.01 (^1H) and 0.1 ppm (^{13}C).

2.2. Synthetic experimental procedure

2.2.1. Synthesis of compounds *1–4*

Symmetrical diarylidene products (**1–4**) were synthesized by the reaction of different aldehyde with cyclohexanone in a 50 mL two-necked round-bottom flask in a ratio of 2:1 M. Dry HCl gas was passed from the content of the flask till it was saturated and turns to red color. The reaction mixture was stirred for 5–10 h. The crude product was diluted with toluene, and washed with $NaHSO_3$ solution. The organic layer was separated, dried with anhydrous Na_2SO_4 and evaporated under low pressure. The residue when distilled under reduced pressure yielded pure compounds **1–4**, which was recrystallized from ethanol (refers to supplementary materials for physical date).

2.2.2. Synthesis of compounds *5–25*

Compounds **5–25** were synthesized by the reaction of different aldehydes with symmetrical ketone. A mixture of cyclohexanone (10.95 mmol), aldehyde (5–7.3 mmol) and DIMCARB (0.2 equivalent) was taken in 100 mL round-bottom flask and stirred for 10 h with vigorous stirring. The DIMCARB was removed from reaction mixture by rotary evaporator at 60 °C. The crude product was extracted 3 times with ether and 1 M HCl solution. The solvent was evaporated by vacuum and the crude product was forwarded for column chromatography to get compounds **5–25**, which were recrystallized from ethanol (refers to supplementary materials for physical date).

2.2.3. Synthesis of compounds *26–31*

A Solution of compounds (monoarylidene **5–25**), and various aldehydes in ethanol (5 mL) was stirred for 5 min at room temperature, after which added sodium hydroxide solution in ethanol (4 mL, 50 mmol) and stirring was continued till the reaction completed. The solvent ethanol was evaporated under reduced pressure. The residue lift was dissolved in ethyl acetate, extracted with $NaHSO_3$ solution and dried with Na_2SO_4. The solvent was evaporated on rota evaporator and the crude product was collected as yellow precipitate, which is further purified by column chromatography and recrystallized from ethanol (refers to supplementary materials for physical date).

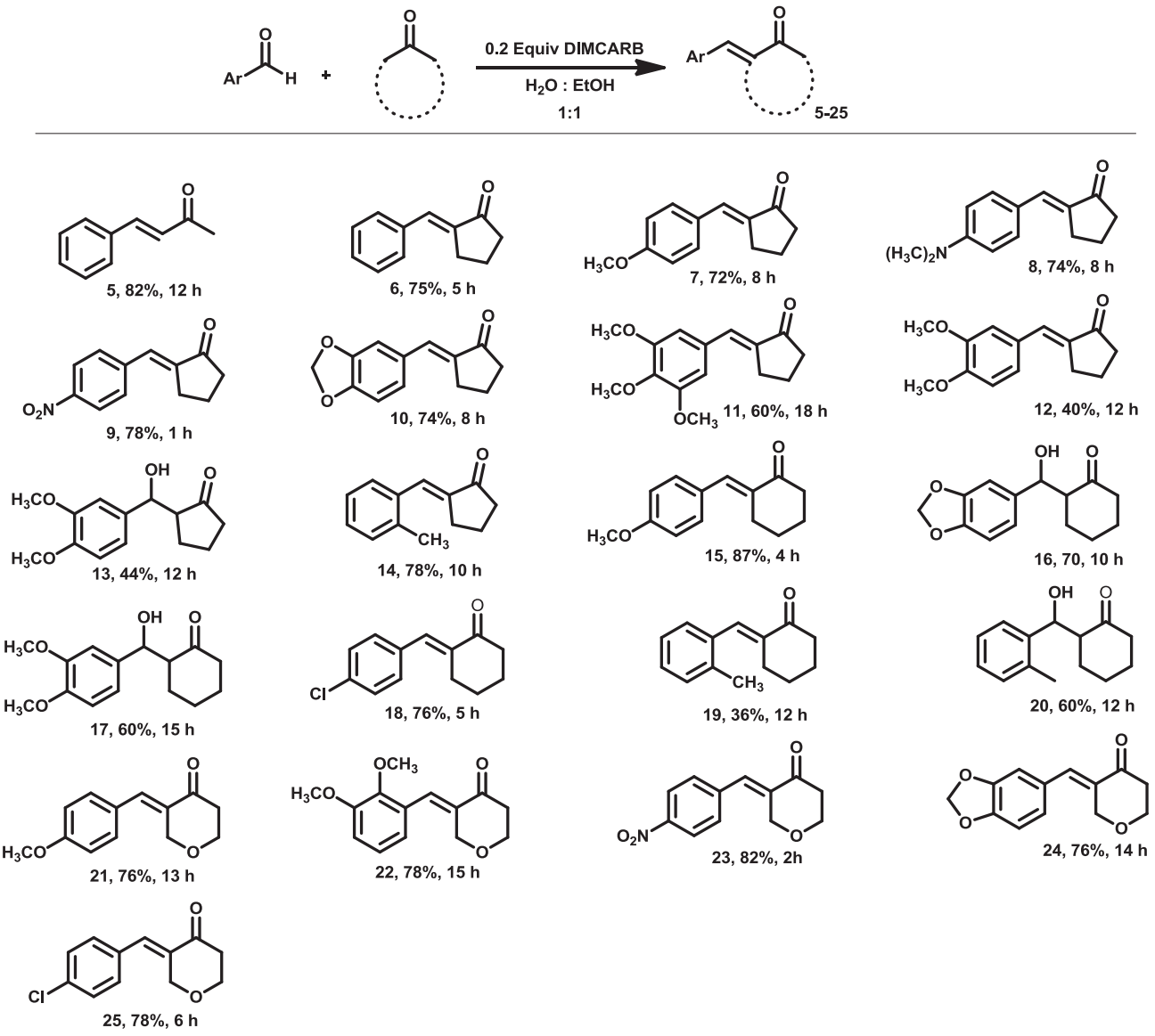
3. Results and discussion

Our initial efforts were to focus on carrying the synthesis of monoarylidene cycloalkanones and then optimizing them for their unsymmetrical diarylcycloalkanones. The model reaction of nitro benzaldehyde with cyclopentanone rapidly gave hydrated intermediary. After some time, or in the result of work up, *E1cb* mechanism produces dehydrated monoarylidene product (Table 1). The reaction carried out in ethanol-water mixture (50:50) with 20 mol percent of DIMCARB at room temperature ends in 2 h. Mild reaction conditions, shorter reaction time, cost-effectiveness, operational simplicity and high yields make this transformation a method of alternative for the straightforward preparation of various monoarylidene products. Comparing with previous methods (Kreher et al., 2003) highlighted herein, a solution is offered to carry mild and green alternative for this key transformation. We observed that the use of water plays an important role in the mechanism, by converting keto form of ketone to its respective enol form for reaction. We stirred aldehyde with DIMCARB in water-ethanol mixture for 5 min, which produced reactive imines specie. The added ketone adopts its enolic form, which readily attacks on imines to give dehydrated product first and

hydrated product later. The substrate scope was analyzed for the reaction in the developed condition. Different cyclic, acyclic ketones, electron donating and withdrawing substituted aromatic aldehydes were used (Scheme 1). It was observed that the reaction of electron-withdrawing group containing aldehydes takes less time by activating carbonyl to form imine than those with electron donator groups. HPLC analysis shows that both products (hydrated and non-hydrated) are interconvertible to each other. We isolated both products and characterized them by spectroscopic methods. To date, no reported procedure for monoarylidene alkanones makes use of such a very mild and green environment and leads to such high product yields. Isolated monoarylidene products were treated with aldehyde in basic condition for the design of unsymmetrical diaryl cycloalkanones in good to excellent yield.

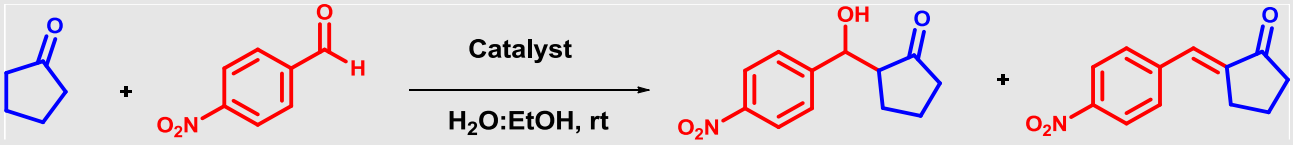
It was verified that DIMCARB, DBU and *N*,*N*-dimethyl amine utilized all the starting material at 0.2 equivalent. So it means that all three bases act as a catalyst. DIMCARB yields *N*,*N*-dimethyl amine which carries the reaction. So it was concluded that liquid crystal DIMCARB is the source of reactive *N*,*N*-dimethyl amine cation and anion which activate both reactants aldehydes and ketones. Further the reaction was carried out in different solvents to see the effect of solvent on reaction (Table 2). There was no reaction observed in water due to the less solubility of aldehyde. It was observed that using dichloromethane only 92 percent of aldehyde was converted into products. Ethanol water mixture (50:50) converts 100 percent of aldehyde into product. Ethanol helps to solubilize the starting material and then it can yield products even by the combination of 50% with water. Mixture of water and ethanol is considered green solvents, so it was selected for further reactions. The products yield was observed from good to excellent.

The catalytic quantity was also calculated for model reaction. It was observed that 100 percent conversion of aldehyde to monoarylidene occurred at all catalyst quantity except 0.2



Scheme 1 Synthesis of monoarylidene ketones from different aldehydes and ketones. Compounds **6–14** are derived from cyclopentanone; **15–20** from cyclopentanone; **21–25** from dihydro-2H-pyran-4(3H)-one; and compound **5** from propanone.

Table 3 Catalytic quantities of DIMCARB used for the synthesis of monoarylidene cycloalkanone.



Entry	Quantity (Mole percent)	Conversion (%)[a]
1	10	50
2	20	100
3	30	100
4	40	100
6	50	100

[a] Calculated by HPLC.

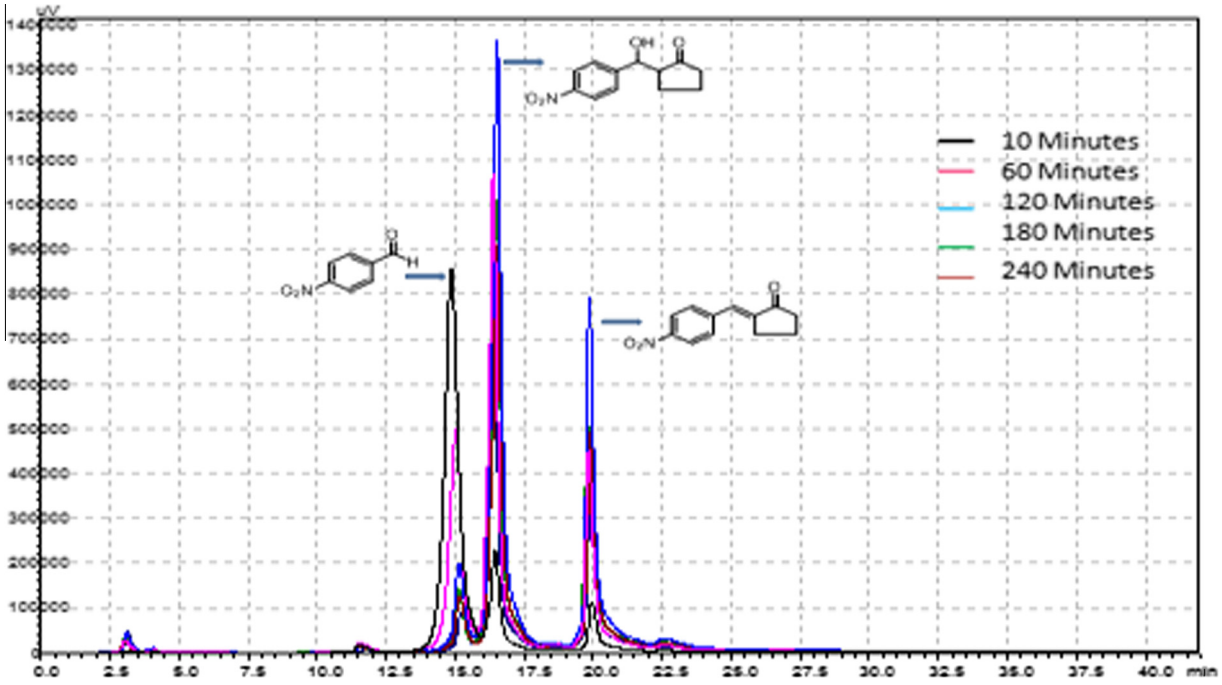


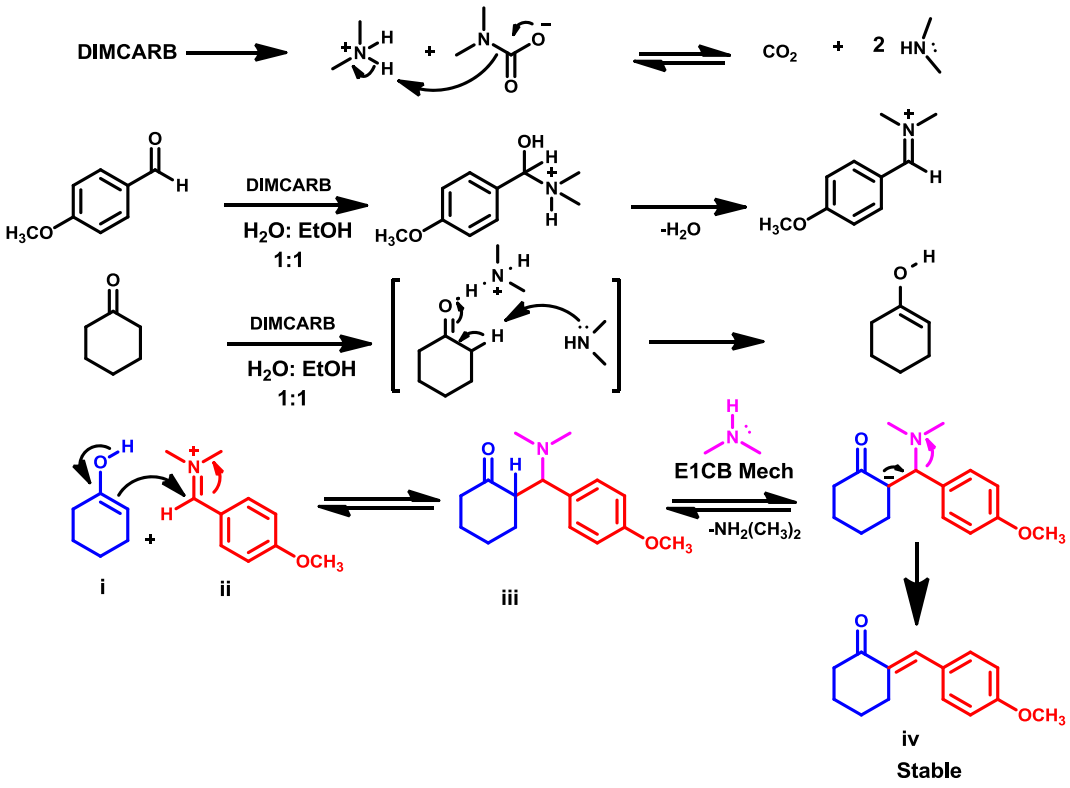
Figure 3 HPLC chromatograms obtained during kinetic study of the model reaction in CH_2Cl_2.

equivalents (Table 3). We carried out further reaction with 20 mol percent due to ineffectiveness. The reaction with 20 mol percent of aldehyde was so clear that most of the time there was no need of column chromatography for purification. Unreacted reactant in case of less reactive aldehyde was removed during the work up procedure by extraction with saturated solution of sodium metabiosulfite.

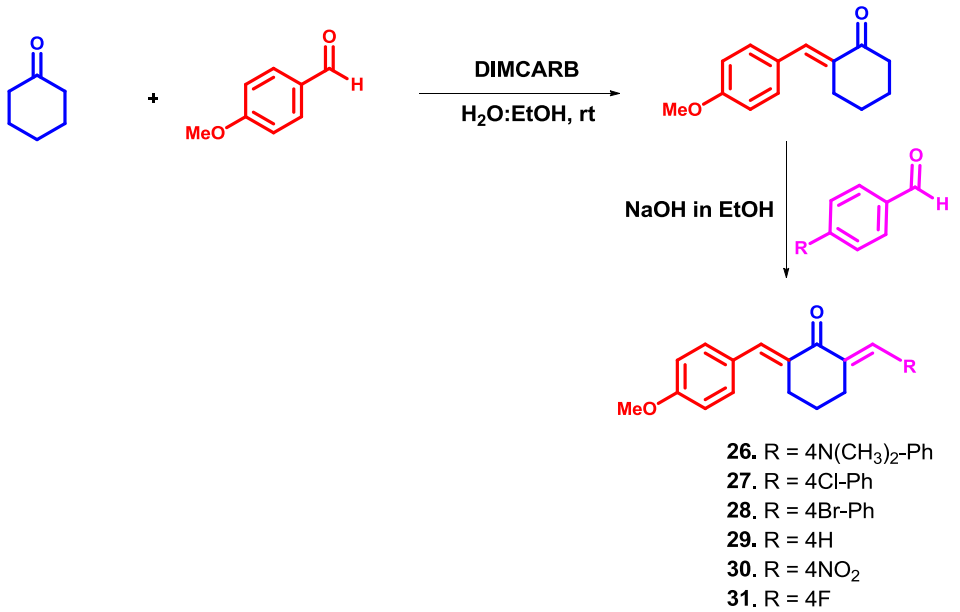
The progress of the reaction for model reaction was also investigated. It was observed that 100 percent conversion was not obtained in dichloromethane by using 1.0 equivalent of DIMCARB. The graph is plotted by different reaction time intervals. The HPLC analysis was carried out after 10, 60, 120, 180, 240 min. Even after 240 min 92 percent conversion occurred. By catalyzing the reaction with 20 mol percent of DIMCARB in ethanol water mixture (50:50), the reactant was converted 100 percent even after 60 min of reaction time (Fig. 3).

3.1. Reaction mechanism

The reaction was further evaluated by mass spectrometer LC-MS to study the mechanism of reaction (refers to data in supplemental material file). The reaction is catalyzed by *N*,*N*-dimethyl amine produced from DIMCARB. For this study we selected moderate reactive aldehyde, anisaldehyde and cyclohexanone in order to explore its mechanism. *N*,*N*-dimethyl amine produced by DIMCARB first reacts with aldehyde yielding iminium species **ii**, which further reacts with enolic form of cyclohexanone **i** to yield intermediate **iii**. Compound **iv** was produced in the result of E_1CB mechanism by dehydration of intermediate compound **iii**. Compound **iii** was stable in the reaction mixture as its enolic form did not process further reaction (Scheme 2). The production of *N*,*N*-dimethyl amine cation and anion from ionic liquid and its attack on the aldehydic and ketonic moieties are also explained.



Scheme 2 Mechanism of the synthesis of mono arylidene by DIMCARB catalyzed reaction.



Scheme 3 Synthesis of unsymmetrical bisarylmethylidene cycloalkanone from monoarylidene ketones.

The reaction of *N*-*N*-dimethyl amine and aldehyde yield iminium compound **ii**. The reaction of compound **i** with **ii** follows Michael mechanism. We have carried out the reaction with HCl and NaOH, which follow Aldolic pathway. This reaction is difficult to control at monoarylidene step, because enol formation takes place at both α-carbon and leads to symmetrical bisarylalkanones (scheme 2). DIMCARB modifies substantially the mechanism of reaction and becomes more selective for monoarylidene compounds by activating the α-hydrogen by forming H-bonding with carbonyl, and provides drawing force for the formation of enolate. So DIMCARB activates both ketones and aldehydes for the formation of monoarylidene products.

The reaction was further optimized successfully for the synthesis of unsymmetrical monocarbonylic analogs of curcumin. One-pot synthesis was carried out by the addition of one molar

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equivalent of aldehyde in reaction mixture after completion of the synthesis of monoarylidene product. NaOH was dissolved in ethanol and was added in the reaction mixture. The diarylidene alkanone (unsymmetrical monocarbonylic analogs of curcumin) was synthesized in good yield. There is a limited literature about the synthesis of unsymmetrical diarylidene compounds. Braga et al. synthesized symmetrical bis arylmethylidene cycloalkanone by catalyzing the reaction with NaOH in ethanol (Braga et al., 2014). This method fails to produce unsymmetrical bis arylmethylidene cycloalkanone. Efficient synthesis of unsymmetrical bisarylmethylidene cycloalkanone could be obtained in good yield by catalyzing the reaction with DIMCARB for the synthesis of monoarylidene product, and then this product can be used as an intermediate for the synthesis of unsymmetrical bisarylmethylidene cycloalkanone (Scheme 3).

4. Conclusion

In conclusion, we have developed mild catalytic system for the synthesis of monoarylidene and diarylidene alkanones. We investigated the role of water applicability using enolic formation of ketones and their reaction with aldehydes leading to wide range of organic compounds. Our method is flexible and is tolerant of various cyclic, acyclic ketones and aldehydes having electron-donating and electron-withdrawing groups at the *ortho*-, *meta*-, and *para*-positions at the aromatic ring. In terms of economical and environmental considerations, we believe that this method holds potentials to synthesize various curcuminoid analogous for pharmaceutical industry.

Acknowledgments

The authors are grateful to Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP Proc Num 2010/11384-6), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), and Coordenação de Aperfeiçoamento de Pessoal de Ensino Superior (CAPES) for financial support and Third World Academy of Science (TWAS) for Ph.D. fellowship.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.arabjc.2016.09.014.

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Please cite this article in press as: Din, Z.U., Rodrigues-Filho, E. Optimized one-pot synthesis of monoarylidene and unsymmetrical diarylidene cycloalkanones. Arabian Journal of Chemistry (2016), http://dx.doi.org/10.1016/j.arabjc.2016.09.014