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Impact of Phase Transfer Catalyst on Ring Annulation of Ethyl Acetoacetate with (E)-1-(2-hydroxy-5-methylphenyl)-3-(p-tolyl)prop-2-en-1-one

Nitin C. Kongre*

*Department of Chemistry, Jawaharlal Nehru Arts, Commerce and Science College, Wadi, RTM, Nagpur University, Nagpur - 440023 (M.S.) India

E-mail: n.kongre@rediffmail.com

Abstract

In the present work, we have reported Michael addition of Ethyl Acetoacetate to (E)-1-(2-hydroxy-5-methylphenyl)-3-(p-tolyl)prop-2-en-1-one **(2)** under solid/liquid phase transfer catalyst TBAB to produce Michael adduct and an annulated compound ethyl (1S,2R)-4-hydroxy-4-(2-hydroxy-5-methylphenyl)-2-(4-methoxyphenyl)-6-oxocyclohexane-1-carboxylate **(4)** in excellent yield, in solvent free green chemical transformation. The annulated cyclic compound **(4)** was the major product obtained via an annulations process of the Michael adducts **(3)**. The results were deduced from organophilicity and approachability of the catalysis by entreating a transition state for the formation of an annulated compound **(4)** due to the formation of chelate with quaternary ammonium cation.

Keywords: Michael reaction; Chalcone; Phase Transfer Catalyst (TBAB); Solvent Free; Annulation

Introduction

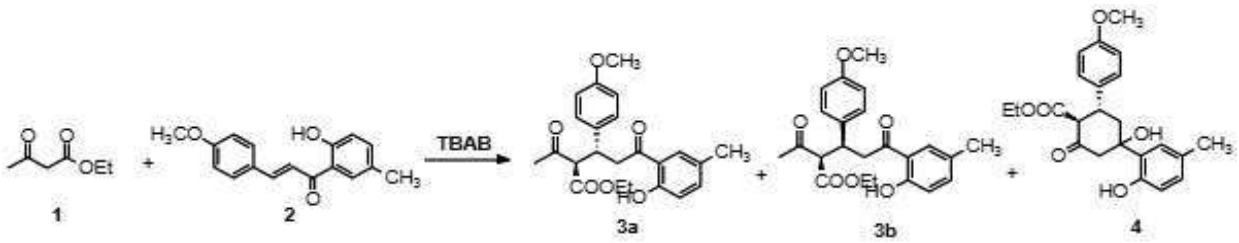
Annulation is the formation of ring within the molecule like Robinson annulation, Danheiser annulation and various cycloaddition reactions in organic synthesis [1]. It is the process of building a ring system onto a Cyclic or non-cyclic established system. Many reactions like Diels-Alder reactions, acid catalyzed poly-olefinic, photochemical, radical and thermal cyclization are not included in broader sense with annulation reactions in general; but they are [2]. The condensation of two open chain chemical entities via two bonds formation in a single molecular framework is the most effectual way to form cyclic analogues [3]. Such transformations may take place either in a concerted manner (Diels-Alder reactions) or in a sequential manner that is unique characteristics of many (3 + 2

annulations) for five-membered ring synthesis. Any of the process is enough once regiochemistry and stereochemistry is controlled for the synthesis [4]. In recent years, the methods of annulation have proved to be irreplaceable utilities to synthetic and medicinal chemists in the syntheses of complex natural products of biological importance [5].

Michael reaction is the addition of nucleophiles (Michael-donor-O, S, P, N) on alkenes, or alkynes attached to electron withdrawing groups (Michael-acceptor) [6]. It is the conjugate addition of carbon nucleophiles to α, β unsaturated compounds that is an important C-C bond formation reaction [7]. This conversion shows a wide scope due to the large variety of acceptors (α, β-unsaturated aldehydes, esters, ketones, phosphonates, sulfones, cyanoester thioesters and nitrostyrenes) and nucleophiles (organometallic reagents, Michael donors, other carbanions) [8]. This nucleophilic addition may take place in enantioselective or non-enantioselective manner. In recent years, due to huge demand for optically active compounds, tremendous progress has been made in the field of asymmetric synthesis, providing the Michael adduct with high enantiomeric purity. It is catalyzed by a large number of acids, bases and transition metals; it is completely atom economical; most of the functionalities of the starting materials are preserved in the products; the starting materials are readily available or are easily prepared. For these reasons, both the intermolecular and intramolecular variants of the Michael reaction are very prominent among methods used for preparing ring systems [9]. Stereochemical and mechanistic aspects of this classical reaction have been the object of intense investigation, mainly focused on the direct intense of enolates or stabilized carbanions [10]. Thus, the objective of this research work is to explore the effect of phase transfer catalyst on ring closure of ethyl acetoacetate with (E)-1-(2-hydroxy-5-methylphenyl)-3-(p-tolyl)prop-2-en-1-one.

Results and discussion

We have reported a study of the effect of the quaternary ammonium cation structure on the annulation, ring closure that occurs between ethyl acetoacetate (donor) **1** and Chalcone (acceptor) **2** under solid/ liquid phase transfer catalysis, under solvent free conditions via Michael addition reaction. This reaction afforded Michael adduct **3** and an annulation product **4**, the later formed via intramolecular cyclization of Michael adduct **3 (Scheme 1)**. We have studied and explored the results in two parts. Those are variation of the reaction parameters and optimization of products yield **3** and **4** in the first part. The second is committed to a study of the effect of catalyst structure in the 6-membered annulation reaction analyzing the ratio of products **3** and **4**.



1 2 3a 3b 4

Scheme 1: Michael addition reaction in the presence of phase of phase transfer catalyst.

Optimization of reaction conditions and study of Stereochemistry of 3 and 4

For optimization of reaction conditions and evaluation of the impact of the addition of a quaternary ammonium salt, the ratio of donor/acceptor and the temperature on the rate of reaction, ethyl Acetoacetate **1** was reacted with Chalcone **2** at 60^0C and room temperature with varying ratios of donor/acceptor as 6:1 and 1:1. The reaction is carried out in solvent free condition in the presence of tetra butyl ammonium bromide (TBAB) using catalytic amount of KOH as base **(Table 1)**. After detailed monitoring of the catalyzed reaction, it was found that no more than 15 minutes were needed to afford products **3** and **4**. In addition, equal stoichiometric amounts of donor/acceptor proved to be sufficient to obtain the product at temperature of 60^0C, and TBAB as catalyst proved to be the optimum reaction condition to obtain products **3** and **4** in 97% yield. The optimized reaction of **1** with chalcone **2** a produced compound **3** as a diastereoisomeric mixture which we did not managed to separate by column chromatography. The relative stereochemistry of the major isomer **3a** was established based on ^{1}H-NMR spectra of **4**, as it was obtained by an intramolecular cyclization of **3a**. The coupling constant of about 12.0 Hz obtained for the hydrogen of the two-stereogenic centres of **4** suggested anti parallel relationships. Thus, the diastereoisomers **3a**, and **3b** show anti and syn relative configuration respectively **(Scheme 1)**. It should be noted that compound **4** was isolated as single diastereoisomer after chromatographic separation.

Table 1. Michael addition of ethyl acetoacetate 1 to chalcone 2

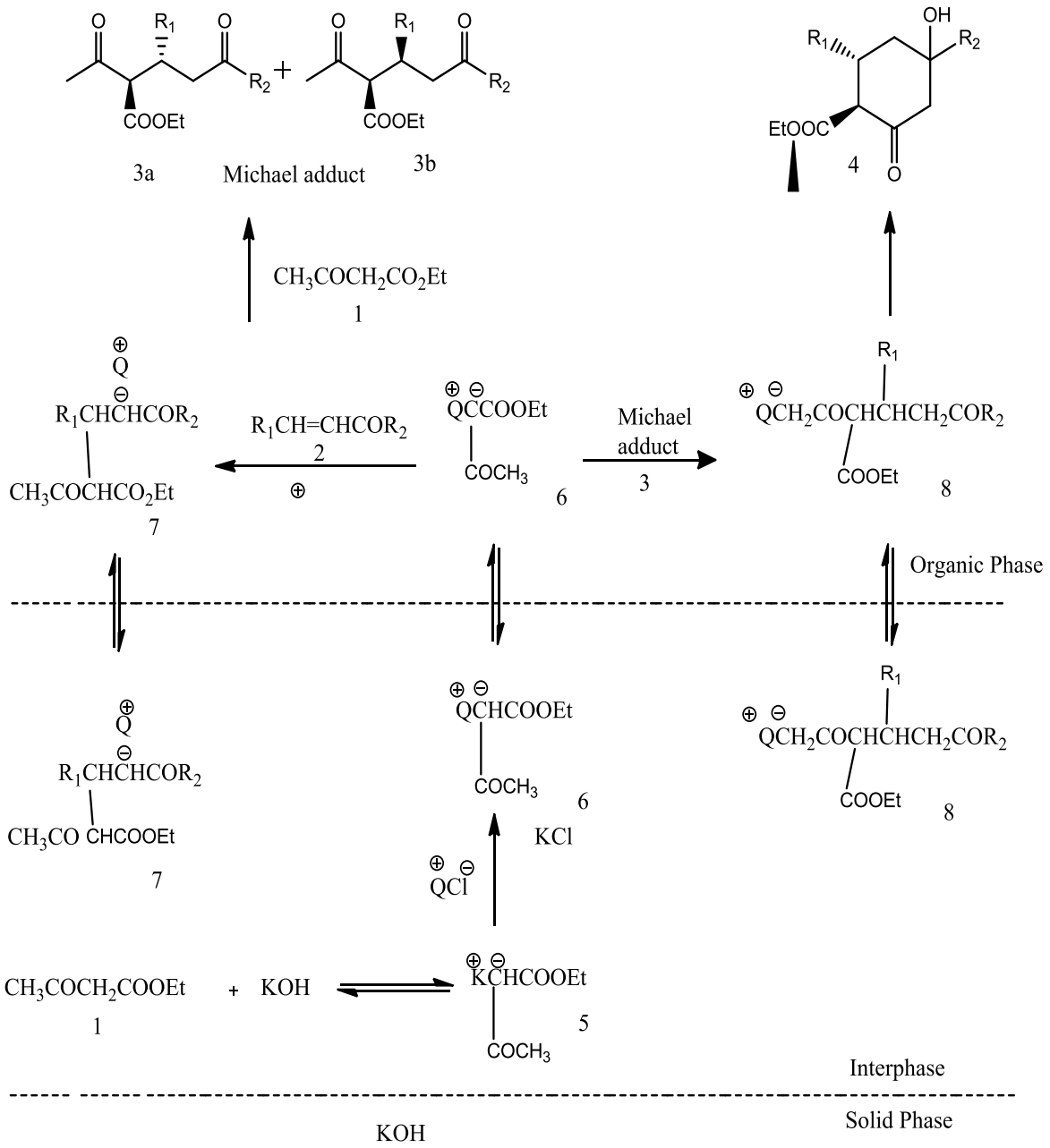
Entry	Ratio Donor: Acceptor	Reaction Time (Min)	Temperature (^{0}C)	Catalyst	Ratio 3/4	Yield (%)
1	1:1	15	60	TBAB	1:9	97%
2	1:1	15	RT	TBAB	1:1	15%
3	6:1	15	60	TBAB	1:3	75%
4	6:1	15	RT	TBAB	1:2	55%

RT = Room Temperature

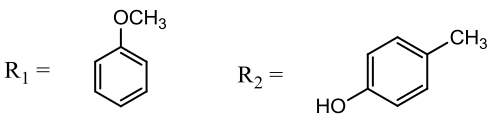
***Study of the effect of catalyst on the ration* 3/4**

It is observed that the cyclic product **4** was formed in more quantity as compared to Michael adduct **3** (Table 1), during the monitoring of the Michael addition of ethyl acetoacetate **1** to chalcone **2** in the presence of TBAB. Moreover, it was possible to observe that the proportion of **4** in the ratio of **3/4** depends on the temperature and ratio of donor/acceptor. In order to account for these results, each reaction condition was separately analyzed and explored. At 60^0C, the thermodynamically more stable cyclic product **4** is favored. Thus, a higher proportion of **4** in ratio **3/4** is obtained when the reaction is conducted under optimal condition (Table 1, entry 1). In this case, the parameter of ratio of donor/acceptor and temperature seems to act with synergism to produce **4** as the major product. The

analysis of data from **(Table 1)** indicates that the reaction was conducted with excess of donor (entry 3, 4), the proportion of cyclic product **4** in the ratio 3/4 was lower as compared to reaction using stoichiometric amount of donor/acceptor (entry 2). A reasonable explanation for these results is based on the competition between the donor 1 and Michael adducts **3** for reaction with the base. The excess of **1** in the reaction increases the formation, of enolate **6** which leads to Michael adduct **3 (Scheme 2).**



Scheme 2. Phase transfer catalysis reaction pathways



The products **3** and **4** are formed as follows: 1) The acid-base reaction of ethyl Acetoacetate 1 and hydroxyl ion from potassium hydroxide generates the ionic potassium salt **5** (K^+ enolate) by an equilibrium process. (2) The quaternary ammonium salt (Q^+Cl^-) stimulates an ionic exchange reaction which convert salt **5** into **6**, which is transferred to the organic phase; at the inter phase. (3) In the organic phase, the enolate **6** reacts with Chalcone **2** giving the Michael adduct enolate **7**. (4) The Michael adduct enolate **7** removes the acidic hydrogen from ethylacetoacetate **1** producing the Michael adduct **3** and forming again the enolate **6**; (5) In the organic phase, the ion pair **6** removes the acidic hydrogen from Michael adduct **3** leading to the enolate adduct **8** which undergoes the cyclization process leading to product **4**. This outcome suggests the formation of a transition state, which leads to cyclic product 4 **(Figure 1),** which involves the contribution of cation Q^+ and K^+.

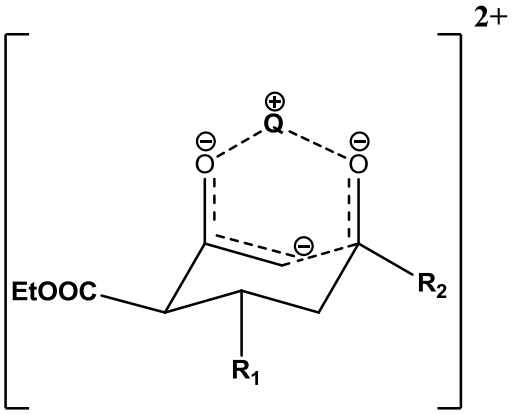


Figure 1. Transition state that leads to cyclic product **4**

The proposed transition state is the coordination of two oxygen atoms with the quaternary ammonium cation Q^+ or K^+ forming a stable 6- membered ring. It is the main feature of the transition state. Therefore, it is proposed that the chelation is more favorable with a small cation as K^+ as compared to a bulky one Q^+. It was hypnotized that increase in the rate of reaction is due to: i) Transference of enolate **6** from an interphase to an organic phase and ii) reaction of **6** with Chalcone **2**, culminating in an enhanced total rate of reaction **(Scheme 2)**.

Because tetra butyl ammonium bromide have 16 carbon atoms and can be considered as catalyst with a reasonable organophilicity and accessibility which promote an efficient transfer of the donor enolate **6** from the inter phase to organic phase. It seems reasonable to suggest that each butyl group attached to the nitrogen atom is properly in size to possess an ideal distance separating cation from anion as well as adequate positive charge density on this central atom ensuring a chelation to give transition state as illustrated in **(Figure 2).**

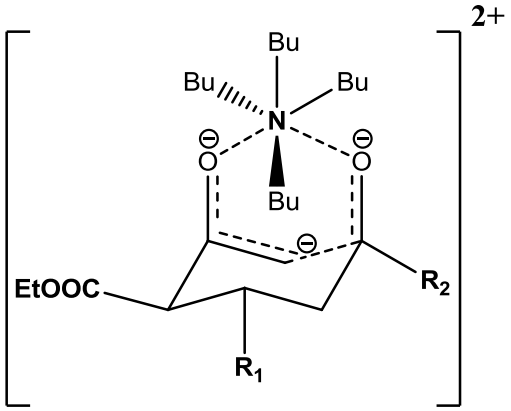


Figure 2. Transition state in the formation of product **4** using TBAB.

Experimental

All solvents were distilled prior to use. The homogenisity of the synthesized compounds was monitored by ascending thin layer chromatography (TLC) on silica gel- G (Merck) coated aluminium plates, visualized by iodine vapour. Developing solvents were n-Hexane-ethylacetate (7:3). Melting points were determined by open capillary method and are uncorrected. ^{1}HNMR and ^{13}CNMR spectra were recorded from $CDCl_3$ solution on a Brucker Avance II 400 (400 MHz) NMR Spectrometer. Chemical shifts are reported in ppm using TMS as an internal standard. IR spectra were obtained on a Shimadzu FTIR spectrophotometer using KBr discs.

General procedure for the Michael addition of ethyl acetoacetate 1 to chalcone 2

A mixture of ethyl acetoacetate (3.80 mmol), chalcone (3.80 mmol), potassium hydroxide (0.38 mmol) and tetra butyl ammonium bromide salt (0.38 mmol), was vigorously stirred by a mechanical stirrer at 60^0C or room temperature in reaction time that varied from 15 min to 4 hrs. After completion of reaction, the reaction mixture was diluted with chloroform (30 mL) and the organic extract was treated with water. The organic layer was separated out and dried over anhydrous sodium sulfate. After removal of solvent, under reduced pressure, the crude product was purified by column chromatography with hexane: acetone using varying polarities to yield products **3** and **4**.

(2R, 3R)-ethyl-2-acetyl-5-(2-hydroxy-5-methylphenyl)-3-(4-methoxyphenyl)-5-oxopentanoate (3)
IR (KBr) ν_{max}/cm^{-1}: 3465, 3110, 1730,1712, 1680, 1657, 1452, 1285, 748, 705; ^{1}H-NMR (400 MHz/ $CDCl_3$) major (3a): δ 1.13 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 3.41 (dd, *J* = 8.2, *J* = 12.2, 1H), 3.34 (dd, *J* = 8.4, *J* = 13.5, 1H), 3.91 (s, 3H, OCH_3), 4.10 (q, 2H, *J* = 8.1, CH_2), 6.41 (s, 1H), 6.80-7.65 (m, Ar-proton), 9.32 (s, 1H); ^{13}CNMR (400MHz/$CDCl_3$): δ 204.8, 193.9, 162.12, 169.38, 152.58, 133.5, 128.8, 113.4-133.01, 54.68, 77.86.

(1S,2R)-ethyl-4-hydroxy-4-(2-hydroxy-5-methylphenyl)-2-(4-methoxyphenyl)-oxocyclohexanecarboxylate (4)

mp. 135-140^{0}C; IR (KBr) ν_{max}/cm^{-1}: 3460, 3210, 1735, 1712, 1685, 1657, 1451, 1281, 745, 703; ^{1}H-NMR (400 MHz/ $CDCl_3$) major (3a): δ 1.12 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.90-3.94 (dd, 2H, *J* = 4.2, *J* = 12 CH_2), 3.62 (m, 1H), 3.65 (d, 1H, *J* = 4.2), 3.72 (d, 1H, *J* = 4.4), 3.91 (s, 3H, OCH_3), 4.01 (q, 2H, *J* = 8.1, CH_2), 6.4 (s, 1H), 6.81-7.68 (m, Ar-proton), 9.31 (s, 1H); ^{13}CNMR [400MHz/$CDCl_3$]: δ 198.9, 168.12, 164.38, 152.58, 113.4-133.01, 54.68, 77.86, cyclized Ca,Cb, Cc, Cd = 158.0, 152.5, 59.68, 43.14.

Conclusion

We have demonstrated Michael addition reaction of ethyl acetoacetate with chalcone via phase transfer catalysis TBAB under optimized solvent free conditions, after variation of the reaction parameters, to obtain products **3** and **4** in excellent yield. We have explained the annulation process based on the stability of a 6-membered cyclic transition state influenced by the structure of tertiary ammonium cation.

Acknowledgement

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