

Phase-transfer-catalyzed Darzen's condensation of chloroacetonitrile with cyclohexanone using aqueous sodium hydroxide and a new phase transfer catalyst

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Received 10 April 1999; received in revised form 24 July 1999; accepted 9 August 1999

Abstract

The kinetics of Darzen's condensation of chloroacetonitrile with cyclohexanone has been studied under phase transfer catalytic conditions using aqueous sodium hydroxide as the base and 2-benzylidene-*N,N,N',N',N',N'*-hexaethylpropane-1,3-diammonium dichloride as a new "multi-site" phase transfer catalyst (MPTC). The reactions were carried out at room temperature (29°C) under pseudo-first order conditions by keeping aqueous sodium hydroxide and cyclohexanone in excess and was monitored by GC. The effect of various experimental parameters on the rate of the reaction has been studied, and based on the results obtained, a suitable mechanism is proposed. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Multi-site phase transfer catalyst; Darzen's condensation; Chloroacetonitrile; Cyclohexanone

1. Introduction

Phase transfer catalysis (PTC) is a versatile, well-established synthetic technique, applied with several advantages to a number of organic biphasic reactions [1,2]. The advances of the same in the recent years have made a remarkable impact in organic syntheses and are being enormously employed to a multitude of organic transformations. "Single-site" phase transfer catalysts, such as quaternary phosphonium and ammonium salts, crown ethers, cryptands etc.,

have been used to carry out reactions between reactants, which exist in different phases. These catalysts were widely used in certain reactions viz. C-alkylation, O-alkylation, dichlorocarbene addition to double bonds, oxidation, reduction, etc. The important considerations in the selection of the catalyst are economy of scale and efficiency of the phase transfer catalysts specifically on the industrial-scale preparation of organic substrates. In order to cater to these needs, "multi-site" phase transfer catalysts (MPTC) have been developed. Idoux et al. [3] synthesized "multi-site" phosphonium PTCs as soluble and polymer-supported catalysts. The catalytic abilities of these MPTCs towards simple Sn₂ reactions and some weak nucleophile–elec-

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trophile SnAr reactions were also reported. The MPTCs offer the potential of providing greater PTC activity and, to effect, a particular synthetic transformation under mild conditions.

Darzen's condensation between α -halocarbanions and carbonyl compounds that leads to the formation of glycidic acid derivatives is a useful tool in organic synthesis. Generally, the α -halo carbanions are generated by the action of dry sodium alkoxides, amide, hydride or other such agents on α -halo esters, nitriles, ketones, etc., in strictly anhydrous organic solvent or liquid ammonia [4]. Reactions involving carbanions that were believed to require strict anhydrous conditions and strong basic agents can be performed in the presence of aqueous sodium hydroxide and quaternary ammonium catalyst. Jonczyk et al. [5] have successfully demonstrated the generation of halocyanomethyl anions and its condensation with carbonyl compounds which gave rise to the formation of glycidic nitriles. The use of crown ether [6] and quaternary ammonium salts [7,8] to catalyze Darzen's condensation with a wide variety of substrates has been documented.

Ohtomi et al. [9] reported the utility of octopus compounds as useful phase transfer catalysts for the synthesis of nitriles from the reaction of alkyl halide and sodium cyanide. They also reported [10] a convenient and efficient Darzen's condensation of ketones with chloroacetonitriles catalyzed by octopus compounds. Colonna et al. [11] reported the Darzen's reactions in an aqueous/organic two-phase system in the presence of chiral catalysts (–)-*N*-alkyl-*N*-methyl ephedrinium halides, supported or not on a polymeric matrix to give optically active α -, β -epoxy-sulphones and nitriles. They have also examined the influence of the asymmetric synthesis of both structural variations and the binding of the ephedrinium catalysts to a polymeric matrix.

We have earlier reported the synthesis [12] of a novel MPTC viz. 2-benzylidene *N,N,N,N',N',N'*-hexaethyl propane-1,3-diammonium dichloride (MPTC) and its utility in some

hydroxide-ion initiated reactions. A kinetic study of dichlorocarbene addition to styrene [13] and C-alkylation of phenylacetone with *n*-butyl bromide [14] using the new MPTC have also been reported. In this paper, we report a kinetic study of Darzen's condensation of chloroacetonitrile with cyclohexanone using the new water-soluble MPTC.

2. Experimental

2.1. Synthesis of 2-benzylidene-*N,N,N,N',N',N'*-hexaethyl propane-1,3-diammonium dichloride (MPTC)

A detailed procedure for the synthesis of MPTC is discussed elsewhere [12,13]. 1,1-Bis(chloromethyl)-2-phenylethene (2 g, 0.01 mol) was dissolved in dry acetonitrile (10 cm³) and transferred into a 150-cm³ three-necked round-bottomed flask. The solution was deaerated and triethylamine (20 cm³) dissolved in acetonitrile (10 cm³) was added to the solution. The resultant mixture gently refluxed for 5 h under inert atmosphere (N₂). To the cold reaction mixture, diethyl ether (20 cm³) was added and a precipitate was collected after 2 h. Then, the precipitated "multi-site" quaternary ammonium salt was filtered and washed repeatedly with ether (three times). The pure white, solid MPTC was stored in a CaCl₂ desiccator.

2.2. Kinetic measurements

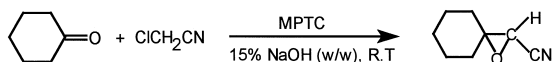
In a typical run, a 150-cm³ three-necked round-bottomed flask was charged with 15 cm³ cyclohexanone, 45 cm³, 15% w/w sodium hydroxide and 32 mg MPTC (0.25 mol% based on the amount of substrate). The mixture was placed in a thermostat at room temperature (29 ± 0.1°C) and stirred mechanically at 200 rpm for 10 min to condition the reaction contents. Chloroacetonitrile, 2 cm³, was added to the reaction mixture and stirring was increased to 400 rpm. Samples were collected from the organic layer

of the mixture at regular intervals of time and analyzed using GC (Varian 3700 Model), with flame ionization detector and using 5% SE-30, Chrom WHP 80/100, 2 m 1/8 in stainless steel column. The kinetics was followed by estimating the disappearance of chloroacetonitrile. The pseudo-first order rate constants were evaluated from the plots of $\log(a - x)$ vs. time.

3. Results and discussion

Darzen's condensation of chloroacetonitrile with cyclohexanone was investigated with emphasis on kinetic aspects using the newly synthesized MPTC (Scheme 1).

The kinetic experiments for the Darzen's condensation of chloroacetonitrile with cyclohexanone were conducted under biphasic conditions with excess of 15% (w/w) aqueous sodium hydroxide and cyclohexanone under pseudo-first order conditions. The reaction was studied at a stirring speed of 400 rpm, in the temperature range 29–44°C. The catalyst was conditioned with aqueous sodium hydroxide and cyclohexanone for 10 min before the reaction was started. Chloroacetonitrile was added to the reaction mixture and the samples were collected from the organic layer at regular intervals of time. The kinetics of Darzen's condensation of chloroacetonitrile with cyclohexanone was followed by the disappearance of chloroacetonitrile using gas chromatograph. The effect of various experimental parameters such as stirring speed, amount of catalyst, substrate concentration, sodium hydroxide concentration and temperature on the reaction rate constants were studied. Based on the experimental results obtained, a suitable mechanism was proposed.



Scheme 1. Darzen's condensation of chloroacetonitrile with cyclohexanone under PTC conditions.

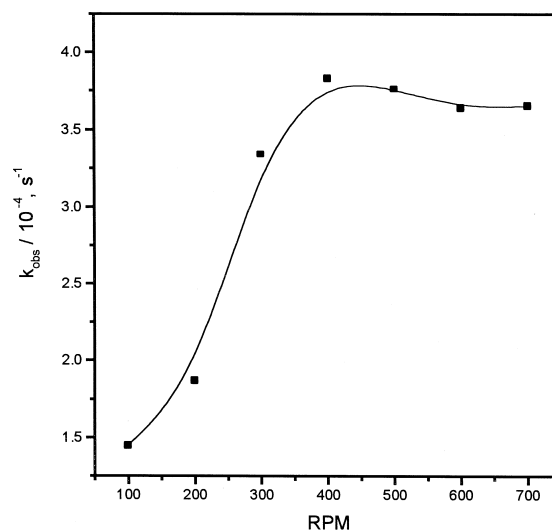


Fig. 1. Dependence of k_{obs} on stirring speed.

3.1. Effect of varying stirring speeds

The effect of varying stirring on the rate of Darzen's condensation of chloroacetonitrile with cyclohexanone was studied in the range 100–700 rpm. From the plots of $\log(a - x)$ vs. time, the pseudo-first order rate constants were evaluated. The experimental results show that the observed reaction rate constants increase linearly with the increase of stirring rate from 100 to 400 rpm. Further increasing the agitation speed does not increase the reaction rate (Fig. 1). The reaction kinetics is controlled by the chemical reaction in the organic phase for stirring rates greater than 400 rpm.

In the kinetic study of oxidation of benzyl alcohol by hypochlorite ion under PTC condition, a similar trend has been reported by Do and Chou [15]. Further, in our study, at stirring level of 400 rpm, anion exchange equilibrium is very fast relative to the organic displacement reaction, and the substrate consumption rate becomes independent of the stirring speed. Below 400 rpm, the requirement for sufficiently rapid mass transfer of the reaction anion is not met and diffusion controlled kinetics is observed. Hence, the constancy of the reaction rate con-

stants on the stirring speed above 400 rpm in the present study is indicative of the extraction mechanism.

3.2. Effect of varying substrate amounts

Kinetic experiments were performed by varying the amount of chloroacetonitrile from 1 (15.84 mmol) to 5 ml (79.21 mmol) and keeping cyclohexanone and 15% w/w NaOH in excess. Pseudo-first-order rate constants are evaluated from the linear plots of $\log(a-x)$ vs. time. The observed reaction rate constants increase as the amount of chloroacetonitrile increases. The results suggest that the substrate concentration in the organic phase is important and is indicative of extraction mechanism. The molar ratios of the substrate to catalyst are given in Table 1. The observed rate constants increase as the substrate:catalyst ratio increases.

3.3. Effect of varying catalyst amounts

The amount of catalyst was varied from 16 to 128 mg (0.125 to 1.00 mol% based on the substrate amount) and the experiments were conducted using 15% w/w aqueous sodium hydroxide solution. The rate constants are calculated from the plots of $\log(a-x)$ vs. time (Fig. 2). The rate constants are linearly dependent on the amount of catalyst used in each reaction. Control experiments for Darzen's condensation reaction in the absence of the catalyst under specified conditions proceed minimally with low conversion. Jonczyk et al. [8] have also reported similar observations in a Darzen's condensation

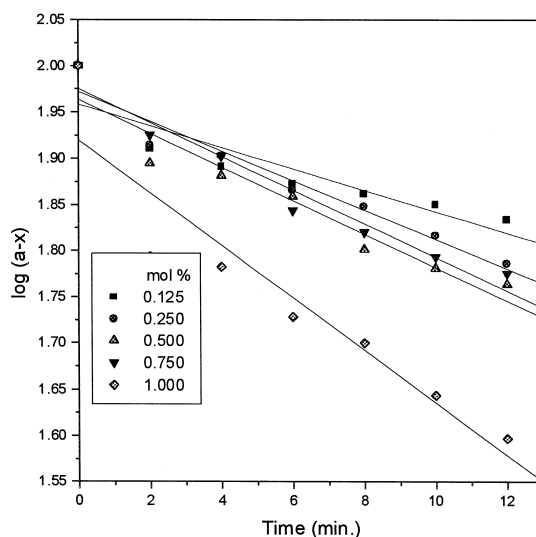


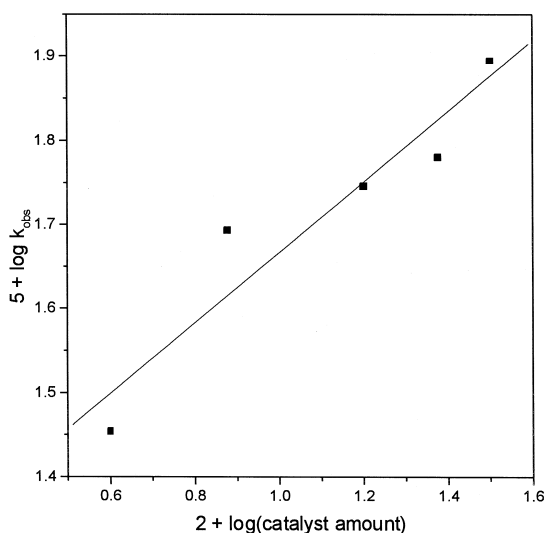
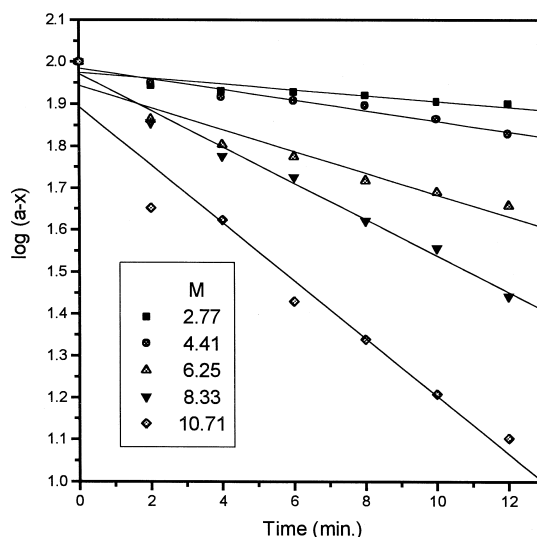
Fig. 2. Effect of catalyst amount variation.

of α -chlorophenyl acetonitrile with benzaldehyde under PTC conditions. Upon addition of the catalyst, product was obtained in good yield. In the study of Br–I exchange reaction of 1-bromo octane, Molinari et al. [16] observed a similar dependence of pseudo-first order rate constants on the amount of heterogenized phosphonium groups. Wang and Yang [17] claimed similar observation in the kinetic study of the synthesis of 4-bromophenyl allyl ether under PTC conditions. A bi-logarithmic plot of the reaction rate constant vs. the concentrations of catalyst gave a straight line having slope 0.4 (Fig. 3). The increased rates are due to the increase in the number of active sites. The linear dependence of reaction rate on catalyst concentration shows that the reaction is believed to proceed through extraction mechanism. In the study [18] of dehydrobromination of phenethyl bromide in the presence of tetrabutylammonium bromide, zero order kinetics with respect to the catalyst was observed.

The dependence of the reaction rate on catalyst concentration was investigated for the ethylation of phenyl acetonitrile by Chiellini et al. [19]. The influence of various catalysts on reaction rate and more specifically their structure

Table 1
Effect of variation of substrate amount

Entry	Substrate amount (mmol)	Substrate: catalyst	$k_{\text{obs}}/10^{-4}$ (s^{-1})
A	15.84	199.72	3.91
B	31.68	399.45	4.30
C	47.52	599.16	4.64
D	63.36	798.89	5.32
E	79.21	998.74	9.01

Fig. 3. Effect of catalyst amount on k_{obs} .Fig. 4. Effect of $[\text{NaOH}]$ variation.

was studied by Halpern et al. [20], taking deoxybenzoin and dimethyl sulphate in the presence of aqueous sodium hydroxide.

3.4. Effect of varying sodium hydroxide concentrations

The rate of Darzen's condensation of chloroacetonitrile with cyclohexanone strongly depends on the strength of the sodium hydroxide. Kinetic experiments were carried out, employing 2.77–10.71 M aqueous sodium hydroxide. Pseudo-first order rate constants are evaluated from the plot of $\log(a-x)$ vs. time (Fig. 4, Table 2). The reaction rate constants are strongly influenced by the concentrations of aqueous NaOH. The observed rate constants tremendously increased with increase in basicity of hydroxide ion. In the study of phenoxide allylation in a phase transfer catalytic system, Wu and Lai [21] observed that the extraction of phenol (using PTC) is more effective if the base concentration in the aqueous alkaline solution is higher. In a kinetic study [17] of the synthesis of 4-bromophenyl allyl ether by PTC, potassium hydroxide is used as a base rather than sodium hydroxide, as KOH enhances the reaction rate.

In this case, the reaction rate initially increases and then decreases gradually when the concentration of KOH increases, due to the catalytic decomposition at higher KOH concentration. In our present study, the rate constant increases with increase of base concentration. A bi-logarithmic plot of the reaction rate against sodium hydroxide concentrations gives a straight line having a slope of 2.0 (Fig. 5). In our study [14] of C-alkylation of phenylacetone using *n*-butyl bromide using MPTC, the kinetic order with respect to aqueous NaOH concentration was found to be 2.0. In the case of isomerisation of allyl benzene [22], the effective kinetic order with respect to aqueous NaOH concentration was reported to be 5.0, where extraction mechanism is operative.

Table 2
Effect of variation of $[\text{NaOH}]$

Entry	$[\text{NaOH}]$ (M)	$k_{\text{obs}}/10^{-4}$ (s^{-1})
A	2.77	1.63
B	4.41	4.20
C	6.25	7.87
D	8.33	15.50
E	10.71	22.38

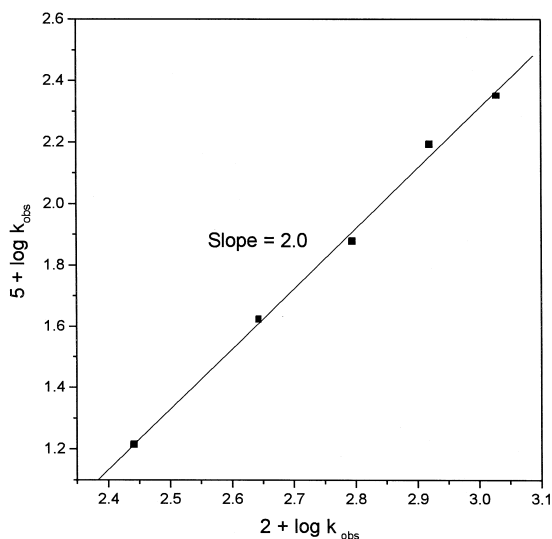


Fig. 5. Effect of [NaOH] on k_{obs} .

3.5. Influence of temperature

The effect of varying temperature on the rate of Darzen's condensation of chloroacetonitrile with cyclohexanone was studied in the temperature range 29–44°C. The kinetic profile of the reaction is obtained by plotting $\log(a-x)$ vs. time (Fig. 6). The rate constants increase with increase in temperature. The energy of activation is calculated from Arrhenius plot, $E_a = 4.9$ kcal mol⁻¹. The other thermodynamic parameters, ΔS^\ddagger , ΔG^\ddagger , and ΔH^\ddagger , were evaluated and were found to be -56.0 cal K⁻¹ mol⁻¹, 23.0 kcal mol⁻¹, and 6.5 kcal mol⁻¹, respectively.

The activation energy for the ethylation of pyrrolidin-2-one under PTC conditions was reported to be 12.4 kcal mol⁻¹ and for this, an interfacial mechanism was proposed [23]. In a comprehensive study [17] of the synthesis of 4-bromophenyl allyl ether, it has been observed that the conversion of allyl bromide increases with increase of temperature and the E_a value was found to be 12.50 kcal mol⁻¹. Do and Chou [15] observed a favorable effect on the extraction of tetrabutyl ammonium hypochlorite ion pair from the aqueous phase into the organic phase on increasing the temperature in the study

of the oxidation of benzyl alcohol by hypochlorite ion under PTC conditions.

The dehydrobromination of phenethyl bromide [18] proceeds more rapidly in the presence of tetraoctyl ammonium bromide. But the zero order kinetics in the presence of catalyst and low energy of activation (8 kcal mol⁻¹) suggested a hydroxide ion extraction mechanism governed by diffusion control. The E_a of intraparticle diffusion of anion exchange resins [24] in aqueous solution is of the order of 5–10 kcal mol⁻¹. Lee et al. [25] studied the effect of temperature on the reaction rate for the formation of phenyl benzoate in the presence of TBAHSO₄ as PTC and without PTC. The activation energies calculated from corresponding Arrhenius plots are, respectively, 8.12 kcal mol⁻¹ with TBAHSO₄ as PTC and 3.55 kcal mol⁻¹ without PTC. In this case, an extraction mechanism has been proposed.

The observed energy of activation for the Darzen's condensation of chloroacetonitrile with cyclohexanone is 4.9 kcal mol⁻¹ and hence, we propose hydroxide ion extraction mechanism for the reaction under study, which is governed by diffusion control.

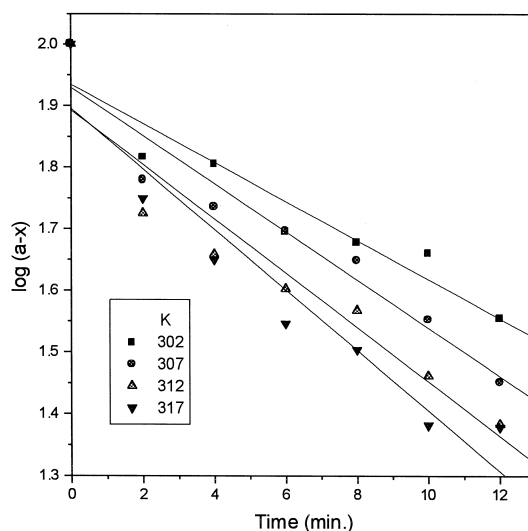


Fig. 6. Effect of temperature variation.

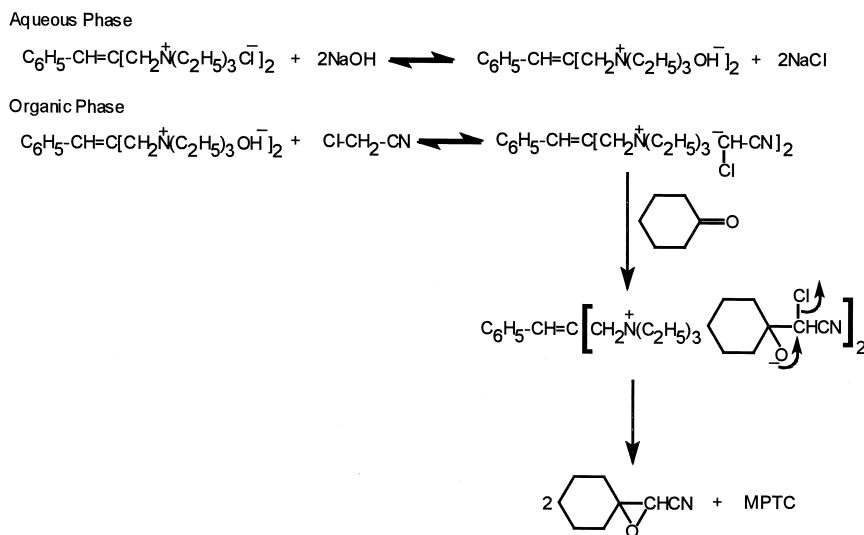
3.6. Mechanism

The Darzen's condensation is a two-step reaction, viz. deprotonation of an active C–H group bearing a chlorine atom (activation by carbonyl, sulphone, benzyl position, nitrile, etc.) and followed by the addition of the carbanion to a carbonyl, then intramolecular attack of the tetrahedral intermediate O[−] anion to displace the chloride and form an oxirane.

A landmark paper by Rabinovitz et al. [26] made a clear distinction in understanding the various mechanisms operative in PTC/OH[−] systems. In determining the valid PTC/OH[−] mechanism of a reaction, one may conduct a simple experiment. Two reaction vessels are set up next to each other under identical conditions; one is charged with an organophillic catalyst (namely tetraoctyl ammonium bromide or chloride) and the other is charged with an accessible (electrostatically available) catalyst, such as butyltriethyl ammonium bromide or chloride. If the organophillic catalyst induces higher reactivity, then the extraction mechanism may be considered valid. One would expect to observe first order kinetics with respect to the substrate and the catalyst if the extraction mechanism is not

diffusion-controlled and is chemically controlled. The interfacial mechanism may be considered valid if the electrostatically accessible catalyst induces higher reactivity. To differentiate between the two mechanisms, an additional run at significantly higher agitation speed is required, since the interfacial mechanism is strongly dependent on stirring speed (in rpm), whereas the chemically controlled extraction mechanism is independent of the stirring speed above a certain value. To distinguish between the diffusion-controlled mechanism and other PTC/OH[−] mechanisms, the kinetic order and the energy of activation of the reaction become valid. An energy of activation above 10 kcal mol^{−1} suggests chemical control (isomerisation [22] — 17 kcal mol^{−1}; alkylation [19] — 20 kcal mol^{−1}; esterification [27] — 14 kcal mol^{−1}). Diffusion-controlled reactions had an energy of activation below 10 kcal mol^{−1} (elimination [18] — 8 kcal mol^{−1}).

From the observed experimental results, the dependency of the rate constants on the stirring speed up to 400 rpm, concentration of the catalyst, base, temperature and a lower E_a value are consistent with a hydroxide ion extraction mechanism.



Scheme 2. Mechanism for the Darzen's condensation of chloroacetonitrile with cyclohexanone under PTC conditions.

The mechanism for the Darzen's condensation of chloroacetonitrile with cyclohexanone may be written as shown in Scheme 2.

Acknowledgements

One of the authors (J.P.J.) is thankful to Dr. Marc E. Halpern (PTC Organics, USA) for his constant encouragement. The financial assistance provided by CSIR, New Delhi, is gratefully acknowledged.

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