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Ultrasound assisted synthesis of *N*-aryl indole under multi-site phase-transfer catalyst: A kinetic study

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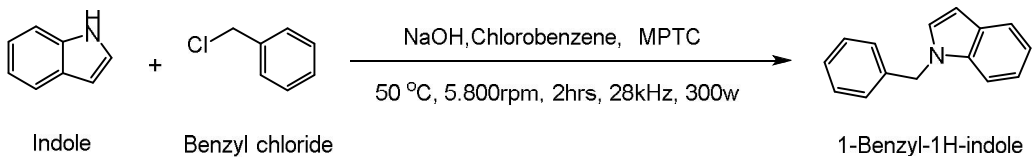
ABSTRACT

The ultrasound assisted preparation of 1-benzyl-1-indole (arylation) from the reaction of benzyl chloride (BC) and indole was carried out successfully using solid sodium hydroxide and catalyzed by multi-site phase-transfer catalyst (MPTC) viz., 1,4-benzyl-1,4-diazoniab-icyclo[2.2.2]octanium dichloride in a solid–liquid reaction condition (SL-PTC). Water was introduced in a trace quantity to the reaction system to avoid a serious hydration of active intermediate. The potentiality of the multi–site phase-transfer catalyst was demonstrated by following the kinetics arylation of indole under pseudo–first order conditions by employing aqueous sodium hydroxide and indole in excess. The reaction was monitored by gas Chromatography. The synthesized MPTC and 1-benzyl-1-indole were characterized by ^{1}H NMR and ^{13}C NMR. The reaction is greatly enhanced in the solid–liquid system, catalyzed by multi-site quaternary ammonium salt (MPTC) and ultrasound irradiation (28 kHz, 300W) in a batch reactor.

GRAPHICAL ABSTRACT



1. Introduction

As the chemical reactants reside in immiscible phases, phase transfer catalysts have the ability to carry out the heterogeneo-us reactions by one of the reactants penetrating from its normal phase (generally aqueous phase) to the organic phase where the reaction takes place, giving a high conversion and selectivity for the desired product under mild reaction conditions.[1] The quaternary onium salts as effective catalysts for enhancing the two-phase reaction occupy a unique niche in organic synthesis and can be regarded as commercially matured discipline with over six hundred applications covering a wide spectrum of industries such as pharmaceut-icals, agrochemicals, dyes, perfumes, flavors, specialty polymers, pollution control, etc.[2–7] As the application of phase-transfer catalysts (PTC) grows, much effort was placed on the development of phase-transfer catalysts with higher catalytic efficiency. To this end, researchers have developed ''multi-site''phase-transfer catalysts (MPTC) for much higher activity than normal phase-transfer catalysts.

Recently, the catalytic behavior of multi-site phase-transfer catalysts have attracted much attention, due to the fact that multiple molecules of the aqueous reactant can be carried into the organic phase once in a reaction cycle, the catalytic efficiency is enhanced.[8–12] Currently, a new analytical and process experimental techniques which are environmental benign techniques viz., ultrasound and microwave irradiation have become immensely popular in promoting various organic reactions.[13–17] Ultrasound irradiation is a transmission of a sound wave through a medium and is regarded as a form of energy enhancing the rate of the reaction due to mass transfer and effective mixing.[18–20] The effect of ultrasonic energies in organic syntheses (homogeneous and heterogeneous reactions) has been boosted in recent years.[21–27] Sonication of multiphase systems accelerates the reaction by ensuring a better contact between the different phases.[28-29] Further, ultrasound irradiation also increases the reaction rate and avoid the use of high reaction temperatures.[30] Nowadays, the environmental benign technology is combined with reaction conditions.[31–33]

Ultrasonic cavitations create a very extreme environment, i.e. extremely high local temperature and pressure, as well as heating and cooling rates for chemical reaction. Under ultrasonic irradiation, the liquid jet could be favorable to be employed for removing the surface-deposited side-product in SLPTC and increasing the formation of the catalytic intermediate. Ultrasound irradiation combined with solid–liquid PTC has revealed significant improvement in the react-ion rate. In PTC reaction system, the overall reaction rate can

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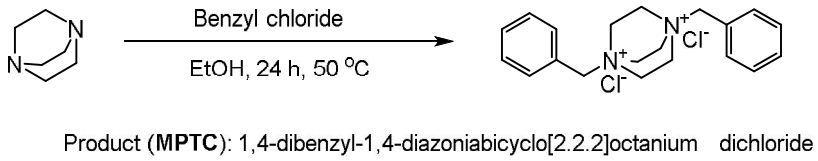
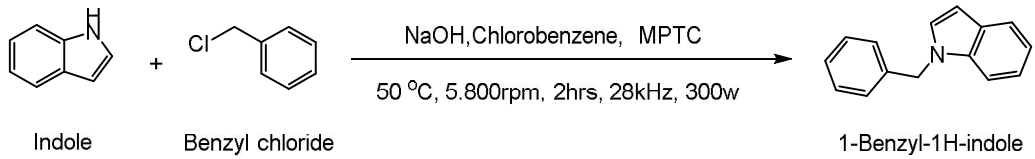
also be effectively raised with multi-site phase-transfer catalyst.[34-35] But the application of ultrasound in SLPTC especially catalyzed by multi-site phase-transfer catalyst was rarely reported. In this work we synthesized the mult-site phase-transfer catalyst (MPTC) viz., 1,4-dibenzyl-1,4-diazo-niabicyclo[2.2.2]octanium dichloride (**Scheme 1**) used as a superior catalyst for the synthesis of 1-benzyl-1-indole (**Scheme 2**) from sodium salt of indole with benzyl chloride (BC) under heterogeneous solid–liquid condition. Since the kinetic study of arylation of indole using benzyl chloride under controlled MPTC reaction conditions will be interesting, we followed the kinetic study using a synthesized multi-site phase-transfer catalyst under ultrasonic condition (28 kHz; 300W).



Product (**MPTC**): 1,4-dibenzyl-1,4-diazoniabicyclo[2.2.2]octanium dichloride

Scheme 1. Synthesis of MPTC.



Scheme 2. Synthesis of 1-benzyl-1-indole.

2. Results and discussion

2.1. Effect of stirring speed

To determine the influences of mass-transfer, the stirring speed was varied from 0 to 500 rpm along with ultrasound irradiation (28 kHz, 300W) using 1,4-dibenzyl-1,4-diazoniabicyclo [2.2.2]octane dichloride (MPTC). In principle, the heterogeneous reaction is dependent on the agitation speed. It can be seen from the (**Table 1**) that the dramatic increase in the reaction rate is produced with a raise in the stirring from 0 to 400 rpm. The possible reason is the interfacial area per unit volume of dispersion increases linearly as the agitation speeds increase.[36]

Table 1. Effect of stirring speed

Entry	Stirring speed (rpm)	k_{app} x 10^{-3}, min^{-1}
1	0	4.32
2	100	11.76
3	200	15.59
4	300	17.38
5	400	19.54
6	500	20.15
7	600	20.43

In fact, the reaction proceeds by accompanying the dissolving ind-N^-Na^+ in chlorobenzene. The dissolving rate of ind-N^-Na^+ in chloro-benzene is highly influenced by the agitation speed. In general, a high concentration of ind-N^-Na^+ dissolving in organic solvent is obtained at a high agitation speed. Therefore, the conversion of benzyl chloride was increased with the increase in the agitation speed up to 400 rpm. For agitation speed higher than 400 rpm, the conversion is not at all influenced by the agitation speed. This verifies that the reaction of ind-N^-Na^+ and benzyl chloride was carried out in a homogeneous solution, i.e. ind-N^-Na^+ first dissolves gradually in chlorobenzene in the presence of MPTC to form Q^{2+}(ind-N^-Na^+) at the inter-phase.

Then, the formed intermediate Q^{2+} (ind-N^-Na^+) reacted with benzyl chloride to produce 1-benzyl-1-indole in the organic phase. Therefore, the agitation speed was set at 400 rpm for studying the reaction phenomena from which the resistance of mass-transfer stays at a constant value. When the reaction was carried out in conventional method, the observed k_{app} value (k_{app} = 5.5 x 10^{-3}, min^{-1}) almost four fold lesser than in the presence of sonication (40 kHz, 300W) and stirring (k_{app} = 19.63 x 10^3, min^{-1}). It is clear from (**Table 1**) that the k_{app} value for the sonication only (without stirring, 0 rpm) is 4.38 x 10^3, min^{-1}. The k_{app} values indicate that the mechanical effects brought up by the use of low frequency ultrasounds are responsible of the enhancement of the kinetics by harsh mixing, enhancement of mass transfer, especially in solid-liquid systems, high erosion of the solid particles occurs and the surface area between the two phase is decreased. Ultrasound decreases the surface area between the two layers.[37]

2.2. Effect of Ultrasonic Power

Sonication was found to increase the rate of the reaction of solid–liquid phase-transfer catalysts (SL-PTC). Ultrasound

influences intense local conditions generated through cavitation bubble dynamics such as the, disappearance, formation and nucleation and of vapour or gas bubbles in its field.[38] In this reaction, the enhancement of mass transfer is mainly due to the supporting mechanical effects i.e., agitation and ultrasound. The presence of ultrasound in SL-PTC system results the cavitational collapse near the solid–liquid interface that disrupts the interface and impels converts of one reactive mass into the other, forming fine emulsion thereafter proceeds to a dramatic enhancement in the interfacial contact area. . It has been reported that a combination of PTC and ultrasound was often better than either of the two techniques alone. In recently, few works are reported that multi-site phase-transfer catalyst (MPTC) combined with ultrasound shows the highest potential to increase the rate of the reaction or conversion.[39]

To study the effect of ultrasound frequency, two different ultrasonic frequencies (28 kHz, 40 kHz) are used, having the same output power of 300W. The reaction is also carried out without ultrasound (conventional method). The mass-transfer resistant plays an important role in interfacial reaction, although the use of ultrasound increases the mixing of the two phases and enhances the mass-transfer.[40-41] The kinetic profile of the reaction is obtained by plottin–ln (1-X) against time. In our experimental condition, without ultrasonic irradiation (silent condition) the k_{app} values is 10.32 x10^3, min^{-1} but in the presence of ultrasonic condition the k_{app} values are 19.54 x 10^3, min^{-1} and 26.59 x 10^3, min^{-1} for 28 kHz (300W) and 40 kHz (300W), respectively (**Table 2**). Hence, the overall k_{app} value was increased by increasing the ultrasonic frequency in the order of 0 kHz (conventional method) <28 kHz (300W) <40 kHz (300W) for our system. Similar trend was observed by Entezari et al.[42-43]

Table 2. Effect of Ultrasonic

Entry	Ultrasonic frequency (300w)	k_{app} x 10^{-3}, min^{-1}
1	0	10.32
2	28	19.54
3	40	26.59

2.3. Effect of the amount of prepared MPTC

The influence of the amount of MPTC (viz., 1,4-dibenzyl-1,4-diazoniabicyclo[2.2.2]octanium dichloride) on the arylation of indole has been studied by varying amount of MPTC from 1 mol% to 3 mol% under ultrasound irradiation (28 kHz, 300 W) keeping other experimental parameters constant. As shown in (**Fig.1**), the rate of conversion is increased with increasing in the amount of MPTC along with ultrasound irradiation (40 kHz, 300W). The increase in the k_{app} value is attributed to the synergic effect of ultrasound, i.e. induce the surface area, change the size, and morphology of phase-transfer catalyst (MPTC). The reaction rate or conversion is increased with increasing the usage of MPTC up to 3 mol%, after that there is no remarkable increase in conversion even increasing the catalyst amount.

It revealed that when more catalyst resulted in much faster initial reaction more inorganic salt produced and deposited on the particle surface, hence reducing the contact of the catalyst and the solid reactant, and hence the reaction rate was quickly diminished and terminated in the late reaction period (>30 min) with slight deviation to pseudo-first-order kinetics. Therefore, all the further experim-ents were done at 3 mol% of catalyst concentration.

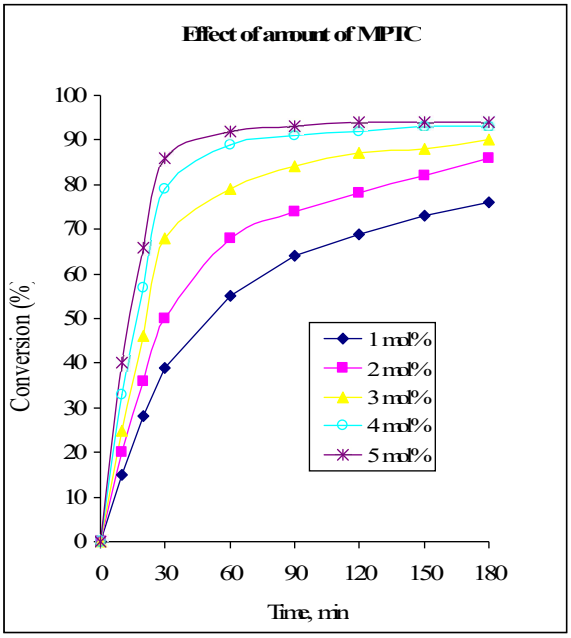


Fig 1. Effect amount of MPTC.

2.3. Effect of the amount of prepared MPTC

For the temperature effect, the temperature is only varied from 40 to 80 °C keeping other operating conditions constant, on the reaction of indole with benzyl chloride. The kinetic profile of the reaction is obtained by plotting -ln (1-X) versus time. It is obvious that the reactivity is increased with an increase in the temperature along with ultrasonic effect. The reason is that the number of reactant molecules which possess higher activated energy at a higher temperature and thus the ultrasonic wave easily passes through the reactor. The other point is that the collision of the reactants at higher temperature is also increased. Hence, the apparent rate constant is increased at higher temperature. Arrhenius plots were made in (**Fig. 2**) of –ln k_{app} against 1/T to get activation energy of 53.71 $kJ.mol^{-1}$. This higher activation energy demonstrates that this ultrasound assisted solid-liquid reaction with multi-site phase-transfer catalyst (MPTC) was kinetically controlled and the mass-transfer resistance between phases was unimportant. This is also indicative of the interfacial mechanism. Hence, we proposed an interfacial mechanism for our present study.[44]

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2.5. Effect of Organic solvents

The influence of various organic solvents on the rate of arylation of indole was followed under otherwise reaction conditions. The polarity of organic solvent affects the dissolution of solid reactant anion in organic solvent. With adding 2 mL of water, the more polar solvent induced the higher activity of phase-transfer catalyst, because a higher content of ($Q^{2+}N^-$) was acquired. From the plot of –ln (1-X) against time, the k_{app} values are obtained. It is clear from the (Table 3) chlorobenzene possesses a higher k_{app} value among the five organic solvents used.

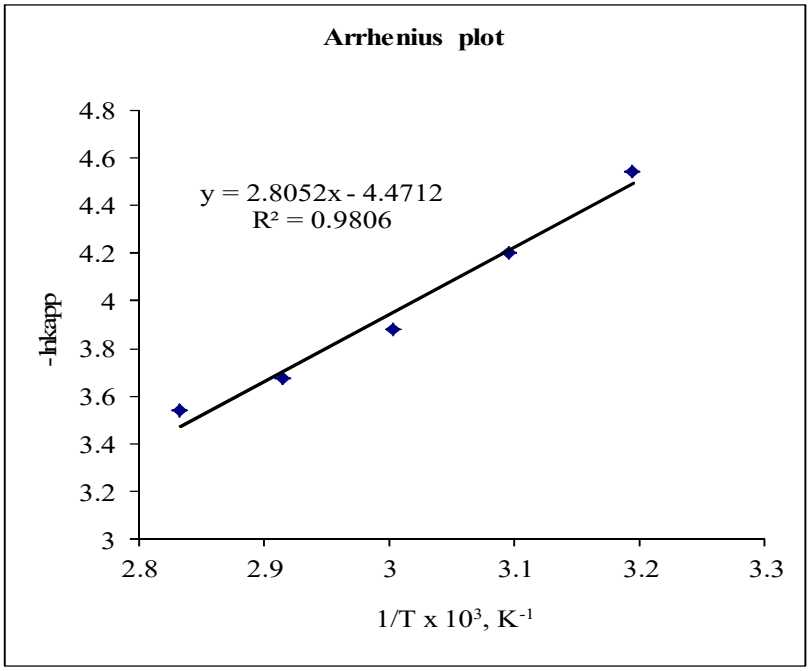

Fig 2. Arrhenius plot.

Table 3. Effect organic solvents.

Entry	Solvent	Dielectric constant	k_{app} x 10^{-3}, min^{-1}
1	Chlorobenzene	5.6	19.54
2	Anisole	4.3	15.80
3	Toluene	2.4	11.23
4	Hexane	2.2	8.50
5	Cyclohexane	2	7.73

2.6. Effect of MPTC and single-site phase-transfer catalysts

Quaternary ammonium salts are generally used as phase-transfer catalysts to promote reaction rate. Several phase-transfer catalysts were employed in addition with MPTC to evaluate their efficacy in the etherification of indole with benzyl chloride at 50^0 C and 400 rpm under ultrasonic condition (28 kHz, 300W). Along with MPTC, The used other six different phase-transfer catalysts were tetrabutyl-ammonium bromide (TBAB), tetrabutylammonium chloride (TBAC), tetrabutylammonium iodide (TBAI), tetrahexyl-ammonium bromide (THAB), tricaprylmethylammonium chloride (Aliquat 336) and tetraoctylammonium bromide (TOAB). Table 4 depicts the apparent rate constants for these seven catalysts. Among these, MPTC shows higher reactivity due to it possess two active sites therefore, the conversion is as fast as compared with other single site PTC's.[37-41]

The greater efficiency of the MPTC is attributed to the higher lipophilic character of the cation (Q^{2+}) supplied by the MPTC catalyst, leading to the formation of an ion-pair ($Q^{2+}N^-$). The ion-pairs are able to enter the organic media in which the displacement reaction takes place. In general, a more oleophilic cation is more effective to transfer anions into the organic phase. Therefore, the order of catalytic reactivity are MPTC > TOAB > THAB > TBAI > TBAB and Aliquat 336 >

TBAC. The accessibility of the positive charge of Aliquat 336, due to the short methyl group, results in a tight ion-pair with the indole anion which in turn reduces the SN^2 reactivity. In addition, the role of counter anion is also important. Comparing the results for TBAB, TBAC and TBAI, the order of the reactivity of these anions is $I^- > Br^- > Cl^-$. Since softer and more oleophilic anions are more effective than harder and less oleophilic anions, the order of catalytic reactivity is TBAI > TBAB> TBAC.

Table 4. Effect of phase transfer catalyst

Entry	Phase transfer catalyst	k_{app} x 10^{-3}, min^{-1}
1	MPTC	19.54
2	TOAB	14.98
3	THAB	13.57
4	TBAI	10.84
5	TBAB	9.12
6	Aliquat-336	7.48
7	TEAC	5.99

2.7. Effect of various sodium hydroxide concentrations

The rate of arylation of indole strongly depends on the strength of the sodium hydroxide. Kinetic experiments were carried out by employing 5 to 20g of NaOH (keeping 2mL water constant) under otherwise similar reaction conditions. The kinetic profile of the reaction is obtained by k_{app} against amount concentration of NaOH. The k_{app} value or conversion tremendously increased with increasing in basicity of OH^- ion (**Fig. 3**). It suggests that the hydroxide ions which are less solvated by water molecules and there by the k_{app} value or conversion is increased.[45]

The reaction rate also increases with the addition of trace water as in other SL–PTC reactions. Because, the amount of the available NaOH increases, resulting in the generation of much more anions [ind-N^-]. The water has a subtle influence on the basicity of the OH^- and the hydration of the ion-pair.

2.8. Effect of water

In solid–liquid system, the addition of small amount of water can be useful in forming the catalytic intermediate for conducting intrinsic reactions. The effect of water on this SLPTC was explored using under 400 rpm and ultrasonic irradiation (28 kHz/300 W), (**Fig. 4**) is the plot of conversion versus volume of water (mL) for different amounts of water added, showing that pseudo-first-order kinetic equation can be successfully used to describe the ultrasound assisted-SLPTC system.

Without adding water, only 40% of product yield was obtained in 120 minute of reaction; but merely with 2mL of water in the system, the product yield largely increased to 90.3%. Continuing to increase the quantity of water, the reaction rate was gradually reduced. When the amount of water was added to 15 mL, the solid–liquid system became a liquid–liquid type, and the product yield greatly decreased to 65%, much lower than that in SLPTC. The increase of reaction rate with small amount of water was mainly due to water solubilizing a small part of solid reactant to increase the production in the inter-phase, thus enhancing the intrinsic reaction rate.

When more water was added, the effective concentration of in the inter-phase would be decreased and the reaction rate was reduced. In the absence of water, the reaction rate of solid reactant and MPTC in the organic phase was slow, resulting in small product yield 40% after 180 min of reaction. With only 2 mL of water, the formation of ($Q^{2+}N^-$) greatly increased and concentrated in the inter-phase and leads to the bulk organic phase where the intrinsic reaction take place.

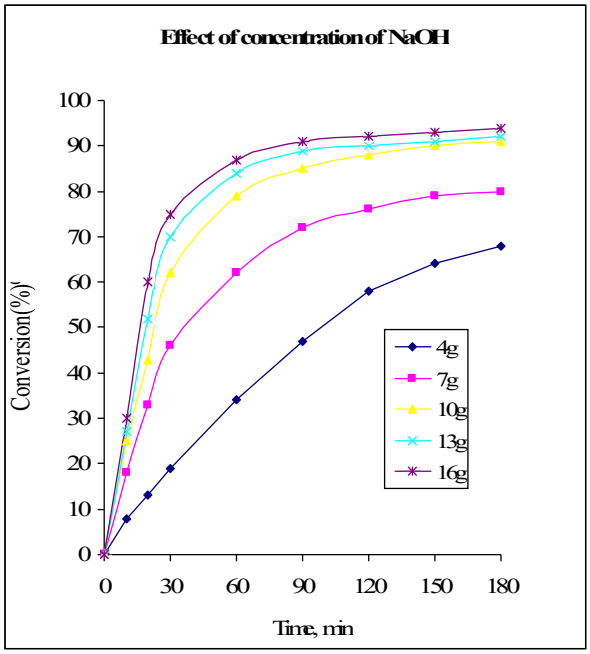

Fig 3. Effect of concentration NaOH.

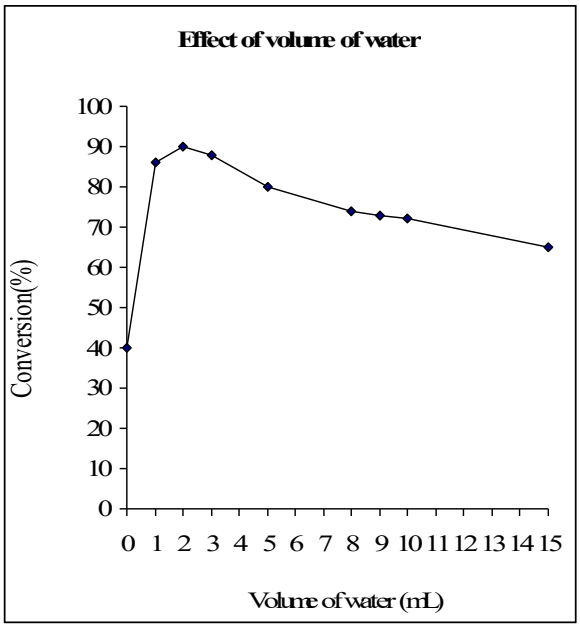

Fig 4. Effect of water valume.

3. Conclusion

From the detailed kinetic study, the following conclusions are stated here,

- The was synthesized 1-benzyl-1-indole successfully from indole and benzyl chloride under ultrasonic-MPTC condition.
- The apparent reaction rates were observed to obey the pseudo-first order kinetics.
- The ultrasonic condition resulted in shorter reaction time, bis-selectivity and high yield.
- The suitable reaction mechanism was proposed from the experimental results.
- The apparent rate constants are increased with increase in the concentration of MPTC and NaOH, ultrasonic frequency, stirring speed and temperature.
- However it decreases with increase in the volume of water.
- Energy of activation was calculated from the Arrhenius plot. The combination of ultrasound and MPTC resulted in better efficacy as compared to the individual operations.

4. Experimental

4.1. Materials

All the reagents, including, indole, DABCO (1,4-diazabicyclo[2.2.2]octane), benzyl chloride, biphenyl, tetrabutylammonium bromide (TBAB), tetrabutylammonium chloride(TBAC), tetrabutylammonium iodide (TBAI), tetrahexylammonium bromide (THAB), tetraoctylammonium bromide (TOAB), tricaprylmethylammonium chloride (Aliqat 336), sodium hydroxide, n-hexane, toluene, chlorobenzene, anisole, ethanol, diethyl ether and other reagents for synthesis were guaranteed grade (GR) chemicals and used without further purification.

4.2. Instrumentation

^{1}H NMR and ^{13}C NMR were recorded on a Bruker 300 MHz and 75 MHz respective using TMS as an internal standard. Gas chromatography was carried out using a GC-Varian 3700 model. Ultrasonic water bath, Equitron, Media Instrument Manufacturing Company, Chennai, India-600004. The ultrasonic generator was a thermostatic bath equipped with dual frequencies (28/40 kHz) and electric power 300 W with 0.0126 W/mL of power density. The details of ultrasonic process equipment are well explained in our previous report.[13] The multi-site phase-transfer catalyst was synthesized according to the literature report.[14] Significantly, it is a colorless solid (hygroscopic in nature) being decomposed in nearly 200 ^{o}C (Scheme 1) and the structure is predicted from ^{1}H and ^{13}C NMR spectra.

4.3. Synthesis of multi-site phase-transfer catalyst (MPTC)

A mixture of 1,4-diazabicyclo[2.2.2]octane (DABCO, 5 g, 44.58 mmol), benzyl chloride (14.11 g, 111.43 mmol) and 80mL of ethanol was placed in a 250 mL three necked round bottomed Pyrex flask. The reaction was carried out at 60°C for 30 hours and was gently refluxed in the nitrogen atmosphere. The solvent was then completely removed under vacuum and onium salt, i.e., 1,4-dibenzyl-1,4- diazoniabicyclo[2.2.2]octane dichloride, (MPTC) was washed with n-hexane (4 x 25 mL). The colorless solid was stored in $CaCl_2$ desiccators. Yield: 92% (**Scheme 1**).
^{1}H NMR (D2O): 4.075 (s, 6H, cyclic-H), 5.055 (s, 2H, benzyl-H), 7.346-7.438 (m, 5H, Ar-H). ^{13}C NMR (D2O): 65.13 (cyclic –C), 69.46 (benzyl-C), 124.92, 126.22, 130.86, 133.55 (Ar-C). Elemental analysis: calculated: C-65.78, H-7.20, Cl-19.45, N-7.69; Found: C-65.75, H-7.17, Cl-19.41, N-7.67.

4.4. Synthesis of 1-benzyl-1-indole

To the well-powdered NaOH (0.25mol) in 2mL water, the indole (15.24mmol) was added under overhead stirring for few minutes to generate the indole anion. Then, benzyl chloride (13.86mmol) and the newly synthesized MPTC (3 mol%) in chlorobenzene (30mL) were added slowly. The reaction mixture was heated at 50^{o}C for 2 hours with vigorous stirring. The formed product was evidenced by thin layer chromatography (TLC). The crude product was isolated by simple extraction with Ethyl acetate (3 x 25 mL). The organic layer was collected and the solvent was evaporated under reduced pressure. The crude product was subjected to chromatography (SiO_2) employing hexane: ethyl acetate (9:1) as an eluent to obtain a pure derivative 1-benzyl-1-indole (**Scheme 2**) in the form of brownish solid. The identity of the product was confirmed by ^{1}H NMR and ^{13}C NMR spectra of the product.
^{1}H NMR ($CDCl_3$): 45.149 (2H, Ar-CH_2), 7.23-7.40 (4H, Ar-CH), 7.30 (1H, Ar-CH), indole (CH_2, CH), 7.30-7.43 (2H), 8.17-8.15 (2H), 7.27 (1H), 7.32 (1H). ^{13}C NMR ($CDCl_3$): 125.06, 127.23, 128.73 (Ar-CH), 54.01 (Ar-CH_2), 135.38 (Ar-C), 136.18, 129.07 (INDOLE-C), 129.07, 101.30, 115.59, 120.72, 121.00, 212.54 (INDOLE-CH).

4.5. Kinetics of the arylation of indole

The reaction was conducted on a 150 mL three-necked Pyrex round-bottom flask which permits agitating the solution, inserting the water condenser to recover organic reactant and taking samples and feeding the reactants. This reaction vessel was suspended at the center of the thermo state. A known quantity of chlorobenzene (30 mL, solvent), sodium hydroxide (0.25 M), 0.5 g biphenyl IS, (internal standard) were introduced into the reactor. Then, 15.24 mmol of indole and 13.86 mmol of benzyl chloride, 3 mol % MPTC (with respect to benzyl chloride limiting reagent) were introduced to the reactor to start the reaction. The reaction mixture was stirred at 400 rpm. The phase separation was almost immediate on arresting the stirring process. Samples were collected from the organic layer of the mixture (by stopping the stirring for 20-30 seconds each time) at regular time intervals. A pinch of anhydrous $CaCl_2$ was placed in the sample vials to absorb any moisture present in the organic layer. Each run consisted of six samples taken over the period ranging from 5 to 30 minutes. The kinetics was followed by estimating the amount of benzyl chloride (limiting reagent) that disappeared using a gas Chromatography (GC-Shimadzu

17A model). The analyzing conditions were as follows; Column, 30 m x 0.525 mm i.d. capillary column containing 100% poly(dimethl siloxanen); injection temperature, 250^{0}C; FID detector (300^{0}C). Yields were determined from standard curve and using biphenyl as internal standard.

4.6. Reaction and mechanism

This paper describes the non-benzonoid aromatic nucleophilic substitution reaction between indole and benzyl chloride which was employed in the presence of MPTC ($Q^{2+}Br^-$). The reaction mechanism is represented in (Scheme 3).

4.7. Definition

The conversion (X) of benzyl chloride (BC) is defined as follows;

$$X=1-[BC]_o/[BC]_{o,t} \qquad (1)$$

Where $[BC]_o$ and $[BC]_{o,t}$ represent the concentration of arylation at time (t), $t = 0$ and $t > 0$, respectively.

4.8. Rate expression

The rate expression for this reaction may be expressed as:

$$-r_{(BC)}=k_{app}[BC]_o \qquad (2)$$

Were k_{app} is the apparent reaction rate constant.

$$-d[BC]_o/dt=-r_{(BC)}=k_{app}[BC]_o \qquad (3)$$

This reaction is carried out in a batch reactor, so the diminution rate of [BC] with time (t) can be expressed on integrating the Equation (3):

$$-\ln[BC]_o/[BC]_{o,t}=-\ln(1-X)=k_{app}t \qquad (4)$$

Using Equation 4, we can get k_{app} value experimentally by plotting –ln (l-X) against time, t.

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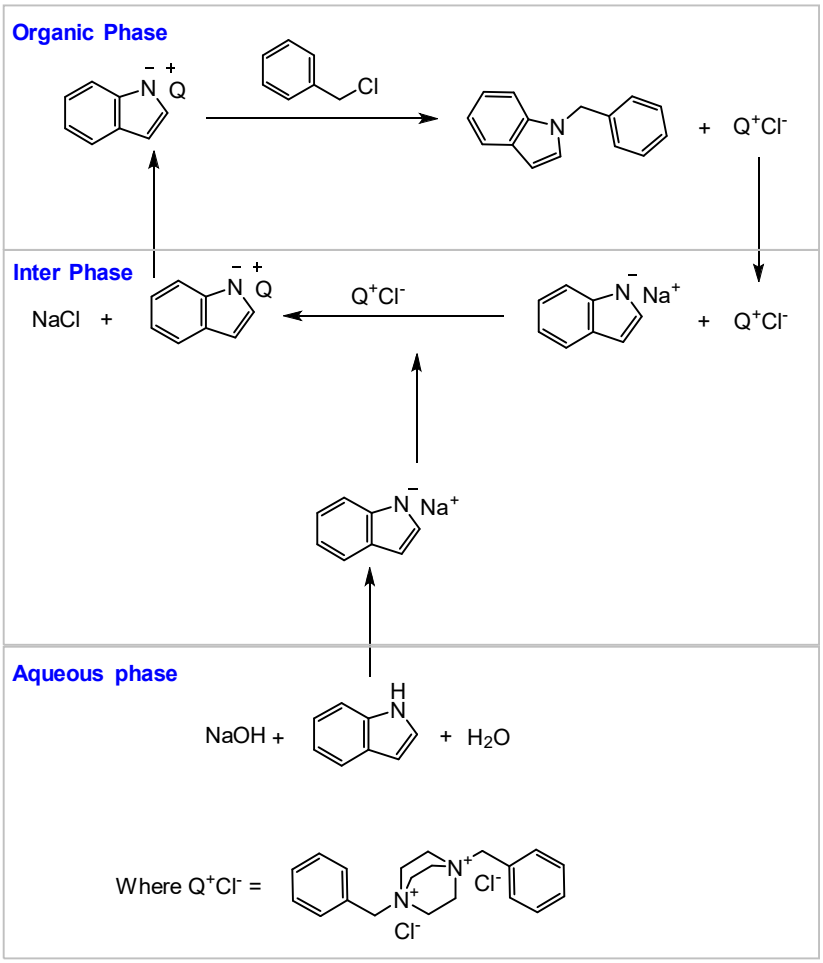

Scheme 3. Suggested mechanism for the synthesis of N-aryl indole using phase transfer catalyst.

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