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KINETIC STUDY OF SUBSTITUTED BENZIMIDAZOLE SYNTHESIZED *VIA* PHASE TRANSFER CATALYSIS

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ABSTRACT:
The interaction of a substituted carbene with azo analogue was studied to obtain Benzimidazole derivative under kinetically controlled phase transfer catalysis conditions. In situ generation of dimethylvinylidene carbene was facilitated by the interaction between 3-chloro-3-methyl-1-butyne and alkali at the interface. Interestingly, insertion of this carbene into the N=N linkage of 2,4-dimethyl-3-arylazo-6-thiopyrimidine afforded newly synthesized desired benzimidazolopyrimidines. The reaction follows the pseudo-first order rate law. Rational mechanism of the reaction is proposed according to the experimental evidence. The compounds were synthesized in excellent yields (70–80%) and their structures were established based on their IR and ^{1}H-NMR spectral data.

KEYWORDS: Benzimidazole; Phase transfer catalyst (PTC); Dimethylvinylidene carbene; Kinetic study.

INTRODUCTION:

Benzimidazole is important pharmacophores and a privileged structure in medicinal chemistry. It is preferred as it provides many pharmacological advantages.[i] The most pronounced benzimidazole is N-ribosyl dimethyl-benzimidazolein vitamin B12.[i-iii] Benzimidazole derivatives are significant with fascinating activities such as analgesic,[iv-vi] anti-inflammatory,[v-viii] anti-bacterial,[ix,x] anti-fungal,[x] anti-viral,[xi-xii] anti-helmenthic,[xiii] anti-convulsant,[xiv, xv] anti-cancer,[xvi, xvii] anti-ulcer,[xviii] anti-hypertensive.[xix] The first benzimidazole in 1872 was reported by Hoebrecker, who obtained 2,5 (or 2,6)-dimethylbenzimidazole by the reduction of 2-nitro-4methyl acetanilide.[xx, xxi]

Phase transfer catalysis has an unquestionable industrial advantage and it offers an exceptional area for fundamental research. In fact, such processes are economically competitive since they allow excellent reaction selectivities and substantially quantitative yields under mild conditions.[xxii, xxiii] Since Jarrous[xxiv] found that quaternary ammonium salts are an efficient catalyst for enhancing the two-phase reactions, many chemists have investigated phase transfer catalysis in numerous reactions such as substitution, displacement, condensation, epoxidation, ylide-mediated reaction, modification of polymer, etc. As a result, phase transfer catalysis is considered to have a great potential for industrial scale applications.

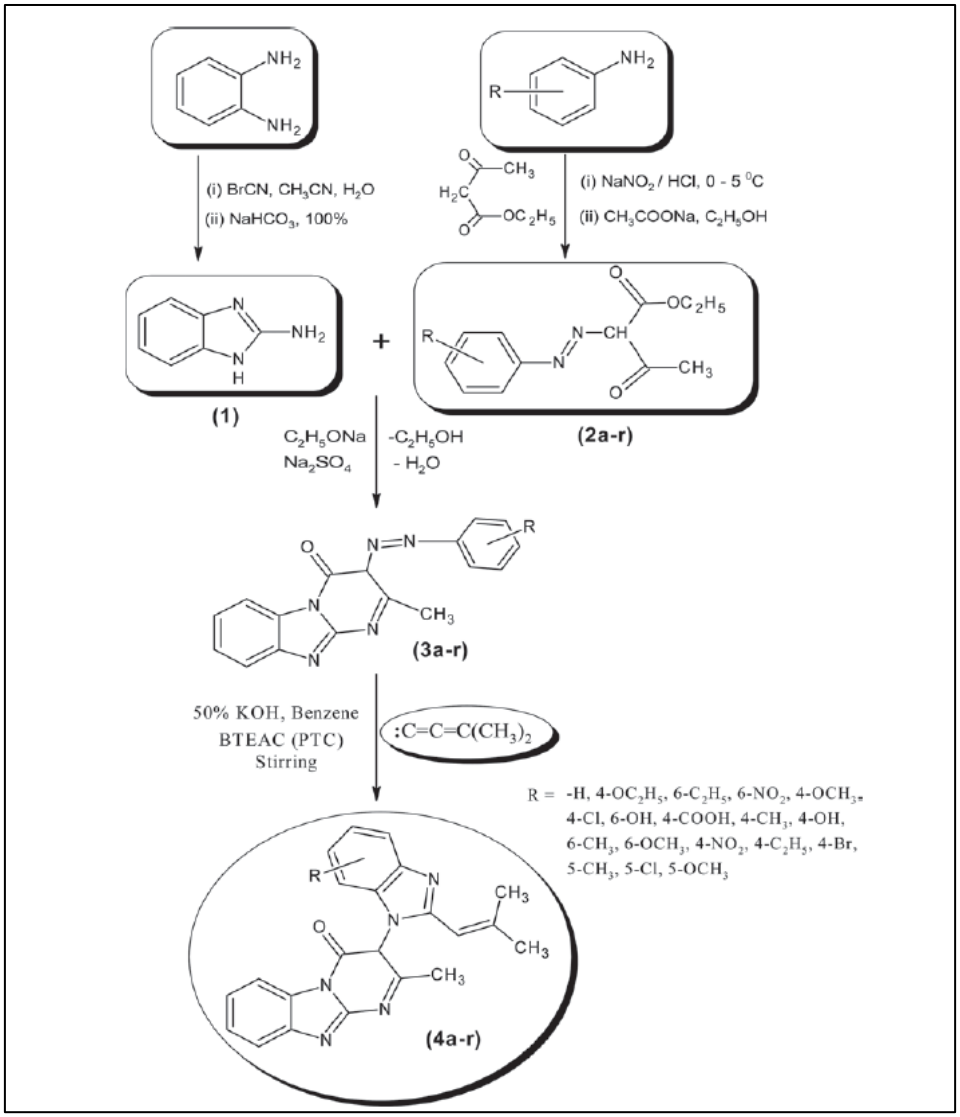
MATERIALS ANS METHODS:

Chemicals, Reagents and Instrumentation:

All the chemicals and other reagents used were of AR grade purity. All the synthesized compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR, FAB-Mass spectroscopy, and elemental analyses. Melting points were observed on an electro-thermal apparatus by open capillary method and are uncorrected. The NMR spectra were observed on Bruker DRX300 instrument (300 MHz) in $CDCl_3$ using TMS as an internal standard. Chemical shifts are observed in δ(ppm) values. All IR spectra were run on Shimadzu 460 spectrophotometer in KBr Discs; frequencies are reported in cm^{-1}. FAB mass spectra (FAB-MS) were observed on a JEOL SX 102 Mass Spectrometer. To ascertain the purity of all the synthesized compounds, analytical thin layer chromatography was performed on (E Merck silica gel G0.50 mm plate no. 5700) using acetonitrile, methanol, and water (50:30:20, v/v) as eluting system.

General procedure for synthesis of Benzimidazole derivative[xxv]

A mixture of 50% of aq. potassium hydroxide (15 mL), benzyl-triethylammonium chloride (BTEAC, 0.57 g, 2.5mmol) and benzene (5 mL) was taken and stirred thoroughly for 30 min. To this mixture, 2-methyl-3-(phenyldiazenyl)pyrimido[1,2-a]benzimidazol-4(3H)-one (**3a–r**, 2.5mmol) was added slowly and stirred for further 5–7 h under nitrogen atmosphere. While stirring was going on, 3-chloro-3-methyl-1-butyne (25mmol) in benzene (5 mL) was added to mixture. The contents were diluted with water (120 mL), followed by extraction with ether (120 mL) to afford crude product. It was purified on an alumina column (benzene as eluent) so as to finally obtain Benzimidazole derivatives (**4a–r**). Their purity was further ascertained upon performing TLC resolution on E Merck silica gel-G plates using acetonitrile, methanol, and water (50:30:20, v/v) as eluting system. An overview of all the synthetic steps is depicted in Scheme 1.



Scheme 1. Synthesis of Benzimidazole derivative

Derivative 4a:

Yield 76%; m.p. 122–123°C; Anal. Calcd. for $C_{22}H_{19}N_5O$: C, 71.53; H, 5.18; N, 18.96%; Found: C, 71.50; H, 5.15; N, 18.96%; IR (υ cm^{-1}): 3085 (C-H, sp^2), 2952 (C-H, sp^3), 1720 (C=O), 1631 (C=C/C=N), 1620, 1522, 1440 (C…C, ring str), 952, 853, 741 (sub. phenyl); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 1.85 (s, 6H, 2 × CH_3, iso-propenyl), 2.02 (s, 3H, CH_3), 4.54 (s, CH, pyrimidine), 5.13 (s, CH, methine), 7.27 (m, 4H, H11, H12, H21, H22), 7.66 (m, 4H, H10, H13, H20, H23); ^{13}C-NMR ($CDCl_3$) δ (ppm): 17.44 (C24), 20.25 (C28), 24.27 (C27), 65.82 (C3), 110.02, 114.12, 115.28, 123.02, 123.26, 130.74, 134.28, 138.91, 139.24 (aromatic ring), 141.64 (C6, C16), 144.66 (C26), 165.16 (C4), 169.57 (C2); FAB-MS: 370 $(M+H)^+$.

PTC Reaction Mechanism and Kinetic Model

3-Chloro-3-methyl-1-butyne anion ($C_5H_7Cl^-$, **1**, Scheme1), which can be converted to dimethylvinylidene carbene (**:**$C=C=C(CH_3)_2$) (**2**, Scheme1) is generated from 3-Chloro -3-methyl-1-butyne in presence of alkaline solution. The organic compound 4,6-dimethyl-5-arylazo-2-thiopyrimidine ($C_{12}H_{12}N_4S$) does not react with dimethylvinylidene carbene to form benzimidazole derivatives because of easy hydrolysis of dimethylvinylidene carbene. Therefore, the addition of PTC to the aqueous solution to generate carbene in organic solution

is essential. An intermediate is formed when 3-chloro-3-methyl-1-butyne reacts with BTEAC (Benzyl triethylammonium chloride - PTC) at the interface of two phases. The intermediate is further treated with 4,6-dimethyl-5-arylazo-2-thiopyrimidine to produce finally 2-methyl-3-[2-(2-methylprop-1-en-1-yl)-1H-benzimidazol1-yl]pyrimido[1,2-a]benzimidazol-4(3H)-one ($C_{21}H_{17}N_5O$).

The reaction mechanism is thus proposed as:

$$C_5H_7Cl + KOH(aq) \rightleftharpoons C_5H_6Cl^-K^+_{(interface)} + H_2O_{(aq)}$$

$$C_5H_6Cl^-K^+_{(interface)} + Ph(CH_2N^+Et_3Cl^-)_{(interface)} \rightleftharpoons Ph(CH_2N^+Et_3C_5H_6Cl^-)_{(org)} + KCl_{(aq)}$$

$$Ph(CH_2N^+Et_3C_5H_6Cl^-)_{(org)} \rightleftharpoons :C=C=C(CH_3)_2 + Ph(CH_2N^+Et_3Cl^-)_{(org)}$$

$$C_{21}H_{17}N_5O + :C=C=C(CH_3)_2 \xrightarrow{k} C_{26}H_{23}N_5O_{(org)}$$

Where, **k** represents the intrinsic rate constant for the reaction of dimethylvinylidene carbene ($:C=C=C(CH_3)_2$) and 4,6-dimethyl-5-arylazo-2-thiopyrimidine ($C_{21}H_{17}N_5O$) to produce the benzimidazole derivatives ($C_{26}H_{23}N_5O$) in the organic solution. Thus, the change rate of 4,6-dimethyl-5-arylazo-2-thiopyrimidine due to reaction is expressed as:

$$\frac{-d[C_{21}H_{17}N_5O]}{dt} = k\,[C_{21}H_{17}N_5O]_o\,[:C=C=C(CH_3)_2]_o \quad \text{.....(1)}$$

Dimethylvinylidene carbene was not detectable during the reaction, however the concentration of dimethylvinylidene carbene was kept at a constant throughout the reaction Thus, eq (1) can be written as:

$$\frac{-d[C_{21}H_{17}N_5O]}{dt} = k_{app}\,[C_{21}H_{17}N_5O]_o \quad \text{.....(2)}$$

where, $\mathbf{k_{app}} = \mathbf{k}\,[:C=C=C(CH_3)_2]_0$ .....(3)

Therefore, the reaction of 4,6-dimethyl-5-arylazo-2-thiopyrimidine and dimethylvinylidene carbene is irreversible and is expressed as:

$$C_{21}H_{17}N_5O \xrightarrow{k_{app}} C_{26}H_{23}N_5O \quad \text{.....(4)}$$

As shown in eq (4), the change rates of these components is:

$$\frac{-d[C_{21}H_{17}N_5O]}{dt} = -k_{app}\,[C_{21}H_{17}N_5O]_o \quad \text{.....(5)}$$

$$\frac{-d[C_{26}H_{23}N_5O]}{dt} = k_{app}\,[C_{21}H_{17}N_5O]_o \quad \text{.....(6)}$$

Eq (5) is integrated as:

$[C_{21}H_{17}N_5O]_o = [C_{21}H_{17}N_5O]_{o,i} \exp(-k_{app},t)$.....(7)

where, $[C_{21}H_{17}N_5O]_{0,i}$ is the initial concentration of 4,6-dimethyl-5-arylazo-2-thiopyrimidine.

The conversion of 4,6-dimethyl-5-arylazo-2-thiopyrimidine, 'X' can be understood as:

$$X = 1 - \frac{[C_{21}H_{17}N_5O]_o}{[C_{21}H_{17}N_5O]_{o,i}} \quad \text{.....(8)}$$

Thus, eq (7) is expressed as:

$-\ln(1-X) = k_{app}.t$.....(9)

The value of $\mathbf{k_{app}}$canbe obtained by plotting the experimental data of-ln (1-X) versus time.

RESULTS AND DISCUSSION:

The purpose of presented work is to study the reaction of 4,6-dimethyl-5-arylazo-2-thiopyrimidine in an alkaline solution with 3-chloro-3-methyl-1-butyne two-phase medium to synthesize requisite benzimidazolopyrimidine derivatives. Dimethylvinylidenecarbene which is produced from the 3-chloro-3-methyl-1-butyne in presence of potassium hydroxide, react with 4,6-dimethyl-5-arylazo-2-thiopyrimidine to yield substituted benzimidazolederivates. The experimental results show a material balance between reactant and product i.e., the consumption of the amount of reactant (4,6-dimethyl-5-arylazo-2-thiopyrimidine) parallels the generation of amount of 4-methyl-3-[2-(2methylprop-1-en-1-yl)-1H-benzimidazol-1-yl]pyrimido[1,2-a]benzimidazol-4(3H)-one. No by-products were noticed during or after the reaction. In absence of PTC, no final product was obtained. The main reason is that dimethylvinylidene carbene can be easily to be hydrolyzed in aqueous solution. Under this situation, no dimethylvinylidenecarbene can react with 4,6-dimethyl-5-arylazo-2-thiopyrimidine to produce the desired product. However, the reaction is dramatically enhanced by adding a small amount of catalyst (BTEAC). The formation of Benzimidazole derivative was established by chemical conversion on catalytic hydrogenation (10% Pd-C) to hexahydro derivatives.

Effect of Stirring Speed

Stirring speed effect on rate of dimethylvinylidene carbene addition to 4,6-dimethyl-5-arylazo-2-thiopyrimidine was studied in the rate 100-1000 rpm in presence of 2.5mmol of catalyst and 15mL of 50% aq. potassium hydroxide. Reaction rate rose sharply with increase in stirring speed. From the plot of ln(a-x) vs. time (Fig.1)**,** the pseudo first order rate constant is evaluated. It is revealed that at 200rpm; the reaction rate is comparatively slower than at higher stirring speed. The increased rates are attributed to increase in interfacial area. The strong rate dependence on stirring speed justifies an interfacial mechanism. Other kinetic investigations were observed at different rpm.

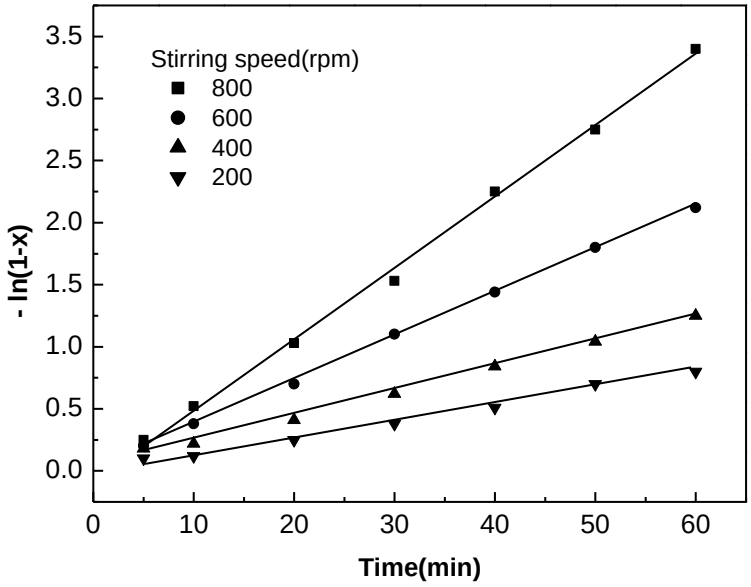


Figure 1. A plot of -ln(1-x) and time with various agitation speeds; 25mmol of 4,6-dimethyl-5-arylazo-2-thiopyrimidine; 15ml of 50% KOH; 2.5mmol BTEAC;25^{0}C

Impact of Catalyst Quantity

The effect of variation in the amount of PTC on rate of dimethylvinylidene carbene addition to 4,6-dimethyl-5-arylazo-2-thiopyrimidine was investigated by differing catalyst amount from 0.5mmol to 2.5mmol. Rate of reaction directly relies on catalyst amount added. A plot of observed rate constant against time of the reaction gives the straight line over a wide range of concentration and its slope is found to be 0.0571 (Fig.2). The increased rate is due to increase in number of active sites. Control experiment was carried out in absence of catalyst under similar conditions and less than 1% conversion was observed within 3hrs. This fact also supports the interfacial mechanism.

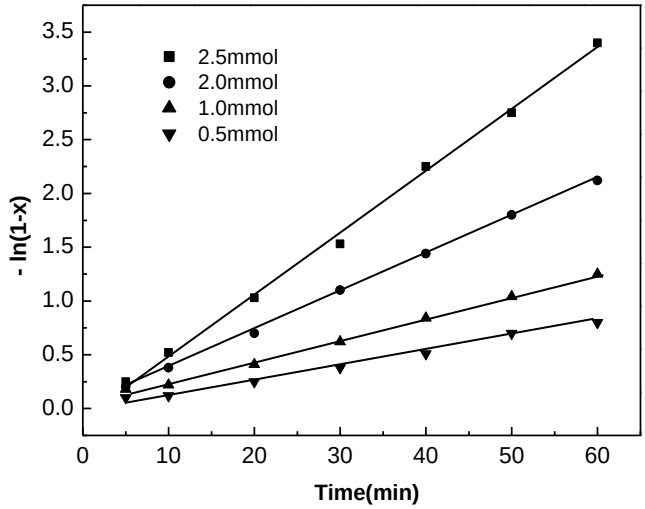


Figure 2. A plot of -ln(1-x) and time of different concentration of BTEAC; 25mmol of 4,6-dimethyl-5-arylazo-2-thiopyrimidine;15ml of 50% KOH;800rpm; 25^{0}C

Effect of Temperature

Temperature effect on reaction rate was investigated by employing 2.5 mmol of the catalyst at 800rpm taking 15ml of 50% KOH. The kinetic profile was studied under various reaction temperatures viz. 20^0,25^0, 30^0 and 35^0C. As expected, the rate increases with increase in temperature as shown in Figure 3. Moreover, the reaction follows a pseudo first order rate law. As depicted in Figure 4, the activation energy data deduced from the plot of –lnk vs 1/T is found to be 9.70kcal/mol.

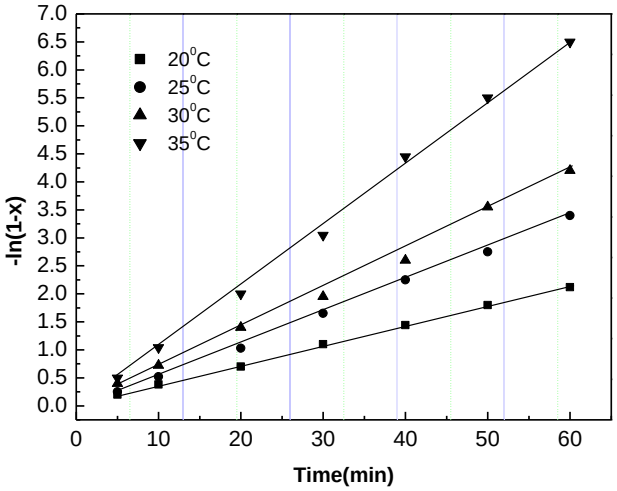


Figure 3. A plot of -ln(1-x) and time of catalyst BTEAC at different temperature; 25 mmol of 4,6-dimethyl-5-arylazo-2-thiopyrimidine; 15 ml of 50%KOH; 800rpm

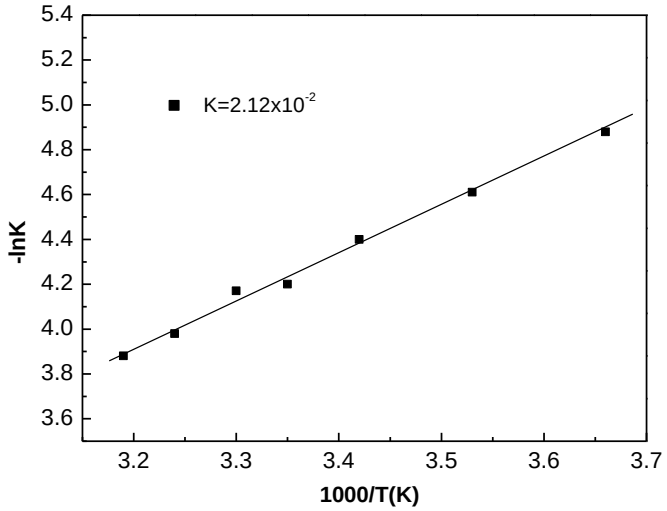


Figure 4. A plot of apparent rate constants and various reaction temperatures of catalyst BTEAC; 25mmol of 2,4-dimethyl-3-arylazo-6-thiopyrimidine; 15ml of 50%KOH; 800rpm; k: $2.12*10^{-2}$; E: 9.70kcal/mol

CONCLUSION:

In this work, a new route to the design of the benzimidazole skeleton has been devised following the phase transfer methodology. A high yield of product and a high reaction rate from the insertion followed by cyclization of 2,4-dimethyl-3-arylazo-6-thiopyrimidine was

obtained as a result of interaction between 3-chloro-3-methyl-1-butyne and 2,4-dimethyl-3-arylazol-6-thiopyrimidine in an alkaline solution catalyzed by benzyl triethyl ammonium chloride.

According to the experimental evidence, the reaction follows an interfacial reaction mechanism, in which the reaction rate is highly dependent on the stirring speed up to 800 rpm. An optimum reaction rate is obtained using 2.5mmol of catalyst. The conversion of Benzimidazole derivative decreases with increase in concentration of 2,4-dimethyl-3-arylazol-6-thiopyrimidine and 3-chloro-3-methyl-1-butyne. The reason is that both the molar ratio of catalyst to 2,4-dimethyl-3-arylazol-6-thiopyrimidine and the concentration of dimethylvinylidene carbene decreases with the increase in amount of 2,4-dimethyl-3-arylazol-6-thiopyrimidine and 3-chloro-3-methyl-1-butyne. However, reaction rate rises with rise in catalyst and alkaline concentration.

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