Calix[*n*]arenes Mediated Phase-Transfer Catalytic Synthesis of Purine Derivatives

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ABSTRACT: A new route was designed to achieve the synthesis of purine derivatives under phase-transfer catalysis conditions using calix[*n*]arenes TAC_nA ($n = 4$, 6, and 8) as phase-transfer catalyst for the first time in this particular type of synthesis. The compounds were synthesized in excellent yields (70%–80%) and the structures were established on the basis of consistent IR, ^1H NMR, FAB-Mass, and elemental analyses data. Their purity has been ascertained by chromatographic resolution using acetonitrile, methanol, and water (50:30:20, v/v) as eluenting system. Moreover, the kinetics of the reaction was studied and it was found to obey first-order kinetics. Effect of various parameters, namely, temperature, amount of catalyst, stirring speed, and so on was also investigated. © 2008 Wiley Periodicals, Inc. Int J Chem Kinet 41: 265–274, 2009

INTRODUCTION

Interaction between two substances located in different phases of a mixture is often inhibited because of the inability of reagents to come together. Traditionally, this problem is solved by the use of an appropriate mutual solvent. An alternative solution to the heterogeneity problem is the introduction of phase-transfer catalysts. The term phase-transfer catalysis (PTC) encompasses several effective techniques of which typical advantages are simplicity, mild conditions, high-reaction rates, high selectivities, and the use of inexpensive reagents [1–3]. PTC is considered to have a great potential for industrial scale applications too. Organic chemists and chemical engineers have been exploiting PTC by virtue to enhance productivity, quality, safety, vis-à-vis from the viewpoint of environmental considerations.

A number of phase-transfer catalysts are being developed to combat the requirement of synthetic chemistry applications [4]. In this context, the potential of calix[*n*]arenes in phase-transfer catalyst mediated synthesis is yet to be explored. Currently, the chemistry of calix[*n*]arenes is growing at a very fast rate and has received increasing attention due to their utilization in supramolecular chemistry. Most of the time, calix[*n*]arenes were reported to promote host–guest interactions in the solvent extraction processes. Investigations are continuously going on to explore the utility of this wonderful system in many disciplines of science [5,6].

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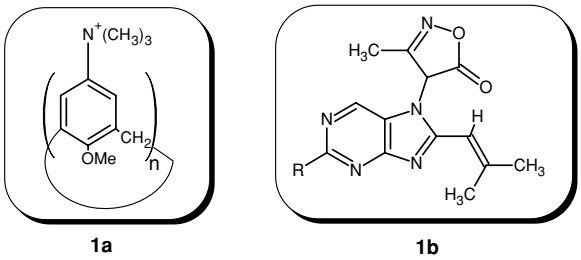


1a **1b**

Figure 1 (**1a**) Structure of calix[*n*]arene TAC_nA ($n = 4$, 6, and 8) and (**1b**) structure of synthesized purines (R = H, Cl, OH).

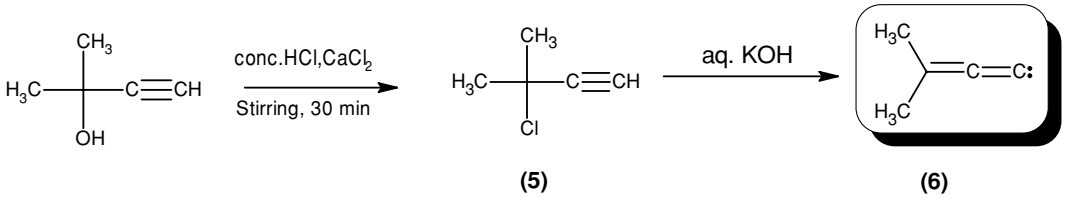
Some functionalized calix[*n*]arenes were also developed as new phase-transfer agents for normal PTC reactions, namely, in Aldol-type condensation and Michael addition reactions in water [7,8]. Calix[4]arene based multisite phase-transfer catalysts exhibited significant high-catalytic activity as compared to single-site phase-transfer catalysts in Darzens condensation, O/N-alkylation reactions and ethyl benzene oxidation [9]. The water-soluble calix[*n*]arenes act as efficient inverse phase-transfer catalysts in the nucleophilic substitution reaction of alkyl and arylalkyl halides with nucleophiles in water [10]. Water-soluble calix[*n*]arene catalytic system provides additional options in the field of biphasic catalysis for synthetic chemistry and process engineering. Hence, keeping in view such considerations, we have explored the potential of supramolecular calix[*n*]arenes **1a** as the effective PTC to synthesize potentially significant purine systems **1b** (Fig. 1).

Purine derivatives are of great importance in biomedical sciences. These are used in the regulation of many biological processes and as constituents of DNA and RNA. Purines, purine nucleosides, and nucleotides participate in the signal transduction and regulation of many biological processes in cells and tissues as ligands of receptors and as second messengers (c-AMP). The interest in modified purine derivatives is immense as pharmacophoric entities. For instance, purine bases and their nucleosides constitute an important group of antineoplastic [11,12], antibiotic [13], and antitubercular [14] agents. Moreover, these compounds have found wide application as adenosine receptor ligands [15,16], antiparasitic agents [17], cyclin-dependent kinase inhibitors [18], antitumor [19], and antiviral compounds [20].

A systematic perusal of literature survey reveals that a number of synthetic routes are available for the construction of substituted purine nucleus deriving from amidines or guanidines with retrosynthetic disconnection at the ring fusion [21], inverse electron demand Diels–Alder cycloaddition (IEDDAC) reaction [22], metal-catalyzed cross-coupling reactions [23], S_NAr displacement in anilines and amines followed by N-alkylation and N-arylation [24]. However, the methods reported so far are tedious with low outcome of the overall yields. Thus in continuation of our work on heterocyclic compounds [25–30] and in quest of developing a synthetic strategy under phase-transfer catalytic condition, a novel route has been designed to obtain 7-[4′-(3′-methylisoxazolyl-5′(4′*H*)-one)-8-(2′-methylprop-1′-en-1′-yl)-7*H*-purine derivatives **8a–c.** The synthesis of designed purine derivatives was achieved by the insertion of a reactive intermediate, namely, dimethylvinylidine carbene (generated in situ, Scheme 1) into the —N=N— moiety of substituted 3-methyl-4-[(*E*)-pyrimidin-4-yldiazenyl]isoxazol-5(4*H*)-one **4a–c** successively followed by cyclization and rearrangement yields appropriately substituted 7-[4′-(3′-methylisoxazolyl-5′(4′*H*)-one)-8-(2′-methylprop-1′-en-1′-yl)-7*H*-purines **8a–c**.

EXPERIMENTAL METHODS

All the chemicals, namely, potassium hydroxide, benzene, ethanol, and other reagents used were of AR grade purity. Calix[*n*]arenes TAC_nA ($n = 4$, 6, and 8) were prepared as per the literature procedure [31,32]. All the synthesized compounds were identified by IR ^{1}H NMR and FAB Mass spectroscopy as well as elemental analysis. Melting points were determined on an electrothermal apparatus by open capillary method and



(5) **(6)**

Scheme 1

are uncorrected. The ^{1}H NMR spectra were recorded on a Bruker DRX300 instrument (300 MHz) in $CDCl_3$ using TMS as an internal standard. Chemical shifts are reported in δ units (ppm) values. All IR spectra were run on a Shimadzu 460 spectrophotometer in KBr Discs; frequencies are reported in cm^{-1}. FAB mass spectra (FAB MS) were recorded on a JEOL SX 102 Mass Spectrometer. To ascertained the purity of all the synthesized compounds, analytical thin layer chromatography was performed on E Merck silica gel G (0.50 mm, plate no. 5700) using acetonitrile, methanol, and water (50:30:20, v/v) as eluent. Elemental analyses were performed on an Elementar Vario EL-III Carlo-Erba-1108 equipment.

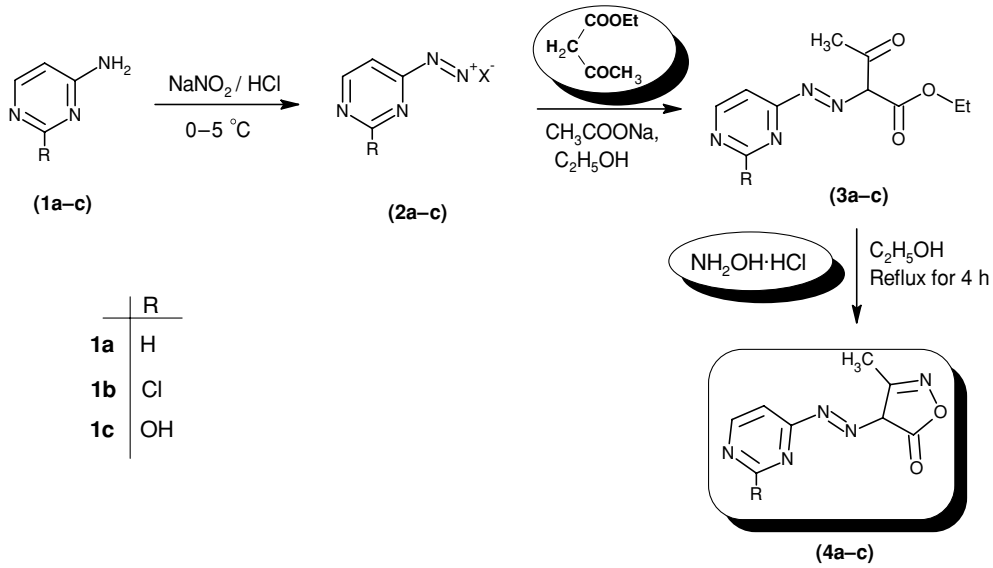
Preparation of 3-Methyl-4-[(*E*)-(5-methylpyridin-2-yl)diazenyl]isoxazol-5(4*H*)-one 4a-c

In a 250-mL round-bottomed flask, solution of 4-aminopyrimidine **1a–c** (10 mmol) in concentrated hydrochloric acid (4.0 mL) and distilled water (4.0 mL) was taken. To this aqueous solution of sodium nitrite (0.69 g, 10 mmol) was added dropwise within 10–15 min at 0–5°C. Meanwhile, ethyl acetoacetate (1.30 g, 10 mmol), sodium acetate (0.82 g, 10 mmol), and ethyl alcohol (20 mL) were taken in another beaker at 0°C. Now, the diazotized solution was added dropwise to this solution under temperature-controlled conditions. The crystals of 1-ethoxy-2-pyrimidinylazo butane -1,3-dione **3a–c** thus obtained were filtered, washed with water, and dried.

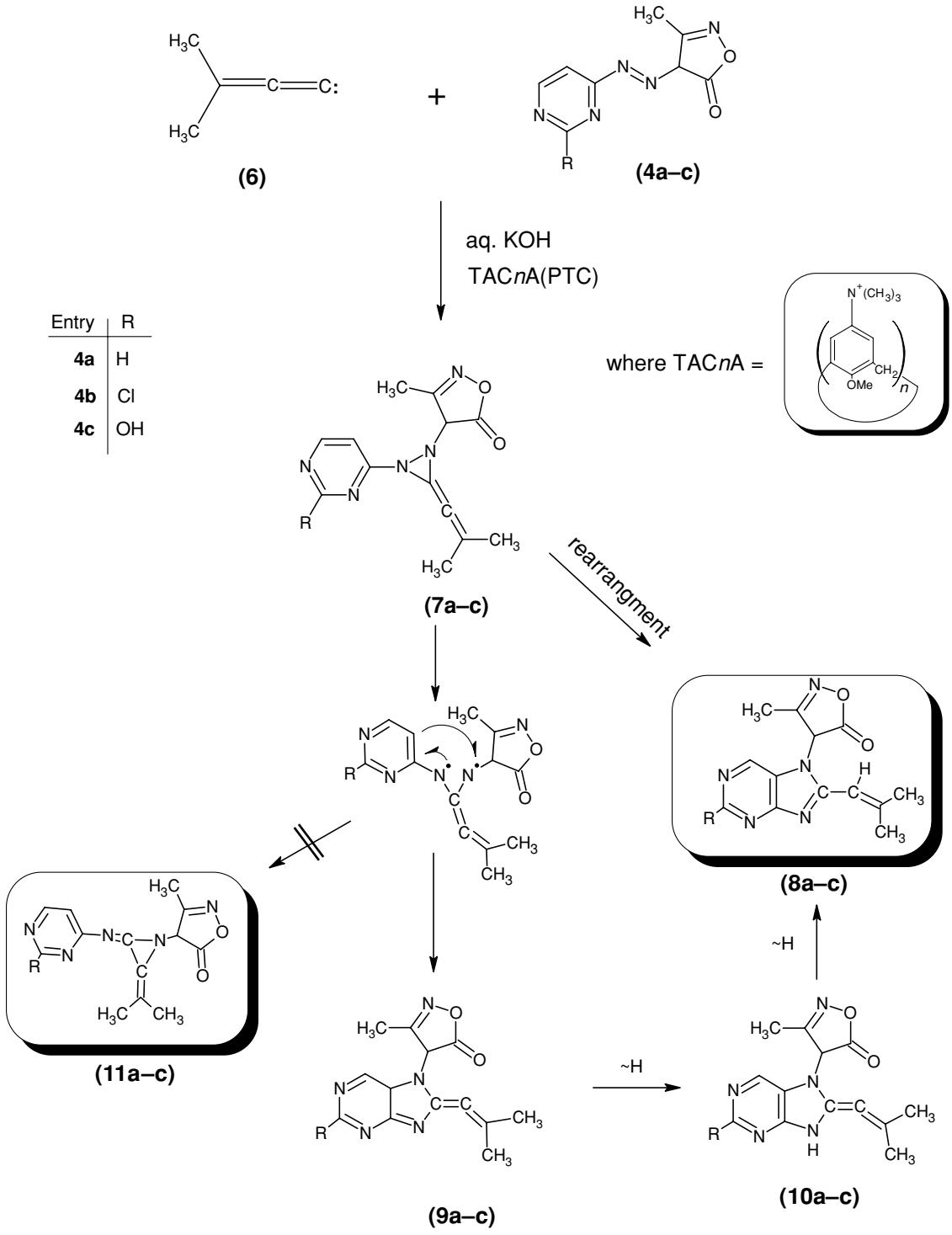
In a 250-mL round-bottomed flask, an equimolar quantity of 1-ethoxy-2-pyrimidinylazo butane-1,3-dione **3a–c** and hydroxylamine hydrochloride were taken together in ethyl alcohol (25 mL) and allowed to undergo refluxation for 3-4 h at 80°C to obtain crystals of required 3-methyl-4-[(*E*)-(5-methylpyridin-2-yl)diazenyl]isoxazol-5(4*H*)-one **4a–c** in good yield (70%–75%). An overview of systematic methodology of schematic pathway is depicted in Scheme 2.

Preparation of 7-[4′-(3′-Methylisoxazolyl-5′(4′*H*)-one)-8-(2′-methylprop-1′-en-1′-yl)-7*H*-purine 8a–c

In a 250-mL three-necked flask fitted with dropping funnel and a mechanical stirrer, a mixture of 50% aq. KOH (25 mL), TAC*n*A as PTC (1.0 mmol), and benzene (5 mL) was taken and stirred for 30 min. To this, 3-methyl-4-[(*E*)-(5-methylpyridin-2-yl)diazenyl]isoxazol-5(4*H*)-one **4a–c** (10 mmol) was added slowly and stirred for further 5–7 h under nitrogen atmosphere. 3-Chloro-3-methyl-1-butyne (25 mmol) in benzene (5 mL) was added slowly to the mixture with continuous stirring. Contents were diluted with water (125 mL), followed by extraction twice with ether to afford crude product, which was then purified on an alumina column. Solid crystals of 1-isoxazolyl-2-[2′-methyl-prop-1-en-1-yl] imidazo[4,5-b] pyridine **8a–c** were then obtained in good yield. An overview of synthetic pathway is depicted in Scheme 2.



Scheme 2


(6)
(4a–c)
aq. KOH
TACnA(PTC)
Entry | R
4a | H
4b | Cl
4c | OH
where TACnA =
(7a–c)
rearrangment
(8a–c)
(11a–c)
(9a–c)
(10a–c)
~H
~H

Scheme 3

Synthesis of 7-[4′-(3′-Methylisoxazolyl-5′(4′*H*)-one)-8-(2′-methylprop-1′-en-1′-yl)-7*H*-purine 8a

mp (°C) 126–127; Yield: 76%; IR (KBr) (cm^{-1}): 3011 (=C—H, sp^2), 2987 (C—H, sp^3), 1738 (C=O), 1629 (C=C/C=N), 1451, 1365 (C—H, bending, sp^3), 1061 (C—O), 1047 (C—N); ^{1}H NMR (δ ppm): 2.51 (s, 6H, —CH_3), 2.83 (s, 3H, —CH_3), 3.02 (s, 1H, —CH-CO—), 4.34 (s, 1H, =CH—), 7.41 (s, 1H, —CH, H_4), 7.53 (s, 1H, —CH, H_2); FAB-MS *m*/*z* 271; Anal. Calcd for $C_{13}H_{13}N_5O_2$: C, 57.56; H, 4.83; N, 25.82. Found: C, 57.51; H, 4.81; N, 25.79.

Synthesis of 2-Chloro-7-[4′-(3′-Methyl-isoxazolyl-5′(4′*H*)-one)-8-(2′-methylprop-1′-en-1′-yl)-7*H*-purine 8b

mp (°C) 119–120; Yield: 75%; IR (KBr) (cm^{-1}): 3019 (=C—H, sp^2), 2980 (C—H, sp^3), 1743 (C=O), 1635 (C=C/C=N), 1458, 1370 (C—H, bending, sp^3), 1069 (C—O), 1050 (C—N); ^{1}H NMR (δ ppm): 2.62 (s, 6H, —CH_3), 2.93 (s, 3H, —CH_3), 3.22 (s, 1H, —CH), 4.54 (s, 1H, =CH—), 7.48 (s, 1H, —CH, H_4); FAB-MS *m*/*z* 306; Anal. Calcd for $C_{13}H_{12}ClN_5O_2$: C, 51.07; H, 3.96; N, 22.91. Found: C, 51.05; H, 3.93; N, 22.89.

Synthesis of 2-Hydroxy-7-[4′-(3′-methyl-isoxazolyl-5′(4′*H*)-one)-8-(2′-methylprop-1′-en-1′-yl)-7*H*-purine 8c

mp (°C) 130–131; Yield: 78%; IR (KBr) (cm^{-1}) 3548 (—OH str.), 3025 (=C—H, sp^2), 2984 (C—H, sp^3), 1739 (C=O), 1624 (C=C/C=N), 1456, 1363 (C—H, bending, sp^3), 1068 (C—O), 1051 (C—N); ^{1}H NMR (δ ppm): 2.53 (s, 6H, —CH_3), 2.83 (s, 3H, —CH_3), 3.04 (s, 1H, —CH—CO—), 4.34 (s, 1H, =CH—), 7.41 (s, 1H, —CH, H_4), 10.31 (s, 1H, —OH); FAB-MS *m*/*z* 287; Anal. Calcd for $C_{13}H_{13}N_5O_3$: C, 54.35; H, 4.56; N, 24.38. Found: C, 54.34; H, 4.56; N, 24.36.

REACTION MECHANISM AND KINETIC MODEL

Kinetic Measurement

For kinetic measurement a 100-mL three-necked flask was used consisting of an agitating device and inlets for thermometer and samples. The reaction aliquots were prepared in volumetric flasks. Reactor was immersed in an isothermal water bath and charged with required quantity of 3-methyl-4-[(*E*)-pyrimidin-4-yldiazenyl]isoxazol-5(4*H*)-one **(4a)**, 50% KOH, PTC in benzene. Stirring was started and organic layer was extracted at regular intervals of time by stopping the stirring intermittently to allow the adequate separation. Each time five samples were taken and completion of reaction was monitored by TLC and HPLC (Fig. 2).

Model for Kinetic Reaction Mechanism

The formation of 7-[4′-(3′-methylisoxazolyl-5′(4′*H*)-one)-8-(2′-methylprop-1′-en-1′-yl)-7*H*-purine **8a–c** can be expressed as

$$C_8H_7N_5O_2 + :C{=}C{=}C(CH_3)_2 \xrightarrow{k} C_{13}H_{13}N_5O_{2\,(org)} \quad (1)$$

From (1) the change rate of the reaction is expressed as

$$\frac{-\mathrm{d}}{\mathrm{d}t}[C_8H_7N_5O_2] = k[C_8H_7N_5O_2]_o[:C{=}C{=}C(CH_3)_2]_o \quad (2)$$

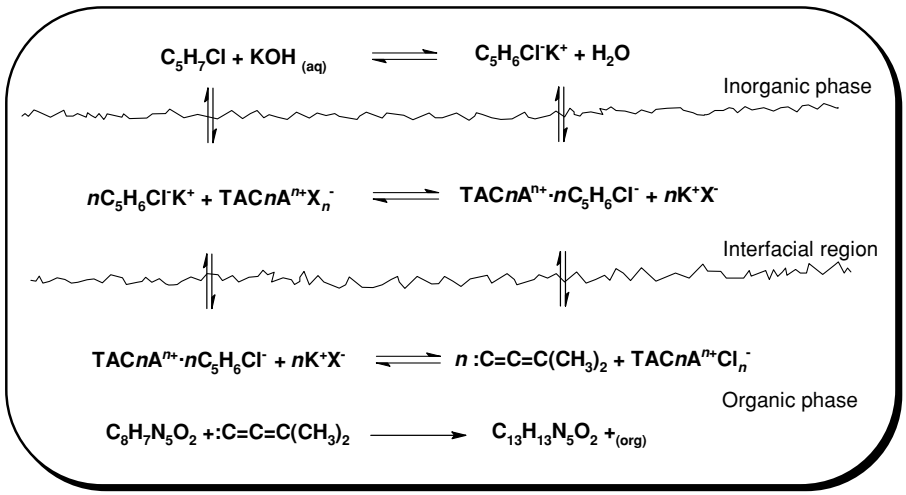


Figure 2 An overview of interfacial reaction mechanism.

where the concentration of dimethylvinylidene carbene was kept constant; Eq. (2) can now become

$$\frac{-\mathrm{d}}{\mathrm{d}t}[C_8H_7N_5O_2] = k_{app}[C_8H_7N_5O_2]_o \quad (3)$$

$$k_{app} = k[:C{=}C{=}C(CH_3)_2]_o \quad (4)$$

Therefore, the reaction of dimethylvinylidene carbene and $C_8H_7N_5O_2$ is irreversible and can be expressed as follows:

$$[C_8H_7N_5O_2] \xrightarrow{k_{app}} [C_{13}H_{13}N_5O_2]_o \quad (5)$$

As shown in Eq. (5), the change rate of these components is

$$\frac{-\mathrm{d}}{\mathrm{d}t}[C_8H_7N_5O_2] = -k_{app}[C_8H_7N_5O_2]_o \quad (6)$$

Eq. (6) can be integrated as

$$\ln \frac{[C_8H_7N_5O_2]_o}{[C_8H_7N_5O_2]_{o,i}} = -k_{app}\, t \quad (7)$$

or

$$[C_8H_7N_5O_2]_o = [C_8H_7N_5O_2]_{o,i} e^{-k_{app} t} \quad (8)$$

The conversion of $C_{13}H_{13}N_5O_2$ is defined as

$$(1 - x) = \frac{[C_8H_7N_5O_2]_o}{[C_8H_7N_5O_2]_{o,i}} \quad (9)$$

Eq. (8) can be modified as

$$-\ln(1 - x) = k_{app}\, t \quad (10)$$

RESULTS AND DISCUSSION

The reaction of 3-methyl-4-[(*E*)-pyrimidin-4-yl diazenyl]isoxazol-5(4*H*)-one **4a** with 3-chloro-3-methyl-1-butyne **5** in the presence of aqueous potassium hydroxide and catalytic amount of TAC_nA (PTC) was carried out. The pseudo-first-order reaction conditions were maintained upon taking into consideration excess amount of 3-chloro-3-methyl-1-butyne and aqueous potassium hydroxide. It was noticed that, in the absence of phase-transfer catalyst, no final product was isolated by the reaction of 3-chloro-3-methyl-1-butyne **5** with 3-methyl-4-[(*E*)-pyrimidin-4-yldiazenyl]isoxazol-5(4*H*)-one **4a** for 2.5 h. The reason was that 3-chloro-3-methyl-1-butyne could be easily hydrolyzed in aqueous solution resulting no reaction with 3-methyl-4-[(*E*)-pyrimidin-4-yl diazenyl]isoxazol-5(4*H*)-one **4a.** However, the addition of small amount of TAC_nA changes the scenario dramatically and the 7-[4′-(3′-methylisoxazolyl-5′(4′*H*)-one)-8-(2′-methylprop-1′-en-1′-yl)-7*H*-purine **8a** was isolated in good yields. The reaction catalyzed by TAC_nA has taken place predominantly in bulk organic phase and/or at benzene–water interface.

Effect of Catalyst

The influence of the catalyst concentration in aqueous solution upon the initial reaction rate is shown in Fig. 3. The catalytic activities of TAC_nA increase in the order of $TAC_4A < TAC_6A < TAC_8A$. It is assumed that these differences are attributable to their cavity sizes. The reaction follows pseudo-first-order reaction rate kinetics.

Effect of Amount of Catalyst

The effect of amount of catalyst was studied by varying the amount of catalyst from 0.5 to 2.5 mmol. As shown in Fig. 4, the rate constant continuously increases as the amount of catalyst was increased. The rate of reaction was directly proportional to the catalyst amounts. A graph of the pseudo-first-order rate constant versus the amount of catalyst (Fig. 4) suggested that the rate of reaction is linearly dependent on the amount of catalyst. The increase in rate was observed owing to the increase in number of active sites for the interaction at the benzene–water interface. The large cavity size in the calix[*n*]arenes system provides stabilization of 3-chloro-3-methyl-1-butyne at the benzene–water interface and increases the probability of interaction.

Effect of Amount of Substrate

Effect of amount of substrate was investigated by varying the substrate concentration from 5 to 25 mmol and keeping constant all other parameters. The effect of amount of substrate is shown in Fig. 5. The observed pseudo-first-order rate constant decreases as the amount of the substrate increases. These results suggest that the concentration of the substrate in organic phase is not important and that at the interface may be vital. The kinetics is not simple with respect to substrate in the reaction in which the interfacial mechanism is operative.

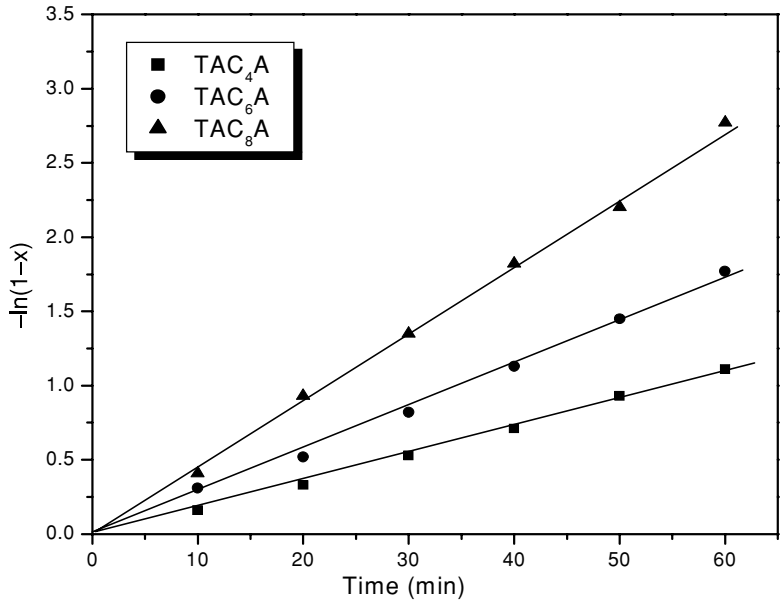


Figure 3 A plot of $-\ln(1-x)$ versus time for different catalysts: 10 mmol of 3-methyl-4-[(*E*)-pyrimidin-4-yldiazenyl]isoxazol-5(4*H*)-one **4a**, 1.0 mmol catalyst, 10 mL of 50% of KOH, 20°C temp, stirring speed = 800 rpm.

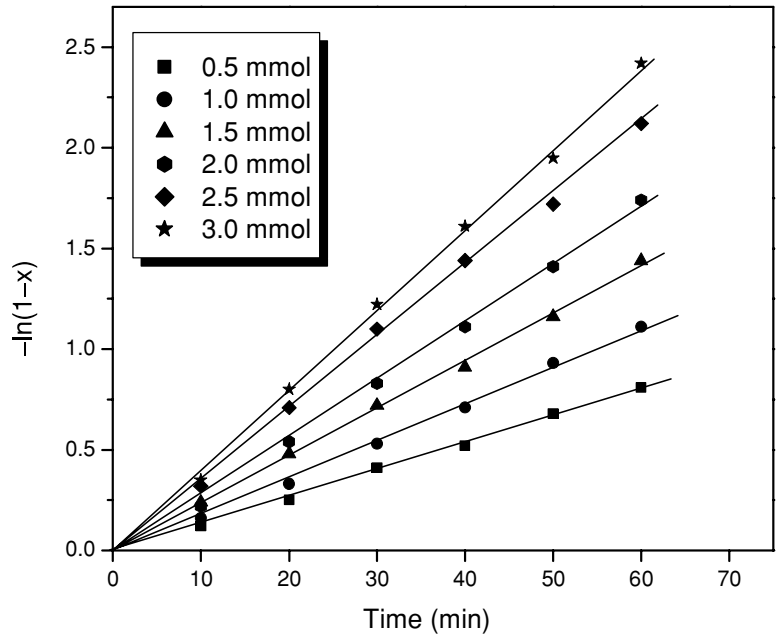


Figure 4 Effect of amount of TAC_4A on the synthesis of 7-[4′-(3′-methylisoxazolyl-5′(4′*H*)-one)-8-(2′-methylprop-1′-en-1′-yl)-7*H*-purine **8a**: 10 mmol of 3-methyl-4-[(*E*)-pyrimidin-4-yldiazenyl]isoxazol-5(4*H*)-one **4a**, 10 mL of 50% of KOH, 20°C temp, stirring speed = 800 rpm.

Effect of Temperature

Temperature is an important factor in affecting the reaction rate, because side reactions could be induced at a temperature higher than 50°C. The effect of temperature on the rate was studied in the range of 20–40°C when the reaction conditions were 10 mmol 3-methyl-4-[(*E*)-pyrimidin-4-yldiazenyl]isoxazol-5(4*H*)-one **4a**, 1.0 mmol of TAC_4A, 10 mL of 50% of KOH, and 800 rpm stirring speed. Evidence of irreversibility and

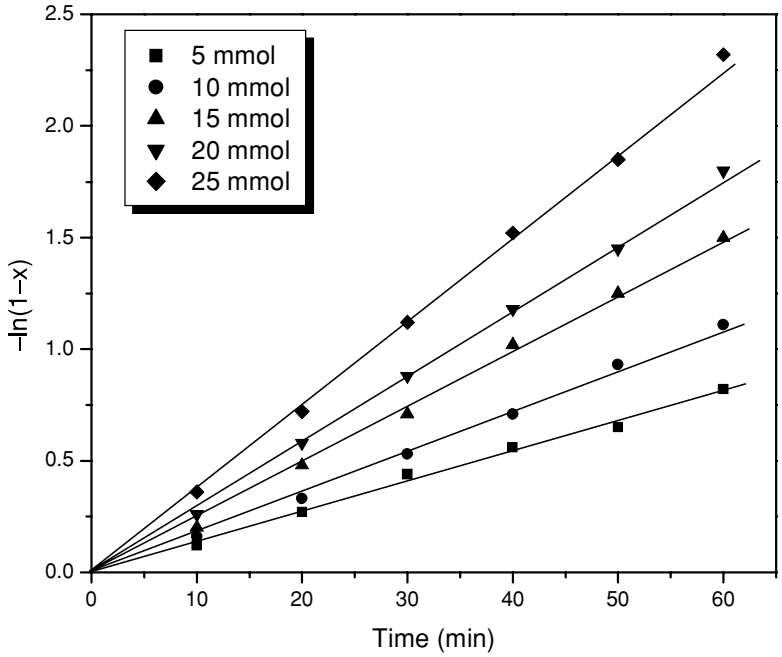


Figure 5 Effect of amount of 3-methyl-4-[(*E*)-pyrimidin-4-yl diazenyl]isoxazol-5(4*H*)-one **4a** on the synthesis of 7-[4′-(3′-methylisoxazolyl-5′(4′*H*)-one)-8-(2′-methylprop-1′-en-1′-yl)-7*H*-purine **8a**: 1.0 mmol of TAC_4A, 10 mL of 50% of KOH, 20°C temp, stirring speed = 800 rpm.

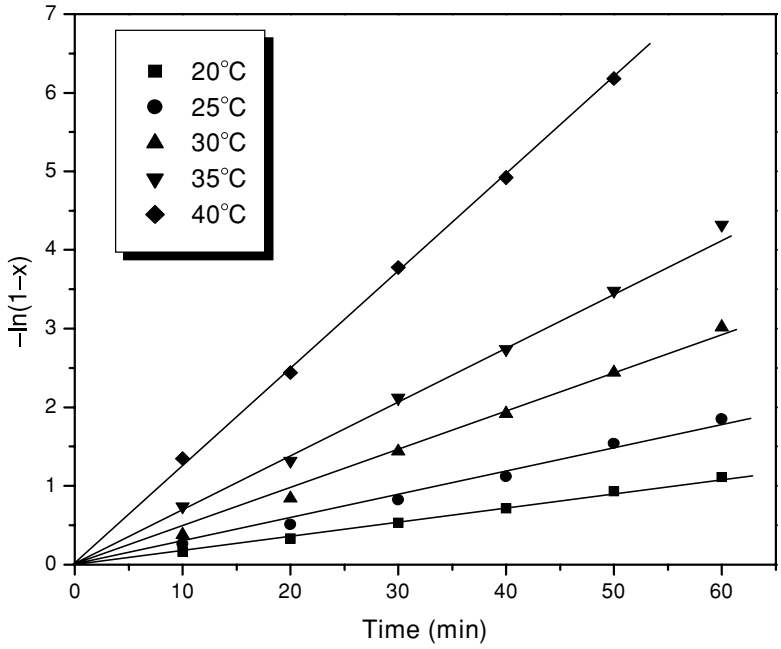


Figure 6 Effect of temperature on the synthesis of 7-[4′-(3′-methylisoxazolyl-5′(4′*H*)-one)-8-(2′-methylprop-1′-en-1′-yl)-7*H*-purine **8a**: 10 mmol of 3-methyl-4-[(*E*)-pyrimidin-4-yl-diazenyl]isoxazol-5(4*H*)-one **4a**, 1.0 mmol of TAC_4A, 10 mL of 50% of KOH, stirring speed = 800 rpm.

pseudo-first-order kinetics was shown in Fig. 6. The plot of $-\ln(1-\times)$ versus time for all of temperatures resulted a straight line. These results also justify the use of Eq. (11) to calculate the constant k_{app}. From Fig. 6 it was also found that the reaction rate is increased with an increase in the temperature. The reason was

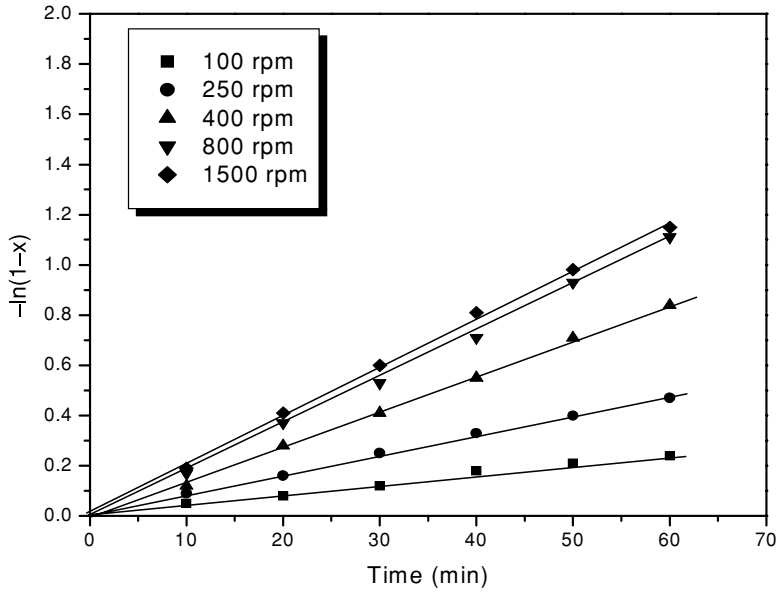


Figure 7 Effect of stirring speed on the synthesis of 7-[4′-(3′-methylisoxazolyl-5′(4′*H*)-one)-8-(2′-methylprop-1′-en-1′-yl)-7*H*-purine **8a**: 10 mmol of 3-methyl-4-[(*E*)-pyrimidin-4-yldiazenyl]isoxazol-5(4*H*)-one **4a**, 1.0 mmol of TAC_4A, 10 mL of 50% of KOH, 20°C temp.

that the energy of reactant molecules is higher and the collision between the molecules is also increased at a higher temperature.

Effect of Stirring Speed

The mass transfer between two phases is an important factor in affecting the rate of reaction. In this work the solution is agitated to enhance the mass transfer of component between two phases. Figure 7 shows the effect of various stirring speeds on the reaction rate. Below 800 rpm, the reaction was highly affected by the stirring speed in which the mass transfer plays an important role. It was increased with an increase in the stirring speed up to 800 rpm. A further increase in the stirring speed shows no significant change in the rate of reaction. The reaction was insensitive to the stirring speed more than 800 rpm.

CONCLUSION

In this work a new route to the synthesis of 7-[4′-(3′-methylisoxazolyl-5′(4′*H*)-one)-8-(2′-methylprop-1′-en-1′-yl)-7*H*-purine **8a–c** has been explored using PTC conditions. Calix[*n*]arenes (TAC*n*A) are used as a new class of PTC. To define the kinetic model, the effects of various parameters were studied and it was stabilized that the reaction follows first-order kinetics. Calix[*n*]arenes are found to play an enormous role in PTC processes due to greater van der Waal interactions and large cavity size (surface area) to fit the interacting molecule, which results in stabilization of interacting molecules and an increase in the rate of reaction.

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