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Graphical Abstract

Organocatalysis by *p*-sulfonic acid calix[4]arene: a convenient and efficient route to 2,3-dihydroquinazolin-4(1*H*)-ones in water

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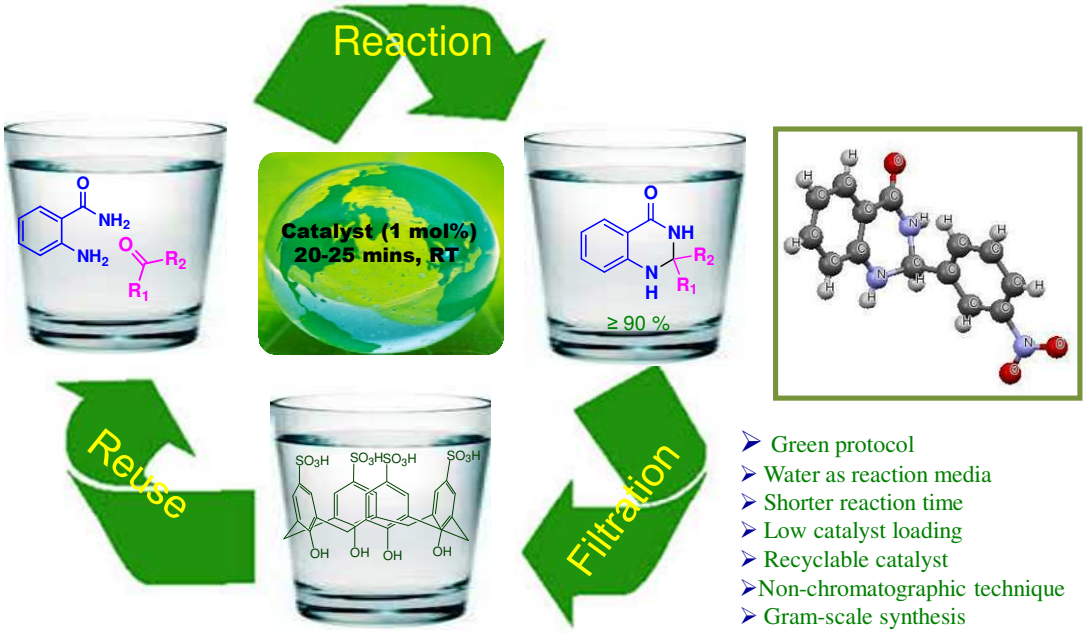

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Organocatalysis by *p*-sulfonic acid calix[4]arene: a convenient and efficient route to 2,3-dihydroquinazolin-4(1*H*)-ones in water

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An efficient and eco-friendly method is reported for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones from the direct cyclocondensation of anthranilamide with aldehydes using *p*-sulfonic acid calix[4]arene (*p*-SAC) as a recyclable organocatalyst in excellent yields in water at room temperature. The catalyst was reusable without significant loss of catalytic efficiency. Operational simplicity, the compatibility with various functional groups, non-chromatographic purification technique, high yields and mild reaction conditions are the notable advantages of this procedure. Large scale reaction demonstrated the practical applicability of this methodology.

Introduction

Catalysis has played a crucial role in the success of the chemistry in the twentieth century.[1] Nowadays organocatalysis is one of the hot research topics in advanced organic chemistry. In the past decade, organocatalysis has opened a new window for carrying out organic transformations and has become a powerful tool in the synthesis of biologically active and structurally complex compounds.[2] Compared with transition-metal catalysts, the cost and toxicity of organocatalysts are low, thus making organocatalysts beneficial for the production of pharmaceutical intermediates.[2,3] Moreover, organocatalysts are tolerant of water and air, are usually easy to use and finally avoidance of expensive metal reagents or catalysts.[4]

The development of eco-friendly methodologies that are environmentally benign and waste-free, as well as being able to produce the desired products in high purity, have received much attention in recent years because of the increasing tendency of the chemical industry towards greener processes.[5] The major drive towards this idea is the replacement of volatile organic solvents by green solvents,[6] as organic solvents are the major contributors to environmental pollution. In this view, water is the most ideal solvent[7] and the use of water in organic reactions as solvent has received much attention.[8] Water is a safe, harmless and environmentally benign solvent in comparison with a large number of harmful organic solvents; the unique physicochemical properties of water can even accelerate some reactions.[9] However, the poor solubility of most organic compounds in water often makes an unfavorable impact on water mediated organic synthesis. Therefore, the development of water-tolerant catalysts that allow organic reactions to be carried out in aqueous media is a challenging task in the field of green catalysis. Aqueous biphasic reaction systems using water-soluble catalysts have the practical advantages that the catalysts can be reused after simple decantation or extraction of the water-insoluble products and the catalysts show high catalytic activity in water.[10] The thought of environmental factor (E-factor) and atom economy have gradually become incorporated into conventional organic synthesis in both industry and academia. Solvents are the main reason for an insufficient E-factor, especially in synthesis of fine chemicals and pharmaceutical industries.[11]

The calixarenes are a class of cyclooligomers formed *via* condensation between *para* substituted phenols and formaldehyde.[12] Calixarenes are good receptors for the complexation with various kinds of guests such as anions, cations and neutral organic/inorganic molecules.[13] Calixarenes have been widely used in sensors, enzyme-mimics, ion carriers, solid-phase support materials, ion selective electrodes, drug-delivery agents etc.[14] The discovery of water-soluble calixarenes as catalyst in organic reaction has attracted the attention of researchers with the objective of faster reaction and use of lower amount of catalyst.[15] In this sense, water-soluble calix[*n*]arenes could be used as surfactant-type Brønsted acid catalyst to facilitate the reactions through the formation of a host-guest complex, with a nucleophile component in the organic-aqueous interfacial layer.[10] So the use of calix[*n*]arenes as catalyst in water is in demand from the aspect of green chemistry. However the use of calixarenes as catalyst in water is very rare.[15*a*]

The *N*-containing heterocyclic compounds play a crucial role in the field of drug scaffolds, synthetic organic chemistry, medicinal chemistry as well as material sciences.[16] 2,3-Dihydroquinazolinone derivatives act as important intermediates in the synthesis of drug molecules, and natural products.[17] These also exhibit various activities such as antitumor, anti-cancer, antibiotic, antidefibrillatory, antipyretic, analgesic, antihypertonic, diuretic, antihistamine, antidepressant, and vasodilating agents[18] (Fig 1).

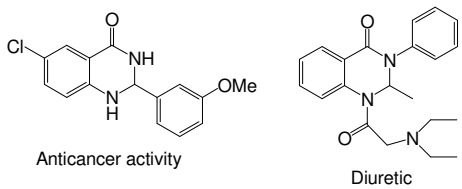
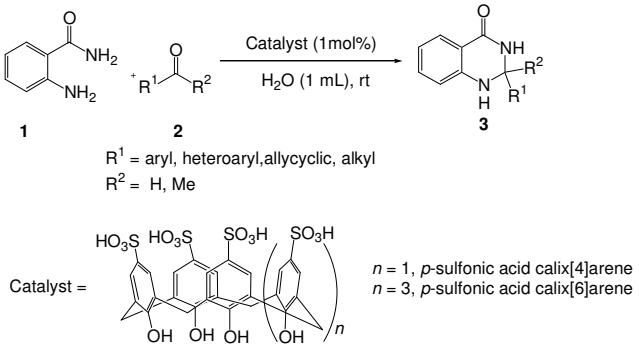


Fig. 1 Biologically important quinazolinone derivatives.

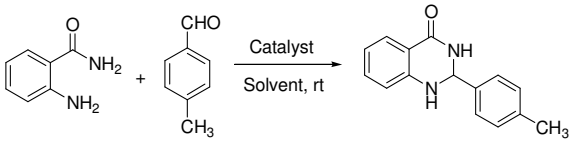
In view of their significant uses, green methodologies for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones should be benefited in the synthetic and medicinal chemistry. Although numerous protocols have been developed for the synthesis of 2,3-dihydroquinazolinones,[19] regardless their efficiency and reliability, most of these methods suffer from one or more of these disadvantages, such as the use of hazardous organic solvents, requires higher temperature, low yields, strongly acidic conditions, expensive moisture sensitive catalysts, and tedious work-up procedure. Therefore, it is important to develop economically and environmentally more viable procedure for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones. Very recently, we have developed an environmentally benign greener strategy using recyclable nano indium oxide as catalyst for the one-pot synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones by a three-component condensation of isatoic anhydride with primary amines or ammonium salts and aromatic aldehydes in ethanol.[19*o*] As a part of our ongoing research for the synthesis of heterocycles through a greener way,[19*o*,20] herein we report a simple and practical metal-free method for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones by the cyclocondensation of anthranilamide with aldehydes using *p*-sulfonic acid calix[4]arene (*p*-SAC) as a recyclable organocatalyst in water at room temperature (Scheme 1).



Scheme 1 Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones.

We started our study with preparing *p*-sulfonic acid calix[*n*]arenes in our laboratory according to the literature procedure.[21] Next the catalytic activity of these organocatalyst were investigated for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones. In order to find out the optimum reaction conditions, we have selected the reaction of anthranilamide **1** and 4-methylbenzaldehyde **2a** as the model reaction (Table 1). To our delight, the desired product **3a** was obtained in 92% yield in presence of 1 mol% *p*-sulfonic acid calix[4]arene (*p*-SAC) in water at room temperature for 20 min (Table 1, entry 1). No further improvement was noticed by increasing the reaction time (Table 1, entry 2). Increasing the amount of catalyst (5 mol%) did not improve the yield noticeably (Table 1, entry 3,) whereas decreasing the amount of catalyst (0.5 mol%) decreased the yield (Table 1, entry 4). To clarify the role of the catalyst (*p*-SAC) in this process, the same reaction was carried out without *p*-SAC (Table 1, entry 5). However the reaction did not proceed at all without the catalyst after 20 min of reaction. Water appeared to be the best choice as solvent among the common solvents like MeOH, MeCN, toluene, DMF, 1,2-DCE (Table 1, entries 6-10). The reaction did not proceed well in absence of any solvent (Table 1, entry 11). The chain length of calixarenes also played a significant role. By increasing the chain length of 4 to 6 (n = 1 to 3) the yield of the desired product decreased noticeably (Table 1, entry 12). To explore the role of *p*-sulfonic acid calix[4]arene (*p*-SAC) we used *p*-hydroxy benzenesulfonic acid (*p*-HSA) as a catalyst. It was observed that *p*-HSA was less efficient than *p*-SAC (Table 1, entry 13). This indicates that the sulfonyl and phenolic groups in calixarene moiety are not solely responsible for fast and efficient reaction. On the other hand, *p*-TSA was not also effective for this conversion (Table 1, entry 14). Phenol was less efficient than *p*-SAC (Table 1, entry 15). Other Brønsted acid catalyst like *p*-dodecylbenzenesulfonic acid (DBSA, Kobayashi's catalyst[2*m*]) was also tested, but no improvement of the yield was observed (Table 1, entries 16). Thus, optimal reaction conditions were obtained using anthranilamide (**1**, 1 mmol), 4-methylbenzaldehyde (**2a**, 1 mmol) in presence of 1 mol% of *p*-sulfonic acid calix[4]arene (*p*-SAC) in water (1 mL) at room temperature for 20 min (Table 1, entry 1).

Table 1 Optimization of the reaction conditions[a]



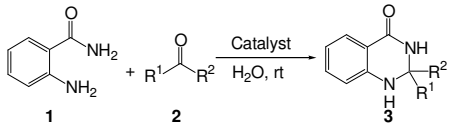
Entry	Catalyst (mol%)	Solvent (1 mL)	Time (min)	Yields (%)[b]
1	*p*-SAC (1)	H_2O	20	92
2	*p*-SAC (1)	H_2O	60	92
3	*p*-SAC (5)	H_2O	20	93
4	*p*-SAC (0.5)	H_2O	20	84
5	-	H_2O	20	n. r.[c]
6	*p*-SAC (1)	MeOH	20	80
7	*p*-SAC (1)	MeCN	20	72
8	*p*-SAC (1)	Toluene	20	38
9	*p*-SAC (1)	DMF	20	75
10	*p*-SAC (1)	DCE	20	32
11	*p*-SAC (1)	-	20	20
12	*p*-Sulfonic acid calix[6]arene [n = 3] (1)	H_2O	20	67
13	*p*-HSA (1)	H_2O	20	60
14	*p*-TSA (1)	H_2O	20	57
15	Phenol (1)	H_2O	20	18
16	DBSA (5)	H_2O	20	58

[a] *Reaction conditions*: 1 mmol of **1** and 1 mmol of **2a** in the presence of catalyst and solvent (1 mL) at room temperature. [b] Isolated yields. [c] No reaction. *p*-SAC = *p*-Sulfonic acid calix[4]arene. *p*-HSA = *p*-Hydroxybenzenesulfonic acid. *p*-TSA = *p*-Toluenesulfonic acid. TBAB = Tetrabutyl ammonium bromide. DBSA = *p*-Dodecylbenzenesulfonic acid.

Next, we studied the scope and limitation of this reaction by employing a wide range of aldehydes (**2**) under optimized reaction conditions. The results are summarized in Table 2. To our delight, the corresponding dihydroquinazolin-4(1*H*)-ones (**3**) were obtained with good to excellent yields in all cases. Aromatic aldehydes with electron-donating as well as electron-withdrawing substituents reacted very well, affording good to excellent yields

of 2,3-dihydroquinazolinones. The chloro- and bromo-substituted benzaldehydes afforded the corresponding products **3d** and **3e** in 87% and 86% yields respectively. Substituent at the *ortho* position of the phenyl ring also afforded the corresponding products with excellent yields (**3j** and **3k**). Heteroaryl aldehyde like 2-thiophenecarboxaldehyde was also compatible under this reaction conditions to give the desired product (**3p**) without polymerization. Gratifyingly, the current methodology is also applicable for the aliphatic aldehydes. Cyclohexane carboxaldehyde gave the desired product (**3q**) with high yield. Butyraldehyde also afforded the corresponding 2,3-dihydroquinazolinone (**3r**) with good yield however longer reaction time is required. Moreover, ketone like acetone also afforded the desired product (**3s**) with moderate yield. The all synthesized compounds have been characterized by spectral and analytical data. Results in Table 2 clearly show that the present protocol is indeed superior to several reported methods in terms of product yields, reaction time, avoiding the use of volatile organic solvents, and reaction temperature. Moreover, we have developed a greener reaction conditions bearing lower E-factor[11,22] of 0.17 and 0.15 in the cases of synthesizing **3a** and **3b** respectively (see Supporting Information).

Table 2 Substrates scopes of the reaction[a]



1 2 3

Entry	R^1	R^2	Products	Time (min)	Yields (%)[b]
1	4-Me-C_6H_4	H	**3a**	20	92, 86[c]
2	Ph	H	**3b**	18	94
3	4-MeO-C_6H_4	H	**3c**	20	90
4	4-Cl-C_6H_4	H	**3d**	22	87
5	4-Br-C_6H_4	H	**3e**	22	86
6	4-NO_2-C_6H_4	H	**3f**	25	82
7	4-MeS-C_6H_4	H	**3g**	20	88
8	4-CN-C_6H_4	H	**3h**	22	86
9	4-OH-C_6H_4	H	**3i**	24	82
10	2-Cl-C_6H_4	H	**3j**	20	90
11	2-OH-C_6H_4	H	**3k**	22	88
12	4-OH-3,5-$(OMe)_2$-C_6H_2	H	**3l**	24	84
13	5-Br-2-OH-C_6H_3	H	**3m**	22	85
14	3-NO_2-C_6H_4	H	**3n**	24	88
15	1-Pyrenyl	H	**3o**	26	82
16	2-Thiophenyl	H	**3p**	22	86
17	Cyclohexyl	H	**3q**	30	82
18	C_3H_7	H	**3r**	40	68
19	CH_3	CH_3	**3s**	90	64

[a] Reaction conditions: **1** (1 mmol), **2** (1 mmol) in water (1 mL) at room temperature in presence of 1 mol% of *p*-SAC. [b] Isolated yields. [c] **1** (20 mmol), **2a** (20 mmol) in water (20 mL) at room temperature in presence of 1 mol% of *p*-SAC.

The dihydroquinazolinones were generally precipitated from the reaction mixtures and the solid precipitation was filtered off and recrystallized from hot ethanol to obtain pure products. This methodology is also applicable on a gram-scale synthesis. We have successfully synthesized the dihydroquinazolinone **3a** in 86% yield by the reaction of anthranilamide (**1**, 20 mmol) and 4-methylbenzaldehyde (**2a**, 20 mmol) (Table 2, entry 1).

Finally the single crystal X-ray diffraction analysis of **3n** was carried out for further confirmation of the structure of product (Fig. 2).[23] In crystalline state the compound shows the 2,3-dihydroquinazoline moiety is planar. The pyrimidine ring is in a flattened half-chair conformation. The nitro-substituted benzene ring forms dihedral angle of 85.91°, with the benzene ring of the dihydroquinazoline group. In the crystal, molecules are arranged in crisscross manner along *a*-axis, with N—O…H hydrogen bonds linking molecules at 2.451 to 2.708 Å in the extended network. Short contacts of hydrogen bonding interaction related to carbonyl oxygen atoms with neighboring hydrogen atoms is observed with O…H distances ranging from 2.080 to 2.636 Å.

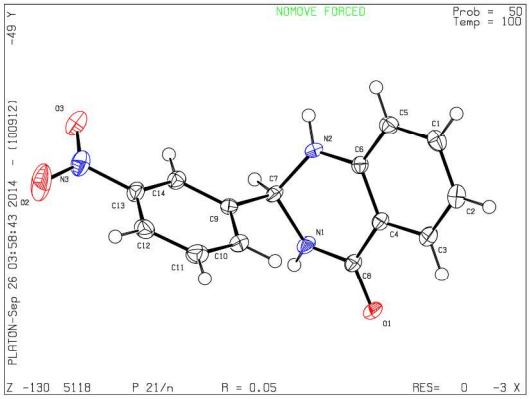


Fig. 2 The single crystal XRD structure of compound **3n.**

Next, we turned our attention towards the recovery and reusability of the catalyst. For this purpose, we have chosen the reaction of anthranilamide (**1**) with 4-methylbenzaldehyde (**2a**) in presence of 1 mol% *p*-sulfonic acid calix[4]arene (*p*-SAC) in water at room temperature as the model reaction. After completion of the reaction distilled water was added to the reaction mixture. The reaction mixture was then filtered off and the catalyst was recovered by evaporating the water. Pure product was obtained by recrystallizing the residue from hot ethanol. The recovered catalyst was reused for a subsequent fresh batch of the reaction. The catalytic activity was checked upto fourth cycle and it showed similar (Table 3).

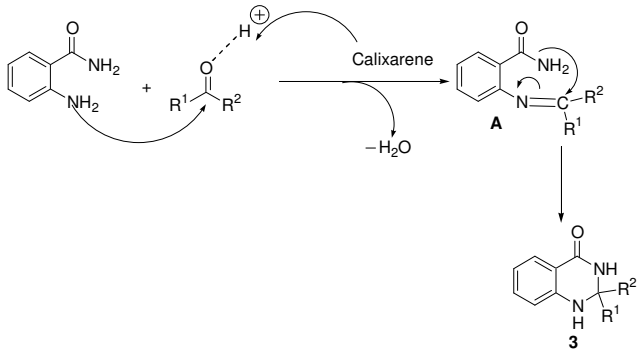
Table 3 Recycling of the *p*-sulfonic acid calix[4]arene (*p*-SAC) for synthesizing **3a**[a]

Entry	Run	Yield (%)[b]
1	1st	92
2	2nd	92
3	3rd	90
4	4th	89
5	5th	87

[a] Carried out with 1 mmol of **1** and 1 mmol of **2a** in presence of catalyst in water (1 mL) at room temperature. [b] Isolated yields.

Based o the literature reports,[19g] a plausible mechanistic pathway to 2,3-dihydroquinazolin-4(1*H*)-ones (**3**) is illustrated in

Scheme 2. In the initial step, condensation of anthranilamide (**1**) with the aldehyde (**2**) gives imine **A**, which upon intramolecular cyclization afforded the final product **3**. The catalyst might activate the aldehyde through the co-ordination with the oxygen of the corresponding carbonyl group which facilitates the subsequent nucleophilic attack by the nitrogen atom on the carbonyl carbon.



Scheme 2 Plausible mechanistic pathway

Conclusions

In summary, we have demonstrated a remarkable catalytic activity of *p*-sulfonic acid calix[4]arene (*p*-SAC) as an organocatalyst for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones by the condensation between various aldehydes and anthranilamide in water at room temperature. This protocol is also applicable on a gram-scale synthesis. Clean reaction, ease of product isolation, short reaction time, mild reaction conditions (room temperature), low catalyst loading, low E-factor, and use of water as solvent are the notable advantages of the present methodology and these features make this procedure to be a green synthetic protocol. We believe that our novel procedure will open up a new practical and convenient route for the synthesis of biologically important 2,3-dihydroquinazolin-4(1*H*)-ones.

Experimental section

General: Melting points were determined on a glass disk with an electric hot plate and are uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were run in in $CDCl_3$ & DMSO-d_6 solutions (Bruker Avance 400). Chemical shift were recorded as δ values in parts per million (ppm), and the signals were reported as s (singlet), d (doublet), t (triplet), m (multiplet) and coupling constants *J* were given in Hz. IR spectra were taken in a Perkin Elmer FTIR-Spectrum 400. Commercially available substrates were freshly distilled before the reaction. Solvents, reagents and chemicals were purchased from Sigma Aldrich and Merck.

General procedure for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones

p-Sulfonic acid calix[4]arene (1 mol%) was added to a solution of anthranilamide (1 mmol) and aldehyde/ketone (1 mmol) in water (1 mL) and the mixture was stirred at room temperature for a specified period of time. After completion of the reaction, cold distilled water (5 mL) was added to the reaction mixture. Then the product was filtered off and the catalyst was recovered by evaporating the water. The recovered catalyst was reused for a subsequent fresh batch of the reaction after reactivation. The crude product was recrystallized from hot ethanol to afford the pure product.

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Notes and references

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†Electronic Supplementary Information (ESI) available: [^{1}H, ^{13}C NMR data and Spectra, crystallographic data, E-factor calculations]. See DOI: 10.1039/b000000x/

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