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Introduction

The quinoxaline-based compounds exhibit a broad spectrum of biological activities¹ and find applications as useful materials.² These have inspired synthetic organic/medicinal chemists to develop new and more efficient synthetic methodologies for the preparation of quinoxaline derivatives. The various approaches (Scheme 1) involve the Lewis/Brønsted acid or Lewis base promoted reaction of *o*-phenylenediamine (commercially available or prepared *in situ* through the reduction of the corresponding *o*-nitroaniline) with (i) 1,2diketone/1,2-ketomonoxime (Route A);³ (ii) α -hydroxyketone/ α -haloketone/1,2-diol or α -methyleno ketone (Route B);⁴ (iii) an appropriately substituted epoxide (Route C);⁵ (iv) substituted alkynes (Route D)⁶ under heating or microwave irradiation.

These routes are associated with the necessity/use of (i) special efforts for the preparation of the starting material or catalyst system, (ii) potentially hazardous additional/auxiliary

Surfactant micelles as microreactors for the synthesis of quinoxalines in water: scope and limitations of surfactant catalysis[†][‡]

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The scope and limitations of surfactants as catalysts for the synthesis of guinoxalines using microreactors made of the surfactants in water has been assessed. The catalytic potential followed the order: non-ionic surfactants > anionic surfactants > Brønsted acid surfactants > cationic surfactants. The non-ionic surfactant, Tween 40, is the most effective catalyst affording excellent yields within a short reaction time at room temperature and is compatible with different variations of the 1,2-diketones and 1,2-diamines. The reaction medium (spent water) containing the catalyst, as well as the catalyst itself (recovered Tween 40) can be reused for five consecutive reactions. The better catalytic efficiency of the surfactant (Tween 40) compared to the various Lewis/Brønsted acids, as well as the surfactant combined Lewis acid, suggests that surfactants, which generate microreactor assemblies at the interface, are better suited as catalytic aids to promote organic reactions in water. The inferior results obtained in organic solvents, which provide a homogeneous reaction mixture compared to those obtained in water, indicate the specific role of water. This has been depicted as a synergistic dual activation through the hydrogen bond mediated formation of supramolecular assemblies involving a water dimer and the reactants. The catalytic assistance of the surfactant could be ascribed to the ability of the surfactant molecule to undergo hydrophobic and hydrogen bond forming interactions with water and the reactants in orienting the reactants at the water interface and encapsulating inside the microreactors to facilitate the cyclocondensation.

> chemicals such as transition/heavy metal based oxidants, (iii) expensive and moisture sensitive reagents/catalysts, (iv) volatile organic solvents, (v) stringent reaction conditions such as high temperature, and (vi) a laborious and complex work-up procedure. In some of the methods, acidic/metallic wastes are generated that are mixed with the effluent water and are a matter of concern since they may cause serious environmental pollution. The contamination of the products with trace amounts of metallic impurities during the metal-



Scheme 1 Synthetic strategies for the construction of the quinoxaline scaffold.

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‡ Experimental section: The glassware to be used in the reactions was thoroughly washed and dried in an oven and the experiments were carried out with the required precautions. Chemicals and all solvents were commercially available and used without further purification. The ¹H and ¹³C NMR spectra were recorded on a 400 MHz NMR spectrometer in CDCl3 with residual undeuterated solvent (CHCl₃: 7.26/77.0) using Me₄Si as an internal standard. The chemical shift (δ) values are given in ppm and J values are given in Hz. The 13C NMR spectra were fully decoupled and were referenced to the middle peak of the solvent CDCl₃ at 77.00 ppm. Splitting patterns were designated as s, singlet; bs, broad singlet; d, doublet; dd, doublet of doublets; t, triplet; and m, multiplet. The mass spectra (MS) were recorded under atmospheric pressure chemical ionization (APCI). The infra-red (IR) spectra were recorded in the range of 4000-600 cm⁻¹ either as neat samples or using KBr for preparing pellets for solid samples. The compounds prepared were routinely checked for their purity on the silica gel GF-254 and visualized under UV light at a wavelength of 254 nm. Melting points were measured using a melting point apparatus and were uncorrected. Evaporation of solvents was performed at reduced pressure, using a rotary evaporator. Preparation of pure water (15 MΩ cm resistivity at 25 °C): The pure water was prepared by subjecting tap water to reverse osmosis and ensuring ionic/organic removal by passing it through a pre-packed cartridge.Preparation of ultrapure water (18.2 MΩ cm resistivity at 25 °C): The ultrapure water was prepared by subjecting the pure water to UV treatment (185/254 nm UV lamp), as well as deionization by passing it through a deionization cartridge, followed by ultra membrane filtration (0.01 µm) under pressures up to 145 psi (10 bar). Ultrapure water (UPW) is generally considered to have a resistivity $\ge 18.2 \text{ M}\Omega \text{ cm}$ at 25 °C, low amounts (ppt) in metals, less than 50 ppt in inorganic anions and ammonia, less than 0.2 ppb in organic anions, and below 1 ppb total organic carbon (TOC) and silica (dissolved and colloidal).General procedure for the synthesis of 2,3-diphenylquinoxaline 3 from the reaction of 1 and 2 in water using Tween 40 as the catalyst (Entry 1, Table 6). To the magnetically stirred solution of Tween 40 (0.32 g, 0.25 mmol, 10 mol%) in water (5 mL), 1a (0.27 g, 2.5 mmol) and 2a (0.52 g, 2.5 mmol, 1 equiv.) were added and the mixture was stirred magnetically at rt until completion (5 min, TLC). The reaction mixture was filtered and the solid residue was washed with water (3 \times 1 mL) and dried under rotary vacuum evaporation to obtain analytically pure 3a (0.69 g, 98%) as a white solid; mp = 125–127 °C; IR (neat) v_{max} = 3401, 1442, 1345, 1261, 1056, 767 cm^{-1} ; ¹H NMR (400 MHz, CDCl₃): δ = 7.77–7.80 (2H, m), 7.50–7.55 (2H, m), 7.32– 7.40 (10H, m); $^{13}{\rm C}$ NMR (100 MHz, CDCl_3): δ = 153.5, 141.2, 139.1, 129.9, 129.8, 129.2, 128.8, 128.2; MS (APCI) m/z 283.32 (M + H)⁺ identical with an authentic sample.3a The remaining compounds were prepared following this general procedure except for 2,3-bis(4-methoxyphenyl)-6-nitroquinoxaline (entry 12, Table 6) and the physical and spectral data were in conformity with the reported data.General procedure for the synthesis of 2,3-bis(4-methoxyphenyl)-6nitroquinoxaline from the reaction of 1b and 2b in water using Tween 40 as the catalyst (Entry 12, Table 6): To the magnetically stirred solution of Tween 40 (0.32 g, 0.25 mmol, 10 mol%) in water (5 mL), 1b (0.38 g, 2.5 mmol) and 2b (0.67 g, 2.5 mmol, 1 equiv.) were added and the mixture was heated under reflux (oil bath, 110 °C) until the completion of the reaction (6 h, TLC). The reaction mixture was filtered and the solid residue was washed with water (3 \times 1 mL) and dried under rotary vacuum evaporation to obtain analytically pure **3a** (0.92 g. 95%) as a yellow solid; mp = 193–194 °C; IR (KBr) $\nu_{\rm max}$ = 3412, 1765, 1556, 1345, 1035, 750 cm⁻¹; ¹H NMR (400 MHz, CDCl3): δ = 9.01 (d, J = 2.4 Hz, 1H), 8.47 (dd, J = 2.3 Hz & 9.1 Hz, 1H), 8.22 (d, J = 9.1 Hz, 1H), 7.54–7.58 (m, 4H), 6.89–6.91 (m, 4H); MS (APCI) m/z 343.41 (M + H)⁺, identical with an authentic

sample.^{24c}Procedure for higher scale synthesis of 3a, recyclability of the spent water containing the catalyst (Tween 40), and catalyst recovery after end use (Table 10): To the solution of Tween 40 (1.3 g, 1 mmol, 10 mol%) in water (40 mL), 1a (1.1 g, 10 mmol) and 2a (2.1 g, 10 mmol, 1 equiv.) were added and the mixture was stirred magnetically at rt until the completion of the reaction (10 min, TLC). The reaction mixture was filtered and the solid residue was washed with water (3×5 mL) and dried under rotary vacuum evaporation to obtain analytically pure 3a (2.76 g, 98%) as a white solid.^{3a} The aqueous filtrate (spent water) was successively used for further reactions (four consecutive fresh batches/runs) to afford 3a in excellent yields (2.67 g, 95%; 2.7 g, 96%, 2. 67 g, 95%, and 2.59 g, 92%, respectively). After the 4th recycling, the spent water was extracted with EtOAc (3×5 mL) to remove the traces of organic contaminants and was subjected to freeze drying to recover the Tween 40 (1.0 g, 82%), which was found to be identical (¹H NMR) to the authentic sample.

catalyzed reactions poses a serious problem in cell/enzymebased biological evaluation. Therefore, there is a need to develop an efficient and environmentally friendly protocol for the synthesis of quinoxaline derivatives as the generation of new hits/leads for potential therapeutic applications requires a convenient, selective and high yielding synthetic method to meet the needs for a timely supply of the designed molecules for biological evaluation.⁷ The considerable influence of green chemistry tools on medicinal chemistry and chemistry research based organisations⁸ drives the requirement to enrich the medicinal chemist's tool box through the improvement of existing transformations for a more general application and making them amenable to parallel chemistry, as well as potentially broadening the diversity of compounds for use in medicinal chemistry purposes.⁹

The development of eco-friendly/green approaches (sustainable development) is an ongoing demand and a subject of current interest due to the adverse effect of the manufacturing processes of drugs and pharmaceuticals on the environment.¹⁰ The major drive towards this initiative is the replacement of volatile organic solvents (VOSs) by green reaction media,¹¹ as VOSs are the major contributors to environmental pollution due to their abundant use (more than 85% of the total mass utilization of a chemical process) and incomplete recovery efficiency (50-80%).12 In this regard, water is the most preferred solvent^{8,13} and the use of water as a non-classical medium for organic reactions has received increasing popularity.¹⁴ However, the poor solubility of most organic compounds in water often makes an adverse impact on water mediated organic synthesis and this has brought to light the use of surfactants¹⁵ in aqueous organic reactions. Herein we describe an extremely efficient and green protocol for the synthesis of functionalized quinoxalines in water using Tween 40 as a catalyst.

Results and discussion

Although the use of surfactants in aqueous organic reactions is popularly correlated with the beneficial effect of the surfactants as solubility aids for the water insoluble organic reactants, the specific role of the surfactants may extend beyond the scope as solubility enhancers.¹⁶ Surfactants often form microreactors at the oil-water interface and find various applications such as ion trapping,¹⁷ size-controlled synthesis of metallic nanoparticles,18 and solubilising reservoirs for drugs, nutraceuticals, anti-oxidants and other compounds.¹⁹ The utility of the microreactors has also been demonstrated in performing organic reactions.²⁰ In a model study, 1,2diaminobenzene 1a was treated with benzil 2a in water in the absence of any additional agent at rt for 1 h (Scheme 2). However, a poor conversion (32% yield) to the desired product of 2,3-diphenylquinoxaline 3a was observed. Therefore, various neutral, anionic, cationic and Brønsted acid surfactants were used to investigate whether they had any beneficial effect on the formation of 3a (Table 1).



Scheme 2 Comparison of the catalytic efficiency of Tween 40 with that of the catalysts reported for quinoxaline formation in aqueous media.

The presence of a suitable surfactant as a catalytic aid was found to be essential, as in the absence of any surfactant a poor result was obtained (entry 1).²¹ Amongst the anionic surfactants, the best results were obtained with sodium dodecylsulfate SDS and sodium dioctylsulfosuccinate SDOSS (entries 2 and 3). Many non-ionic surfactants (entries 15–23) exhibited very good catalytic activities. However, the cationic surfactants (entries 7–14), as well as the Brønsted²² acid type surfactant (entry 6), gave moderate results. Although the reported procedure used the non-ionic surfactant PEG-600 as a cosolvent with water (5 mL of 1 : 1 PEG-600 and water for 1 mmol of 1,2-diketone) for quinoxaline synthesis,²³ lesser yields are obtained when using various PEGs in a catalytic amount (entries 40–48).

In order to determine the most effective catalyst from the panel of the surfactants (*e.g.*, SDS, SDOSS, Triton X 100, Triton X 110, Triton X 114, Triton SP 135, Triton SP 190, Tween 20, Tween 40, Tween 60, and Tween 80) that afforded very good yields (>80%) (Table 1), the electron deficient 1,2-diamine-4-nitrobenzene **1b** was used as a less nucleophilic, diamine representative, treated with **2a** in the presence of these surfactants in water at rt for 5 h (Table 2).

The initial study of performing the reaction for 5 h (Table 2) clearly demonstrated the better catalytic potential of the nonionic surfactants. Tween 40, Triton SP 135, and Triton SP 190 are found to be the most effective catalysts, affording the desired product, 6-nitro-2,3-diphenylquinoxaline **3b**, in 88, 80, and 76% yields, respectively. To have a clear distinction, the reactions were performed for 1 h and Tween 40, Triton SP 135, and Triton SP 190 emerged as the most effective catalysts affording 88, 78, and 75% yields, respectively. Further lowering the reaction time to 0.5 h also could not distinguish between the catalytic potential of these three surfactants.

To distinguish the catalytic potential of Tween 40, Triton SP 135, and Triton SP 190, the reaction of **1b** was carried out with 4,4'-dimethoxybenzil **2b**, which has fewer electrophilic carbonyl groups compared to those in **2a**, in the presence of the selected catalysts (Table 3).

The desired product, 2,3-bis(4-methoxyphenyl)-6-nitroquinoxaline **3c**, was not formed at room temperature in the presence of these surfactants (Table 3, entries 1–3). However, **3c** was obtained in 68, 55, and 92% yields, respectively, when the reactions were carried out under reflux (Table 3, entries 4– 6). The requirement for catalytic assistance by the surfactants

Table 1 Catalytic efficiency of various surfactants for the synthesis of **3a** from **1a** and **2a** in water^a

	$ \begin{array}{c} $	N Ph
Entry	Surfactant	Yield (%) ^b
1	None	32 ^c
2	Sodium dodecylsulfate (SDS)	91
3	Sodium dioctylsulfosuccinate (SDOSS)	90
4	Sodium <i>N</i> -laurovlsarcosine (SNLS)	72
5	Sodium deoxycholate (SDC)	67
U	Brønsted acid	07
6	Dodecylbenzenesulfonic acid (DBSA) Cationic	68
7	Benzalkonium chloride	58
8	Cetvl trimethyl ammonium bromide	62
9	Hexadecyl pyridinium chloride	60
10	Tetrabutylammonium fluoride	58
11	Tetrabutylammonium chloride	53
12	Tetrabutylammonium bromide	50
13	Tetrabutylammonium iodide	42
14	Adogen-464	49
	Non-ionic	
15	Triton X 100	85
16	Triton X 110	95
17	Triton X 114	90
18	Triton SP 135	92
19	Triton SP 190	95
20	Tween 20	92
21	Tween 40	96
22	Tween 60	90
23	Tween 80	85
24	Span 20	62
25	Span 40	65
26	Span 60	63
27	Span 80	62
28	Myrj 49	45
29	Brij ® 93	40
30	Brij S 100	56
31	Labrasol	62
32	Gelucire® 44/14	52
33	Compritol [®] 888	55
34	Capryol	52
35	Labrafil® M2125CS	58
36	Igepal CO-630	50
37	Merpol HCS	52
38	Tetronic 90R4	56
39	β-Cyclodextrin	64
40	PEG-200	55
41	PEG-400	52
42	PEG-600	55
43	PEG-1000	58
44	PEG-2000	53
45	PEG-4600	50
46	PEG-8000	52
47	PEG-10000	53
48	PEG-20000	41

^{*a*} **1a** (0.10 g, 1 mmol) was treated with **2a** (0.21 g, 1 mmol, 1 equiv.) in water (5 mL) for 1 h at rt in the presence of different surfactants (20 mol%). ^{*b*} The isolated yield of **3a**. ^{*c*} The reaction was carried out without any surfactant.

was clearly demonstrated, since **3c** was not obtained in the absence of the surfactant either at rt or under reflux (Table 3, entries 7 and 8).

O ₂ N	$NH_2 + O Ph$ $NH_2 + O Ph$ $1b 2a$	Water, r Surfactan	$t \rightarrow 0_2 N$	N N N Bh
		Yield (%) after ^b	
Entry	Surfactant	5 h	1 h	0.5 h
1	SDS	55	31	
2	SDOSS	45	24	
3	Triton X 114	52	30	
4	Triton SP 135	80	78	77
5	Triton SP 190	76	75	75
6	Triton X 100	56	28	
7	Triton X 110	62	35	
8	Tween 20	66	46	
9	Tween 40	88	88	81
10	Tween 60	60	41	
11	Tween 80	71	52	
12	None	nil		

Table 2 Comparison of the catalytic potential of a few selected surfactants for guinoxaline synthesis in water from **1b** with **2a**^a

^a 1b (0.15 g, 1 mmol) was treated with 2a (0.21 g, 1 mmol, 1 equiv.) in the presence of the surfactant (20 mol%) in water (5 mL) at rt for different time intervals. ^b Isolated yield of **3b**.

The catalytic potential of SDS and SDOSS was assessed further for the formation of 3c (Table 3). Not surprisingly, no product formation was observed when using either SDS or SDOSS during the reaction of 1b with 2b in water at rt for 5 h (Table 3, entries 9 and 10). However, 3c was obtained in 62 and 56% yields when the reactions were performed in water under reflux for 5 h in the presence of catalytic amounts of SDS and SDOSS, respectively (Table 3, entries 11 and 12). Thus, Tween 40 was found to be the most effective catalyst for the preparation of quinoxaline in water. It was observed that apart from its distinctly superior catalytic potential compared to other surfactants, the use of Tween 40 offers advantages in many other aspects. The Tween surfactants are stable, possess a relatively non-toxic profile and are widely used as detergents, emulsifiers and excipients in a number of domestic, scientific, pharmacological and pharmaceutical applications or products, because of its stability.

The reaction of **1b** with **2b** was performed in the presence of Tween 40 in different organic solvents (non-polar, weakly polar, polar, aprotic polar and a few alcohols as protic polar) in which the reactants, as well as the surfactant, are soluble and a homogeneous reaction mixture is formed. However, these led to poor yields and in fact no product formation took place in some of these solvents (Table 3, entries 14, 17, 22, 25, 29, 32, 39, 44, 47) indicating that when the reaction is run in aqueous media, water also plays a role in promoting the reaction. Thus, the role of the surfactant (e.g. Tween 40) could be not only to help solubilize the water insoluble organics (the substrates/ reactants) in the aqueous medium, but it may also play some specific role in promoting the reaction in the aqueous medium. The observation that the use of surfactants may

Table 3 The comparison of the catalytic potential of a few selected surfactants
during the reaction of 1b with 2b to form 3c in water ^a

	~ .00	CH₃	OCH3
Í		Surfactant	
0 ₂ N		Water, rt O ₂ N	N N
-			U OCH
1	b 2b	203	3c
Entry	Surfactant	Solvent	Yield $(\%)^b$
1	Triton SP 125	Water	nil
1)	Triton SP 100	Water	nil
3	Tween 40	Water	nil
1	Triton SP 135	Water	68 ^c
5	Triton SP 190	Water	55 ^c
5	Tween 40	Water	92^c
7	None	Water	nil
8	None	Water	nil^{c}
9	SDS	Water	nil
10	SDOSS	Water	nil
11	SDS	Water	62^c
12	SDOSS	Water	56 ^c
13	Tween 40	PhMe	32^c
14	Tween 40	Dioxane	trace ^c
15	Tween 40	DCM	18^c
16	Tween 40	EtOAc	20^c
17	Tween 40	DMF	nil ^c
18	Tween 40	MeOH	25^c
19	Tween 40	t-BuOH	31 ^c
20	Tween 40	neat	trace ^a
21	Triton SP 135	PhMe	30^{c}
22	Triton SP 135	Dioxane	trace
23	Triton SP 135	DCM	15°
24	Triton SP 135	EtOAc	20°
25	Triton SP 135	DMF	nil
26	Triton SP 135	MeOH	22°
27	Triton SP 135	t-BuOH	25
28	Triton SP 190	PhMe	26
29	Triton SP 190	Dioxane	trace
5U 21	Triton SP 190	DCM EtOAc	15 22 ⁰
20	Triton SP 190	DME	$\frac{22}{\text{nil}^c}$
22	Triton SP 190	MeOH	26 ^c
33	Triton SP 190	t-BuOH	20°
35	SDS	PhMe	2.2 ^c
36	SDS	Dioxane	trace ^c
37	SDS	DCM	16 ^c
38	SDS	EtOAc	18 ^c
39	SDS	DMF	trace ^c
40	SDS	MeOH	26 ^c
41	SDS	t-BuOH	25^c
43	SDOSS	PhMe	24^c
14	SDOSS	Dioxane	trace ^c
45	SDOSS	DCM	15^c
46	SDOSS	EtOAc	18 ^c
47	SDOSS	DMF	trace ^c
48	SDOSS	MeOH	20^{c}
19	SDOSS	t-BuOH	23^c

^a **1b** (0.15 g, 1 mmol) was treated with **2b** (0.27 g, 1 mmol, 1 equiv.) in the presence of the selected surfactants (20 mol%) in different solvent (5 mL) at rt (unless otherwise specified) for 5 h.^b Isolated yield of **3c**. ^c The reaction was carried out under reflux conditions (oil bath 110 $^{\circ}$ C). ^d The reaction was carried out neat at 110 $^{\circ}$ C (oil bath).

not be limited only to their role as solubility aids was highlighted earlier in a communication from this laboratory. This communication describes a non-heme model for oxygen

Table 4 Evaluation of various reaction parameters for the Tween 40 catalysedreaction of 1a and 2a to form 3a in aqueous media at rt^a

Entry	Reaction medium	Amt $(mol\%)^b$	Time (min)	Yield (%)
1	Normal water	20	60	98
2	Distilled water ^d	20	60	98
3	Pure water ^e	20	60	97
4	Ultrapure water ^f	20	60	97
5	Degassed water ^g	20	60	98
6	Normal water	2	60	45
7	Normal water	5	5	72
8	Normal water	10	5	95
9	Normal water	15	5	95
10	Normal water	20	5	96

^{*a*} **1a** (0.10 g, 1 mmol) was treated with **2a** (0.21 g, 1 mmol, 1 equiv.) in the presence of Tween 40 in the specified reaction medium (5 mL) at rt. ^{*b*} The amount of Tween 40 used with respect to **1**. ^{*c*} The isolated yield of **3a**. ^{*d*} Glass distilled water. ^{*e*} The pure water was obtained by purification of normal/tap water through reverse osmosis and ionic/organic removal and has the resistivity of 15 MΩ cm at 25 °C. ^{*f*} The ultrapure water was obtained by further subjecting pure water to UV treatment (185/254 nm), deionization and ultra membrane filtration (0.01 µm under pressure up to 145 psi (10 bar) and has the resistivity of 18.2 MΩ cm at 25 °C. ^{*g*} The degassed water was obtained by bubbling N₂ gas into the glass distilled water with sonication.

activation, a fact that has brought a new dimension to the field of surfactant catalysis.¹⁶ The distinct advantages in rate acceleration (in terms of product yields) in aqueous media compared to organic solvents was further revealed/established when the results of the reactions catalyzed by other surfactants such as Triton SP-135, Triton SP-190, SDS, and SDOSS in aqueous media were compared with those performed in organic solvents (Table 3, entries 20–44).

The influence of the various reaction parameters such as the amount of catalyst, reaction time, and the source of water (e.g., normal/tap, double glass distilled, pure, ultrapure and degassed) as the reaction medium was studied to derive the optimal operational conditions during the reaction of 1a with 2a to form 3a (Table 4). In order to avoid any catalytic influence/assistance, due to the presence of traces of metal ions, dissolved gases or any organic impurities, the reactions were performed in normal/tap water, double glass distilled water, pure water, ultrapure water, and degassed water (Table 4, entries 1-5). As comparable results were obtained when using water from various sources, subsequent studies were performed in normal water. A 10 mol% of Tween 40 was found to be the optimal amount required, affording a 95% yield of 3a in 5 min. The use of lower amounts (2 or 5 mol%) afforded lower yields.

The water/surfactant value^{18b,c} has a significant influence in controlling the size of the microreactor and is expected to have implications on the rate of organic reactions. Thus, the effect of the amount of water, used as the reaction medium, on the product yield was evaluated during the Tween 40 catalysed reaction of **1b** with **2a** to form **3b** (Table 5).

The water/surfactant ratio significantly altered the product yield and the best results were obtained for values from

Table 5 The effect of the water/surfactant ratio on quinoxaline formationduring the Tween 40 catalysed reaction of 1b with 2a to form $3b^a$



^{*a*} **1b** (0.15 g, 1 mmol) was treated with **2a** (0.21 g, 1 mmol, 1 equiv.) in the presence of Tween 40 (20 mol%), in different amounts of water so that the water/surfactant varies, at rt for 1 h. ^{*b*} Isolated yield of **3b**.

1:0.03 to 1:0.25. The product yield decreased when using a larger amount of water (water/surfactant value < 1:0.03). A decrease in product yield was also observed with lesser quantities of water (water/surfactant value 1:1).

The catalytic potential of Tween 40 was explored for the diversified synthesis of quinoxalines in water (Table 6). The reactions were carried out with different variations of the 1,2-diamine substrate (aromatic, hetroaromatic, alicyclic and aliphatic 1,2-diamines), as well as of the 1,2 diketone system (1,2-diaryl-, 1,2-heteroaryl-, aryl alkyl-, and 1,2-dialkyl-1,2-diketones).

The reaction proceeded smoothly with differently substituted 1,2-diaminobenzenes containing electron donating groups (methyl, methoxy), electron withdrawing groups (nitro, cyano), and halogen substituents (fluorine, chlorine, bromine), affording excellent yields (85-95%) in a short time (5-20 min). The exceptions are o-phenylenediamines with electron withdrawing groups (entries 7 and 8, Table 6) that require a longer reaction time (30-45 min). In the case of heteroaromatic 1,2-diamines such as 2,3-diamino- and 3,4diamino-pyridines, excellent yields were obtained but after longer reaction times (entries 14-16, Table 6) than those required for 1,2-diaminobenzene for similar 1,2-dicarbonyl substrates. The reactions also worked well with aliphatic-1,2diamines such as ethylenediamine and cyclohexane-1,2-diamine. With respect to the 1,2-diketone system, benzil and its substituted analogues such as 4,4'-dimethoxybenzil, a heteroaromatic 1,2-diketone such as furil, a 1-alkyl-2-aryl-1,2-diketone such as 3-phenylpropane-2,3-dione, as well as aliphatic diketones such as hexane-3,4-dione and butane-2,3-dione were used and excellent results were obtained. The product isolation/purification is simple and straightforward. After the completion of the reaction (TLC), the solid mass was filtered off and washed with water to afford the quinoxaline. In most of the cases the product obtained after filtration was pure

Table 6 Tween 40 catalysed synthesis of different quinoxaline derivatives in water^a

Entry	1,2-Diamine	1,2-Diketone	Product	Time (min)	Yield (%) ^b
	R^2 NH_2 R^1 NH_2	O O R ³	$R^{2} \qquad N \qquad R^{3}$ $R^{1} \qquad N \qquad R^{3}$		
1 2 3 4 5 6 7 8 9 10 11 12 13	$R^{1} = H; R^{2} = H$ $R^{1} = OMe; R^{2} = H$ $R^{1} = Cl; R^{2} = H$ $R^{1} = Cl; R^{2} = H$ $R^{1} = Br; R^{2} = H$ $R^{1} = F; R^{2} = H$ $R^{1} = RO_{2}; R^{2} = H$ $R^{1} = RO_{2}; R^{2} = H$ $R^{1} = R^{2} = Cl$ $R^{1} = R^{2} = H$ $R^{1} = NO_{2}; R^{2} = H$ $R^{1} = R^{2} = H$ $R^{1} = R^{2} = H$	$R^{3} = H$ $R^{3} = OMe$ $R^{3} = OMe$	$R^{1} = R^{2} = R^{3} = H$ $R^{1} = Me; R^{2} = R^{3} = H$ $R^{1} = OMe; R^{2} = R^{3} = H$ $R^{1} = Cl; R^{2} = R^{3} = H$ $R^{1} = Br; R^{2} = R^{3} = H$ $R^{1} = RO_{2}; R^{2} = R^{3} = H$ $R^{1} = CN; R^{2} = R^{3} = H$ $R^{1} = R^{2} = Me; R^{3} = H$ $R^{1} = R^{2} = Cl; R^{3} = H$ $R^{1} = R^{2} = Cl; R^{3} = H$ $R^{1} = R^{2} = H; R^{3} = OMe$ $R^{1} = NO_{2}; R^{2} = H; R^{3} = OMe$	5 5 5 5 5 30 45 5 5 20 6 h 20	98 95 96 95 96 80 85 95 91 90 95 ^c 91
14	NH2 NH2			2 h	88
15	Br NH ₂ NH ₂		Br	2 h	86
16	N N NH ₂ NH ₂			2 h	85
17	NH ₂ NH ₂	O Me	N Me	15	85
18	NH ₂ NH ₂	O Me Me	N N Me	1 h	92
19	NH ₂ NH ₂	O Me O Me	N Me N Me	1 h	92

Table 6 (Continued)



^{*a*} The 1,2-diamine (2.5 mmol) was treated with the 1,2 diketone (2.5 mmol, 1 equiv.) in the presence of Tween 40 (10 mol%) in water (5 mL) at rt for the stipulated time. ^{*b*} Isolated yield of the quinoxaline. ^{*c*} The reaction was carried out under reflux condition (oil bath, 110 $^{\circ}$ C).

(NMR, MS) and purification was done through crystallisation in EtOH or EtOH-water.

As various Lewis acid catalysts are known to be tolerated in aqueous media, it was decided to use Lewis acid catalysts instead of the surfactant (Tween 40), so as to derive a comparative catalytic potential between Tween 40 and the water tolerant Lewis acids for the quinoxaline formation in water. Hence, acidic catalysts with different water tolerances were tested against Tween 40 for the synthesis of **3a** by the reaction of **1a** with **2a** in water (Table 7). The water tolerant acidic catalysts were chosen from different classes such as heterogeneous/solid acids (silica, alumina, clay and zeolite) and metal Lewis acids [Sc(OTf)₃, Ln(OTf)₃, Yb(OTf)₃ and InF₃]. Tween 40 was found to be superior to all of the tested catalysts as it gave an excellent yield in a short time, whereas with the other catalysts tested, they either gave an inferior yield or required a longer reaction time.

It was observed that there are a few reports on the use of acid catalysts for quinoxaline formation in an aqueous medium.²¹ However, these involve the use of different Lewis acids as catalysts which raises the query of whether these are generalised Lewis-acid catalysed reactions or they have any specific advantage in using water as the reaction medium. Hence, three sets of reactions were designed (Scheme 2) for quinoxaline formation in water involving the cyclo-condensation of (i) **1a** and **2a**, (ii) **1b** and **2a**, and (iii) **1a** and **2b** and the efficiencies of these reported catalysts²¹ were compared with that of Tween 40 (Table 8).

In each case, the reactions were performed following the conditions (reaction time and temperature) mentioned in the reported procedure,²⁴ as well as for the conditions developed under the present study for the Tween 40 catalysed reaction (Table 8). In all of these three model reactions, the present methodology using Tween 40 in water was found to be distinctly superior to all of the reported procedures using solid

acids or metal Lewis acids, as well as the surfactant combined Lewis acid in aqueous media.

The results (Table 3) of the present study revealed that for the Tween 40 catalysed reactions, inferior yields are obtained when replacing water with organic solvents, indicating that for reactions in water the surfactant may play a specific role in promoting the reaction (Table 3). Therefore, it generated curiosity as to whether there could be a similar advantage in using water over organic solvents for the reported Lewis/ Brønsted acid-catalyzed procedures.²⁴

Table 7 The comparison of the catalytic potential of Tween 40 and a few water tolerant acidic catalysts for quinoxaline formation in water from the reaction of **1a** with $2a^a$

Entry	Catalyst	Yield $(\%)^b$
1	SiO ₂ (60–120)	35
2	SiO_2 (100–200)	35
3	$SiO_{2}(230-400)$	38
4	Al_2O_3 (Acidic)	36
5	Al_2O_3 (Neutral)	35
6	Al_2O_3 (Basic)	35
7	KSF	45
8	Zeolite Y	46
9	Zeolite K L^{-1}	42
10	Zeolite ZSM 5	44
11	Zeolite K L^{-1}	40
12	Zeolite Na/Fau	36
13	Zeolite NH ₄ -Y	35
14	$Sc(OTf)_3$	65
15	$Ln(OTf)_3$	68
16	Yb(OTf) ₃	65
17	InF ₃	66
18	Tween 40	98

^{*a*} **1a** (0.10 g, 1 mmol) was treated with **2a** (0.21 g, 1 mmol, 1 equiv.) in the presence of different catalysts (10% w/w for solid acids or 10 mol% for metal salt derived Lewis acids) in water (5 mL) at rt for 5 min. ^{*b*} Isolated yield of **3a**.

Table 8 Comparison of the efficiency of the reported Lewis/Brønsted acid-catalysed procedures of quinoxaline formation in water with that of the Tween 40	
catalysed reactions ^a	

Entry	Cat.	1,2-Diamine	1,2-Diketone	Quinoxaline	Time (min)	Yield $(\%)^b$
1	CAN ^{24a}	1a	2a	3a	10	$82^{c} (98)^{d}$
2	CAN	1a	2a	3a	5	68 ^e
3	CAN	1a	2b	3 d	10	$65^{c} (88)^{d}$
4	CAN	1a	2b	3 d	20	72^e
5	CAN	1b	2a	3 b	60	70
6	CAN	1b	2a	3 b	30	52
7	${\rm InCl_3}^{24a}$	1a	2a	3a	30	$85^c (98)^d$
8	InCl ₃	1a	2a	3a	5	55^e
9	InCl ₃	1a	2b	3 d	60	72
10	InCl ₃	1a	2b	3 d	20	60^e
11	InCl ₃	1b	2a	3b	60	70
12	InCl ₃	1b	2a	3b	30	58^e
13	$CuSO_4 \cdot 5H_2O^{24a}$	1a	2a	3a	15	$85 (96)^d$
14	$CuSO_4 \cdot 5H_2O$	1a	2a	3a	5	65 ^e
15	CuSO ₄ ·5H ₂ O	1a	2b	3 d	12	$70 (90)^d$
16	CuSO ₄ ·5H ₂ O	1a	2b	3 d	20	75 ^e
17	CuSO ₄ ·5H ₂ O	1b	2a	3 b	30	$79^{e} (94)^{d}$
18	K 10^{24a}	1a	2a	3a	2.5 h	$72^{c} (100)^{d}$
19	K 10	1a	2a	3a	5	35 ^e
20	K 10	1a	2b	3d	2.5 h	68
21	K 10	1a	2b	3d	20	35^e
22	K 10	1b	2a	3b	6 h	$62(70)^d$
23	K 10	1b	2a	3b	30	35^{e}
24	$Zr(DS)_4^{24a}$	 1a	2a	3a	30	$79 (94)^d$
25	$Zr(DS)_4$	1a	2a	3a	5	52^e
26	$Zr(DS)_4$	 1a	2 b	3d	35	$75 (93)^d$
27	$Zr(DS)_4$	1a	2b	3d	20	50^{e}
28	$Zr(DS)_4$	1b	2a	3h	90	$72(86)^d$
29	$Zr(DS)_4$	1b	2a	3h	30	35 ^e
2.4	Amberlyst 15^{24a}	19	2a 2a	3a	20	$82^{c,f}$ (99) ^{d,f}
25	Amberlyst 15	19	24	39	20	52 ^g
25	Amberlyst 15	19	2a	3a	5	56 ^{c,f}
20	Amberlyst 15	19	2a	3a	5	24^g
27	Amberlyst 15	10	2a 2b	3d	5	$60^{c,f}$
20	Amberlyst 15	10	26 2b	3d	60	traceg
30	Amberlyst 15	10	20 2b	3d	20	25 ^c f
21	Amberlyst 15	10	20 2b	24	20	trace
22	Amberlyst 15	1a 1b	20	3u 2h	20	62 ^c f
32	Amberlyst 15	10	2a	30 2b	60	traces
24	Amberlyst 15	10	24	30 21a	80	20 ^c f
34 25	Amberlyst 15	10 1b	2a 2a	30 21a	3U 20	30°
33	Allibertyst 15	10	2a 2a	3D 20	3U F	uace ^o
30	Tween 40	18	2a 2h	58 A	5	98
3/	Tween 40	18	20	3 a	20	88
38	Tween 40	1b	2a	3b	30	80

^{*a*} The 1,2-diamine (1 mmol) was treated with 1,2-diketone (1 mmol, 1 equiv.) in water (5 mL) at rt in the presence of the catalyst. ^{*b*} Isolated yield of the corresponding quinoxaline. ^{*c*} The yield obtained in the present study by performing the reaction following the reported procedure. ^{*d*} The figure in the parenthesis is the yield as reported in the respective literature. ^{*e*} The yield obtained in performing the reaction using the reported catalyst for the time period required for the Tween 40 catalysed reaction under the present study. ^{*f*} In the reported procedure using this catalyst the reactions were carried out at 70 °C. ^{*g*} The reaction was performed at rt under the present study.

Hence, we performed two sets of reaction (Scheme 3) for quinoxaline formation in various organic solvents involving the reaction of (i) **1a** and **2a**, and (ii) **1b** and **2a**, in the presence of these reported catalysts²¹ and compared the results with those obtained when performing the reaction in water in the presence of the said catalyst (Table 9).

Surprisingly all of these catalysts performed better/equally in organic solvents (particularly MeOH and MeCN) compared to water. These results imply that the surfactants are best suited as a catalytic aid in promoting organic reactions in water rather than in organic solvents, implying the fact that solubility is not the sole reason for the observed advantages of using surfactants in aqueous organic reactions. On the other hand, the better/equal catalytic potency of the Lewis/Brønsted acids and surfactant combined Lewis acids in organic solvents over those in water suggests that perhaps the Lewis/Brønsted



Scheme 3 The comparative catalytic efficiency of a few Lewis/Brønsted acids for quinoxaline formation in water and in organic solvents.

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Table 9 The efficiency of the catalysts, reported for quinoxaline formation in water, in various organic solvents as well as in water for the reaction of the 1,2-diamines **1a** or **1b** with the 1,2-diketone **2a** to form **3a** or **3b**^a

Entry	Cat	Diamine	Product	Solvent	Time (h)	Yield (%) ^b
1	K10	1a	3a	Water	2.5	72
2	K10	1a	3a	MeOH	2.5	85
3	K10	1a	3a	MeCN	2.5	76
4	K10	1a	3a	DCM	2.5	65
5	K10	1a	3a	Dioxane	2.5	60
6	K10	1a	3a	Toluene	2.5	46
7	K10	1a	3a	DMF	2.5	52
8	K10	1b	3b	Water	6	62
9	K10	1b	3b	MeOH	6	70
10	K10	1b	3b	MeCN	6	65
11	K10	1b	3b	DCM	6	35
12	K10 K10	10	30	Dioxane	6	41
13	K10 K10	1D 11	3D 31-	Toluene	6	30
14	K10 7*(DS)	10	30	DMF	0	41
15	$ZI(DS)_4$ Zr(DS)	10	3a 20	MOU	0.5	72
10	$ZI(DS)_4$ Zr(DS)	10	3a 20	MeOn	0.5	65
17	$ZI(DS)_4$ Zr(DS)	1a 1a	3a 2a	DCM	0.5	42
10	$Zr(DS)_4$ Zr(DS)	1a 1a	3a 2a	Diovane	0.5	43
20	$Zr(DS)_4$	1a 1a	3a 3a	Toluene	0.5	40 21
20	$Zr(DS)_4$ $Zr(DS)_4$	1a 1a	3a 3a	DMF	0.5	20
21	$Zr(DS)_4$ $Zr(DS)_4$	1a 1h	3h	Water	1.5	72
23	$Zr(DS)_4$ $Zr(DS)_4$	10 1h	3h	MeOH	1.5	62
24	$Zr(DS)_4$	1b 1h	3h	MeCN	1.5	55
25	$Zr(DS)_4$	1b	3b	DCM	1.5	32
26	$Zr(DS)_4$	1b	3b	Dioxane	1.5	30
27	$Zr(DS)_4$	1b	3b	Toluene	1.5	14
28	$Zr(DS)_4$	1b	3b	DMF	1.5	15
29	CuSO ₄ ·5H ₂ O	1a	3a	Water	0.25	85
30	CuSO ₄ ·5H ₂ O	1a	3a	MeOH	0.25	90
31	CuSO ₄ ·5H ₂ O	1a	3a	MeCN	0.25	88
32	CuSO ₄ ·5H ₂ O	1a	3a	DCM	0.25	65
33	CuSO ₄ ·5H ₂ O	1a	3a	Dioxane	0.25	70
34	$CuSO_4 \cdot 5H_2O$	1a	3a	Toluene	0.25	52
35	$CuSO_4 \cdot 5H_2O$	1a	3a	DMF	0.25	61
36	$CuSO_4 \cdot 5H_2O$	1b	3b	Water	0.5	79
37	$CuSO_4 \cdot 5H_2O$	1b	3b	MeOH	0.5	85
38	$CuSO_4 \cdot 5H_2O$	1b	3b	MeCN	0.5	75
39	$CuSO_4 \cdot 5H_2O$	1b	3b	DCM	0.5	50
40	$CuSO_4 \cdot 5H_2O$	1b	3b	Dioxane	0.5	46
41	CuSO ₄ ·5H ₂ O	1b	3b	Toluene	0.5	36
42	$CuSO_4 \cdot 5H_2O$	1b	3b	DMF	0.5	40
43	InCl ₃	1a	3a	Water	0.5	85
44	InCl ₃	1a	3a	MeOH	0.5	96
45	InCl ₃	1a	3a	MeCN	0.5	84
46	InCl ₃	1a	3a	DCM	0.5	61
47	InCl ₃	1a	3a	Dioxane	0.5	68
48	InCl ₃	1a	3a	Toluene	0.5	60
49	InCl ₃	1a	3a	DMF	0.5	72
50	InCl ₃	10	30	water	1	70
51	InCl ₃	10	30	MeOH	1	81
52	InCl ₃	10	30	MeCN	1	/1
53	InCl ₃	1D 1h	3D 21-	DCM	1	55
54	InCl	10 1h	3D 2h	Toluono	1	60
55	InCl ₃	10 1h	30 21-	DME	1	65
50	Amborlyst 15	10	3D 20	Water	1	00 00 ^C
58	Amberlyst 15	1a 1a	3a 3a	MeOU	20 min	02 88 ⁰
50	Amberlyst 15	1a 1a	3a 3a	MeCN	20 min	80 ^c
59 60	Amberlyst 15	1a 1a	3a 3a	DCM	20 min	68 ⁰
61	Amberlyst 15	1a 1a	3a 3a	Diovana	20 min	65 ^c
62	Amberlyst 15	1a 1a	3a 3a	Toluene	20 min	42 ^c
63	Amberlyst 15	1a 1a	3a 3a	DMF	20 min	50 ^c
64	Amberlyst 15	1a 1h	3a 3h	Water	20 mm 1	62 ^c
65	Amberlyst 15	10 1h	3h	MeOH	1 1	70 ^c
66	Amberlyst 15	1b	3b	MeCN	1	68 ^c
67	Amberlyst 15	1b	3b	DCM	1	50°

Table 9 (Continued)

Entry	Cat	Diamine	Product	Solvent	Time (h)	Yield $(\%)^b$
68	Amberlyst 15	1b	3b	Dioxane	1	46 ^c
69	Amberlyst 15	1b	3b	Toluene	1	35 ^c
70	Amberlyst 15	1b	3b	DMF	1	32 ^c
71	CAN	1a	3a	Water	10 min	72
72	CAN	1a	3a	MeOH	10 min	91
73	CAN	1a	3a	MeCN	10 min	80
74	CAN	1a	3a	DCM	10 min	62
75	CAN	1a	3a	Dioxane	10 min	68
76	CAN	1a	3a	Toluene	10 min	48
77	CAN	1a	3a	DMF	10 min	52
78	CAN	1b	3b	Water	1	70
79	CAN	1a	3a	MeOH	1	84
80	CAN	1a	3a	MeCN	1	71
81	CAN	1a	3a	DCM	1	51
82	CAN	1a	3a	Dioxane	1	65
83	CAN	1a	3a	Toluene	1	30
84	CAN	1a	3a	DMF	1	46

^{*a*} The 1,2-diamine (1 mmol) was treated with **2a** (0.21 g, 1 mmol, 1 equiv.) in the presence of the catalyst (10% w/w or 10 mol%, whichever is applicable) in the specified solvent (5 mL) at rt (unless otherwise mentioned). ^{*b*} Isolated yield of the corresponding quinoxaline. ^{*c*} The reaction was carried out at 70 °C (oil bath).

acids are better suited for applications in organic solvents. It may further be concluded that without any distinct comparison of the catalytic efficiency in organic solvents vs. water, a mere use of an aqueous medium may not reflect the projected greener advantage.

The recyclability of the spent water containing the surfactant, as well as the surfactant (Tween 40) itself was studied for the model reaction of **1a** with **2a**. After each reaction the product was isolated by filtration. The filtrate (aqueous layer containing the Tween 40) was reused for four subsequent fresh reaction batches. Excellent results were obtained without any significant loss of product yield (Table 10). After the final use, the spent water containing the catalyst (Tween 40) was subjected to freeze drying to recover the Tween 40 (recovery 82%) and was found to be identical (NMR) with the authentic (unused) sample of Tween 40.

The better performances of the surfactant (*e.g.*, Tween 40) in aqueous media rather than that in organic solvents

Table 10 Recyclability of the spent water containing the catalyst (Tween 40)during the Tween 40 catalysed reaction of 1a with 2a to form 3a in water^a

Entry	Run	Yield $(\%)^b$
1	Fresh	98
2	1st recycle	95
3	2nd recycle	96
4	3rd recycle	95
5	4th recycle	92 $(91)^c$

^{*a*} **1a** (1.1 g, 10 mmol) was treated with **2a** (2.1 g, 10 mmol, 1 equiv.) in the presence of Tween 40 (1.3 g, 1 mmol, 10 mol%) in water (40 mL) at rt. ^{*b*} Isolated yield of **3a**. ^{*c*} Isolated yield of **3a** using the recovered Tween 40.

Fig. 1 The role of water during quinoxaline formation in aqueous media.

highlighted the distinct rate acceleration by water. Understanding the role of water in promoting organic reactions is yet to be fully recognised. Various factors such as enforced hydrophobic interactions, high cohesive energy density of water and the hydrogen bond (HB) effect have been attributed to water for its unique ability to enhance the rate of an organic reaction.²⁵ Amongst the various factors, the HB effect has gained popularity to account for "on water" catalysis.^{26,27} However, the non-HB effect has also been invoked.²⁸ The advantage of using water as the reaction medium may be attributed to its superior HB donor (HBD) ability²⁹ in facilitating the condensation between the amine group of the 1,2-diamine and the carbonyl group of the 1,2diketone, through the formation of the hydrogen bonded supramolecular assembly I (Fig. 1). The intermittently formed imine II may in turn undergo intramolecular condensation between the adjacent amine and carbonyl groups through a hydrogen bond mediated supramolecular assembly involving the water dimer akin to I to form the quinoxaline.

The hydrogen bond induced formation of the supramolecular clusters involving the reactants and water molecule(s) have been postulated in various water-mediated organic reactions,²⁶ water catalysis of radical-molecule gas-phase reactions³⁰ and epoxide-opening cascades.³¹ The poor results in the organic solvents could be due to their inferior HBD values. Thus, water accelerates the cyclocondensation process through HB-assisted synergistic dual activation.³²

The specific catalytic effect exhibited by Tween 40 could be due its HB formation ability both in the form of HBDs (through the terminal/free hydroxyl groups) and HB acceptors (HBAs) (through the carbonyl and polyoxyethylene ethereal oxygen atoms). The surfactant molecule undergoes HB formation with the dangling OH groups³³ of the interfacial water and encapsulates, through HB, the reactants (the 1,2diamine and 1,2-dicarbonyl substrates) inside the microreactor for acceleration of the cyclocondensation leading to the formation of quinoxalines.

Conclusions

In summary, we describe in this study a simple, extremely efficient, and green protocol for the synthesis of quinoxalines from various 1,2-diketones and 1,2-diamines in water at room temperature catalysed by a surfactant. The catalytic potential of various surfactants were in the order: non-ionic surfactants > anionic surfactants > Brønsted acid surfactants > cationic surfactants, where Tween 40 proved to be the best catalyst. The

advantages such as (i) no requirement of an additional reagent, (ii) non-flammable and non-toxic reaction medium, (iii) high yields, (iv) short reaction time, (v) room temperature reaction, (vi) virtually no waste generation, (vii) use of cheap, readily available and non-toxic Tween 40 as the catalyst, and (viii) ease of product isolation/purification fulfils the 'triple bottom line philosophy'34 of green chemistry and makes the present methodology environmentally benign. In general, the catalytic potential of Tween 40 was found to be superior compared to some of the water tolerant Lewis/Brønsted acid catalysts, as well as the reported methods of quinoxaline synthesis in water in the presence of Lewis/Brønsted acid catalysts and surfactant combined Lewis acids. From this study it can be concluded that surfactants are the best suited agents/catalysts to promote or accelerate organic reactions in water and that Lewis or Brønsted acid catalysts are better suited to promote reactions in organic solvents. The superiority of water as the reaction medium is attributed to its role in hydrogen bond mediated synergistic activation of the 1,2diamine and the 1,2-dicarbonyl in facilitating the condensation, wherein the surfactant (Tween 40) also plays a critical role in forming hydrogen bonds with the dangling OH groups of the interfacial water, providing a close proximity to the reactants in encapsulating them inside the microreactor through hydrogen bond formation. Since the concern is to develop environmentally benign protocols, the various features such as stability, cost and toxicity profile of the surfactants were looked into.

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