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Robust Cationic Quaternary Ammonium Surfactant-Catalyzed Condensation Reaction for (*E*)-3-Aryl-1-(3-alkyl-2-pyrazinyl)-2-propenone Synthesis in Water at Room Temperature

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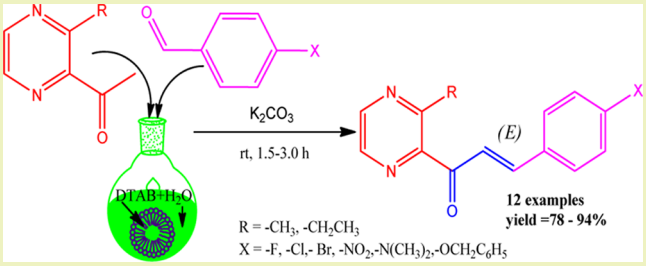
Supporting Information

ABSTRACT: An efficient, convenient, and environmentally benign method for synthesis of novel (*E*)-3-aryl-1-(3-alkyl-2-pyrazinyl)-2-propenone in aqueous micellar medium at room temperature has been developed. Initially, the reaction between 2-acetyl-3-methylpyrazine (**1a**; 1 mmol) and 4-bromobenzaldehyde (**2c**; 1 mmol) was separately conducted with 10 mol % cationic quaternary ammonium surfactants (CQAS), namely, methyltrioctylammonium chloride (MTOAC), methyltrioctylammonium bromide (MTOAB), cetylpyridinium chloride (CPC), cetylpyridinium bromide (CPB), dodecyltrimethylammonium bromide (DTAB), and hexadecyltrimethylammonium bromide (CTAB). An 89.0% maximum yield was noted with DTAB due to higher a catalyzing effect on the reaction. The other surfactants used for the same reaction have produced only 50−86% yield. DTAB was found to be a most efficient catalyst because of the higher yield in the reaction. Therefore, applying DTAB, the various reaction conditions such as effect of concentration (2.5−20 mol %), temperature (rt-reflux), and reusability of aqueous micellar medium were investigated. Thus, the 15 mol % DTAB used for synthesis of a series (**3a**−**3l**) of compounds at room temperature produced a 78−94% yield. The method using DTAB allows for the preparation of a variety of aryl propenones with better yield and purities, making any further purification unnecessary. DTAB is also considered environmentally benign and may lead to developing a new option of synthesis in green chemistry. The structures were confirmed by FTIR, ^{1}H NMR, ^{13}C NMR, LCMS (Q-TOF), and elemental analysis.



KEYWORDS: *Benign synthesis, Cationic surfactant, Chalcone, Micelle, Pyrazine*

INTRODUCTION

For the past few decades, benign processes using water as a solvent for several organic reactions and transformations have been considered for developing and promoting new synthetic methodology.[1,2] The water as a medium for reaction has become an area of growing interest due to its nontoxic, nonvolatile, nonflammable, nonexplosive, noncarcinogenic, cheap, and environment friendly nature[1] without any sophistication like an inert environment, higher temperature, and typical workup.[3] Synthesis in water as a solvent could be termed as "N-synthesis". Because of today's concern for environmental issues, where most of the organic solvents are volatile, carcinogenic, toxic, and have many adverse effects on health and the environment, water is being preferred,[1,2] although the use of water has constraints owing to a limited solubility of many organic reactants for reaction. Hence, the hydrophobic effect and cohesive energy of water are considered as the main reasons for increasing reactivity of the reactants that are partially soluble or insoluble in water.[4,5] To overcome such solubility limitations, surfactants in water are preferred for reactions.[6,7] In the past, micellar solutions have been proven to be a thrust area of research, and the catalytic potential of micellar aggregates has received special attention for synthesis of mesoporous nanoparticles, carbon nanotubes,[8] heterocyclic compounds,[9] Lewis acid-catalyzed reactions,[10] and others. The surfactants in aqueous medium develop micelles or vesicular cavities and act as phase transfer catalysts.[9] On completion of the reaction, surfactants are removed by using water without a use of any organic solvent.[10] Such features fascinated us to choose the cationic quaternary ammonium surfactant (CQAS), which could pave a new path for organic synthesis by reducing the use of organic solvents with a higher reaction rate.[11] Thus, in the light of the above, we have reported on the Claisen−Schmidt condensation reaction of aromatic aldehydes with pyrazine moiety containing aromatic ketones in aqueous micellar media. The substituted pyrazines are an important class of aromas and fragrances found in natural sources such as fruits and vegetables with several biomedical applications.[12]

The Claisen−Schmidt condensation reaction is an important synthetic reaction for preparing the carbon−carbon bond of

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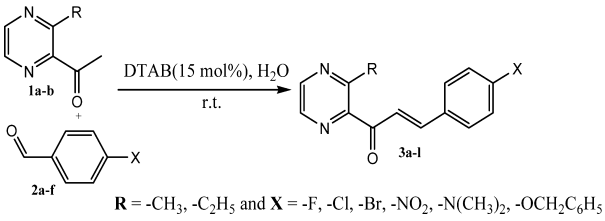
α,β-unsaturated ketones (chalcones) and their derivatives. These α,β-unsaturated ketones and derivatives are important precursors for synthesis of pyrimidines, pyrazolines, isoxazolines, flavonoids, isoflavonoids, and other bioactive heterocyclic compounds.[13] In addition, they also possess different biological activities where some of the chalcones exhibit antimicrobial,[14] anti-inflammatory,[14] antimalarial,[15] anticancer,[16] antileishmanial,[17] antioxidant,[14] antifungal, and antibacterial behaviors,[18] and the inhibition of leukotriene B4.[19] Partly, the chalcones are reported to exhibit anti-HIV, antituberculosis, and agrochemical activities.[20−22] Such peculiar features attract significant interest of chemists, biochemists, and pharmacologists in this particular group of compounds. In general, the Claisen−Schmidt and aldol condensation reactions are conducted with a strong acid or base or high cost catalysts like $LiNO_3$/natural phosphate,[23] Amberlyst-15, Bamboo char sulfonic acid,[24] $SOCl_2$/EtOH,[25] $Cu_3(BTC)_2(H_2O)_3$,[26] zinc oxide,[27] or a Zn−Al hydrotalcite adhering ionic liquid[28] in organic solvents that consume a longer time, higher temperature, inert environment, and sophisticated workup along with some impurities.[3,29] The above-mentioned difficulties create hurdles in conducting reactions even with efficient catalysts aimed at the product under ordinary experimental conditions. Thus, in the present work, we have optimized the best reaction conditions for the Claisen−Schmidt condensation reaction using the DTAB (Scheme 1) aqueous micellar medium at room temperature. The compounds have shown promising antibacterial activities, screened with gram positive, gram negative, and fungal strain.

Scheme 1. Synthesis of (*E*)-3-Aryl-1-(3-alkyl-2-pyrazinyl)-2-propenone in Water



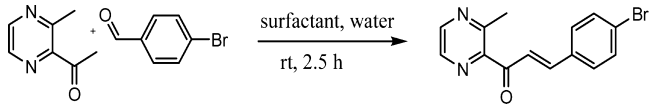
R = -CH_3, -C_2H_5 and **X** = -F, -Cl, -Br, -NO_2, -$N(CH_3)_2$, -$OCH_2C_6H_5$

RESULTS AND DISCUSSION

For the last many years, applications of chalcones in pharmaceuticals and life sciences for developing highly potential molecules for curing diseases have been the center of attraction. For designing and developing several chalcones having heterocyclic moieties with benign methodology, we were looking to find a common method for their synthesis with high yields, less time, and high purities. Such environmently friendly synthetic approaches are always beneficial, and thus, the chalcones preparation using the condensation of 2-acetyl-3-alkylpyrazine and para-substituted aldehydes in water with CQAS was chosen.

Initially, the reaction between an equimolar ratio of a 2-acetyl-3-methylpyrazine (**1a**; 200 mg, 1 mmol) and 4-bromobenzaldehyde (**2c**; 185 mg, 1 mmol) was considered as a model reaction for optimization of reaction conditions. The 10 mol % MTOAC, MTOAB, CPC, CPB, DTAB, and CTAB were separately used as catalyzed for the model reaction at ambient temperature. MTOAC and MTOAB produced 61.0% and 50.5% yields, respectively (Table 1, entries 1−2), whereas CPC, CPB, DTAB, and CTAB produced 86.0%, 82.5%, 89.0%, and 82.0% yields, respectively (Table 1, entries 3−6). Out of all the surfactants, DTAB produced an 89.0% higher yield than the other surfactants. (Table 1, entry 6).

Table 1. Optimization of Reaction Conditions with Surfactants[a]



entry	surfactant	temp[b]	base	mol %	time (h)	yield (%)[c]
1	MTOAC	rt	K_2CO_3	10	2.5	61.0
2	MTOAB	rt	K_2CO_3	10	2.5	50.5
3	CPC	rt	K_2CO_3	10	2.5	86.0
4	CPB	rt	K_2CO_3	10	2.5	82.5
5	DTAB	rt	K_2CO_3	10	2.5	89.0
6	CTAB	rt	K_2CO_3	10	2.5	82.0
7	DTAB	rt	K_2CO_3	2.5	2.5	69.5
8	DTAB	rt	K_2CO_3	5.0	2.5	75.5
9	DTAB	rt	K_2CO_3	15	2.5	92.0
10	DTAB	rt	K_2CO_3	20	2.5	93.5
11	DTAB	50	K_2CO_3	15	2.5	82.0
12	DTAB	70	K_2CO_3	15	2.5	64.0
13	DTAB	reflux	K_2CO_3	15	2.5	50.0
14	DTAB	rt	neat	15	8.0	traces
15	DTAB	rt	NaOH	15	2.5	59.0
16	ML[d]	rt	–	–	3.0	78.0

[a]Reaction conditions: 2-acetyl-3-methylpyrazine (1.0 mmol), 4-bromobenzaldehyde (1.0 mmol), and K_2CO_3 (1.0 mmol) in H_2O (10 mL). [b]rt = 32−34 °C. [c]Isolated yield. [d]Reaction was carried out in mother liquor (ML) of 15 mol % DTAB (entry 9).

On getting better results with DTAB, the concentration of DTAB was experimented for higher yield. The yield was increased by 69.5%, 75.5%, 89.0%, 92.0%, and 93.5% for an increase in concentration from 2.5 to 20 mol % DTAB, respectively (Table 1, entries 7−10). Thus, 15 mol % DTAB was considered for further reaction condition optimization because at 20 mol % DTAB, no considerable increase in yield was obtained. (Table 1, entry 10). Along with the DTAB concentration effect on yield, the effect of temperature was experimented by conducting reaction at room temperature (rt) to reflux (Table 1, entries 11−13); yield was decreased from 92.0% to 50.0%, respectively. It seems that a disruption of micelles at higher temperature might decrease the rate of reaction and probably successful collisions may not occur due to higher kinetic energy of the reactants. Apart from the above investigations, the reaction was also conducted in the absence of K_2CO_3, which required a longer time with the formation of a trace amount of the product (Table 1, entry 14). However, in the presence of NaOH (1 mmol), the desired product was obtained with a 59.0% yield (Table1, entry 15).

Initially, the reaction in the presence of 15 mol % DTAB had produced a 92% yield (Table 1, entry 16), which is referred to as a first run. When the model reaction was conducted using the filtrate micellar media of the first run, a 78.0% yield was observed. The filtrate of the first run, referred to as the mother liquor, reduced the yield by 14%. The reduction in reaction catalyzing efficiency of DTAB may be attributed to disruption of micelles. Thus, the cationic surfactant can be used as an efficient catalyst for a carbon−carbon bond formation reaction.

The reaction mass consisting of reactants that initially floated in water became homogenized upon addition of DTAB and with mechanical stirring formed a turbid emulsion (Figure 1a,

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b). Later, the addition of K_2CO_3 produced a light yellow precipitate signifying product formation (Figure 1c).

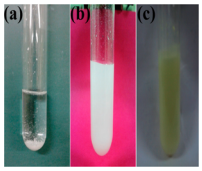


Figure 1. (a) Water and reactants (1:1 ratio) only. (b) Reaction mass after addition of DTAB (15 mol %) surfactant. (c) Yellow precipitate due to product formation.

The above-mentioned observations indicate that there is formation of micelles or micelle-like colloidal aggregates. When normal micelles are formed in water (Figure 2) on surfactant dissolution, the hydrophobic chain is located away from the aqueous region and the polar head moves toward the aqueous peripheral[30] as is depicted in Figure 3.

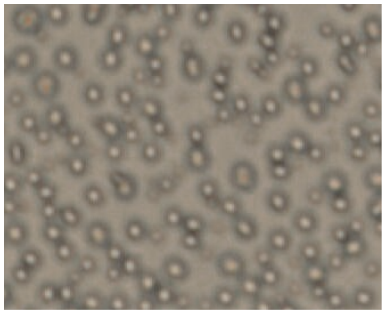
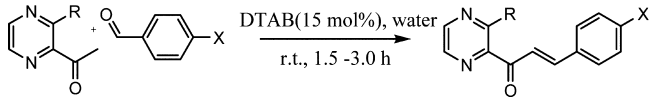


Figure 2. Optical micrograph image of the reaction mass.

Formation of droplets in aqueous media was confirmed by optical microscopy[31] (Figure 2). Because of hydrophobic interactions of DTAB with reactants, droplets with hydrophobic interior were formed in emulsion.[32] The aldehyde and ketone that act as a hydrophobic reaction sites were further concentrated within the droplets because the water molecules were repelled. Such molecular reorientations enhanced the rate of equilibrium with an increase in collisions via a concentration effect. The water molecules that were generated during the condensation reaction might have been removed from the droplet due to the hydrophobic nature of their interior.[32] In micelles, aldehyde and ketone are pushed away from the water to hydrophobic domains causing effective collisions between reactants and inducing a reaction rate that is responsible for rapid reactions in aqueous medium.[31,33]

On getting successful results with DTAB for synthesis of (*E*)-3-(4-bromophenyl)-1-(3-methylpyrazin-2-yl)prop-2-en-1-one, the approach was extended to overall scope and versatility of the method for synthesis of structurally different electron-donating and -withdrawing para-substituted aldehydes and acetylpyrazines **3a−3l** (Scheme 1). The reaction was completed within 1.5−3.0 h with a 78−94.0% yield (Table 2, entry 1−12).

Table 2. Physical Data of Novel (*E*)-3-Aryl-1-(3-alkyl-2-pyrazinyl)-2-propenones[a]



entry	comp.	R	X	time (h)	yield (%)[b]	mp (°C)
1	3a	$-CH_3$	−F	2.0	78.0	113−115
2	3b	$-CH_3$	−Cl	2.0	88.5	128−130
3	3c	$-CH_3$	−Br	2.5	92.0	136−138
4	3d	$-CH_3$	$-NO_2$	1.5	86.5	190−192
5	3e	$-CH_3$	$-N(CH_3)_2$	3.0	93.5	114−116
6	3f	$-CH_3$	$-OCH_2Ph$	2.5	94.0	141−143
7	3g	$-C_2H_5$	−F	2.0	84.5	105−107
8	3h	$-C_2H_5$	-Cl	2.5	87.0	115−117
9	3i	$-C_2H_5$	−Br	2.0	91.0	95−97
10	3j	$-C_2H_5$	$-NO_2$	2.5	85.5	199−201
11	3k	$-C_2H_5$	$-N(CH_3)_2$	2.5	82.0	105−107
12	3l	$-C_2H_5$	$-OCH_2Ph$	3.0	90.0	118−120

[a]Reaction conditions: 2-acetyl-3-alkylpyrazine (1.0 mmol), aldehyde (1.0 mmol), and K_2CO_3 (1.0 mmol) in H_2O (10 mL) at rt (32−34 °C). [b]Isolated yield.

The structures of compounds were confirmed using FTIR, ^1H NMR, ^{13}C NMR, LCMS (Q-TOF), and CHNS/O analysis (Supporting Information).

Antibacterial and Antifungal Activity. The compounds **3a−3l** were screened for their antibacterial activity against human pathogenic bacteria, viz., gram positive (*S. aureus*; ATCC 33591) and gram negative (*E. coli*; ATCC 25922), by

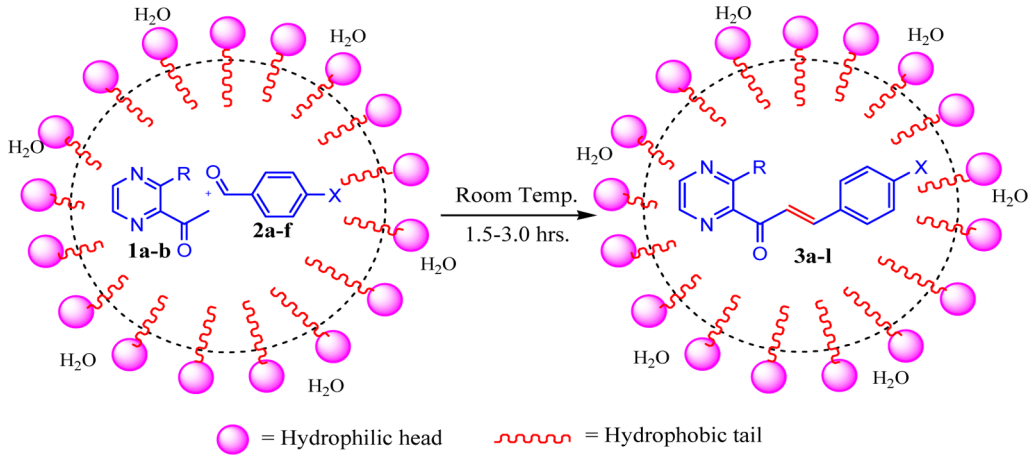


Figure 3. Micelle-promoted condensation reaction for synthesis of (*E*)-3-aryl-1-(3-alkyl-2-pyrazinyl)-2-propenones.

disc diffusion method[34] using DMSO as solvent at 200 μg/mL concentration on Mueller Hinton agar media (Himedia, India). The compounds were also screened for their antifungal activity against *C. albicans* (ATCC 14053). Antifungal activity was assessed by the disc diffusion method.[35] Saboraud dextrose agar (SDA, Himedia, India) was used as the basal medium. The zone of inhibition was measured in millimeters (mm) after 24 h incubation at 37 °C and pH 7.4 (Table 3).

Table 3. Antibacterial and Antifungal Activities of Compound 3a−3l[a]

	zone of inhibition (mm)		
entry	*S. aureus*[b]	*E. coli*[c]	*C. albicans*[d]
3a	32	20	02
3b	22	04	04
3c	44	40	04
3d	46	38	05
3e	30	04	00
3f	18	06	00
3g	20	03	02
3h	22	08	05
3i	17	07	00
3j	22	03	04
3k	24	03	00
3l	25	00	00
ampicillin	28	–	–
gentamycin	–	15	–
fluconazole	–	–	19

[a]Data represent the mean of three replicates for each concentration. DMSO was used as positive control. [b]Compounds with zone ≥28 mm are sensitive and ≤28 mm are resistant against *S. aureus*. [c]Compounds with zone ≥15 mm are sensitive and ≤12 mm are resistant against *E.coli*. [d]Compounds with zone ≥19 mm are sensitive against *C. albicans*.

The zones of inhibition were compared with the standard drugs ampicillin, gentamycin, and fluconazole. Disc with DMSO was used as positive control. The in vitro antibacterial and antifungal studies agreed that the **3a**, **3c**, **3d**, and **3f** compounds are highly sensitive against gram positive strains, while **3a**, **3c**, and **3d** show better sensitivity against gram negative strains than the standard drug.

CONCLUSIONS

In conclusion, we have developed an efficient, convenient, clean, and green synthetic method with DTAB surfactant for the Claisen−Schmidt condensation reaction in aqueous micellar medium, which affords the corresponding products in 78−94% yield with minimal environmental impact. This method was extended for a series of structurally different aldehydes and ketones for carbon−carbon bond formation in water as a new option for synthesis of various compounds. Thus, the developed method could be applied for several other carbon−carbon bond formation reactions in water with cationic surfactants. The studies for in vitro antibacterial and antifungal activities were made, and the compounds **3a**, **3c**, **3d**, and **3f** have been proven to be highly sensitive against gram positive strains. The compounds **3a**, **3c**, and **3d** show a better sensitivity against gram negative strains.

ASSOCIATED CONTENT

Supporting Information

General details of chemicals and instrumentations, experimental procedure, characterization data of compounds, and copies of ^{1}H and ^{13}C NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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