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Organic Reactions in "Green Surfactant": An Avenue to Bisuracil Derivative

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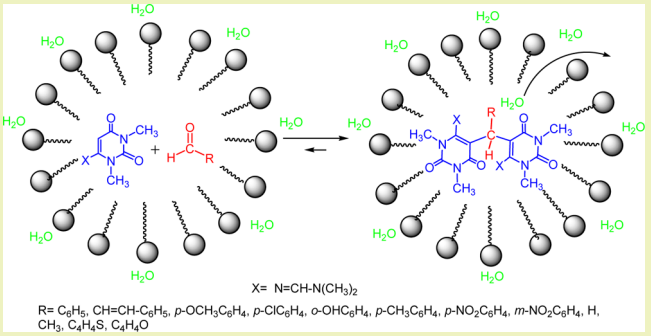
Supporting Information

ABSTRACT: An environmentally benign and chemoselective nucleophilic addition of 6-[(dimethylamino)-methyleneamino]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione with aldehydes (aromatic, aliphatic, and heterocyclic) using a "green surfactant" isolated from *P. aeruginosa* OBP1 in water at room temperature is described. In this protocol, products (i.e., bisuracils) were obtained in moderate to good yields. Ketones failed to provide any product(s). The biosurfactant is easily recyclable. The structures of the products (i.e., bisuracils) were established using various spectroscopic techniques, elemental analysis, and single-crystal X-ray analysis. Amide-iminol tautomerism in the product is detected by NMR spectroscopy and conclusively supported by single-crystal X-ray analysis.



KEYWORDS: *Pyrimidine, Nucleophilic, P. aeruginosa, Biosurfactant, Rhamnolipids, Water, Amide-iminol*

INTRODUCTION

The powerful color "green" refers to nature, life, balance, harmony, fertility, growth, safety, peace, and prosperity. Maintaining the sanctity of "green", green chemistry leads to an approach that eliminates or minimizes the ill effects of chemistry by improvising the existing methodologies or discovering newer greener methodologies. So, practicing green chemistry is the need of the hour. In the wake of such awareness, lots of environmentally benign techniques have been developed or discovered during the past few years. In this regard, organic reactions using water[1−3] have invoked considerable attention because they mimic nature and provide environmentally benign conditions along with the other advantages. A very recent review by Varma et al. focuses on in-water and on-water organic reactions.[4]

The uracil scaffold and its derivatives are known to have a wide spectrum of bioactivities that have helped chemists and biologists to move forward with harmony.[5−12] The nucleophilic nature of the C-5 position of uracil and its derivatives is well-known,[13−20] and its reactivity is greatly influenced by the nature of substituents in the uracil skeleton. In fact, this is one of the strategies adopted for the synthesis of bioactive 5-substituted uracil derivatives.[7] It is observed that the presence of an amino group at C-6 position increases the nucleophilicity of the C-5 position in comparison to unsubstituted uracil.[21,22] Hence, synthetic modification of uracil via the C-5 position by varying the substituents at the C-6 position is one of the key strategies employed for the diversity-oriented synthesis of uracil based compounds.

In recent years, surface-active molecules (e.g., biosurfactant) as high value microbial products are gaining popularity and interest due to their broad range of functional properties and the diverse synthetic capabilities of microbes. Such molecules tend to accumulate at the interface of air−liquid, liquid−liquid, or liquid−solid and form a thin molecular film at the junction of the two media that ultimately lowers the interfacial tension and surface tension.[23] At the interface of two media, such molecules interact with each other possessing different degrees of polarity. The hydrogen bonding between the molecules causes a decrease in the surface tension and critical micelle concentration (CMC). These properties create microemulsions leading to micelle formation in which hydrocarbons become soluble in water or water in hydrocarbons and makes the surfactant more applicable in industrial processes like wetting and phase dispersion, detergency, foaming, emulsification, etc.[24] The use of biosurfactant seems to offer more potential than chemically synthesized equivalents because of their unique structural diversity; high specificity; higher biodegradability,

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biocompatibility, and digestibility; ecofriendlyness; reusability; stability over different extreme conditions such as high temperature, pH, and salinity; less toxicity; widespread applicability; and production from renewable sources, mainly from wastes.[25−27] Hence, the biosurfactant can be regarded as a "green surfactant". In this work, we have used the rhamnolipids (mixture of monorhamnolipids and dirhamnolipids) (Figure 1),

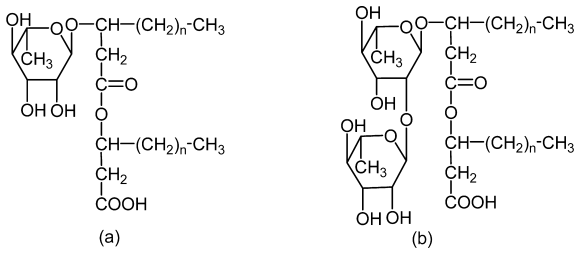


Figure 1. Structure of rhamnolipids: (a) monorhamnolipid and (b) dirhamnolipid.

a major class of biosurfactant, which is produced by *P. aeruginosa* OBPI.[28] The rhamnolipid biosurfactant is a transparent liquid with a light to dark amber tint color and a mild, sweet, soapy odor.

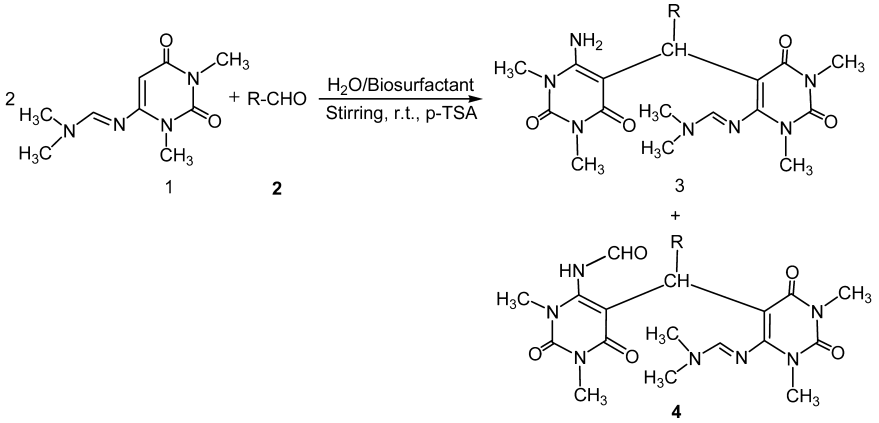
Biosurfactants are widely used in industrial, environmental, and biological and medical applications.[25−27,29−34] Specially, application of biosurfactant in organic transformation is still not explored and to the best of our knowledge, for the first time, we have used biosurfactant in organic transformation, although synthetic chemists have been using "synthetic surfactants" for years. We believe this methodology will open a new vista in the regime of sustainable green synthetic methodology. Synthesis of heterocycles of biological significance is a never ending active field of research. In our research program, owing to the ample bioactivities associated with pyrimidine compounds, we are considerably interested in developing newer methodologies for the synthesis of pyrimidine derivatives.[35−41] In this connection, we reported the formation of bisuracil derivatives in water by exploiting the nucleophilic behavior of 6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (1) at the C-5 position in the absence of biosurfactant.[42] The marine sea hare *Dolabella auricularia*[43] is the natural source of extraction for bisuracil and their analogues. Some of the *N*-substituted bisuracil analogues are associated with promising bioactivities.[44]

RESULTS AND DISCUSSION

6-[(Dimethylamino)methyleneamino]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (**1**) and benzaldehyde (**2a**; R═-C_6H_5) were chosen as the model substrates (Scheme 1) for optimization, and the results are elaborated in Table 1. Initially, we examined the reaction between (**1**) and (**2a**) in water (Scheme 1, in the absence of biosurfactant). But the reaction did not proceed at all under this condition (entry 1, Table 1). Using *p*-toluene sulfonic acid (*p*-TSA) as catalyst or applying heat also did not help the reaction to proceed (entries 2 and 3, Table 1). Interestingly, when we carried out the reaction using the biosurfactant produced by *P. aeruginosa* OBPI in water, the reaction proceeded but with very low yield (entry 11, Table 1). However, notably, when we added *p*-TSA as catalyst, the yield of the product was found to increase (entries 12 and 13, Table 1). A number of solvents were also screened (entries 4−9, Table 1). However, no product formation was noticed in those solvents. Fifteen mol % *p*-TSA was found to be the optimum amount to give the best yield of the product (entry 14, Table 1) in the presence of biosurfactant. Reaction in synthetic surfactant, SDS produced moderate yield (entry 10, table 1).

6-[(Dimethylamino)methyleneamino]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (**1**) is an interesting molecule having a azadiene unit.[36−42] In the reaction, a mixture of products, bisuracils **3** and **4**, were obtained in poor yield. In view of poorer yield, 15 mol % of *p*-TSA was added to increase the yield of the products (Table 1). In the presence of biosurfactant, the solubility of uracil and aldehydes in water increases. The best solubility was observed at CMC. Notably, the reaction was very clean providing **3a** (R═C_6H_5) as the major product and a trace amount of **4a**. The structure of **3a** was confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, elemental analyses, and single-crystal X-ray analysis.

Scheme 1. Synthesis of Bisuracil Derivatives 3 and 4 in the Presence of Bbiosurfactant



R= C_6H_5, CH=CH- C_6H_5, *p*-$OCH_3C_6H_4$, *p*-ClC_6H_4, *o*-OHC_6H_4, *p*-$CH_3C_6H_4$, *p*-$NO_2C_6H_4$, *m*-$NO_2C_6H_4$, H, CH_3,

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Table 1. Optimization of Reaction Condition for Model Reaction between 1 and 2a

entry	reaction condition	time (h)	Yield %[a] of **5a**
1	water, rt	48	No product formation
2	water, reflux	48	No product formation
3	water, reflux, 15 mol % *p*-TSA	12	Trace amount of product
4	CH_3CN, reflux	12	No product formation
5	CH_3CH_2OH, reflux	12	No product formation
6	CH_3OH, reflux	12	No product formation
7	DMF, reflux	12	No product formation
8	toluene, reflux	12	No product formation
9	$C_6H_5NO_2$, reflux	12	No product formation
10	water, SDS,[b] rt	12	56
11	water, biosurfactant,[c] rt	12	25
12	water, biosurfactant,[c] rt, 5 mol % *p*-TSA	12	40
13	water, biosurfactant,[c] rt, 10 mol % *p*-TSA	8	60
14	water, biosurfactant,[c] rt, 15 mol % *p*-TSA	4	75

[a]Yield % is referred to isolated yields and calculated from (mol of product)/(mol of initial substrate) × 100. [b]SDS = sodium dodecyl sulfate. [c]At CMC.

Table 2. Synthesis of Bisuracil Derivatives 3 and 4 in the Presence of Biosurfactant According to Scheme 1

entry	carbonyl compounds (**2**)	time (h)	yield % of product **3**[a]	yield % of product **4**[a]
a	C_6H_5CHO	3.5	75	Trace
b	$C_6H_5CH{=}CHCHO$	10	25	Trace
c	*p*-$OCH_3C_6H_4CHO$	3	trace	93
d	*p*-ClC_6H_4CHO	2	95	no product formation
e	*o*-OHC_6H_4CHO	5	trace	75
f	*p*-OHC_6H_4CHO	5	trace	85
g	*p*-$CH_3C_6H_4CHO$	4	15	87
h	*p*-$NO_2C_6H_4CHO$	4.5	96	trace
i	*m*-$NO_2C_6H_4CHO$	4.5	60	37
j	$C_5H_4O_2$	3	73	25
k	C_5H_4OS	3.5	trace	93
l	$HO(CH_2O)_nH$ (n = 6−100)	10	trace	no product formation
m	CH_3CHO	10	trace	no product formation
n	$CH_3(CH_2)_2CHO$	10	trace	no product formation
o	$CH_3(CH_2)_3CHO$	10	trace	no product formation
p	$(CH_3)_2CO$	48	no product formation	no product formation
q	$CH_3COC_6H_5$	48	no product formation	no product formation
R	$C_6H_5COC_6H_5$	48	no product formation	no product formation

[a]Yield % is referred to isolated yields and calculated from (mol of product)/(mol of initial substrate) × 100.

The ^{1}H NMR peaks of **3a** at δ 2.80 (s, 3H), 3.02 (s, 3H), 3.28 (s, 3H), 3.33 (s, 3H), 3.36 (s, 3H), and 3.39 (s, 3H) ppm are due to the six *N*-methyl groups. The peak at δ 5.69 (s, 1H) ppm is due to the −CH proton. The broad singlet peak at δ 5.93 (br s, 2H) ppm is due to $-NH_2$ protons. The multiplets within δ 7.09−7.24 ppm are due to five aromatic protons, and the peak at δ 8.41 (s, 1H) ppm is due to −N=CH. The $-NH_2$ group was confirmed by shaking with D_2O, i.e., the $-NH_2$ peak disappeared in the ^{1}H NMR spectrum upon shaking with D_2O.

Having these interesting results in hand, the reaction was extended to other differently substituted aromatic, aliphatic, and heterocyclic aldehydes and ketones (**2a**−**r**) under the same optimized reaction conditions. Out of the two, one product was obtained always predominantly or exclusively. The results are summarized in Table 2 (entries **a**−**r**). To our delight, all the aldehydes (entries **2a**−**o**, Table 2) reacted with equal ease within short times, furnishing the products 6-amino-6′-(dimethylamino)methyleneamino-1,1′,3,3′-tetramethyl-5,5′-(phenylidene)-bis-[pyrimidine-2,4(1*H*,3*H*)-dione] derivatives **3a**−**k** and **4a**−**k** in good yields except **2b** and without side product(s) formation. To note, the same reaction did not proceed in water in the absence of biosurfactant, thereby proving the necessity of biosurfactant. The reaction failed with ketones (entries **p**−**r**, Table 2); neither **3** nor **4** were formed. With aliphatic aldehydes (entries **l**−**o**, Table 2), the reaction was not at all satisfactory. Product **3** was obtained in trace amounts, and product **4** was not found at all.

Single-crystal X-ray analysis further confirmed the structure of the products. The ORTEP diagram for compound **3h** (R= *p*-$NO_2C_6H_4$) is shown in Figure 2. Suitable crystals of **3h** were obtained by slow evaporation from ethanol solution.

Interestingly, the ^{1}H NMR spectrum of **4c** shows that in solution it remains in iminol form ($CDCl_3$, 25 °C) exclusively. No amide form was detected. The peak at δ 10.49 (s, 1H, exchangeable with D_2O) ppm is due to hydroxyl proton. Peaks at δ 7.30 (s, 1H) and 7.29 (s, 1H) ppm are due to azomethine protons. Peaks at δ 7.10 (d, J 8.72 Hz, 2H) and 6.82 (d, J 8.72 Hz, 2H) ppm are due to aromatic protons. The peak at δ 5.47 (s, 1H) ppm is due to the methine proton. Peaks at δ 3.79 (s, 3H), 3.42 (s, 3H), 3.40 (s, 3H), 3.39 (s, 3H), 3.34 (s, 3H), 3.10

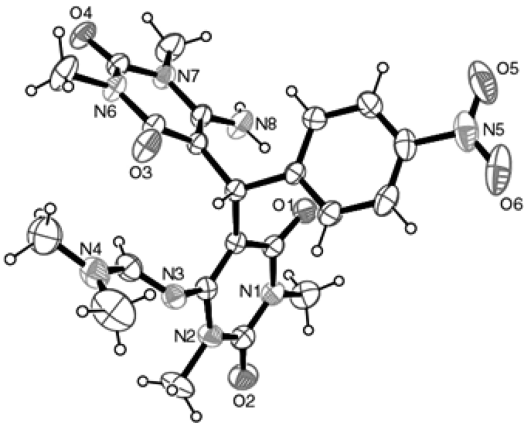


Figure 2. ORTEP diagram of **3h**.

(s, 3H), and 2.76 (s, 3H) ppm are due to six *N*-methyls and one methoxy group. No aldehydic peak was observed. However, single-crystal X-ray analysis of **4c** shows that in the solid state (Figure 3) it remains in amide form exclusively. This can be explained with the help of amide-iminol prototopic tautomerism in **4**, which is shown in Scheme 2.

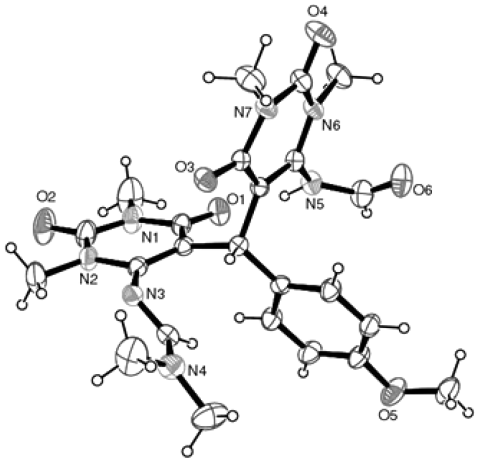


Figure 3. ORTEP diagram of **4c**. **4c** remains in amide form exclusively in the solid state.

ORTEP diagrams for compounds **4c** (R=*p*-$OCH_3C_6H_4$) and **4j** (R=C_4H_3S) are shown in Figures 3 and 4, respectively. Suitable crystals of **4c** and **4j** were obtained by slow evaporation from ethanolic solution.

To gain more insight into the reaction, a competitive reaction involving equimolar 6-amino-1,3-dimethyluracil (**5**), **1**, and **2a** (R=C_6H_5) was studied (Scheme 3). Here, we expected three products: **3a**, **4a**, and **6a**. However, we got **4a** in trace amount,

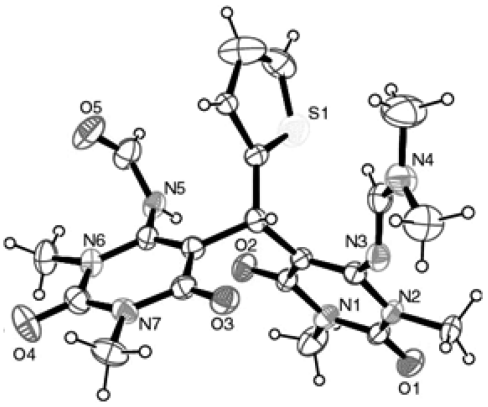


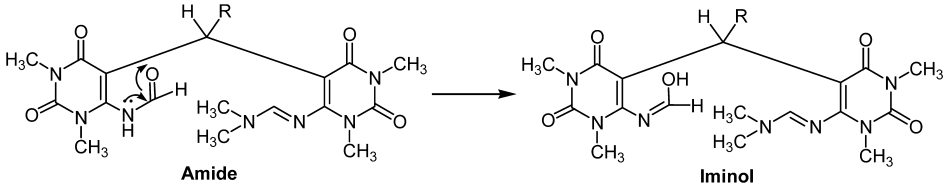
Figure 4. ORTEP diagram of **4j**. **4j** remains in amide form exclusively in the solid state.

6a as the major product, and **3a** as the minor product. This suggests that the reactivity of **5** is more as compared to **1**.

To extend the scope and limitations of the reaction further, we also studied the reaction of **1** with dicarbaldehydes (**7**) (Scheme 4). The results are summarized in Table 3 (entries a and b). In the case of an aliphatic dicarbaldehyde (glutaraldehyde; entry b, Table 3) we obtained the bis-uracil adduct (**8b**) as the major one (25%), but in the case of *p*-benzenedicarbaldehyde (entry a, Table 3), we obtained the bisuracil adduct (**8a**) predominantly, along with little amount of *N*-formylated bisuracil derivative (**9**). In both cases, only one aldehydic group reacted as evidenced by the appearance of the aldehydic peak at δ 9.96 ppm in the ^{1}H NMR spectrum and at δ 192 ppm in the ^{13}C NMR spectrum of both **8** and **9**. Unreacted amount of **1** was recovered from the reaction mixture.

Why does the reaction occur in the presence of biosurfactant at CMC? There might be two factors responsible for it. First, the equilibrium of the nucleophilic reaction is shifted far to the right in the presence of biosurfactant. The aromatic aldehyde molecules being hydrophobic in nature form a highly structured solvation layer in the aqueous environment in the absence of biosurfactant. This results in the reduced entropy condition with high free energy content in the existing physiochemical environment. Gradual addition of surfactant into the reaction mixture to an extent of CMC led to the formation of a hydrophobic pocket within the bulk water solvent due to hydrophobic interior of micelle, which paves the way for bringing the reactants to close proximity facilitating the product formation (Scheme 5). The biosurfactant usually interferes with the existing solubility of solvation layer, which led to the other probable interactions and chemical events that might be responsible for the release of binding energy. The binding energy in turn helps in expediting the reaction toward

Scheme 2. Amide-Iminol Tautomerism in 4[a]



[a]In solution it remains in enol form, and in solid state it remains in keto form.

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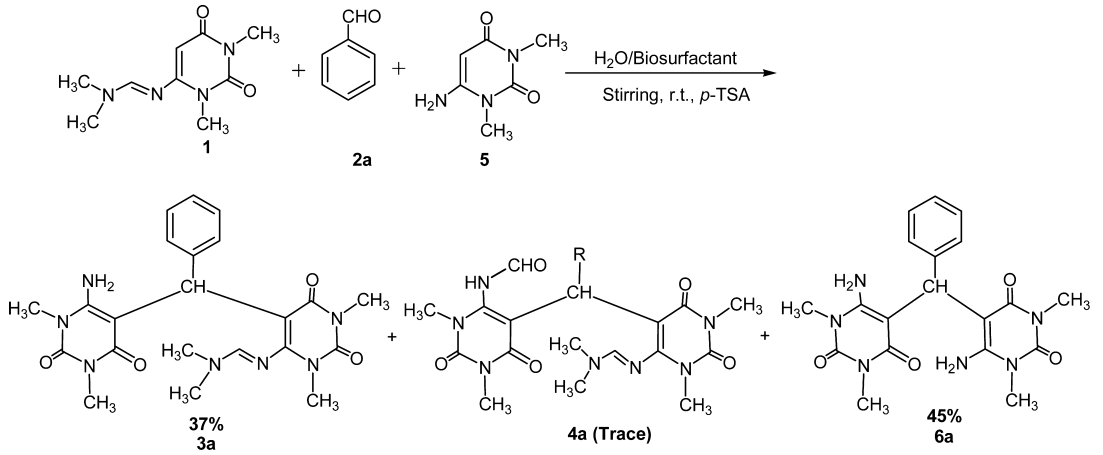
Scheme 3. Competitive reaction among 1, 5, and 2a



Scheme 4. Synthesis of Bisuracil Derivatives 8 and 9 in the Presence of Biosurfactant

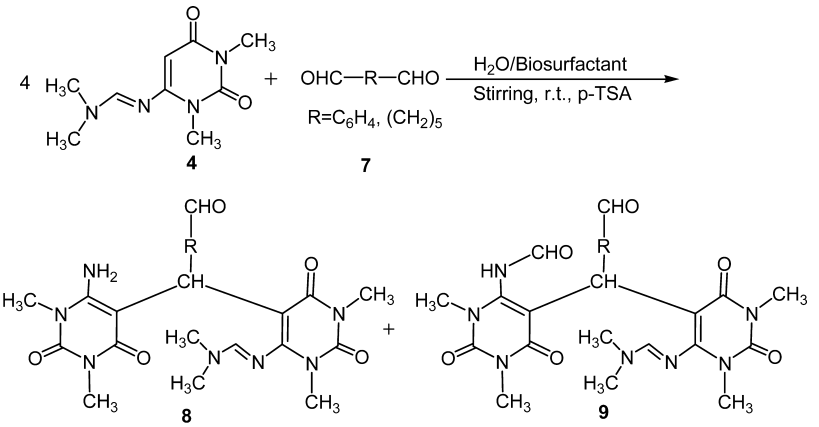
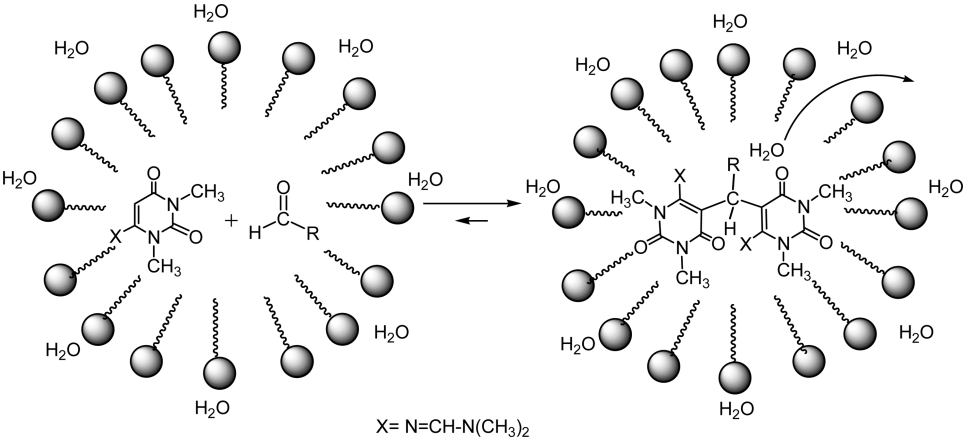


Table 3. Synthesis of Bisuracil Derivatives 8 and 9 in the Presence of Biosurfactant (Scheme 4)

entry	dicarbonyl compounds (7)	time (h)	yield % of product 8[a]	yield % of product 9[a]
a	*p*-(CHO)C_6H_4(CHO)	5	65	28
b	CHO$(CH_2)_5$CHO	10	25	Trace

[a]Yield % is referred to isolated yields and calculated from (mol of product)/(mol of initial substrate) × 100.

Scheme 5. Reaction between Uracil Derivative (1) and Aldehydes (2) in the Presence of Biosurfactant in Water



completion in the presence of catalyst. Second, mechanistically,[42] it is believed that the reaction proceeds through the nucleophilic attacks by the 5-position of **1** at the carbon center of the aldehyde (**2**), followed by the elimination of water molecule. Then, a second uracil molecule attacks via its 5-position affording the products. Dehydration has successfully

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been achieved in water due to the hydrophobic nature of the biosurfactant interior (Scheme 5).[45] Organic substrates (uracil and aldehydes) in water would form emulsion droplets (solvation layer), which possess a hydrophobic interior, through hydrophobic interactions. Because aldehydes are more reactive than ketones toward nucleophilic attack, the reaction occurs with aldehydes only. Again, aromatic aldehydes are more hydrophobic than aliphatic ones because of the presence of the aromatic benzene ring. Therefore, aromatic aldehydes provided the products in good yields, but aliphatic aldehydes afforded only trace amounts of the products.

The catalyst, *p*-TSA protonates the aldehydic oxygen in **2** and thereby makes the carbonyl carbon more electrophilic.

One of the most important economic considerations in the context of sustainable green chemistry is recovery and recyclability. The biosurfactant has been recovered and recycled several times repeatedly.

CONCLUSION

In conclusion, the nucleophilic addition of 6-[(dimethylamino)-methyleneamino]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (**1**) with aldehydes (**2**) was achieved using "green surfactant" isolated from *P. aeruginosa* OBP1 in water at room temperature. The methodology is highly efficient, environmentally friendly, and quite general for aromatic, aliphatic, and heterocyclic aldehydes. Chemoselectivity of the reaction is also demonstrated. Much focus has been paid to "designer surfactants",[46] but looking at the sustainability issues, the scientific community should realize the vast potential of "biosurfactants". The general belief is that dehydration reactions require anhydrous conditions. However, this difficulty has been successfully eliminated by using biosurfactant.

In spite of the immense potential of biosurfactants in organic synthesis over synthetic surfactants, their uses are still not explored. So, there are many scopes of exploration in this regard and as a possible replacements to synthetic surfactants.

EXPERIMENTAL SECTION

General Experimental Details. Melting points were determined on a melting point apparatus and are uncorrected. IR spectra were recorded as KBr pallets on a FT-IR spectrophotometer in the range 4000−600 cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded on a 400 MHz NMR spectrophotometer using tetramethylsilane (TMS) as the internal standard. Chemical shift values are expressed in ppm. Coupling constants are expressed in hertz. The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; and m, multiplet. X-ray intensity data were collected on a CCD area-detector diffractometer with Mo Kα radiation (λ = 0.71073 Å). The structures were solved by SHELX97 and refined by full-matrix least-squares on F^2 (SHELX97).[47] Reactions were monitored by thin layer chromatography using aluminum-backed plates coated with silica gel and visualized under UV light at 254 and/or 360 nm and/or iodine vapor. Elemental analyses were carried out in a CHN analyzer. Mass spectra were recorded on a time-of-flight mass spectrometer using electrospray ionization (ESI).

Crystallographic Information. CCDC-849125 (for **3h**), −849124 (for **4c**) and −849126 (for **4j**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

ASSOCIATED CONTENT

Supporting Information

Synthesis of 6-[(dimethylamino)methylene]1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (**1**), synthetic procedure for the bis-uracil (**3**) and (**4**), determination of CMC of the biosurfactant, recycling procedure of biosurfactant, biosurfactant recovery, spectroscopic and analytical data of compounds, and copies of ^1H and ^{13}C NMR spectra for compounds. 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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