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An efficient non-ionic surfactant catalyzed multicomponent synthesis of novel benzylamino coumarin derivative via Mannich type reaction in aqueous media

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ABSTRACT

An efficient non-ionic surfactant catalyzed multicomponent synthesis of novel benzylamino coumarin derivatives has been developed from secondary amines, aromatic aldehyde, and 4-hydroxy coumarin via Mannich type reaction in aqueous media. In this Mannich type reaction, surfactant forms stable colloidal medium to stabilize iminium ion which undergoes nucleophilic addition of 4-hydroxy coumarin to give benzylamino coumarin in very good yields.

Recently, aqueous environment has attracted much attention in organic synthesis.[1] Water exhibits unique reactivity and selectivity, which cannot be attained in conventional organic solvents.

In recent years, multicomponent reactions (MCRs), involving three or more reactants in one-pot have been used to synthesize structurally diverse bioactive heterocyclic compounds.[2] The advantages of multicomponent reactions are high atom-economy, structural diversity, operational simplicity, and lack of waste products in a multi-step reaction.

Coumarins and its derivatives are an important class of heterocyclic compounds, which are widely distributed in various natural products.[3] They show wide range of biological activities such as anti-HIV, antimalarial, insecticides, and antioxidants.[4] Among various derivatives of 4-hydroxy coumarin, 3-(benzyl)-substituted compounds have been used in important clinical applications (Fig. 1).[5] Therefore, we tried to synthesize 3-(benzyl)-substituted coumarins via Mannich type reaction.

Mannich reaction[6] is one of the most powerful synthetic methods for carbon–carbon bond-forming reactions for the synthesis of novel nitrogen containing organic molecules.

In 1953, Robertson and Link reported the Mannich reaction on 4-hydroxy coumarins.[7] They obtained the Mannich base along with bis coumarin as the major product. This is due to high reactivity of 3-position of 4-hydroxy coumarins (Scheme 1).

In our preliminary work on multicomponent reactions (MCRs) for the synthesis of various biologically important heterocyclic compounds,[8] we wish to report herein a highly efficient procedure for the preparation of 3-substituted coumarin derivatives via one pot three-component Mannich type reaction using non-ionic surfactant (Triton X-100) in aqueous media (Scheme 2).

We selected benzaldehyde, 4-hydroxy coumarin, and piperdine as a model reaction in methanol at room temperature. Surprisingly, we obtained bis product **5** as a major product whereas, **4** was formed as a minor product (10% yield). Various solvents were used to improve the yield of **4** and reduce the formation of **5**.

In non-polar solvents such as dichloromethane, tetrahydrofuran, and acetonitrile, both **5** and **4** were obtained in poor yield. However, in polar solvents like ethanol, DMF and DMSO, **5** was obtained in higher yield in comparison to **4**. When the reaction was performed in water at room temperature, no product was formed. On heating the reaction mixture gave **5** in high yield while **4** was obtained in poor yield. However, when the reaction was carried out under solvent-free condition at 100 °C, we found that only product **5** was formed in high yield.

When benzaldehyde, 4-hydroxy coumarin, and piperdine were stirred at room temperature using water as solvent and Triton X-100 (5 mol %) as a surfactant the yield of **4** was improved. However, it was found that the amount of Triton X-100 ($C_{14}H_{22}O(C_2H_4O)n$) where n = 9–10, influenced the yield of **4**. Further studies revealed that on increasing the amount of surfactant, the yield of the product **4** also increased (Table 1). The best results were obtained when 20 mol % of catalyst was used (only **4** was formed).

In order to study the effect of surfactant,[9] various ionic (cationic and anionic) and non-ionic surfactants were tested for the reaction of benzaldehyde, 4-hydroxy coumarin, and piperdine in water, and

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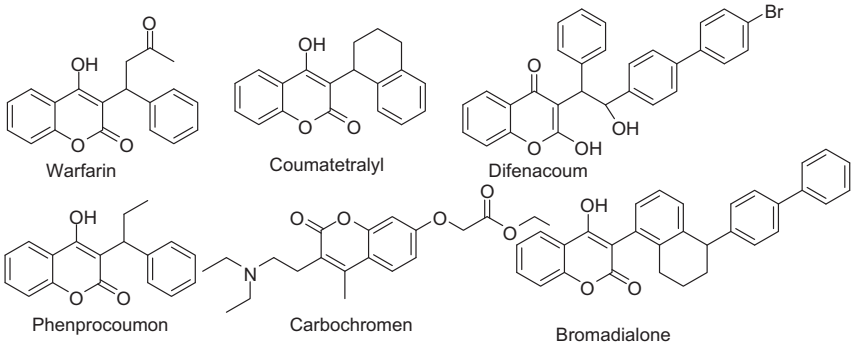
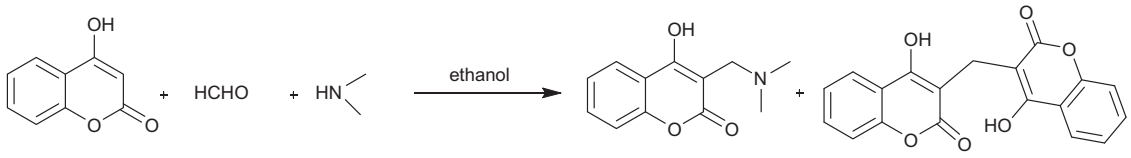
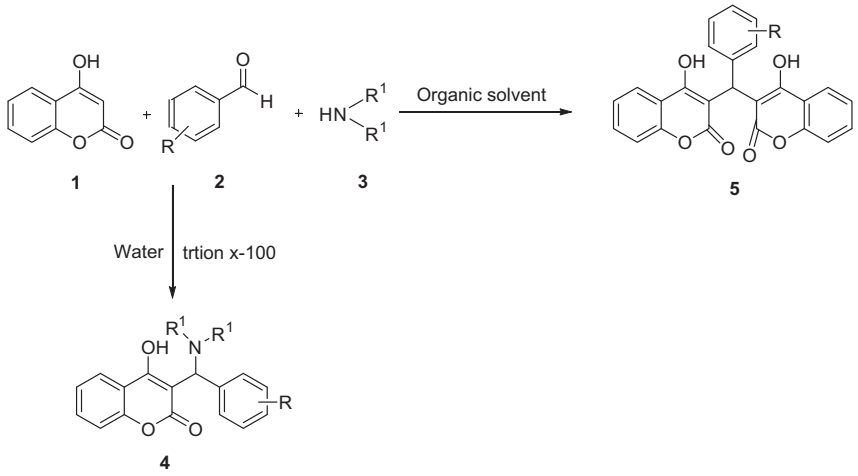


Figure 1. Biologically active 3-substituted coumarin.



Scheme 1. Synthesis of 3-substituted aminomethyl-4-hydroxy coumarin.



Scheme 2. Synthesis of benzylamino coumarin derivatives catalyzed by surfactant (Triton X-100).

Table 1
Effect of solvents on synthesis of benzylamino coumarin[a]

Entry	Solvents	Yield of **5**[c] (%)	Yield of **4**[c] (%)
1	MeOH	52	10
2	EtOH	52	10
3	DCM	20	8
4	THF	22	8
5	ACN	25	10
6	DMF	50	12
7	DMSO	52	10
8	MeOH[b]	62	8
9	Water[b]	80	9
13	No solvent	85	—
10	Water/Triton X-100[d]	20	64
11	Water/Triton X-100[e]	8	78
12	Water/Triton X-100[f]	—	89

[a] The reaction was conducted with benzaldehyde (5 mmol), 4-hydroxy coumarin (5 mmol), and piperdine (5 mmol) at room temperature.
[b] Reaction was carried out with heating.
[c] Isolated yield.
[d] Triton X-100 (5 mol %).
[e] Triton X-100 (10 mol %).
[f] Triton X-100 (20 mol %) in water (10 ml).

the results are summarized in Table 2. In the presence of SDS, the desired product was obtained in very low yield (entry 1, Table 2). Addition of catalytic amount of Lewis acid (boric acid) and Brønsted acid (*p*-toluenesulfonic acid, methane sulfonic acid) did not improve the yield of **4**; whereas, *p*-dodecylbenzenesulfonic acid (DBSA), which acts both as Brønsted acid and surfactant gave products **5** and **4**.

Scandium tris-(dodecyl sulfate) $Sc(DS)_3$ which acts as Lewis acid-surfactant-combined catalysts (LASCs)′, and cetyltrimethylammonium bromide (CTAB) which acts as cationic surfactant were employed as catalysts for the formation of desired product in water at room temperature in separate reactions. Unfortunately, **5** was obtained as major product. A combination of two surfactants Triton X-100/$Sc(DS)_3$, Triton X-100/CTAB, Triton X-100/DBSA has also been used during the reaction, but they did not catalyze the reaction efficiently.

Therefore, Triton X-100 was found to be the best surfactant for the synthesis of benzylamino coumarin derivatives in water.

With the successful optimization of the synthesis of 3-substituted coumarin with benzaldehyde, piperidine, and 4-hydroxycoumarin we further studied the reactions of different aromatic

Table 2
Effect of catalyst/surfactant on synthesis of benzylamino coumarin[a]

Entry	Catalyst	Yield of **5**[b] (%)	Yield of **4**[b] (%)
1	SDS	60	10
2	Boric acid	56	8
3	TsOH	69	8
4	MSA	65	8
5	DBSA	70	12
6	$Sc(DS)_3$	55	14
7	CTAB	60	16
8	Triton X-100	—	89
9	Triton X-100/$Sc(DS)_3$[c]	55	30
10	Triton X-100/CTAB[c]	60	34
11	Triton X-100/DBSA[c]	57	28

[a] The reaction was conducted with benzaldehyde (5 mmol), 4-hydroxy coumarin (5 mmol), piperdine (5 mmol) and Triton X-100 (20 mol %) in water (10 ml) at room temperature for 6 h.
[b] Isolated yield.
[c] 10:10 mol % were used.

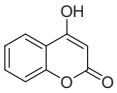
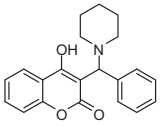
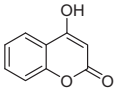
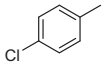
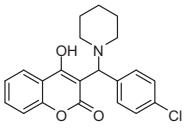
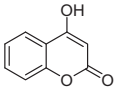
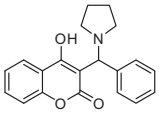
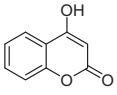
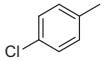
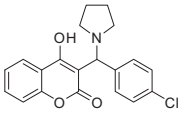
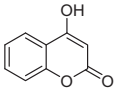
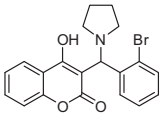
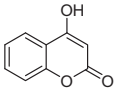
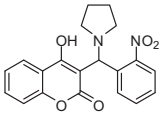
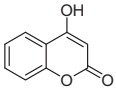
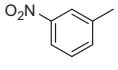
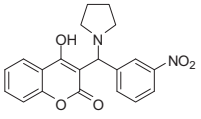
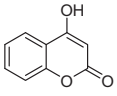
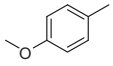
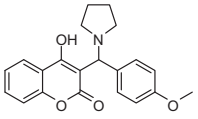
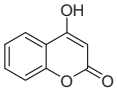
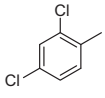
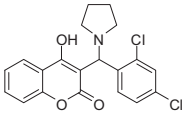
aldehydes, secondary amine and 4-hydroxy coumarin under similar conditions.[10] It was found that only **4** was formed without the formation of bis coumarin (**5**). The results are shown in Table 3.

The formation of the desired product indicates that surfactants play an important role to stabilize the imine intermediate which is formed by aldehyde and secondary amine. Subsequent nucleophilic addition of 4-hydroxy coumarin results in the formation of only one product (**4**). This imine formation is the most attractive feature of our reaction in aqueous medium (Scheme 3).

In contrast to the other surfactant/catalysts, Triton X-100 does not interact with reagent to provide a micelle due to which equilibrium position shifts toward the imine side. The water molecules generated by imine formation, are expelled from the micelle due to hydrophobic nature of their interior.

In conclusion, we have demonstrated an easy, efficient, and green protocol for the synthesis of novel benzylamino coumarin derivatives in water.[11] Non-ionic surfactant (Triton X-100) is a

Table 3
Triton X-100 catalyzed synthesis of benzylamino coumarin derivative[a]

Entry	**1**	**2**	**3**	Product[b] (**4**)	Time (h)	Yield[c] (%)
1				 4a	6	89
2				 4b	5	92
3				 4c	6	90
4				 4d	5	91
5				 4e	5	87
6				 4f	4	85
7				 4g	4	85
8				 4h	6.5	89
9				 4i	4	90

(*continued on next page*)

Table 3 (*continued*)

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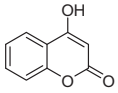
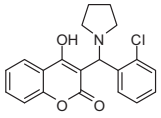
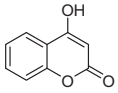
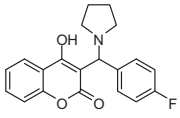
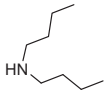
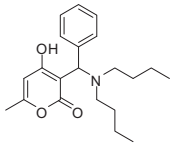
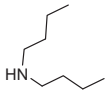
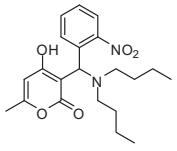
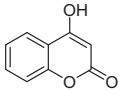
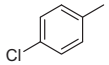
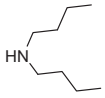
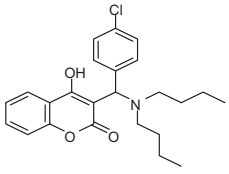
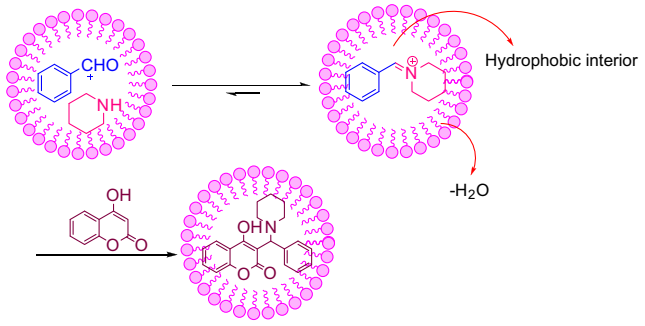
10				 4j	5	90
11				 4k	3.5	93
12				 4l	4.5	87
13				 4m	3.5	84
14				 4n	5	90

[a] The reaction was conducted with benzaldehyde (5 mmol), 4-hydroxy coumrin (5 mmol), piperdine (5 mmol), and Triton X-100 (20 mol %) in water (10 ml) at room temperature for given hours.
[b] All products were characterized by ^{1}H, ^{13}C NMR, IR and mass spectroscopy.
[c] Isolated yield.



Scheme 3. Micelle-promoted multicomponent synthesis of benzylamino coumarin.

useful surfactant to form a stable colloidal medium which stablises imine intermediate to accelerate the reaction in water. The advantages of this method are the improvement in the synthesis of benzylamino coumarin derivative without formation of any side product as seen with the use of organic solvent.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.040.

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10. General procedure for the synthesis of compound **4**. In a typical experiment, the aldehyde (5 mmol), secondary amine (5 mmol), 4-hydroxy coumarin (5 mmol) and Triton X-100 (20 mol %) were taken in water (10 ml) in a round-bottom flask. The reaction mixture was vigorously stirred at room temperature. After the reaction was completed, the solid compound obtained was filtered off and the crude products were purified by recrystallization from

EtOH. In case of liquid (**4n**) the reaction mixture was extracted with EtOAc, dried over sodium sulfate and evaporated under vacuum. The residue was purified by silica gel column with hexane/ethyl acetate (2:3) as eluent to afford the corresponding product.

11. Analytical data for few representative compounds. *4-hydroxy-3-(phenyl (piperidin-1-yl)methyl)-2H-chromen-2-one*(**4a**): White solid; mp: 182–184 °C ^{1}H, 300 MHz ($CDCl_3$): δ 1.64–1.90 (m, 6H), 2.37 (t, 1H, J = 12.36 Hz), 2.78 (t, 1H, J = 12.03), 2.99 (d, 1H, 12.03), 3.85 (d, 1H, J = 11.94), 5.12 (s, 1H), 7.24 (d, J = 7.77 Hz), 7.34–7.26 (m, 2H), 7.48–7.43 (m, 1H), 7.61 (m, 2H), 8.01 (d, 1H, J = 8.43). 13C, 75 MHz ($CDCl_3$): 173.83, 164.20, 154.08, 136.04, 131.28, 129.15, 124.15, 122.98, 120.87, 116.55, 94.84, 76.58, 71.43, 53.85, 50.53, 29.66, 24.35, 23.36, 22.59. ESIMS: m/z 336 (M+H). IR (KBr): 3255, 1671, 1625, 1498, 1393, 1217, 1167, 751 cm^{-1}. Anal. Calcd for $C_{21}H_{21}NO_3$ C, 75.20; H, 6.31; N, 4.18; Found: C, 75.12; H, 6.23; N, 4.13. *3-((4-Chlorophenyl)(piperidin-1-yl)methyl)-4-hydroxy-2H-chromen-2-one* (**4b**): White solid; mp: 188–190 °C ^{1}H, 300 MHz ($CDCl_3$): δ 1.69–1.90 (m, 6H), 2.41 (t, 1H, J = 12.20 Hz), 2.80 (t, 1H, J = 12.0 Hz), 3.01(d, 1H, 12.60), 3.84 (d, 1H, J = 11.96 Hz), 5.11 (s, 1H), 7.20–7.32 (m, 5H), 7.43–7.47 (m, 1H), 7.43–7.48 (m, 1H), 7.99 (d, 1H, J = 6.58 Hz).^{13}C, 75 MHz ($CDCl_3$): 173.55, 164.0, 154.07, 135.13, 134.69, 131.44, 130.44, 129.34, 124.12, 123.08, 120.59, 116.57, 94.84, 70.58, 53.87, 50.56, 40.97, 24.38, 22.58. ESIMS: m/z 370 (M+H). IR (KBr): 3253, 1673, 1627, 1494, 1392, 1213, 1164, 754 cm^{-1}. Anal. Calcd for $C_{21}H_{20}ClNO_3$: C, 68.20; H, 5.45; N, 3.79. Found: C, 68.11; H, 5.38; N, 3.63. *4-Hydroxy-3-(phenyl(pyrrolidin-1-yl)methyl)-2H-chromen-2-one* (**4c**): White solid; mp: 170–172 °C ^{1}H, 300 MHz ($CDCl_3$): δ 2.08 (br, 4H), 2.72 (br, 1H), 3.14 (br, 2H) 3.64 (br, 1H), 5.20 (s, 1H), 7.19–7.26 (m, 2H), 7.30–7.33 (m, 3H), 7.41–7.46 (m, 1H), 7.68–7.71(m, 2H), 7.99 (d, 1H, J = 7.71 Hz). ^{13}C, 50 MHz ($CDCl_3$): 173.85, 164.03, 154.08, 137.73, 131.23, 129.02, 128.96, 128.25, 124.07, 122.94, 121.10, 116.48, 95.49, 75.14, 70.55, 23.72, 23.28. ESIMS: m/z 322 (M+H). IR (KBr): 3257, 1670, 1624, 1497, 1396, 1219, 1169, 749 cm^{-1}. Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.67; H, 5.88; N, 4.28. *4-Hydroxy-3-((3-nitrophenyl)(pyrrolidin-1-yl)methyl)-2H-chromen-2-one* (**4g**): Yellow solid; mp: 188–190 °C ^{1}H, 300 MHz ($CDCl_3$ + DMSO-d_6): δ 2.11 (br, 4H), 3.31 (br, 4H), 5.62 (s, 1H), 7.13–7.20 (m, 2H), 7.39–7.56 (m, 2H), 7.99 (d, 1H, J = 7.62 Hz), 8.14 (t, 2H, J = 6.99 Hz), 8.71 (s, 1H). ^{13}C, 50 MHz ($CDCl_3$ + DMSO-d_6): 172.96, 163.02, 153.03, 147.11, 139.28, 133.19, 130.06, 128.75, 123.60, 122.08, 121.67, 121.57, 120.83, 115.13, 92.93, 76.36, 66.74, 52.77, 22.63. ESIMS: m/z 367 (M+H). IR (KBr): 3252, 1670, 1622, 1492, 1390, 1219, 1162, 759 cm^{-1}. Anal. Calcd for $C_{20}H_{18}N_2O_5$: C, 65.57; H, 4.95; N, 7.65. Found: C, 65.48; H, 4.83; N, 7.58. *4-Hydroxy-3-((4-methoxyphenyl)(pyrrolidin-1-yl)methyl)-2H-chromen-2-one* (**4h**): White solid; mp: 140 °C ^{1}H, 300 MHz ($CDCl_3$): δ 2.07 (br, 4H), 2.72 (br, 1H), 3.13 (br, 2H), 3.61 (br, 1H), 3.76 (s, 3H), 5.15 (s, 1H), 6.82 (br, 2H), 7.21–7.27 (m, 2H), 7.43 (br, 1H), 7.59 (br, 2H), 7.97 (br, 1H). ^{13}C, 50 MHz ($CDCl_3$): 173.31, 163.09, 153.10, 147.07, 139.21, 133.14, 130.09, 128.70, 123.62, 122.11, 121.63, 121.59, 120.81, 115.09, 92.91, 76.32, 66.70, 55.89, 52.72, 22.60. ESIMS: m/z 352 (M+H). IR (KBr): 3251, 1674, 1621, 1500, 1399, 1213, 1161, 754 cm^{-1}. Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.65; H, 5.92; N, 3.89. *3-((Dibutylamino)(phenyl)methyl)-4-hydroxy-6-methyl-2H-pyran-2-one* (**4l**): White solid; mp: 151–152 °C ^{1}H, 300 MHz ($CDCl_3$): δ 0.72 (t, 6H, J = 7.2 Hz), 1.15–1.25 (m, 4H), 1.49–1.62 (m, 4H), 2.11 (s, 3H), 2.84 (t, 4H, J = 7.5 Hz), 5.75 (s, 1H), 5.83 (s, 1H) 7.06–7.19 (m, 5H), ^{13}C, 50 MHz ($CDCl_3$): 169.25, 159.69, 128.01, 126.48, 125.58, 106.11, 102.48, 48.04, 35.38, 28.03, 19.73, 19.43, 13.30. ESIMS: m/z 344 (M+H). IR (KBr): 3251, 1668, 1629, 1492, 1389, 1212, 1161, 754 cm^{-1}. Anal. Calcd for $C_{20}H_{17}Cl_2NO_3$: C, 61.55; H, 4.39; N, 3.59. Found: C, 61.48; H, 4.28; N, 3.48.