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A Mild and Efficient Route to 3-Vinylchromones in Aqueous Micellar media

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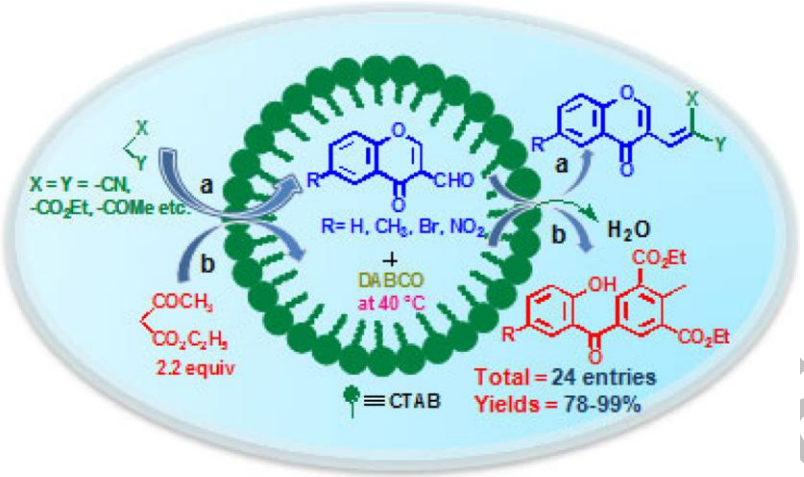
Abstract

A simple, mild and eco-friendly method has been developed for the synthesis of 3-vinylchromones from 4-oxo-4*H*-1-benzopyran-3-carboxaldehyde (3-formylchromone) by simple Knoevenagel condensation with various active methylene compounds (AMC) in aqueous micellar media in the presence of catalytic amounts of CTAB and DABCO. In case of malonic acid as AMC, the reaction resulted formation of only Doebner decarboxylated products under the standard reaction condition. It has been also observed that 3-formylchromone derivatives primarily undergo tandem Knoevenagel and Michael reactions in the presence of >2 equiv. of ethyl acetoacetate to produce benzophenone derivatives, by opening of pyran ring, as the sole product in high yields.



Key words: micellar media, surfactants, Knoevenagel condensation, Doebner decarboxylation, active methylene compounds, 3-vinylchromones.

INTRODUCTION

Chromone is the structural scaffold of a variety of bioactive compounds of synthetic as well as of natural origin with great pharmaceutical importance.[1, 2] From a synthetic viewpoint, 3-formylchromone remains as the key starting material for many of these important heterocyclic systems because of the availability of three electron deficient sites: the C-2 carbon, the aldehyde carbon and the C-4 carbon of the carbonyl group (Figure 1A). Therefore, 3-formylchromone is able to serve as a heterodiene as well as a dienophile or a Michael acceptor based on the available substrates and reaction condition leading to the construction of a great variety of heterocyclic systems.[3] At the same time, chemical modification of this scaffold is a delicate issue as valuable pharmacophores derived from this moiety are vulnerable to a number of nucleophiles, organic bases or strong acids due to its high reactivity.[4] Therefore, development of mild conditions for

further functionalization of C-3 position of 3-formylchromone and pharmacological utilization draws significant research interests till date.[5] In particular, Knoevenagel condensation reactions of 3-formylchromones with compounds having active methylene group leading to formation of 3-vinylchromones were well studied.[6] Such types of condensations are mostly achieved by conventional methods in organic medium in the presence of acids or bases. However, present environmental concerns demand greener alternatives to construct these important heterocycles. So far, there are only limited numbers of green approaches for vinylation of 3-formylchromones by Knoevenagel condensation [7] including a catalyst free process in water at elevated temperature.[7b] Therefore, the development of a new and efficient "green" protocol for this purpose is worthy pursuit.

In the context of "green chemistry and its 12 principles" water as solvent has gained immense popularity due to being inexpensive, non-toxic, non-flammable, widely abundant in nature and environmentally benign. The main problem of insolubility of most of the organic compounds in water is commonly solved by the use of surface-active compounds.[8] They form a micellar, colloidal, or other organized phase hydrophobic interior of which acts as a confined nanoreactor and bring the organic reagents in close proximity to allow the reaction to occur.[9] In particular, dehydration reactions, which often require anhydrous conditions and therefore, one of the most challenging tasks to accomplish in water, have been successfully carried out by our group[10] and others[11] in aqueous media in the presence of catalytic amounts of surfactants. Knoevenagel condensation is eventually a dehydration reaction and there are several reports of carrying

out this reaction in water catalyzed by a surfactant.[12] However, to the best of our knowledge, Knoevenagel condensation of 3-formylchromone leading to 3-vinylchromones was not explored in a micellar medium.

RESULTS AND DISCUSSION

We report herein, CTAB catalyzed efficient synthesis of 3-vinylchromones by simple Knoevenagel condensation of 3-formylchromones with various active methylene compounds in aqueous media in the presence of DABCO as co-catalyst (Scheme 1). The main role of CTAB is to form micelles in aqueous media that act as nanoreactors to carry out organic reactions. Although most of the active methylene compounds are moderately to freely soluble in water, 3-formylchromones have very limited aqueous solubility. Therefore, condensation reaction could proceed in an aqueous medium only at higher temperature.[7b] We anticipated, a micellar medium will be helpful to carry out such reactions more efficiently at a much milder condition because both the reactants would preferably stay in close proximity inside the hydrophobic interior of the micelles allowing the reaction to proceed spontaneously. Indeed, the methodology worked out well for various 3-formylchromones and compounds containing active methylene group. Interestingly, 3-formylchromones in condensation with ethyl acetoacetate mainly produce benzophenone derivatives by opening of pyran ring via tandem Knoevenagel and Michael reactions (Scheme 1).

We started our investigation with a focus on standardizing the reaction conditions. First, the formation of the emulsion droplets were examined by taking optical micrograph of

different surfactant containing aqueous solutions of reaction mixtures after 5 min of stirring at room temperature (Figure 2A). Dynamic light scattering (DLS) experiments of those solutions confirmed that the size of emulsion droplets is in the nanometer range (225-420 nm) (Figure 2B). Then the suitable condition for the Knoevenagel condensation was established by thorough screening of various surfactants, organic bases and reaction temperature. We selected four different class of surfactants viz. SDS (anionic), DBSA (Brønsted acid), CTAB (cationic), and Triton X-100 (neutral) and conducted a model reaction between equimolar mixture of 3-formylchromone (**1a**) and diethylmalonate (**2a**) to find out the most suited surfactant for this reaction. It was found that three surfactants (SDS, CTAB, and Triton X-100) out of four could initiate the formation of the desired product (**3a**) but the reaction was very sluggish at room temperature (Table 1, entry 1-3). Even gentle warming of the reaction mixture was not very effective in terms of the rate of formation of **3a** (Table 1, entry 5-7). On the other hand, DBSA failed to initiate the reaction even after 12 h (Table 1, entry 4, 8). However, addition of 10 mol% of a suitable amine (such as DABCO) as co-catalyst boosted the rate of product formation by several fold (Table 1, entry 9-13). Furthermore, significant enhancement in rate was observed when the same reaction was carried out at 40 °C (Table 1, entry 10) instead of room temperature (Table 1, entry 9). In these cases, the model reaction was carried out using 10 mol% of CTAB as the surfactant. Among several different amines DABCO was found to be most suitable in terms of yield and time required for completion of the reaction. Presumably, DABCO, being more hydrophobic in nature, prefers to stay inside the hydrophobic interior of micelles as compared to other bases used for this purpose and therefore, it could act as a better catalyst for this reaction. Once DABCO was identified

as most suitable co-catalyst, the same model reaction was carried out with different surfactants and it was found that all the surfactants (10 mol%) could catalyze the condensation reaction in the presence of 10 mol% of DABCO at 40 °C to afford the desired product (**3a**) in moderate to good yields (Table 1, entry 10, 14-16). Both DBSA and SDS were found less efficient as catalyst for this reaction, whereas, yields of the final product were high for both CTAB and Triton X-100. As expected, catalytic ability of DBSA-DABCO combination is poor as DBSA reduces the catalytic activity of DABCO by protonation (Table 1, entry 15). Among the rest, CTAB catalyzes the reaction better, presumably due to stronger binding of the CTAB with the substrates, which is expected as CTAB has higher hydrocarbon content in its core region than others.[13] As a part of our study, we also varied mol% of both CTAB and DABCO, and changed temperature to arrive at the ideal reaction condition. As mentioned in table 1, decrease in concentration of CTAB (Table 1, entry 20) or DABCO (Table 1, entry 17) in the reaction mixture slows down the reaction, whereas, use of excess CTAB (Table 1, entry 21) and DABCO (Table 1, entry 18, 19) hardly shows any effect on the reaction rate or the yield of final product (**3a**). At the same time, the reaction temperature above 40 °C did not make a significant difference in the reaction rate and the yield (Table 1, entry 22, 23). Therefore, use of 10 mol% of CTAB as catalyst and 10 mol% of DABCO as co-catalyst and gentle heating (at 40 °C) was considered as optimum condition for further studies.

To test the generality of this method, various 3-formylchromones were treated with different compounds containing active methylene group in the presence of CTAB (10 mol%) and DABCO (10 mol%) at the optimized reaction condition. All the

substrates were found to undergo smooth reaction to afford 3-vinylchromones in high yields within few hours (Table 2). Each of the 3-vinylchromones was thoroughly characterized by ^{1}H NMR, ^{13}C NMR, ESI-MS, IR and CHN analysis, and compared with the reported data. It was found that a substitution at the aromatic ring of 3-formylchromones does not have much influence in the final yield of the products. This is presumably because of the fact that the substituent is located far away from the reaction center. However, presence of electron withdrawing group does influence a little on the reactivity of the corresponding 3-formylchromone derivatives. Thus, the reactions involving 3-formyl-6-nitro-chromone (**1d**) completed in shorter time (Table 2, entry 18, 19, 20) than similar reactions with unsubstituted 3-formylchromones (Table 2, entry 1, 5, 6). Among active methylene compounds malononitrile (**2d**) reacted much faster than the others to produce the desired condensation products in high yields (Table 2, entry 4, 10). Interestingly, however, condensation of 3-formylchromones with malonic acid (**2f**) afforded Doebner decarboxylated products (**3f**, **3l**, **3q** and **3t**; Table 2, entry 6, 12, 17 and 20, respectively) as the only isolated product as revealed by spectral studies and CHN analysis. The coupling constant (J = 15.6 Hz) of H-atoms across the olefinic double bond revealed that they bear *trans* geometry.[6d] As reported by Nohara et al.,[2d] these chromone derivatives bearing an acrylic acid residue at C-3 display antiallergic activity. These compounds were previously achieved only by refluxing the reaction mixture in pyridine. We observed that the micellar medium is suitable to spontaneously carry out an *in situ* decarboxylation to afford these products in high yields. Moreover, the yields of these bioactive

compounds using this method were much higher than the previously reported procedure.[2d, 6d] Although the yields were highly satisfactory for all the other entries, the reaction between ethyl acetoacetate (EAA) and 3-formylchromone did not afford the condensation product, **3b** in high yield (Table 2, entry 2). It was observed that the major product of the reaction between equimolar mixture of **1a** and **2b** was a benzophenone derivative (**4a**). The formation of the benzophenone derivative, **4a** by opening of pyran ring by Knoevenagel condensation followed by Michael reaction was previously reported by W. D. Jones et al. in ethanolic medium in the presence of one equiv of organic base in poor yield.[14]

Encouraged by the fact that 3-formylchromone mainly undergoes tandem Knoevenagel and Michael reaction in the presence of EAA to produce benzophenone derivative, **4a** several reactions were carried out between various 3-formylchromones (1 equiv) and excess EAA (2.2 equiv) to ensure formation of benzophenone derivatives (**4**) as the main product (Table 3). As expected, the reactions produced the benzophenone derivatives (**4**) in high yields. None of the simple Knoevenagel condensation product (**3**) was observed in the final reaction mixture. Presumably, the benzophenone derivatives are formed by stepwise attack of two molecules of EAA to 3-formylchromones (Figure 3). At first, EAA undergoes Knoevenagel condensation to form expected 3-vinylchromones (**3**). Next, another molecule of EAA goes for Michael addition followed by opening of the chromone ring and cyclization to afford the benzophenone derivatives, **4**. Once again, it was found that the nature of the substitutions in the aryl ring of chromone moiety does not have great influence on the reactivity and the yield of the final product. All the

reactions were completed within 2 h and the yields were in the range 82-90%. Although variation was made only in the chromone moiety, it is expected that a variety of acylacetate esters ($RCOCH_2COOR'$) would also undergo similar reactions to produce a benzophenone derivative.

CONCLUSION

A facile and 'green' method has been developed for the synthesis of 3-vinylchromones from 3-formylchromones using different active methylene compounds in organized aqueous media in the presence of CTAB as surfactant and DABCO as mild basic catalyst. A broad range of vinyl derivatives from various 3-formylchromones were obtained using this method. In case of malonic acid, Doebner decarboxylated products and in case of excess ethyl acetoacetate, benzophenone derivatives were obtained as major products. Overall, this method is environmentally benign, cheap, safe, high yielding, and a much improved method than other available methods for the synthesis of 3-vinylchromones from 3-formylchromones.

EXPERIMENTAL SECTION

A Representative Procedure For The Synthesis Of 3-Vinylchromones (3): Synthesis Of *3-[(6-Methyl-4-Oxo-4H-1-Benzopyran-3-Yl)-Methylene]-Pentan-2,4-Dione* (3k).

To a solution of CTAB (18.2 mg, 0.05 mmol) in H_2O (2 mL) were added 6-methyl-3-formylchromone (94.0 mg, 0.5 mmol), DABCO (5.6 mg, 0.05 mmol), and acetyl acetone (51.3 µL, 0.5 mmol) successively at room temperature in a 10 mL round-bottom flask. The reaction mixture was sonicated for 2 min and then stirred at 40 °C for 40 min. The

reaction was monitored by TLC. The crude product was extracted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuum. The crude product was purified by column chromatography (silica gel, 60-120 mesh) using a mixture of ethyl acetate and hexane (1:5) as the eluent.

Light yellow solid, mp. 138-139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.34 (s, 3H), 2.45 (s, 3H), 2.46 (s, 3H), 7.36 (d, *J* = 8.5 Hz, 1H), 7.49-7.52 (m, 2H), 8.0 (s, 1H), 8.26 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 21.1, 26.4, 31.4, 118.1, 118.6, 123.3, 125.6, 130.9, 135.8, 136.4, 144.3, 154.3, 156.8, 175.6, 197.4, 204.2; IR (KBr): 3066, 1702, 1650 cm^{-1}; MS (ESI): *m/z* 271 $(M + H)^+$. *Anal.* Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.24; H, 5.27.

A Representative Procedure For The Synthesis Of Benzophenone Derivatives (4): Synthesis Of *Diethl-5-(2-Hydroxy-5-Methylbenzoyl)-2-Methyl-1,3-Benzenedicarboxylate* (4b).

To a solution of CTAB (18.2 mg, 0.05 mmol) in H_2O (2 mL) were added 6-methyl-3-formylchromone (94.0 mg, 0.5 mmol), DABCO (5.6 mg, 0.05 mmol), and ethyl acetoacetate (140 µL, 1.1 mmol) successively at room temperature in a 10 mL round-bottom flask. The reaction mixture was sonicated for 2 min and then stirred at 40 °C for 2 h. The crude product was extracted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuum. The crude product was purified by column chromatography (silica gel, 60-120 mesh) using 8% ethyl acetate in hexane as the eluent.

Light yellow solid, mp. 75-77 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.42 (t, J = 8.0 Hz, 6H), 2.29 (s, 3H), 2.82 (s, 3H), 4.42 (q, J = 8.0 Hz, 4H), 7.02 (d, J = 8 Hz, 1H), 7.33 (d, J = 2.5 Hz, 1H), 7.38 (dd, J_1 = 2.5 Hz, J_2 = 8.0 Hz, 1H), 8.19 (s, 2H), 11.68 (s, 1H, exchangeable); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.2, 18.2, 20.5, 61.7, 118.4, 128.2, 132.8, 132.9, 133.3, 135.2, 137.9, 143.3, 161.2, 167.0, 199.3; IR (KBr): 2983, 1725, 1639 cm^{-1}; MS (ESI): *m/z* 371 $(M + H)^+$. *Anal.* Calcd. for $C_{21}H_{22}O_6$: C, 68.10; H, 5.99. Found: C, 67.89; H, 6.00.

SUPPORTING INFORMATION

Full characterization data of all compounds and selected ^{1}H & ^{13}C NMR spectra for this article can be accessed on the publisher's website. Please make the words "publisher's website" a live DOI link.

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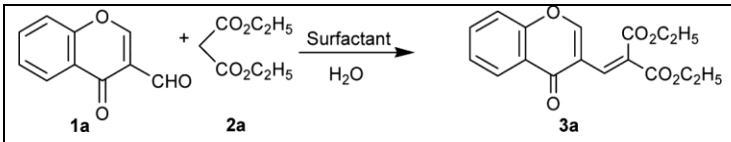
Table 1. Effect of surfactant, temperature and base:

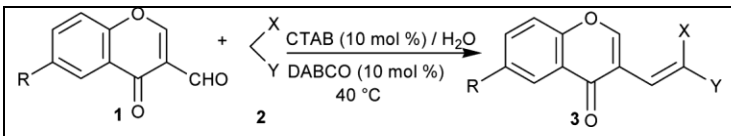


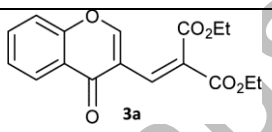
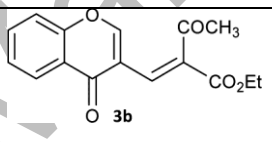
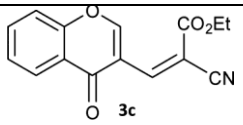
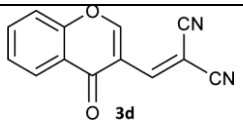
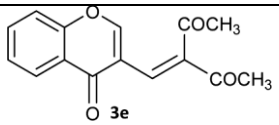
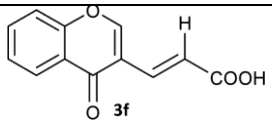
Entry	Surfactant	mol % of surfactant	Base	mol % of base	Time (h)	*T* (°C)	Yield of 3a (%)
1	SDS	10	-	-	12	rt	10[a]
2	CTAB	10	-	-	12	rt	16[a]
3	Triton X-100	10	-	-	12	rt	12[a]
4	DBSA	10	-	-	12	rt	nd
5	SDS	10	-	-	12	40	24[a]
6	CTAB	10	-	-	12	40	36[a]
7	Triton X-100	10	-	-	12	40	28[a]
8	DBSA	10	-	-	12	40	nd
9	CTAB	10	DABCO	10	4	rt	56[a]
10	CTAB	10	DABCO	10	1	40	78
11	CTAB	10	Piperidine	10	2.5	40	76
12	CTAB	10	Pyrrole	10	4	40	80
13	CTAB	10	L-Proline	10	6	40	72
14	SDS	10	DABCO	10	2	40	60
15	DBSA	10	DABCO	10	4	40	42[a]
16	Triton X-100	10	DABCO	10	2	40	71

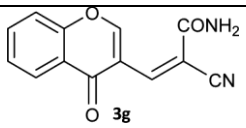
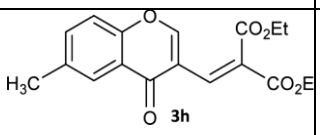
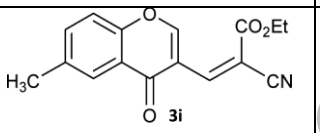
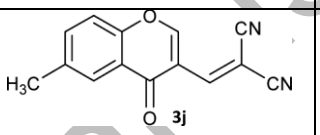
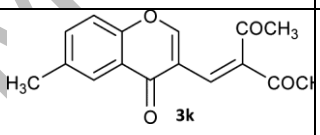
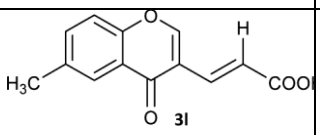
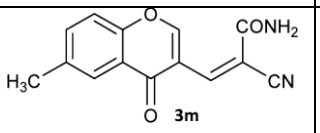
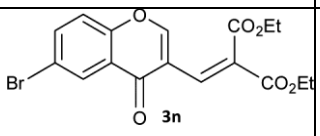
17	CTAB	10	DABCO	05	2.5	40	68
18	CTAB	10	DABCO	20	1	40	75
19	CTAB	10	DABCO	100	0.75	40	82
20	CTAB	5	DABCO	10	3	40	48[a]
21	CTAB	20	DABCO	10	1	40	82
22	CTAB	10	DABCO	10	1	50	76
23	CTAB	10	DABCO	10	1	60	80

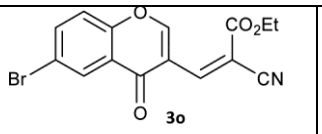
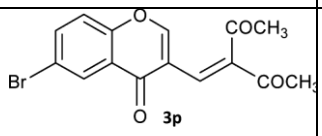
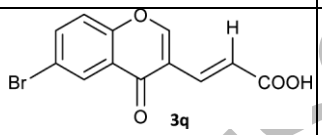
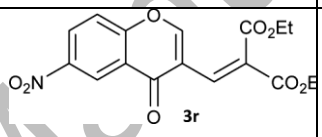
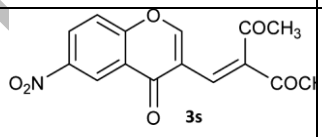
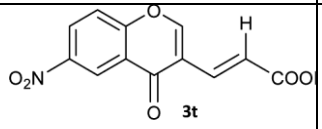
[a]Incomplete conversion, starting material left out; nd: not determined

Table 2. Condensation of 3-formylchromones with active methylene compounds (AMC):



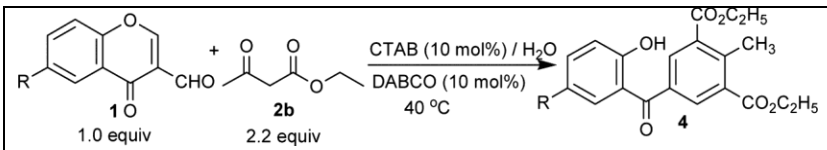
Entry	R	X	Y	AMC	Product	Time (min)	% Yield	Ref.
1	H	-$CO_2C_2H_5$	-$CO_2C_2H_5$	**2a**	 **3a**	60	78	15
2	H	-$COCH_3$	-$CO_2C_2H_5$	**2b**	 **3b**	60	22[a]	14
3	H	-CN	-$CO_2C_2H_5$	**2c**	 **3c**	15	79	7c
4	H	-CN	-CN	**2d**	 **3d**	10	81	7c
5	H	-$COCH_3$	-$COCH_3$	**2e**	 **3e**	30	83	14
6	H	-COOH	-COOH	**2f**	 **3f**	150	88	6d

7	H	-CN	-$CONH_2$	**2g**		20	85	7c
8	6-Methyl	-$CO_2C_2H_5$	-$CO_2C_2H_5$	**2a**		75	82	15
9	6-Methyl	-CN	-$CO_2C_2H_5$	**2c**		15	96	7c
10	6-Methyl	-CN	-CN	**2d**		10	83	7c
11	6-Methyl	-$COCH_3$	-$COCH_3$	**2e**		40	79	--
12	6-Methyl	-COOH	-COOH	**2f**		180	83	6d
13	6-Methyl	-CN	-$CONH_2$	**2g**		30	85	7c
14	6-Bromo	-$CO_2C_2H_5$	-$CO_2C_2H_5$	**2a**		40	92	--

15	6-Bromo	-CN	-$CO_2C_2H_5$	**2c**	 **3o**	15	99	--
16	6-Bromo	-$COCH_3$	-$COCH_3$	**2e**	 **3p**	30	84	--
17	6-Bromo	-COOH	-COOH	**2f**	 **3q**	120	98	6d
18	6-Nitro	-$CO_2C_2H_5$	-$CO_2C_2H_5$	**2a**	 **3r**	40	90	--
19	6-Nitro	-$COCH_3$	-$COCH_3$	**2e**	 **3s**	15	90	--
20	6-Nitro	-COOH	-COOH	**2f**	 **3t**	60	93	2d

[a]The reaction produced benzophenone derivative, **4a** in 32% yield.

Table (3) Condensation of 3-formylchromones with ethyl acetoacetate:



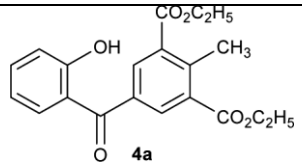
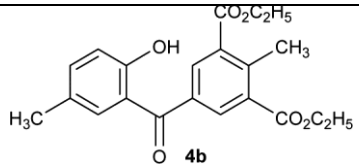
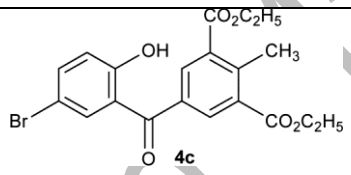
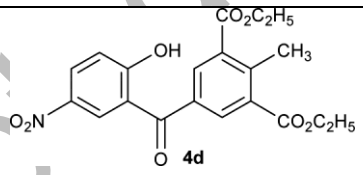
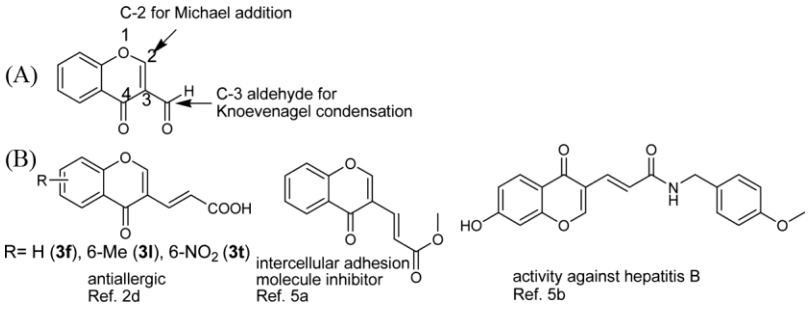
Entry	R	Product	Time (h)	%Yield	Ref.
1	H		1.5	82	14
2	6-Methyl		2.0	88	--
3	6-Bromo		1.5	83	--
4	6-Nitro		1.0	90	--

Figure 1. A) 3-Formylchromone and its various reactive centers, B) some pharmacologically active 3-vinylchromone derivatives.



Scheme 1. Condensation of 3-formylchromones using various active methylene compounds (AMCs) in micellar media.

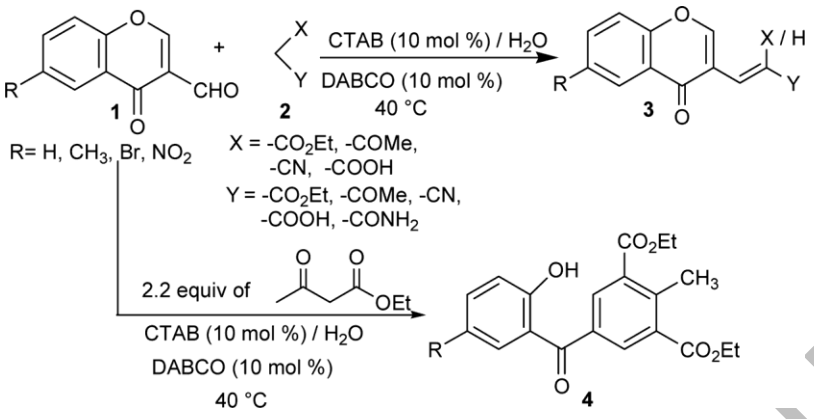
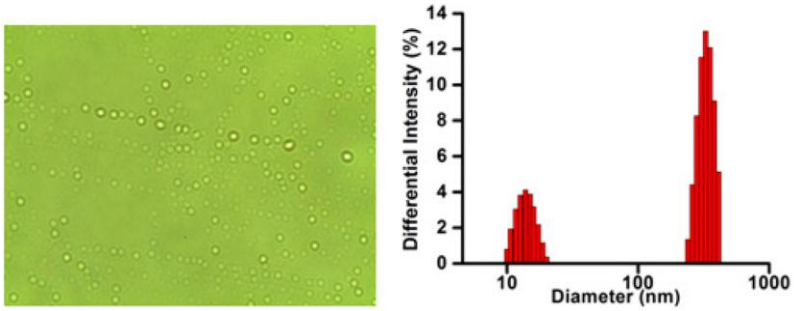


Figure 2. A) A typical optical micrograph of vesicles formed in an aqueous solution of different 3-formylchromones and active methylene compounds in the presence of CTAB, B) DLS data of CTAB showing formation of aggregates.



(A) (B)

Figure 3. Mechanitic pathway of the formation of benzophenone derivative (**4a**) in micellar media.