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Microwave-accelerated Wittig olefination of β-chloroacroleins

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ABSTRACT

The first microwave assisted Wittig reactions of β-chloroacroleins with a stabilized ylide are described here. A combination of sodium ethoxide and toluene was found to be optimum and using this reaction condition a number of alkenyl-substituted benzopyran/benzo[*b*]oxepine/2-chromenone derivatives were prepared within few minutes. The microwave mediated process was found to be comparable with the conventional Wittig reaction in terms of product yields. All the products isolated were found to have *E*-geometry around the C=C bond.

1. Introduction

3-Alkenyl benzopyrans (**I**, Fig. 1), reported to be powerful activators of PPARα and PPARγ (two of the three isoforms of 'Peroxisome Proliferator-Activated Receptors'), are useful for the treatment of dyslipidaemia, atherosclerosis, and diabetes.[1] Benzopyran **II** was also explored as potential antitumor agent.[2]

Because of our interest[3] in the development of novel anti-atherosclerotic agents we became interested in the synthesis of benzopyran/benzo[*b*]oxepine derivative **III** (Fig. 2) that can be functionalized further for Structure–Activity Relationship (SAR) studies. In pursuance of our research[4,5] on the usage of β-chloroacrolein derivative **IV** (generated from ketone **V**, Fig. 2) as a starting material for various organic transformations we decided to explore its utility for the preparation of our target compound **III**.

The use of microwave mediated[6] chemical transformation has become a powerful tool in organic synthesis[7] because of milder reaction conditions, significantly low reaction times, enhanced selectivity, and the possibility of carrying out reactions under

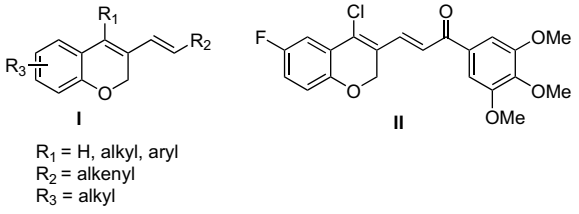

Figure 1. 3-Alkenyl benzopyrans of pharmacological interest.

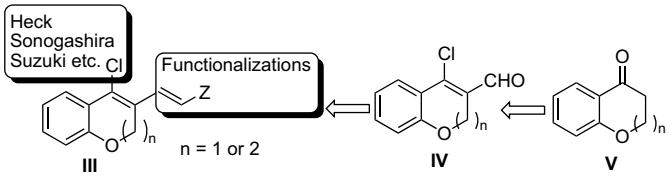

Figure 2. Planned route to benzopyran/benzo[*b*]oxepine derivative **III** and its possible functionalization.

a solvent-free conditions.[8] Construction of C–C double bond via Wittig reaction (one of the versatile and widely used methodology in organic synthesis)[9,10] on the other hand has been a key synthetic step in the preparation of many carbocyclic/heterocyclic structures including natural products and drugs. Extensive efforts have been devoted to modify the conventional method in order to improve the functional group tolerability and product yields. Thus, Wittig reaction of aromatic aldehyde with a stabilized ylide (Wadsworth–Emmons condensation) can be carried out using a range of reagents or catalysts, e.g., cadmium iodide,[11] bis(*p*-ethoxyphenyl)telluroxide (BEPTO),[12] BMPTO,[13] NH_4OAc,[14] $SnCl_2/Na_2SO_3$,[15] $SnCl_2$,[15] $Ti(OR)_4$,[16] *p*-toluenesulfonic acid (PTSA),[17] and NaOH(S).[18] Variations of reaction conditions, e.g., increasing temperature[19] or pressure,[20] irradiation with light,[21] sonication,[22] use of silica gel[23] or ionic solvents[24] have also been reported. The use of water as a solvent in Wittig reaction has been explored recently.[25,26] Notably, Wittig reaction of ketones or aldehydes with stabilized organophosphorus reagents under a microwave condition is less common.[27–30] While the condensation of acrolein with triphenylphosphorane reagents under a conventional Wittig reaction condition has been reported[31–34] the process, however, often encountered with low yields of product due to the acrolein polymerization and therefore β-chloropropionaldehyde was used as a suitable acrolein equivalent in such

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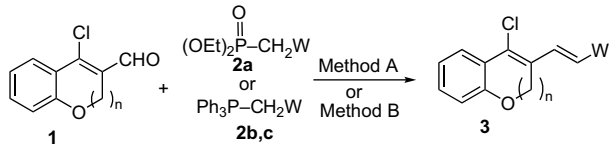


Scheme 1. Wittig olefination of β-chloroacroleins.

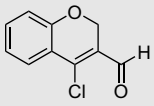
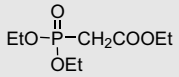
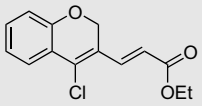
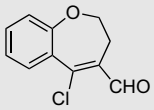
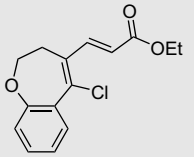
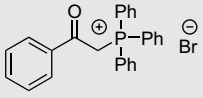
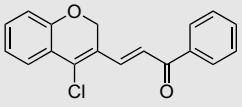
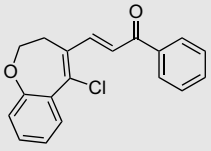
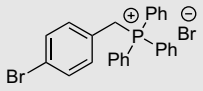
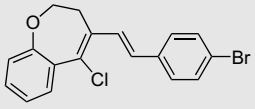
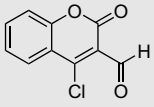
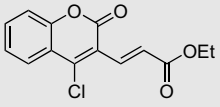
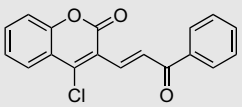
reactions.[35] We have observed that β-chloroacrolein **IV** undergoes both conventional and microwave-accelerated Wittig reaction with stabilized ylides smoothly affording the alkene derivative **III** in good yields. Herein we report our detailed study on the olefination of β-chloroacrolein[36,37] and to the best of our knowledge this is the first example of microwave-accelerated Wittig reaction employing β-chloroacrolein as a carbonyl component.

2. Results and discussion

In order to assess the applicability of β-chloroacrolein in conventional Wittig reaction we examined the reaction of 4-chloro-2*H*-chromene-3-carbaldehyde **1a** (**1**, n=1) with a stabilized ylide **2a** [W=–CO_2Et] (Scheme 1 and Table 1). Thus a mixture of **1a** (2.57 mmol), (diethoxy phosphoryl)-acetic acid ethyl ester **2a** (3.85 mmol), and sodium ethoxide (5.14 mmol) in toluene (5 mL) was stirred at 80 °C and the reaction was monitored. The reaction proceeded smoothly and the complete conversion of aldehyde **1a** to alkene **3a** was observed after 12 h (method A). No side reactions such as polymerization of aldehyde leading to the formation of side products were observed.

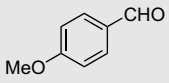
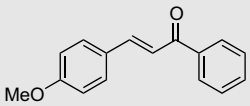
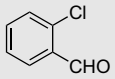
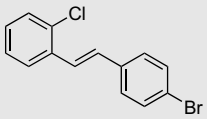
The desired product **3a** was isolated in 95% yield after usual work up and purification (entry 1, Table 1). While the present reaction was carried out using sodium ethoxide as a base and toluene as a solvent, the use of other bases like potassium *tert*-butoxide and potassium carbonate and solvents such as THF, DMF, and DMSO was also examined. However, the best result was achieved by using the combination of sodium ethoxide and toluene. Encouraged by these results we decided to conduct this reaction under microwave. Accordingly, the reaction of **1a** (2.57 mmol) with **2a** (3.85 mmol) in the presence of sodium ethoxide (5.14 mmol) in toluene (1.0 mL) was carried out in a commercially available domestic microwave oven (method B). Under microwave irradiation the reaction was completed within 5.0 min affording the desired product **3a** in 85% yield (entry 1, Table 1). This dramatic reduction of reaction time

Table 1
Synthesis of alkenyl-substituted benzopyran/benzo[*b*]oxepine/2-chromenone derivatives[a] (**3**)

Entry	β-Chloroacroleins (**1**)		Ylides (**2**)		Products (**3**)		Yield[b] (%)/Time	
							Method A	Method B
1		**1a**		**2a**		**3a**	95/12 h	85/5.0 min
2		**1b**		**2a**		**3b**	75/8 h	75/5.0 min
3		**1a**		**2b**		**3c**	78/6 h	75/5.0 min
4		**1b**		**2b**		**3d**	74/8 h	73/5.0 min
5		**1b**		**2c**		**3e**	70/8 h	68/5.0 min
6		**1c**		**2a**		**3f**	71/12 h[c]	65/5.0 min
7		**1c**		**2b**		**3g**	67/12 h[c]	61/5.0 min

[a] Method A: reactions were carried out by using **1** (1.0 equiv), **2** (1.5 equiv), and sodium ethoxide (2.0 equiv), in toluene at 80 °C. Method B: reactions were carried out by using **1** (1.0 equiv), **2** (1.5 equiv), and sodium ethoxide (2.0 equiv), in toluene under microwave radiation.
[b] Isolated yields.
[c] The reaction was carried out at room temperature.

Table 2
Synthesis[a] of chalcone (**5a**) and stilbene (**5b**)

Entry	Aromatic aldehydes (**4**)		Ylides (**2**)	Products[b] (**5**)		Yield[c] (%)/time	
						Method A	Method B
1		**4a**	**2b**		**5a**	88/6.0 h	78/5.0 min
2		**4b**	**2c**		**5b**	78/8.0 h	73/5.0 min

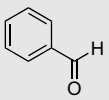
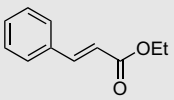
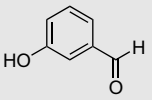
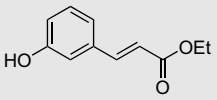
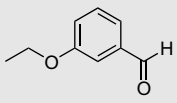
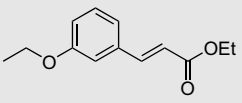
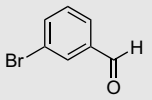
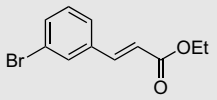
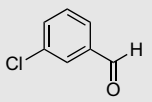
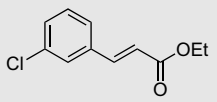
[a] For methods A and B, see footnote of Table 1.
[b] Identified by ^{1}H NMR, IR, and MS.
[c] Isolated yields.

without affecting the product yield significantly prompted us to evaluate the reactivity of other β-chloroacroleins and ylides under both conventional and microwave promoted Wittig reaction conditions. The results of this study are summarized in Table 1.

As can be seen from Table 1 that 4-chloro-2*H*-chromene-3-carbaldehyde (**1a**) showed good reactivity toward other ylide, e.g., phenacyl triphenylphosphonium bromide (**2b**) in addition to **2a** (entry 1 vs 3, Table 1) both under conventional and microwave promoted Wittig reaction condition. Like earlier observation the microwave mediated process was completed within 5.0 min affording the corresponding product **3c** in 75% yield. The use of other β-chloroacrolein derivatives, e.g., 5-chloro-2,3-dihydro benzo[*b*]oxepine-4-carbaldehyde (**1b**, n=2) and 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde (**1c**) was also successful, which afforded novel 4-alkenyl-substituted 2,3-dihydro benzo[*b*]oxepines (**3b**, **3d**, and **3e**) and 3-alkenyl-substituted 2-oxo-2*H*-chromenes (**3f** and **3g**) in good yields when reacted with ylides **2a**, **2b**, and 4-(bromobenzyl)triphenyl phosphonium bromide (**2c**) under both the conditions (entries 2 and 4–7, Table 1). Notably, the chloro group was tolerated in all these cases. The starting aldehyde, i.e., β-chloroacroleins (**1**) used were readily prepared from the corresponding ketones by a Vilsmeier–Haack–Arnold reaction[38,39] as reported in the literature. All the ylides used are commercially available.

We have shown that β-chloroacroleins (**1**) participated smoothly in C=C bond forming reaction under both conventional and nonconventional (microwave mediated) Wittig reaction conditions affording conjugated olefins (**3**) in good yields. Although the Wittig reaction is known to proceed at a slow reaction rate when nonpolar solvents are employed,[23] we were able to reduce the reaction time from hours to minutes under microwave irradiation in spite of using toluene as a solvent. All the products (**3**) isolated after purification were well characterized by spectral data. Based on ^{1}H NMR data [coupling constants ('*J*' values) of olefinic protons] the geometry of the newly formed double bond was assigned as *E*. For example, J=16.4 Hz in the case of compound **3a** (see Experimental section for complete ^{1}H NMR data). The *E*- or *Z*-geometrical selectivity of Wittig reaction of aldehydes with stabilized or nonstabilized ylides has been studied extensively.[40,41] *E*-Alkenes were

Table 3
Synthesis[a] of ethyl cinnamates (**7**)

Entry	Aromatic aldehydes (**6**)		Ylides (**2**)	Products[b] (**7**)		Yield[c] (%)/Time	
						Method A	Method B
1		**6a**	**2a**		**7a**	80/4.0 h	78/5.0 min
2		**6b**	**2a**		**7b**	75/5.0 h	80/6.0 min
3		**6c**	**2a**		**7c**	73/5.0 h	89/5.0 min
4		**6d**	**2a**		**7d**	65/6.0 h	60/5.0 min
5		**6e**	**2a**		**7e**	75/6.0 h	80/5.0 min

[a] For methods A and B, see footnote of Table 1.
[b] Identified by ^{1}H NMR, IR, and MS.
[c] Isolated yields.

generally found to be the major products when a stabilized ylide was reacted with an aldehyde in a solvent ranging from hexane to DMF or DMSO.[42] In the present case, we failed to isolate the corresponding *Z*-isomers even in trace quantity and analysis of the crude products by using ^{1}H NMR remained inconclusive. However, the formation of *Z*-isomers as minor products could not be ruled out as isolated yields of *E*-isomers were not always quantitative.

Having generated 1,3-butadiene moiety as integral part of benzopyran/benzo[*b*]oxepine/2-chromenone derivatives (**3**) by using stabilized phosphorus ylides (**2**) successfully we then decided to expand the scope of this methodology further. Moreover, while the reaction of a range of stabilized ylides, e.g., $Ph_3P{=}CHY$ [Y=CO_2Et, CON(Me)OMe, CN, COMe, etc.] with various aromatic/heteroaromatic aldehydes has been examined earlier, the use of ylide **2b** and **2c** has not been explored. Since ylides **2b** and **2c** reacted smoothly with β-chloroacroleins (**1**) under the condition of methods A and B we therefore reacted **2b** and **2c** with an aromatic aldehyde (**4**) separately under the same reaction conditions. The results of this study are summarized in Table 2. Ylide **2b** afforded chalcone **5a** (entry 1, Table 2) whereas ylide **2c** provided stilbene **5b** (entry 2, Table 2) and the yields were found to be good in both the cases. Finally, encouraged by the outcome of the reaction of ylide **2a** with **1**, we treated **2a** with a variety of aromatic aldehydes (**6**) under the condition of methods A and B (Table 3) and a number of ethyl cinnamates were obtained in good yields.

3. Conclusions

In summary, we have investigated the Wittig reaction of β-chloroacroleins with a number of stabilized phosphorus ylides to afford alkenyl-substituted benzopyran/benzo[*b*]oxepine/2-chromenone derivatives in good yields. The process provides an easy access to the compounds containing 1,3-butadiene moiety. A combination of toluene as a solvent and sodium ethoxide as a base was found to be optimum. The reactions were carried out both under conventional and microwave conditions. Only few minutes were needed to obtain the desired product under microwave irradiation in comparison to the several hours required by the conventional method. Applicability of this process was demonstrated in the synthesis of chalcone and stilbene derivatives. The present work on C=C bond formation via Wittig reaction might prove to be a key step in the synthesis of diversity based benzopyran/benzo[*b*]oxepine/2-chromenone derivatives of potential pharmacological interest.

4. Experimental

4.1. General

Unless stated otherwise, reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F_{254}), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (60–120 mesh) using distilled petroleum ether and ethyl acetate. ^{1}H and ^{13}C NMR spectra were determined in DMSO-d_6 solution using 200 and 400, and 50 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ=0.0) as internal standard and expressed in parts per million. Spin multiplicities are given as s (singlet), d (doublet), t (triplet), and m (multiplet) as well as br (broad). Coupling constants (*J*) are given in hertz. Infrared spectra were recorded on an FTIR spectrometer. Melting points were determined by using thermal analysis and differential scanning calorimetry (DSC) was generated with the help of DSC-60A detector. MS spectra were obtained on a mass spectrometer. Chromatographic purity by HPLC was determined by using area normalization method and the condition specified in each case: column, mobile phase (range used), flow rate, detection wavelength, and retention times. All the reagents used are commercially available except β-chloroacroleins that were prepared according to a known procedure.[38,39]

4.2. Synthesis of alkenyl-substituted benzopyran/benzo[*b*]oxepine derivatives

*4.2.1. Typical procedure for the preparation of **3a***

4.2.1.1. Method A. To a solution of 4-chloro-2*H*-3-chromenecarbaldehyde (2.57 mmol) in toluene (5 mL) was added sodium ethoxide (5.14 mmol) and the mixture was stirred at 25 °C for 15 min under a nitrogen atmosphere. The mixture was cooled to 15 °C and triethyl phosphono acetate (3.85 mmol) was added. The resulting reaction mixture was then stirred at 80 °C for 12 h. After completion of the reaction (as indicated by TLC, mobile phase: ethyl acetate–petroleum ether), solvent was removed under reduced pressure and the residue was purified by column chromatography using light petroleum ether–ethyl acetate to furnish the desired product.

4.2.1.2. Method B. To a mixture of 4-chloro-2*H*-3-chromenecarbaldehyde (2.57 mmol) in toluene (1.0 mL) was added sodium ethoxide (5.14 mmol) at 25 °C under a nitrogen atmosphere. The thick slurry was stirred with glass rod at 25 °C for 15 min and cooled to 15 °C. Then triethyl phosphono acetate (3.85 mmol) was added and the resulting thick reaction mixture was then irradiate in a domestic microwave oven (LG Electronics, model: MC 808 war, 3 L capacity) for 5.0 min. After completion of the reaction (as indicated by TLC, mobile phase: ethyl acetate–petroleum ether) the mixture was diluted with toluene (10 mL) and filtered. The filtrate was collected, concentrated under reduced pressure, and the residue was purified by column chromatography using light petroleum ether–ethyl acetate to give the desired product.

4.3. 3-(4-Chloro-2*H*-chromen-3-yl)-acrylic acid ethyl ester (3a)

This compound was obtained as off white solid; mp 90–92 °C; R_f (20% ethyl acetate in *n*-hexane): 0.59; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.7 (d, *J*=16.4 Hz, 1H), 7.6 (d, *J*=7.6 Hz, 1H), 7.3 (d, *J*=7.6 Hz, 1H), 7.08 (t, *J*=7.6 Hz, 1H), 6.96 (d, *J*=8.0 Hz, 1H), 6.30 (d, *J*=16.4 Hz, 1H) 5.1 (s, 2H), 4.2 (q, *J*=6.8 Hz, 2H), 1.25 (t, *J*=6.8 Hz, 3H); IR (cm^{-1}, KBr) 3068, 2978, 2864, 1709, 1599, 1178, 970, 754; *m*/*z* (ES Mass) 265 (M^+, 100%); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 165.8, 154.8, 135.6, 132.0, 130.5, 125.5, 124.4, 122.2, 120.9, 120.7, 115.9, 65.5 (CH_2), 60.3 (CH_2), 14.1 (CH_3); HPLC 98.3%, column: Xterra MS C18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/0, 30/85, 35/85, 36/0; flow: 1.0 mL/min, UV 215 nm, retention time 19.3 min; HRMS (ESI): calcd for $C_{14}H_{14}ClO_3$ $(M+H)^+$ 265.0631, found 265.0627.

4.4. 3-(5-Chloro-2,3-dihydro-benzo[*b*]oxepin-4-yl)-acrylic acid ethyl ester (3b)

This compound was obtained as white solid; mp 92–94 °C; R_f (20% ethyl acetate in *n*-hexane): 0.56; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.92 (d, *J*=15.6 Hz, 1H), 7.6 (d, *J*=8.0 Hz, 1H), 7.43 (t, *J*=8.0 Hz, 1H), 7.27 (t, *J*=7.6 Hz, 1H), 6.42 (d, *J*=15.6 Hz, 1H), 4.49 (t, *J*=6.4 Hz, 2H), 4.2 (q, *J*=7.2 Hz, 2H), 2.6 (t, *J*=6.0 Hz, 2H), 1.25 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 166.1, 154.7, 139.2, 133.3, 133.2, 131.6, 131.4, 129.6, 124.1, 122.4, 120.9, 78.9 (CH_2), 60.2 (CH_2), 27.6 (CH_2), 14.1 (CH_3); IR (cm^{-1}, KBr) 3412, 2910, 2881, 1722,

1713, 130, 1173, 1040, 761; *m*/*z* (ES Mass) 279 (M+1, 100%); HPLC 99.55%, column: ZORBAX XDB-C8 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/15, 25/90, 30/90, 31/35, flow 1.0 mL/min, UV 215 nm, retention time 8.6 min; HRMS: calcd for $C_{11}H_{12}O_3$ 193.0865, found 193.0866.

4.5. 3-(4-Chloro-2*H*-chromen-3-yl)-1-phenyl-propenone (3c)

This compound was obtained as off white solid; mp 132–133 °C; R_f (20% ethyl acetate in *n*-hexane): 0.6; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 8.07 (d, *J*=16.4 Hz, 1H), 7.96 (d, *J*=7.6 Hz, 2H), 7.6–7.5 (m, 4H), 7.3–7.27 (m, 1H), 7.04–7.0 (m, 1H), 6.95 (d, *J*=16.4 Hz, 1H), 6.89–6.82 (m, 1H), 5.1 (s, 2H); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 189.8, 155.5, 137.6, 137, 133.7, 132.9, 131.7, 128.6 (2C), 128.4 (2C), 126.07, 123.9, 122.8, 122.0, 121.4, 115.9, 66.1 (CH_2); IR (cm^{-1}, KBr) 3046, 2853, 1653, 1571, 1303, 1213, 1010, 755; *m*/*z* (ES Mass) 297.1 (M+1, 100%); HPLC 98.2%, column: Xterra MS C18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/0, 30/85, 35/85, 36/0; flow 1.0 mL/min, UV 215 nm, retention time 20.9 min; HRMS (ESI): calcd for $C_{18}H_{14}ClO_2$ $(M+H)^+$ 297.0682, found 297.0691.

4.6. 3-(5-Chloro-2,3-dihydro-benzo[*b*]oxepin-4-yl)-1-phenyl-propenone (3d)

This compound was obtained as yellow solid; mp 150–152 °C; R_f (10% ethyl acetate in *n*-hexane): 0.79; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.15–8.13 (m, 2H), 8.06 (d, *J*=15.2 Hz, 1H), 7.7–7.6 (m, 5H), 7.47–7.42 (m, 1H), 7.31–7.26 (m, 1H), 7.12 (d, *J*=9.2 Hz, 1H), 4.58 (t, *J*=6.4 Hz, 2H), 2.78 (t, *J*=6.4 Hz, 2H); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 189.1, 154.6, 138.7, 137.3, 134.2, 134.1, 133.2, 131.8, 131.4, 129.5, 128.7 (2C), 128.5 (2C), 124.3, 124.0, 122.3, 78.1 (CH_2), 27.8 (CH_2); IR (cm^{-1}, KBr) 3063, 2877, 2324, 1657, 1580, 1287, 1229, 1017, 702; *m*/*z* (ES Mass) 311 (M+1, 100%); HPLC 99.07%, column: Xterra MS C18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/0, 30/85, 35/85, 36/0, flow 1.0 mL/min, UV 215 nm, retention time 19.8 min; HRMS (ESI): calcd for $C_{19}H_{16}ClO_2$ $(M+H)^+$ 311.0839, found 311.0835.

4.7. 4-[2-(4-Bromo-phenyl)-vinyl]-5-chloro-2,3-dihydro-benzo[*b*]oxepine (3e)

This compound was obtained as yellow oil; R_f (10% ethyl acetate in *n*-hexane): 0.61; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.62 (d, *J*=7.6 Hz, 1H), 7.53 (d, *J*=14.8 Hz, 2H), 7.37–7.2 (m, 4H), 7.06 (d, *J*=9.2 Hz, 1H), 6.64 (d, *J*=14.8 Hz, 1H), 6.58 (d, *J*=12.0 Hz, 1H), 4.32 (t, *J*=6.4 Hz, 2H), 2.3 (t, *J*=6.0 Hz, 2H); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 154.8, 135.6, 135.5, 131.6, 130.6, 130.4, 130.3, 130.1, 129.4, 129.2, 128.7, 126.9, 123.6, 122.1, 121.8, 121.2, 77.6 (CH_2), 32.4 (CH_2); IR (cm^{-1}, KBr) 3412, 1663, 1482, 1444, 1007, 1025.9; *m*/*z* (ES Mass) 362 (M+1, 100%), 363 (M+2); HPLC 97.05%, column: Xterra MS C18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/0, 30/85, 35/85, 36/0, flow 1.0 mL/min, UV 215 nm, retention time 24.8 min. Elemental analysis found: C, 59.62; H, 3.93. $C_{18}H_{14}BrClO$ requires: C, 59.78; H, 3.90.

4.8. 3-(4-Chloro-2-oxo-2*H*-chromen-3-yl)acrylic acid ethyl ester (3f)

This compound was obtained as white solid; mp 124–125 °C (lit. [39b] 125–126 °C); ^{1}H NMR (DMSO-d_6, 200 MHz) δ 8.01 (d, *J*=16.0 Hz, 1H), 7.7–7.3 (m, 4H), 7.02 (d, *J*=16.0 Hz, 1H), 4.20 (q, *J*=6.8 Hz, 2H), 1.25 (t, *J*=7.2 Hz, 3H); *m*/*z* (ES Mass) 279 (M+1, 100%).

4.9. 4-Chloro-3-(3-oxo-3-phenyl propenyl)chromen-2-one (3g)

This compound was obtained as light yellow solid; mp 140–141 °C (lit.[39b] 139–142 °C); ^{1}H NMR (DMSO-d_6, 200 MHz) δ 8.05 (d, *J*=16.3 Hz, 1H), 7.98 (d, *J*=7.5 Hz, 2H), 7.6–7.3 (m, 7H), 7.05 (d, *J*=16.3 Hz, 1H); *m*/*z* (ES Mass) 311 (M+1, 100%).

4.10. 3-(4-Methoxy-phenyl)-1-phenyl-propo-2-en-1-one (5a)

This compound was obtained as light yellow solid; mp 74–76 °C; R_f (20% ethyl acetate in *n*-hexane): 0.46; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.0 (d, *J*=8.4 Hz, 2H), 7.76 (d, *J*=16.0 Hz, 1H), 7.6–7.57 (m, 3H), 7.55–7.47 (m, 2H), 7.43 (d, *J*=16.0 Hz, 1H), 6.95 (d, *J*=8.8 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 190.5, 161.6, 144.6, 138.5, 132.5, 130.1, 128.8, 128.4 (2C), 128.4 (2C), 127.6, 119.8, 114.4 (2C), 55.4 (CH_3); IR (cm^{-1}, KBr) 3308, 2954, 2941, 1657, 1511, 1263, 1017, 984, 825; *m*/*z* (ES Mass) 239 (M+1, 100%); HPLC 97.9%, column: Xterra MS C18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/0, 30/85, 35/85, 36/0, flow 1.0 mL/min, UV 215 nm, retention time 15.7 min; HRMS (ESI): calcd for $C_{16}H_{15}O_2$ $(M+H)^+$ 239.1072, found 239.1077.

4.11. 1-(4-Bromostyryl)-2-chlorobenzene (5b)

This compound was obtained as yellow oil; R_f (10% ethyl acetate in *n*-hexane): 0.79; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.59–7.15 (m, 6H), 7.04 (d, *J*=8.8 Hz, 1H), 6.73 (d, *J*=12.4 Hz, 1H); IR (cm^{-1}, KBr) 2961, 2925, 1585, 1486, 1472, 1072, 1050; *m*/*z* (ES Mass): 292 (M^+, 100%), 293 (M+1); HPLC 99.07%, column: Xterra MS C18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/0, 30/85, 35/85, 36/0; flow 1.0 mL/min, UV 215 nm, retention time 19.8 min. Elemental analysis found: C, 57.34; H, 3.40. $C_{14}H_{10}BrCl$ requires: C, 57.27; H, 3.43.

4.12. 3-Phenyl-acrylic acid ethyl ester (7a)

This compound was obtained as light brown liquid; R_f (20% ethyl acetate in *n*-hexane): 0.7, ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.74–7.67 (m, 3H), 7.45–7.42 (m, 3H), 6.65 (d, *J*=16.4 Hz, 1H), 4.22 (q, *J*=6.8 Hz, 2H), 1.28 (t, *J*=6.8 Hz, 3H); IR (cm^{-1}, KBr) 3062, 2937, 2981, 1713, 1638, 1366, 1311, 1257, 1176, 1038, 768; *m*/*z* (ES Mass) 177 (M+1, 100%); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 165.9, 144.0, 137.0, 130.0, 128.6 (2C), 128.2, 128.0, 118.0, 59.8 (CH_2), 13.9 (CH_3); HPLC: 98.47%, column: Luna C18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/35, 25/80, 35/80, 36/35; flow 1.0 mL/min; UV 220 nm, retention time 18.1 min; HRMS: calcd for $C_{11}H_{13}O_2$ $(M+H)^+$ 177.0916, found 177.0918.

4.13. 3-(3-Hydroxy-phenyl)-acrylic acid ethyl ester (7b)

This compound was obtained as light cream solid; mp 76–77 °C; R_f (20% ethyl acetate in *n*-hexane): 0.48; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.97 (s, 1H), 7.56–7.52 (m, 3H), 6.8 (d, *J*=16.0 Hz, 1H), 4.16 (q, *J*=6.8 Hz, 2H), 1.2 (t, *J*=7.2 Hz, 3H); IR (cm^{-1}, KBr) 3534, 3286, 2983, 1682, 1603, 1279, 1168, 830; *m*/*z* (ES Mass) 193 (M+1, 100%); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 160.5, 159.8, 144.5, 130.2 (2C), 125.07, 115.7 (2C), 114.3, 59.7 (CH_2), 14.22 (CH_3); Column: Xterra MS C18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/0, 30/85, 35/85, 36/0, flow 1.0 mL/min, UV 215 nm, retention time: 8.6 min; HRMS (ESI): calcd for $C_{11}H_{12}O_3$ $(M+H)^+$ 193.0865, found 193.0866.

4.14. 3-(3-Ethoxy-phenyl)-acrylic acid ethyl ester (7c)

Light yellow oil; R_f (10% ethyl acetate in *n*-hexane): 0.52; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.66–7.62 (m, 2H), 7.6 (d, J=15.6 Hz, 1H), 6.95 (d, J=8.8 Hz, 2H), 6.47 (d, J=16.0 Hz, 1H), 4.18 (q, J=7.6 Hz, 2H), 1.3 (t, J=7.6 Hz, 3H), 1.25 (t, J=7.2 Hz, 3H); IR (cm^{-1}, KBr) 2980, 2934, 1708, 1604, 1251, 1172, 1403, 826; *m*/*z* (ES Mass) 221 (M+1, 100%); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 166.3, 160.3, 144.0, 129.9 (2C), 126.4, 115.2, 114.7 (2C), 63.22 (CH_2), 59.7 (CH_2), 14.5 (CH_3), 14.2 (CH_3); HPLC 99.69%, Column: Xterra MS C18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/0, 30/85, 35/85, 36/0, flow 1.0 mL/min; UV 215 nm, retention time 16.0 min; HRMS (ESI): calcd for $C_{13}H_{16}O_3$ $(M+H)^+$ 221.1178, found 221.1188.

4.15. 3-(3-Bromo-phenyl)-acrylic acid ethyl ester (7d)

This compound was obtained as off white solid; mp 36–38 °C; R_f (20% ethyl acetate in *n*-hexane): 0.75; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.97 (s, 1H), 7.4 (d, J=7.6 Hz, 1H), 7.64–7.6 (m, 2H), 7.37 (t, J=8.0 Hz, 1H), 6.73 (d, J=16.0 Hz, 1H), 4.2 (q, J=7.2 Hz, 2H), 1.26 (t, J=6.8 Hz, 3H); IR (cm^{-1}, KBr) 2979, 1709, 1641, 1556, 1310, 1180, 1035, 785; *m*/*z* (ES Mass) 255 (M), 257 (M+2); ^{13}C NMR (DMSO-d_6, 200 MHz) δ 171.2, 148, 141.8, 138.2, 136.2, 136.1, 132.5, 127.6, 125.2, 65.5 (CH_2), 19.5 (CH_3); HPLC 99.7%, Column: ZORBAX XDB-C8 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/15, 25/90, 30/90, 31/35, flow 1 mL/min; UV 215 nm, retention time 19.4 min; HRMS (ESI): calcd for $C_{11}H_{12}BrO_2$ 255.0021, found 255.0031.

4.16. 3-Chloro phenyl-acrylic acid ethyl ester (7e)

This compound was obtained as off white colored low melting solid; mp 33–35 °C; R_f (20% ethyl acetate in *n*-hexane): 0.7; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.84 (s, 1H), 7.7 (d, J=7.6 Hz, 1H), 7.65 (d, J=16.4 Hz, 1H), 7.49–7.42 (m, 2H), 6.72 (d, J=16.0 Hz, 1H), 4.2 (q, J=7.2 Hz, 2H), 1.26 (t, J=7.6 Hz, 3H); IR (cm^{-1}, KBr) 2982, 2903, 1713, 1640, 1566, 1313, 1201, 1180, 1036, 787; *m*/*z* (ES Mass) 211; ^{13}C NMR (DMSO-d_6, 200 MHz) δ 165.8, 142.5, 136.1, 133.6, 130.4, 129.8, 127.7, 126.7, 119.7, 60.0 (CH_2), 40.0 (CH_3); HPLC 99.4%, Column: Xterra MS C18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in acetonitrile, gradient (T/%B)=0/0, 30/85, 35/85, 36/0, flow 1 mL/min, UV 215 nm, retention time 16.8 min; HRMS (ESI): calcd for $C_{11}H_{12}ClO_2$ 211.0526, found 211.0527.

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