CHAPTER 3

A Practical Synthesis of 3-Functionalized Coumarins from *o*-Cresols and Active Methylene Compounds under Metal and Catalyst-Free Conditions using *tert*-Butyl Hydrogen Peroxide

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3.1 Introduction

Coumarin scaffold is a well-regarded parent compound found in several natural products (Murray et al. 1989, Brahmachari et al. 2010) and bioactive molecules (Hoult et al. 1996). Coumarin derivatives possess a wide range of biological activities including antibacterial (Creaven et al. 2010), antifungal (Kayser et al. 1997), anti HIV (Bhavsar et al. 2011, Bedoya et al. 2005), antioxidant (Vazquez et al. 2013, Kontogiorgis et al. 2003), antimutagenic (Kontogiorgis et al. 2005), anticancer (Zhi et al. 2014, Wu et al. 2014), anti-inflammatory (Timonen et al. 2011, Melagraki et al. 2009), analgesic (Khode et al. 2009), antibiotic activities (Chimenti et al. 2006). Coumarin scaffold is also incorporated in insecticides (Moreira et al. 2007), fragrances & perfumes (Aslam et al. 2010), agrochemicals (Schonberg et al. 1954, Adronov et al. 2000) and additives in foods and cosmetics (Frosch et al. 2002, Brahmachari et al. 2015). Numerous carboxy coumarins are used as triplet oxygen sensitizers (Peroni et al. 2002) and fluorescent probes (Specht et al. 1982). Hence, coumarin is a very imperative building block for combinatorial library synthesis. **Figure 3.1** represents some biologically active compounds like Novobiocin, Hymechromone, Acenocoumaral, Ensaculin (KA 672), Batoprazine and Warfarin having coumarin moiety.

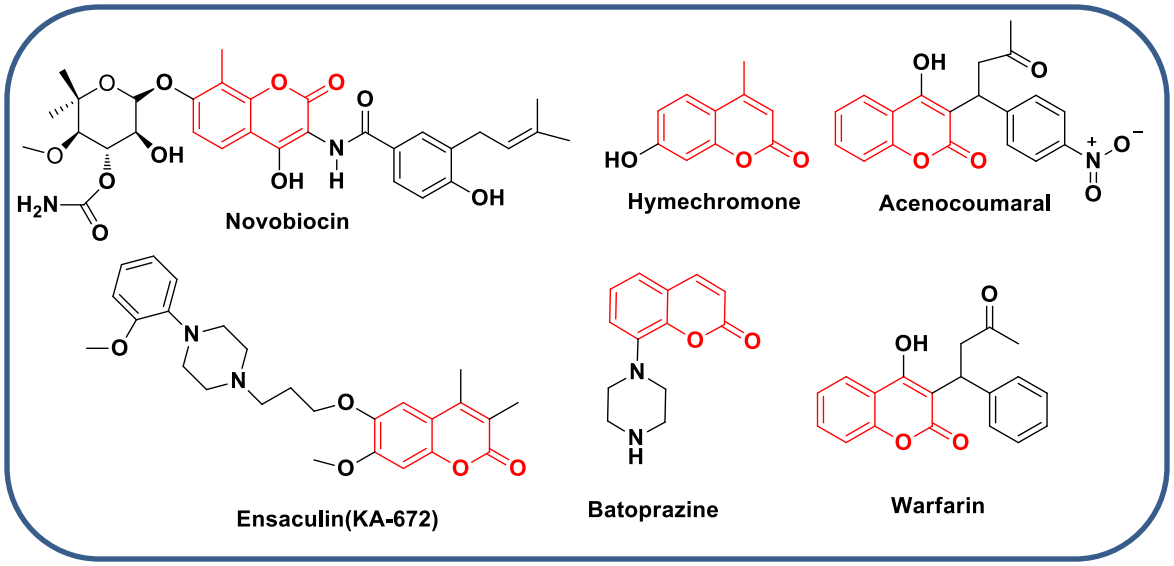


Figure 3.1: Biologically active molecules containing coumarin moiety.

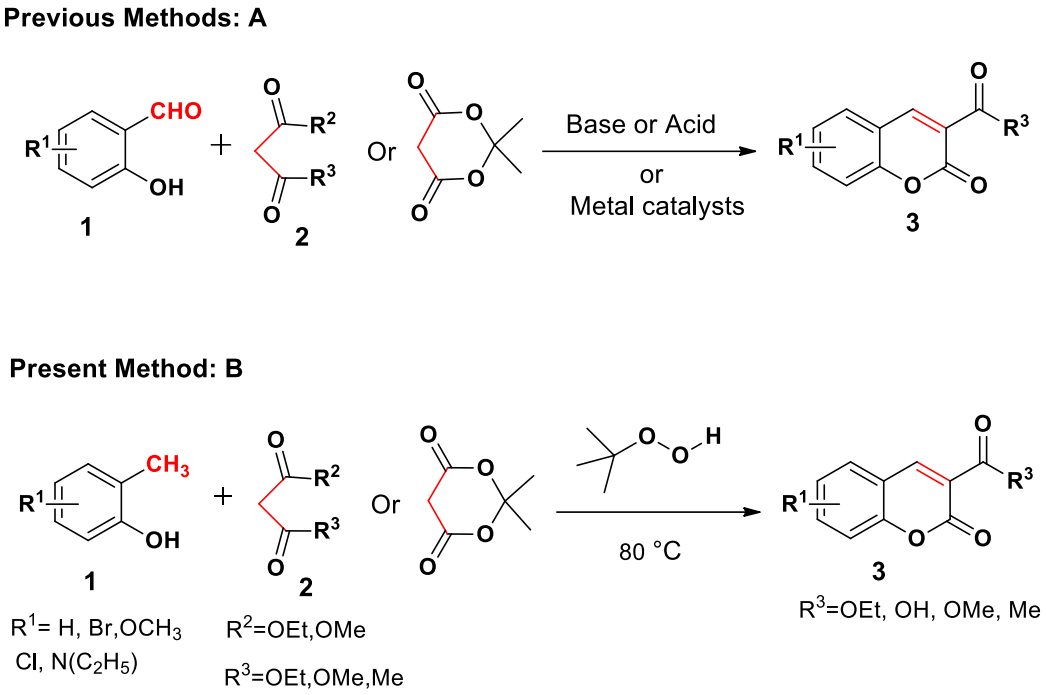
Synthesis of these oxygen containing heterocyclic compounds are usually executed by numerous methods such as von Pechmann (Pechmann et al. 1884), Perkin (Johnson et al. 2004), Wittig reaction (Yavari et al. 1998) and Baylis-Hilmann reaction (Kaye et al. 2003). Knoevenagel condensation is not only an alternative method but also an efficient method for the synthesis of 3-substituted coumarins from salicylaldehyde with active methylene compounds like meldrum acid, malonate esters, ethyl cyanoacetate (Jones et al. 2004) etc. Synthesis of 3-substituted coumarins via Knoevenagel condensation was achieved using different metal and metal-free catalyst like $ZrCl_4$ (Valizadeh et al. 2011), Mg-Al hydrotalcite (Bandgar et al. 1999), mesoporous molecular sieve MCM-41(Heravi et al. 2010), *p*-toluenesulfonic acid (Kumar et al. 2014), natural clay (Bandgar et al. 1999),

L-proline (Karade et al. 2007), NaOH (Zhang et al. 2004), piperidine (Volmajer et al. 2005), $MgFe_2O_4$ nanoparticles (Ghomi et al. 2018) (**Scheme 3.1, A**). However, most of these methods have their own merits and demerits.

Recently, the oxidative functionalization of methyl arenes has emerged as an efficient and alternative approach to access a wide range of functional groups including amides, esters, ketones, nitriles etc. (Vanjari et al. 2015, Zhou et al. 2009). Ready availability, high stability and easy handling are the major advantages of methyl arenes when compared to its aldehydes analogues. Despite the potential, so far no method has been developed for the oxidative synthesis of coumarins from the stable *ortho*-hydroxy methylarenes (*i.e. o*-cresols) via direct sp^3 C-H bond functionalization reactions with active methylene compounds.

As a well-known oxidant, *tert*-butyl hydrogen peroxide (TBHP) has found wide applications in several oxidation reactions to generate C–C, C–N, C–O, C–S and N–N bonds (Sun et al. 2018, Zheng et al. 2015, Guntreddi et al. 2014, Sun et al. 2016, Yuan et al. 2014, Jiang et al. 2019, Yu et al. 2016, Yang et al. 2017, Wu et al. 2017, Kumar et al. 2019, Li et al. 2017, Hill et al. 1983). TBHP has attracted much attention because of its easy availability, cost-effectiveness, easy handling, etc. In this context, we have recently explored the TBHP promoted transamidation reactions (Mishra et al. 2019). In continuation, here we report the synthesis of 3-functionalized coumarins from *o*-cresols and

active methylene compounds using *tert*-butyl hydrogen peroxide (TBHP) as an oxidant under solvent free condition (**Scheme 3.1, B**).



Scheme 3.1: Previous & present method for the synthesis of coumarin.

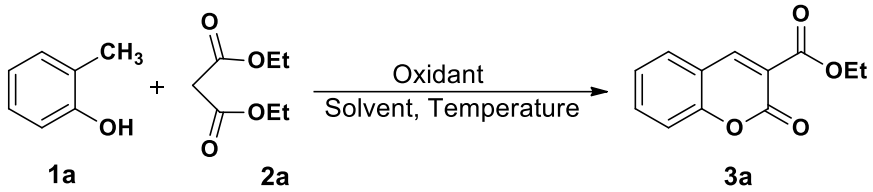
3.2 Results and Discussion

In order to optimize reaction conditions, *o*-cresol **1a** (1.0 mmol) and diethylmalonate **2a** (1.2 mmol) were chosen as the model substrates and subjected to the oxidative condensation reaction. The effect of different parameters including reaction medium, oxidant and its loading as well as temperature was examined on the model reaction. Initially, the condensation of *o*-cresol and diethylmalonate was performed using TBHP (5

equiv.) in different polar solvents like water, acetonitrile, 1,4-dioxane, dichloromethane, chloroform (**Table 3.1, entries 1-5**) and also in non-polar solvents like hexane, benzene (**Table 3.1, entries 6,7**) at its refluxed temperature. The reaction proceeded smoothly in all the solvents tested in this study and gave the desired product **3a** in 40-75% yield.

In order to improve the yield of the product in a greener way, we have switched to the solvent free condition. The model reaction was investigated under solvent free condition using TBHP (5 equiv.) as an oxidant at different temperatures. No product was obtained at room temperature (25 °C). Hence, the reaction was carried out at higher temperature 50-100 °C (**Table 3.1, entries 8-12**). At 50 and 70 °C, the desired product **3a** was obtained in 45, 70% yield while at 80 °C the reaction provides 91% yield (**Table 3.1, entry 11**). Any further increase in reaction temperature did not show significant change on reaction time and yield of the product (**Table 3.1, entry 12**). It is important to mention that the reaction temperature affect the yield of the product which is possibly due to the different rate of radical generation via thermal breakdown. Further, we have investigated the reaction progress by varying amount of TBHP from 2-6 equiv. (**Table 3.1, entries 11, 13-16**). The best result was obtained with 4 equiv. of TBHP (**Table 3.1, entry 14**) which provides the desired product in 91% yield within 2.5 h.

Table 3.1: Optimization of solvents, oxidants and temperature[a]



1a 2a 3a

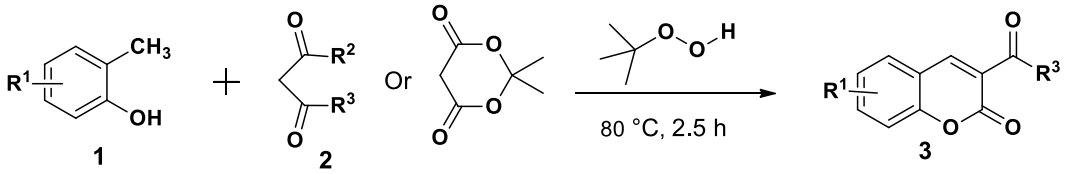
Entry	Solvent	Oxidant (Equiv.)	Temperature (°C)	Time (h)	Yield[b] (%)
1	Water	TBHP (5)	Reflux	5	75
2	Acetonitrile	TBHP (5)	Reflux	7	69
3	1,4-dioxane	TBHP (5)	Reflux	6	65
4	Dichloromethane	TBHP (5)	Reflux	5	40
5	Chloroform	TBHP (5)	Reflux	6	67
6	Hexane	TBHP (5)	Reflux	6	65
7	Benzene	TBHP (5)	Reflux	7	66
8	Solvent free[c]	TBHP (5)	rt	7	NR
9	Solvent free	TBHP (5)	50	6	45
10	Solvent free	TBHP (5)	70	4	70
11	Solvent free	TBHP(5)	80	2.5	91
12	Solvent free	TBHP (5)	100	2.5	91
13	Solvent free	TBHP (6)	80	2.5	91
14	**Solvent free**	**TBHP (4)**	**80**	**2.5**	**91**
15	Solvent free	TBHP (3)	80	2.5	50
16	Solvent free	TBHP (2)	80	2.5	20
17	Solvent free	CAN (4)	80	2.5	NR
18	Solvent free	Oxone (4)	80	2.5	NR
19	Solvent free	DDQ (4)	80	2.5	NR
20	Solvent free	Chloranil (4)	80	2.5	NR

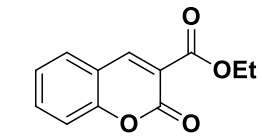
[a] **Reaction Condition:** *o*-cresol (1.0 mmol), diethylmalonate (1.2 mmol) and oxidizing agent. [b] Isolated yield. [c] No additional solvent.

The model reaction of *o*-cresol and diethylmalonate was also investigated with different organic/inorganic oxidizing agents such as ceric ammonium nitrate (CAN), oxone, DDQ and chloranil under solvent free condition at 80 °C (**Table 3.1, entries 17-20**), but not a trace of the product was obtained. Formation of model compound **3a** is confirmed by the ^{1}H & ^{13}C NMR spectroscopy (**Figure 3.2 and 3.3**).

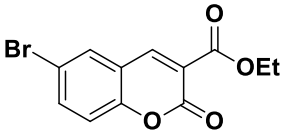
With these optimized conditions, the substrate scope of this methodology was explored with diethylmalonate and different substituted *o*-cresol. *o*-Cresol with different electron donating *viz.* ethyl 8-methoxy-2-oxo-2H-chromene-3-carboxylate (**3d**), ethyl 7-(diethylamino)-2-oxo-2H-chromene-3-carboxylate (**3e**) (**Table 3.2**, entries **3d** and **3e**) as well as electron withdrawing groups *viz.* ethyl 6-bromo-2-oxo-2H-chromene-3-carboxylate (**3b**), ethyl 6-chloro-2-oxo-2H-chromene-3-carboxylate (**3c**), (**Table 3.2,** entries **3b** and **3c**) undergo subsequent transformation smoothly in good yields (87-90%).We have also tested the other active methylene compounds like dimethylmalonate, ethyl acetoacetate, meldrum acid. To our delight, these substrates participated efficiently in the oxidative coupling reaction and provided the desired products in good yields (**Table 3.2**, entries **3f-3s**) *viz.* 3-acetyl-2H-chromen-2-one (**3f**), 3-acetyl-6-bromo-2H-chromen-2-one (**3g**), 3-acetyl-6-chloro-2H-chromen-2-one (**3h**), 3-acetyl-8-methoxy-2H-chromen-2-one (**3i**), 3-acetyl-7-(diethylamino)-2H-chromen-2-one (**3j**), 2-oxo-2H-chromene-3-carboxylic acid (**3k**),

Table 3.2: TBHP mediated synthesis of coumarin under solvent free condition[a]

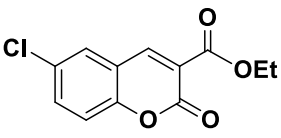




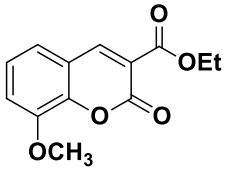
3a: 91%[b]



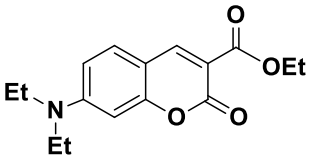
3b: 90%



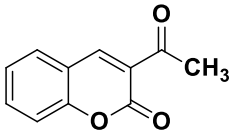
3c: 89%



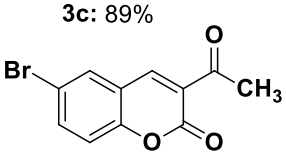
3d: 88%



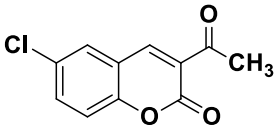
3e: 87%



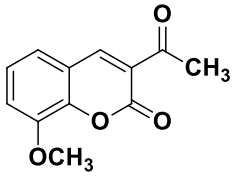
3f: 90%



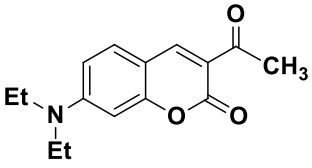
3g: 90%



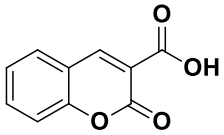
3h: 89%



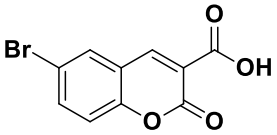
3i: 86%



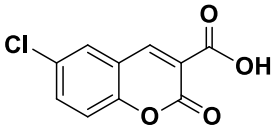
3j: 80%



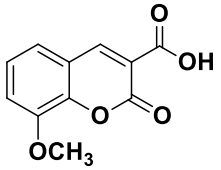
3k: 90%



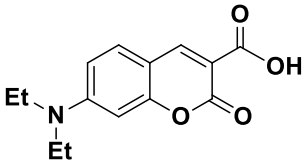
3l: 89%



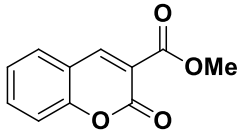
3m: 88%



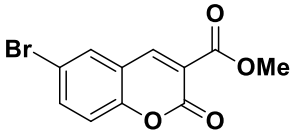
3n: 87%



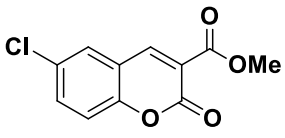
3o: 82%



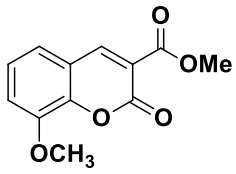
3p: 90%



3q: 89%



3r: 87%



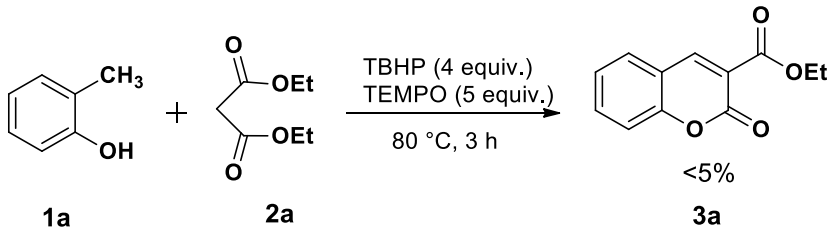
3s: 87%

[a]**Reaction conditions**: *o*-cresol derivatives (1.0 mmol), active methylene compounds (1.2 mmol), TBHP (4 equiv.) were heated at 80 °C. [b]Isolated yield

6-bromo-2-oxo-2H-chromene-3-carboxylic acid (**3l**), 6-chloro-2-oxo-2H-chromene-3-carboxylic acid (**3m**), 8-methoxy-2-oxo-2H-chromene-3-carboxylic acid (**3n**), 7-(diethylamino)-2-oxo-2H-chromene-3-carboxylic acid (**3o**), methyl 2-oxo-2H-chromene-3-carboxylate (**3p**), methyl 6-bromo-2-oxo-2H-chromene-3-carboxylate (**3q**), methyl 6-chloro-2-oxo-2H-chromene-3-carboxylate (**3r**) and methyl 8-methoxy-2-oxo-2H-chromene-3-carboxylate (**3s**).

3.3 Mechanistic Study & Controlled Experiments

In order to establish the reaction mechanism, a controlled experiment was performed with radical scavenger TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (**Scheme 3.2**) under the same optimized reaction conditions with 5 equiv. of TEMPO, less than 5% of the desired product (**3a**) was obtained. This observation shows that the reaction proceeds through radical pathway.

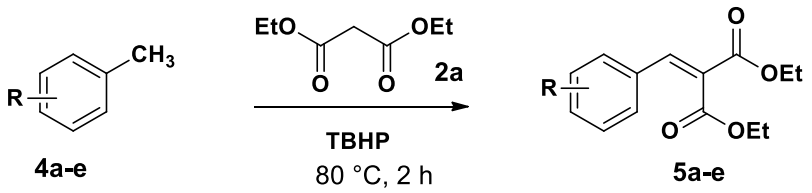


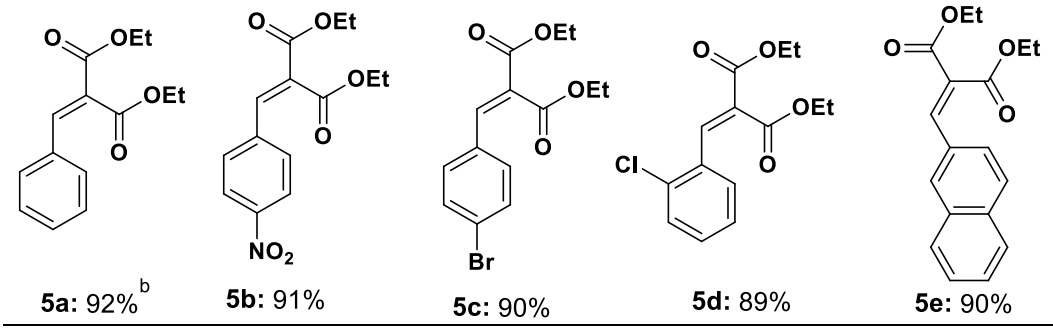
Scheme 3.2: Control experiment with TEMPO.

Next control reaction was performed between toluene (**4a**) and diethylmalonate (**2a**) in the presence of TBHP under optimized reaction conditions. The desired Knoevenagel

product **5a** was obtained in 92% yield. In fact, not only toluene but also many other methyl arenes underwent oxidative coupling with diethylmalonate (**2a**) and provided Knoevenagel products (**Table 3.3**, entries **5b**-**5e**) *viz.* diethyl 2-benzylidenemalonate (**5a**), diethyl 2-(4-nitrobenzylidene)malonate (**5b**), diethyl 2-(4-bromobenzylidene)malonate (**5c**), diethyl 2-(2-chlorobenzylidene)malonate (**5d**) and diethyl 2-(naphthalen-2-ylmethylene)malonate (**5e**) in good yields. It is clear from above observation that initially toluene oxidizes into benzaldehyde and then it reacts with diethylmalonate to give Knoevenagel product.

Table 3.3: Conversion of toluene derivatives into corresponding Knoevenagel products[a]

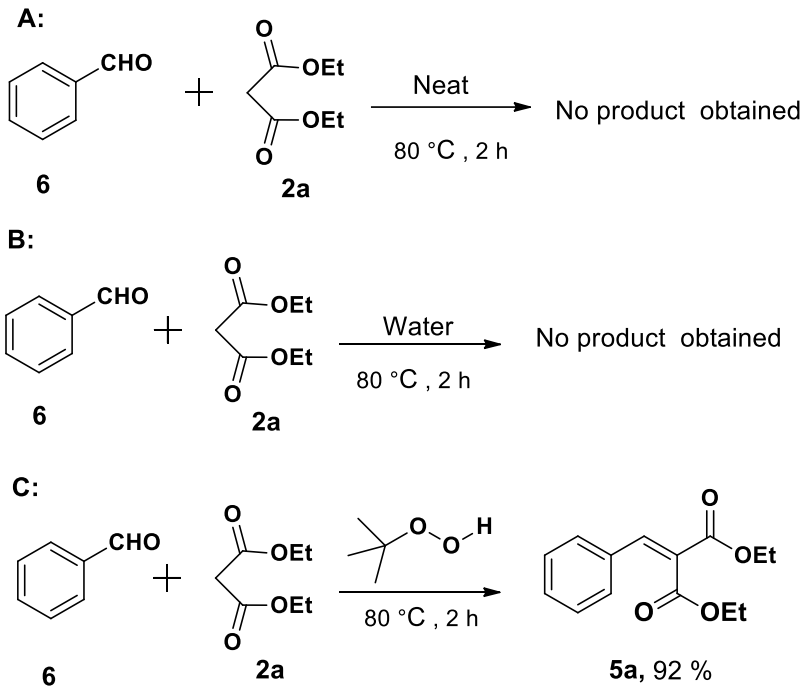




[a]**Reaction conditions**: Toluene derivative (1.0 mmol) active methylene (1.2 mmol) TBHP (4 equiv.) were heated at 80 °C. [b] Isolated yield**.**

To investigate the role of TBHP in Knoevenagel condensation of benzaldehyde (6) and diethylmalonate was performed in the absence of TBHP under solvent free condition at

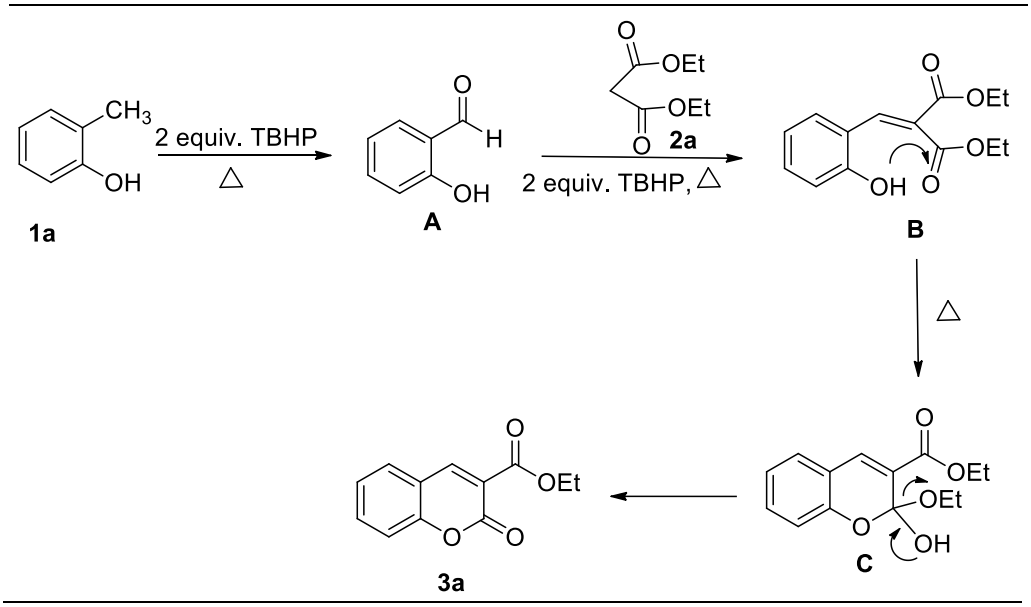
80 °C (**Scheme 3.2, A**). This reaction did not provide the desired product even after 2 h. Further, the reaction was performed only in water in the absence of TBHP to make sure that the reaction is not promoted by water. No product was obtained while starting material was remained as such (**Scheme 3.2, B**) which indicates that water did not take part in Knoevenagel condensation. However, when the same reaction was carried out in the presence of TBHP desired product was obtained in good yield (**Scheme 3.3, C**). These results indicate that TBHP took part not only in the oxidation of methyl arene to aldehyde but also in Knoevenagel condensation reaction.



Scheme 3.3: Controlled experiment with and without TBHP.

3.4 Plausible Reaction Mechanism

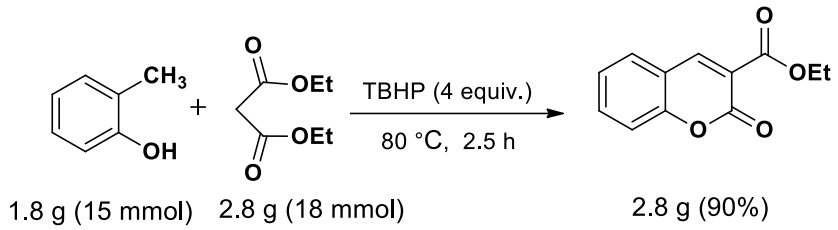
Based on the controlled experiments, a plausible reaction mechanism is proposed in Scheme **3.4.** In the presence of TBHP, *o*-cresol oxidizes to salicylaldehyde (**A**) (Rao et al. 2009, Rout et al. 2014) which reacts with active methylene compound (**2a**) giving the Knoevenagel product (**B**) which rearranges to give final product **3a**.



Scheme 3.4: Plausible reaction mechanism.

3.5 Scalability of the Protocol

To validate the prospective synthetic application of this process the synthesis of **3a** was carried out on gram scale *o*-cresol (**1a**) (1.8 g, 15.0 mmol), diethyl malonate (**2a**) (2.8 g, 18.0 mmol) and TBHP (4 equiv.), which gave the desired Product in good yield of 2.8 g (90%) under the optimum condition (**Scheme 3.5**).



Scheme 3.5: Gram scale synthesis of coumarin.

3.6 Experimental Section

3.6.1 General procedure for the synthesis of coumarin derivatives (3a-s)

o-Cresol (1.0 mmol), active methylene compound (1.2 mmol) and TBHP (70% aq., 4 equiv.) was stirred at 80 °C. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), concentrated and subjected for silica gel (60-120 mesh) column chromatography purification (SiO_2: hexane/ethyl acetate) to obtain the pure desired products.

3.6.2 General procedure for the synthesis of 5a-e

Toluene (1.0 mmol), active methylene compound (1.2 mmol) and TBHP (70% aq., 4 equiv.) was stirred at 80 °C. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), concentrated and

subjected for silica gel (60-120 mesh) column chromatography purification (SiO_2: hexane/ethyl acetate) to obtain the desired products.

3.6.3 Procedure for control experiment with TEMPO

o-Cresol (**1a**) (1.0 mmol), active methylene compound (1.2 mmol) and TEMPO (5.0 mmol) was stirred at 80 °C for 30 min to which 4 equiv. of *tert*-butyl hydrogen peroxide (TBHP) was added. The reaction was further stirred for 180 min and diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), concentrated and subjected for silica gel (60-120 mesh) column chromatography purification (SiO_2: hexane:EtOAc) to obtain **3a**.

3.6.4 Gram-scale procedure for the synthesis of coumarin derivatives

o-Cresol (**1a**) (1.8 g, 15.0 mmol), diethyl malonate (**2a**) (2.8 g. 18.0 mmol) and TBHP (70% aq., 4 equiv.) was stirred at 80 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, it was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4), the solvent was evaporated under vacuum and the product was purified by column chromatography on silica gel (60-120 mesh, hexane/ethyl acetate) gave the desired products (**3a**) in 90% yield (2.85 g).

3.7 Analytical Data

3.7.1 Ethyl 2-oxo-2H-chromene-3-carboxylate (3a): White crystalline solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); yield 198 mg (91%); m.p. 90-91 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.46 (s, 1H), 7.57 (dd, 2H), 7.27 (t, 2H), 4.34 (q, 2H), 1.34 (t, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 163.1, 156.8, 155.2, 148.7, 134.4, 129.6, 124.9, 118.3, 117.9, 116.7, 62.0, 14.3; Anal. calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.00; H 4.59.

3.7.2 Ethyl 6-bromo-2-oxo-2H-chromene-3-carboxylate (3b): White crystalline solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); yield 266 mg (90%); m.p. 162-163 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.45 (s, 1H), 8.01 – 7.44 (m, 2H), 7.27 (d, 1H), 4.43 (q, 2H), 1.42 (t, , 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 162.7, 156.1, 154.0, 147.2, 137.0, 131.6, 119.5, 119.4, 118.6, 117.4, 62.3, 14.3; Anal. calcd for $C_{12}H_9BrO_4$: C, 48.51. H, 3.05; Found: C, 48.47; H, 3.03.

3.7.3 Ethyl 6-chloro-2-oxo-2H-chromene-3-carboxylate (3c): White crystalline solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); yield 224 mg (89%); m.p. 174-176 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.45 (s, 1H), 7.59 (d, 2H), 7.33 (t, 1H), 4.42 (q, 2H), 1.41 (t, 3H); **^{13}C**

NMR (126 MHz, $CDCl_3$) δ (ppm): 162.7, 156.1, 153.5, 147.2, 134.2, 130.2, 128.5, 119.6, 118.9, 118.3, 62.3, 14.3; Anal. calcd for $C_{12}H_9ClO_4$: C, 57.05, H, 3.59; Found: C, 56.99, H, 3.57.

3.7.4 Ethyl 8-methoxy-2-oxo-2H-chromene-3-carboxylate (3d): Yellow crystalline solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); yield 218 mg (88%); m.p. 89-90 ^oC; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.43 (s, 1H), 7.19 (d, 1H), 7.11 (d, 1H), 7.10 (s, 1H), 4.33 (q, 2H), 3.90 (s, 3H), 1.34 (t, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 163.2, 156.2, 148.9, 147.1, 145.0, 124.8, 120.7, 118.5, 115.9, 62.1, 56.4, 14.3; Anal. calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 62.85; H, 4.85.

3.7.5 Ethyl 7-(diethylamino)-2-oxo-2H-chromene-3-carboxylate (3e): Yellowish solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (60:40); yield 251 mg (87%); m.p. 76 ^oC; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.44 (s, 1H), 7.34 (d, 1H), 6.60 (dd, 1H), 6.43 (d, 1H), 3.89 (s, 2H), 3.43 (q, 4H), 1.22 (t, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 165.0, 158.5, 158.4, 153.0, 149.7, 131.2, 109.6, 108.3, 107.7, 96.6, 52.3, 45.1, 12.4; Anal. calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.37; H, 6.60; N, 4.81.

3.7.6. 3-Acetyl-2H-chromen-2-one (3f): Yellowish solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); yield 169 (90%); m.p. 120-122 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.45 (s, 1H), 7.90 – 7.42 (m, 2H), 7.35 – 7.20 (m, 2H), 2.67 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 195.6, 159.4, 155.4, 147.6, 134.5, 130.3, 125.1, 124.6, 118.4, 116.8, 30.7; Anal. calcd for $C_{11}H_8O_3$: C, 70.21; H, 4.29. Found: C, 70.16; H, 4.26.

3.7.7. 3-Acetyl-6-bromo-2H-chromen-2-one (3g): White solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); yield 239 mg (90 %); m.p. 231-232 ^{o}C; **^{1}H NMR** (500 MHz, DMSO) δ (ppm): 8.60 (s, 1H), 8.21 (s, 1H), 7.89 (d, 1H), 7.44 (d, 1H), 2.59 (s, 3H); **^{13}C NMR** (126 MHz, DMSO) δ (ppm): 195.4, 158.4, 154.1, 146.1, 137.1, 133.1, 125.9, 120.5, 118.8, 116.8, 30.4.; Anal. calcd for $C_{11}H_7BrO_3$: C, 49.47; H, 2.64. Found: C, 49.41; H, 2.62.

3.7.8 3-Acetyl-6-chloro-2H-chromen-2-one (3h): Yellow solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); yield 197 mg (89%); m.p. 210-211 ^{o}C; **^{1}H NMR** (500 MHz, DMSO) δ (ppm): 8.59 (s, 1H), 8.06 (s, 1H), 7.77 (s, 1H), 7.50 (s, 1H), 2.57 (s, 3H); **^{13}C NMR** (126 MHz, DMSO) δ (ppm): 195.1, 158.1, 153.3, 145.8, 133.9, 129.6, 128.6, 125.5, 119.6, 118.2, 30.1; Anal. calcd for $C_{11}H_7ClO_3$: C, 59.35; H, 3.17. Found: C, 59.30; H, 3.13.

3.7.9 3-Acetyl-8-methoxy-2H-chromen-2-one (3i): Yellow solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); yield 187 mg (86%); m.p. 162-163 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.41 (s, 1H), 7.33 – 6.72 (m, 3H), 3.92 (s, 3H), 2.66 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 195.7, 158.8, 147.8, 147.1, 145.1, 124.9, 124.7, 121.4, 118.9, 115.9, 56.4, 30.7; Anal. calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.0; H, 4.59.

3.7.10 3-Acetyl-7-(diethylamino)-2H-chromen-2-one (3j): Yellow solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (60:40); yield 207 mg (80%); m.p. 151-153 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.41 (s, 1H), 7.37 (d, 1H), 6.60 (d, 1H), 6.44 (s, 1H), 3.44 (dd, 4H), 2.65 (s, 3H), 1.22 (t, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 195.8, 161.0, 158.8, 153.1, 147.9, 132.0, 116.1, 109.9, 108.2, 96.6, 45.2, 30.7, 12.5; Anal. calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.42; H, 6.59; N, 5.35.

3.7.11 2-Oxo-2H-chromene-3-carboxylic acid (3k): Yellow crystalline solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); m.p. 189-190 °C; yield 171 mg (90%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 11.40 (s, 1H), 8.72 (s, 1H), 7.38 (dd, 2H), 7.06 – 6.95 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 164.8, 159.9, 133.6, 132.7, 119.8, 117.4, 117.3; Anal. calcd for $C_{10}H_6O_4$: C, 63.16; H, 3.18. Found: C, 63.09; H, 3.15.

3.7.12 6-Bromo-2-oxo-2H-chromene-3-carboxylic acid (3l): Yellow solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); yield 241 mg (89%); m.p. 197-199 °C; **^{1}H NMR** (500 MHz, DMSO) δ (ppm): 11.14 (s, 1H), 8.94 (s, 1H), 7.90 (s, 1H), 7.54 (d, 1H), 6.95 (d, 1H); **^{13}C NMR** (126 MHz, DMSO) δ (ppm): 160.7, 159.9, 157.6, 142.1, 135.5, 132.0, 131.5, 131.0, 120.6, 118.95, 110.6; Anal. calcd for $C_{10}H_5BrO_4$: C, 44.64; H, 1.87. Found: C, 44.57; H, 1.84.

3.7.13 6-Chloro-2-oxo-2H-chromene-3-carboxylic acid (3m): Yellow solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); yield 197 mg (88%); m.p. 121-122 °C; **^{1}H NMR** (500 MHz, DMSO) δ (ppm): 11.14 (s, 1H), 8.94 (s, 1H), 7.77 (s, 1H), 7.42 (d, 1H), 7.00 (d, 1H); **^{13}C NMR** (126 MHz, DMSO) δ (ppm): 164.1, 160.94, 157.3, 132.8, 128.7, 123.2, 120.0, 118.5; Anal. calcd for $C_{10}H_5ClO_4$: C, 53.48; H, 2.24. Found: C, 53.41; H, 2.22.

3.7.14 8-Methoxy-2-oxo-2H-chromene-3-carboxylic acid (3n): Yellow solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); yield 191 mg (87%); m.p. 218-220 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 11.56 (s, 1H), 8.69 (s, 1H), 7.00 (d, 2H), 6.92 (t, 1H), 3.93 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 164.9, 149.8, 148.4, 124.1, 119.5, 117.4, 115.2, 56.3; Anal. calcd for $C_{11}H_8O_5$: C, 60.00; H, 3.66. Found: C, 59.52; H, 3.63.

3.7.15 7-(Diethylamino)-2-oxo-2H-chromene-3-carboxylic acid (3o): Orange crystal; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (60:40); yield 214 mg (82%); m.p. 220-222 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 11.83 (s, 1H), 8.45 (s, 1H), 7.09 (d, 1H), 6.25 (d, 1H), 6.22 (s, 1H), 3.39 (q, 4H), 1.20 (t, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 161.5, 161.0, 151.3, 133.4, 107.0, 104.0, 97.9, 44.6, 12.8; Anal. calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.30; H, 5.76; N, 5.33.

3.7.16 Methyl 2-oxo-2H-chromene-3-carboxylate (3p): White solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); yield 183 mg (90%); m.p. 116-117 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.53 (s, 1H), 7.63 – 7.58 (m, 2H), 7.31 (dd, 2H), 3.91 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 163.6, 156.7, 155.2, 149.2, 134.5, 129.6, 124.9, 117.8, 117.8, 116.7, 52.9; Anal. calcd for $C_{11}H_8O_4$: C, 64.71; H, 3.95. Found: C, 64.67; H, 3.93.

3.7.17 Methyl 6-bromo-2-oxo-2H-chromene-3-carboxylate (3q): White solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); yield 250 mg (89%); m.p. 183-184 ^{o}C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.45 (s, 1H), 7.73 (dd, 2H), 7.24 (d, 1H), 3.95 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 163.3, 156.0, 154.1, 147.6, 137.1, 131.7, 119.4, 119.2, 118.6, 117.5, 53.1; Anal. calcd for $C_{11}H_7BrO_4$: C, 46.67; H, 2.49. Found: C, 46.60, H, 2.47.

3.7.18 Methyl 6-chloro-2-oxo-2H-chromene-3-carboxylate (3r): White solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); yield 207 mg (87%); m.p. 197-198 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.45 (s, 1H), 7.75 – 7.70 (m, 2H), 7.24 (d, 1H), 3.95 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 163.3, 156.0, 154.1, 147.6, 137.1, 131.7, 119.4, 119.2, 118.6, 117.5, 53.1; Anal. calcd for $C_{11}H_7ClO_4$: C, 55.37; H, 2.96. Found: C, 55.30; H, 2.94.

3.7.19 Methyl 8-methoxy-2-oxo-2H-chromene-3-carboxylate (3s): Yellow solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (90:10); yield 203 mg (87%); m.p. 123-124 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.50 (s, 1H), 7.26 – 7.21 (m, 1H), 7.17 (s, 1H), 7.15 (d, 1H), 3.94 (s, 3H), 3.91 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 163.6, 156.1, 149.3, 147.0, 144.8, 124.8, 120.6, 118.3, 118.0, 115.9, 56.3, 52.8; Anal. calcd for $C_{12}H_{10}O_5$: C, 61.54; H, 4.30. Found: C, 61.47; H, 4.27.

3.7.20 Diethyl 2-benzylidenemalonate (5a): Yellow liquid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (95:5); yield 92%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.73 (s, 1H), 7.44 (s, 2H), 7.38 (s, 2H), 4.33 (q, 2H), 4.29 (q, 2H), 1.33 (t, 3H), 1.28 (t, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 166.8, 164.2, 142.2, 133.0, 130.6, 129.5, 128.9, 126.4, 61.8, 61.7, 14.2, 13.9; Anal. calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.68; H, 6.48.

3.7.21 Diethyl 2-(4-nitrobenzylidene)malonate (5b): Yellow solid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (95:5): yield 91%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.64 (s, 1H), 7.50 (d, 2H), 7.31 (d, 2H), 4.31 (dd, 4H), 1.30 (dd, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 166.5, 164.0, 140.8, 132.1, 131.9, 130.9, 127.0, 125.1, 61.9, 61.8, 14.2, 14.0; Anal. calcd for $C_{14}H_{15}NO_6$: C, 57.34; H, 5.16; N, 4.78. Found: C, 57.28; H, 5.13; N, 4.76.

3.7.22 Diethyl 2-(4-bromobenzylidene)malonate (5c): Yellow liquid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (95:5); yield 90%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.24 – 8.21 (m, 2H), 7.75 (s, 1H), 7.60 (d, 2H), 4.33 (q, 4H), 1.34 (t, 3H), 1.28 (t, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 165.7, 163.4, 148.5, 139.3, 139.2, 130.1, 130.1, 124.0, 62.3, 62.2, 14.2, 14.0; Anal. calcd for $C_{14}H_{15}BrO_4$: C, 51.40; H, 4.62. Found: C, 51.32; H, 4.59.

3.7.23 Diethyl 2-(2-chlorobenzylidene)malonate (5d): Yellow liquid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (95:5); yield 89%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.02 (s, 1H), 7.44 – 7.41 (m, 2H), 7.31 (t, 1H), 7.23 (d, 1H), 4.24(q, 2H), 4.32 (q, 2H), 1.34 (t, 3H)), 1.18 (t, 3H); ^{13}C **NMR** (126 MHz, $CDCl_3$) δ (ppm): 165.9, 163.7, 139.3, 134.7, 132.1, 131.2, 129.9, 129.3, 128.9, 126.9, 61.9, 61.7, 14.2, 13.9; Anal. calcd for $C_{14}H_{15}ClO_4$: C, 59.48; H, 5.35. Found: C, 59.40; H, 5.31.

3.7.24 Diethyl 2-(naphthalen-2-ylmethylene)malonate (5e): Brown liquid; the residue was purified by column chromatography in silica gel eluting with hexane:EtOAc (95:5); yield 90%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.91 (s, 1H), 7.86 (s, 1H), 7.77 (t, 3H), 7.48 (dd, 2H), 4.34 (q, 2H), 4.29 (q, 2H), 1.31 (t, 3H), 1.26 (t, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 166.8, 164.2, 142.2, 134.1, 133.0, 130.9, 130.4, 128.7, 128.5, 127.7, 127.7, 126.8, 126.3, 125.3, 61.8, 61.7, 14.2, 14.0; Anal. calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.39; H, 6.05.

3.8 Spectral Data of Synthesized Products

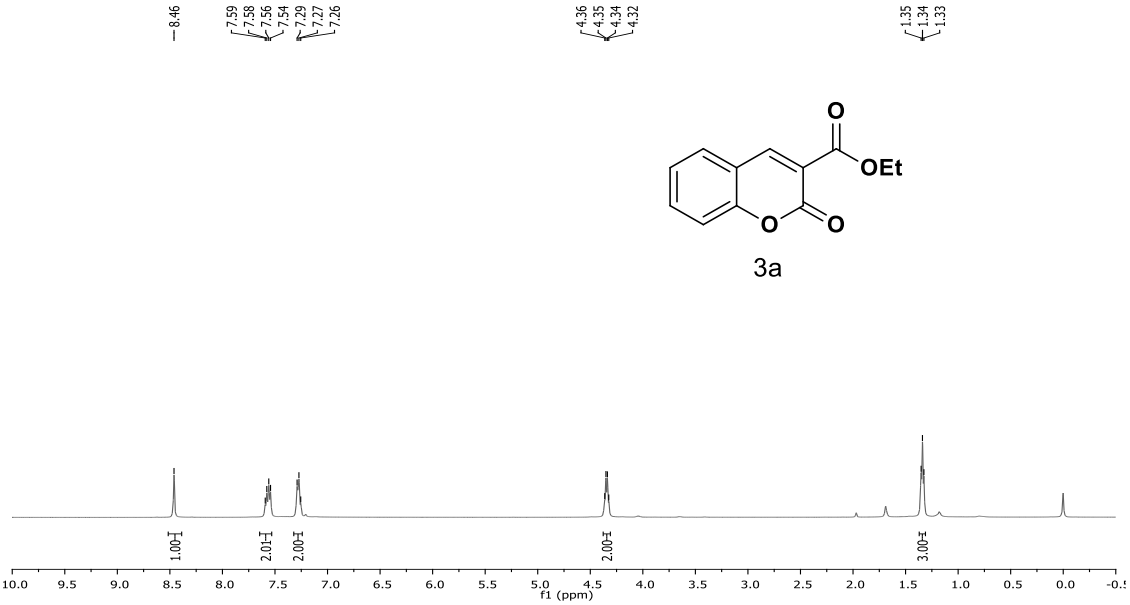


Figure 3.2: ^{1}H NMR spectrum of coumarin (**3a**).

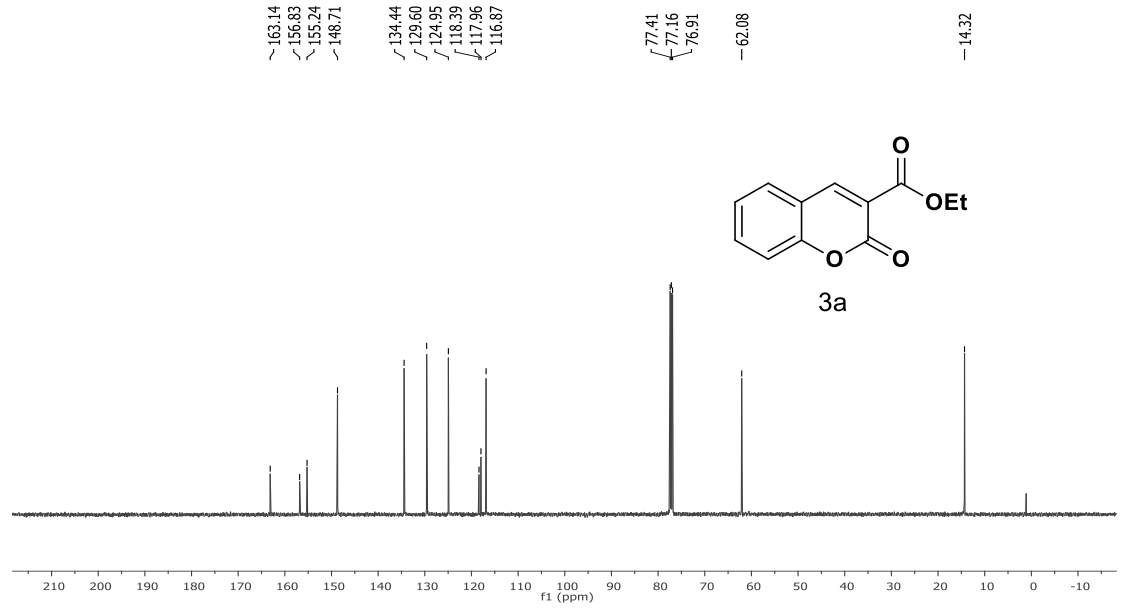


Figure 3.3: ^{13}C NMR spectrum of coumarin (**3a**).

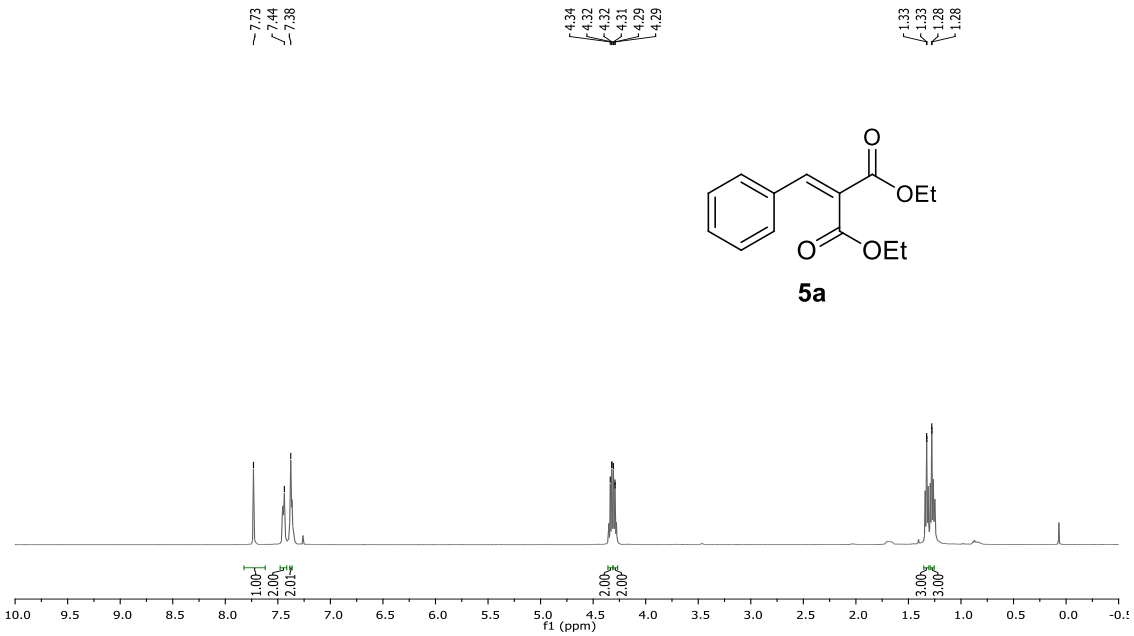


Figure 3.4: ^{1}H NMR spectrum of **5a**.

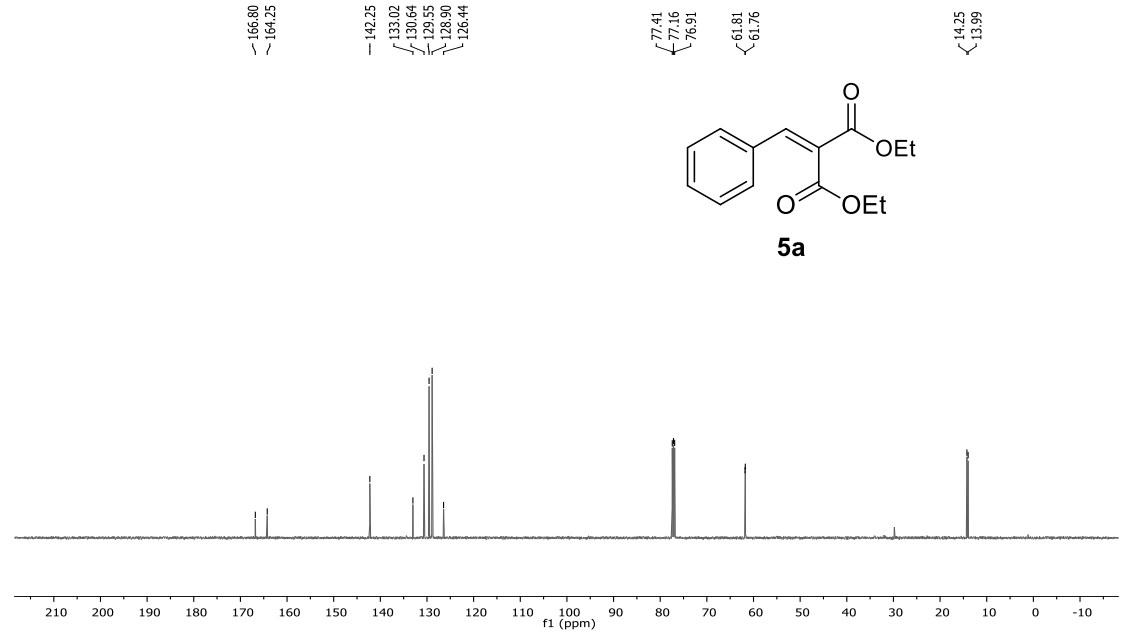


Figure 3.5: ^{13}C NMR spectrum of **5a**.

3.9 References

Adronov, A., S. L. Gilat, J. M. Frechet, K. Ohta, F. V. Neuwahl and G. R. Fleming, "Light harvesting and energy transfer in laser dye-labeled poly(aryl ether)dendrimers," *Journal of the American Chemical Society,* **122**(6) (2000) 1175-1185.

Aslam, K., M. K. Khosa, N. Jahan and S. Nosheen, "Short communication: synthesis and applications of Coumarin," *Pakistan journal of pharmaceutical sciences,* **23**(4) (2010) 449-454.

Bandgar, P. B, "Solvent-free one-pot rapid synthesis of 3-carboxycoumarins using focused microwaves," *Green Chemistry*, **1**(5) (1999) 243-245.

Bandgar, P. B., L. S. Uppalla and D. S. Kurule, "Solvent-free one-pot rapid synthesis of 3-carboxycoumarins. Using focused microwaves," *Green Chemistry*, **1**(5) (1999) 243-245.

Bedoya, L. M., M. Beltrán, R. Sancho, D. A. Olmedo, S. S.-Palomino, E. D. Olmo, J. L. L.-Perez, E. Munoz, A. S. Feliciano and J. Alcami, "4-Phenylcoumarins as HIV transcription inhibitors," *Bioorganic & medicinal chemistry letters,* **15**(20) (2005) 4447-4450.

Bhavsar, D., J. Trivedi, S. Parekh, M. Savant, S. Thakrar, A. Bavishi, A. Radadiya, H. Valaa, J. Lunagariyaa, M. Parmara, L. Paresha, R. Loddob and A. Shaha, "Synthesis and in vitro anti-HIV activity of N-1,3-benzo[d]thiazol-2-yl-2-(2-oxo-2H-chromen-4-yl)acetamide derivatives using MTT method," *Bioorganic & medicinal chemistry letters,* **21** (11) (2011) 3443-3446.

Brahmachari, G., "Handbook of pharmaceutical natural products," Vol. 1. Weinheim: Wiley-VCH, 2010.

Brahmachari, G., "Room Temperature One-Pot Green Synthesis of Coumarin-3-Carboxylic Acids in Water: A Practical Method for the Large-Scale Synthesis, " *ACS Sustainable Chemistry & Engineering*, **3** (2015) 2350-2358.

Chimenti, F., B. Bizzarri, A. Bolasco, D. Secci, P. Chimenti, S. Carradori, A. Granese, D. Rivanerab, D. Lillib, M. M. Scaltritoc and M. I. Brenciagliab, "Synthesis and in vitro selective anti-Helicobacter pylori activity of N-substituted-2-oxo-2H-1-benzopyran-3-carboxamides," *European journal of medicinal chemistry*, **41**(2) (2006) 208-212.

Creaven, B. S., E. Czegledi, M. Devereux, E. A. Enyedy, A. F. A. Kia, D. Karcz and A. Kellett, "Biological activity and coordination modes of copper (II) complexes of Schiff base-derived coumarin ligands," *Dalton Transactions*, **39**(45) (2010) 10854-10865.

Frosch, P. J., J. D. Johansen, T. Menne, C. Pirker, S. C. Rastogi, K. E. Andersen, M. Bruze, A. Goossens, J. P. Lepoittevin and I. R. White, "Further important sensitizers in patients sensitive to fragrances I. Reactivity to 14 frequently used chemicals," *Contact dermatitis*, **47**(2) (2002) 78-85.

Ghomi, J. S. and Z. Akbarzadeh, "Ultrasonic accelerated Knoevenagel condensation by magnetically recoverable $MgFe_2O_4$ nanocatalyst: A rapid and green synthesis of coumarins under solvent-free conditions," *Ultrasonics sonochemistry*, **40** (2018) 78-83.

Guntreddi, T., R. Vanjari and K. N. Singh,"Direct conversion of methylarenes into dithiocarbamates, thioamides and benzyl esters," *Tetrahedron*, **70**(25) (2014) 3887-3892.

Heravi, M. M., N. Poormohammad, Y. S. Beheshtiha, B. Baghernejad and R. Malakooti, "The synthesis of 2-iminochromenes using mesoporous molecular sieve MCM-41 as a heterogeneous and recyclable catalyst," *Bulletin of the Chemical Society of Ethiopia*, **24**(2) (2010) 273-276.

Hill, J. G., B. E. Rossiter and K. B. Sharpless, "Anhydrous *tert*-butyl hydroperoxide in toluene: the preferred reagent for applications requiring dry TBHP," *The Journal of Organic Chemistry*, **48**(20) (1983) 3607-3608.

Hoult, J. R. S. and M. Paya, "Pharmacological and biochemical actions of simple coumarins: natural products with therapeutic potential," *General Pharmacology: The Vascular System*, **27**(4) (1996) 713-722.

Jiang, X., B. Zhu, K. Lin, G. Wang, W.-K. Su and C. Yu, "Metal-free synthesis of 2, 2-disubstituted indolin-3-ones," *Organic & biomolecular chemistry*, **17**(8) (2019) 2199-2203.

Johnson, J. R., "The Perkin Reaction and Related Reactions," *Organic Reactions*, **1**(2004) 210-265.

Jones, G., "The Knoevenagel Condensation," *Organic reactions*, **15** (2004) 204-599.

Valizadeh, H., M. Mahmoodian and H. Gholipour," $ZrCl_4$/[bmim]BF_4-catalyzed condensation of salicylaldehydes and malononitrile: Single-step synthesis of 3-cyanocoumarin derivatives," *Journal of Heterocyclic Chemistry*, **48**(4) (2011) 799-802.

Karade, N. N., S. V. Gampawar, S. V. Shinde and W. N. Jadhav, "L-Proline Catalyzed Solvent-Free Knoevenagel Condensation for the Synthesis of 3-Substituted Coumarins." *Chinese Journal of Chemistry*, **25**(11) (2007) 1686-1689.

Kaye, P. T., M. A. Musa and X. W. Nocanda, "Efficient and chemoselective access to 3-(chloromethyl)coumarins via direct cyclisation of unprotected Baylis-Hillman adducts," *Synthesis*, **2003** (04) (2003) 531-534.

Kayser, O. and H. Kolodziej, "Antibacterial activity of extracts and constituents of Pelargonium sidoides and Pelargonium reniforme," *Planta medica*, **63**(06) (1997) 508-510.

Khode, S., V. Maddi, P. Aragade, M. Palkar, P. K. Ronad, S. Mamledesai, A. H. M. Thippeswamy and D. Satyanarayana, "Synthesis and pharmacological evaluation of a novel series of 5-(substituted)aryl-3-(3-coumarinyl)-1-phenyl-2-pyrazolines as novel anti-inflammatory and analgesic agents," *European journal of medicinal chemistry*, **44**(4) (2009) 1682-1688.

Kontogiorgis, C. A. and D. J. H.-Litina,"Synthesis and antiinflammatory activity of coumarin derivatives," *Journal of medicinal chemistry*, **48**(20) (2005) 6400-6408.

Kontogiorgis, C. and D. H. Litina, "Biological evaluation of several coumarin derivatives designed as possible anti-inflammatory/antioxidant agents," *Journal of Enzyme Inhibition and Medicinal Chemistry*, **18**(1) (2003) 63-69.

Kumar, D., S. Kumari, S. Gajaganti, V. Srivastava and S. Singh, "Et_3N-Promoted Cascade Sp^3 C-H Bond Functionalization of Methyl Arene with Active Methylene Compounds Under Solvent-Free Condition," *ChemistrySelect*, **4**(7) (2019) 2225-2228.

Kumar, S., "A solvent free approach for Knoevenagel condensation: facile synthesis of 3-cyano and 3-carbethoxycoumarins," *Green Processing and Synthesis*, **3**(3) (2014) 223-227.

Li, Y. F., "*tert*-butyl hydroperoxide (TBHP): A versatile oxidizing agent in organic synthesis," *Synlett*, **2007**(18) (2007) 2922-2923.

Melagraki, G., A. Afantitis, O. I.-Markopoulou, A. Detsi, M. Koufaki, C. Kontogiorgis and D. J. H.-Litina, "Synthesis and evaluation of the antioxidant and anti-inflammatory activity of novel coumarin-3-aminoamides and their alpha-lipoic acid adducts," *European journal of medicinal chemistry*, **44**(7) (2009) 3020-3026.

Mishra, A., S. Chauhan, P. Verma, S. Singh and V. Srivastava, "TBHP-Initiated Transamidation of Secondary Amides via C− N Bond Activation: A Metal-Free Approach," *Asian Journal of Organic Chemistry*, **8**(6) (2019) 853-857.

Moreira, M. D., M. C. Picanço, L. C. D. A. Barbosa, R. N. C. Guedes, M. R. D. Campos, G. A. Silva and J. C. Martins, "Plant compounds insecticide activity against Coleoptera pests of stored products," *Journal of the Brazilian Chemical Society*, **42**(7) (2007) 909-915

Murray, R. D. H.,"Coumarins," *Natural product reports*, **6**(6) (1989) 591-624.

Pechmann, H. V, "New pictorial way of cumarine. synthesis of daphnetin, " *Reports of the German Chemical Society*, **17**(1) (1884) 929-936.

Peroni, E., G. Caminati, P. Baglioni, F. Nuti, M. Chelli and A. M. Papini, "A new lipophilic fluorescent probe for interaction studies of bioactive lipopeptides with membrane models," *Bioorganic & medicinal chemistry letters*, **12**(13) (2002) 1731-1734.

Rao, K. T. V., P. S. N. Rao, P. Nagaraju, P. S. S. Prasad and N. Lingaiah, "Room temperature selective oxidation of toluene over vanadium substituted polyoxometalate catalysts," *Journal of Molecular Catalysis A: Chemical*, **303**(2009) 84-89.

Rout, S. K., S. Guin, W. Ali, A. Gogoi and B. K. Patel, "Copper-catalyzed esterification of alkylbenzenes with cyclic ethers and cycloalkanes via C (sp3)–H activation following cross-dehydrogenative coupling," *Organic letters*, **16**(2014) 3086-3089.

Schonberg, A. and N. Latif, "Furochromones and coumarins. XI. The molluscicidal activity of bergapten, isopimpinillin and xanthotoxin," *Journal of the American Chemical Society*, **76(**23) (1954) 6208-6208.

Specht, D. P., P. A. Martic and S. Farid, "Ketocoumarins: a new class of triplet sensitizers," *Tetrahedron*, **38**(9) (1982) 1203-1211.

Sun, J., D. Z.-Negrerie and Y. Du, "Oxidative Coupling of Enamines and Disulfides via Tetrabutylammonium Iodide/*tert*-Butyl Hydroperoxide-Mediated Intermolecular Oxidative C (sp^2)- S Bond Formation Under Transition Metal-Free Conditions," *Advanced Synthesis & Catalysis*, **358**(13) (2016) 2035-2040.

Sun, J., H. Ge, X. Zhen, X. An, G. Zhang, D. Z.-Negrerie, Y. Du and K. Zhao, "TBHP/AIBN-Mediated Synthesis of 2-Amino-thioazoles from Active Methylene Ketones and Thiourea under Metal-free Conditions," *Tetrahedron*, **74**(17) (2018) 2107-2114.

Timonen, J. M., R. M. Nieminen, O. Sareila, A. Goulas, L. J. Moilanen, M. Haukka, P. Vainiotalo, E. Moilanen and P. H. Aulaskari, "Synthesis and anti-inflammatory effects of a series of novel 7-hydroxycoumarin derivatives," *European journal of medicinal chemistry*, **46**(9) (2011) 3845-3850.

Vanjari, R. and K. N. Singh, "Utilization of methylarenes as versatile building blocks in organic synthesis," *Chemical Society Reviews*, **44**(22) (2015) 8062-8096.

Vazquez, R. S., R. F. Guíñez, M. J. Matos, L. Santana, E. Uriarte, M. Lapier, J. D. Maya and C. O. Azar, "Synthesis of coumarin–chalcone hybrids and evaluation of their antioxidant and trypanocidal properties," *Medicinal Chemistry Communications*, **4**(6) (2013) 993-1000.

Volmajer, J., R. Toplak, I. Leban and A. M. L. Marechal, "Synthesis of new iminocoumarins and their transformations into N-chloro and hydrazono compounds," *Tetrahedron*, **61**(29) (2005) 7012-7021.

Wu, L.-J., F.-L.Tan, M. Li, R.-J. Song and J.-H. Li, "Fe-Catalyzed oxidative spirocyclization of *N*-arylpropiolamides with silanes and TBHP involving the formation of C–Si bonds," *Organic Chemistry Frontiers*, **4**(3) (2017) 350-353.

Wu, X.-Q., C. Huang, Y.-M. Jia, B.-A. Song, J. Li and X.-H. Liu, "Novel coumarin-dihydropyrazole thio-ethanone derivatives: design, synthesis and anticancer activity," *European journal of medicinal chemistry*, **74** (2014) 717-725.

Yang, Y., Y. Bao, Q. Guan, Q. Sun, Z. Zha and Z. Wang, "Copper-catalyzed S-methylation of sulfonyl hydrazides with TBHP for the synthesis of methyl sulfones in water," *Green Chemistry*, **19**(1) (2017)112-116.

Yavari, I., R. H. Shoar and A. Zonouzi, "A new and efficient route to 4-carboxymethylcoumarins mediated by vinyltriphenylphosphonium salt, "*Tetrahedron Letters*, **39**(16) (1998) 2391-2392.

Yu, J., D. Z.-Negrerie and Y. Du, "TBHP/$CoCl_2$-Mediated Intramolecular Oxidative Cyclization of N-(2-Formylphenyl) amides: An Approach to the Construction of 4*H*-3, 1-Benzoxazin-4-ones," *European Journal of Organic Chemistry*, **2016**(3) (2016) 562-568.

Yuan, Y., W. Hou, D. Z.-Negrerie, K. Zhao and Y. Du, "Direct oxidative coupling of enamines and electron-deficient amines: TBAI/TBHP-mediated synthesis of substituted diaminoalkenes under metal-free conditions," *Organic letters*, **16**(20) (2014) 5410-5413.

Zhang, M. and A. Q. Zhang, "Catalyzed Preparation of Ylidenemalononitriles and 3-Cyanocoumarin in Water," *Synthetic communications*, **34**(24) (2004) 4531-4535.

Zheng, L., Z.-Z. Zhou, Y.-T. He, L.-H. Li, J.-W. Ma, Y.-F. Qiu, P. –X, Zhou, X.-Y. Liu, P.-F. Xu and Y.-M. Liang, "Iodine-Promoted Radical Cyclization in Water: A Selective Reaction of 1, 6-Enynes with Sulfonyl Hydrazides," *The Journal of organic chemistry*, **81** (1) (2015) 66-76.

Zhi, Q. D., J. B. Shi, B. A. Song and X. H. Liu, "Novel 2 H-chromen derivatives: design, synthesis and anticancer activity," *RSC Advances*, **4**(11) (2014) 5607-5617.

Zhou, W., Z. Liangren and N. Jiao, "Direct transformation of methyl arenes to aryl nitriles at room temperature,"*Angewandte Chemie International Edition*, **48**(38) (2009) 7094-7097.