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Feasible pathways for the multi-dimensional synthesis of carboxylic acid from benzo-pyrone methyl ketone

Aruna Yarva[a,*], Lavanya Nagamalla[a], Kavitha K[a,b], Aparna Pasula[b], Srikrishna Devulapally[b] & Pramod Kumar Dubey[b]

[a]Department of Humanities and Sciences, Hyderabad Institute of Technology and Management, Medchal, Hyderabad, Telangana 502 401, India

[b]Department of Chemistry, Jawaharlal Nehru Technological University Hyderabad, College of Engineering, Kukatpally, Hyderabad, Telangana 500 085, India

*E-mail: yarvaaruna@gmail.com

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3-Acetyl coumarin derivatives are the key synthons to the numerous numbers of heterocyclic compound syntheses. Due to the wide spectrum applications of benzopyran derivatives in pharma, research, food technology and material science there is a multitude number of methodologies feasible to synthesize benzo pyrone heterocyclic derivatives. This article articulates the synthesis and molecular structure confirmation of oxidative product starting from methyl ketone compound by haloform reaction. Design of benign path ways for instance room temperature, reflux conditions and water bath mediated synthesis of desired compounds in expected yields is the foremost intent of the article. Solvent and catalyst optimization studies were carried to elevate the product yield and to precede the reaction in sustainable way. Furthermore compounds are confirmed by spectroscopic analytical methods such as ^{1}H NMR, ^{13}C NMR, IR and HRMS spectroscopy. This article paves the way to researchers to explore these analogues to explore disparate medicinal applications.

Keywords: Methyl ketone, Haloform reaction, Multi-dimensional synthesis, Phase transfer catalyst, Benzo-pyrone

Coumarin and its derivatives are the plant extracted products and many heterocyclic compounds are synthesized from 3-acetyl-2*H*-chromen-2-one. There are so many references to find out the proficient applications of 3-acetyl-2*H*-chromen-2-one. Heterocyclic compounds synthesized from 3-acetyl-2*H*-chromen-2-one are pyridine derivative[1], applied in spectrometric determination of iron[2], Synthesis of quinolone derivatives having anti-bacterial and anti-fungal activities[3], synthesis of chalcones[4], dihydro pyridine carbonitriles[5] and Pyramidines[6] etc. Gist of chemical modification of 3-acetyl Coumarin are manifested in Fig. 1.

Study of haloform reactions was started in the year of 1822. Haloform reaction on methyl ketone was performed in disparate methods namely Br_2 dissolved in water[7] in presence of sodium hydroxide, Aston *et al*. reported haloform reaction with of sodium hypo bromite[8], iodoform reaction by treating iodine dissolved in potassium iodide[9], halogenation reaction of methyl ketone with hypobromite or hypochlorite[10], haloform reaction of methyl ketone with bromine in water in the presence of 1,3-dioxane[11], Haloform reaction with sodium hypochlorite under phase transfer catalysis[12], haloform reaction of aldehydes and ketones pentaflouro enolates[13], chloral with calcium hydroxide[14], iodine dissolved in sodium hydroxide[15], advanced haloform reactions[16]. In order to perform haloform reaction in the presence of alkali there is a search for the stability of coumarin lactone ring in presence of base. Noster *et al*. reported[17] the analysis of reaction conditions in terms of concentration of alkali screening, they observed that 20% NaOH aqu. solution will not cleave the lactone ring.

Furthermore there is a search for the biological importance data of 3-acetyl coumarin, it is efficient in exhibiting anti-fungal activity[18], antitumor activity[19], Cytotoxic activity against selected cell lines[20], gram positive, gram negative bacteria and *in vitro* anti-oxidant activity studies[21], anti-bacterial[22], anti-oxidant activity[23] and nuero protective properties[24]. Consolidation of desperate routes for the transformation of methyl ketones into haloform are delineated in the Fig. 2.

Rajendra Prasad *et al*.[25] delineated the anti-microbial activity of 3-acetyl coumarin against *B. Pumilis*, *B. Subtilis*, *E. Coli*, *A. Niger*, *R. Oriza*.

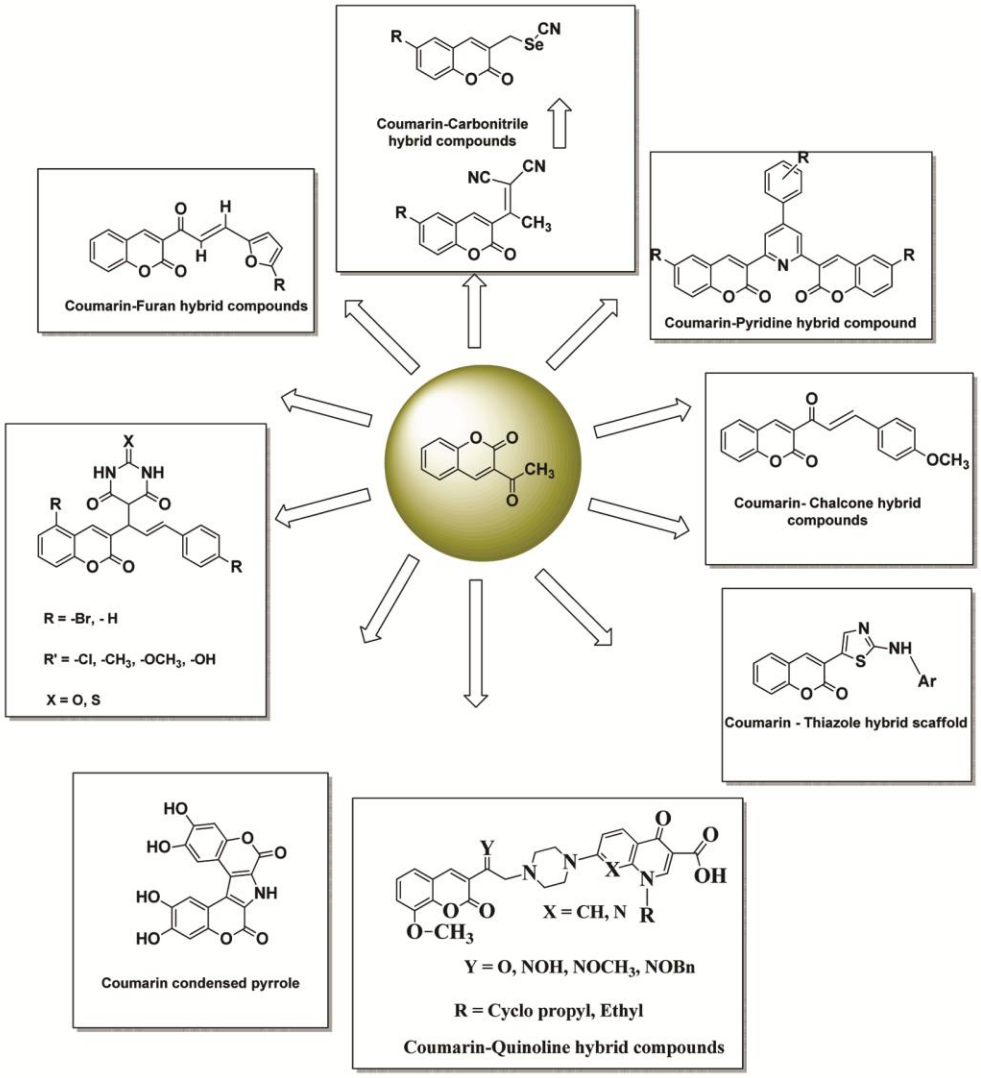


Fig. 1 — Assortment of chemical modifications of 3-acetyl coumarin employed as a key synthon

Rajesh *et al*. reported[26] the synthesis and anti-microbial activity against Staphylococcus Aureus and Staphylococcus pyogenic. Anees *et al*. reported[27] the synthesis and evaluation of *in vitro* anti-hepato carcinoma activity of 3-acetyl coumarin derivatives and their DNA protein binding properties.

Based on all the keen literature survey on the 3-acetyl-2*H*-chromen-2-one in terms of its applications in synthetic organic chemistry as a useful synthon for various heterocyclics, exploration studies of biological activity review, it is taken as research objective and performed haloform reaction of the 3-acetyl-2*H*-chromen-2-one. Though there are lot many methods to synthesize coumarin based carboxylic acid derivatives but no report was found on haloform reaction of 3-acetyl coumarin to subsequent carboxylic acid. Being the method of synthesis chosen is laboratory viable, feasible, single step with green chemistry protocols; this method of synthesis is the profitable path way in terms of product yield, reaction times and quality of the product. This article also emphasizes the reaction optimization studies, method development for the sustainable synthesis of the title compound.

Experimental Details

Melting points were determined from digital melting point apparatus, TLC analysis of the compounds was carried by Aluminium foil coated with silica gel-G supplied by Akshaya company, TLC plates were monitored under UV lamp. ^{1}HNMR spectra were recorded in DMSO-D_6 solvent using TMS as an internal standard compound at 400 MHz frequency. High resolution mass spectra were

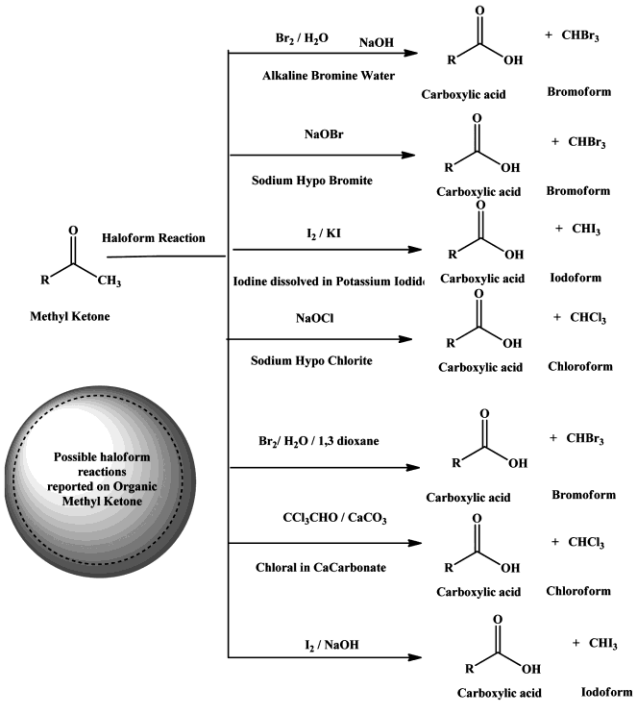


Fig. 2 — Collation of reported haloform reactions on Organic methyl ketones

recorded on Agilent-LCMS instrument. Infrared spectras were recorded on Brooker-FTIR instrument.

Synthetic procedure for the preparation of target compounds

Synthesis of 6-bromo-2-oxo-2H-chromene-3-carboxylic acid from 3-acetyl-6-bromo-2H-chromen-2-one with tetrabutyl ammonium tri bromide (TBATB) as brominating agent (2c)

Equimolar ratio (1:1) of 3-acetyl-6-bromo-2*H*-chromen-2-one and tetra butyl ammonium tribromide (TBATB) were dissolved in ethanol taken in round bottom flask, catalytic amount of 3 M phase transfer catalyst tetra butyl ammonium bromide (TBAB) solution was added reaction was stirred at room temperature for 60 min. Completion of the reaction was preliminarily identified by TLC in chloroform mobile phase under short length UV light.

Synthesis of 6-bromo-2-oxo-2H-chromene-3-carboxylic acid from 3-acetyl-6-bromo- 2H-chromen-2-one with Iodine dissolved in potassium iodide as Iodinating agent (2c)

1 (mmol) of 3-acetyl-6- bromo- 2*H*-chromen-2-onetreated with excess of liquid iodinating agent i.e., solution of I_2/KI in ethanol solvent and added with catalytic amount of 3 M tetrabutyl ammonium bromide and reaction mixture was stirred at RT for 60 min. TLC method is used for the preliminary identification of product formation. Final product formation further confirmed by spectroscopic analysis.

Synthesis of 6-bromo-2-oxo-2H-chromene-3-carboxylic acid from 3-acetyl-6-bromo-2H-chromen-2-one with bromine water (2c)

100 g of 3-acetyl-6-bromo- 2*H*-chromen-2-one was added with excess of bromine dissolved in water and added with catalytic amount of 3 M tetrabutyl ammonium bromide. Furthermore reaction mixture was stirred at room temperature for 60 min of time duration. TLC method is used to identify the completion of the reaction. Products were further confirmed by spectroscopic analysis.

Synthesis of 6-bromo-2-oxo-2H-chromene-3-carboxylic acid from 3-acetyl-6-bromo-2H-chromen-2-one with bromine water under alkaline conditions (2c)

100 g of 3-acetyl-6-bromo-2*H*-chromen-2-one acid was added with excess of bromine dissolved in water and added with catalytic amount of 3 M sodium hydroxide. Furthermore reaction mixture was stirred at room temperature for 4 h. Compound is preliminary identified by the Thin Layer Chromatography. products were further confirmed by spectroscopic analysis.

Synthesis of 6-bromo-2-oxo—2H-chromene-3-carboxylic acid from 3-acetyl-6- bromo-2H-chromen-2-one with TBATB with TBAB (2c)

100 g of 3-acetyl-6-bromo-2*H*-chromen-2-one was added with tetra butyl ammonium bromide (TBATB) and added with catalytic amount of 3 M TBAB. Furthermore reaction mixture was heated on the water bath with shaker for thirty minutes. Further reaction completion primarily identified by TLC in hexane and ethyl acetate mobile phase under UV light. Products were further confirmed by spectroscopic analysis.

Synthesis of 6-bromo-2-oxo—2H-chromene-3-carboxylic acid from 3-acetyl-6- bromo-2H-chromen-2-one with bromine water with TBAB (2c)

100 g of 3-acetyl-6-bromo- 2*H*-chromen-2-one was added with excess of bromine dissolved in water and added with catalytic amount of 3 M TBAB. Furthermore reaction mixture was heated on the water bath on shaker for thirty minutes. Further reaction completion primarily identified by TLC in hexane and ethyl acetate mobile phase under UV light. Products were further confirmed by spectroscopic analysis.

Preparation of reagents

Bromine water solution (Br_2/ H_2O): 25 mL of liquid bromine is dissolved in 500 mL of water. It is

used for the bromination of 3-acetyl coumarin.

Iodine dissolved in Potassium Iodide (I_2 / KI) solution: 3 g of potassium iodide is dissolved in 500 mL of water and 1.5 g of granules of Iodine was added in small lots.

3 M Sodium hydroxide solution (NaOH):60 g of sodium hydroxide dissolved in 500 mL of water to prepare 3M sodium hydroxide solution.

3 M Sodium bi carbonate solution ($NaHCO_3$): 126.03 g of sodium bicarbonate dissolved in 500 mL of water to prepare 3 M sodium bicarbonate solution.

3 M Tetra Butyl Ammonium Bromide (TBAB): 30. 0 g of TBAB dissolved in 31.02 mL of water to prepare 3 M TBAB solution.

3 M Sodium Carbonate (Na_2CO_3) solution: 31.77 g of sodium carbonate dissolved in 100 mL water to prepare 3 M sodium Carbonate.

3 M Potassium hydroxide (KOH) solution: 84.165 g dissolved in 500 mL distilled water to prepare 3 M KOH solution.

TLC mobile phase preparation: Prepared mobile phase with the composition 70: 30 ratio Ethyl Acetate and Hexane.

Tetrabutyl ammonium tribromide solid preparation (TBATB): 9.7 g of tetrabutyl ammonium bromide dissolved in 120 mL water, 3.0 g sodium bromate was added in small lots, drop by drop addition of HBr to the reaction mixture until the solidification is started. Reaction mixture is stirred at room temperature until orange colour solid is developed in RB.

Spectroscopic analysis

2-Oxo-2H-chromene-3-carboxylic acid

Ash colour compound. MF: $C_{10}H_6O_4$,Yield: 3-01 g (95%); MP: 209-211°C (Ethyl Acetate): IR (KBr): 1736 cm^{-1} (strong, sharp, -CO- of carboxylic acid); 1614 cm^{-1} (strong, sharp, -CO- of coumarin ring); ^{1}H NMR(400 MHz, DMSO-d6 / TMS): δ = 7.42- 7.84 (complex, m, 4 H, Ar-H), 8.55 (s, 1H,Ar-H of lactone ring), 11.0 (s, -COOH hydrogen). ^{13}C NMR (100 MHz, DMSO-d6/ TMS): 116.1, 118.1, 118.2, 125.4, 127.9, 128.3, 148.5, 153.0, 155.7, 166.2 HRMS calculated for MF: $C_{10}H_6O_4[M+H^+]$: 190.026610 u and observed = 190. 027820 u.

2-Oxo-2H-chromene-3-carboxylic acid

Ash colour compound. MF: $C_{10}H_5BrO_4$, Yield: 2.98 g (94%); MP: 243-245°C (ethyl acetate): IR (KBr): 1736 cm^{-1} (strong, sharp, -CO- of carboxylic acid); 1614 cm^{-1} (strong, sharp, -CO- of coumarin ring); ^{1}H NMR (400 MHz, DMSO-d6 / TMS): δ = 7.39- 8.19 (complex, m, 3 H, Ar-H), 8.45 (s, 1H,Ar-H of lactone ring), 11.0 (s, 1H, -COOH hydrogen). ^{13}C NMR (100 MHz, DMSO-d6/ TMS): 118.1, 118.8, 119.7, 121.5, 124.9, 130.3, 134.5, 152.0, 155.7, 166.7, HRMS calculated for MF: $C_{10}H_5BrO_4$,$[M+H^+]$: 267.932036 u. and observed = 267.027920 u.

3-Oxo-3H-benzo[f]chromene-2-carboxylic acid

Ash colour compound. MF: $C_{14}H_8O_4$, Yield: 2.98 g (94%); MP: 300-310°C (ethyl acetate): IR (KBr): 1736 cm^{-1} (strong, sharp, -CO- of carboxylic acid); 1614 cm^{-1} (strong, sharp, -CO- of coumarin ring); ^{1}H NMR (400 MHz, DMSO-d6 / TMS): δ = 7.42- 8.16(complex, m, 6 H, Ar-H), 8.45 (s, 1H,Ar-H of lactone ring), 11.0 (s, 1-H, -COOH hydrogen). ^{13}C NMR (100 MHz, DMSO-d6/ TMS): 115.5, 117.1, 118.6, 122.3, 123.6, 126.5, 128.9, 128.3, 130.1, 130.3, 148.5, 150.0, 155.7, 166.3, HRMS calculated for MF: $C_{14}H_8O_4[M+H^+]$: 240.057175 u.and observed = 240.057950 u.

7-Hydroxy-2-oxo-2H-chromene-3-carboxylic acid

Ash colour compound. MF: $C_{10}H_6O_5$, Yield: 2.98 g (94%); MP: 382-386°C (ethyl acetate): IR (KBr): 1736 cm^{-1} (strong, sharp, -CO- of carboxylic acid); 1614 cm^{-1} (strong, sharp, -CO- of coumarin ring); ^{1}H NMR (400 MHz, DMSO-d6 / TMS): δ = 5.35 (s, 1-H, -OH), 6.62- 7.57(complex, m, 3 H, Ar-H), 8.45 (s, 1H,Ar-H of lactone ring), 11.0 (s, 1-H, -COOH hydrogen). ^{13}C NMR (100 MHz, DMSO-d6/ TMS): 102.5, 110. 7, 112.1, 130.2, 134.3, 147.6, 157. 3, 158.5, 159.9, 165.3, HRMS calculated for MF: $C_{10}H_6O_5$,$[M+H^+]$: 206.017440 u. and observed = 206. 078960 u.

7-Chloro-2-oxo-2H-chromene-3-carboxylic acid

Ash colour compound. MF: $C_{10}H_5ClO_4$, Yield: 2.98 g (94%); MP: 252-256°C (ethyl acetate): IR (KBr): 1736 cm^{-1} (strong, sharp, -CO- of carboxylic acid); 1614 cm^{-1} (strong, sharp, -CO- of coumarin ring); ^{1}H NMR (400 MHz, DMSO-d6 / TMS): δ = 7.36- 8.02 (complex, m, 3 H, Ar-H), 8.45 (s, 1H,Ar-H of lactone ring), 11.0 (s, 1-H, -COOH hydrogen). ^{13}C NMR (100 MHz, DMSO-d6/ TMS): 118.5, 123. 7, 126.1, 129.2, 131.3, 134.6, 147. 3, 151.5, 159.9, 165.3, HRMS calculated for MF: $C_{10}H_5ClO_4$,$[M+H^+]$: 223.017440 u. and observed = 223.049760 u.

7-Nitro-2-oxo-2H-chromen-3-carboxylic acid

Ash colour compound. MF: $C_{10}H_5NO_6$, Yield: 2.98 g (94%); MP: 267-269°C (ethyl acetate): IR (KBr): 1736 cm^{-1} (strong, sharp, -CO- of carboxylic acid); 1614 cm^{-1} (strong, sharp, -CO- of coumarin ring); ^{1}H

NMR (400 MHz, DMSO-d6 / TMS): δ = 7.36- 8.02(complex, m, 3 H, Ar-H), 8.45 (s, 1H,Ar-H of lactone ring), 11.0 (s, 1-H, -COOH hydrogen). ^{13}C NMR (100 MHz, DMSO-d6/ TMS): 118.5, 123. 7, 126.1, 129.2, 131.3, 134.6, 147. 3, 151.5, 159.9, 165.3, HRMS calculated for MF: $C_{10}H_5NO_6$,[M+H$^+$]: 235.017440 u. and observed = 235.048760 u.

8-Methoxy-2-oxo-2H-chromene-3-carboxylic acid: MF

$C_{11}H_8O_5$, MP calculated: 255-256°C.(ethyl acetate): IR (KBr): 1736 cm^{-1} (strong, sharp, -CO- of carboxylic acid); 1614 cm^{-1} (strong, sharp, -CO- of coumarin ring); ^{1}H NMR (400 MHz, DMSO-d6 / TMS): δ = 3.83 (s, 3H, -OCH$_3$) 7.18- 7.40(complex, m, 3 H, Ar-H), 8.52 (s, 1H,Ar-H of lactone ring), 11.0 (s, 1-H, -COOH hydrogen). ^{13}C NMR (100 MHz, DMSO-d6/ TMS): 55.8, 113.9, 118.5, 120. 7, 121.1, 121.2, 126.3, 140.6, 148.3, 155.5, 166.3, HRMS calculated for MF: $C_{10}H_5NO_6$,[M+H$^+$]:220.017540 u. and observed = 220.058760 u.

Results and Discussions

In continuation to our previous research[28-39], In the initial attempt of haloform reaction, the reaction was started by taking 3-acetyl-6-bromo-2*H*-chromen-2-one (1) and subjected to haloform reactions with various halogenating agents such as bromine water, TBATB and Iodine dissolved in potassium iodide in methanol solvent media with catalytic amount of phase transfer catalyst Tetra Butyl Ammonium Bromide (TBAB) at room temperature reaction conditions in three distinct reaction flasks. Progress of the reaction is monitored by TLC (Scheme 1).

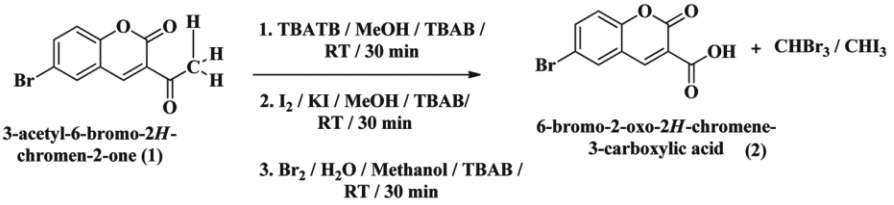
Reaction mechanism of haloform reaction

Haloform reactions are the common identification test for the methyl ketone. Compound **(1)** is treated with halogen and base, methyl ketone is oxidized to the corresponding carboxylic acid under given set of reaction conditions[4] by the formation of haloform as the subsided product (Scheme 2).

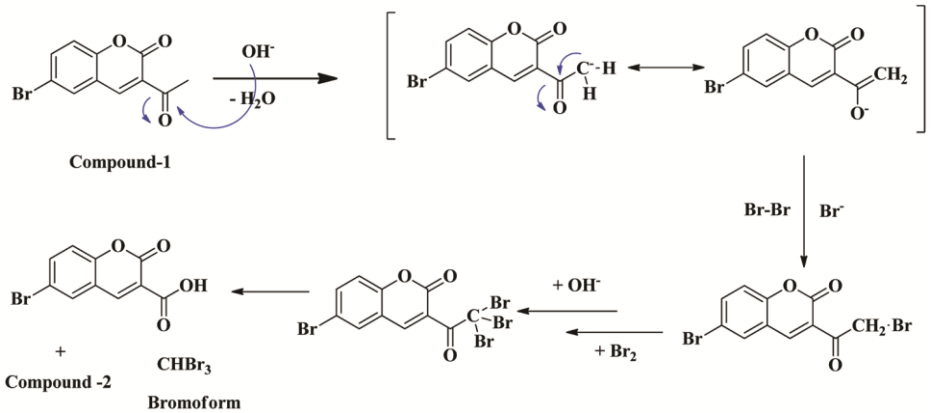
Method development

In addition to the above experiment, it is needed to screen the reaction conditions and yield of the product to develop the facile, multi-component, one-pot reaction under benign conditions. Hence, optimization of reaction conditions were carried in terms of time consumption for the completion of the reaction, reaction conditions, catalyst and yield of the product as shown in the Table 1. Column chart of graphical representation of Reaction condition optimization data substantiated in the Fig. 3.

Based on reaction screening and optimization data, it is confirmed that Br_2/ H_2O under alkaline catalytic conditions at running temperature 298 K is sufficient and superior among all for the synthesis of target compound in high yield under green pathway (Scheme 3).



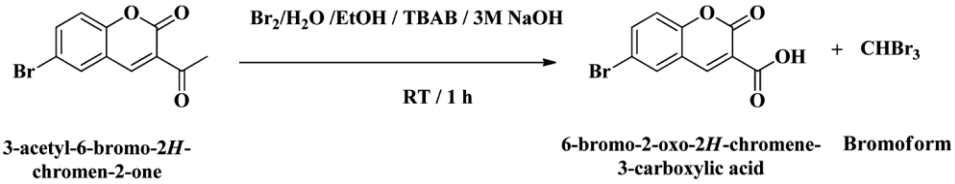
Scheme 1 — Haloform reaction of 3-acetyl-6-bromo-2*H*-chromen-2-one with different halogenating agents



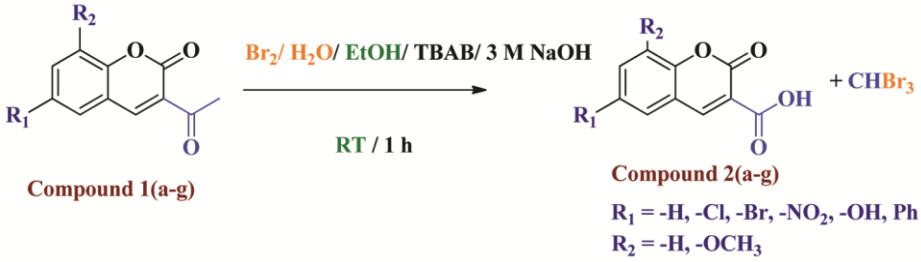
Scheme 2 — Reaction mechanism for the formation of compound (**2**) from compound (**1**)

Table 1 — Optimization of reaction conditions

S. No.	Methyl ketone derivative	Time of the reaction	Reaction conditions	Reagent used	Catalyst	Isolated yield
1	3-acetyl-6-bromo-2*H*-chromen-2-one	60[1]	RT	TBATB	TBAB	60%
2	3-acetyl-6-bromo-2*H*-chromen-2-one -one	60[1]	RT	I_2/KI	TBAB	50%
3	3-acetyl-6-bromo-2*H*-chromen-2-one	60[1]	RT	Br_2/H_2O	TBAB	99%
4	3-acetyl-6-bromo-2*H*-chromen-2-one	4 h	RT	TBATB	NaOH	30%
5	3-acetyl-6-bromo-2*H*-chromen-2-one	4 h	RT	Br_2/H_2O	NaOH	98%
6	3-acetyl-6-bromo-2*H*-chromen-2-one	4 h	RT	I_2/KI	NaOH	20%
7	3-acetyl-6-bromo-2*H*-chromen-2-one	60[1]	RT	TBATB	$NAHCO_3$	NIL
8	3-acetyl-6-bromo-2*H*-chromen-2-one -one	60[1]	RT	I_2/KI	$NAHCO_3$	NIL
9	3-acetyl-6-bromo-2*H*-chromen-2-one	60[1]	RT	Br_2/H_2O	$NAHCO_3$	NIL
10	3-acetyl-6-bromo-2*H*-chromen-2-one	60[1]	RT	TBATB	Na_2CO_3	NIL
11	3-acetyl-6-bromo-2*H*-chromen-2-one -one	60[1]	RT	I_2/KI	Na_2CO_3	NIL
12	3-acetyl-6-bromo-2*H*-chromen-2-one	60[1]	RT	Br_2/H_2O	Na_2CO_3	NIL
13	3-acetyl-6-bromo-2*H*-chromen-2-one	30[1]	Water bath	I_2/KI	TBAB	10%
14	3-acetyl-6-bromo-2*H*-chromen-2-one	30[1]	Water bath	TBATB	TBAB	50%
15	3-acetyl-6-bromo-2*H*-chromen-2-one	30[1]	Water bath	Br_2/H_2O	TBAB	70%



Scheme 3 — Haloform reaction of compound (**1**) to yield corresponding carboxylic acid



Scheme 4 — Accomplishing haloform reaction on compound **1(a-g)** to oxidative product

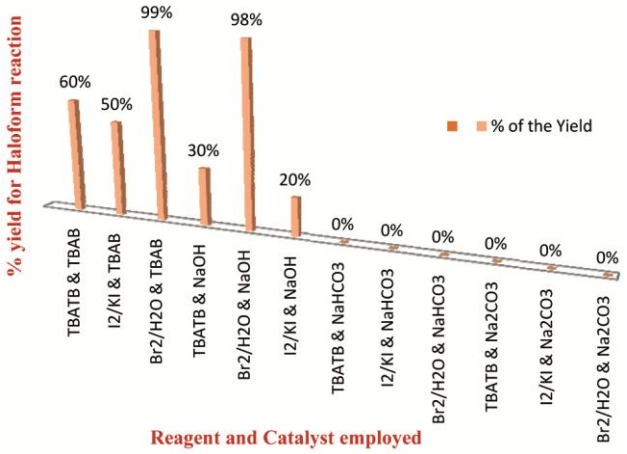


Fig. 3 — Optimization of reaction conditions for haloform reaction of compound (**1**)

Encouraged with above set of optimized reaction conditions and productivity, this methodology was further extended to various derivatives of the 3-acetyl-2*H*-chromen-2-one (**1**) to perform haloform reaction to achieve the product in excellent yield in short reaction time (Scheme 4).

Conclusion

In summary, though haloform reaction is simple and most common in synthetic organic chemistry; no report of reaction on 3-acetyl coumarin was noticed on thorough literature search. Hence in this article, research work is focused on purely benign pathways in order to achieve the target compound. After multiple attempts with various catalysts, solvents and reactions conditions the efficient methodology is

established for the synthesis of target compounds. Among all, it is observed that Br_2/ H_2O under alkaline catalytic conditions at running temperature 298 K is sufficient and superior to rest of the conditions. Hence library of target synthetic analogous were synthesized by the virtue of established methodology. These synthesized scaffolds will become the future research object for extending distinctive applications.

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