ARTICLE

Facile Synthesis of Chromenone from α-Oxoketene Dithioacetal Catalyzed by Trifluroacetic Acid in Aqueous Medium

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ABSTRACT

An efficient chromenone synthesis by two component condensation of α-oxoketene dithioacetal and 2-hydroxy-1-benzaldehyde by catalytic amount of trifluroacetic acid in aqueous medium. The experimental procedure is simple, environmentally benign and gives good to excellent yield of products. This work may not only lead to environmentally benign systems but also will provide a newer aspect of organic chemistry in aqueous medium.

KEYWORDS

Chromenones, α-Oxoketene dithioacetal, Water medium, Trifluroacetic acid.

INTRODUCTION

Chromenone is an oxygen heterocycle widely distributed throughout the plant kingdom [1]. Compound containing the chromenone moiety displays wide-range of biological and therapeutic properties [2-7]. Furthermore, they are used as additives in food, perfumes, cosmetics, optical brighteners and dispersed fluorescent and laser dyes [8], antioxidant [9,10], antimicrobial, anti-HIV therapy [11], antitumor [12] and anticoagulant [13].

Several synthetic strategies are known in the literature for the synthesis of chromenone derivatives like Pechmann [14], Perkin [15], Reformatsky [16], Wittig [17] and Knoevenagel [18] condensation reaction. Many improved methodologies are developed to make these classical reactions efficacious, like variations in terms of catalyst and reaction conditions. However, they usually suffer from harsh reaction conditions and non-environmental friendly solvents. In continuation of our interest in the synthesis of coumarin [19-21], we now report an environmentally benign route for the synthesis of chromenone derivatives starting from a readily available α-oxoketene dithioacetal **2a** and the 2-hydroxybenzaldehydes (salicylaldehyde) **1a** in aqueous medium.

The method described has the benefits of operational simplicity and excellent yields of the targeted molecule. This work may not only lead to environmentally benign system but

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also will provide a newer aspect of organic chemistry in aqueous medium.

EXPERIMENTAL

The melting points were determined on a Mel-temp II laboratory device and are uncorrected. IR spectra were recorded on a Shimadzu IR-408 spectrometer in KBr pellets. ^{1}H NMR spectra were recorded on a Bruker FT-NMR-DRX300 ppm (δ) (300 MHz) and chemical shifts are reported. Analytical thin layer chromatographies (TLCs) were carried out by pre-coated silica gel (E. Merck, Kiesegel 60F254 layer thickness 0.25 mm).

General procedure for synthesis of 3a-k: A mixture of 2-hydroxy-1-benzaldehyde (10 mmol), α-oxoketene dithioacetal (10 mmol) and trifluoroacetic acid (0.2 mmol) was refluxed in aqueous medium for 6 h. The progress of the reaction was monitored by thin layer chromatography and complete transformation was observed in 6 h. The reaction mixture was extracted with ethyl acetate (20 mL) and washed several time with water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude products were subjected to column chromatography using ethyl acetate/ petroleum ether (1:9) as eluent to give the pure product.

3-Benzoyl-2*H*-2-chromenone (3a): Colourless solid; IR (KBr, ν_{max}, cm^{-1}): 3023, 1710, 1620, 1245, 754 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 8.08 (s, 1H), 7.89 (d, 2H), 7.51-7.69 (m, 3H), 7.49 (d, 2H), 7.26-7.49 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 191.6 158.4, 154.7, 145.4, 136.2, 133.8, 133.6, 129.5, 129.2, 128.6, 126.9, 124.9, 118.1, 116.0. Anal. calcd. for $C_{16}H_{10}O_3$: C, 76.79; H, 4.03. Found: C, 76.65; H, 4.01.

3-Benzoyl-6-methyl-2*H*-2-chromenone (3b): Colourless solid; IR (KBr, ν_{max}, cm^{-1}): 3035, 2993, 1721, 1656, 1605, 1248, 686 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 8.03 (s, 1H), 7.88 (d, 2H), 7.28-7.64 (m, 6H), 2.43 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 191.8, 152.9, 145.5, 136.3, 134.8, 134.7, 133.7, 129.6, 128.8, 128.6, 126.9, 117.9, 116.6, 115.4, 20.7. Anal. calcd. for $C_{17}H_{12}O_3$: C, 77.26; H, 4.58. Found: C, 77.35; H, 4.55.

3-Benzoyl-6-chloro-2*H*-2-chromenone (3c): Colourless solid; IR (KBr, ν_{max}, cm^{-1}): 3034, 1725, 1635, 1237, 683 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 7.95 (s, 1H), 7.82 (d, 2H), 7.53-7.62 (m, 2H), 7.46 (d, 2H), 7.43 (br s, 1H), 7.33 (t, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 190.6, 157.3, 153.2, 143.5, 136.0, 133.9, 133.2, 130.2, 129.6, 128.6, 126.7, 128.2, 119.3, 118.4. Anal. calcd. for $C_{16}H_9O_3Cl$: C, 67.50; H, 3.36. Found: C, 67.45; H, 3.36.

3-(4-Methyl benzoyl)-2*H*-2-chromenone (3d): Colourless solid; IR (KBr, ν_{max}, cm^{-1}): 3034, 1713, 1606, 1241, 762 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 8.05 (s, 1H), 7.78 (d, 2H), 7.55-7.68 (m, 2H), 7.31-7.43 (m, 2H), 7.27 (d, 2H), 2.43 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 191.2, 158.3, 155.1, 145.0, 144.9, 133.6, 133.5, 129.8, 129.3, 129.1, 126.9, 124.9, 118.2, 116.9. 21.9.

6-Methyl-3-(4-methyl benzoyl)-2*H*-2-chromenone (3e): Colourless solid; IR (KBr, ν_{max}, cm^{-1}): 3033, 2917, 1715, 1651, 1605, 1252, 781 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 7.99 (s, 1H), 7.78 (d, 2H), 7.8 Hz, 2H), 7.25-7.46 (m, 5H), 2.43 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): 191.4, 158.9, 152.9, 145.1, 144.8, 134.7, 134.6, 133.72, 129.8, 129.3, 128.8, 127.2, 117.9, 116.6, 21.8, 20.7. Anal. calcd. for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07. Found: C, 77.62; H, 5.13.

6-Chloro-3-(4-methyl benzoyl)-2*H*-2-chromenone (3f): Colourless solid; IR (KBr, ν_{max}, cm^{-1}): 3104, 2993, 1725, 1650, 1606, 1287, 775 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 7.92 (s, 1H), 7.74 (d, *J*) 8.1 Hz, 2H), 7.54-7.58 (m, 2H), 7.34 (d, *J*) 8.1 Hz, 2H), 7.26 (d, *J*) 8.4 Hz, 1H), 2.49 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 190.4, 157.5, 153.2, 144.9, 143.2, 133.5, 133.2, 130.2, 129.8, 129.4, 128.9, 128.1, 119.4, 118.4, 21.9. Anal. calcd. for $C_{17}H_{11}O_3Cl$: C, 68.35; H, 3.71. Found: C, 68.47; H, 3.76.

3-(4-Chloro benzoyl)-2*H*-2-chromenone (3g): Colourless solid; IR (KBr, ν_{max}, cm^{-1}): 3059, 1713, 1656, 1608, 1237, 754 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 8.33 (s, 1H), 7.87 (d, *J*) 8.4 Hz, 2H), 7.79 (d, *J*) 7.3 Hz, 1H), 7.68 (t, *J*) 7.3 Hz, 1H), 7.50 (d, *J*) 8.4 Hz, 2H), 7.35-7.43 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 189.8, 157.5, 154.1, 145.5, 138.9, 134.4, 133.2, 130.7, 129.5, 128.4, 125.8, 124.5, 117.9, 116.0. Anal. calcd. for $C_{16}H_9O_3Cl$: C, 67.50; H, 3.19. Found: C, 67.52; H, 3.16.

3-(4-Chloro benzoyl)-6-methyl-2*H*-2-chromenone (3h): Colourless solid; IR (KBr, ν_{max}, cm^{-1}): 3062, 2917, 1713, 1675, 1605, 1243, 765 cm^{-1}; ^{1}H NMR (300 MHz, CDC_{l3}): 8.08 (s, 1H), 7.81 (d, *J*) 8.4 Hz, 2H), 7.48-7.31 (m, 5H), 2.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 190.2, 158.2, 152.4, 145.5, 139.6, 134.5, 134.4, 134.2, 130.4, 128.5, 128.4, 125.7, 117.3, 116.1, 20.2. Anal. calcd. for $C_{17}H_{11}O_3Cl$: C, 68.35; H, 3.71. Found: C, 68.41; H, 3.81.

6-Chloro-3-(4-chloro benzoyl)-2*H*-2-chromenone (3i): Colourless solid; IR (KBr, ν_{max}, cm^{-1}): 3050, 2993, 1725, 1635, 1243, 765 cm^{-1}. ^{1}H NMR (300 MHz, DMSO): 8.37 (s, 1H), 7.95 (d, 2H), 7.94 (br s, 1H), 7.74 (d, 1H), 7.58 (br, 2H), 7.50 (d 1H). ^{13}C NMR (75 MHz, DMSO): 190.2, 157.5, 152.8, 144.4, 138.9, 134.6, 133.0, 131.3, 128.7, 128.6, 128.5, 126.9, 119.6, 118.2. Anal. calcd. for $C_{16}H_8O_3Cl_2$: C, 60.22; H, 2.52. Found: C, 59.89; H, 2.51.

3-(4-Bromo benzoyl)-2*H*-2-chromenone (3j): Colourless solid; IR (KBr, ν_{max}, cm^{-1}): 3033, 1713, 1656, 1608, 1237, 754 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 8.31 (s, 1H), 7.68 (d, 2H), 7.59 (d, 1H), 7.48 (t, 1H), 7.42 (d, 2H), 7.32-7.41 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 190.7, 158.6, 155.2, 144.6, 139.9, 135.4, 134.6, 129.8, 128.7, 127.6, 124.7, 123.4, 117.5, 117.5. Anal. calcd. for $C_{16}H_9O_3Br$: C, 58.38; H, 2.76. Found: C, 58.31; H, 2.16.

3-(2-Thienyl)-2*H*-2-chromenone (3k): Colourless solid; IR (KBr, ν_{max}, cm^{-1}): 3032, 1721, 1655, 1610, 1236, 753 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 8.13 (s, 1H), 7.57 (d, 2H), 7.46 (d, 1H), 7.18-7.12 (m, 2H), 7.10 (t, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 181.7, 153.7, 148.6, 143.9, 138.4, 134.6, 129.8, 128.7, 128.3, 127.1, 125.5, 122.9, 121.7, 120.4. Anal. calcd. for $C_{13}H_8O_2S$: C, 68.40; H, 3.53. Found: C, 68.38; H, 3.43.

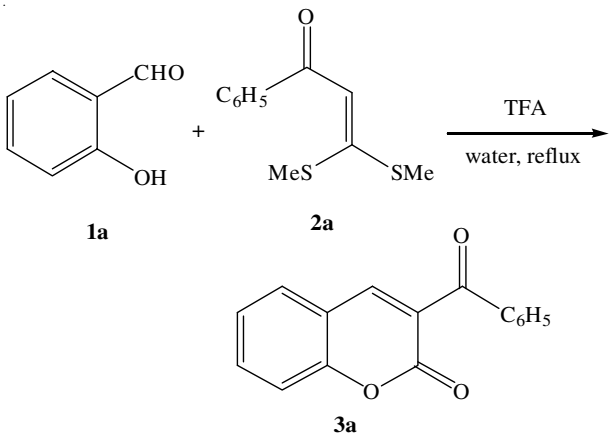
RESULTS AND DISCUSSION

Investigation was initiated by refluxing equimolar amount of 2-hydroxy-1-benzaldehyde (**1a**) and α-oxoketene dithioacetal (**2a**) as the model substrates in aqueous medium by using catalytic amount of 0.2 mmol trifluroacetic acid (TFA), the desired product 3-benzoyl-2*H*-chromen-2-one (**3a**) was obtained in 93 % yield (**Scheme-I**). The reaction was also subjected in

other media like acetronitrile, dimethyl sulfoxide, dichloromethane but no product was obtained. We also attempted under basic condition like triethyamine, aniline, pyrrolidine, morpholine and in absence of any catalyst no product was obtained. By increasing the catalytic amount from 0.2 to 0.3 mmol and prolong refluxing cannot improved the yield of the products (Table-1). Thus we optimized the reaction condition by refluxing in aqueous medium with catalytic amount of 0.2 mmol trifluroacetic acid for 6 h. The same reaction condition was successfully extended to a wide range of α-oxoketene dithioacetal **2b-e** and other variety of 2-hydroxy-1-benzaldehyde **1b-c** to afford the corresponding chromenones **3b-k** in good to excellent yields (Table-2).

All the structures are confirmed from the spectral analysis like IR, ^{1}H NMR, ^{13}C NMR spectra. From IR spectrum, the stretching frequency at 3023 cm^{-1} indicates the presence of aromatic C-H, the peak at 1710 cm^{-1} and 1620 cm^{-1} for two C=O group. In the ^{1}H NMR spectrum the peak at 8.08 ppm indicates the presence of vinvlic protron and in ^{13}C NMR spectrum the peak at 191.6 ppm corresponds to the benzoyl carbonyl and peak at 158.4 ppm correspond to lactone carbonyl.

The α-oxoketene dithioacetals are the three carbon synthon having electrophilic centres and nucleophilic centre. Thus, condensation reaction of α-oxoketene dithioacetal (**2**) with the salicylaldehydes (**1**), having nucleophilic oxygen and electrophilic carbonyl carbon, could result and subsequent hydrolysis and dehydration could lead to 3-aroylchromenones.



1a **2a** **3a**

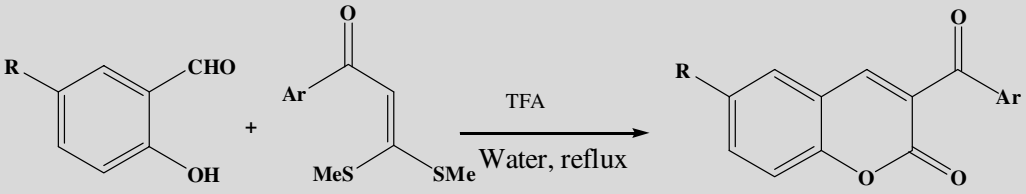
Scheme-I: Synthesis of 3- benzoylchromenone **3a**[a] [[a]Reaction conditions: **1a** (10 mmol), **2a** (10 mmol), trifluoroacetic acid (0.2 mmol), distilled water, reflux, yield of **3a** (93 %)]

Plausible mechanism: The mechanism involved etherification followed by hydrolysis and dethiomethylation to give enolate **B**. The enolate **B** undergo intramolecular Aldol condensation followed by dehydration to give the product.

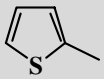
TABLE-1
EVALUATION OF DIFFERENT CATALYTIC SYSTEMS IN OPTIMIZATION OF THE 3-AROYLCOUMARINS SYNTHESIS

Entry	Catalyst (equiv)	Solvent	Yield (%)
1	Trifluroacetic acid (0.2 mmol)	Water	93
2	Trifluroacetic acid (0.3 mmol)	Water	90
3	Trifluroacetic acid (0.2 mmol)	Acetronitrile, DMSO, dichloromethane	No reaction
4	Aniline, pyrrolidine, morpholine,	Water	No reaction
5	No catalyst	–	No reaction
6	Et_3N (0.2 mmol)	Water	No reaction

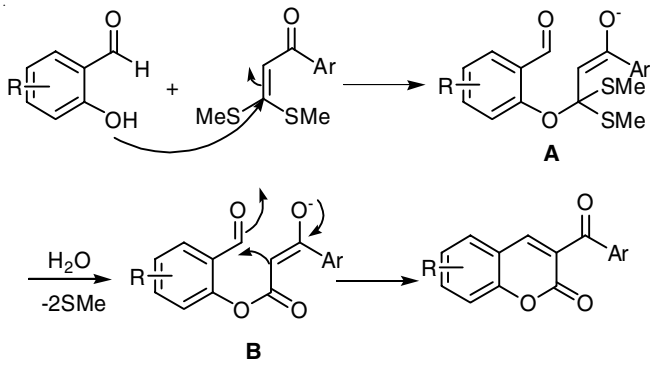
TABLE-2
TRIFLUROACETIC ACID CATALYZED SYNTHESIS OF CHROMENONES (**3a-I**) IN AQUEOUS MEDIUM[a]



1a-c **2a-e** **3a-k**

Entry	Ar	R	Products	Yields
1	C_6H_5	H	**3a**	93
2	C_6H_5	CH_3	**3b**	92
3	C_6H_5	Cl	**3c**	90
4	4-MeC_6H_4	H	**3d**	94
5	4-MeC_6H_4	CH_3	**3e**	93
6	4-MeC_6H_4	Cl	**3f**	91
7	4-ClC_6H_4	H	**3g**	90
8	4-ClC_6H_4	CH_3	**3h**	89
9	4-ClC_6H_4	Cl	**3i**	87
10	4-BrC_6H_4	H	**3j**	93
11		H	**3k**	85

[a]Reaction conditions: **1** (10 mmol), **2** (10 mmol), trifluoroacetic acid (0.2 mmol) under refluxed condition in distilled water



Conclusion

The facile synthesis of different chromenone derivatives by the reaction of 2-hydroxy-1-benzaldehydes is successfully performed with easily accessible α-oxoketene dithioacetals in the presence of catalytic amount of trifluroacetic acid under refluxing condition in aqueous medium. This scheme offers an environmentally benign method for the synthesis of chromenones.

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