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Efficient Synthesis of 3-Substituted Coumarins as Potential Anti-Microbial Agents

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Abstract: **A series of 3-carboxycoumarins and 3-Cyanocoumarins molecules containing coumarin ring structure were synthesized. The synthesized compounds were elucidated by HNMR, CNMR. Many groups of researchers using a number of various methodologies, but some of them are required long reaction time, use of toxic reagents and solvents. Here in, we report our results on the synthesis of 3-carboxycoumarins and 3-Cyanocoumarins by using malonic acid and ethyl 2-cyanoacetate with different substituted Salicylaldehydes in the presence of Potassium 1, 2, 3, 6-Tetrahydrophthalimide catalyst, mild, efficient and easy available reagents in aqueous media.**

Keywords: **Anti-microbial, Efficient, Coumarin, Potassium 1, 2, 3, 6-Tetrahydrophthalimide.**

I. INTRODUCTION

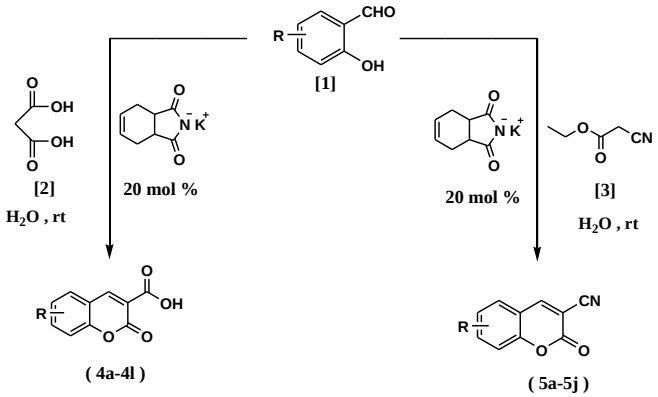
The coumarins are important heterocyclic moiety, present in various bio-active compounds, used as a precursor for synthesis of important organic compounds in the pharmaceutical industry. The coumarins well-known natural product which contains oxygen heteroatom and isolated from many plants (Kostova et al., 2005). In addition coumarins containing *carboxyl* and *cyano* groupin heterocyclic frameworknamely 3-carboxycoumarins and 3-Cyanocoumarins, represents a significant class of biologically valuable pharmacological compounds such as antimicrobial (Zaha et al., 2002) antifungal (Sardari et al., 2000), anti-HIV (Kashman et al., 1992) and tumour growth in vivo (Chimenti et al., 2004) and Antioxidant activity (Kontogiorgis et al., 2003).Their metal complexes of these biologically active compounds are also known and possesses good biological properties. Many of these 3-substituted coumarins are very well-known products that exhibit a broad range of properties like anti-inflammatory (Melagraki et al., 2002), analgesic (Khode et al., 2009), antibacterial (Creaven et al., 2010), anticancer (Reddy et al., 2004), and anticoagulant (Kidane et al., 2004), agents. A broad range of coumarins typically used as the purpose of some insecticides (Brahmachari et al., 2015), fragrances and perfumes (Frosch et al., 2002), vasorelaxants (Vilar et al., 2006). Some coumarins derivatives are used as photo chemotherapeutic drugs for psoralen plus ultraviolet-A-radiation therapy (Dalla et al., 2002). It was also reported that 3-substituted coumarins includes some other properties such as preventing asthma and antisepsis (Cao et al., 1998), agrochemicals, and pesticides (Egan, et al., 1990) .The synthesis of these potential pharmacologically active 3-substituted coumarins carried out in the laboratory by many groups of researchers using a number of various methodologies. Some of reported and reaction proceeds via well-known reactions pathway Perkin (Johnson, et al., 2004), Knoevenagel (Brufola, et al., 1996), and Claisen reactions (Cairns et al., 1994). These syntheses carried out the reaction between different substituted salicylaldehydes with compound containing active methylene group in the reactants. Various synthetic methodologies have been reported recent years to provide 3-substituted coumarins and its derivatives which involve Stannous Chloride (Karami, et al., 2012), heterocyclic base piperidine (Bogdał et al., 1998), ammonium chloride (Valizadeh, et al., 2005), ammonium acetate in reaction medium (Scott, et al., 2000), piperidinium acetate catalyse reaction also reported (Song, et al., 2003) . Apart from this use of some ionic liquid technique and exchange resins (Valizadeh, 2007; De et al., 1999), Lithium perchlorate and lithium bromide catalyzed synthesis (Bandgar, et al., 2002), using choline chloride/urea (Harishkumar, et al., 2011), potassium phosphate (Undale, et al., 2012), alkali as aqueous form (Fringuelli, et al., 2003), propylphosphonic anhydride (Augustine, et al., 2012), L-Histidine and L-arginine (Rahmati et al., 2010), and some

inorganic metals Zirconyl chloride octahydrate (Bardajee, et al., 2010), Calcium oxide (Lu, et al., 2004), in the presence of magnesium oxide or zinc oxide (Moison et al., 1987), give desired synthesis of 3- substituted coumarins and its derivatives.

Water is one of the most abundant, environmentally benign solvent, and widely used as solvent in various reactions. In recent years, need of new methodologies which includes, simple, facile, recyclable catalysts, eco-friendly solvent, atom economy, low reaction costs, easy handling of reactions are preferred in synthetic organic chemistry.1, 2, 3, 6-tetrahydrophthalimide is a commercially available, chemical compound and its potassium salt prepared in laboratory and can be used as base in appropriate conditions (Pandey, et al., 2018). Considering above valuable facts and applications our group reported the synthesis of 3-carboxycoumarins and 3-Cyanocoumarins derivatives catalysed by Potassium 1, 2, 3, 6-Tetrahydrophthalimide in aqueous media at room temperature.

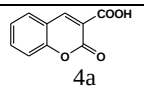
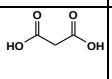
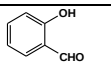
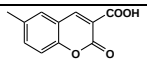
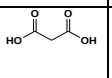
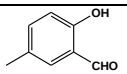
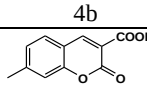
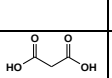
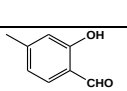
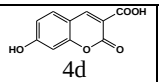
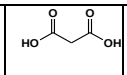
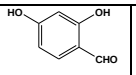
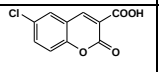
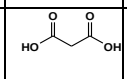
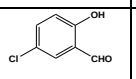
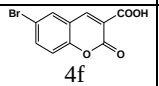
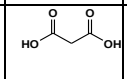
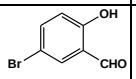
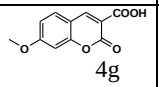
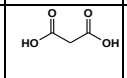
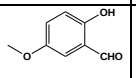
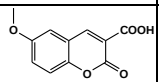
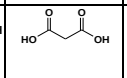
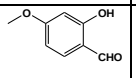
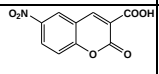
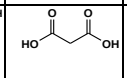
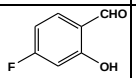
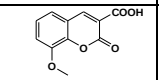
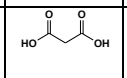
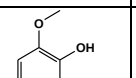
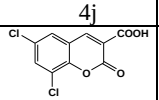
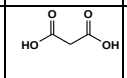
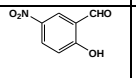
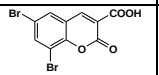
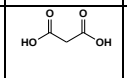
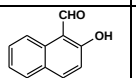
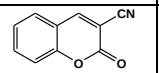
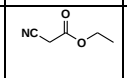
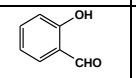
II. Manuscript Organization

In general, manuscripts may contain Title, Authors' names, Affiliation, E-mail address, Abstract, Keywords, Introduction, Literature Survey, Proposed Approach, Results and Discussion, Conclusion, Experimental Section, Acknowledgments, References and Endnotes. However, authors can organize the contents of the manuscript according to their requirements.



Reaction Scheme

Table 1. synthesised compounds and their physical analysis

Entry	**Product**	**Reactant**	**Reactant**	**Yield (%)**	**mp˚C**
1.	 4a			95	191-193
2.	 4b			93	168-170
3.	 4c			90	169-171
4.	 4d			91	260-262
5.	 4e			95	117-119
6.	 4f			90	198-200
7.	 4g			93	194-196
8.	 4h			91	193-195
9.	 4i			98	201-203
10.	 4j			89	194-196
11.	 4k			92	200-202
12.	 4l			93	241-243
13.	 5a			94	180-182
14.	5b			90	201-203
15.	5c			89	226-228
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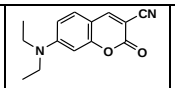
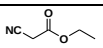
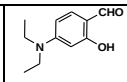
17.	5e			92	246-248
18.	5f			94	229-231
19.	5g			91	190-192

20.	 5h			92	210-212

III. MATERIALS AND METHODS

All the chemicals and reagents were obtained from commercial sources Avera Chemicals Pvt Ltd and Sigma Aldrich and used without further purification. Melting points are uncorrected and were determined in open capillaries. IR spectra were recorded using Perkin Elmer model-446 FTIR in KBr. ^{1}HNMR (Nuclear Magnetic Resonance) 400 MHz and ^{13}CNMR 100 MHz spectra were recorded on a Bruker DRX-500 Avance spectrometer in CDCl3, as a solvent, at appropriate temperature. The chemical shifts are given relative to tetramethylsilane (TMS) as internal standard and values are expressed in ppm. The reaction progress was monitored and the purity of compounds was monitored by TLC on silica gel.

A. General Procedure for The Synthesis of 3-Substituted Coumarins

An equimolar mixture (1mmol), of substituted salicylaldehydes and ethyl cyanoacetate/malonic acid mixed with appropriate amount ofpotassium 1, 2, 3, 6-tetrahydro - phthalimide in 5 ml of water (table2). The reaction mixture was stirred at room temperature for the time mentioned (1-5hr). The completion of reaction monitored with TLC, product was filtered collected and washed with cold water. Product purified with hot ethanol, the yield of desired products were between 85-95%.

Table 2. Optimization table of experiments

Entry	**Catalyst (mol %)**	**Time (h)**	**Temperature (□C)**	**Water: ethanol**	**Yield (%)**
1.	5	5	40	5:5	40
2.	10	5	40	5:5	50
3.	15	5	40	5:5	55
4.	20	5	40	5:5	60
5.	20	5	40	water	70
6.	30	5	40	water	80
7.	30	6	Rt	water	85
8.	20	5	Rt	water	95
9.	25	5	Rt	water	90

Impact of catalyst, time, temperature, and water in synthesis of substituted coumarins.

B. Supporting Information

2-oxo-2H-chromene-3-carboxylic acid: (4a)

IR (KBr, cm^{-1}): 3450, 1755, 1690, 1615, 1564, 1483, 1260; ^{1}H-NMR(400 MHz, DMSO-d6, δ ppm):7.14 (t, J = 8.4, 7.6 Hz 2H), 7.68 (d, J = 8.4 Hz 1H), 7.84 (d, J = 8.4 Hz1H), 8.80 (, s 1H), 13.06 (bs, 1H). ^{13}CNMR(100 MHz, DMSO-d6, δ ppm): 115.94, 117.75, 117.84, 124.67, 129.82, 134.84, 148.52, 154.10, 156.75, 163.74;

6-methyl-2-oxo-2H-chromene-3-carboxylic acid: (4b)

IR (KBr, cm^{-1}): 3450, 3040, 1750, 1698, 1618, 1562, 1485, 1250; ^{1}HNMR(400 MHz, DMSO-d6,δppm) 2.48 (s,3H);7.28(dd,J=8.2,1.8Hz,1H),7.44(d,J=8.2Hz,1H),7.60(d,J=1.8Hz,1H),8.56(s,1H),13.46(bs,1H) ^{13}CNMR(100 MHz, DMSO d6,δppm):21.63,116.30,118.15,118.68,130.23,134.54,135.54,148.67, 153.08, 157.26, 164.65;

7-Methyl-2-oxo-2H-chromene-3-carboxylic Acid: (4c)

IR (KBr, cm^{-1}): 3050−2750, 1746, 1677, 1628, 1560, 1425, 1228; ^{1}HNMR(400 MHz, DMSO-d6, δ ppm): 2.46 (s, 3H), 7.28 (d, J = 8 Hz, 1H), 7.32 (s, 1H), 7.78 (d, J = 8 Hz, 1H), 8.84 (s, 1H), 13.25 (bs, 1H).^{13}CNMR(100 MHz, DMSO-d6, δ ppm): 21.62, 116.35, 118.21, 118.55, 130.13, 134.55, 135.68, 148.68, 153.13, 157.26, 164.40;

7-hydroxy-2-oxo-2H-chromene-3-carboxylic acid: (4d)

IR (KBr, cm^{-1}):3635, 3385, 3280, 30554, 1750, 1677, 1614, 1564, 915, 856, 752; ^{1}HNMR(400 MHz, DMSO-d6, δ ppm): 11.05 (br s, 1H), 8.62 (s, 1H),7.69 (d, J = 8.8 Hz, 1H), 6.80 (dd, J = 8.8 and 2.4 Hz,1H), 6.68(d, J = 2.0Hz, 1H); ^{13}CNMR(100 MHz, DMSO-d6, δ ppm): 164.65, 164.32, 158.04 ,157.38, 149.80, 132.43, 114.39, 112.74 ,111.20 , 102.25;

6-chloro-2-oxo-2H-chromene-3-carboxylic acid: (4e)

IR (KBr, cm-1):3500−3340, 3048, 1749, 1690, 1625, 1565, 1474, 1262 ^{1}HNMR(400 MHz, DMSO-d6, δ ppm): 7.44 (d, J = 8 Hz, 1H), 7.72 (dd, J = 8, 1.8Hz, 1H), 8.08 (d, J = 1.8 Hz, 1H), 8.70 (s, 1H), 13.40 (bs, 1H):13C-NMR(100MHz,DMSO-d6,δppm):117.78,119.21,119.20,128.27,128.88,133.40,147.19,152.92,156.20,163.54;

6-Bromo-2-oxo-2H-chromene-3-carboxylic acid: (4f)

IR (KBr, cm^{-1}):3510−3320, 3047, 1752, 1692, 1610, 1550, 1474, 1268; ^{1}HNMR(400 MHz, DMSO-d6, δ ppm): 7.42, (d, J = 8 Hz, 1H), 7.73 (d, J = 8 Hz, 1H), 8.08 (s 1H), 8.62 (s, 1H), 13.29 (bs, 1H); ^{13}CNMR(100 MHz, DMSO-d6, δ ppm): 116.34, 118.62, 119.50, 123.52, 131.16, 131.19, 147.05, 153.27, 159.23, 163.36;

7-Methoxy-2-oxo-2H-chromene-3-carboxylic Acid: (4g)

IR (KBr, cm^{-1}): 3185, 3043, 1744, 1692, 1622, 1562, 1478, 1260; ^{1}HNMR(400 MHz, DMSO-d6, δ ppm): 4.03, (s, 3H), 7.16 (m, 2H), 7.94 (d, J = 8 Hz, 1 H), 8.88 (s, 1H), 13.24 (bs, 1H). ^{13}CNMR(100 MHz, DMSO-d6, δ ppm): 165.15, 164.50, 157.66, 157.29, 149.40, 131.88, 114.22, 113.62, 112.05, 100.64, 56.60;

6-Methoxy-2-oxo-2H-chromene-3-carboxylic Acid: (4h)

IR (KBr, cm^{-1}): 3520−3240, 3042, 1748, 1692, 1620, 1562, 1480, 1268; ^{1}HNMR(400 MHz,DMSO-d6, δ ppm): 3.83 (s, 3H); 6.94 (dd, J = 8, 1.6 Hz, 1H), 7.06 (d, J = 1.6 Hz, 1H), 7.47 (d, J = 8 Hz, 1H), 8.62 (s, 1H), 13.22(bs, 1H). ^{13}CNMR(100 MHz, DMSO-d6, δ ppm): 164.42, 157.43, 156.15, 149.26, 148.40, 122.48, 118.82, 118.72, 117.58, 112.18, 56.20;

6-nitro-2-oxo-2H-chromene-3-carboxylic acid: (4i)

IR (KBr, cm-1): 3458, 3053, 2934, 1754, 1678, 1625, 1564, 1228, 1078, 856, 7545; ^{1}HNMR(400 MHz, DMSO-d6, δ ppm): 8.86 (d, *J* = 2.4 Hz, 1H), 8.76 (s, 1H), 8.42 (dd, *J* = 2.4, 2.8 and 9.0 Hz, 1H), 7.68(d, *J* = 9.2 Hz, 1H); ^{13}CNMR(100 MHz, DMSO-d6, δ ppm): 164.04, 158.46, 155.46, 146.38 ,144.14, 128.45, 126.25 , 122.15, 118.88, 118.14;

8-Methoxy-2-oxo-2H-chromene-3-carboxylic Acid: (4j)

IR (KBr, cm^{-1}): 3520−3245, 3024, 2984, 2948, 1754, 1681, 1600, 1584, 1478 ^{1}HNMR(400 MHz, DMSO-d6, δ ppm): 3.91

(s, 3H), 6.88 (t, J = 8.4 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 8.61 (s, 1H), 13.15 (bs, 1H). ^{13}CNMR(100 MHz, DMSO-d6, δ ppm):165.15, 164.54, 157.63, 157.22, 149.44, 131.89, 114.32, 113.58, 112.21, 100.56, 56.66;

6, 8-dichloro-2-oxo-2H-chromene-3-carboxylic acid: (4k)

IR (KBr, cm^{-1}):3478, 3059, 2930, 1758, 1696, 1615, 1453, 1214, 988; ^{1}HNMR(400 MHz, DMSO-d6, δ ppm): 8.16 (d, J = 2.4 Hz 1H), 8.26 (d, J = 2.4 Hz 1H), 8.69 (s, 1H), 13.48 (bs, 1H). ^{13}CNMR(100 MHz, DMSO-d6, δ ppm): 110.49, 116.66, 120.49, 121.38, 132.22, 138.62, 147.31, 150.80, 155.74, 163.85;

6, 8-dibromo-2-oxo-2H-chromene-3-carboxylic acid: (4l)

IR (KBr, cm-1):3480, 3068, 2927, 1763, 1694, 1619, 1454, 1218, 988; ^{1}HNMR(400 MHz, DMSO-d6, δ ppm): 8.16 (d, J = 2.4 Hz 1H), 8.22 (d, J = 2.4 Hz 1H), 8.69 (s, 1H), 13.52 (bs, 1H). ^{13}CNMR(100 MHz, DMSO-d6, δ ppm): 110.48, 116.67, 120.45, 121.39, 132.12, 138.62, 147.20, 150.86, 155.70, 163.84;

2-oxo-2H-chromene-3-carbonitrile: (5a)

IR (KBr, cm^{-1}): 2233, 1717, 1648; ^{1}HNMR(400 MHz, DMSO-d6, δ ppm): 7.32 (m, 2H), 7.58 (dd, *J* = 7.46, 1.62 Hz, 1H), 7.74 (dd, *J*= 7.54, 1.45 Hz, 1H), 8.31 (s, 1H). ^{13}CNMR(100 MHz, DMSO-d6, δ ppm): 103.52, 112.05, 117.15, 117.03, 128.10, 128.25, 135.05, 152.10, 155.20, 156.08;

6-Bromo-2-oxo-2H-chromene-3-carbonitrile: (5b)

IR (KBr, cm^{-1}): 2333, 1754, 1648;^{1}HNMR(400 MHz, DMSO-d6, δ ppm): 7.18 (d, *J*= 7.36 Hz, 1H), 7.38 (dd, *J*= 7.36,1.96 Hz, 1H), 7.46 (d, *J*= 1.96 Hz,1H), 8.80 (s, 1H); ^{13}CNMR(100 MHz, DMSO-d6, δ ppm): 105.50, 114.33, 116.05, 120.10, 128.16, 131.15, 138.07, 152.25, 157.90, 160.32;

8-Methoxy-2-oxo-2H-chromene-3-carbonitrile:(5c)

IR (KBr, cm^{-1}): 2255, 1748, 1641; ^{1}HNMR(400 MHz, DMSO-d6, δ ppm): 3.92 (s, 3H), 7.23–7.42 (m, 3H), 8.86 (s, 1H); ^{13}CNMR(100 MHz, DMSO-d6, δ ppm): 67.10, 11.25, 102.23, 115.58, 116.27, 120.58, 127.89, 132.13, 137.68, 153.53, 158.92, 160.34;

7-Methoxy-2-oxo-2H-chromene-3-carbonitrile. (5d)

IR (KBr, cm^{-1}): 2229, 1726, 1638;^{1}HNMR(400 MHz, DMSO-d6, δ ppm): 3.93 (s, 3H), 7.12 (dd, J= 8.71, 2.39 Hz, 1H), 7.14 (d, J= 2.39 Hz, 1H), 7.78 (d, J= 8.71 Hz, 1H), 8.86 (s, 1H); 13CNMR(100 MHz, DMSO-d6, δ ppm): 63.75, 105.55, 115.35, 116.68, 120.23, 127.84, 130.34, 137.76, 153.56, 158.30, 159.20;

7-Hydroxy-2-oxo-2H-chromene-3-carbonitrile. (5e)

IR (KBr, cm^{-1}):3398, 2229, 1720, 1635; ^{1}HNMR(400 MHz, DMSO-d6, δ ppm): 7.14 (dd, J= 8.85, 2.41 Hz, 1H),7.16 (d, J= 2.41 Hz, 1H), 7.79 (d, J= 8.85 Hz, 1H), 8.76 (s,1H), 8.81 (s, 1H);^{13}CNMR(100 MHz, DMSO-d6, δ ppm): 104.28, 114.48, 117.80, 121.20, 128.10, 133.35, 138.65, 154.54,159.50, 161.50;

8-Hydroxy-2-oxo-2H-chromene-3-carbonitrile: (5f)

IR (KBr, cm^{-1}): 3384, 2255, 1745, 1640;^{1}HNMR(400 MHz, DMSO-d6, δ ppm): d 7.20–7.35 (m, 3H), 8.74 (s, 1H), 8.87(s, 1H);^{13}CNMR(100 MHz, DMSO-d6, δ ppm): 104.56, 114.43, 115.33, 119.90, 128.05, 131.13, 136.95, 152.28, 157.02, 160.35;

7-Diethylamino-2-oxo-2H-chromene-3-carbonitrile (5g)

IR (KBr, cm^{-1}): 2220, 1715, 1642; ^{1}HNMR(400 MHz, DMSO-d6, δ ppm): 1.24 (t,J= 6.87 Hz, 6H), 3.44(q, J= 6.86 Hz, 4H), 6.45 (d, J = 2.3 Hz, 1H), 6.62 (dd, J= 8.89, 2.45 Hz, 1H), 7.32 (d, J= 8.89 Hz,1H), 7.99 (s, 1H); ^{13}CNMR(100 MHz, DMSO-d6, δ ppm): 15.25, 56.64, 105.55,115.35, 116.630, 120.24, 127.86, 130.34, 137.78, 153.58,158.34, 159.15;

IV. Results And Discussion

A general, efficient method the synthesis of some 3-carboxycoumarins and 3-Cyanocoumarins by using malonic acid and ethyl 2-cyanoacetate with different substituted Salicylaldehydes in the presence of Potassium 1,2,3,6-Tetrahydrophthalimide catalyst, mild, efficient and easy available reagents in aqueous media. The present investigation focused various solvent and temperature mentioned in optimisation table. The synthesis was conducted using water and ethanol in appropriate ratio which gives different yields in different conditions and temperature which results desired products in good yields. The best results obtained in the solvent water at room temperaturein20mol% catalyst Potassium 1,2,3,6-Tetrahydrophthalimid.On increasing the mol % of catalyst Potassium 1,2,3,6-Tetrahydrophthalimide at room temperature from 20 mol% to 25 mol% the observed results give lower yields

Conclusions

We have demonstrated a rapid and an efficient synthetic route for potassium 1, 2, 3, 6-tetrahydrophthalimide catalyzed synthesis of 3-carboxycoumarins and 3-Cyanocoumarins in water as solvent at room temperature. The current technology has the advantages of operational simplicity, and neither used hazardous materials, nor metal are required to this synthesis provide good to high yield of products.

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