The Pharma Innovation Journal 2018; 7(1): 123-127

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2018; 7(1): 123-127

www.thepharmajournal.com
Received: 15-11-2017
Accepted: 19-12-2017

Santosh G Badne1
Department of Chemistry
Shri Shivaji College of Arts, Commerce and Science, Akola, Maharashtra, India

Gajanan W Belsare
Department of Chemistry
Shri Shivaji College of Arts, Commerce and Science, Akola, Maharashtra, India

Correspondence
Santosh G Badne1
Department of Chemistry
Shri Shivaji College of Arts, Commerce and Science, Akola, Maharashtra, India

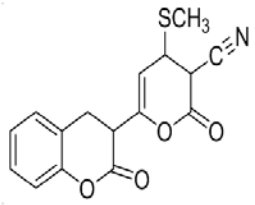
A study of newly synthesized via green chemistry approach towards 4-methylsulfanyl-2-oxo-6-(-2-oxo-2-h chromene-3-yl)-2h pyran-3-carbonitrile and their derivatives and antibacterial activities

Santosh G Badne1 and Gajanan W Belsare

Abstract
3-actyl coumarin was prepared by a well known name reaction Knovengel reaction in basic condition. A mixture of Salicylaldehyde and ethyl acetoacetate was mixed and piperdine was added into that mixture slowly. This mixture was stirred well and kept at freezing temperature for 2-3 hours. A yellow coloured Solid was separates out. In addition to that we have been planned to synthesize a new heterocyclic compound 4-methylsulfanyl-2-oxo-6-(-2-oxo-2-H Chromene-3-yl)-2H pyran-3- Carbonitrile (I) by reaction of 3-acetyl coumarin with ethyl-2-cyano,3,3-bismethyl thioacrylate in prescence of KOH without solvent only by constant grinding at room temperature for 3- 4 Hours. Solid separates out with appreciable yield. Thereafter it has been planned to synthesize 4-substitued derivatives. The parent compound which will show the nucleophillic substitution reaction at 4-position. The derivative was prepared by the reaction of parent Compound (I) and Substituted Anilines, Phenols Nitro Compounds etc.

Keywords: Coumarin, Bismethyl Thioacrylate, Carbonitrile, Aniline, phenols.

1. Introduction
Coumarin and its derivatives represents one of the most active classes of compounds possessing a wide spectrum of biological activity. [3] Coumarins also have the super thermal stability and outstanding optical properties including extended spectral response, high quantum yields and superior photo stability. Optical applications of these compounds such as laser dyes nonlinear optical chromophores, fluorescent whiteners, fluorescent probes, polymer science, optical recording and solar energy collectors have been widely investigated. Compounds containing a coumarin moiety display a broad spectrum of biological activities such as antimicrobial, antifungal, anti-coagulant, anti-HIV and insecticidal properties. Classical routes to coumarins incorporate Pechman, Knoevenagel, Perkin, Reformatsky, and Wittig condensation reactions.

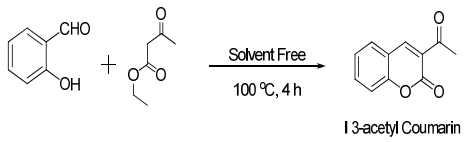


4-methylsulfanyl2-oxo--6-(2-oxo-2H-chromen-3-yl)-2H-pyran-3-carbonitrile

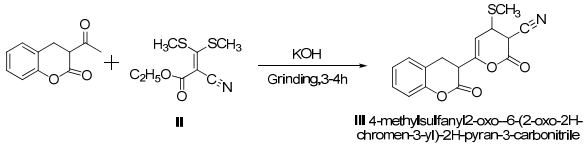
The synthesis of 3-substituted coumarin was particularly accomplished by the century old Knoevenagel reaction consisting of the condensation between 2-hydroxy benzaldehydes and active methylene compounds which was originally catalysed by weak bases under homogeneous reactions conditions. 3-acetyl coumarin was prepared by a Knoevenagel reaction in basic condition. A mixture of salicyldehyde and ethyl aceto acetate was mixed and piperidine was added into the mixture. This mixture was stirred well and kept at freezing temperature for 2-3 h. A yellow colour solid will separate out which when was recrystalised with alcohol. In our synthesis of parent compound, we use the Ethyl 2-cyano-3,3-bis

(methylthio) acrylate reagent. Ethyl 2-cyano-3, 3-bis (methylthio) acrylate was prepared by the reaction of ethyl cyano acetate, carbon disulfide and dimethyl sulphate in the presence of a base. The electron attracting groups on C2 position makes it very useful reagent for the preparation of hetrocyclic compounds. Moreover, Ethyl 2-cyano-3, 3-bis (methylthio) acrylate can also be prepared efficiently using sodium ethoxide as a base. We prepare Ethyl 2-cyano-3,3-bis (methylthio) acrylate reagent by using ice cold solution of KOH in 10 ml water and 30 ml DMF was added with cooling and stirring 0.1 mol. of ethyl cyano acetate followed 0.1 mol. of CS_2. The mixture was stirred for one hour at room temperature, cooled and treated drop wise addition with 0.1 mol. of dimethyl sulphate maintaining the temperature at >5 °C. The reaction mixture was allowed to stand at room temperature for 12 h and poured into ice cold water. The solid obtained was filtered washed with water dried and recrystalised from ethanol. Heterocyclic compounds have shown many excellent biological activities in both area of medicine and pesticide. The synthetic method is one of the focused fields concerning pharmaceutical and pesticidal researches at present. With the theme of green synthesis, some advantages of organic solvent-free heterocyclic synthesis in high yield, good selectivity and easy operation, low cost and environmental friendship were introduced. And the developments in the recent four years of solvent-free reaction in heterocyclic synthesis study have been reviewed.

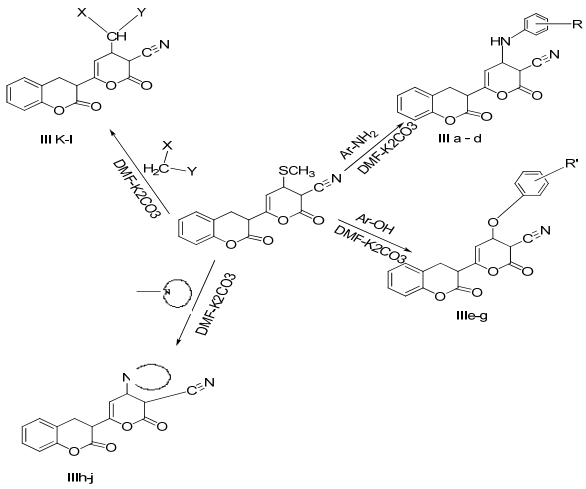
Scheme 1



Scheme 2



Scheme 3: Synthetic protocol of newly synthesized 4-methylsulfanyl2-oxo--6-(2-oxo-2H-chromen-3-yl)-2H-pyran-3-carbonitrile derivatives



Organic synthesis under solvent-free conditions has been an area of growing interest because solvents are often expensive, hazardous, difficult to remove in case of solvents with high boiling points, and are agents that pollute the environment. Unfortunately many of the solvents are used in synthesis are volatile organic compounds (VOCs) which lead to environmental damage, through pollution, risks to human health and to resource depletion, we need to develop and apply more environmentally friendly approaches. Due to enormous advantages of solvent free reactions, new solvent free approaches are being discovered for eco-friendly synthesis of many compounds. In view of Green Chemistry approach, the solvent free reaction of 3-Acetyl coumarins with ethyl -2-cyano-3, 3- bis (methyl thio)-acrylate in presents of aq. KOH gave corresponding 3-(2-oxo-4-methylsulfanyl-2H-pyran-3-carbonitrilo) coumarins, Structures of all the compounds has been confirmed on the basis of their IR, NMR and mass spectral data and has been screened for their antimicrobial activity.

2. Experimental section

2.1 Material and Methods

Chemicals: Chemicals used in the synthesis of the titled compounds were purchased from SpectroChem and Research lab. They were N,N dimethyl formamide, KOH, conc. HCl, acetic acid substituted aromatic aldehydes, Piperidine, ethyl cyano acetate, dimethyl sulphate, substituted amine, aniline, phenols and active methylene compound.

2.2 Instruments and Software

The melting points of the organic compounds were determined by open capillary in a heavy liquid paraffin bath. FT-IR spectra were recorded on Bruker spectrophotometer by using KBr pellets. **1**HNMRspectra were recorded on sophisticated multinuclear NMR Spectrometer Brucker Ascend 500 with TMS as an internal standard DMSO-d6 used as Solvent and Mass spectra were recorded on Mass spectrometer of Bruker, from Department of Chemistry, Shri Shivaji College, Akola, Indian Institute of Chemical Technology Hyderabad and CDRI Lucknow.

2.3 Typical procedure for the preparation of 3-acetyl-2-*H*-chromene-2-one (I)

A mixture of ortho-hydroxy benzaldehyde (1.0 mmol) and ethyl acetoacetate (1.0 mmol) and Starch sulphuric acid (40 mg) was stirred at 100 °C temperatures under solvent free conditions for 4 h. The reaction progress was monitored by TLC using hexane:ethyl acetate (4:6) as the mobile phase. After completion of the reaction, the reaction mixture was mixed with hot ethanol (5 ml) and filtered. Starch sulphuric acid was recovered by filtration after the addition of ethanol to the stirred reaction mixture. Conventional elemental analysis showed the presence of sulfur, indicating sulfur had not leached out. Filtrate was cooled in ice to obtain pale yellow colored 3-acetyl coumarin with 95% yield; m.p. = 121–124 °C. ^{1}H NMR (400 MHz, DMSO-d_6, *ô* ppm, J Hz) 2.58 (s, 3H, ACOCH3), 7.44–7.78 (m, 4H, Ar-H), 8.64 (s, 1H, pyran-H). MS: m/z (%) 389.24 (M++1, 100%) base peak.

2.4 Procedure for the one-pot preparation of 4-methylsulfanyl 2-oxo--6-(2-oxo-2H-chromen-3-yl)-2H-pyran-3-carbonitrile (III) towards a green approach

In this context it has been planned to synthesize a new heterocyclic compound, 4-methyl sulfanyl-2-oxo-6-(2-oxo-2H-chromen-3yl)-2H-pyran-3-carbonitrile(III) by reaction of

3-acetyl-2-*H*-chromene-2-one with ethyl-2-cyano-3, 3-bismethyl thioacrylate in presence of aqueous KOH with constant grinding at room temperature for 3-4 h. The reaction progress was monitored by TLC using hexane: ethyl acetate (4:6) as the mobile phase. After completion of the reaction, the reaction mixture was keep it for overnight on the next day solid which get separated out was dried in air with 80% yield; m.p. = 193–195 ºC.I.R 3161 cm^{-1} Hetero Ar- Stretch 705 cm^{-1};Aliphatic C-H Streach;1887 cm^{-1} C-S Stretch; 1668 cm^{-1} C=O Stretch; 2247 cm^{-1} C ≡ N Stretch 1711 cm^{-1} (C=O of ester), 1064 cm^{-1} (C-O) ^{1}H NMR (400 MHz, DMSO-d_6, d ppm, J Hz) 2.09 (s, 2H, SCH3), 7.02–7.09 (, Ar-H), 3.64 (s, 1H, methyne H). MS: m/z (%) 309.04 (M+1, 100%) base peak.

2.5 Synthesis of 2-oxo--6-(2-oxo-2H-chromen-3-yl)-4-phenylamino-3, 4 dihydro-2*H*-pyran-3-carbonitrile derivatives (IIIa-d)

The parent compound which will show the substitution reaction at 4-position consist of replicable methylthio group at 4-position. The derivative was prepared by refluxing the mixture of 4-methyl sulfanyl-2-oxo-6-(2-oxo-2H-chromen-3yl)-2H-pyran-3-carbonitrile and 4 substituted aniline/4-nitro aniline/4-hydroxy aniline/4-chloro aniline(III a-d) in presence of solvent DMF and catalyst anhydrous K_2CO_3, refluxing oil bath >160 ºC temperature for 4-5 h. Cool it at room temperature, then pour in ice cold water and filter. Solid Separates out and dry. With more than 80% yield; and found difference in melting point. I.R spectrum shows the absence of –SCH3 stretch.

2.6 Synthesis of 2-oxo--6-(2-oxo-2H-chromen-3-yl)-4-phenoxy-3,4-dihydro 2*H*-pyran-3-carbonitrile (III e-g)

The parent compound which will show the substitution reaction at 4-position consist of replicable methylthio group at 4-position. The derivative was prepared by refluxing the mixture of 4-methyl sulfanyl-2-oxo-6-(2-oxo-2H-chromen-3yl)-2H-pyran-3-carbonitrile and phenoxy compounds phenol /4-nitro phenol/4-chloro phenol

(IIIe-g) in presence of solvent DMF and catalyst anhydrous K_2CO_3, refluxing oil bath >160 ºC temperature for 4-5 h. Cool it at room temperature, then pour in ice cold water and filter. Solid Separates out and dry. With more than 80% yield; and found difference in melting point. I.R spectrum shows the absence of –SCH3 stretch. IR (KBr): 2209 cm^{-1} (CN), 1711 cm^{-1} (C=O of ester), 1694 cm^{-1} (cyclic C=O)

2.7 Synthesis of 2-oxo--6-(2-oxo-2H-chromen-3-yl)-4—N-Heteryl-3,4-dihydro 2*H*-pyran-3-carbonitrile (III h-i)

Similarly the other N-heteryl derivatives of compound **(III)** were prepared by the reaction of compound 4-methyl sulfanyl-2-oxo-6-(2-oxo-2H-chromen-3yl)-2H-pyran-3-carbonitrile independently with morpholine and piperdine to yield compounds (III-h-i). With more than 80% yield; and found difference in melting point. I.R spectrum shows the absence of –SCH_3 stretch. IR (KBr): 2216 cm^{-1} (CN), 1708cm^{-1} (C=O of ester), 1683 (cyclic C=O)

2.8 Synthesis of 2-oxo--6-(2-oxo-2H-chromen-3-yl)-4—active methylene compound-3, 4-dihydro 2*H*-pyran-3-carbonitrile (IIIj-l)

Similarly treatment of compound (III) with other compounds containing active methylene group like ethyl cyano acetate, ethyl acetoacetate and malononitrile afforded corresponding 4-substituted derivatives (III-j-l) of compound (III). The structures of these newly synthesized compounds were confirmed by elemental analysis, IR, ^{1}H-NMR and Mass spectral data. IR(KBr) : 2209 cm^{-1} (CN), 1711 cm^{-1} (C=O of ester), 1694 cm^{-1} (cyclic C=O), 1077 cm^{-1} (C-O)

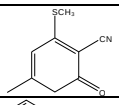
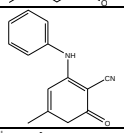
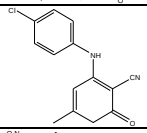
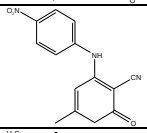
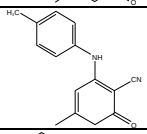
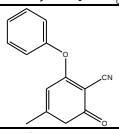
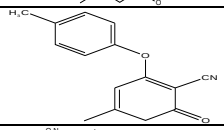
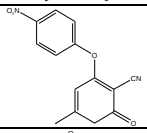
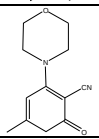
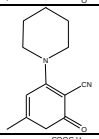
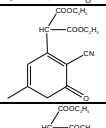
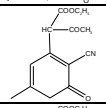
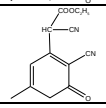
3. Result and Discussion

In summary of novel series of 4-methyl sulfanyl-2-oxo-6-(2-oxo-2H-chromen-3yl)-2H-pyran-3-carbonitrile derivatives were synthesized. The employed green chemistry method offers high reaction yields, short reaction time and mild conditions. The reaction progressed smoothly and provided excellent yields in all cases. All synthesized compounds were easily purified and recrystlized from respective solvents. The purity of the compound was confirmed by TLC and elemental analysis. Furthermore, a biological activity of the 4-substituted derivatives shows good to excellent antibacterial and anti fungal inhibitory activities. The structure of the final products were well characterized by using spectral (IR, 1H NMR, and MS) and elemental analysis data.IR spectra shows characteristic peaks of these derivatives with 2200-2235 cm^{-1} corresponding to CN, while 1705-1730 cm-1 exhibited the cyclic ester of the coumarin nucleus and another observed between 1060-1150 cm^{-1} was assigned to C-O stretching frequency. The ^{1}H NMR spectrum of DMSO exhibited a singlet nearer 5.19 ppm, which was attributed to the- SCH_3 group, another characteristic peak of these derivatives showed nearer to 7.9 ppm which indicated a proton of the pyran nucleus. Peaks between 7.02–7.09 ppm were observed for respective aromatic protons. The ESIMS spectra of the compound (IIIa-l), show corresponding (M+1) peak and (M+2) peak in the case of aniline, phenoxy, active methylene compound and chloro substituted compounds. We hypothesized that mechanistically the reaction has the green chemistry approach, proceeds through the substitution reaction between the 2^O carbon of 3, 3-bis methyl thio acrylate and attacks the carbon cation of the 3-acetyl group of coumarin, at a time when a ring transformation takes place. This processes occurred due to the presence of KOH as the catalyst. The third step was synthesis of derivatives, and for synthesis of derivatives here we had use K_2CO_3 as catalyst and the reaction is on controlled temperature. In the parent compound at 4 positions Methylthio group is the best leaving group therefore it shows the substitution type reaction with this removal of methyl thio group and we substitute various substituted Anilines, phenols, Active methylene compounds and N-heteryl derivatives we had synthesized.

4. Biological Evaluation

All newly synthesized 4-methylsulfanyl2-oxo-6-(2-oxo-2H-chromen-3-yl)-2H-pyran-3 carbonitrile derivatives (III a-l) were examined for antimicrobial activity against two gram positive bacterial strains(staphylococcus aureus, Pseudomonas aeroginosa) two gram negative bacterial strains (Escherichia coli) as well as three fungal strains (Aspergillus clavatus and Aspergillus Niger) using the agar agar dilution method Chlorampinicol were used as slandered controlled drug for antibacterial activity, whereas Nystain were used as slandered control drugs for antifungal activity.

Table 1

Sr. No.	Compounds	Zone of inhibition in mm		
		Escherichia coli	***Staphylococcus aureus***	***Pseudomonas aeroginosa***
1		*14mm*	*16mm*	*10.5mm*
2		*12mm*	*13mm*	*9mm*
3		*11mm*	*12mm*	--
4		*12mm*	*14mm*	*10mm*
5		*13mm*	*16mm*	*12mm*
6		*12mm*	*13mm*	*10.7mm*
7		*11mm*	--	*11mm*
8		*13mm*	*14mm*	*10mm*
9		*14mm*	*15mm*	*11mm*
10		*15mm*	*17mm*	*13mm*
11		*13mm*	*14mm*	*11mm*
12		*14mm*	*16mm*	*12mm*
13		*13.03mm*	*14mm*	--
14	*Chlorampinicol*	*15mm*	*18mm*	*13mm*

5. Conclusion

The screening results revealed that the compounds 3a-l showed significant antimicrobial activity. In particular compounds 3d and 3k showed moderate to considerable antibacterial and antifungal activities against all the organisms and are comparable to that of standard drugs Chloramphenicol respectively.

6. Acknowledgment

We are grateful to the Principal of Shri Shivaji College of Arts, Commerce and Science, Akola for their guidance and providing laboratory facilities for our research work. We also thankful of Analyst of CDRI Lucknow to provide me facilities of NMR and Mass.

7. References

1. Ram VJ, Singha UK, Guru PY. Chemotherapeutic agents XI: synthesis of pyrimidines and azolopyrimidines as leishmanicide, European Journal of Medicinal Chemistry. 1990; 25(6):533-538.
2. Yoshinori Tominaga. Synthesis of heterocyclic compounds using ketene dithioacetals Trends in Heterocyclic Chemistry. 1991; 2:43-83.
3. Patil, VS, Nadre KP, Ghosh S, Rao VJ, Chopade BA, Bhosle SV *et al.* Synthesis and glycosidase inhibitory activity of novel(2-phenyl-4H-Benzopyrimido[2,1-b]-thiazole-4-yliden)acetonitrile derivatives. Bioorg. Med. Chem. Lett. 2012; 22:7011-7014.
4. Rajesh H, Vekariya Kinjal D, Patel Smita D, Rajani, Hitesh D, Patel A. one pot three component synthesis of coumarin hybrid thiosemicarbazone derivatives and their antimicrobial evolution;; Journal of the Association of Arab Universities for Basic and Applied Sciences. 2017; 23:10-19.
5. Anastas PT, Kichhoff M. Origins Current Status and future challanges of Green Chemistry Acc.Chem Res. 2002; 35:686.
6. Arora RB, Mathur CN. Relationship between structure and Anti-Coagulant Activity of Coumarin Derivatives; British Journal of pharmacology. 1963; 20:29-35.
7. VishnuJi Ram, Pratibha Srivastava, Atul Goel. Synthesis of bridged head azolo[3,2-a]pyrimidines and imidazo[2,1-b]thiazines through ring transformation of 2H-pyran-2-ones;; Tetrahedron. 2003; 59(36):7141-7146
8. Shrihari P, Sanap, Sougata Ghosh, Amit M, Jabgunde, Rahul V *et al.* Dhavale Synthesis, computational study and glycosidase inhibitory activity of polyhydroxylated conidine alkaloids—a bicyclic iminosugar. Organic & Biomolecular Chemistry. 2010; 8(14):3307.
9. Rajendra Prasad Y, Ravi Kumar P, Asha Deepti CH, venkata ramana M. Synthesis and Antimicrobial Activity of Some Novel Chalcones of 2-Hydroxy -1-Acetonapthone and 3-Acetyl Coumarin. E-Journal of Chemistry. 2006; 3(4):236-241.
10. Raviraj A, Kusanurmanjunath Ghatemanohar V, Kulkarni. Synthesis of spiro[indolo-1,5-benzodiazepines] from 3-acetyl coumarins for use as possible antianxiety agents. 2004; 116(5):265-270.
11. Nageswara Sastry VD, Seshadri, TR. Reactivity of the double bond in coumarins and related unsaturated carbonyl compounds Proceedings of the Indian Academy of Sciences – Section A July 1942.