Research Journal of Chemical Sciences ISSN 2231-606X
Vol. **2(8),** 21-25, August **(2012)** *Res.J.Chem.Sci.*

DABCO Promoted Multi-Component one-pot Synthesis of Xanthene Derivatives

Paliwal Pradeep, Jetti Srinivasa Rao and Jain Shubha*
Laboratory of Heterocycles, School of Studies in Chemistry and Biochemistry, Vikram University, Ujjain-456010, INDIA

Available online at: www.isca.in
Received 10th April 2012, revised 21st April 2012, accepted 28th April 2012

Abstract

The reaction of dimedone with various heteroaryl aldehydes afforded the corresponding heteroaryl substituted xanthene derivatives. Reaction proceeds via initial Knoevenagel, subsequent micheal and final heterocyclization reactions using 1,4-diazabicyclo(2.2.2)octane (DABCO) as catalyst. Short reaction time, environmentally friendly procedure, no need to use cumbersome apparatus for the purification of the products and excellent yields are the main advantages of this procedure which makes it more economic than the other conventional methods.

Keywords: Multi-component, DABCO, Xanthene.

Introduction

In the past few decades, the synthesis of new heterocyclic compounds has been a subject of great interest due to the wide applicability of them. The importance of multi-component reactions in organic synthesis has been recognized, and considerable efforts have been focused on the design and development of one-pot procedures for the generation of libraries of heterocyclic compounds[1-2]. Multi-component reactions (MCRs) have emerged as an important tool for building of diverse and complex organic molecules through carbon-carbon and carbon-heteroatom bond formations taking place in tandem manner[3]. Particularly, in the last three decades a number of three and four-component reactions have been developed[4,5].

Xanthene derivatives are very important heterocyclic compounds and have been widely used as dyes[6] and fluorescent materials for visualization of bio-molecules and laser technologies due to their useful spectroscopic properties[7]. They have also been reported for their agricultural bactericide activity[8,9], anti-flammatory effect[10] and antiviral activity[11]. These compounds are also utilized as antagonists for paralyzing action of zoxazolamine and in photodynamic therapy[12]. Due to their wide range of applications, these compounds have received a great deal of attention in connection with their synthesis.

A wide variety of methods for the preparation of the xanthenes have been reported[13-19]. However, many of these methods are associated with several short comings such as long reaction times (16 h to 5 days), expensive reagents, harsh conditions, low product yields, and use of toxic organic solvents. Diazabicyclo [2.2.2] octane (DABCO) is an inexpensive, non toxic and commercially available catalyst that can be used in laboratory without special precautions[20-22]. But, it has not been used much as a catalyst in xanthene synthesis, only a few reports are therein the literature[23-25]. This promoted us to develop a new synthetic method for heteroaryl substituted xanthenes using DABCO as a catalyst.

We have been interested in the synthesis of heterocyclic systems[26] and application of DABCO in organic synthesis[27]. In this article, we wish to report a facile condensation of heteroaryl aldehyde (**1**) or 5,5'-dimethyl**-**1,3-cyclohexanedione (dimedone, **2**), and in the presence of a catalytic amount of DABCO to produce a variety of 1,8-Dioxo-octahydroxanthenes derivatives in excellent yields scheme-1.

Material and Methods

The chemicals used in the synthesis of the octahydroxanthene-1, 8-diones were obtained from the Merck and Aldrich Chemical Co. All chemicals and solvents used for the synthesis were analytical reagent grade. Reactions were monitored by thin layer chromatography on 0.2 mm silica gel F-252 (Merck) plates. Melting points were determined by open capillary method and were uncorrected. ^{1}H (400 MHz) and ^{13}C (200 MHz) spectra were recorded on Bruker3000 NMR spectrometer in CDCl3/DMSO-d_6 (with TMS for ^{1}H and $CDCl_3$ as internal references) unless otherwise specified stated. The electro spray mass spectrum was recorded on a MICROMASS QUATTRO II triple quadraupole mass spectrometer.

General procedure for the synthesis of heteroaryl substituted xanthenes: A mixture of 5-membered, heteroarylaldehyde **1** (1 mmol), 5, 5-dimethylcyclohexane-1, 3-dione **2** (2 mmol) and DABCO (0.05 g) in H_2O (20 mL) was refluxed for 30 minutes table-1. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature and the solid filtered off and washed with H_2O. The crude product was purified by recrystallization from 95% ethanol.

2,2,5,5-Tetramethyl-9-(furan-2-yl)-3,4,5,6,7,9-hexahydro-1*H* -xanthene-1,8(2*H*)-dione (3a): This compound was obtained as white solid. m.p. 168-169^{0}C; ^{1}H NMR (400 MHz, CDCl3) δ: 1.0148 (s, 6H, 2×CH3), 1.0844 (s, 6H, 2×CH3), 2.2355 (s, 4H, 2×CH2), 2.4251 (s, 4H, CH2), 4.9415 (s, 1H, CH), 6.1594-6.1817 (m, 2H, ArH), 7.1338-7.1393 (d, 1H, ArH); IR ν: 3071 (Ar-H), 2845 (C-H), 1730 and 1673 (C=O), 1602 (C=C), 1180

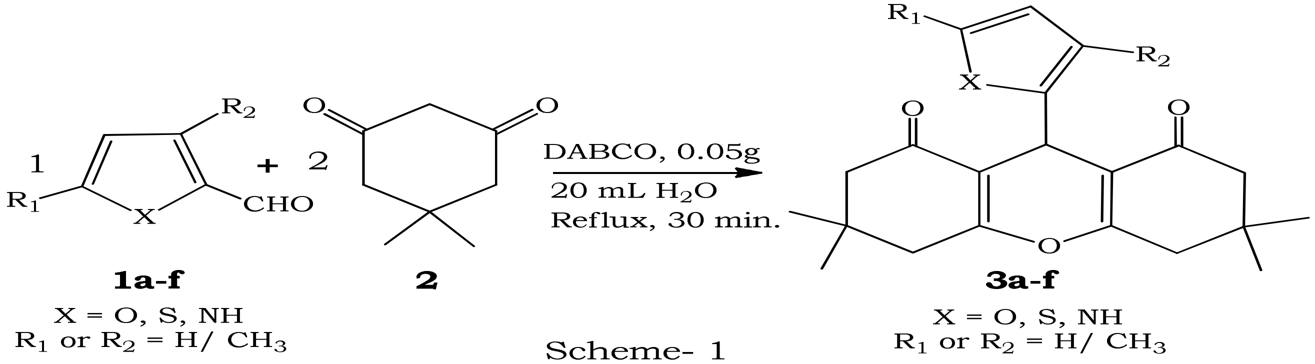
(COC) cm^{-1}. EI-MS (*m/z*): 340 (M^+). Anal. calcd for $C_{21}H_{24}O_4$: C 74.09, H 7.11; found C 74.03, H 7.07.

2,2,5,5-Tetramethyl-9-(3-methyl, thiophen-2-yl)-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (3d): This compound was obtained as white solid. m.p. 156-157°C; 1H NMR (400 MHz, CDCl3) δ: 1.100 (s, 12H, 4×CH3), 3.035 (s, 3H, Ar-CH3), 2.281 (s, 4H, 2×CH2), 2.544 (s, 4H, 2×CH2), 4.875 (s, 1H, CH), 6.478 (d, 1H, ArH), 6.824 (d, 1H, ArH),; IR ν: 3042 (Ar-H), 2963 (C-H), 1730 (C = O), 1607 and 1588 (C=C), 1150 (C-O-C) cm^{-1}. EI-MS (*m/z*): 370 (M^+). Anal. calcd for $C_{22}H_{26}O_3S$: C 71.32, H 7.07, S 8.65; found C 71.28, H 7.09, S 8.69.

2,2,5,5-Tetramethyl-9-(1*H*-pyrrol-2-yl)-3,4,5,6,7,9-hexahydro -1*H*-xanthene-1,8(2*H*)-dione (3f): This compound was obtained as white solid (ethanol-H_2O). 88-90°C m.p.; ^1H NMR (400 MHz, CDCl3) δ: 1.0188-1.1460 (m, 12H, 4×CH3), 2.1545 (br s, 8H, 4×CH2, 5.6014 (s, 1H, CH), 6.9571-6.9708 (s, 1H, ArH), 6.6982-6.7108 (d, 1H, ArH), 9.5708 (br s, 1H, NH), 6.1628 (dd, 1H, ArH); IR ν: 3397, 3328 (N-H), 3065 (Ar-H), 2978 (C-H), 1680 (C = O), 1604 and 1469 (C = C), 1145 (COC) cm^{-1}. EI-MS (*m/z*): 339 (M^+). Anal. calcd for $C_{21}H_{25}NO_3$: C 74.31, H 7.42, N 4.13; found C 74.26, H 7.46, N 4.15.

Results and discussion

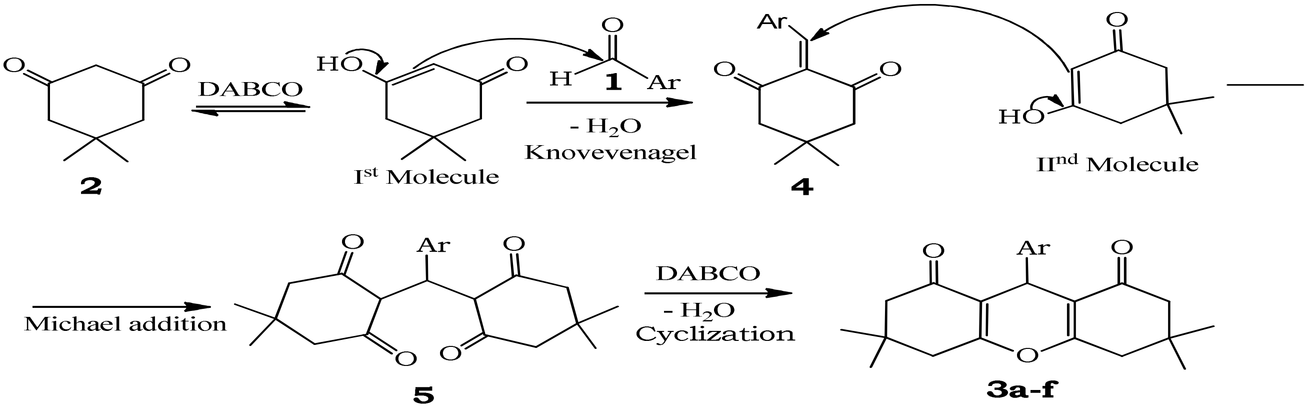
The formation of the compound 3 was assumed to proceed via formation of a Knoevenagel product which on addition of IInd molecule to give Michael adduct intermediate followed by cyclization according to scheme-2. A α,α'-bis(arylidene) cycloalkanones 4 was firstly condensed with dimedone 2 to afford the intermediate 5 on addition of IInd molecule of dimedone, this step can be regarded as a Michael addition. Then, the intermediate 5 cyclized by nucleophilic attack of the OH group on the C=C moiety and gave the intermediate 6. Finally, the expected product 3 was afforded.



Scheme- 1

Table-1
Synthesis of heteroaryl substituted xanthenes using of 0.05g DABCO

Entry	Aldhyde	Time (min.)	Product	Yield (%)	M.p.(°C)
1	Furfural(1a)	30	3a	94	168-169
2	5-methyl, furfural(1b)	30	3b	92	158-160
3	Thienaldehyde(1c)	30	3c	95	142-144
4	3-methyl, thienaldehyde(1d)	30	3d	96	156-157
5	5-methyl, thienaldehyde(1e)	30	3e	94	145-147
6	Pyrrol-2-caroxaldehyde(1f)	30	3f	87	88-90



Scheme- 2

To optimize the catalytic system, the synthesis of (**3d**) from the condensation of 3-methyl, thiophen-2-carboxaldehyde and dimedone in water was used as a model reaction. Firstly, we study the relation between the rate of the model reaction and the best results were obtained in water table-2.

Table-2
Effect of various solvents on xanthene synthesis

Entry	Solvent	Yield (%)
1	Ethanol	93
2	Methanol	81
3	ACN	62
4	Ethyl Acetate	74
5	Water	96

a)Reaction of 3-methyl, thienaldehyde **1d** (1 mmol) and dimedone **2** (2 mmol) in presence of 0.05g DABCO base catalyst after 30 min. reflux.

The best catalytic activity of DABCO was optimized to be 0.05g and any excess of the catalyst, beyond this proportion, did not show further increase in the conversion and yield. The optimized conditions were used for the synthesis of 3, 4, 6-tetrahydro-3,3,6,6-tetramethyl-9-heteroaryl-2H-xanthane-1,8 (5H,9H)-dione derivatives. It was found that this method is effective with a variety of substituted heteroaryl aldehydes independently of the nature of the substituent on the aromatic ring tables-3.

Table-3
Effect of various amount of DABCO catalyst on xanthenes synthesis

Entry	Amount of DABCO^a	Yield (%)^b
1	No catalyst	Trace
2	0.01 g	87
3	0.02 g	90
4	0.03 g	90
5	0.04 g	94
6	0.05 g	96
7	0.10 g	93

a) Reaction of 3-methyl, thienaldehyde **1d** (1 mmol) and dimedone **2** (2 mmol) in presence of different amount of DABCO base catalyst under reflux condition. b) Isolated yield after 30 min. reflux.

Conclusion

In summary, we have reported a high yielding, simple, convenient, straight forward and practical one-pot procedure for the synthesis of **3**a-f in aqueous media. All starting materials are readily available from commercial sources. Moreover, there is no need for dry solvents or protecting gas atmospheres. Using DABCO as catalyst offers advantages including simplicity of operation, easy work-up, time minimizing, and high yields of products. The procedure is very simple and can be used as an alternative to the existing procedures.

Acknowledgement

The authors are thankful to Director, SAIF, IIT Mumbai for spectral analysis and Dr. Asutosh K. Pandey, Depatment of Environment and polymer Science National Chemical Laboratory, Pune (Maharashtra) for valuable suggestions.

References

1. Orru R.V.A. and Greef M., Recent advances in solution-phase multicomponent methodology for the synthesis of heterocyclic compounds, *Synthesis*, 1471-1499 **(2003)**
2. Domling A., Recent developments in isocyanide-based multicomponent reactions in applied chemistry, *Chem. Rev.*, **106**, 17-89 **(2006)**
3. Domling A. and Ugi I., Multicomponent reacitons with isocyanides, *Angew. Chem. Int. Ed.*, **39**, 3168-3210 **(2000)**
4. Masquelin T., Bui H., Stephenson G., Schwerkoske J. and Hulme C., Sequential Ugi/Strecker reactions via microwave assisted organic synthesis: novel 3-center-4-component and 3-center-5-component multi-component reactions, *Tetrahedron Lett.* **47**, 2989-2991 **(2006)**
5. Djandé A., Kiendrébéogo M., Compaoré M., Kaboré L., Nacoulma G.O., Aycard J. and Saba A., Antioxidant potential of 4-acyl isochroman-1,3-diones, *Res. J. Chem. Sci.,* **1(5)**, 88-90 **(2011)**
6. Menchen S.M., Benson S.C., Lam, J.Y.L., Zhen, W., Sun D., Rosenblum B.B., Khan S.H. and Taing M.U.S. *Patent*, US 6583168 **(2003)**
7. Knight C.G. and Stephens T., Xanthene-dye-labelled phosphatidylethanolamines as probes of interfacial pH, *Biochem J.*, **258,** 683-689 **(1989)**
8. Bhattachary A.K., Rana K.C., Microwave assisted synthesis of 14-aryl-14*H*-dibenzo[a,j] xanthenes catalysed by *p*TSA in solution and solvent-free conditions, *Mendeleev Commun.*, **17**, 247-248 **(2007)**
9. Mulongo G., Mbabazi J., Odongkara B., Twinomuhwezi H. and Mpango G.B., New biologically active compounds from 1, 3-Diketones, *Res. J. Chem. Sci.*, **1(3)**, 102-108 **(2011)**
10. Karimi-Jaberi Z. and Hashemi M.M., One step synthesis of 14-alkyl- or aryl-14H-dibenzo[a,j]xanthenes using sodium hydrogen sulfate as catalyst, *Monatsh. Chem.*, **139**, 605-608 **(2008)**
11. Seyyedhamzeh M., Mirzaei M. and Bazgir A., Solvent-free synthesis of aryl-14H-dibenzo[a,j]xanthenes and 1,8-Dioxo-octahydro-xanthenes using silica sulfuric acid as catalyst, *Dyes Pigm.*, **76**, 836-839 **(2008)**
12. Sirkecioglu O., Talinli N. and Akar A., Chemical aspects of santalin as a histological stain, *J. Chem Res (S)*, 502 **(1995)**

13. Wang J.Q. and Harvey R.G., Synthesis of polycyclic xanthenes and furans via palladium-catalyzed cyclization of polycyclic aryltriflate esters, *Tetrahedron*, **58**, 5927-5931 **(2002)**

14. Stetler H. and Forest W., New Methods of Preparative Organic Chemistry, Academic Press NY, **2**, 51-54 **(1963)**

15. Casiraghi G., Casnati G., Catellani M. and Corina M.A.A., Convenient one-step synthesis of xanthene derivatives, *Synthesis,* 564-564 **(1974)**

16. Anand S., Shallu G., Poonam G. and Sharma R.L., Synthetic studies of some varied structural systems of biologically potent polynitrogen heteropolycyclics, *Ind. J Chem.* **49B**, 1243-1256 **(2010)**

17. Majid M.H., Hamideh A., Khadijeh B., Mina S., Hossein A.O. and Fatemeh F.B., Solvent-free synthesis of xanthenes derivatives by preyssler type heteropolyacid, *Bull. Chem. Soc. Ethiop.*, **25(3)**, 399-406 **(2011)**

18. Muharrem K., Aldol Condensation and Michael Addition of 4,4-Dimethylcyclohexane-1,3-dione and Aromatic Aldehydes, Unconventional Substituent Effects, *Chinese Journal of Chemistry*, **29**, 2355–2360 **(2011)**

19. Ilangovan A., Malayappasamy S., Muralidharan S. and Maruthamuthu S., A highly efficient green synthesis of 1, 8-dioxooctahydroxanthenes, *Chemistry Central Journal*, **5**, 81-86 **(2011)**

20. Baghernejad B., 4-Diazabicyclo [2,2,2] octane (DABCO) as a useful catalyst in organic synthesis, *European Journal of Chemistry*, **1(1)**, 54-60 **(2010)**

21. Hua Y., Rui T., Ye L., Organic reactions catalyzed by 1,4-diazabicyclo [2.2.2] octane (DABCO), *Frontiers of Chemistry in China*, **3(3)**, 279-287 **(2008)**

22. Da-Zhen X., Yingjun L., Sen S. and Yongmei W., A simple, efficient and green procedure for Knoevenagel condensation catalyzed by [C_4dabco][BF_4] ionic liquid in water, *Green Chem.* **12**, 514-517 **(2010)**

23. Bigdeli M., Clean synthesis of 1,8-dioxooctahydroxanthenes promoted by DABCO-bromine in aqueous media, *Chinease Chemical Letters*, **21**, 1180-1182 **(2010)**

24. Saeed B., Sorour R., Morteza B. and Jurgen H.G., DABCO-catalyzed efficient synthesis of naphthopyran derivatives via One-Pot three-component condensation reaction at room temperature, *Synth. Commun.*, **38(7),** 1078-1089 **(2008)**

25. Ka Y.L., Jeong M.K. and Jae N.K., Synthesis of 2,3,4, 4a-Tetrahydroxanthen-1-ones and 3,3a-dihydro-2H cyclopenta[b]chromene-1-ones from the reaction of salicylaldehyde and 2-cyclohexen-1-one and 2-cyclopenten-1-one, *Bull. Korean Chem. Soc.,* **24(1)**, 17-18 **(2003)**

26. Jain S., Babu G.N., Jetti S.R., Harshada S. and Suryaprakash D., Synthesis, antitubercular and antifungal activities of heteroaryl -substituted oxirance derived from Baylis - Hillman adducts, *Med Chem Res.* (In press), doi:10.1007/s00044-011-9802-2 (**2011**)

27. Jain S., Paliwal P. and Babu G.N., DABCO promoted one-pot synthesis of dihydropyrano(*c*)chromene and pyrano[2,3-*d*]pyrimidine derivatives and their biological activities, *J Saudi Chem. Soc.,* (In press) http://dx.doi.org/10.1016/j.jscs.2011.10.023 (**2011**)

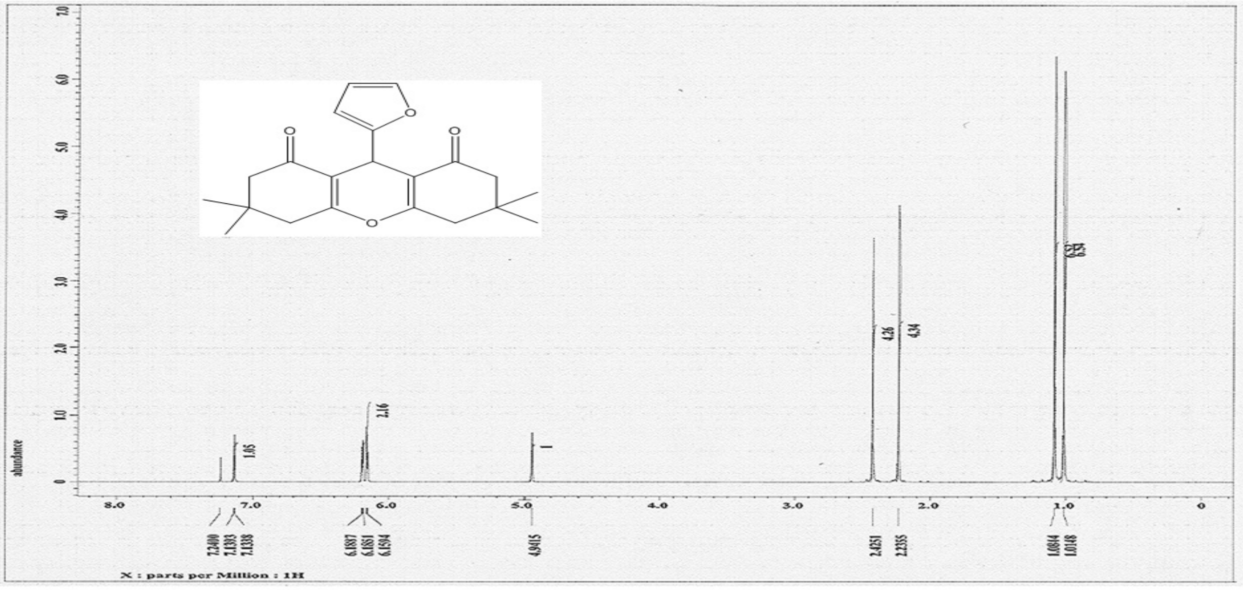


Figure-1
1H NMR SPECTRUM

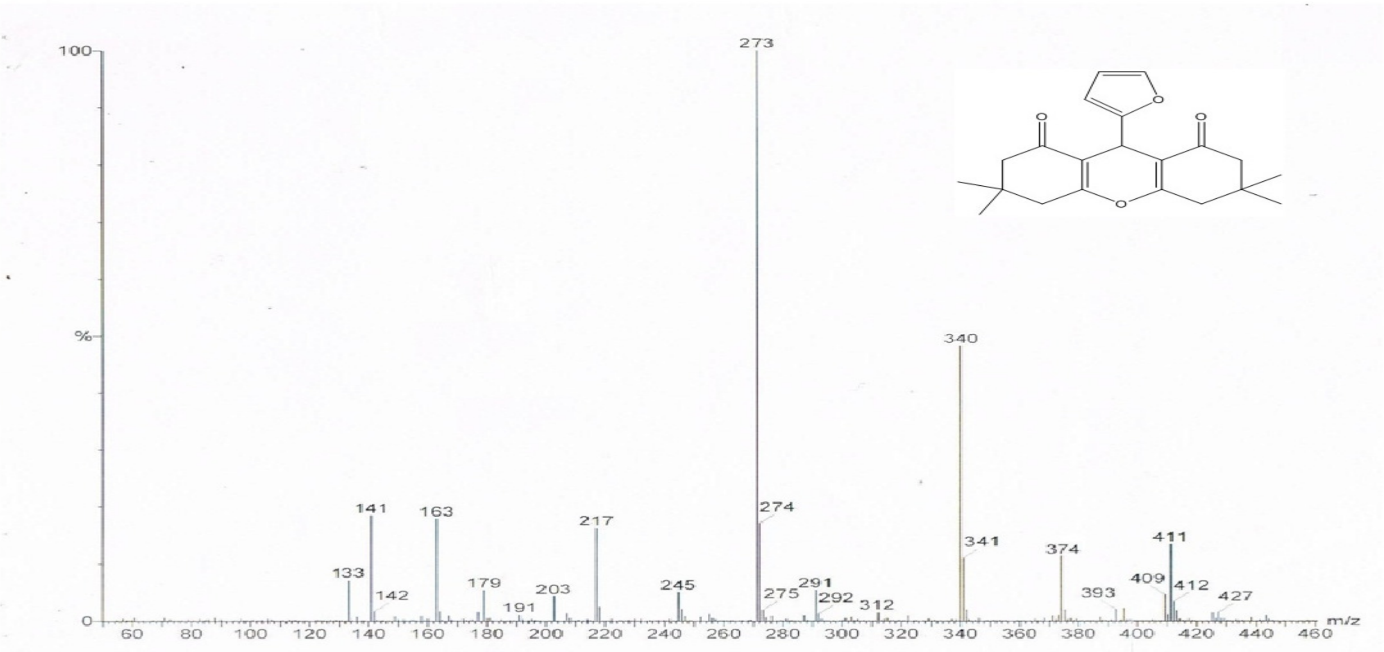


Figure-2
Mass Spectrum

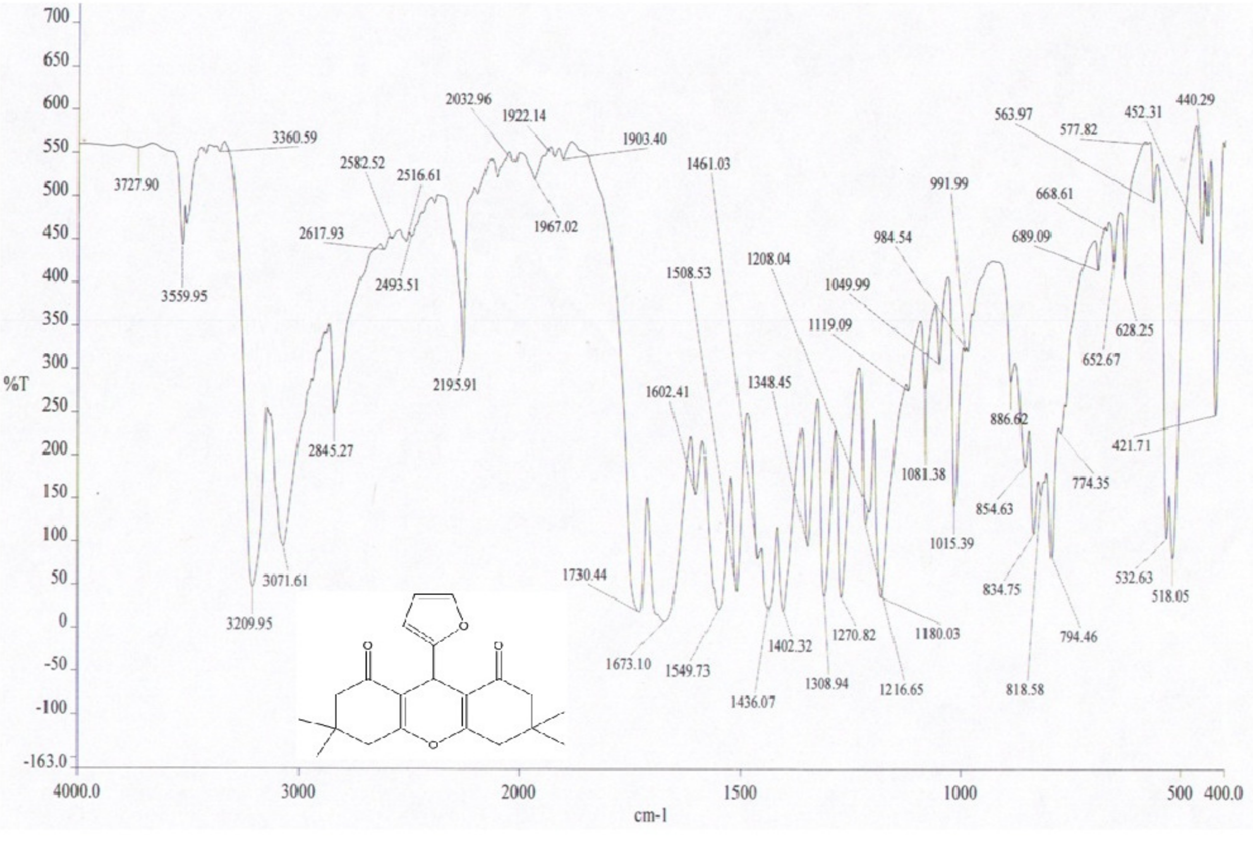


Figure-3
IR Spectrum