International Research Journal of Engineering and Technology (IRJET) e-ISSN: 2395-0056
Volume: 07 Issue: 08 | Aug 2020 www.irjet.net p-ISSN: 2395-0072

Synthesis of Functionalized Coumarins in Water by using *β*-Cyclodextrin–Glycerin as Reaction Medium

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Abstract : In the present work 3-acetoacetylcoumarin derivatives were synthesized at ambient temperature by reaction between substituted salicylaldehyde and 4-hydroxy-6-methyl-2Hpyran-2-one by using *β*-Cyclodextrin–glycerin as reaction medium. The existing organic transformation involves Knoevenagel condensation reaction followed by intramolecular ring opening and then cyclisation.

Keywords: 3-acetoacetylcoumarins, *β*-Cyclodextrin, glycerin, ambient temperature.

1. Introduction

The recent heterocyclic chemistry comprises coumarins based organic molecules which shows far-reaching spectrum of biological activity such as diuretic, spasmolytic, [1-3], anticonvulsant [4], antitumor [5], antimicrobial [6] and anti-HIV [7] in addition to insecticidal properties [8]. Chemistry of coumarins has very much promising industrial applications such as laser dye [9], optical brighteners [10, 11] additives in food and cosmetics [12, 13]. The previously used protocols for synthesis of 3-acetoacetylcoumarins derivatives are ionic liquids [14], piperidine [15], triethylamine [16], potassium fluoride (KF)–alumina [17] in organic solvents.

Some of the reported methods of for synthesis of 3-acetoacetylcoumarins derivatives suffer drawbacks like use of expensive catalyst, hazardous solvents, prolonged reaction time, elevated temperature, tedious work up procedure. These weaknesses can be overcome by using water as reaction medium in organic transformation [18, 19].

Many organic reactions showed improved rate of reaction in water due to hydrophobic effects, but the low solubility of organic compounds restricts the use of water as solvent in organic synthesis [20]. Many inorganic catalysts perform better in aqueous medium rather than organic solvents [21]. However, glycerin is very promising solvent, in which many organic compounds are readily soluble than in water and alcohol [22].

Supramolecules forms inclusion complex with guest molecule and can be utilized in various actions such as extraction, purification, reaction catalyst, food industry, perfume industry, drug delivery [23]. Cyclodextrins (CD's) are cyclic oligosaccharides which show host-guest complexation by binding organic substrates in its hydrophobic cavity [24]. Among the other CD's, *β*-CD has been extensively used in organic synthesis as catalyst [25-28]. In continuation of our work for using *β*-CD-glycerin system in organic transformation [29] here we synthesize 3-acetoacetylcoumarin derivatives.

2. Experimental Section

2.1 Material and Methods

β-CD was bought from Himedia and all remaining chemicals from Sigma Aldrich, Spectrochem, s. d. Fine chemical Limited (India). These chemicals were used by itself exclusive of extra purification. Melting points were determined by an open capillary method and are uncorrected. Infrared spectra were recorded on Perkin Elmer FT-IR spectrometer (KBr discs ~5% w/w). NMR spectra were recorded on Bruker Avon 300 MHz spectrometer using $CDCl_3$ as solvent and Tetramethylsilane as internal reference.

2.2 General procedure for synthesis of 3-acetoacetylcoumarins

In a 50 mL round bottom flask, *β*-CD (0.227 gm) was added to 15 mL aq. 50% glycerin (*v*/*v*) and heated (35-40 °C) under stirring to obtain homogeneous solution. To this homogeneous solution salicylaldehyde (0.122 gm, 1 mmol) and 4-Hydroxy-6-methyl-2*H*-pyran-2-one (0.126 gm, 1 mmol) were added. Resulting mixture was stirred at 40 °C for appropriate duration. The reaction was monitored with TLC by using Petroleum Ether: Ethyl acetate (8:2) as mobile phase. After completion of reaction

the product was isolated by simple filtration followed by washing with water (15 mL x 3). The isolated dried crude product recrystallized with 95% EtOH to afford the corresponding pure 3-acetoacetylcoumarin derivative.

3. Results and discussion

Initially we carried out the model reaction by reacting equimolar quantity of salicylaldehyde and 4-Hydroxy-6-methyl-2*H*-pyran-2-one without use of beta cyclodextrin at room temperature in water. However, there is no any product formation observed which supports the crucial role of -CD (table 3.1). With 0. 1 mmol (0.227 gm) of *β*-CD as catalyst gave only 20 % yield of the corresponding product. As the concentrations of *β*-CD in reaction medium increases the duration of completion of reaction reduces however there is no any drastic change in the yield of product. This might be partial solubility of the *β*-CD in water which lead to incomplete formation of inclusion complex with reagents.

Table 3.1 Optimization of the -CD for the synthesis of 3-acetoacetylcoumarin

Sr. No.	-CD (mmol)	Temp. (℃)	Time (h)	Yield [a, b] (%)
1	--------	25	12	Nil
2	-------	25	12	Nil
3	0.1	25	10	20
4	0.2	25	8	52
5	0.5	25	8	64
6	0.7	25	6	66
7	1.0	25	5	66

a) Reacting substrates: salicylaldehyde (1 mmol), 4-Hydroxy-6-methyl-2H-pyran-2-one (1 mmol) in 15 mL water;
b) Isolated yield of the product.

Next, we carried out several reactions with various concentrations of aq. glycerin solution for the model reaction. There is no any product formation observed with the concentration below 40% (v/v) at room temperature for model reaction. However, at 40%, 50 % the product formation was observed with poor yield. The aq. glycerin solution gave good results at elevated temperature (40 ℃) among these aq. 50 % glycerin (v/v) brought better results compared with other concentrations (table 3.2).

Table 3.2 Optimization of the concentration of aq. glycerin

Sr. No.	aq. glycerin % (*v/v*)	Temp. (℃)	Time (h)	Yield [a, b] (%)
1	10	25	15	Nil
2	20	25	15	Nil
3	30	25	15	Nil
4	40	25	15	10
5	50	25	12	30
6	10	40	15	10
7	20	40	12	25
8	30	40	10	35
9	40	40	8	45
10	**50**	**40**	**6**	**75**
11	60	40	7	72
12	70	40	5	70

a) Reacting substrates: salicylaldehyde (1 mmol), 4-Hydroxy-6-methyl-2H-pyran-2-one (1 mmol) in 15 mL aq. glycerin; b) Isolated yield of the product.

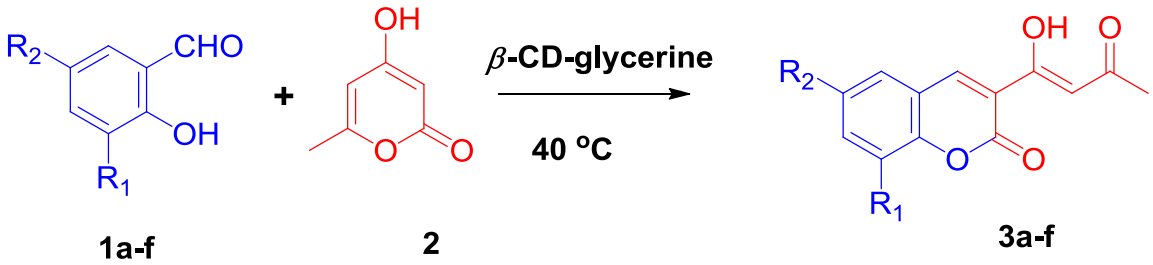
Our next goal was to use *β*-CD in combination with aq. 50 % glycerin (*v*/*v*). No formation of desired product in absence of *β*-CD, showing its participation in the reaction medium was crucial. The model reaction showed excellent results with 0.1 mmol of *β*-CD in combination with aq. 50 % glycerin (*v*/*v*) (table 3.3). With increase in *β*-CD concentration there is no any drastic change in the yield of product was observed hence we utilize this optimized condition for formation of various derivatives of the 3-acetoacetylcoumarin.

Table 3.3 Optimization of -CD - aq. glycerin concentration

Sr. No.	aq. glycerin % (*v*/*v*)	-CD (mmol)	Temp. (℃)	Time (h)	Yield [a, b] (%)
1	50	0.0	25	12	30
2	50	0.1	25	8	45
3	50	0.0	40	6	75
4	**50**	**0.1**	**40**	**1**	**98**
5	50	0.2	40	1	97
6	50	0.5	40	1	97
7	50	0.7	40	1	98
8	50	1.0	40	1	98

a) Reacting substrates: salicylaldehyde (1 mmol), 4-Hydroxy-6-methyl-2*H*-pyran-2-one (1 mmol) in 15 mL aq. Glycerin; *β*-CD; b) Isolated yield of the product.

The scope of the reaction was studied with substituted salicylaldehyde with diverse functional groups such as -OMe, -OEt, -NO_2, and -Cl to synthesize the corresponding 3-acetoacetylcoumarins in good to excellent yield (**Scheme 1**). The 3,5-dichloro salicylaldehyde reacted slowly and gave the corresponding 3-acetoacetylcoumarins in poor yield. The results are tabulated in below (table 3.4).



Scheme 1 Synthesis of 3-acetoacetylcoumarins.

Table 3.4 Synthesis of 3-acetoacetylcoumarins derivatives [a]

Entry	R_1	R_2	Product	Time (h)	Yield [b] (%)	M.P. [c] (°C)
1	H	H	3a	2.0	98	144-146
2	H	NO_2	3b	1.5	96	210-212[14, 30]
3	OMe	H	3c	2.0	97	172-174[14, 30]
4	OEt	H	3d	2.5	98	202-204

5	Cl	Cl	3e	3.0	89	200-202[14, 30]
6	2OH-naphthalene-1-carbaldehyde		3f	3.5	94	222-224

a) Reaction conditions: salicylaldehyde (1 mmol), 4-Hydroxy-6-methyl-2*H*-pyran-2-one (1 mmol), 0.1 mmol *β*-CD-aq. 50 % glycerin (*v/v*) in 15 mL solution stirred at 40 °C;
b) Isolated yield of product; c) Melting point match with literature value.

In a plausible mechanism, 2-hydroxybenzaldehyde (**1**) undergoes Knoevenagel condensation with 4-Hydroxy-6-methyl-2H-pyran-2-one (**2**) to give corresponding intermediate 3-salicylidenepyrane-2,4-dione. This intermediate undergoes a ring-opening reaction mediated by a nucleophilic attack of the phenolic OH group onto the lactone carbonyl followed by intramolecular cyclization yielding the desired final product 3-acetoacetylcoumarin (**Figure 1**).

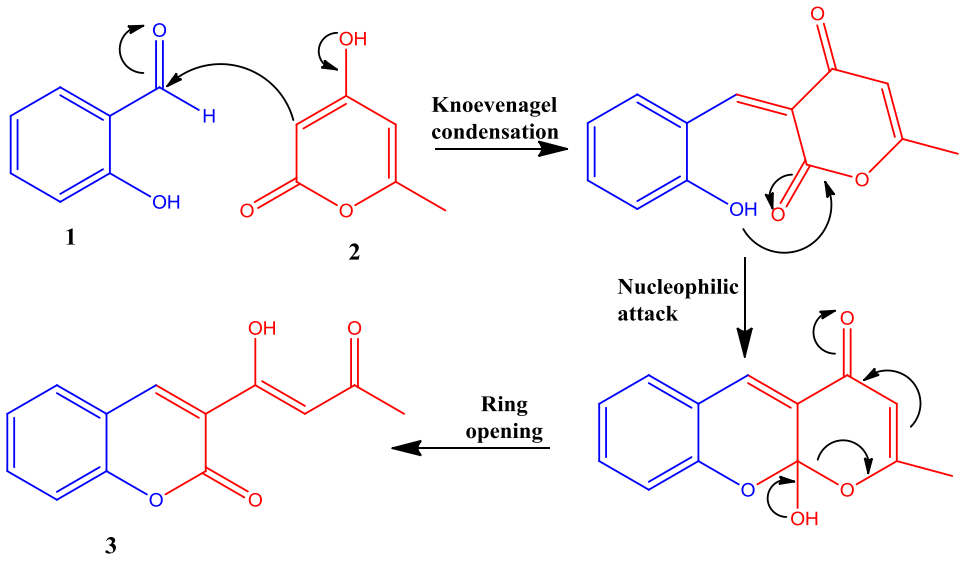


Figure 1 Plausible reaction mechanism for synthesis of 3-acetoacetylcoumarin.

3.1 Spectral analysis of synthesized 3-acetoacetylcoumarin derivatives

8-Nitro-3-acetoacetylcoumarin (**3b**); IR (KBr, cm^{-1}): ν_{max} 1740, 1612, 1575, 1530, 1480, 1425, 1344, 1280, 1187, 1107, 999, 925, 822; ^1H NMR (300 MHz, $CDCl_3$): δ 15.74 (1H, s), 8.72 (1H, s), 8.47-8.60 (2H, m), 7.51 (1H, d, J= 9.3), 7.01 (1H, s), 2.32 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.67, 169.81, 157.43, 156.48, 144.37, 143.69, 129.86, 128.14, 127.58, 125.16, 122.83, 118.50, 117.85, 102.22, 27.89.

8-Methoxy-3-acetoacetylcoumarin (**3c**); IR (KBr, cm^{-1}): ν_{max} 1748, 1608, 1558, 1507, 1363, 1183, 1116, 1034, 816; ^1H NMR (300 MHz, $CDCl_3$): δ 15.92 (1H, s), 8.65 (1H, s), 7.29-7.32 (1H, m), 7.17-7.22 (2H, m), 7.07 (1H, s), 4.01 (3H, s), 2.30 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.89, 171.80, 157.50, 146.92, 145.66, 144.00, 124.80, 120.72, 119.12, 115.37, 101.77, 56.32, 27.62.
6,8-Dichloro-3-acetoacetylcoumarin (**3e**); IR (KBr, cm^{-1}): ν_{max} 1740, 1600, 1568, 1412, 1365, 1273, 1183, 1096, 1011, 829; ^1H NMR (300 MHz, $CDCl_3$): δ 15.72 (1H, s), 8.53 (1H, s), 7.60 (1H, d J= 3.0 Hz), 7.52 (1H, d J= 3.0 Hz), 7.00 (1H, s), 2.30 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.39, 170.20, 156.31, 148.59, 142.49, 131.50, 130.07, 125.00, 121.57, 121.50, 120.27, 102.17, 27.80.
2-(1-hydroxy-3-oxobut-1-en-1-yl)-3*H*-benzo[f]chromen-3-one (**3f**); IR (KBr, cm^{-1}): ν_{max} 1738, 1602, 1560, 1470, 1432, 1350, 1271, 1177, 1092, 966, 820; ^1H NMR (300 MHz, $CDCl_3$): δ 16.00 (1H, bs), 9.00 (1H, s), 8.38 (1H, d, J= 9.0), 8.10 (1H, d, J= 9.0), 7.95 (1H, d, J= 6), 7.77 (1H, t, J= 7.8 Hz, J= 7.8 Hz), 7.63 (1H, t, , J= 7.5 Hz, J= 7.5 Hz), 7.49 (1H, d, J= 9Hz), 2.31 (3H, s), 7.12 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.40, 171.64, 157.16, 154.91, 139.96, 135.79, 130.26, 129.40, 129.19, 129.08, 126.60, 121.74, 118.97, 116.48, 113.04, 101.49, 27.47.

4. Conclusion

In conclusion, the current protocol for synthesis of 3-acetoacetylcoumarin is eco-friendly and advantageous process as the -CD as well as glycerin both are biodegradable, nontoxic, inexpensive and easily available. 3-acetoacetylcoumarins synthesized in water at ambient temperature. This technique serves as green approach from environment viewpoint which is a major requirement of various chemical industries nowadays.

Acknowledgement

We gratefully acknowledge the unconditional support and providing the required laboratory facilities, some chemicals and various machineries from the *D.K.T.E. S's. Textile and Engineering Institute,* Ichalkaranji, 416115, M.S., India.

References:

1] Foye, W. O. Principi Di Chemico Farmaceutica; Piccin: Padova, Italy, **1991**; p 416.

2] Mane, A.; Patil, A.; Kamat, S.; Salunkhe, R. *Chemistry Select* **2018**, 3, 6454.

3] Bonsignore, L.; Loy, G.; Secci, D.; Calignano, A. *Eur. J. Med. Chem.* **1993**, 28, 517.

4] El-Nagger, A. M.; Abdel-El-Salam, A. M.; Latif, F. S. M.; Ahmed, M. S. A. *Pol. J. Chem.* **1981**, 55, 793.

5] Middleton, E.; Kandaswami, C. Harborne, J. B., Ed.; Chapman Hall: London, U.K., **1994**; p 619.

6] Ohemeng, K. A.; Schwender, C. F.; Fu, K. P.; Barrett, J. F. *Bioorg. Med. Chem. Lett.* **1993**, 3, 225.

7] Kashman, Y.; Gustafson, K. R.; Fuller, R.; Cardellina, J. H.; McMahon, J. B.; Currens, M. J.; Buckheit, R. W.; Hughes, S. H.; Cragg, G. M.; Boyd, M. R. *J. Med. Chem.* **1992**, 35, 2735.

8] Mitra, A.; Misra, S. K.; Patra, A. New Synthesis of 3-Alkyl Coumarins. *Synth. Commun.* **1980**, 10, 915-919.

9] Maeda, M. Laser Dyes, Academic Press, New York, **1994**.

10] Zahradnik, M. The Production and Application of Fluorescent Brightening Agents, Wiley and Sons, **1992**.

11] Sun, W. C.; Gee, K. R.; Haugland, R. P. *Bioorg. Med. Chem. Lett.* **1988**, 8, 3107.

12] Meuly, W. C. Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 7, 3rd Ed., John Wiley & Sons, New York, **1979**, p. 196.

13] Sethna, S. M.; Shah, N. M. *Chem. Rev.* **1945**, 36, 1.

14] Shi, D-Q.; Zhou, Y.; Rong, S-F.; *Synth. Commun.* **2009**, 39, 3500.

15] Alizadeh, A.; Ghanbaripour, R. *Synth. Commun.* **2014**, 44: 1635.

16] Hirsch, B.; Hoefgen, N. German Patent (East) DD 218,892, 1985. *Chem. Abstr.* **1985**, 103, 123357z.

17] Wang, X. S.; Zeng, Z. S.; Zhang, M. M.; Shi, D. Q.; Tu, S. J. *J. Chem. Res., Synop.* **2006**, 602.

18] a) Karamthulla, S.; Pal, S.; Khana, Md. N.; Choudhury, L. H. *RSC Adv.* **2014**, 4, 37889; b) Pawar, A.; Mane, A.; Patil, A.; Kamat, S.; Salunkhe, R. *Chem. Sci. Rev. Lett.* **2018**, 7(26), 635.

19] a) Kamat, S.; Salunkhe, R.; Choudhari, P.; Dhavale, P.; Mane, A.; Lohar, T. *Res. Chem. Intd.* **2018**, 44(2), 1351-1362; b) Patil, A.; Mane, A.; Kamat, S.; Lohar, T.; Salunkhe, R. *Res. Chem. Intd.* **2019**, **44**, 3441-3452.

20] a) Lohar, T.; Mane, A.; Kamat, S.; Salunkhe, R. *Polycyclic Aromatic Compounds,* **2020**, 40 (4), 1210; b) Chigare, R.; Patil, J.; Kamat, S. *IRJET*, **2019**, 6(6), 974.

21] a) Indi, Y.; wasif, A. *IJFTR*, **2018**, 43, 120; b) Chigare, R.; Patil, J.; Kamat, S. *IRJET*, **2020**, 7(5), 3764.

22] a) Dı´az-Alvarez, A.; Francos, J.; Lastra Barreira, B.; Crochet, P.; Cadierno, V. *Chem. Commun.* **2011,** 47, 6208; b) Sadek K.; Mekheimer R.; Hameed A.; Elnahas F.; Elnagdi M. *Molecules*. **2012**, 17, 6011.

23] Patil, J.; Chigare, R.; Kamat, S. *IRJET*, **2020**, 7(5), 2921.

24] a) Szejtli, J. *Chem. Rev.* **1998**, 98, 1743; b) Shibu, E. S.; Pradeep, T. *Chem. Mater.* **2011**, 23 (4), 989; c) Connors, K. A. *Chem. Rev.* **1997**, 97, 1325.

25] Wu, J.; Du, X.; Ma, J.; Zhang, Y.; Shi, Q.; Luo, L.; Song, B.; Yang, S.; Hu, D. *Green Chem.* **2014**, 16, 3210.

26] Azath, A. I.; Puthiaraj, P.; Pitchumani, K. *ACS Sustainable Chem. Eng.* **2013**, 1, 174.

27] Zhao, W.; Zhong, Q. *J Incl Phenom Macrocycl Chem.* **2012**, 72, 1.

28] Takahashi K., *Chem. Rev.* 1998, 98 (5), 2013.

29] Kamat, S.; Mane, A.; Arde S.; Salunkhe, R. *IJPCBS*. **2014**, 4(4), 1012.

30] Chavan, H.; Bandgar, B. *ACS Sustainable Chem. Eng.* **2013**, 1, 929.