IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

DESIGN AND SYNTHESIS OF SOME AMINO COUMARIN DERIVATIVES BY USING MILD CATALYST

Kadlag A. G.

Department of Chemistry, S. N. Arts, D. J. M. Commerce and B. N. S. Science College, Sangamner.

ABSTRACT

Coumarin possesses a number of biological activities like antimicrobial, anti-inflammatory, analgesic, antioxidant, anticancer, antimalarial etc. Coumarin belongs to a group of benzpyranes, which consist of a benzene ring joined to a pyran nucleus. In the present study amino derivatives bearing coumarin nucleus are synthesized from 7-hydroxy -4- methyl coumarin by using mild catalyst, CAN which is water soluble salt. The formed compounds have been evaluated by physical methods like melting point, thin layer chromatography, elemental analysis and functional group analysis.

Keywords: Coumarin, Ceric Ammonium Nitrate (CAN), iron power, nitro coumarin, amino coumarin derivatives.

ISSN 2349-7203
IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
HUMAN

INTRODUCTION

Coumarin (2H-1-benzopyran-2-ones) is important oxygen containing fused heterocycles used in drugs and dyes [1]. Coumarins be bound their class name to 'coumarou' the vernacular name of the Tonka bean (Dipteryx odorata willd, Fabaceae), from which coumarin itself was isolated in1820 [2]. They are the family of lactones containing benzpyran skeletal framework that have enjoyed isolation from plant as well as total synthesis in the laboratory [3]. The incorporation group as a fused component into parent coumarin alters the property of parent coumarin and converts it into a more useful product[4]. Coumarin is plant flavonoids widely distributed in nature. Natural coumarins are known to have antidiabetic activity [5], anabolic antioxidant and hepato protective activities [6]. Substituted coumarins derivatives have been reported to have variety of biological activities.

The synthesis of coumarins and their derivatives has attracted considerable attention from organic and medicinal chemists from many years as a large number of natural and synthetic products contain this heterocyclic nucleus[7-11]. A considerable number of natural and synthetic coumarin derivatives have been reported to exert antimicrobial [7, 8] antifungal [9, 10], and cytotoxic [11], antitumor [12- 13], antibacterial [14- 15,] anticoagulant [16], anti-inflammatory [17] properties. They have also shown to be useful as anti- HIV agents and as CNS active compounds [18]. In addition these compounds are used as additives to food and cosmetics [19], dispersed fluorescence and lasers [20]. Coumarins are present in remarkable amounts in plants, although their presence has also been detected in microorganisms and animal sources [18.]

Thus the synthesis of this heterocyclic nucleus is of much interest. I am interested in designing synthesizing amino coumarin compounds bearing coumarin nucleus attached to benzoxazol moieties.

MATERIALS AND METHODS

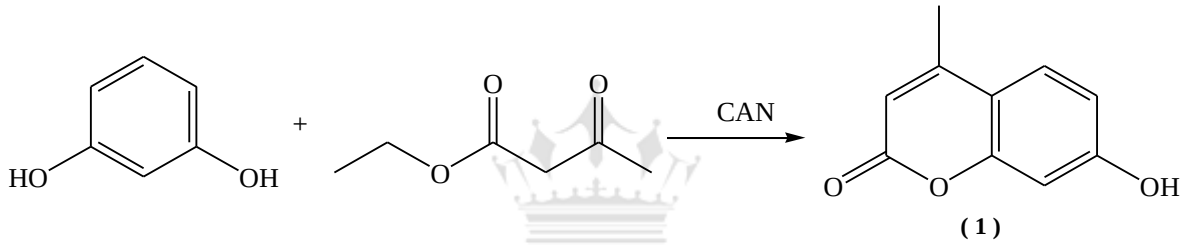
The chemicals are used as of analytical grade i.e. Resorcinol, Ethylacetoacetate, Ceric ammonium nitrate, Conc. H_2SO_4, Conc. HNO_3, Conc HCl, Iron powder, Ethanol, Glacial acetic acid, benzaldehyde, pthalic anhydride.

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

All the melting points were determined in open capillaries and are uncorrected. The purity of compounds was checked by TLC on silica gel by using aluminum sheet and was purified by column chromatography. The elemental analysis was carried out by chemical methods.

Synthesis of 7- Hydroxy-4-Methyl Coumarin (1)

Resorcinol (1.1 gm, 0.01 mol) was dissolved completely in ethylacetoacetate (1.35 gm, 0.01 mol) in a 50 ml dry round bottom flask. Ceric Ammonium Nitrate (CAN)(0.5 gm) was added to this mixture and mixed thoroughly using a glass rod. Then the mixture was heated for 3 – 4 hr. at 60^0C. Then mixture was cooled to room temperatureand 50 ml water was added to it and kept overnight. White solids were filtered and wash with cold water. Then the crude product was recrystallized from ethanol. The Yields: 85%, Melting point: 192 ^{0}C, Molecular Formula: $C_{10}H_8O_3$.



(1)

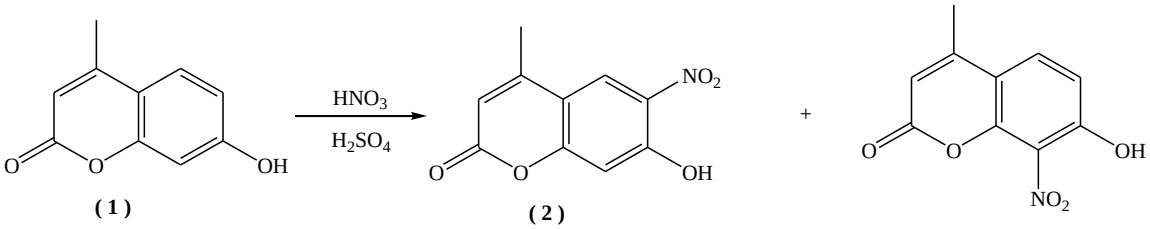
Scheme 1

Synthesis of 6-nitro-7-Hydroxy-4-Methyl Coumarin (2)

The nitration of 7-hydroxy-4-methyl Coumarin using concentrated nitric acid and sulphuric acid at 5^0C gave two nitro isomers i.e. 7-hydroxy-4-methyl-8-nitro Coumarin & 7-hydroxy 4 methyl-6-nitro Coumarin. In a conical flask 7-hydroxy-4-methyl Coumarin (1 gm) was dissolved in conc. H_2SO_4 (10 ml.) and then keep the flask in an ice bath. When the temperature inside the flask is below 10^0C, add 4ml of nitrating mixture (1 ml of concentrated nitric acid and 3 ml of concentrated sulphuric acid) taking care that the temperature does not rise above 10 ^{0}C. After the addition was completed, removed the flask from the ice bath and keep it at room temperature for an hour. The flask shaked occasionally during this period and then poured with stirring in a beaker containing crushed ice. The crude product filtered which is a mixture of 6 and 8 nitro derivatives and washed with cold water. Transfer the crude mixture in a conical flask containing ethanol and boiled. The residue is 6-nitro-4-methyl-7

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

hydroxy coumarin, m.p 260-262 ^{0}C and filtrate contains 8 nitro derivative.Concentrated the filtrate, and cooled in an ice bath, 8 nitro derivativecrystallized out. Yields: 60%, Melting point: 260 - 262^{0}C, Molecular Formula: $C_{10}H_7NO_5$.

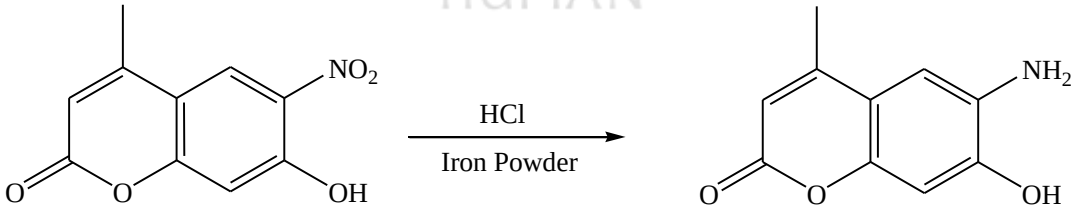


(1) (2)

Scheme 2

Synthesis of 6-Amino-7-hydroxy-4-methyl Coumarin (3)

Iron powder (4 gm) was added portion wise with stirring to a hot mixture of 6 nitro-7-hydroxy-4- methyl Coumarin (2.21 gm, 0.01 moles) in ethyl alcohol (10 ml) and concentrated hydrochloric acid (15 ml) at reflux temperature. After completion of the addition, the refluxing was continued for 6 hours. Upon cooling a white precipitate formed, which was filtered off, washed with water, dried and recrystallized. Yields: 50%, Melting point: 284^{0}C, Molecular Formula: $C_{10}H_9NO_3$.



(2) (3)

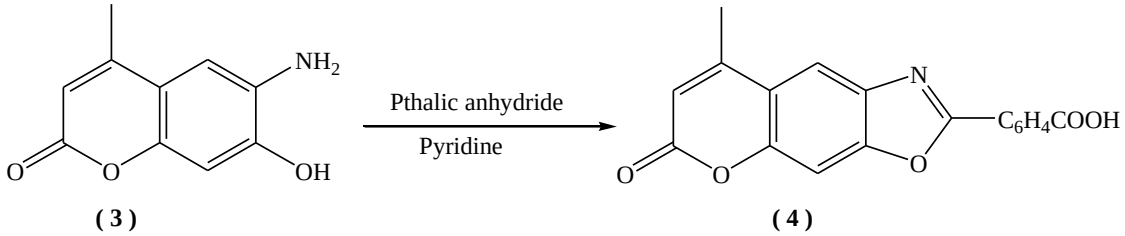
Scheme 3

Synthesis of 8-methyl-2-[p-benzoate]-6H-pyrano [6, 7-d] benzoxazol-6-ones (4)

To a solution of 6 amino derivative (**3**) (0.42 gm, 0.002 mole) in pyridine (10 ml), an (0.300 gm, 0.002 mole)pthalic anhydride was added. The reaction mixture was refluxed for 10 hrs, the pyridine was distilled under reduced pressure, and the residue was washed with water and dissolved in NaOH solution (5%, 10 ml). The reaction mixture wasfiltered off and neutralized

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

by dilute hydrochloric acid. The precipitate formed was filtered off, washed with water, dried and recrystallized.Yields: 82%, Melting Point: >300^{0}C, Molecular Formula: $C_{18}H_{11}NO_5$.

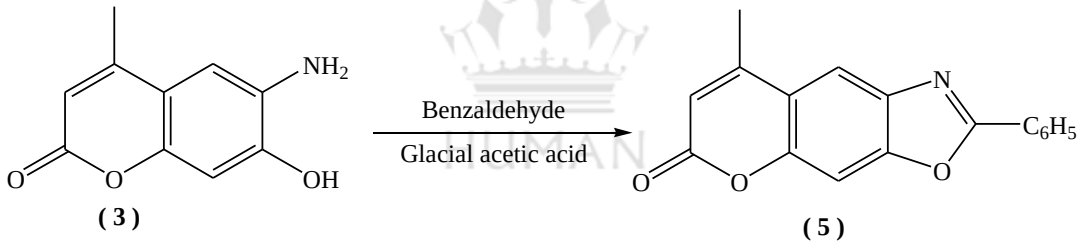


(3) (4)

Scheme 4

Synthesis of 6-methyl-2-benzayl-8H-pyrano [2, 3-e] benzoxazol-8-one (5)

In a solution of **3** (0.42 gm, 0.002 mole) in glacial acetic acid (20 ml), add benzaldehyde (0.212 gm, 0.002mole) and was refluxed for 15 hours, cooled, poured into ice/cold water. The precipitate formed was filtered off and recrystallized. Yield: 65%, Melting point: 232 ^{0}C**,** Molecular Formula having $C_{17}H_{11}NO_3$.



(3) (5)

Scheme 5

RESULTS AND DISCUSSION

From the literature survey it reveals that the coumarin have been reported for number of pharmacological activities and some molecules have shown significant and some compounds show moderate and good activities. Here we have synthesized some amino coumarin compounds bearing coumarin nucleus attached to benzoxazol moieties. The purity of the synthesized compounds was preliminary checked by their physical constant, elemental analysis and functional group analysis.

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Table 1: The Melting Point, % of yield, molecular formula of synthesized compounds

Compound No.	Melting Point	Yield (%)	Molecular Formula
1	192	85	$C_{10}H_8O_3$
2	262	60	$C_{10}H_7NO_5$
3	284	50	$C_{10}H_9NO_3$
4	>300	82	$C_{18}H_{11}NO_5$
5	232	65	$C_{17}H_{11}NO_3$

CONCLUSION

In this study 6-methyl-2-[p-benzoate]-8H-pyrano [2, 3-e] benzoxazol-8-ones (4) and 6-methyl-2-benzayl-8H-pyrano [2, 3-e] benzoxazol-8-one (5) were successfully synthesized. However further studies are needed to evaluate the biological activity and establish molecular mechanisms, which are responsible for their biological activity.

ACKNOWLEDGEMENTS

The author express their thanks and gratefully acknowledges to Head of Department & Principal, S. N. Arts, D. J. M. Commerce & B. N. S. Science College, Sangamner forhis continuous encouragement.

REFERENCES

1. Rajasekaran S, Rao G.K., Pai S.P.N. Ranjan A (2011), International journal of chem tech research,3(2),555-559.
2. Nachiket S.D., Shashikant R.P, Dengale S.S., Musmade D.S., Shelar M, Tambe V, M Hole M, (2010), Der Pharma Chemica,2(2), 65-71.
3. Olayinka A.O., Obinna N.C.,(2010) Journal of Heterocyclic Chemistry, , 47,179-187.
4. Brahnbhatt D.I.,Gajera J.M., Pandya V.P., Patel M.A (2007), Ind. J. chem.46(B),869 871.
5. Sharma R, Arya V, J (2011)Chem. Pharm. Res., 3(2),204-212.
6. Murrey R.D.P, D Medez, Brown S A(1982), The natural coumarins occurrences, chemistry and biochemistry, John Wiley Interscience, Newyork.
7. czerpack R, Skolska S (1982) Effect of selected synthetic regulators on Pseudomonas aeruginosa growth in liquid culture Med Dosw Microbiolgy, 34, 37-50.
8. Jund L, Corse J, King A S, Bayne H, Mihrag K(1971) Antimicrobial properties of 6,7-dihydroxy, 7-8-dihydroxy, 6-hydroxycoumarins phytochemistry 10, 2971-2974.
9. El-Ansary S L, Aly E I, Halem M A (1992) New coumarin derivatives as antibacterial agents Egypt J Pharm Sci, 33, 379-390.
10. Reddy Y D, Somayojulu V V, (1981) Synthesis, spectra and physiological activity of 7H-pyrano [3,2-c]benzoxazole-7-one J Ind Chem Soc, 58, 599-601.

11. Weber U S, Steffen B, Siegers C(1998) Antitumor activities of coumarin, 7-hydroxy-coumarin and its glucuronide in several human tumor cell lines Res Commun Mol Pathol Pharmacol, 99, 93-206.
12. Raev L, Voinov E, Ivanov I, Popov D,(1990) Antitumor activity of some coumarin derivatives Pharmazie, 45, 696-698.
13. Nofal Z M, El-Zahar M, Abd El-Karim S, (2000) Novel coumarin derivatives with expected biological activity, Molecules, 5, 99-113.
14. Agrody A M, Abd Latif M S, Hady N A, Fakery A H, Badair A H, (2001) Heteroaromatisation with 4-hydroxycoumarin part 2, Molecules, 6, 519-527.
15. Patibha S, Shreeya P, (1999) Synthesis, Characterization and antimicrobial studies of some novel 3- arylazo-7-hydroxy-4-methylcoumarin Indian J Chem, 38B, 1139-1142.
16. Manolov I, Danchev N D,(1995) Synthesis, toxicological and pharmacological assessment of some 4-hydroxycoumarin Eur J Med Chem Ther, 30, 531-536.
17. Emmanule Giota A A, Fylaktakidou K C, Hadjipavlou Latina D J, Litinas K E, Nicolaides D N, (2001) J Heterocycle Chem, , 38, 717-722.
18. Borges F, Roleira F, Milhazes N, Santana L, Uriarte E,(2005) Simple coumarins and analoues in medicinal chemistry: occurrence, synthesis and biological activity, Curr Med Chem, 12, 887-916.
19. Kennedy R O, Thorens R D, Coumarins (1997) Biology, Applications and Mode of Action, Wiley & Sons Chichester, UK.
20. Zahradnik M(1997) The Production and Applications of Fluorescent Brightening Agent, Wiley & Sons Chichester, UK.
21. Cacic M, Molnar M, Balic T, Draca N(2009) Design and synthesis of some Thiazolidin -4- ones, Molecules,14, 2501-2513.
22. Sobhi M Gomha, Khaled D Khalil (2012) A Convenient ultrasound promoted synthesis of some new thiazole derivatives bearing a coumarin nucleus and their cytotoxic activity, Molecules, 17, 9335-9347.
23. Ramaganesh C K, Yadav D Bodke, Venkatesh K B(2010) Synthesis and biological evaluation of some innovative coumarin derivatives containing thiazolidin-4-one ring, Indian J Chemistry, 49B, 1151-1154.
24. Patel K.C (2011) Synthesis and biological evaluation of coumarinyl sydnone derivatives, E-Journal of Chemistry, 8, 113-118.