A Short Review on Recent Advances In The Synthesis, Characterization, Applications of Coumarin Derivatives

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Abstract- *Coumarins (2H-chromen-2-ones) are heterocylic compounds and it is used for important biological and pharamaceutial properties such as antimicrobial, antioxidant, anti-inflammatorry and antitumor activities. Coumarins and their derivations have been prepared by various methods like perkin condensation, pechnann condensation, knoevenagel condensation, witting and refornatsky reactions, claisen rearrangement, among others. Coumarin compounds were characterized by using FTIR and 1H NMR spectroscopy. Many synthesis of coumarin derivatives via Knoevenagel condensation and Pechmann condensation with good to excellent yield and high purity. In this review article, we have mentioned various methods for the coumarin derivative synthsis via Knoevenagel condensation and also by Pechmann condensation.*

Keywords- Coumarin derivatives, 2H-chromen-2-ones, Knoevenagel condensation, Pechmann condensation, Perkin reaction, characterization, applications.

I. INTRODUCTION

Chemically, coumarins (2H-1-benzopyran-2 one) belong to the subgroup of lactones.[1] Coumarin compounds are an important class of oxygen-containing heterocyclic moiety.[3] It is found as secondary metabolites in some micro organism and plants.[3] Natural coumarins can be divided into six basic groups as follows.[3]

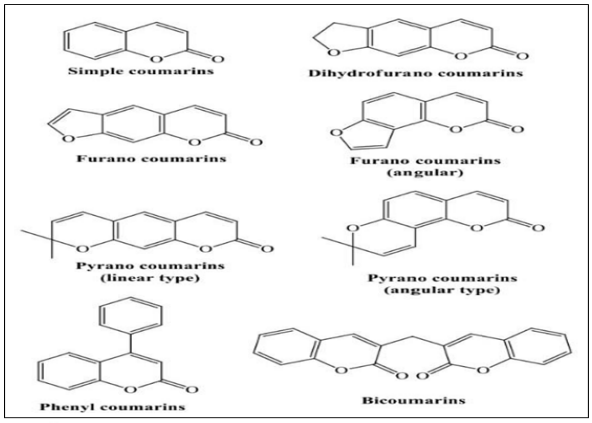


Figure 1. Six basic groups of natural coumarins.

Coumarins are significantly well known as they exhibit valuable biological properties such as anti-inflammatory,antibacterial,analgesic,antifungal,antioxidant,anticancer,antimicrobial,anti- HIV.[2] Along with these applications, coumarin compounds have widely applied in other fields, such as food and dyes industries,fragrance and cosmetic.[3] Coumarins could be synthesized with many different methods like perkin reaction, knoevenagel condensation, pechmann condensation, witting reaction,bayis-Hillman reaction,claisen rearrangement and vilsmeier-Haack and Suzuki cross-coupling reaction.[1] The conventional methods for coumarin synthesis require drastic conditions.[4]

Numerous methods can be used to characterize coumarine derivatives.[2] These are two methods can be used such as fourier-transform infrared (FTIR)spectroscopy and proton nuclear magnetic resonance (^{1}HNMR)spectroscopy.[2] Coumarin derivatives applications were reviewed,including their biological activities,toxicology activity and coumarin derivatives in fragrance. The results obtained were then compared and evaluated.[2]

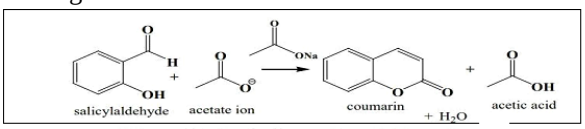
II. SYNTHSIS METHODS OF COUMARIN DERIVATIVES

There are different methods used to synthsize coumarin derivaties. These methods include perkin reaction,

pechnn condensation, witting reaction and knoevenagel reaction.[2]

A. Perkin reaction

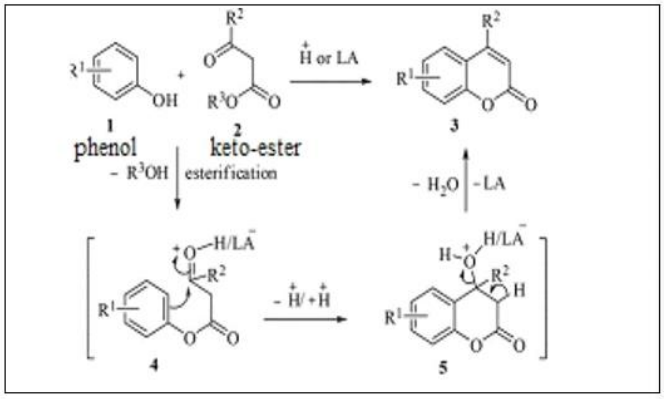
It is commonly performed using salicylaldehyde with carboxylic acid anhydride as a base catalyst.[2] The perkin reaction is might be simple and most direct method to synthesize coumarin derivatives.[2] However, it is difficult to be carried out due to the limitations, such as limitated range for substrate and strong acids. Scheme 1 shows synthesis of coumarin by perkin reaction with salicylaldehyde as the starting material.[2]



Scheme 1. Synthesis of coumarin by Perkin reaction

B. **Pechmann condensation**

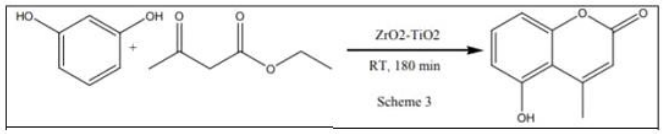
It is one of the common methods used to synthesize 4-methyl coumarin derivatives.[2] The synthesis of coumarin derivatives using phenol as the starting material with either carboxylic acid or ester containing β-carbonyl group.[2] In the conventional production of coumarins by the pechmann reaction, concentrated sulfuric acid is used as the catalyst.[8] Scheme 2 shows the mechanism of synthesis of coumarin by pechmann condensation.[2]



Scheme 2. Mechanism of coumarin synthesis by Pechmann condensation [19]

Pechmann reaction is commonly used to synthesize coumarin due to mild reaction condition mple starting materials and outstanding yields of the products in short reaction times.2 Lewis acids, such as GaI_3, $ZrCl_4$, $InCl_3$, and $Sm(NO_3)_3$ have been utilized as catalysis in pechmann condensation.2 Zirconium salt are used as homogenous catalysis in various organic transformations.[2]

Scheme 3 khan et al. reported the synthesis of coumarin compounds through pechmann reaction in a solvent-free condition at room temperature using zirconia-based heterogenous catalyst(ZrO_2-TiO_2).3



Scheme 3 pechmann reaction in solvent free condition.

C. **Knoevenagel condensation**

Knoevenagel condensation reaction is a classical organic synthesis. All the active methylene containing compounds used in this study cleanly gave high yields of products.[5] It is a modified aldol condensation of aldehyde or ketone with active hydrogen compound in the presence of a basic catalyst such as piperidine, pyribine, ammonia, or sodium ethoxide in organic solvents, resulting in carbon-carbon formation.[2] Scheme 4 shows the synthesis of ethyl coumarin-3-carboxylate by knoevenagel condensation. However, it gives low yield as well as dangerous and toxic solvents like pyridin

III. CHARACTERIZATION THECHNIQUES

A. Fourier-transform infrared (FTIR) spectroscopy

FTIR gives qualitative information such as functional groups and characterizes covalent bonding information.[2] Wahy and his co-researches characterized four novel coumarin derivatives using FTIR.[2] The first compound, 7,7-(propane-1,3- diylsis(oxy)bis(4-methyl-2H-chromen-2-one) (A1) posses wider band at 1722 cm^{-1} due to C=O stretching of α,β-unsaturated ester. Compound B1, 7,7-(1,3-phenylene bis(methylene)bis(4- methyl-2H-chromen-2-one), exhibits strong peak at 1716 cm^{-1}. This is caused by C=O stretching of α,β-unsaturated ester.[2]

B. Proton Nuclear Magnetic Resonance (^{1}H NMR) spectroscopy

The structures of all synthesized compounds were determined by high- resolution ^{1}H NMR spectroscopy.[6] It is used to determine the type and number of hydrogen atoms in molecule.[2] ^{1}H NMR uses radio waves as source of energy.[2] Moghanian and his co-researches conducted a study on the characterization of 8-formyl-7-hydroxy-4-methyl coumarin(A2) using ^{1}H NMR spectroscopy.[2]

IV. APPLICATIONS

Coumarins can be used in several applicatioins.[2] These are anti-inflammatory, anticoagulant, antimicrobial, anticancer and antiviral.[6] Table I lists some of the coumarin derivatives and their application in biological activities.[2]

TABLE I:COUMARIN DERIVATIVES AND THEIR APPLICATION IN BIOLOGICAL ACTIVITIES

Coumarin derivatives	**Applications**
7,8-dihydroxy-4-methyl coumarin	Antioxidant
6-(3-(4-chloro phenyl)-acryloyl)-5-hydroxy-4-methyl-coumarin	Anti-HIV(Reverse transcriptase inhibitors)
7-hydroxy coumarin	Anticoagulant, Antibacterial
4-chloro-3-formayl coumarin and 4-chloro-3-cyano coumarin	Anticancer
3-acetyl-6-bromo-coumarin	Antimicrobial

V. CONCLUSION

This review highlights important biological applications and synthesis of coumarin derivatives through the Knoevenagel condensation and pechmann condensation reaction.[3] FTIR can be used in the characterization of coumarin derivatives.[2] ^{1}H NMR is utilized to determine information of structure, reaction state and chemical environment of coumarin derivatives.[2] Various functional groups in coumarin derivatives lead to useful biological activities and toxicology application.[2] This review useful to some extent to the researches working in this field of coumarin derivative and related compounds.[3] This efficient method is environmental friendly because of avoiding use toxic solvents and using choline chloride as a cheap, biologically degradable and non-toxic molecule.[7]

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