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Chemistry of biologically important flavones☆

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ABSTRACT

The syntheses of flavones with biologically important functional groups like *C*-glycoside, isoprenyl, and hydroxy functionalities at different positions available to medicinal chemists for SAR studies are reviewed. Some rearrangements and transformations facilitating the functionalization of flavones are also discussed.

Contents

1. Introduction

Flavones are natural products of the benzopyran class constituting an important group of oxygen heterocycles, ubiquitously present in fruits and vegetables. We inadvertently consume them in our daily diet and they have a positive impact on our health. Quercetin is well known for its antioxidant activity while the rohitukine **2** has anti-inflammatory and immunomodulatory activities.[1] Rohitukine was later modified into flavopiridol **1**, an anticancer agent presently in clinical trials.[2]

The various biological activities exhibited by the flavones are dependent on the nature and position of the substituents on the flavone skeleton. They have attracted significant attention of chemists to develop various synthetic strategies. As the chemistry of the flavones has not been discussed in depth, the synthetic protocols and transformational chemistry of flavones, will be surveyed in this report.

The flavones exhibit a great diversity in their biological activities due to their unique ability to modulate various enzyme systems.[3] Some of the important natural and synthetic flavones **1**–**12** of pharmacological importance have been shown in Fig. 1. The

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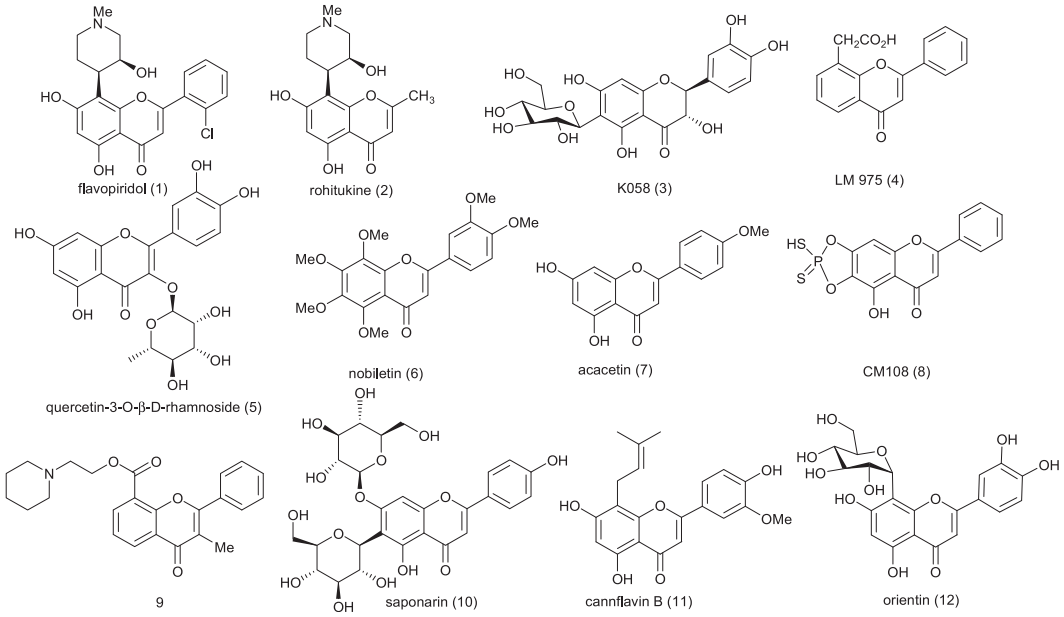


Fig. 1. Some important flavonoids of pharmacological significance.

flavones are active against metabolic and infectious diseases and demonstrate anti-inflammatory, anti-estrogenic, antimicrobial,[4] anti-allergic, antioxidant,[5] vascular, antitumor, and cytotoxic[6] activities.

2. Synthetic protocols for flavones

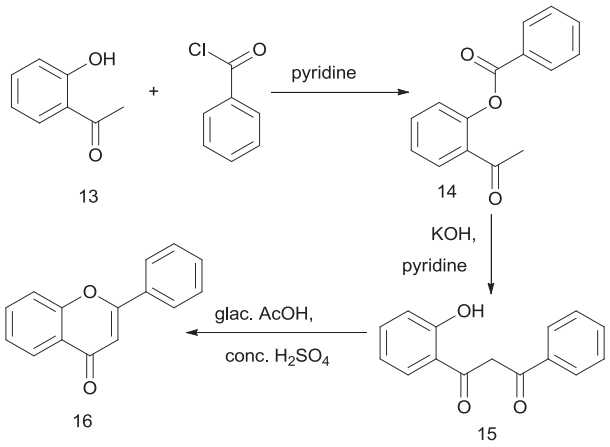
A number of methods for the synthesis of various flavones are available, which broadly can be categorized into two groups involving β-diketones and chalcones as penultimate intermediates derived from *o*-hydroxyacetophenones.

Most of the current syntheses of flavonoids are based on β-diketones emanating from the pioneering work of Robinson[7] and Venkataraman.[8] In spite of the number of steps involved in both the methods, they constitute the most popular strategies for flavone syntheses. All of these methods involve the formation of a β-diketone intermediate through a base-catalyzed acylation of acetophenone followed by an acid-catalyzed cyclodehydration.

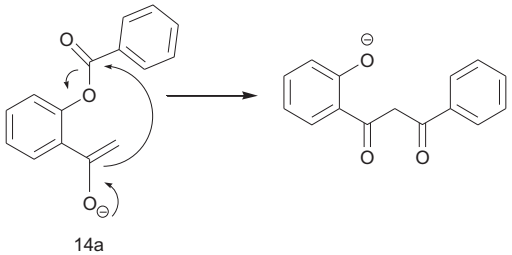
The Baker–Venkataraman rearrangement is one of the fundamental reactions that involves conversion of *o*-hydroxyacetophenone **13** into phenolic ester **14**, which undergoes an intramolecular Claisen condensation in the presence of a base to form β-diketone **15** (Scheme 1).[9]

The rearrangement proceeds via the formation of an enolate **14a** followed by an intramolecular acyl transfer (Scheme 2). A wide range of bases have been employed in the formation of β-diketones. The β-diketones thus formed are cyclized to flavones under relatively harsh acidic conditions, e.g., heating with concentrated sulfuric acid in glacial acetic acid.

Allan and Robinson[7] synthesized flavones through the reaction of *o*-hydroxyacetophenone with aromatic acid anhydrides and sodium salts of aryl acids used in the anhydrides. This led to the formation of two products **16** and **20**. The formation of these products was explained through a hemiketal intermediate **17**. The hemiketal **17** under basic conditions gave the flavone **16**, but the hemiketal **17** also opens to form ω-benzoyl-*o*-hydroxyacetophenone **15**, which has an acidic proton and further reacts with the acid anhydride to form a triketone **18** leading to hemiketal **19**, which undergoes dehydration to yield 3-benzoyl-flavone (**20**) (Scheme 3).[10] The formation of 3-benzoyl-flavone was avoided by heating 2-benzoyloxy-acetophenone (**14**) in anhydrous glycerol.[11]



Scheme 1. Typical synthesis of flavones via β-diketone intermediate.



Scheme 2. Baker–Venkataraman rearrangement.

When there are electron withdrawing groups on the ring A, a milder base is required for the β-diketone formation. Thus, Tang et al. synthesized 6-nitroflavones by utilizing potassium carbonate followed by 5% KOH in ethanol for the β-diketone formation.[12] Further, Saxena et al. used potassium carbonate under phase-transfer-catalyzed (PTC) conditions for the synthesis of β-diketone intermediates and p-toluenesulphonic acid for the cyclodehydration step.[13] The reaction failed to get satisfactory results