Synthesis of exocyclic $\alpha,\beta$-unsaturated ketones

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Dedicated to Professor Dr. Sándor Antus on the occasion of his 60th birthday
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Abstract
This review describes synthetic procedures for the preparation of selected groups of the most important exocyclic $\alpha,\beta$-unsaturated ketones. Some of these $\alpha,\beta$-enones, víz. aurones and 3-benzylidene-4-chromanones belong to the natural products. The others are synthetic substances which are convenient and especially important intermediates for the stereoselective synthesis of polycyclic ring systems. To illustrate the utility of any special procedures, relevant examples have been included. However, it is not the aim of the present review article to list and evaluate all the papers published in this field. Owing to the huge number of papers, such a goal would be an almost unrealizable task.

Keywords: Arylideneclanones, 2-arylidene-1-indanones, 2-arylidene-1-tetralones, 2-arylidene-1-benzosuberones, aurones, 1-thioaurones, 3-arylidene-4-chromanones, 3-arylidene-1-thio-4-chromanones, 3-arylideneflavanones, 3-arylidene-1-thioflavanones

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Introduction

α,β-Unsaturated ketones are versatile and convenient intermediates for the synthesis of a wide variety of heterocyclic compounds. The α,β-enone moiety of the molecule is a favourable unit for dipolar cycloaddition with numerous reagents providing heterocyclic compounds of different ring sizes with one or several heteroatoms. Their reactions with dinucleophiles usually result in the formation of polycyclic ring systems which may be the skeleton of important heterocyclic compounds.

Among the α,β-unsaturated ketones, chalcones and their analogues are especially important starting materials or intermediates for the synthesis of naturally occurring flavonoids and various nitrogen-containing heterocyclic compounds. For this reason, their syntheses have been compiled and discussed in various accounts.

Exocyclic α,β-unsaturated ketones are convenient starting materials for the synthesis of heterocyclic compounds of polycyclic skeletons. Their 1,3-dipolar cycloadditions with different dipoles provide important nitrogen-containing spiroheterocyclic ring systems. Another versatile utilization is the reaction of exocyclic α,β-enones with dinucleophiles to afford polycyclic fused ring systems, e.g. tricyclic pyrazolines, tetracyclic benzothiazepines, tetracyclic benzodiazepines, thiazines, pyrimidines, quinazolines and so on. In the present review article the most common and useful procedures for the preparation of selected exocyclic α,β-unsaturated ketones utilized as intermediates for the synthesis of well known heterocyclic ring systems are compiled and discussed.

1. Preparation of arylidenecyclanones

Arylidenecyclanones are frequently used α,β-unsaturated ketones. Their most important synthesis is based on the reaction of the appropriate cyclic ketone with aldehydes, the well known aldol reaction, which was discussed in detail by Nielsen and Houliham. For this reason, in this review article examples will be shown only for the synthesis of selected groups, viz. arylidenecyclopentanones, arylidenecyclohexanones and some hetero-analogues.

Cyclopentanone (1) was allowed to react with substituted benzaldehydes in alcoholic solution in the presence of sodium or potassium hydroxide and a mixture of 2-benzylidenecyclopentanone (2) and 2,5-dibenzylidenecyclopentanone (3) was formed. The latter products were separated by the utilization of their different solubility in alcohol (Scheme 1).

![Scheme 1](image-url)
Cyclohexanone (4) was reacted with aldehydes under similar alkaline reaction conditions to afford 2-benzylidene cyclohexanones (5) and 2,6-dibenzylidene cyclohexanones (6) (Scheme 2)\(^{63-71}\) which can be easily separated.

![Scheme 2](image)

2-Benzylidene cyclohexanone (5) was synthesized in excellent yield by the reaction of the silyl enol ether (7) of cyclohexanone and benzaldehyde dimethyl acetal (8) using SnCl\(_2\) catalyst in methylene chloride solution (Scheme 3).\(^{72}\)

![Scheme 3](image)

2,5-Dibenzylidene cyclopentanones (3) and 2,6-dibenzylidene cyclohexanones (6) have also been synthesized by the RuCl\(_3\) catalyzed aldol condensation of substituted benzaldehydes and ketones 1 and 4.\(^{73}\)

3,5-Dibenzylidene-4\(H\)-pyran-4-ones (11, X = O) and 3,5-dibenzylidene-4\(H\)-1-thiopyran-4-ones (12, X = S) were synthesized by the reaction of tetrahydro-4\(H\)-pyran-4-one (9, X = O) or tetrahydro-4\(H\)-1-thiopyran-4-one (10, X = S) with substituted benzaldehydes either in alkaline\(^{74-79}\) or in acidic\(^{80,81}\) reaction conditions (Scheme 4).

![Scheme 4](image)
2. Synthesis of 2-arylidene-1-indanones

2-Arylidene-1-indanones (14) are important intermediates for the synthesis of a wide variety of heterocyclic ring systems. For this reason, it is useful to have simple and convenient procedures for their preparation. Most of the hitherto utilized syntheses are based on the condensation of 1-indanones (13) with aldehydes in the presence of catalyst to afford E-2-arylidene-1-indanones (E-14) (Scheme 5).

\[ \text{R}^1 = \text{R}^2 = \text{H}, \text{R}^1 = \text{R}^2 = \text{Me}, \text{R}^1 = \text{H}, \text{R}^2 = \text{Ph} \]

Scheme 5

In most cases sodium or potassium hydroxide is used as catalyst\textsuperscript{8,25,26,82-91} and E-2-arylidene-1-indanones (E-14) are obtained in good yields. Various inorganic acids, viz. H\textsubscript{2}SO\textsubscript{4}, H\textsubscript{3}PO\textsubscript{4} or HCl also have been utilized to catalyze the condensation reaction to obtain E-2-arylidene-1-indanones (E-14).\textsuperscript{92-97} It should be mentioned that acetic anhydride also has been used to facilitate the condensation of indanones with benzaldehydes.\textsuperscript{98}

Recently Basavaiah and Reddy\textsuperscript{99} have introduced a simple one-pot procedure for the preparation of E-2-arylidene-1-indanones (E-14) starting from tert-butyl 3-aryl-3-hydro-2-methylenepropanoate (15). Compound 15 was allowed to react with a catalytic amount of conc. H\textsubscript{2}SO\textsubscript{4} in benzene followed by reaction of the intermediates formed with trifluoroacetic anhydride in methylene chloride to afford E-2-arylidene-1-indanones (E-14) (Scheme 6).

\[ \text{Scheme 6} \]
E-2-Arylidene-1-indanones (E-14) have been photosomerized by irradiation with UV light to obtain Z-2-arylidene-1-indanones (Z-14) (Scheme 5). The two diastereomers can be easily differentiated by 1H-NMR spectroscopic measurements.

The above discussed procedures made possible the preparation of both diastereomers of the 2-arylidene-1-indanones (14) which can be used as intermediates for the stereospecific synthesis of a wide variety of heterocyclic ring systems.

3. Synthesis of 2-arylidene-1-tetralones

Similarly to the 2-arylidene-1-indanones (14), 2-arylidene-1-tetralones (17) are useful intermediates for the synthesis of polycyclic ring systems. For this reason, several synthetic methods have been developed for their preparation starting from 1-tetralone (16). Condensation of the ketone and aldehyde components is performed in the presence of catalyst to yield E-2-arylidene-1-tetralones (E-17) (Scheme 7). The majority of compounds E-17 have been synthesized by the condensation of 1-tetralone (16) with aromatic aldehydes in alcoholic solution in the presence of sodium or potassium hydroxide. Another alkaline catalyst is piperidine which has also been used in several cases to obtain E-2-arylidene-1-tetralones (E-17). Also, as acidic catalysts, H2SO4 and H3PO4 have been utilized for this condensation. No significant difference was observed if different catalysts were used for the same purpose.

\[
\begin{align*}
\text{16} & \quad + \quad \text{OHC} - \text{Ar} & \quad \rightarrow & \quad \text{E-17} & \quad \text{hv} & \quad \rightarrow & \quad \text{Z-17}
\end{align*}
\]

Scheme 7

E-2-Arylidene-1-tetralones (E-17) have been converted into Z-2-arylidene-1-tetralones (Z-17) by photoisomerization (Scheme 7). In this way both diastereomers became available as starting materials for the preparation of polycyclic organic compounds.

4. Synthesis of 2-arylidene-1-benzosuberones

E-2-Arylidene-1-benzosuberones (E-19) were synthesized by the condensation of 1-benzosuberone (18) with aromatic aldehydes either by using alkaline or acidic catalysts (Scheme 8). E-2-Arylidene-1-benzosuberones (E-19) have been converted into their Z-isomers (Z-19) by photoisomerization (Scheme 8).
Synthesis and chemical transformations of the 2-arylidene-1-benzosuberones (19) have hitherto received less attention than those of the related 2-arylidene-1-indanones (14) and 2-arylidene-1-tetralones (17).

5. Synthesis of aurones

Aurones belong to the naturally occurring flavonoids and, therefore, their syntheses are usually described in comprehensive books of flavonoids. Since aurones can be considered oxanalogues of the 2-arylidene-1-indanones (14), it seemed expedient to include the most important procedures used for their preparation.

First, the Algar-Flynn-Oyamada reaction based on the oxidative cyclization of 2'-hydroxychalcones should be mentioned since one of the products is aurone. Another procedure described by Donnelly et al. is also based on the reactions of chalcones. 2'-acetoxychalcones are first bromomethylated and the ring closure of the bromodihydro-chalcones provides aurones. However, none of these procedures can be considered as rational methods for the synthesis of aurones.

The most common synthetic procedures are based on the condensation of coumaran-3-ones (20) with benzaldehydes in the presence of catalyst to afford Z-aurones (21). Sodium hydroxide, hydrochloric acid or $H_3PO_4$ were used as catalysts for this condensation (Scheme 9).

Farkas et al. performed the condensation of the appropriate coumaran-3-one (20) with substituted benzaldehydes in hot acetic anhydride to obtain Z-aurones (Z-21) and their glycosides.
All the naturally occurring aurones are the \( Z \)-diastereomers (\( Z-21 \)) which can be converted into the \( E \)-diastereomers (\( E-21 \)) by photoisomerization.\[^{143}\] The stereochemistry of the aurone diastereomers has been elucidated by NMR spectroscopic measurements and by X-ray diffraction analysis.\[^{143-145}\]

6. Synthesis of 1-thioaurones

1-Thioaurones, synthetic thio analogues of the naturally occurring aurones are scarcely mentioned in the chemical literature. Nonetheless, the synthesis of both their diastereomers has already been published in several papers.\[^{139,146-149}\] 1-Thiocoumaran-3-ones (\( 22 \)) are allowed to react with substituted benzaldehydes in the presence of H\(_3\)PO\(_4\)\[^{139}\] or in piperidine\[^{146}\] to afford \( Z \)-1-thioaurones (\( Z-23 \)) (Scheme 10). \( Z \)-1-Thioaurones (\( Z-23 \)) have also been obtained by the conversion of 1-thioflavanone 1-oxide in a mixture of acetic anhydride and sodium acetate.\[^{148}\]

![Scheme 10](image)

Recently, a convenient one-step synthesis has been published.\[^{149}\] Equimolar amounts of (2-methylthio)benzoic acid (\( 24 \)) and aromatic aldehydes were allowed to react with two equivalents of LDA in THF at 0 °C to yield \( Z \)-1-thioaurones (\( Z-23 \)) (Scheme 11).

![Scheme 11](image)

\( Z \)-1-Thioaurones (\( Z-24 \)) have been converted into \( E \)-1-thioaurones (\( E-23 \)) (Scheme 11) by photoisomerization. The two diastereomers can be differentiated by spectroscopic methods.
7. Synthesis of 3-arylidene-4-chromanones

Synthetic 3-arylidene-4-chromanones (26) are known from the early twentieth century. Some of their representatives have also been isolated as natural products belonging to the homoisoflavonoids. The traditional synthesis of the $E$-3-arylidene-4-chromanones ($E$-26) is based on the condensation of 4-chromanones (25) with aromatic aldehydes in the presence of a catalyst (Scheme 12). This procedure can be subdivided according to the catalyst used. For a long time, in the majority of cases, acid-catalyzed condensation of the two components was accomplished. As catalyst, $\text{H}_2\text{SO}_4$, $\text{H}_3\text{PO}_4$ and $\text{HCl}$ were used. In many cases an alkoholic solution of the two reaction partners was saturated with anhydrous hydrogen chloride and then the mixture was left to stand to afford the desired $E$-3-arylidene-4-chromanone ($E$-26). However, the acid-catalyzed reaction is not always convenient for the synthesis of some analogues of $E$-26.

![Scheme 12](image)

For this reason, this condensation has also been performed under various reaction conditions. Farkas et al. accomplished the reaction of the appropriate ketone and aldehyde in hot acetic anhydride, which is a very simple and convenient method, but sometimes it requires a prolonged (e.g. 80 h) refluxing. This disadvantage may be a reason that this method has not become a widely used one.

Another procedure used for the synthesis of $E$-3-arylidene-4-chromanones ($E$-26) is the base-catalyzed condensation of 4-chromanones (25) with aromatic aldehydes. In their studies, Pfeiffer et al. used sodium hydroxide and sodium methoxide as catalysts. Woods and Dix heated a mixture of 4-chromanone (25), aromatic aldehyde and anhydrous potassium acetate which provided the appropriate $E$-3-arylidene-4-chromanone ($E$-26) on treatment of the reaction mixture with acid.

In our own studies, piperidine was used as catalyst to afford $E$-3-arylidene-4-chromanones ($E$-26). However, it should be mentioned that in the case where piperidine is used as catalyst, an exo-endo double bond migration takes place if the benzaldehyde has strong electron acceptor substituent(s). In such a case, 3-benzyl-4-chromone (homoisoflavone) (28) is the
sole isolable product instead of the expected \( E \)-3-arylidene-4-chromanone (\( E-26 \)). Recently, pyrrolidine was used as catalyst for this condensation.\(^{182}\) Basavaiah et al.\(^{99,183}\) synthesized \( E \)-3-arylidene-4-chromanones (\( E-26 \)) by the ring closure of an acrylic acid derivative (\( 27 \)) with trifluoroacetic anhydride in methylene chloride (Scheme 13).

### Scheme 13

\( E \)-3-Arylidene-4-chromanones (\( E-26 \)) have been isomerized into their \( Z \)-diastereomers (\( Z-26 \)) upon UV irradiation.\(^{184-186}\) The two diastereomers can easily be differentiated by NMR spectroscopic measurements.

\( E \)-3-Benzylidene-4-chromanones (\( E-26 \)) can be converted into the corresponding 3-benzyl-4-chromones (homoisoflavones) (\( 28 \)) under various reaction conditions (Scheme 14). The piperidine-catalyzed exo-endo double bond transposition has already been mentioned.\(^{179,181}\) Donnelly et al.\(^ {187}\) performed such reactions in \( \text{N,N} \)-dimethylformamide with potassium carbonate. Andrieux et al.\(^ {188}\) prepared 3-benzyl-4-chromones (\( 28 \)) from 3-benzylidene-4-chromanones (\( 26 \)) by double bond migration promoted by rhodium trichloride trihydrate.

On all these bases, it can be concluded that the 3-arylidene-4-chromanones (\( 26 \)) are not only useful intermediates for the synthesis of various heterocyclic ring systems but also for the preparation of naturally occurring homoisoflavones and their synthetic analogues.

### Scheme 14

8. **Synthesis of 3-arylidene-1-thio-4-chromanones**

3-Arylidene-1-thio-4-chromanones (\( 30 \)) have hitherto received much less attention than the related 3-arylidene-4-chromanones (\( 26 \)). Their synthesis is based on the condensation of 1-thio-4-chromanones (\( 29 \)) with aromatic aldehydes mainly under acidic reaction conditions.\(^{127,189-195}\)
We have accomplished this condensation by using piperidine catalyst.\textsuperscript{178,179} As described for the condensation of the 4-chromanone (25) with aromatic aldehydes,\textsuperscript{178,179} in the case of benzaldehydes bearing strongly electron-withdrawing substituent(s), an exo-endo double bond transposition also takes place, resulting in the formation of 3-benzyl-1-thio-4-chromones (31) instead of 3-benzylidene-1-thio-4-chromanones (30) (Scheme 15).\textsuperscript{179,196} It means that these reaction conditions are adequate for the synthesis of 3-benzyl-1-thio-4-chromones (1-thiohomoisoflavones) in special cases.

![Scheme 15](image)

3-Arylidene-1-thio-4-chromanones (30) synthesized under the above-discussed reaction conditions are Z-isomers in each case. In these isomers the carbonyl and aryl groups are on the opposite sides of the exocyclic double bond. Prior to our own study,\textsuperscript{197} their E-diastereomers had not been reported in the literature. Z-3-arylidene-1-thio-4-chromanones (Z-30) were photoisomerized to afford E-3-arylidene-1-thio-4-chromanones (E-30) (Scheme 16), however, where a methoxy or ethoxy group was present in the p-position of the phenyl group, 3-methylene-1-thioflavanone (32) was formed. This is an unprecedented transformation of these 1-thiochromanone derivatives that provides a new method for the preparation of compounds 32.

![Scheme 16](image)

9. Synthesis of 3-arylideneflavanones

3-Arylideneflavanones (termed flavindognides) (34) are well known flavanone derivatives. Their first representatives were synthesized by Katschalowsky and Kostanecky in 1904.\textsuperscript{198} For a long
time, \( E-3 \)-Arylideneflavanones (\( E-34 \)) were synthesized solely by the acid-catalyzed condensation of flavanones (33) and aromatic aldehydes (Scheme 17).\(^{198-205}\) The reaction usually has been performed in alcoholic solution saturated with anhydrous hydrochloric acid at various temperatures and for different reaction times. For this condensation, use of glycine as catalyst was also described in one case.\(^{206}\) It was reported that in some cases the base-catalyzed condensation of a hydroxyacetophenone with a benzaldehyde gave 3-benzylideneflavanone as a coproduct of the corresponding hydroxy-chalcone.\(^{207-209}\)

![Scheme 17](image)

Prior to our own study,\(^{210}\) neither inorganic nor organic bases had been used as catalysts for the preparation of 3-arylideneflavanones (34) by the condensation of flavanones (33) with aromatic aldehydes. We have introduced a very simple base-catalyzed condensation for the synthesis of \( E-3 \)-arylideneflavanones (\( E-34 \)). A mixture of equimolar amounts of flavanone (33) and aromatic aldehyde and a few drops of piperidine was allowed to react at 150\(^\circ\)C and \( E-3 \)-arylideneflavanone (\( E-34 \)) was obtained in good yield without any purification.\(^{180,210}\) Later, this simple and convenient method was used by other groups\(^{11,12,211}\) to prepare \( E-3 \)-arylideneflavanones (\( E-34 \)). It should be mentioned also that if benzaldehydes with strongly electron-withdrawing substituent(s) are used, 3-benzylflavones (35) can be prepared instead of \( E-3 \)-benzylideneflavanones (\( E-34 \)) by using a higher amount of piperidine for longer reaction times (Scheme 18).\(^{212}\)

![Scheme 18](image)
\textit{E-3-Arylideneflavanones (E-34)} prepared by the above-discussed procedures have been converted into \textit{Z-3-arylideneflavanones (Z-34)} (Scheme 17) by photoisomerization.\textsuperscript{205,213-215} The two diastereomers can be differentiated easily by NMR spectroscopic measurements.

10. Synthesis of 3-arylidene-1-thioflavanones

3-Arylidene-1-thioflavanones (37) have hardly been described in the literature. A very few representatives were synthesized by the acid-catalyzed condensation of 1-thioflavanones (36) with substituted benzaldehydes (Scheme 19).\textsuperscript{189,216,217} Similarly to the synthesis of other exocyclic $\alpha,\beta$-unsaturated ketones, we have used piperidine catalyst for the condensation of 1-thioflavanone (36) with substituted benzaldehydes to obtain \textit{Z-3-benzylidene-1-thioflavanones (Z-37)} (Scheme 19).\textsuperscript{218}

\begin{center}
\textbf{Scheme 19}
\end{center}

However, this procedure can be used only for the synthesis of \textit{Z-3-benzylidene-1-thioflavanones} substituted with electron donating or slightly electron-withdrawing substituent(s) in the benzylidene moiety. Where benzaldehydes substituted with strongly electron-withdrawing substituent(s) were used, 3-benzyl-1-thioflavones (38) were obtained as the sole isolable products (Scheme 20).\textsuperscript{196,218} It is worth mentioning that this is the first synthesis of the latter.

\begin{center}
\textbf{Scheme 20}
\end{center}

\textit{Z-3-Arylidene-1-thioflavanones (Z-37)} have been converted into their \textit{E}-isomers (\textit{E-37}) by photoisomerization.\textsuperscript{197,215} The two diastereomers can be differentiated by NMR spectroscopy.
11. Closing remarks

In this short review article the most important procedures used for the synthesis of both diastereomers of selected groups of α,β-unsaturated ketones have been compiled and discussed. These α,β-enones are useful intermediates for the stereoselective syntheses of a wide variety of heterocyclic compounds with a polycyclic skeleton. A major aim of the present review article has been to concentrate on exocyclic α,β-unsaturated ketones derived from heterocyclic ketones, víz. coumaran-3-ones, 4-chromanones and their thio analogues.

Literature data published until the end of June 2003 have been included to help the reader to find information appropriate for the synthesis of a particular exocyclic α,β-unsaturated ketone.

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