A comprehensive review of the oxidative cyclisation of 2’-hydroxychalcones to aurones and flavones

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Abstract

The oxidative cyclisation reactions of 2’-hydroxychalcones to corresponding aurones and flavones are discussed. While Hg^{2+}, Cu^{2+} and Tl^{3+}-mediated oxidative cyclisation of 2’-hydroxychalcones selectively give aurones, I_{2}, Se^{4+}, In^{3+}, Cu^{+} and Fe^{3+}-mediated reactions preferable give flavones. The general mechanisms of these oxidative cyclisation reactions are proposed.

Keywords: 2’-hydroxychalcones, aurones, flavones, oxidative cyclisation

Introduction

Substituted 2’-hydroxychalcones are widely distributed in the plant kingdom. They are also accessed through synthesis by the Claisen-Schmidt reaction of 2-hydroxyacetophenone and benzaldehyde or their derivatives in the presence of aqueous NaOH, KOH or Ba(OH)\_2. Enzyme-catalysed cyclisation of 2’-hydroxychalcones is a central reaction in the biosynthesis of aurones and flavanones. The biosynthesis of 2’-hydroxychalcone 1 and its subsequent elaboration into either aurone 2 or flavanone 3 is summarized in scheme 1. The biogenesis of substituted 2’-hydroxychalcones involves the chalcone synthase-catalysed reaction of three molecules of malonyl CoA and cinnamyol CoA. 2’-hydroxychalcones then either isomerise to corresponding flavanones which in turn are oxidased to flavones or directly oxidized to give aurones. Inspired by the natural oxidative cyclisation of 2’-hydroxychalcones, chemists have developed procedures for the synthesis of aurones and flavones from 2’-hydroxychalcones. Hence, the aim of this article is to compare and contrast these procedures with regards to their percentage yields and duration of the reactions.

Scheme 1: The biosynthetic relationships of 2’-hydroxychalcone, aurones and flavones

Oxidative cyclisation of 2’-hydroxychalcones to aurones

Aurones are a rare class of natural occurring flavonoids and have been isolated from flowering plants, ferns, mosses and marine brown algae. Both the Z (5) and E (6) isomers (figure 1) are found in nature with the thermodynamically more stable Z isomer more abundant.
Transition metal salts-mediated oxidative cyclisation of 2'-hydroxychalcones is a reliable reaction for the synthesis of aurones. The reaction is thought to proceed by coordination of the transition metal salt of type M-Y to the double bond of chalcone 7 making the α-carbon susceptible to an intramolecular electrophilic reaction with the 2’-hydroxy group to give intermediate 8. A facile E1CB-type elimination then proceeds to give the more thermodynamic stable aurone isomer 5, scheme 2.

As a result of the extensive studies of a number of research groups, three transition metal salts Hg(OAc)2, CuBr2 and Tl(NO3)3 have become important and useful reagents for oxidative cyclisation of 2'-hydroxychalcone derivatives to aurones. A typically Hg(OAc)2-mediated cyclisation of 2’-hydroxychalcone involves refluxing a solution of chalcone 7 in pyridine in the presence of molar equivalent of Hg(OAc)2 to give aurone 5 as the only detectable product in 78% yield, scheme 3 [16-18]. Under these reaction conditions, chalcones 9, 10, and 11 amongst others were converted to aurones 12, 13, and 14 respectively in high yields. The reaction is equally effective when DMSO is used as the solvent instead of pyridine [19, 20]. However, when acetic acid is used as the solvent in the Hg(OAc)2-mediated cyclisation reaction of 2'-hydroxychalcones, the reaction gave a mixture of aurones (major products) and flavanones [21].

CuBr2 has also proved to be an effective agent for the oxidative cyclisation of 2’-Hydroxychalcones to give aurones. The efficient synthesis of aurones 5, 12, 13 and 14 in yields of 72-80% by Agrawal and Soni involved the CuBr2-mediated oxidative cyclization of chalcones 7, 9, 10 and 11 respectively, scheme 4 [16]. Although this reaction took a much longer time than the Hg(OAc)2-mediated oxidative cyclisation described in scheme 3, it afforded the aurones in comparable yields. An alternative approach explored by Ameta and co-workers involved refluxing a solution 2'-hydroxychalcones and CuBr2 in a DMF-H2O mixture (4:1 v/v) instead of DMSO to give the corresponding aurones in lower yields of 63-73%. [22]

The use of thallium (III) nitrate in the oxidative rearrangement of 2’-hydroxychalcones to corresponding isoflavones is well documented [23-25]. However, in 1995 Thakkar and Cushman reported a Tl(NO3)3-mediated cyclisation of 2’-hydroxychalcones to aurones as the only products [26]. Recently, Thanigaimalai and co-workers carried out extensive studies on the same reaction [27]. The reaction involved treatment of a solution of chalcone 15 in MeOH with two molar equivalent of Tl(NO3)3 followed by stirring for 24 h. Subsequent addition of two molar equivalent of HCl (2 M) to the reaction mixture and stirring at 65 °C for 5 h gave aurone 16 in 75% yield after column chromatography. Replacing the -NO2 group in chalcone 15 with other electron-withdrawing groups such as -Cl, -CHO, and -CO2Me gave the corresponding aurones in low yields of 43% or less. However when the -NO2 group was replaced by electron-donating groups such as -OH, -OCH2OCH3 and OCH3 only isoflavone 17 was isolated [27].

**Oxidative cyclisation of 2’-hydroxychalcones to flavones**

Flavones are structurally isomers of aurones and are widely distributed in nature. Although several methods for the synthesis of flavones have been reported, the oxidative cyclisation of 2’-hydroxychalcones remains an important route to flavones. The speculative general mechanisms for this oxidative cyclisation of 2’-hydroxychalcones are summarized in scheme 6. One mechanism involves chalcone 7 undergoing an intramolecular oxo-Michael addition reaction to give an enolate which is trapped by the reagent X-Y to give intermediate 18. A facile elimination reaction then proceeds to give flavone 20. Alternatively, 2’-hydroxychalcone 7 isomerizes into flavanone 19 which then undergo oxidation to give flavone 20.
Scheme 6: Speculative general mechanisms of oxidative cyclisation of 2'-hydroxychalcones to flavones

The I$_2$-DMSO reagent has featured prominently in the cyclisation of 2'-hydroxychalcones to flavones. It is assumed that I$_2$ acts as the reagent X-Y in scheme 6. DMSO on the other hand has been documented as an oxidant mostly of primary alcohols to corresponding aldehydes [28-31]. It is therefore reasonable to assume that the role of DMSO in I$_2$-DMSO reagent is to act as a co-oxidant to regenerate I$_2$ as shown in scheme 7. From scheme 6, a molecule of HI is liberated when chalcone 7 cycles to give intermediate 18. This molecule of HI then undergoes an addition reaction with DMSO to give intermediate 21. Subsequent protonation of intermediate 21 gives cation 22 which undergoes a nucleophilic reaction with I to regenerate I$_2$, scheme 7.

To mitigate against the disappointing low yields of the classical I$_2$-DMSO-mediated cyclisation of 2'-hydroxychalcones to corresponding flavones, synthetic chemists have investigated modifications to the procedure. To this end, Lokhande and co-workers have described the rapid I$_2$-DMSO-mediated deprotection of 2'-allyloxychalcone 25 and subsequent oxidative cyclisation to give flavone 30 in 86% yield, scheme 9 [34]. Molar equivalent of iodine was used in this procedure. Likewise, allyloxychalcones 26, 27, 28 and 29 amongst others were converted to the flavones 31, 32, 33 and 34 respectively in 85-97% yields [34]. These results suggested that this procedure was tolerated by alkoxy, halo and nitro substituents on the aromatic rings of the 2'-hydroxychalcones.

Another method that gave synthetically useful yields involved silica gel-supported I$_2$ (SiO$_2$-I$_2$) as the oxidant, scheme 10 [35]. The SiO$_2$-I$_2$ reagent was prepared by dissolving I$_2$ (2.5 g) in minimum amount of dichloromethane and to this solution was added silica gel (25 g). The mixture was then made homogeneous and air-dried. With the required oxidant in hand, the oxidative cyclisation of chalcone 35 was achieved by heating it with the SiO$_2$-I$_2$ reagent without any solvent to give flavone 39 in 80% yield [35]. The tolerance of the procedure to various functional groups was demonstrated by exposing chalcones 36, 37 and 38 amongst others to the SiO$_2$-I$_2$ reagent to give flavones 40, 41 and 42 respectively in 68-92% yields, scheme 10 [35]. The best yield of 92% was achieved when 37 with R$_1$ = CH$_3$ and R$_2$ = R$_3$ = H was used as the substrate. It is important to note that under this reaction conditions, extra hydroxyl groups on ring A do not stop the reaction from proceeding. Chalcone 38 with the highly electron-withdrawing nitro substituent on ring B gave a significantly lower yield of the corresponding flavone 42 when compared to the other substrates.
NH₄I is a white crystalline powder that turns yellow when exposed to moist air owing to its decomposition giving iodine and ammonia. This in situ generation of iodine from the decomposition of NH₄I was used by Kulkarni and co-workers to achieve the oxidative cyclisation of 2'-hydroxychalcone to flavone 20 in 92% yield [36]. The reaction involved heating a mixture of chalcone 7 and NH₄I under solvent-free conditions at 120 °C for one hour. The reaction was found to be tolerant to halo, methoxy, dialkynino and nitro groups as shown by the conversion of chalcones 43, 44, 45, 46 and 47 amongst others to the corresponding flavones 48, 49, 50, 51 and 52, scheme 11 [36].

In addition to iodine, transition metals have been reported to be effective agents for the cyclisation of 2'-hydroxychalcones to flavones. Selenium (IV) reagents for example have proved to be very efficient oxidative agents in the cyclisation of 2'-hydroxychalcones to flavones under microwave irradiation. Gupta and co-workers have used silica gel-supported indium (III) halides in the conversion of 2'-hydroxychalcones to flavones in good yields. The Indium (III) halides used were InCl₃ and InBr₃ [43]. A typical procedure involved dissolving chalcone 7 in minimum amount of ethyl acetate and this was added to silica gel-supported In³⁺ halide. The solvent was then removed by evaporation and the resulting solid was heated at 130-140 °C. The solid was transferred to a column and elution with a mixture of hexane and ethyl acetate gave flavone 20 in 96% yield [43]. Under these reaction conditions, chalcones 1, 59, 60 and 61 amongst others were converted to flavones in high yields, scheme 15. The positions and nature of the R groups were generally well tolerated.

In another approach to the cyclization of 2'-hydroxychalcones to flavones using transition metals, Ahmad and co-workers have used silica gel-supported indium (III) halides in the conversion of 2'-hydroxychalcones to flavones in good yields. The Indium (III) halides used were InCl₃ and InBr₃ [43]. A typical procedure involved dissolving chalcone 7 in minimum amount of ethyl acetate and this was added to silica gel-supported In³⁺ halide. The solvent was then removed by evaporation and the resulting solid was heated at 130-140 °C. The solid was transferred to a column and elution with a mixture of hexane and ethyl acetate gave flavone 20 in 96% yield [43]. Under these reaction conditions, chalcones 1, 59, 60 and 61 amongst others were converted to their corresponding flavones in high yields, scheme 15. The positions and nature of the R groups were generally well tolerated.

Scheme 11: NH₄I-mediated oxidative cyclisation of 2'-hydroxychalcones

Gulacsí and co-workers were able to execute a synthesis of flavone 54 in 62% yield relying on the hypervalent iodine reagent phenyliodinium acetate (PIDA)-mediated oxidative cyclisation of chalcone 53, scheme 12 [37]. Just over 2.5 mole equivalent of PIDA was used in this reaction. Subsequent removal of the MOM protecting groups under acidic conditions gave natural occurring flavone yinanghuo-C isolated from Vancouveria hexandra [38] and Epimedium sagittatum [39]. This procedure was also applied to the preparation of two other prenylated flavones kanzonol-D and kanzonol-E isolated from Glycyrrhiza eurycarpa [40].

Scheme 12: PIDA-mediated oxidative cyclisation of 2'-hydroxychalcone 53

Lamba and co-workers were also able to cyclize 2'-hydroxychalcone 7 using a different Se (IV) reagent Na₂SeO₃ under microwave irradiation to give flavone 20 in slightly higher yield (85%) and shorter reaction time compared to that reported Gupta and co-workers. Comparable yields were achieved under thermal conditions but the reaction times were significantly longer (over 1 hour) [42]. The tolerance of this procedure to various functional groups was demonstrated by cyclizing chalcones 44, 55 and 56 amongst others to flavones 49, 57 and 58 respectively in yields of 75% and better, scheme 14 [42].
In their approach to flavones, Du and co-workers relied on Cul-catalyzed cyclisation of 2’-hydroxychalcones in the ionic liquid [bmim] [NTf2] as a solvent. In the event, a mixture of catalytic amount of Cul and chalcone 7 in [bmim] [NTf2] was heated and stirred for 48 hours to give flavone 20 in 92% yield [44]. To demonstrate the scope and generality of this procedure, a variety of 2’-hydroxychalcones including 37, 66, 67, 68 and 69 were converted to the corresponding flavones in high yields as shown in scheme 16.

Kumar and co-workers have utilized FeCl3·6H2O to mediate the cyclisation of 2’-hydroxychalcones to flavones in moderate yields. The procedure involved treatment of a solution of chalcone 7 in methanol with FeCl3·6H2O (2.5 molar equivalent) and refluxing the mixture until the completion of the reaction as indicated by TLC. Working-up the reaction and purifying the crude product by column chromatography gave flavone 20 in 55% yield [45]. Likewise, subjection of chalcones 55, 74 and 75 amongst others to Kumar and co-workers’ procedure gave flavones 57, 76 and 77 respectively in 55-62% yields. In addition to I2, transition metals and peroxides, a number of other reagents have proved to be efficient in the oxidative cyclisation of 2’-hydroxychalcones to flavones. For example, Hishono and co-workers employed a diphenyl disulfide (PhSSPh)-mediated reaction in the cyclisation of chalcone 7 to yield flavone 20 in good yield of 80% [59]. Using this procedure, chalcones 38, 47, 55, 81 and 82 were successfully cyclized to flavones 41, 52, 57, 83 and 84 respectively in yields ranging from low to high, scheme 20. The yields of this reaction were negatively affected when R3 was an electron withdrawing nitro group. The other drawback for this procedure was the high temperatures at which the reactions were performed.

Peroxides have proved to be efficient reagents for the oxidative cyclisation of 2’-hydroxychalcones to corresponding 3-hydroxy-flavones. For example, oxidative cyclisation took place when a solution of chalcone 7 in ethanol was mixed with excess aqueous NaOH followed by slow addition of excess H2O2 and stirring at room temperature giving the corresponding flavone 78 in 65% yield, scheme 18 [46, 47]. Likewise, chalcones 35 and 55 amongst others were cyclized to flavones 79 and 80 respectively in acceptable yields. Under microwave irradiation, these reactions proceeded to completion within seven minutes [46].

Unlike H2O2, the peroxide sodium perborate (SPB) facilitates the oxidative cyclisation of chalcones without oxygenation at position 3. Ganguly and co-workers have reported such a reaction involving conversion of chalcone 7 to flavone 20 in 65% [48]. An array of chalcones including 35, 55 and 74 were also converted to their corresponding flavones 39, 57 and 76 in moderate yields, scheme 19.

In addition to L2, transition metals and peroxides, a number of other reagents have proved to be efficient in the oxidative cyclisation of 2’-hydroxychalcones to flavones. For example, Hishono and co-workers employed a diphenyl disulfide (PhSSPh)-mediated reaction in the cyclisation of chalcone 7 to yield flavone 20 in good yield of 80% [59]. Using this procedure, chalcones 38, 47, 55, 81 and 82 were successfully cyclized to flavones 41, 52, 57, 83 and 84 respectively in yields ranging from low to high, scheme 20. The yields of this reaction were negatively affected when R3 was an electron withdrawing group. Hence, the lowest yield of 19% was achieved when R3 was the electron-withdrawing nitro group. The other drawback for this procedure was the high temperatures at which the reactions were performed.

**Scheme 16: Cul-catalysed oxidative cyclisation of 2’-hydroxychalcones**

**Scheme 17: FeCl3·6H2O-mediated oxidative cyclisation of 2’-hydroxychalcones**

**Scheme 18: H2O2-mediated oxidative cyclisation of 2’-hydroxychalcones**

**Scheme 19: SPB-mediated oxidative cyclisation of 2’-hydroxychalcones**

**Scheme 20: PhSSPh-mediated oxidative cyclisation of 2’-hydroxychalcones**
As a further alternative approach, Zambare and co-workers described an oxalic acid catalyzed cyclisation of 2'-hydroxychalcones to corresponding flavones. This simple and efficient method involved treatment of a solution of chalcone 7 in ethanol with catalytic amount of oxalic acid and refluxing the reaction mixture to give flavone 20 in 95% yield. The reaction was equally effective for cyclisation of chalcones bearing electron-donating or electron-withdrawing groups such as 47, 55, 85, and 86 giving flavones 52, 57, 87 and 88 respectively in high yields, scheme 21. It is important to note that the acid-catalysed isomerization of 2'-hydroxychalcones to corresponding flavonones is well documented. The most likely oxidant for the conversion of the flavanones to corresponding flavones in Zambare and co-workers procedure is atmospheric molecular oxygen.

Scheme 21: Oxalic acid-catalysed oxidative cyclisation of 2'-hydroxychalcones

**Conclusion**

Although a number of procedures are available for the synthesis of aurones and flavones, this review highlights the importance of the oxidative cyclisation of 2'-hydroxychalcones to these biologically relevant compounds. The Hg(OAc)₂-mediated oxidative cyclisation of 2'-hydroxychalcones is the most reliable reaction for the synthesis of aurones while the I₂-mediated reaction is the most used for the synthesis of flavones. This review has also highlighted the advantage of reactions under microwave irradiation over thermal reactions. While thermal reactions proceed to completion in hours, corresponding microwave reactions proceed to give the products under 10 minutes.

**Acknowledgements**

The author thanks the University of Botswana library for providing access to journal articles cited in this review paper.

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