International Journal of Chemical Studies

P-ISSN2349–8528
E-ISSN 2321–4902
IJCS 2015; 3(3): 53-59

Received: 26-08-2015
Accepted: 28-09-2015

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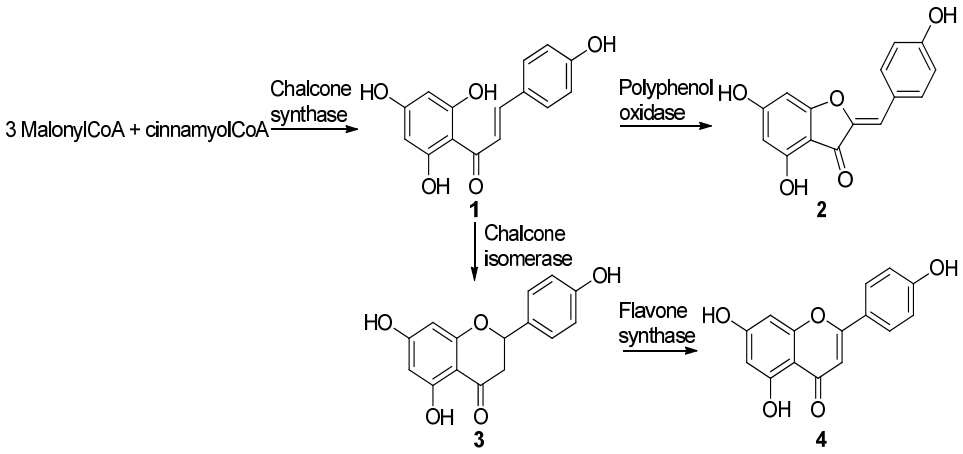
A comprehensive review of the oxidative cyclisation of 2'-hydroxychalcones to aurones and flavones

Ishmael B Masesane

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 [1-6]. 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 $Ba(OH)_2$ [7-11]. 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 [12-14]. Inspired by the natural oxidative cyclisation of 2'-hydrochalcones, 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.

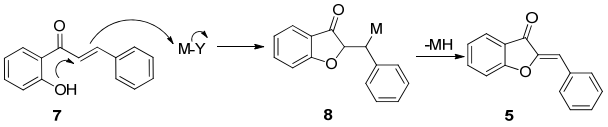


Scheme 1: The biosynthetic relationships of 2'-hydroxychalcone, aurones and flavones

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.[15] Both the Z (**5**) and E (**6**) isomers (figure 1) are found in nature with the thermodynamically more stable Z isomer more abundant.

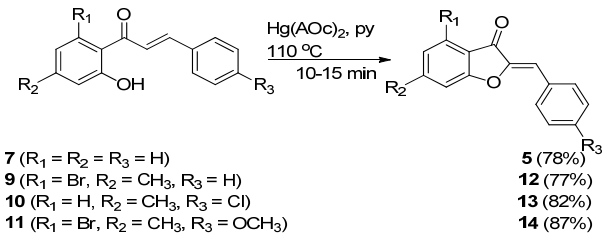
Fig 1: Geometric isomers of an aurone

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 *intra*-molecular 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.



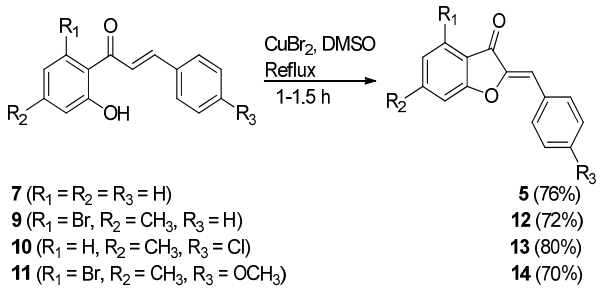
Scheme 2: Possible mechanism for the oxidative cyclisation of chalcone **7**

As a result of the extensive studies of a number of research groups, three transition metal salts $Hg(OAc)_2$, $CuBr_2$ and $Tl(NO_3)_3$ 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].



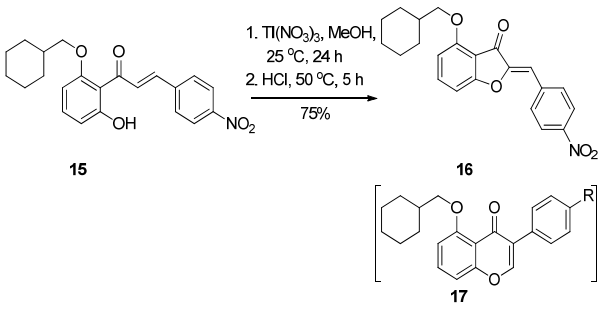
Scheme 3: $Hg(OAc)_2$-mediated Oxidative cyclisation of 2'-hydroxychalcones

$CuBr_2$ 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 $CuBr_2$-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 $CuBr_2$ in a DMF-H_2O mixture (4:1 v/v) instead of DMSO to give the corresponding aurones in lower yields of 63-73%.[22]



Scheme 4: $CuBr_2$-mediated oxidative cyclisation of 2'-hydroxychalcones

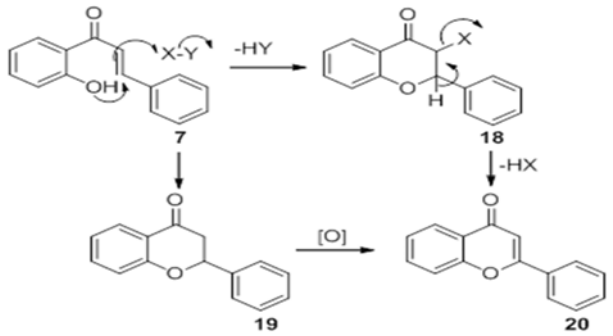
The use of thallium (III) nitrate in the oxidative rearrangement of 2'-hydroxychalcones to corresponding isoflavones is well documented [23-25]. However, in 1995 Thakkar and Cushman reported a $Tl(NO_3)_3$-mediated cyclisation of 2'-hydroxychalcones to aurones as the only products [26]. Recently, Thanigaimalai 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 $Tl(NO_3)_3$ 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 -NO_2 group in chalcone 15 with other electron-withdrawing groups such as –Cl, -CHO, and -CO_2Me gave the corresponding aurones in low yields of 43% or less. However when the –NO_2 group was replaced by electron-donating groups such as –OH, -OCH_2OCH_3 and OCH_3 only isoflavone 17 was isolated [27].



Scheme 5: $Tl(NO_3)_3$-mediated oxidative cyclisation of 2'-hydroxychalcones

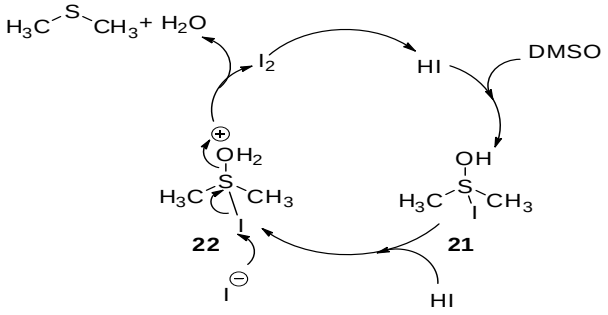
Oxidative cyclisation of 2'-hydroxychalcones to flavones

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.



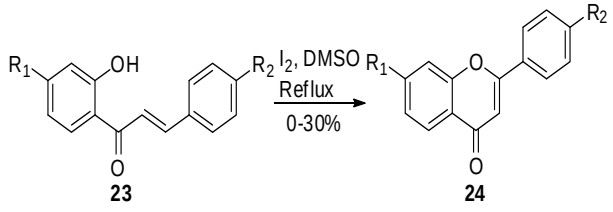
Scheme 6: Speculative general mechanisms of oxidative cyclisation of 2'-hydroxychalcones to flavones

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.



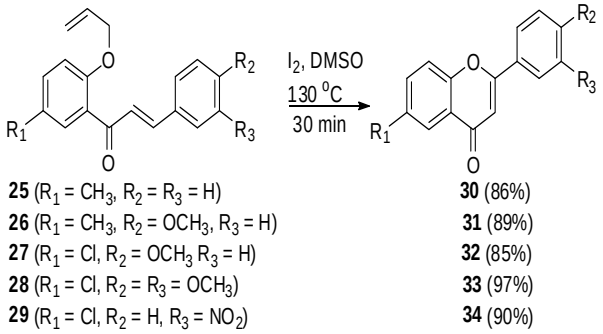
Scheme 7: DMSO-mediated regeneration of I_2

The classical I_2-DMSO-mediated oxidative cyclisation of 2'-hydroxychalcones involves refluxing chalcones of type 23 in DMSO in the presence of catalytic amount of iodine giving the corresponding flavones of type 24 in low yields of about 30%, scheme 8 [9, 32]. This reaction is tolerant to methoxy-, halo- and methyl- groups on any of the two aromatic rings but fails when R_1 or/and R_2 are free hydroxyl groups. Recently, it was reported that the presence of two halo substituents on ring A and methoxy groups on ring B of chalcone 23 led to considerable increase in the yield of the corresponding flavone [33].



Scheme 8: I_2-DMSO-mediated oxidative cyclisation of 2'-hydroxychalcones

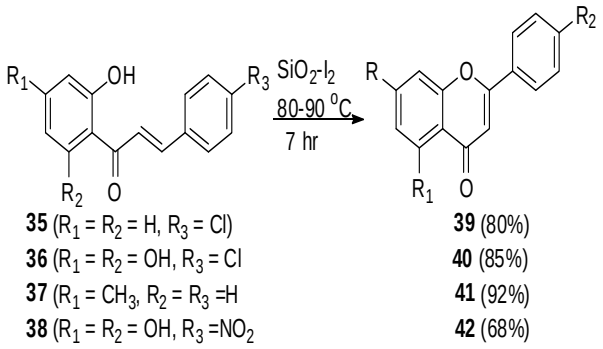
To mitigate against the disappointing low yields of the classical I_2-DMSO-mediated cyclisation of 2'-hydroxychalcones to corresponding flavones, synthetic chemists have investigated modifications to the procedure. To this end, Lokhande and co-workers have described the rapid I_2-DMSO-mediated deprotection 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.



25 (R_1 = CH_3, R_2 = R_3 = H) **30** (86%)
26 (R_1 = CH_3, R_2 = OCH_3, R_3 = H) **31** (89%)
27 (R_1 = Cl, R_2 = OCH_3 R_3 = H) **32** (85%)
28 (R_1 = Cl, R_2 = R_3 = OCH_3) **33** (97%)
29 (R_1 = Cl, R_2 = H, R_3 = NO_2) **34** (90%)

Scheme 9: I_2-DMSO-mediated deprotection and oxidative cyclisation of 2'-allyloxychalcones

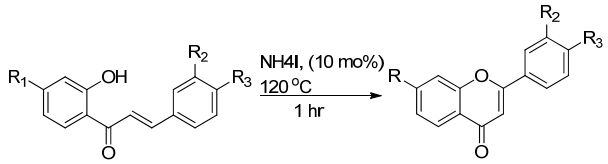
Another method that gave synthetically useful yields involved silica gel-supported I_2 (SiO_2-I_2) as the oxidant, scheme 10 [35]. The SiO-I_2 reagent was prepared by dissolving I_2 (2.5 g) in minimum amount of dichloromethane and to this solution was added silica gel (25 g). The mixture was then made 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.



35 (R_1 = R_2 = H, R_3 = Cl) **39** (80%)
36 (R_1 = R_2 = OH, R_3 = Cl **40** (85%)
37 (R_1 = CH_3, R_2 = R_3 =H **41** (92%)
38 (R_1 = R_2 = OH, R_3 =NO_2 **42** (68%)

Scheme 10: SiO_2-I_2-mediated oxidative cyclisation of 2'-hydroxychalcones

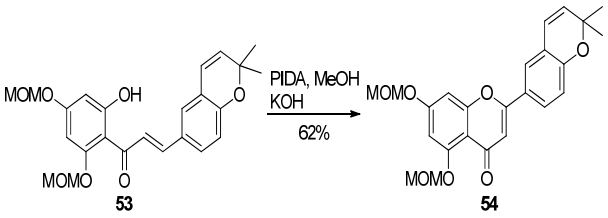
NH_4I is a white crystalline powder that turns yellow when exposed to moist air owing to its decomposition give iodine and ammonia. This *in situ* generation of iodine from the decomposition of NH_4I was used by Kulkarni and co-workers to achieve the oxidative cylisation of 2'-hydroxychalcone **7** to flavone 20 in 92% yield [36]. The reaction involved heating a mixture of chalcone 7 and NH_4I under solvent-free conditions at 120 ºC for one hour. The reaction was found to be tolerant to halo, methoxy, dialkyamino 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]



7 ($R_1 = R_2 = R_3 = H$) **20** (92%)
43 ($R_1 = R_2 = H$, $R_3 = Cl$) **48** (94%)
44 ($R_1 = R_3 = OCH_3$, $R_2 = H$) **49** (79%)
45 ($R_1 = OH$, $R_2 = H$ $R_3 = OCH_3$ **50** (67%)
46 ($R_1 = R_2 = H$, $R_3 = N(CH_3)_2$) **51** (72%)
47 ($R_1 = R_2 = H$, $R_3 = NO_2$) **52** (75%)

Scheme 11: NH_4I-mediated oxidative cyclisation of 2'-hydroxychalcones

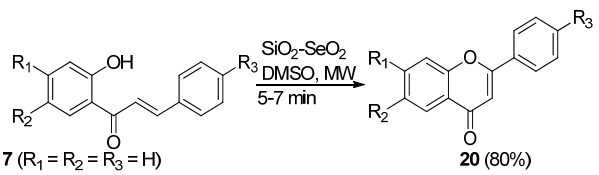
Gulacsi and co-workers were able to execute a synthesis of flavone 54 in 62% yield relying on the hypervalent iodine reagent phenyliodinium acetate (PIDA)-mediated oxidative cyclisation of chalcone 53, scheme 12 [37]. Just over 2.5 mole equivalent of PIDA was used in this reaction. Subsequent removal of the MOM protecting groups under acidic conditions gave natural occurring flavone yinyanghuo-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[37] isolated from *Glycyrrhiza eurycarpa* [40].



53 **54**

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

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 described a procedure for the oxidative cyclisation of 2'-hydroxychalcone 7 using silica gel-supported SeO_2 (SiO_2-SeO_2) under microwave irradiation to give flavone 20 in 80% yield.[41] The wide scope of this procedure was demonstrated by cyclizing 2'-hydroxychalcones 45, 47, 55 and 56 with an array of functional groups to their corresponding flavones 50, 52, 57 and 58 in high yields, scheme 13. Low yields and long reaction times were recorded when the reactions were attempted under thermal conditions [41].



7 ($R_1 = R_2 = R_3 = H$) **20** (80%)
45 ($R_1 = OH$, $R_2 = H$, $R_3 = OCH_3$) **50** (77%)
47 ($R_1 = R_2 = H$, $R_3 = NO_2$) **52** (82%)
55 ($R_1 = R_2 = H$, $R_3 = OCH_3$) **57** (79%)
56 ($R_1 = H$, $R_2 = CH_3$, $R_3 = OCH_3$) **58** (88%)

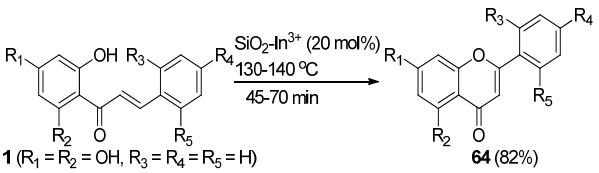
Scheme 13: Se (IV)-mediated oxidative cyclisation of 2'hydroxychalcones

Lamba and co-workers were also able to cyclize 2'-hydroxychalcone 7 using a different Se (IV) reagent Na_2SeO_3 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].

7 ($R_1 = R_2 = R_3 = H$) **20** (85%)
44 ($R_1 = OCH_3$, $R_2 = H$, $R_3 = OCH_3$) **49** (75%)
55 ($R_1 = R_2 = H$, $R_3 = OCH_3$) **57** (80%)
56 ($R_1 = H$, $R_2 = CH_3$, $R_3 = OCH_3$) **58** (80%)

Scheme 14: Na_2SO_3-mediated oxidative cyclisation of 2'-hydroxychalcones

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 $InCl_3$ and $InBr_3$ [43]. A typical procedure involved dissolving chalcone 7 in minimum amount of ethyl acetate and this was added to silica gel-supported In^{3+} halide. The solvent was then removed by evaporation and the resulting solid was heated at 130-140 ºC. 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.



1 ($R_1 = R_2 = OH$, $R_3 = R_4 = R_5 = H$) **64** (82%)
7 ($R_1 = R_2 = R_3 = R_4 = R_5 = H$) **20** (96%)
59 ($R_1 = R_2 = R_4 = H$, $R_3 = R_5 = Cl$) **62** (98%)
60 ($R_1 = R_2 = R_3 = R_5 = H$, $R_4 = OH$) **63** (85%)
61 ($R_1 = R_2 = OCH_3$, $R_3 = R_5 = H$, $R_4 = NO_2$) **65** (80%)

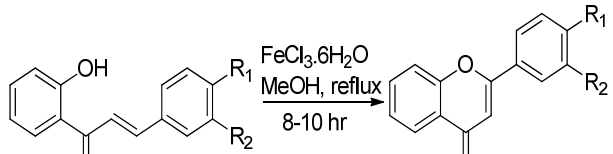
Scheme 15: In^{3+}-catalyzed oxidative cyclisation of 2'-hydroxychalcones

In their approach to flavones, Du and co-workers relied on CuI-catalyzed cyclisation of 2'-hydroxychalcones in the ionic liquid [bmim] [NTf_2] as a solvent. In the event, a mixture of catalytic amount of CuI and chalcone **7** in [bmin] [NTf_2] 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.

7 (R_1 = R_2 = R_3 = H) — **20** (92%)
37 (R_1 = CH_3, R_2 = R_3 = H) — **41** (89%)
66 (R_1 = F, R_2 = R_3 = H) — **70** (91%)
67 (R_1 = Br, R_2 = R_3 = H) — **71** (98%)
68 (R_1 = NO_2, R_2 = R_3 = H) — **72** (87%)
69 (R_1 = H, R_2 = R_3 = Cl) — **73** (90%)

Scheme 16: CuI-catalysed oxidative cyclisation of 2'-hydroxychalcones

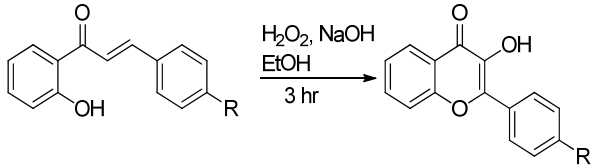
Kumar and co-workers have utilized $FeCl_3.6H_2O$ to mediate the cyclisation of 2'-hydroxychalcones to flavones in moderate yields. The procedure involved treatment of a solution of chalcone **7** in methanol with $FeCl_3.6H_2O$ (2.5 molar equivalent) and refluxing the mixture until the completion of 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, scheme 17. The $FeCl_3.6H_2O$-mediated cyclization of 2'-hydroxychalcones to flavones was found to be sensitive to solvents. The reaction failed when aprotic solvents such as THF, DMSO, DMF and toluene were used instead of the alcoholic protic solvents [45].



7 (R_1 = R_2 = H) — **20** (55%)
55 (R_1 = OCH_3, R_2 = H) — **57** (58%)
74 (R_1 = CH_3, R_2 = H) — **76** (55%)
75 (R_1 = R_2 = OCH_3) — **77** (62%)

Scheme 17: $FeCl_3.6H_2O$-mediated oxidative cyclisation of 2'-hydroxychalcones

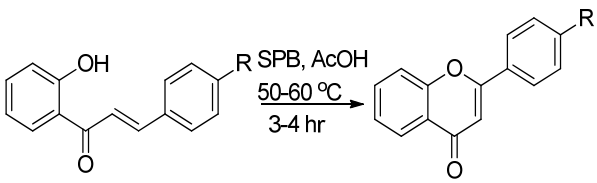
Peroxides have proved to be efficient reagents for the oxidative cyclisation of 2'-hydroxychalcones to corresponding 3-hydroxyflavones. For example, oxidative cyclisation took place when a solution of chalcone **7** in ethanol was mixed with excess aqueous NaOH followed by slow addition of excess H_2O_2 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].



7 (R = H) — **78** (65%)
35 (R = Cl) — **79** (65%)
55 (R = OCH_3) — **80** (72%)

Scheme 18: H_2O_2-mediated oxidative cyclisation of 2'-hydroxychalcones

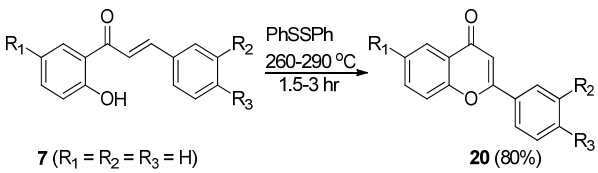
Unlike H_2O_2, the peroxide sodium perborate (SPB) facilitates the oxidative cyclisation of chalcones without oxygenation at position 3. Ganguly and co-workers have reported such a reaction involving conversion of chalcone 7 to flavone 20 in 65% [48]. An array of chalcones including 35, 55 and 74 were also converted to their corresponding flavones 39, 57 and 76 in moderate yields, scheme 19.



7 (R = H) — **20** (65%)
35 (R = Cl) — **39** (58%)
55 (R = OCH_3) — **57** (55%)
74 (R = CH_3) — **76** (55%)

Scheme 19: SPB-mediated oxidative cyclisation of 2'-hydroxychalcones

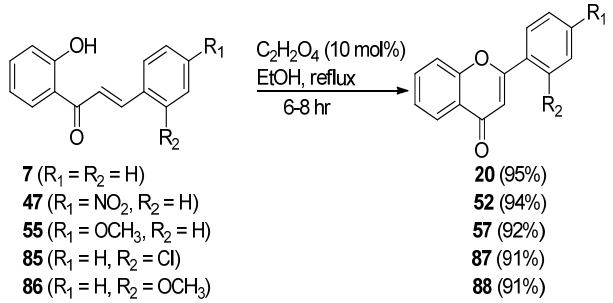
In addition to I_2, transition metals and peroxides, a number of other reagents have proved to be efficient in the oxidative cyclisation of 2'-hydroxychalcones to flavones. For example, Hishono and co-workers employed a diphenyl disulfide (PhSSPh)-mediated reaction in the cyclisation of chalcone **7** 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 R_3 was an electron withdrawing group. Hence, the lowest yield of 19% was achieved when R_3 was the electron-withdrawing nitro group. The other drawback for this procedure was the high temperatures at which the reactions were performed.



7 (R_1 = R_2 = R_3 = H) — **20** (80%)
37 (R_1 = CH_3, R_2 = R_3 = H) — **41** (74%)
47 (R_1 = R_2 = H, R_3 = NO_2) — **52** (19%)
55 (R_1 = R_2 = H R_3 = OCH_3) — **57** (63%)
81 (R_1 = R_2 = H, R_3 = C_6H_5) — **83** (82%)
82 (R_1 = R_3 = H, R_2 = OCH_3) — **84** (52%)

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 [50]. 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 [51-54]. 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 I_2-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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