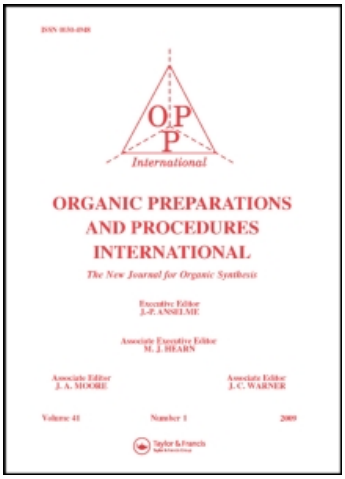

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INTRODUCTION

o-Hydroxyaryl ketones are very interesting molecules both because of their many industrial applications[1-4] and also because of their usefulness as synthons in organic synthesis. The presence of a phenolic hydroxyl and an acyl group *ortho* to each other at the benzene ring allows for the formation of novel heterocycles as well as other non-heterocyclic aromatic compounds. The products are usually obtained in good yields using simple experimental conditions. They possess interesting biological or industrial applications. It is also worth noting that *o*-hydroxyaryl ketones are readily available low cost materials. Some of them exist in nature.[5] The most popular method for their synthesis is the Fries rearrangement.[6-8] Recently, an interesting review was published dealing with the uses of the Fries rearrangement for the preparation of hydroxyarylketones.[9]

The purpose of the this review is to present the progress that has been made in organic synthesis using of *o*-hydroxyaryl ketones as starting materials. We attempt to cover all the reported general synthetic methods that afford products in high yields. Cases of total synthesis of natural products, in lower yields, are also included. Finally some of their applications will be discussed.

I. SYNTHESIS OF HETEROCYCLIC DERIVATIVES

1. Containing Oxygen

a. Chromones

o-Hydroxyacetophenones **1** are very useful precursors of chromones (benzopyran-4-ones) **3**. 1,3-Diketones **2**, formed either by direct acylation at the active methyl group or initial phenolic ester formation followed by rearrangement, are the main intermediates. Cyclization of the 1,3-diketones to chromones **3** occurs by means of acid (Eqs. 1-10).[10-21, 23-35, 37] As early as 1892 the reaction of 2-hydroxy-4-methoxyacetophenone with acetic anhydride and fused sodium was first reported[10] to give 7-methoxy-2-methylchromone directly. However, the method was not general and several subsequent reports appeared dealing with this reaction.[11-13]

The acylation of aromatic *o*-hydroxy ketones **1** with aliphatic ethyl esters in the presence of metallic sodium, and subsequent ring closure of the resulting diketone by means of hydrogen bromide in glacial acetic acid, was found to be very effective in the synthesis of chromones (Eq. 1).[14] Further development of this method appeared later by *Mozingo*[15,16] when he prepared 2-ethylchromone by substituting powdered sodium in xylene for sodium metal and concentrated hydrochloric acid / acetic acid for the final ring closure. Attempts at using *o*-hydroxypropiophenone in order to prepare the 3-

methyl derivatives **3** (Y = Me) were not successful. In 1973, *Kabuto et al.*[17] reported the synthesis of 2-substituted chromones with bulky substituents. In 1984, *Gamill*[18] reported the condensation of *o*-hydroxyacetophenone **1** (R = H) with ethyl methylthioacetate and sodium hydride to prepare the corresponding 1,3-diketone **2** with 43% yield. This diketone was later treated with acid by *Whiting*[19] to give 2-methylthiomethyl chromone, which led to an interesting six step rotenoid synthesis.

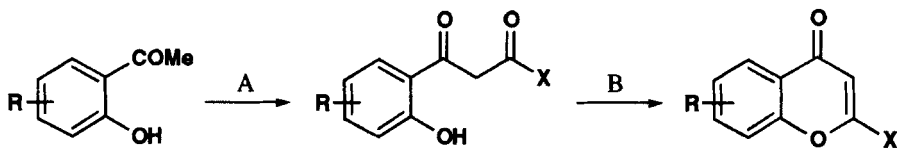
2-Styrylchromones (**3**, X = PhCH=CH) have been synthesized by initial condensation of the appropriate *o*-hydroxyacetophenones **1** with cinnamoyl chloride to give the corresponding cinnamate. The cinnamate undergoes a base-catalyzed intramolecular acyl transfer, the *Baker-Venkataraman* rearrangement, to give 1-(*o*-hydroxyphenyl)-5-phenyl-4-pentene-1,3-dione, followed by acid catalyzed cyclization (Eq. 2).[20,21]

In 1989, *Makrandi et al.*[22] reported a modified preparation of 2-styrylchromones under phase transfer catalysis conditions (Eq. 3). The *o*-hydroxyacetophenones were condensed with cinnamic anhydrides in the presence of tetra-*n*-butyl ammonium hydrogen sulfate in a benzene-aqueous potassium carbonate biphase medium. The 1,3-diketones obtained were subsequently cyclodehydrated by *p*-toluenesulfonic acid in dimethyl sulfoxide to give 2-styrylchromones in 65-80% yield. This method seems to be superior to the previous one involving fewer steps and shorter reaction periods and resulting in high yields. The *Baker-Venkataraman* rearrangement is very useful in the conversion of *o*-hydroxyaryl ketones to chromones and it was thoroughly investigated by *Kraus et al.*[23] It had been used earlier by the same researchers for an earlier synthesis of 2-arylchromones (**3**, X = Ar, Eq. 3), commonly called flavones, in 92-95% yield.[24,25] Water was removed from the reaction by azeotropic distillation before the addition of TsOH.

1,3-Diketones **2** (X = Ar) were alternatively cyclodehydrated by iodine in dimethyl sulfoxide to afford flavones in high yields (87-95%).[26] Furthermore, 1,3-diketones can also be converted to flavones in up to 57% yield by treatment with alcohol solutions of Co[N^1,N^7-4-azaheptamethylenebis(salicylidene-iminato)].[27] 7-Hydroxy-2-flavone **3** (R = 7-OH, Eq. 4) was converted in two subsequent steps to a biologically important epoxide derivative in 57% yield.[28]

Recently, the synthesis of some 2-benzylchromones (**3**, X = CH_2Ar) were reported[29] from 1,3-diketones obtained from reaction of *o*-hydroxyacetophenones and phenylacetic acid *via* the *Baker-Venkataraman* rearrangement (Eq. 4). Chromones were obtained in overall yields of 50-62%. They contain either a methyl group, or a halogen atom, or both in the benzopyran moiety because the presence of such groups often enhances the biological activity.[30] The same procedure was followed for the preparation of flavones (**3**, X = Ar) starting from *o*-hydroxyacetophenones **1** and *o*-methoxybenzoic acid and using phosphorus oxychloride as the condensing agent.[31] Acidification with cold dilute sulfuric acid gave the chromones **3** directly in high yields (80-95%) without isolation of the 1,3-diketones **2**.

Analogously, the synthesis of twenty-one methyl-, methoxy-, nitro- and halogen- 3-methyl-2-substituted chromones was achieved starting from substituted *o*-hydroxypropiophenone.[32]



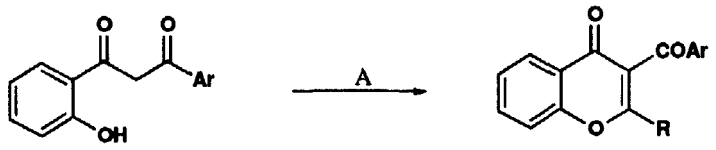
1 2 3 (1-5)

Eq.	R	A	X	B
1	H; 4-MeO	Na or NaH XCO_2Et	Me; Et; *t*-Bu; *t*-Pt; $MeSCH_2$	HCl / AcOH or HBr / AcOH
2	H	a. XCOCl; b. K_2CO_3	PhCH=CH	HCl
3	H; 4-MeO; 4-MeO-5-Me; 5-Me	$n\text{-}Bu_4NHSO_4 / C_6H_6$ $K_2CO_3 / (XCO)_2O$	PhCH=CH; *p*-MeO-C_6H_4CH=CH; *p*-MeO-C_6H_4 *p-m*-$(MeO)_2C_6H_3$	*p*-TsOH / DMSO
4	4-Me; 3-Cl; 3-Br-5-Br b. KOH / pyridine	a. $POCl_3$ / pyridine XCO_2H; *o*-MeO-C_6H_4	CH_2Ph; *p*-MeO-C_6H_4;	H_2SO_4 or HCl / AcOH
5	H; 4-Me; 5-Me; 4,6-$(Me)_2$; 4-MeO; 5-Br	NaOMe $(MeO)_2CHCO_2Me$	**2** : X = $C(OMe)_2$ **3** : X = CN	1. MeOH / H^+ 2. NH_2OH / H_2O 3. $(F_3CCO)_2O$

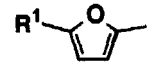
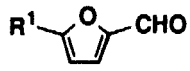
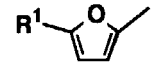
Furthermore, a convenient and general route to 2-cyanochromones, key intermediates in the preparation of highly active 2-(tetrazol-5-yl)-chromones, was published by *Ortar et al.*[33] The reaction involves initial acylation with methyl dimethoxyacetate, which cyclizes to the chromone without isolation of the intermediate 1,3-diketone. Conversion to the nitrile is accomplished in one-pot *via* hydrolysis of the acetal, formation of the aldoxime and dehydration (Eq. 5). The yields obtained were high (75-88%).

1,3-Diketones, prepared from reaction of *o*-hydroxyacetophenone with aroyl chlorides, were useful intermediates in preparing 3-aroylchromones for photochemical studies.[34,35] The diketone underwent condensation either with anhydrides[33] (Eq. 6 and 7) or furylaldehydes[35,36] (Eq. 8 and 9) to give 3-aroylchromones. 1,3-Diketones **2** can also undergo chlorination with sulfuryl chloride and simultaneous ring closure to give 3-chloroflavones as shown in Eq. 10.[37]

The active methyl group of *o*-hydroxyacetophenones can also undergo condensation with benzaldehydes or their equivalents to give substituted chalcones (benzylideneacetophenones) **4** (X = Ar). Oxidative cyclization of the hydoxychalcone gives the corresponding 3-hydroxyflavones (Eq. 11).[37]

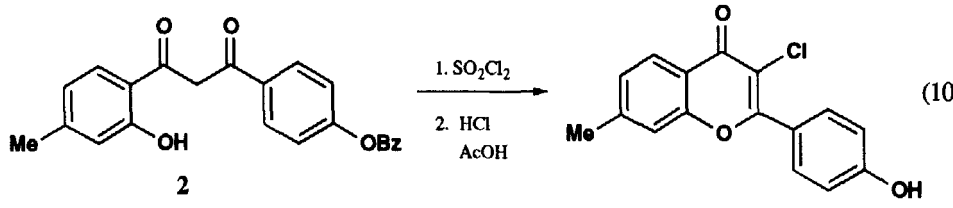


2 3 (6-9)

Eq.	A				R
6	HCO_2Na				H
	HCO_2COMe				
7	$MeCO_2Na$				Me
	$((MeCO)_2O$				
8	a. 		pyridine DMAP	b. DBU / EtOH	
9	a. 		piperidine EtOH	b. SeO_2 / dioxane	

Ar = Ph; 4-MeO-C_6H_4; 3,4,5-$(MeO)_3$-C_6H_2; 2-HO-5-Me-C_6H_3; 2-Me-C_6H_4

R^1 = H; CH_2Br; CH_2OH; CHO; CO_2H; CO_2Me

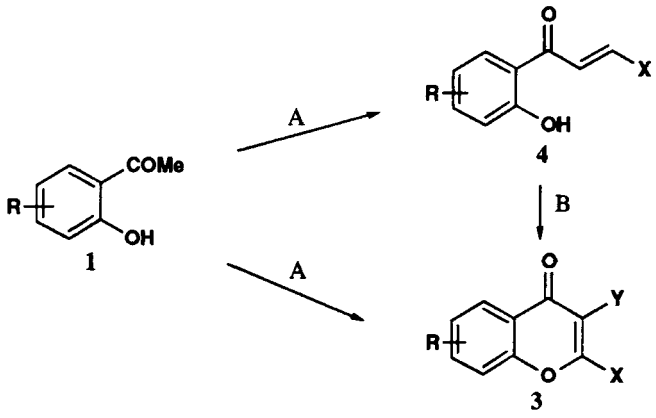


2 (10)

The direct conversion of *o*-hydroxyacetophenones to flavones occurs on reaction with benzaldehydes in perchloric acid in the presence of orthoformates (Eq. 12).[38]

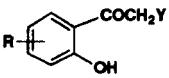
The synthesis of the parent chromone (3, R = X = Y = H) was previously reported by reaction of *o*-hydroxyacetophenone either with dimethylformamide dimethylacetal[39] in xylene in 71% yield (Eq. 13), or using Gold's reagent ($Me_2NCH{=}\overset{+}{N}HCH{=}\overset{+}{N}Me_2$ Cl^-) and LDA[40] in 37% yield (Eq. 14). Condensation of *o*-hydroxyacetophenone with triethyl orthoformate and perchloric acid gave also chromone as shown in Eq. 15.[41] The latter reaction was later extended to cyclization with orthoformate esters to give chromones which possess a methyl at the C-2 position (Eq. 16).[42] This procedure provides a convenient route to 3-hydroxychromone which is otherwise tedious to prepare.

Recently, 2,6-dihydroxyacetophenone was used to achieve the synthesis of some aminoalkoxychromones of biological interest (Eq. 17).[43]

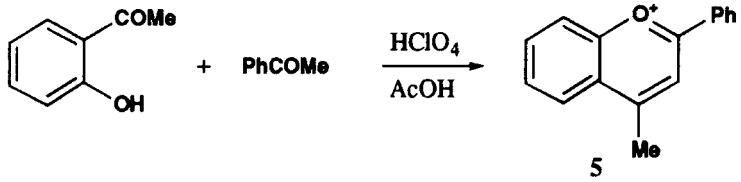


(11-17)

Eq.	A	B	R	X	Y
11	NaOH XCHO	H_2O_2 / NaOH	H; 4-Me; 5-Me; 4-*i*-Pr; 5-*i*-Pr; 3-MeO; 4-MeO; 5-MeO; 6-MeO	*p*-$PhCH_2O$-C_6H_4; *p*-MeO-C_6H_4 *p*-Cl-C_6H_4	OH
12[a]	XCHO $HC(OEt)_3$ / $HClO_4$	____	H; 4-HO; 5-COMe	3-CO_2H-4-HO-C_6H_3; Ph; 3,4-$(MeO)_2C_6H_3$	H
13[a]	$Me_2NCH(OMe)_2$	____	H	**3**: X = H	H
14[a]	$Me_2NCH{=}NCH{=}NMe_2Cl$ LDA / THF	____	H	**3**: X = H	H
15[a]	$HC(OEt)_3$ / $HClO_4$	____	H	**3**: X = H	H
16[a,b]	$XC(OEt)_2$ / $HClO_4$	____	5-Me; 4-MeO; 3-HO; 3-Cl	**3**: X = H; Me	Me, MeO; OH; Ph
17	1. K_2CO_3 $Cl(CH_2)_nBr$ 2. Na / HCO_2Et	1. HCl 2. R^1R^2NH [c] $NaHCO_3$	**1**: R = 6-HO **4**: R = 5-$O(CH_2)_4Cl$ **3**: R = 5-$O(CH_2)_4NR^1R^2$	**4**: X = HO **3**: X = H	H

a) *o*-Hydroxyacetophenones **1** gave chromones **3** directly in these cases. b) *o*-Hydroxyarylketone **1** has the structure  for Eq. 16. c) The secondary amines are substituted phenylpiperazines, heteroaromatic piperazines and phenyltetrahydro-pyridines.

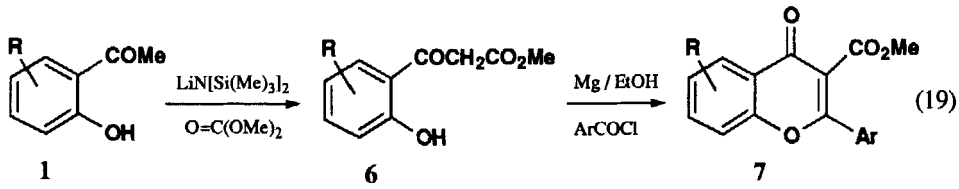
The reaction of *o*-hydroxyacetophenone with acetophenone in the presence of perchloric acetic acid led to the formation of 4-methylflavylium perchlorate (**5**) in 57% yield (Eq. 18).[44]



5 (18)

Several naturally occurring flavonoids such as quercetin (3,5,7,3',4'-pentahydroxyflavone) are known to inhibit a wide range of protein kinases. *o*-Hydroxyacetophenones were used to synthesize a series of flavonoid analogues with more enhanced and selective inhibitory activity. The route

involved treatment of *o*-hydroxyacetophenones **1** with an excess of lithium bis(trimethylsilyl)-amide followed by addition of dimethyl carbonate to give the β-ketoesters **6** (Eq. 19). These were transformed through the reaction of their magnesium chelates with aroyl chlorides into a series of flavones **7**, which were subsequently elaborated into a variety of flavonoids.[45]

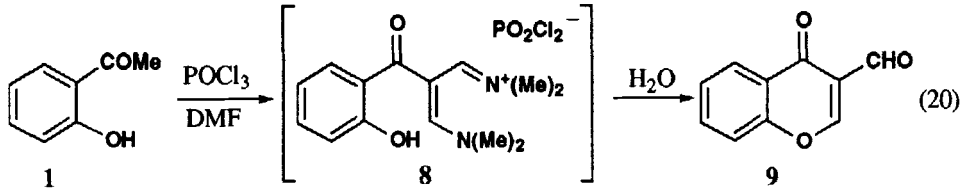


1 6 7 (19)

R = H; 4-MeO; 5-MeO

Ar = 3,4,5-$(MeO)_3$-C_6H_2; 3,5-$(MeO)_2$-C_6H_3; 3,4-$(MeO)_2$-C_6H_3; 4-MeO-C_6H_4; 4-Br-C_6H_4

Research by *Harnisch*[46] and *Nohara et al.*[47,48] independently in the early 1970's showed that the *Vilsmeier-Haack* reaction of *o*-hydroxyacetophenone gave chromone-3-carboxaldehyde (**9**) in one step. The reaction proceeds through double formylation of the methyl group to give the product in 81% yield.

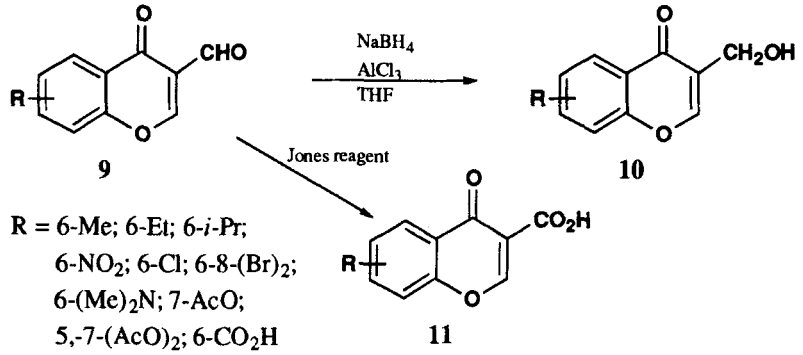


1 8 9 (20)

A variety of chromones depress the release of mediators for tissues involved in the antigen-antibody reaction. Since the presence of a carbonyl group at the C-3 position is important for this activity, the *Vilsmeier* synthesis of 3-formylchromones was further explored. It was concluded that the reaction is general for *o*-hydroxyacetophenones containing electron attracting or releasing groups, but *o*-hydroxyacetophenones carrying a methoxy group at the C-4' position, or carrying one or more hydroxy groups, give low yields of products. This was accounted for by formylation at the electron-rich aromatic ring and the formation of tarry material.

Nohara et al[48] further demonstrated that subsequent reduction or oxidation gave access to novel 3-hydroxymethylchromones **10** and rarely reported 3-carboxy-chromones **11**, respectively (Eq. 21).

Recently, a route to 5,7-dihydroxychromone (**14**), an interesting flavonoid decomposition product that has been found as a constituent in certain plant extracts, was reported.[49] The synthesis was achieved in 18% yield by reaction of 2,4,6-trihydroxyacetophenone (**12**) with ethyl oxalyl chloride and subsequent hydrolysis of the ester **13** with hydrochloric acid followed by thermal decarboxylation (Eq. 22).



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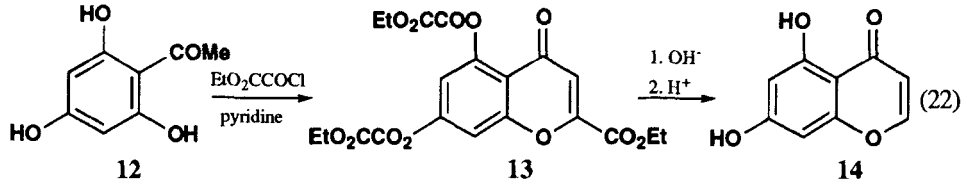
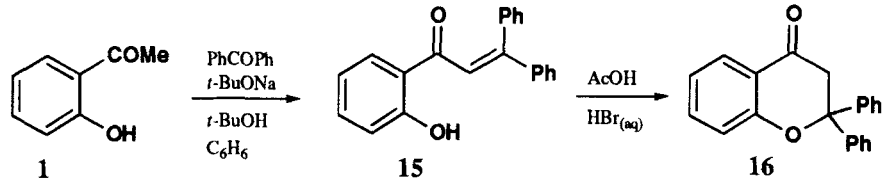


(22)

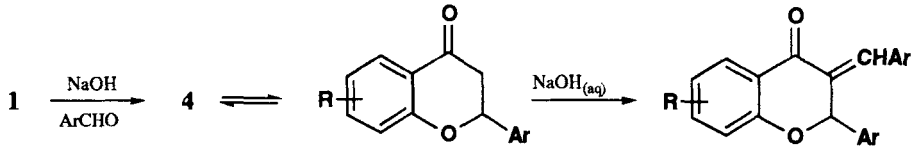
In addition to the synthesis of chromones, *o*-hydroxyacetophenone has been also used to prepare chromanones (2,3-dihydrochromones).[50-64]

For example, *o*-hydroxyacetophenone reacts with benzophenone to form *o*-hydroxy-β-phenylchalcone (**15**) in 74% yield, which cyclizes to 2,2-diphenylchromanone (**16**) by heating in acid (Eq. 23).[50]



(23)

Condensation of *o*-hydroxyaryl ketones **1** with aromatic aldehydes in aqueous sodium hydroxide gave an one step synthesis of 3-benzalchromanones **18** (Eq. 24). The reaction is general and the yield for **18** increases (17 to 51%) when the aldehyde contains an electron withdrawing group.[51]

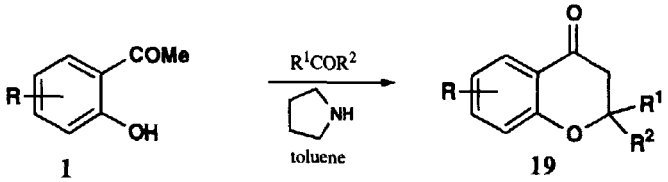


(24)

R = H; 4-MeO; 5-HO

Ar = *p*-MeO-C_6H_4; *p*-NO_2-C_6H_4; *p*-Cl-C_6H_4

Furthermore, *o*-hydroxyacetophenones **1** react with aliphatic aldehydes and ketones in the presence of pyrrolidine to give 4-chromanones **19** (Eq. 25).[52,53] When cycloalkanones were used as the ketone, 2-spiro substituted derivatives were obtained. These can also be obtained by the reaction of *o*-hydroxyacetophenone with pyrrolidine enamines. A characteristic example is shown in Eq. 26.[54-56]

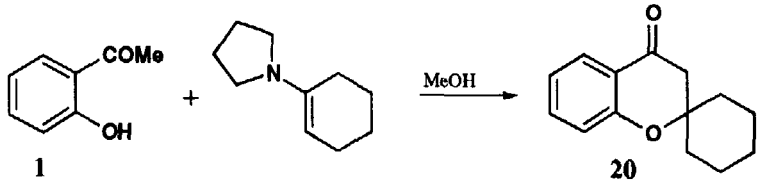


1 **19** (25)

R = H; 4-HO; 3,5-$(Cl)_2$; 5-HO-3,4,6-$(Me)_3$

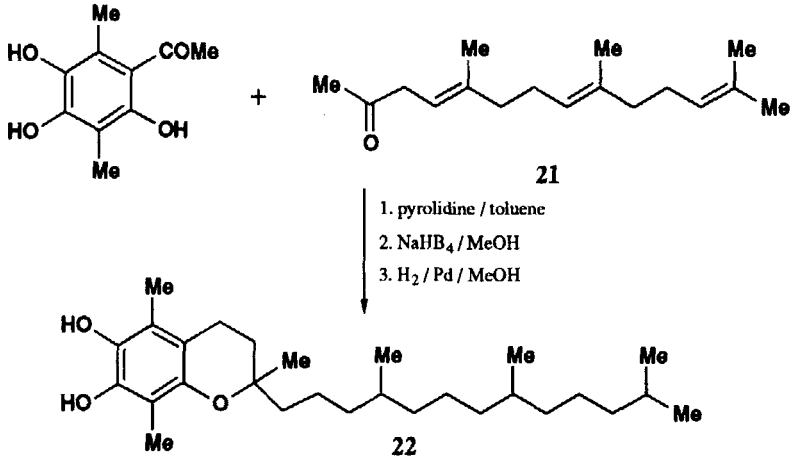
R^1 = *n*-C_6H_{13}; *i*-Pr; -$(CH_2)_3NEt_2$ R^2 = H; Me

R^1, R^2 = -$(CH_2)_5$-; -$(CH_2)_4$-



1 **20** (26)

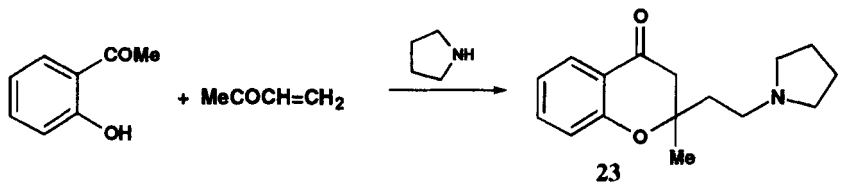
The above reactions were thoroughly investigated and the scopes and limitations were presented in a review by *Kabbe et al.*[56] The mild conditions employed allow for the synthesis of molecules bearing labile substituents. This is demonstrated in the 3-step synthesis of Vitamin-E **22** shown in Eq. 27.[52] Most of the other chromone syntheses involve acid catalysis which would lead to cyclization of the isoprenoid side-chain.[57]



(27)

22

The reactions of 1,2-unsaturated ketones or glyoxalic acid were found to be exceptions to the results described above (Eq. 28 and 29).[56]



(28)

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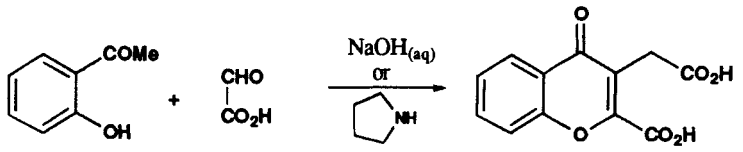
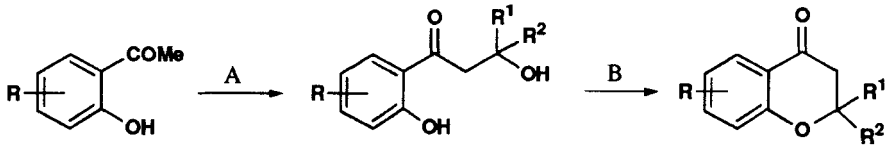


(29)

24

In 1979 *Banerji et al.*[58] described a facile synthesis of 2,2-dialkylchromanones **19** *via* reaction of lithium enolates of *o*-hydroxyacetophenones (Eq. 30) with ketones. The intermediates, β-hydroxy ketones **25**, were isolated and underwent facile cyclodehydration on refluxing in methanolic hydrochloric acid to give chromones **19** in high yields (68-90%). However, *Banerji's* approach, as well as *Kabbe's* condensation, both proved inefficient with base-sensitive carbonyl derivatives.

Alternatively, in 1991 *Kelly et al.*[59] were able to synthesize chromanones from enolizable aldehydes and ketones by employing a *Mukaiyama* aldol condensation with bis-silyl enol ethers. β-Hydroxy ketones **25**, obtained in 81-92% yields, were subsequently cyclized to the chromanones **18** under acidic conditions in 66-94% yields (Eq. 31).

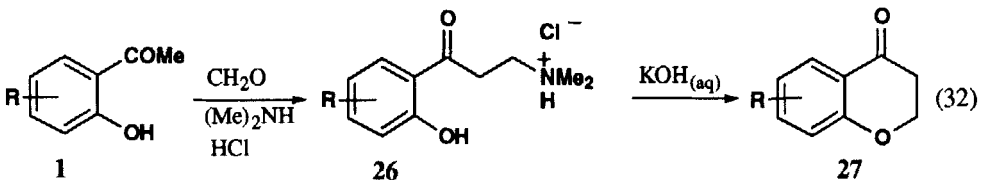


(31-32)

1 25 19

Eq.	A	B	R	R^1	R^2
30	LDA / R^1COR^2 THF	HCl / MeOH	H; MeO; 4,6-$(MeO)_2$	Me; *n*-Pr	Me; Et; *i*-Bu; *n*-Pr
31	1. LDA / THF TMSCl / TEA 2. $TiCl_4$ / R^1COR^2 CH_2Cl_2	H_2SO_4 / AcOH	H	H, Me	Ph, Bz, $BzCH_2$ -$(CH_2)_5$-

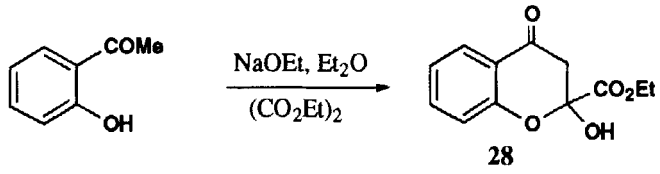
In 1989 *Waigh et al.*[60] reported that Mannich base hydrochlorides **26**, formed from *o*-hydroxyacetophenone by reaction with formaldehyde and dimethylamine under acidic conditions, could cyclize to chromanones **27** on titration with potassium hydroxide in 34-50% yields (Eq. 32). This is complementary to the *Kabbe* condensation which fails with formaldehyde.



1 26 27

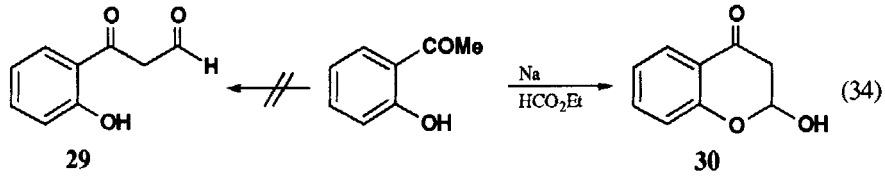
R = H; 4-Cl; 5-Cl; 4,5-$(Cl)_2$

Furthermore, the reaction of *o*-hydroxyacetophenone with oxalic acid diethyl ester led to the 2-hydroxychromanone **28** (Eq. 33).[61]



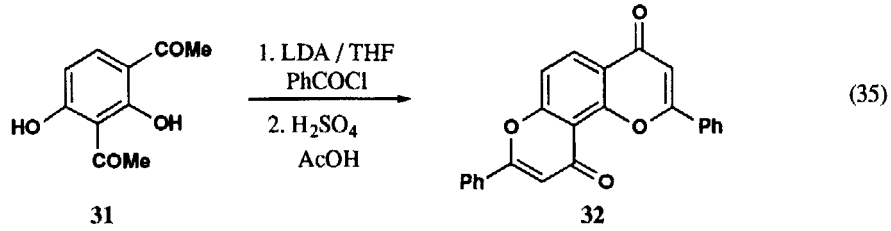
28

In 1988 it was reported[62] that the reaction of *o*-hydroxyacetophenone with ethyl formate in the presence of sodium gave 2-hydroxychromanone (**30**), which had earlier been erroneously identified[63] as the isomeric 1,3-dione **29** (Eq. 34).

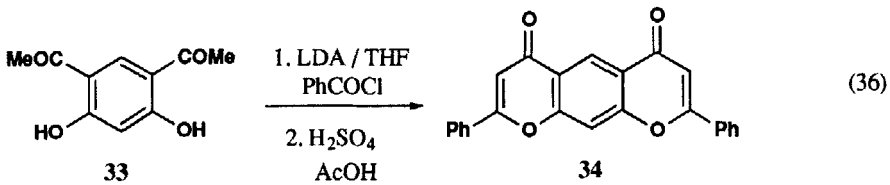


29 **30**

Recently, *Banerji et al.*[64] explored the synthetic potential of enolates generated from compounds with more than one *o*-hydroxyacetyl moiety, and thus a new synthetic approach towards benzodipyrans **32** and **34** was described (Eq. 35 and 36). The key step involves cross condensation between the enolates of 2,4- and 4,6-diacetylresorcinols **31** and **33**, respectively, with electrophiles such as benzoyl chloride.



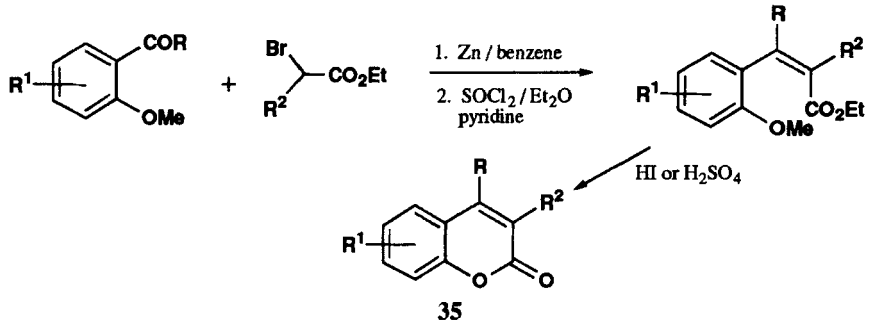
31 **32**



33 **34**

b. Coumarins (Benzopyran-2-ones)

o-Methoxyaryl ketones were reported in 1938 by *Chakrararti et al.*[65,66] to undergo the *Reformatsky* reaction with α-bromo esters followed by dehydration to give unsaturated cinnamic esters, which were then converted to 3,4-dialkylcoumarins **35** by treatment with acid (Eq. 37).



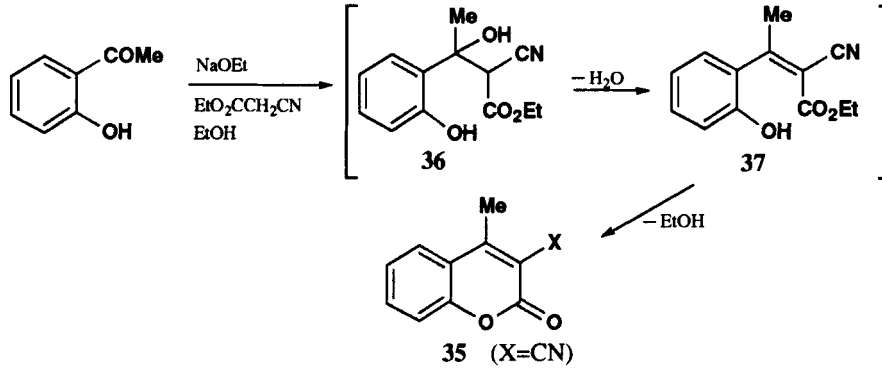
(37)

35

R = Me, Et R^2 = H, Me

R^1 = 4-Cl, 5-Cl, 5-Br, 3-Me, 5-Me, 3-Me-5-Cl, 4-Me-5-Cl, 3-Cl-5-Me

Later, in 1953, *Schroeder et al.*[67] reported that *o*-hydroxyacetophenone in the presence of sodium ethoxide undergoes condensation with the active methylene group of ethyl cyanoacetate to form 3-cyano-4-methylcoumarin (**35**, X = CN) in 79% yield (Eq. 38). The reaction presumably proceeds *via* the formation of the aldol condensate **36**. Dehydration of **36** would form the intermediate **37** which by intramolecular condensation yields coumarin.

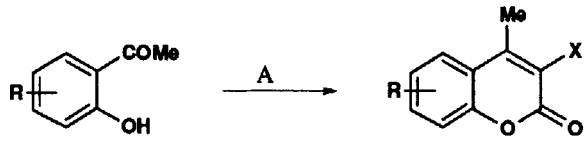


(38)

35 (X=CN)

o-Hydroxyacetophenones can also afford coumarins by reaction with a variety of other reagents.[68-77] For example, reaction of *o*-hydroxyacetophenone with the cumulated phosphorane shown in Eq. 39 led to 4-methylcoumarin in 78% yield.[68] Somewhat higher yields and easier work-up and isolation of coumarins were reported later in a conceptually similar reaction involving reaction of the preformed phenoxide with trimethylsilylketene instead of the phosphorane (Eq. 40).[69]

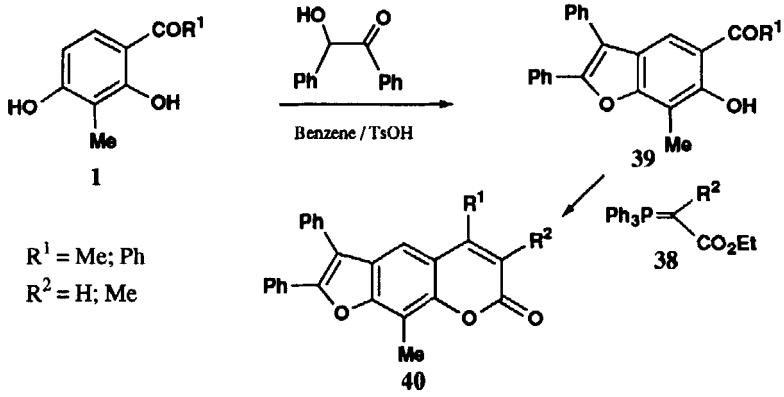
Furthermore, it was reported recently that *o*-hydroxyacetophenones undergo direct ring closure upon heating with the neat phosphorane ester shown in Eq. 41 to produce the 4-methyl-3-benzylcoumarins **35** (X = $PhCH_2$) in 46-58% yield.[70]



1 35 (39-40)

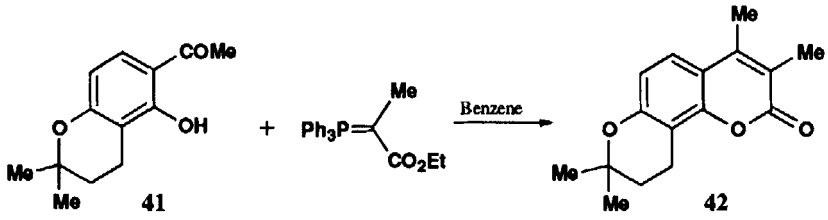
Eq.	A	R	X
39	$Ph_3P{=}C{=}C{=}O$ / Benzene	H	H
40	1. NaH / DMF 2. $Me_3SiCH{=}C{=}O$	H, 4-OH	H
41	$Ph_3P{=}C(CH_2Ph)CO_2Et$	5-Me, 5-MeO	$PhCH_2$

Ahluwalia et al.[71,72] also used *o*-hydroxyaryl ketones **1** to synthesize coumarins for biological testing. Thus, condensation of *o*-hydroxyaryl ketones with benzoin in the presence of TsOH followed by *Wittig* reaction with phosphorane esters **38** led to the formation of **40** in 50-74% yields (Eq. 42).

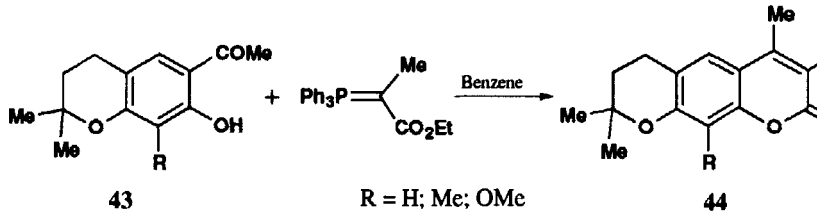


(42)

Similarly, the *Wittig* reaction of **41** and **43** afforded the coumarins **42** and **44** in 55% and 47-71% yields respectively (Eq. 43 and 44).[72]

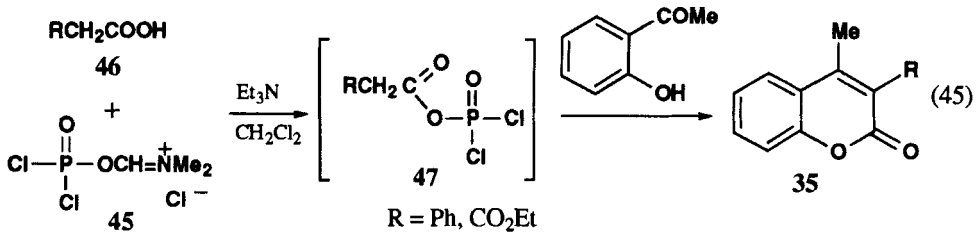


(43)

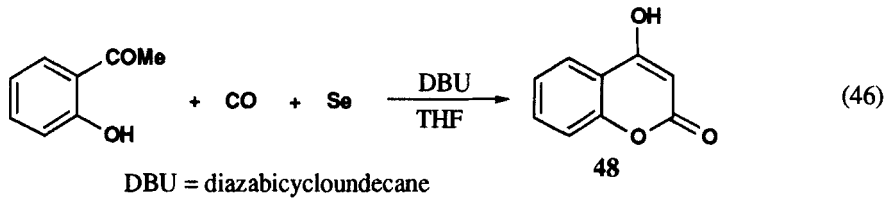


(44)

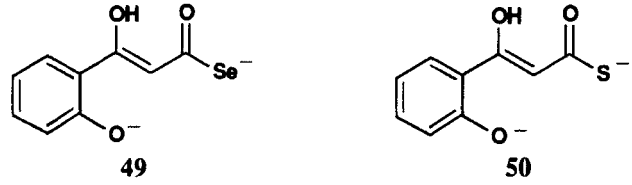
The *Vilsmeier* salt **45** is an alternative phosphorus reagent that has been used in a convenient one-pot annelation of *o*-hydroxyacetophenone to give 3,4-substituted coumarins **35** in 86-90% yields (Eq. 45).[73] The reaction seems to proceed *via* esterification of the carboxylic acid **46** to give the mixed phosphoric carboxylic acid anhydride **47** as an activated species. Subsequent aldol type reaction of the resulting intermediate yields the coumarins **35**.



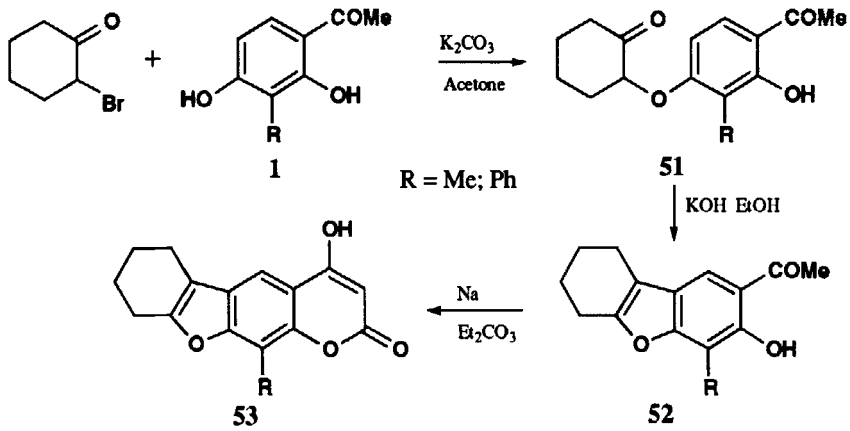
Selenium-assisted C-carbonylation of o-hydroxyacetophenone with carbon monoxide in the presence of a strongly basic tertiary amine gave 4-hydroxycoumarin (**48**) in quantitative yield (Eq. 46).[74] It was suggested that the reaction proceeds *via* the intermediate **49**.



Similarly, sulfur-assisted carbonylation of *o*-hydroxyacetophenone provided a facile method for the synthesis of 4-hydroxycoumarins **48**.[75] In this case the carbonylation proceeded under milder reaction conditions (80°, 10 Kgr / cm^2) than those for selenium-assisted carbonylation (90°, 30 Kgr / cm^2) and afforded the product in 95% yield. Several substituted *o*-hydroxyacetophenones were used as starting materials. An analogous intermediate **50** to the selenium case was suggested to serve as the key intermediate of the reaction.



Recently, 4-hydroxycoumarins **53** were synthesized mainly for biological purposes as shown in Eq. 47. The yield was reported to be about 50%.[76]



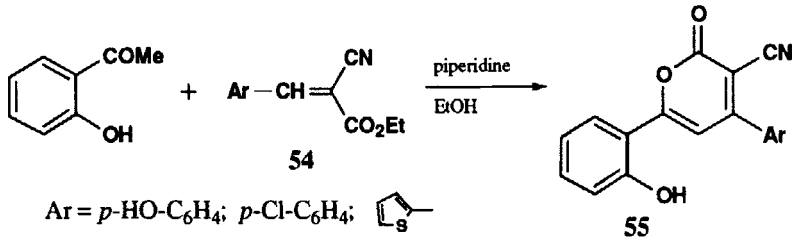
(47)

Finally, 3-phenyl-4-styrylcoumarins were recently synthesized by phase-transfer catalyzed reaction of 2'-hydroxychalcones **4** with phenylacetic anhydride in 65-75% yields.[77] Similar phase-transfer conditions were employed to synthesize 2-styrylchromones (see Eq. 3).

c. Other Oxygen Heterocycles

Besides the extended use of *o*-hydroxyaryl ketones in the synthesis of chromones and coumarins, their application to the preparation of a great variety of other heterocycles has also been reported. Thus, the synthesis of a variety of interesting oxygen containing heterocycles, such as pyrone derivatives,[78,79] benzofurans,[80] coumaranones,[81] benzoxepins,[82,83] benzoxanthones,[84] and quinones[84] was achieved.

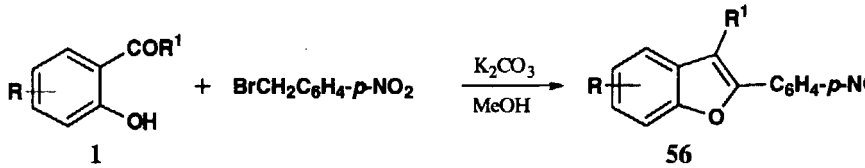
o-Hydroxyacetophenone was found to lead to 3-cyano-2-pyrone derivatives **55** under treatment with cinnamonitriles **54** (Eq. 48).[78,79]



(48)

Ar = *p*-HO-C_6H_4; *p*-Cl-C_6H_4;

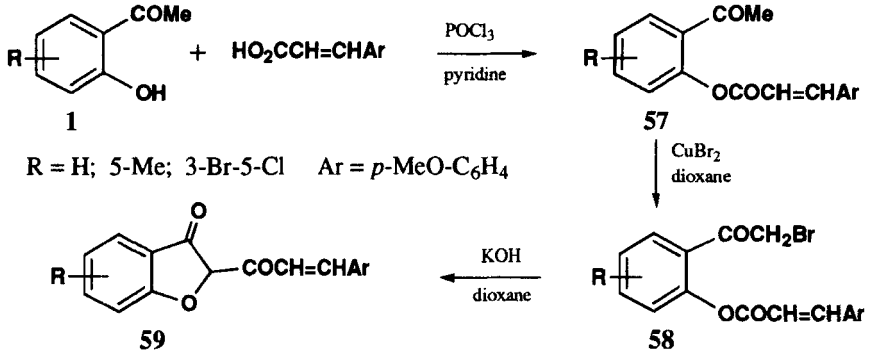
Reaction of **1** with *p*-nitrobenzyl bromide in the presence of freshly ignited potassium carbonate gave the 2-(*p*-nitrophenyl)benzofurans **56** in good yields, 60-75% (Eq. 49).[80]



(49)

R = H; 4-Me; 5-Me; 5-Br; 5-Cl; 3-Br-5-Me; 3-Br-5-Cl R^1 = Me; Et

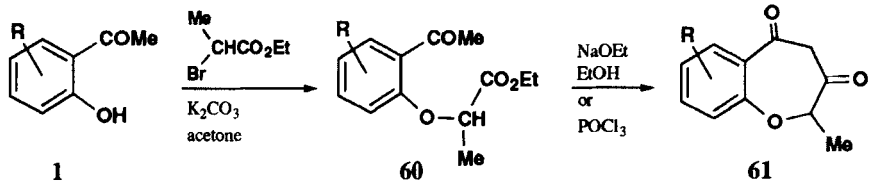
Coumaranone derivatives were obtained from *o*-hydroxyaryl ketones **1** as shown in Eq. 50. Esterification with *p*-methoxycinnamic acid gave the esters **57** which were brominated to yield the cinnamoyl-2'-bromoacetophenones **58**. Subsequent *Baker-Venkaraman* rearrangement led to the formation of cinnamoylcoumaran-3-ones **59**, in 55-62% yields (Eq. 50).[81]



1 **57** **58** **59**

R = H; 5-Me; 3-Br-5-Cl Ar = *p*-MeO-C_6H_4 (50)

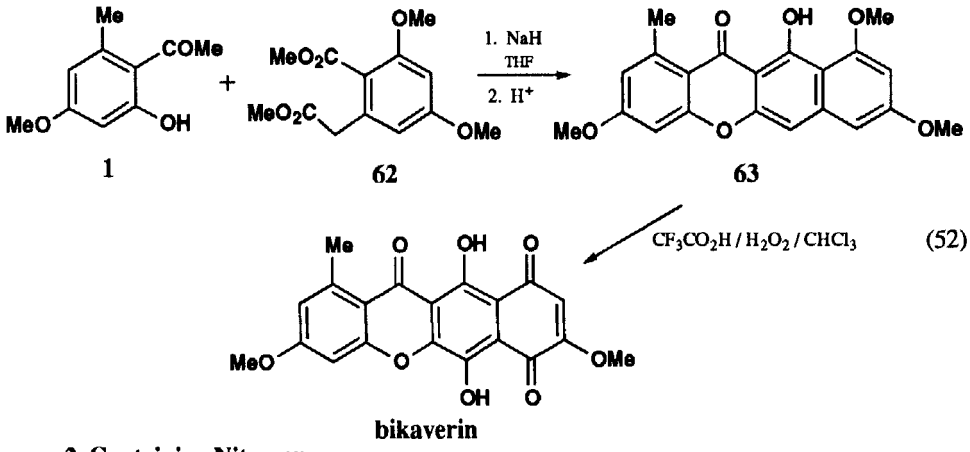
The use of *o*-hydroxyacetophenones in the preparation of substituted benzoxepine-3,5-diones **61**, intermediates in the synthesis of a sesquiterpenoid aplysin, was reported by *Pickles et al.*[82,83] The route involves alkylation with ethyl 2-bromopropionate to give the ester **60**. Cyclisation occurs either with ethanolic sodium ethoxide or partially by treatment with phosphorus oxychloride. The range of the yields was 42-78%. The same α-bromoester was also used in a *Reformatsky* reaction to give coumarins (see Eq. 37).



1 **60** **61** (51)

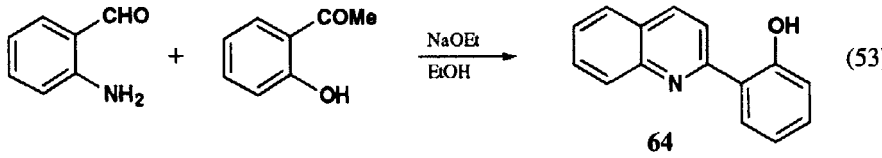
R = H; 3-Cl; 4-Me; 5-Cl; 5-Br; 5-*t*-Bu

In 1983 the two step synthesis of bikaverin, a biologically interesting fungal red pigment with a unique highly oxidized benzoxanthone structure, was published.[84] The precursor to bikaverin, the substituted benzoxanthone **63**, is obtained by a base-catalyzed reaction between 4-methoxy-6-methyl-2-hydroxyacetophenone (**1**) and the homophtalate **62** in about 25% yield. Subsequent oxidation with trifluoroperacetic acid gave bikaverin in about 35% yield. It is notable that the independent syntheses by *Barton et al.*[85] and *Kato et al.*[86] starting from common chemicals such as orcinol, orsellinic acid and vanillin, proceed through a dozen individual steps or more.

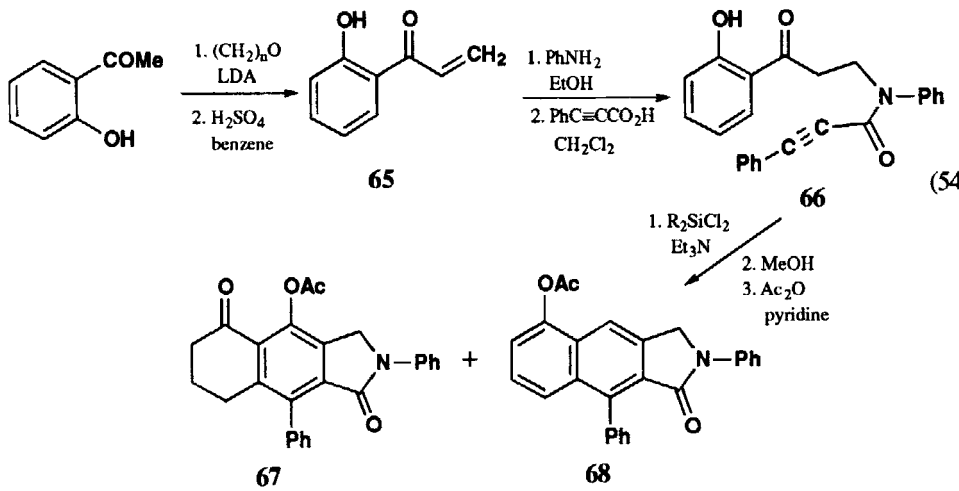


2. Containing Nitrogen

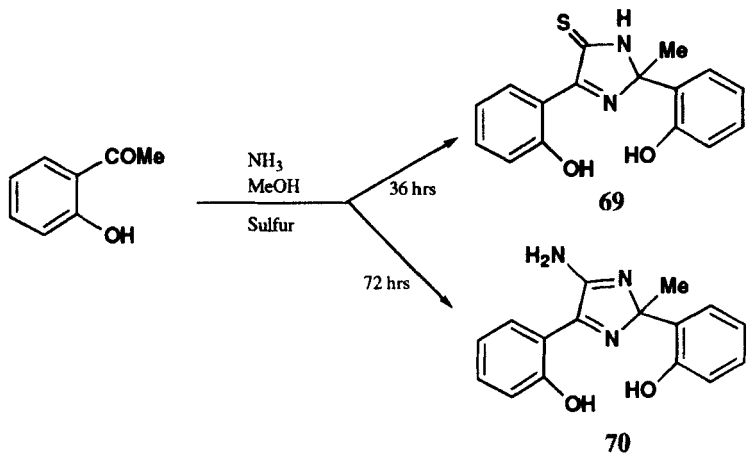
In 1959, 2-(*o*-hydroxyphenyl)quinoline (**64**) was synthesized by the reaction of *o*-hydroxyacetophenone with *o*-aminobenzaldehyde (Eq. 53).[87]



o-Hydroxyacetophenone were the starting material in the preparation of a mixture of benzoisondole derivatives **67** and **68**. The key step involves a novel intramolecular [4 + 2] cycloaddition of a silylene protected 1,3-diol (Eq. 54).[88]

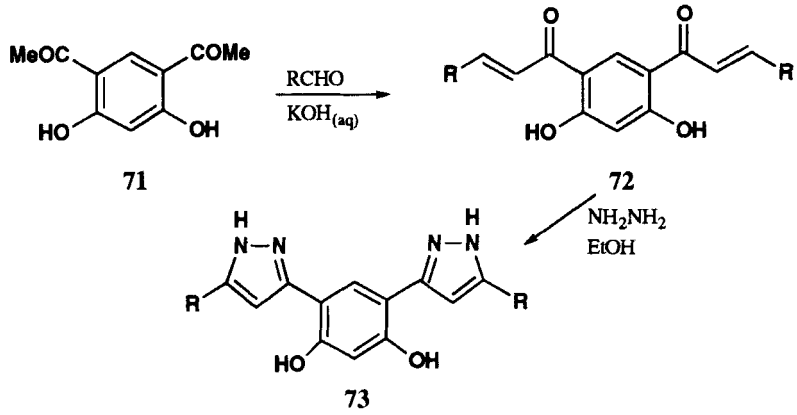


o-Hydroxyacetophenone was also the starting material in the preparation of imidazoles **69** and **70** (Eq. 55).[89] Imidazole **69** was obtained in 22% yield. Further reaction afforded the 5-amino derivative **70** in 24% yield.



69 70 (55)

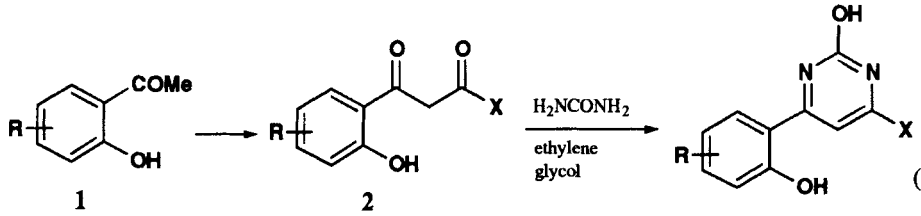
4,6-Diacetylresorcinol (**71**) led to the formation of pyrazole derivatives **73** by condensation with aromatic aldehydes in the presence of aqueous potassium hydroxide and subsequent refluxing with hydrazine hydrate (Eq. 56). The reaction proceeds *via* the formation of dichalcones **72**. Pyrazoles **73** were obtained in good yields (62-75%).[90]



71 72 73 (56)

R = Ph, 2-Cl-C_6H_4; 4-Cl-C_6H_4; 2,4-Cl_2-C_6H_3; 4-MeO-C_6H_4; 3,4-$(MeO)_2$-C_6H_3

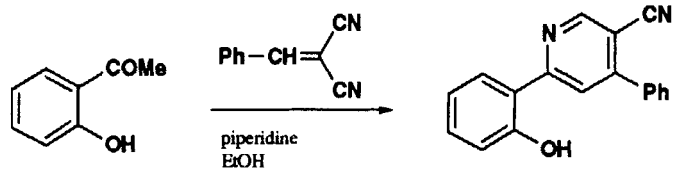
1,3-Diketones **2**, prepared from *o*-hydroxyacetophenones as described earlier,[20] were cyclised with urea in ethylene glycol to give pyrimidines **74** in 55-80% yields (Eq. 57).[91]



1 2 74 (57)

R = H; 4-MeO; 4-EtO; 4-MeO-5-NO_2; 4-MeO-5-Br;
3-Br-4-MeO-5-NO_2; 4-EtO-5-NO_2; 4-EtO-5-Br; 3-Br-4-EtO-5-NO_2
X = C_6H_5; *p*-MeO-C_6H_4

3-Cyanopyridine **75** was obtained in 60% yield by treatment of *o*-hydroxyacetophenone with benzylidenemalononitrile (Eq. 58) in a similar fashion to the 3-cyano-2-pyrone derivatives **55** described earlier (Eq. 48).[78]

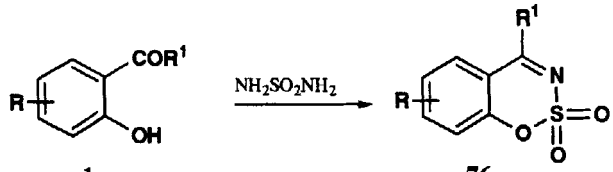


1 **75** (58)

3. Containing More Than One Kind of Heteroatom (O, N, S)

Another field in which *o*-hydroxyaryl ketones have found application has been in the synthesis of heterocycles bearing more than one kind of heteroatom.

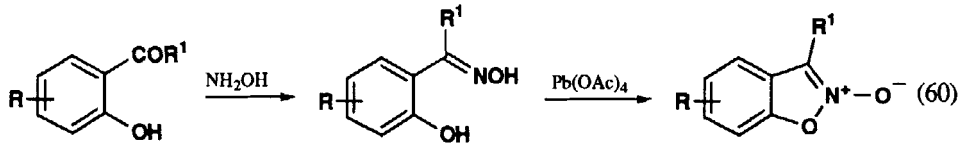
1,2,3-Benzothiazine 2,2-dioxides **76** were prepared in 30-42% yield by fusion of *o*-hydroxyaryl ketones **1** with sulfamide (Eq. 59).[92]



1 **76** (59)

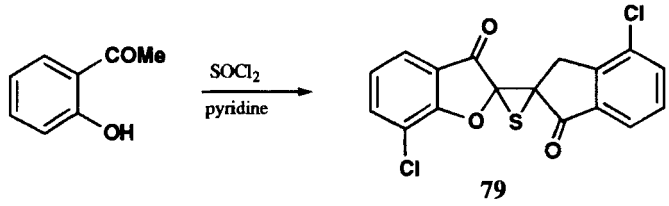
R = H; 4-MeO R¹ = Me; Ph

Cyclisation of the oximes **77** of *o*-hydroxyaryl ketones with lead tetraacetate gave benzisoxazole *N*-oxides **78** (Eq. 60).[93]

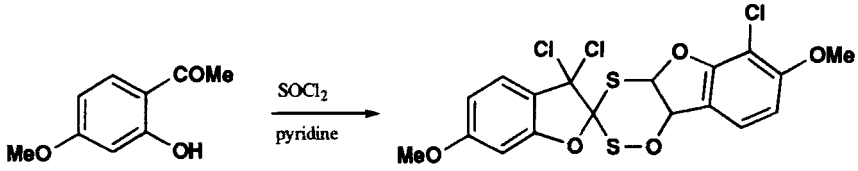


1 **77** **78** (60)

Reaction of *o*-hydroxyacetophenone with an excess of thionyl chloride in the presence of a catalytic amount of pyridine at room temperature afforded the thiirane **79**, whilst 4-methoxy-2-hydroxyacetophenone gave **80** when subjected to the same conditions (Eq. 61 and 62).[94] Though the yields were not high, being 27 and 34% for **79** and **80** respectively, the accomplishment of these complicated spiro skeleton in a single step from readily available materials was quite significant. Possible mechanisms were also suggested.[94]



79 (61)

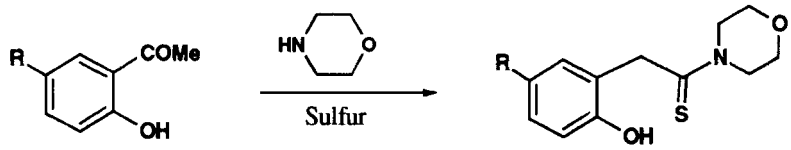


80 (62)

4. Heterocycles not Involving Formation of a New Ring

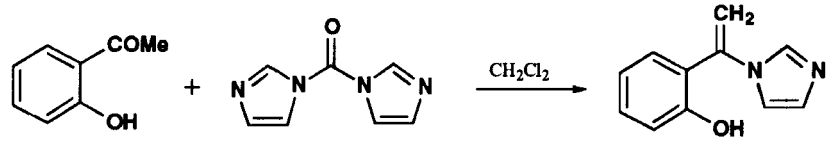
A number of papers dealing with condensations of *o*-hydroxyaryl ketones with heterocyclic compounds have been published.

For example, thiomorpholides **81** were formed from *Willgerodt-Kindler* reaction of *o*-hydroxyacetophenones with sulfur in refluxing morpholine (Eq. 63).[95] These thioamides were used to prepare 4-ethoxycarbonylchroman-3-one, a key intermediate in the synthesis of rotenoids. The yields for the preparation of **81** were not specified.



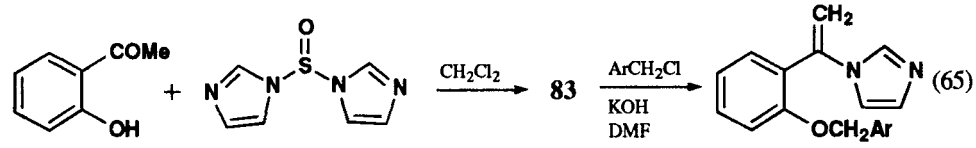
(R = H, Me) **81** (63)

Reaction of *o*-hydroxyacetophenone with N,N'-carbonylimidazole (**82**) resulted in the formation of imidazole derivative **83** (Eq. 64).[96]



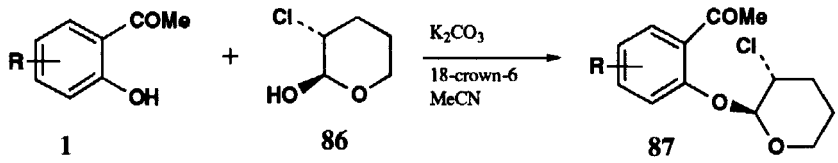
82 **83** (64)

Similarly, reaction of *o*-hydroxyacetophenone with the sulfoxide **84**, prepared from imidazole and thionyl chloride, and subsequent treatment with *m*-chlorobenzyl chloride in the presence of potassium hydroxide led to the formation of **85** (Eq. 65).[97]



84 Ar= *m*-Cl-C_6H_4 **85** (65)

Treatment of *o*-hydroxyacetophenones **1** with tetrahydropyranols **86** resulted in the synthesis of tetrahydropyranyl ethers **87** in 27-70% yield (Eq. 66).[98]

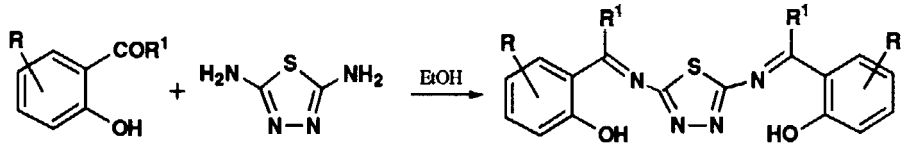


(66)

1 **86** **87**

R = H; 4,6-$(MeO)_2$

Finally, azomethines **89** were prepared by the coupling of *o*-hydroxyaryl ketones **1** with diaminothiadiazole (**88**), in 60-75% yield (Eq. 67).[99]



(67)

1 **88** **89**

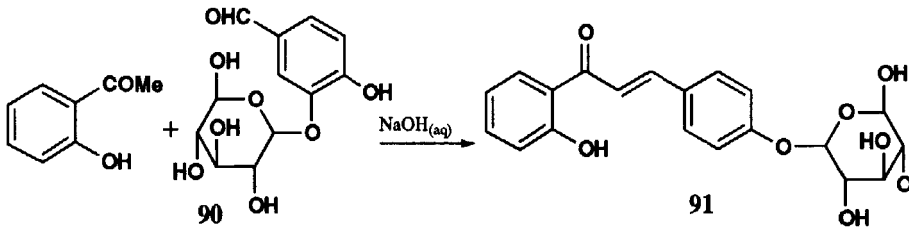
R = H; 3-NO_2; 3-Br R^1 = Me; Ph

II. SYNTHESIS OF NON-HETEROCYCLIC DERIVATIVES

1. Chalcones

Chalcones are one the most useful type of products derived from *o*-hydroxyaryl ketones. Their use as intermediates in the synthesis of chromones was discussed earlier.[37,39,40,43,50,51,77,88,90] The interest in 2'-hydroxychalcones as antibiotics[100] has stimulated efforts to synthesize and isolate chalcones starting from *o*-hydroxyaryl ketones. Usually the reaction involves condensation of *o*-hydroxyaryl ketones with aldehydes in an alkaline media.

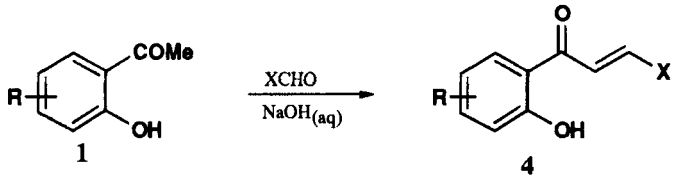
In 1943, *Reichel et al.*[101] reported the synthesis of 2'-hydroxychalcone glycoside **91** in 54% yield by the reaction of *o*-hydroxyacetophenone with the glycoside **90** (Eq. 68).



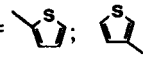
(68)

90 **91**

Recently, additional 2'-hydroxychalcones have been synthesized for biological purposes.[102,103] Condensation of substituted *o*-hydroxyacetophenones **1** with thiophenecarboxaldehydes gave the thienylchalcones **4** in yields higher than 70% (Eq. 69).[102]



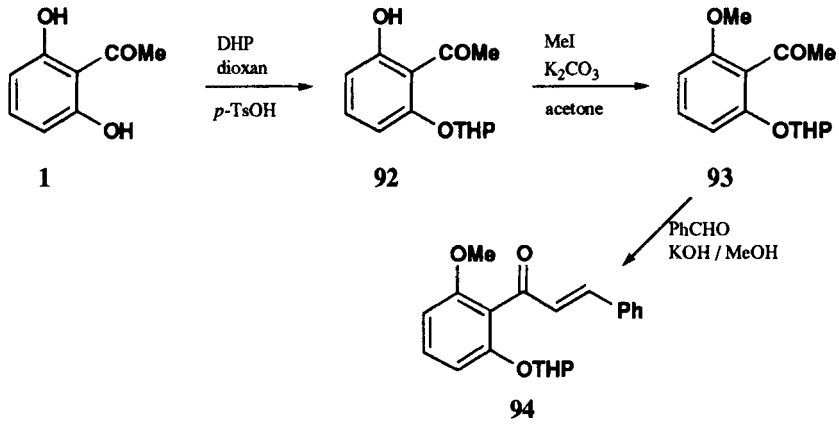
1 4 (69)

R = H; 4-NO_2; 5-NO_2 X= 

Analogously, chalcones **4** were obtained when 2-hydroxy-4,5-dimethylacetophenone was condensed with substituted benzaldehydes in the presence of potassium hydroxide.[103,104] Yields were not given but it was reported that they were good. The same procedure was followed later for the preparation of some chromones, as previously shown in Eq. 11.[40]

A common problem in the above Claisen-Schmidt condensations it that the desired 2'-hydroxychalcones **4** cyclise to chromones under the homogenous basic experimental conditions used for their preparation.[105,106] In 1987, *Alcantara et al.*[106] described a general method of synthesis of **4** using interfacial solid-liquid conditions without unwanted secondary reactions. The method involved a barium hydroxide catalyst (C-200) and chalcones **4** were isolated in 24-89% yield.

In a recent publication dealing with the synthesis of 2'-hydroxychalcone epoxides, chalcone **94** was prepared (Eq. 70). The hydroxy group was protected by a tetrahydropyranyl group which could be removed using slightly aqueous acidic dioxane.[107] Epoxidation was achieved with alkaline hydrogen peroxide.



1 92 93 (70)

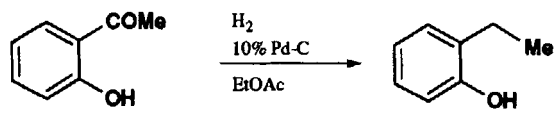
94

2. 1,3-Diketones

1,3-Diketones **2** are one of the most useful class of products obtained easily from *o*-hydroxyaryl ketones. Characteristic reactions for their preparation as well as their further use in organic synthesis, especially in heterocyclic formation, have been discussed above.[14-38, 92]

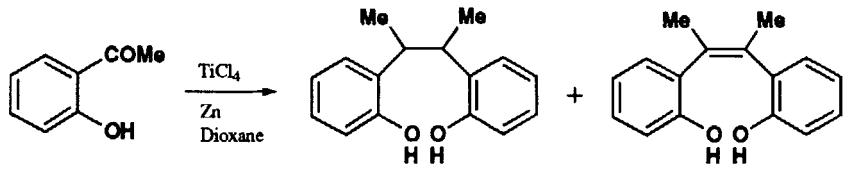
3. Reduction Products

o-Hydroxyacetophenone can be reduced to *o*-ethylphenol (**95**) in 78% yield by hydrogenation in the presence of 10% palladium-charcoal in ethyl acetate at 80° (Eq. 71).[108]



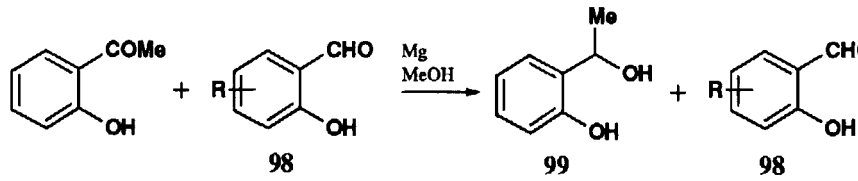
95 (71)

Diarylalkane **96** was the main product obtained from the reductive deoxygenation of *o*-hydroxyacetophenone with low valent titanium. The yield was 58%. Diarylalkene **97** was formed as a minor product in 12% yield (Eq. 72).[109]



96 **97** (72)

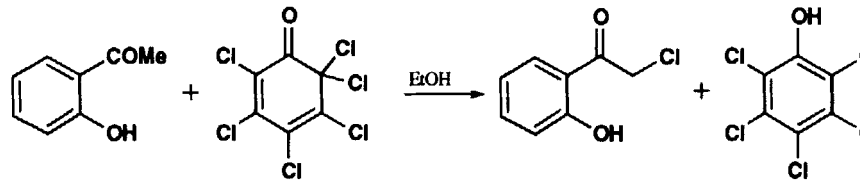
Furthermore, *o*-hydroxyacetophenone was reduced to **99** by magnesium-methanol (Eq. 73).[110] This reagent was found to selectively reduce a phenolic keto group in the presence of a phenolic aldehyde. Thus, in a mixture of the two, secondary alcohol **99** was obtained in 95-97% yield, whereas aldehydes **98** were recovered quantitatively.



98 **99** **98** (73)

4. 2'-Chloro-*o*-hydroxyaryl Ketones

An interesting selective 2'-chlorination of *o*-hydroxyacetophenone has also been reported using hexachloro-2,4-cyclohexadienone **100** and is delineated in Eq. 74.[111] The chloromethylaryl ketone **101** was obtained in 66% yield, with pentachlorophenol **102** formed as the by-product.

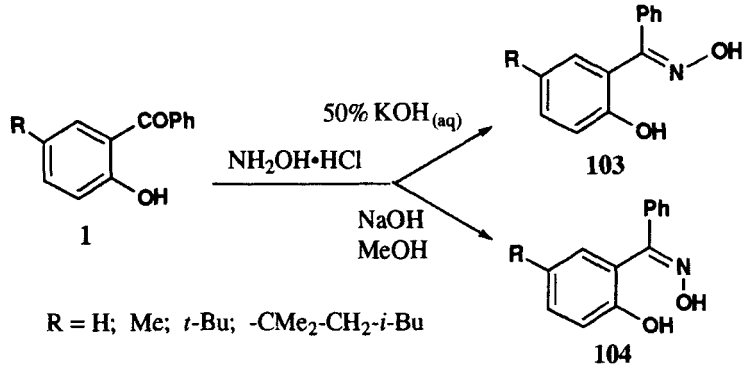


100 **101** **102** (74)

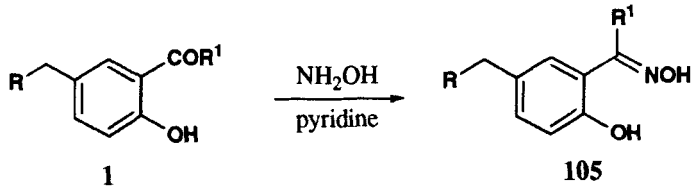
5. Nitrogen Derivatives

The synthesis of several nitrogen derivatives of *o*-hydroxyaryl ketones, such as oximes, amides, hydrazones and carbonyl hydrazones have been reported and the main aspects of this field are presented below.[112-122]

Oximes were synthesized in good yields by standard methods by reaction of the corresponding ketone with hydroxylamine either in alkaline ethanol or in pyridine.[112-115] Characteristic examples are shown in Eqs. 75 and 76. According to the conditions employed, the reaction led preferentially to either the *E*- or *Z*-isomers, **103** and **104** respectively, in yields of 52-81%.

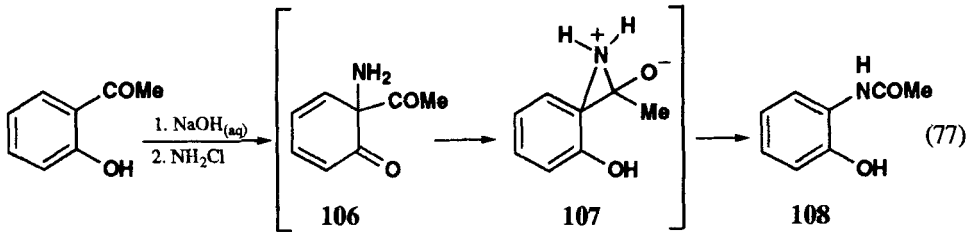


(75)



(76)

Rearrangement of the sodium salt of *o*-hydroxyacetophenone by monochloramine yielded 2-acetamidophenol **108** in 93% yield (Eq. 77).[116] The reaction pathway probably involves nucleophilic displacement on chloramine by the cyclohexadienone anion to produce **106**.



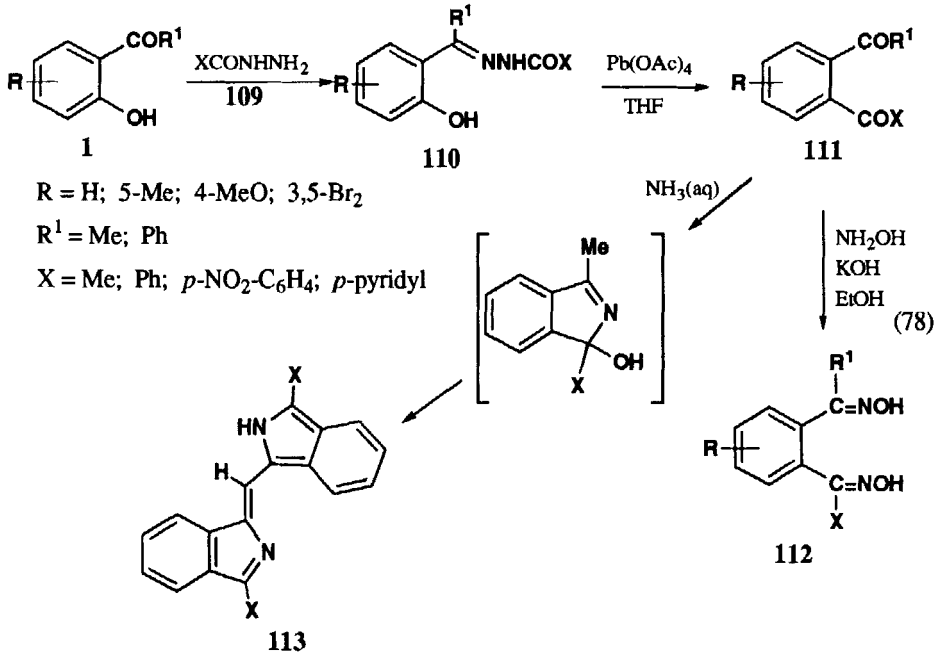
(77)

Hydrazones of o-hydroxyaryl ketones are easily prepared by condensation of the ketones with the appropriate hydrazine usually in alcohol.[117,118]

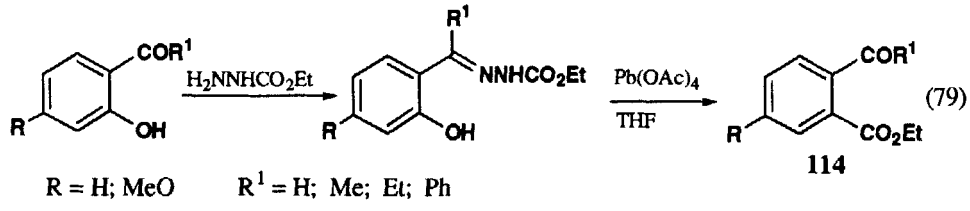
Recently, the synthesis of the carbonyl hydrazones **110** by treatment of o-hydroxyaryl ketones **1** with the appropriate hydrazide **109** was reported (Eq. 78).[119,120] Hydrazones **110** were prepared in 75-98% yield, and exhibited some interesting electron impact mass spectra.[121]

6. 1,2-Diacyl- and 1,2-3-Triacylbenzenes

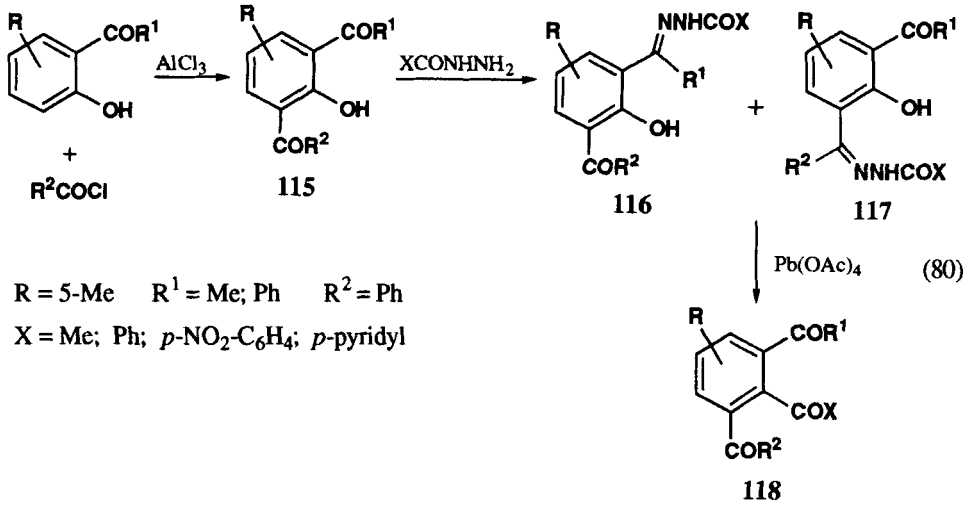
Hydrazones **110,** obtained from *o*-hydroxyaryl ketones **1**, unexpectedly rearranged to 1,2-diacylbenzenes **111** under treatment with lead tetraacetate at room temperature in high yields (60-95%) (Eq. 78).[119] Cross-over experiments showed that the reaction is intramolecular and the mechanism of this two step "replacement" of phenolic hydroxyl by an acyl group was established by labeling experiments.[122] 1,2-Diacylbenzenes **111** were further used for the synthesis of their dioximes **112** (Eq. 78)[123] and for condensation reactions with aqueous ammonia yielding imadazole derivative **113** (X = 4-pyridyl).[124] Alternatively, [(diacetoxy)-iodo]benzene, a reagent with similar reactivity to lead tetraacetate, can also be used for the conversion of aroyl-hydrazones to 1,2-diacylbenzenes.[125]



Similarly, *o*-acylarylcarboxylic esters **114** can be prepared from lead tetraacetate treatment of ethoxycarbonyl hydrazones (Eq. 79).[120]



The synthetic potential of the lead tetraacetate reaction was extended to the synthesis of 1,2,3-triacylbenzenes **118** (Eq. 80).[126] The unseparated isomeric mixtures of **116** and **117** were converted to 1,2,3-triacylbenzenes **118** in 63-92% yields.



R = 5-Me R^1 = Me; Ph R^2 = Ph
X = Me; Ph; *p*-NO_2-C_6H_4; *p*-pyridyl

(80)

III. APPLICATIONS OF *o*-HYDROXYARYL KETONES AND DERIVATIVES

o-Hydroxyaryl ketones have found applications in various fields. They are extensively used as absorbers of uv radiation for the protection of polymeric materials from degradation induced by sunlight,[1] and as effective sunscreens in cosmetic preparations.[2] In addition they are employed for the spectroscopic estimation of V(V), Ti(IV), Cu(II), NI(II) and Co(II).[4,5]

Heterocycles prepared from *o*-hydroxyaryl ketones have properties that have attracted the interest of medicinal chemists. Thus, *o*-hydroxyaryl ketones can lead to chromone, flavone and chromanone derivatives which have been investigated for their biological activities.

For example, recently it was shown that aminoalkoxychromones act as dopamine autoreceptor agonists and are thus potential antipsychotics.[43] 5,7-Dihydroxy-3-acetylchromones and flavones depress the release of mediators (histamine etc.) for tissues involved in the antigen-antibody reaction.[47] 5,7-Dihydroxychromone, a natural product which can be synthesized from *o*-hydroxyaryl ketones, is a germination and growth inhibitor.[49] Natural flavones possessing 3-methoxy and 4'-hydroxyl groups show potent antiviral activity against poliomyelitis and rhinovirues.[37] They operate by interfering with an early step in viral RNA synthesis. 3-Methoxycarbonyl-2-arylflavones possessing an hydroxyl substituent at the *para* position of the 2-aryl ring were shown to inhibit *in vitro* protein-tyrosine kinease, which plays a role in the regulation of normal cell growth.[45] Various flavone derivatives show hypolipidemic activity as tested in albino rats.[38] Furthermore, (3-phenyl-7-flavonoxy)propanolamines have reduced spontaneous antihypertensive activity in rats by lowering arterial blood pressure.[28] Finally, 2-ethoxycarbonyl-2-hydroxychromanones have displayed antibiotic activity.[61]

Coumarins are another class of compounds known for their various medicinal properties.[71,72] Especially noteworthy is that 7,8-dimethoxy-4-methylcoumarins were active as antibacterial agents against *S. aureus* and *E. Coli.*,[128] and coumarin **53** is a photochemotherapeutic agent in the treatment of psoriasis.[76]

Chalcones also possess biological activities;[130] the presence of an enone function in the 2'-hydroxychalcones confers on them antibiotic activity.[100]

Bikaverin (Eq. 52) is a fungal pigment possessing a number of interesting properties such as *in vitro* growth inhibition of various tumor cell types,[84,129] whereas pyrimidines **74** also showed a strong inhibition against *S. aureus* and *E. Coli.*[91]

Other non-medicinal uses of these derivatives include the use of 3-aroyl-2-furylchromones as photoactive fluorophones for fluorescent probes.[34,35] Treatment of chromone-3-carboxaldehyde (**9**) with tertiary aromatic amines followed by oxidation gave cationic dyes.[46] Photochromic[54] and thermochromic[55] properties were also found in 2-spirochromanones **19**. 1,2-Diacetylbenzene is a selective reagent for the qualitative and quantitative determination of amines and amino acids.[131] Finally, oximes **105** of *o*-hydroxyaryl ketones are used in analytical chemistry for copper extraction from acidic solution.[115]

IV. CONCLUSIONS

The versatility of *o*-hydroxyaryl ketones **1** has been demonstrated in the chemistry presented in this review. *o*-Hydroxyaryl ketones have been shown to be valuable starting materials in the synthesis of various compounds such as chromones, coumarins, benzofurans, benzoxepins, benzoxanthones, quinones, quinolines, benzoisoindoles, imidazoles, pyrimidines, pyridines, thiazoles, chalcones, 1,3-diketones, alkanes, alkenes, 1,2-diacyl- and 1,2,3-triacylbenzenes, o-acylarylcarboxylic esters, as well as of a number of interesting natural products. Polyhydroxylated flavones such as quercetin,[45] 5,7-dihydroxychromone (**14**)[49] and hydroxylated 4'-methoxyflavones[37] are commonly found in nature. Furthermore, the synthesis of bikaverin and vitamin E were significant contributions to synthetic organic chemistry.

Most of the procedures involve condensation of *o*-hydroxyaryl ketones **1** with acid anhydride, acid chloride, carboxylic acid or carbonyl compounds in the presence of a base. *o*-Hydroxyacetophenone was the most commonly used starting material due to its active acetyl group.

The operational simplicity, together with the easy accessibility of the starting materials, make these syntheses either unique or favorable compared with other reported methods.

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