Synthesis and chemical reactivity of 2-methylchromones

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Abstract

2-Methylchromones, although scarce in nature, constitute a group of oxygen heterocyclic compounds which have shown significant biological activities. Their transformations into other biologically active compounds have been exploited. This review describes the work on the synthesis and reactions of 2-methylchromones as well as their biological evaluation.

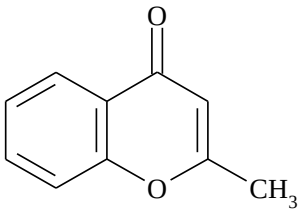
Keywords: 2-Methylchromones, synthesis, chemical reactivity, biological activity

Contents

1. Introduction

Chromones and their derivatives are well known naturally occurring oxygen-containing heterocyclic compounds which perform important biological functions in nature. It is known that certain natural and synthetic chromone derivatives possess important biological activities, such as antitumor,[1] antihepatotoxic, antioxidant,[2] anti-inflammatory,[3] antispasmolytic, estrogenic[4] and antibacterial activities.[5] These applications have stimulated a continuous search for the synthesis of new compounds in this field and led already to the appearance of some drugs on the market.[6]

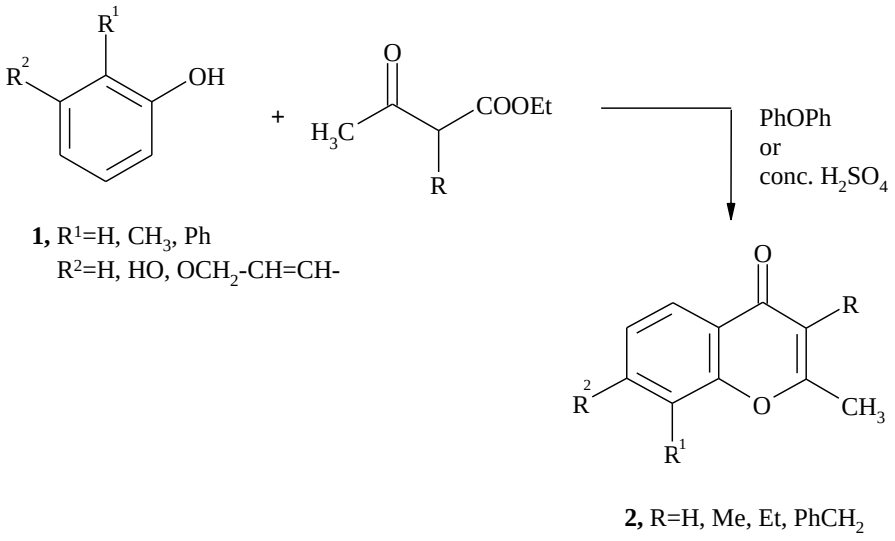
2-Methylchromones are one of the scarcest classes of natural chromones. Although 2-methylchromones constitute a small family of naturally occurring compounds, their synthesis should be extensively studied. To our knowledge, there is not any review summarizing the literature on the synthesis and chemistry of 2-methyl-chromones. This review aims, therefore, to cover the work on the synthesis and reactions of 2-methylchromones as well as their biological evaluation.



2. Preparation of 2-methylchromones

2.1 From phenols

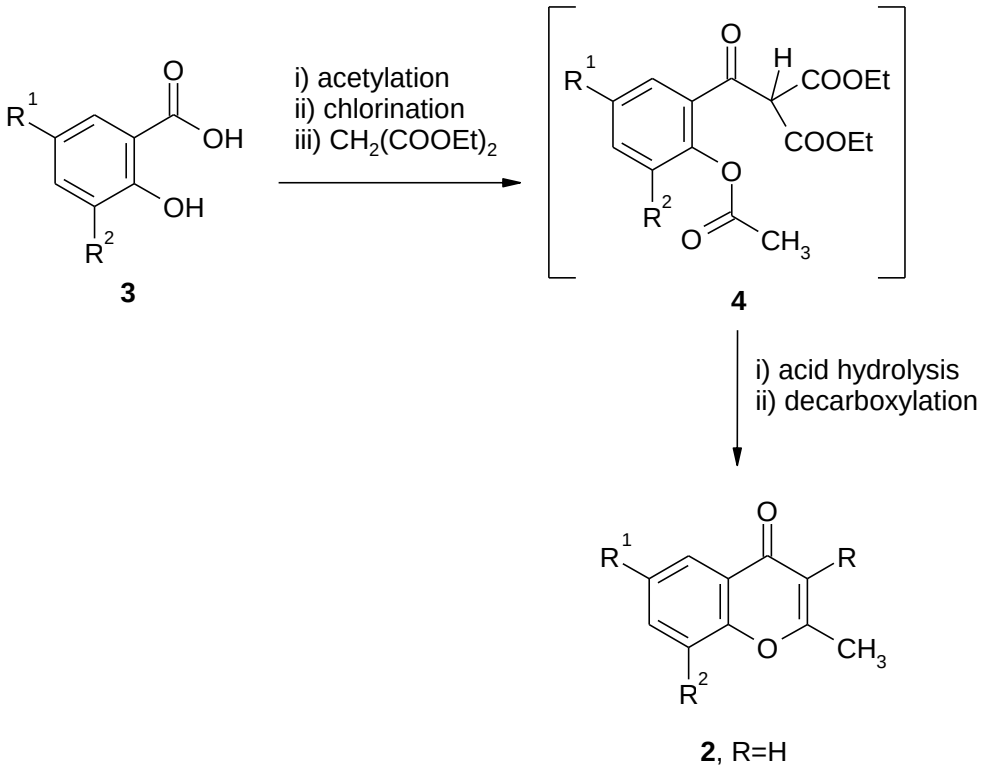
The Simonies reaction involved the reaction of phenols **1** with β-ketoester in the presence of diphenyl ether or concentrated H_2SO_4 to form 2-methylchromones **2** by losing ethanol and water molecules (Scheme 1).[7-10]



Scheme 1

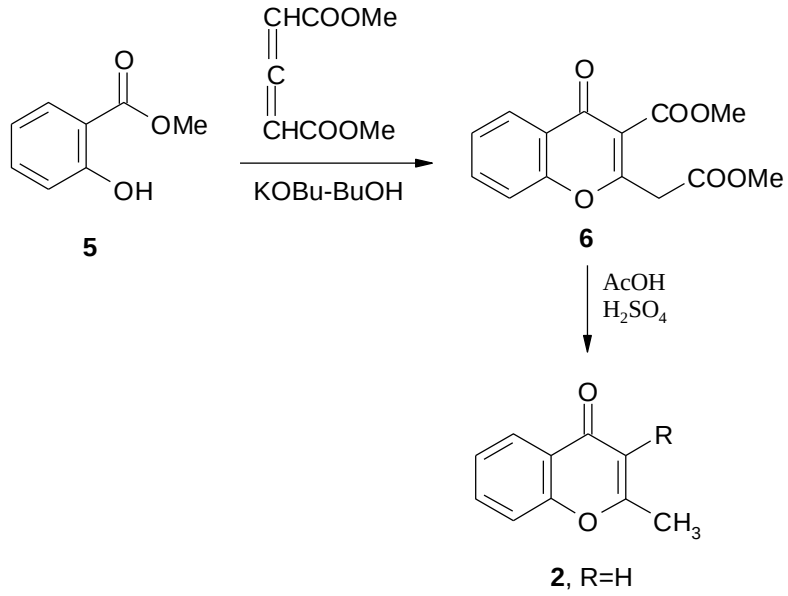
2.2 From salicylic acids

Treatment of salicylic acids **3** *via* successive acetylation, chlorination and reaction with diethylmalonate gave intermediates **4** which underwent acid catalyzed hydrolysis and decarboxylation to give 2-methylchromones **2** (Scheme 2).[11]



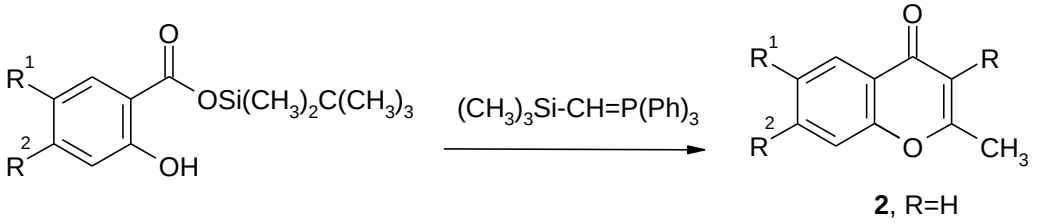
Scheme 2

Dimethylpenta-2,3-dienedioate reacted with methyl salicylate **5** to give the chromone **6** which underwent hydrolysis with acetic acid containing a trace of sulfuric acid, followed by decarboxylation to give 2-methylchromone **2** in 84% yield (Scheme 3).[12]



Scheme 3

O-Acetylsalicylic acid *tert*-butyldimethylsilyl esters **7** underwent condensation with (trimethylsilyl)methylenetriphenylphosphorane followed by an intramolecular Wittig olefination to give substituted 2-methylchromones **2** (Scheme 4).[13]



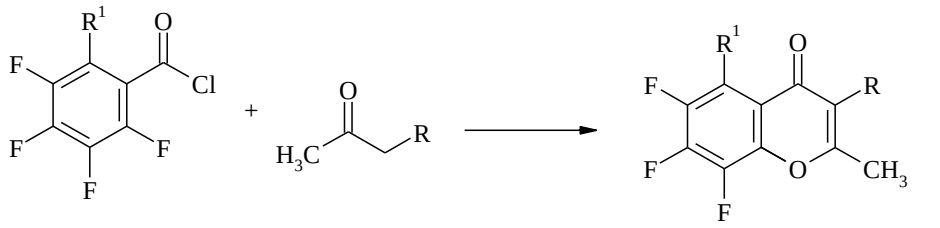
7, R^1, R^2=H, Cl, Me

2, R=H

Scheme 4

2.3 From benzoyl chlorides

2-Methylchromones **2** were synthesized by reaction of fluorobenzoyl chlorides **8** with the corresponding 1,3-dicarbonyl derivatives under basic conditions (Scheme 5).[14-16]

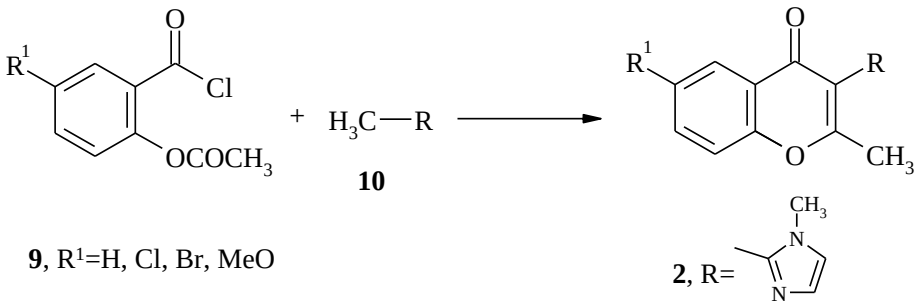


8, R^1=H, F

2, R=COMe, COEt, CONHPh
4-MeC_6H_4NHCO
2-MeC_6H_4CO

Scheme 5

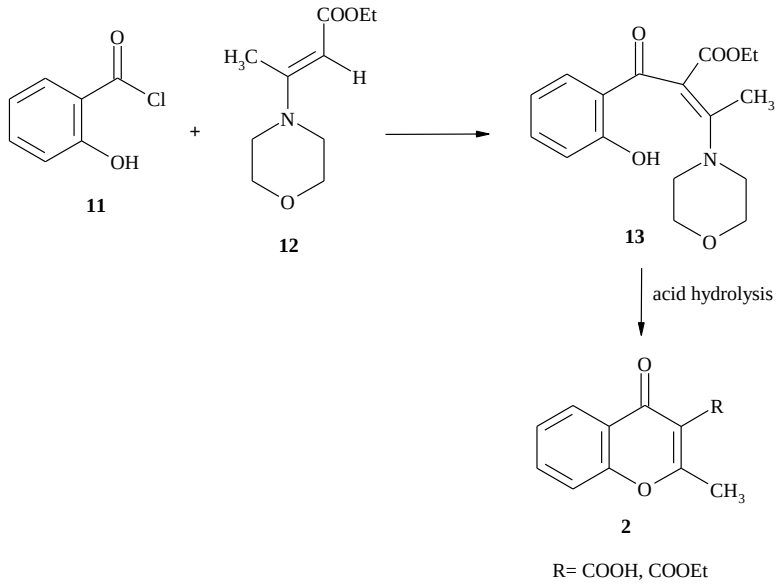
Paolo and Antonio described the synthesis of 2-methyl-3-(1-methyl)-1*H*-imidazol-4*H*-chromones **2** starting from 2-acetoxybenzoyl chlorides **9** and 1,2-dimethylimidazole **10** (Scheme 6).[17]



9, R^1=H, Cl, Br, MeO

Scheme 6

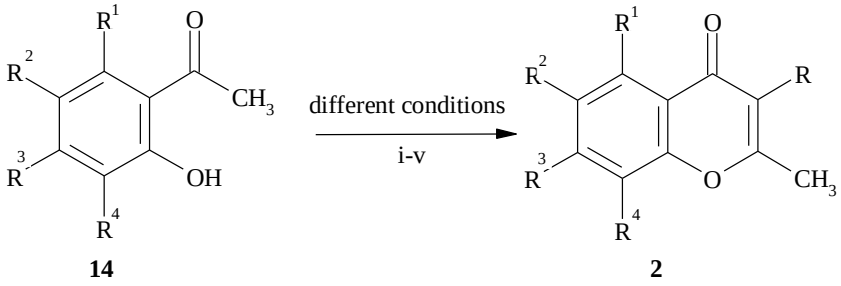
The direct condensation of salicyloyl chloride **11** with enamine **12** gave quantitative yield of morpholine derivative **13**, which was converted to 3-carboxy/carboethoxy-2-methylchromone **2** under acid hydrolysis (Scheme 7).[18,19]



Scheme 7

2.4 From 2-hydroxyacetophenone derivatives

Treatment of 2-hydroxyacetophenones **14** with certain reagents under different conditions afforded 2-methylchromones **2** (Scheme 8).[20-29]

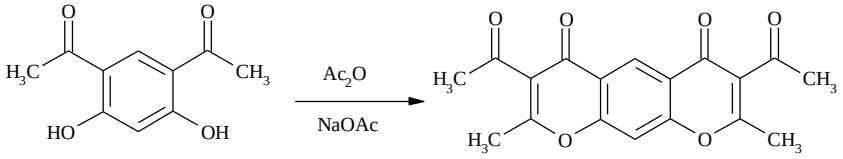


i) Ac_2O-NaOAc
ii) AcCl-DBU-pyridine
iii) a. $LiCH_2CO_2C(CH_3)_3$
b. acid hydrolysis
iv) a. AcCl-$NaOCH_3$
b. Br_2-CCl_4
c. $P(OCH_3)_3$
v) a. DMFDMA
b. Ac_2O

R^1	R^2	R^3	R^4
H	H	MeO	CN
H	CN	MeO	H
H	NO_2	H	H
H	H	HO	MeO
H	H	O	allyl

Scheme 8

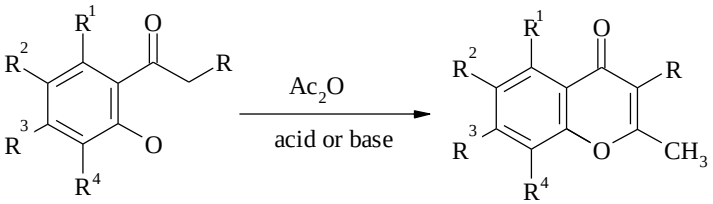
The action of acetic anhydride and sodium acetate on 4,6-diacetylresorcinol **18** yielded unpurified 3,7-diacetyl-2,8-dimethyl-4*H*,6*H*-pyrano[3,2-*g*]chromene-4,6-dione **19** as reported by Gulati and Venkatarman (Scheme 9).[30]



18 **19**

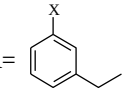
Scheme 9

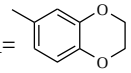
The ring closure of α-substituted-2-hydroxyacetophenones **20** was performed by acetic anhydride in the presence of a trace amount concentrated sulfuric acid or pyridine or triethylamine to give 2-methylchromones **2** (Scheme 10).[31-38]

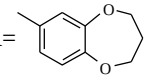


20 **2**

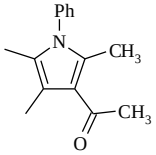
R=H, R^1=H, R^2=Me, R^3=R^4=H
R=Me, R^1=H, R^2=H, COCH=CH-Ar, R^3=R^4=H
R=NO_2, R^1=R^2=R^3=R^4=H

R=  R^1=H, R^2=OMe, R^3=R^4=H
X=CO_2Me, NHCOMe

R=  R^1=H, R^2=H, Et, Pr, R^3=OH, R^4=H

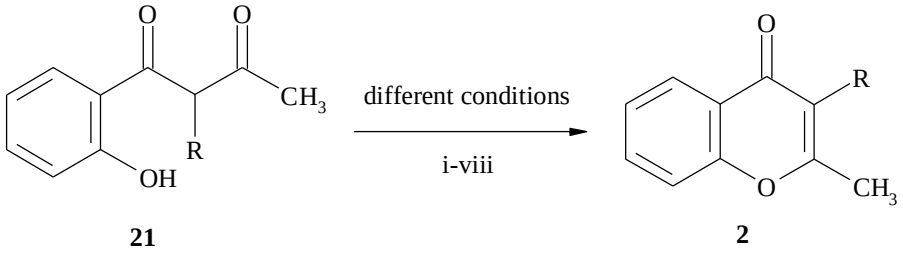
R=  R^1=H, R^2=OH,OMe, R^3=H, OH, R^4=H

R=  R^1=R^2=R^3= R^4=H

R=COCH=CHPh R^1=R^2=H, R^3 R^4= 

Scheme 10

Cyclization of β-diketones **21** under certain conditions such as distillation,[39] acetic anhydride,[19,24,40-44] acidic,[45-53] basic media,[54] microwave,[55] iodine-DMSO,[56] DMSO-heat[57] and bromine[58] gave 2-methylchromones **2** (Scheme 11).



21 **2**

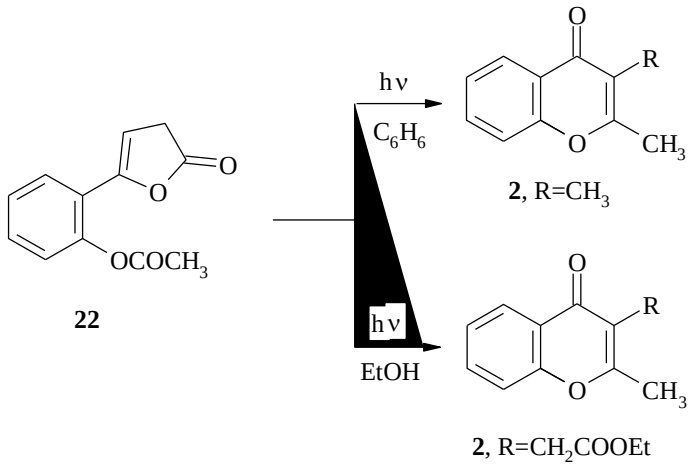
R=H, $COCH_3$, COOEt, Br

i) Distillation at 165 °C
ii) Ac_2O-AcONa
iii) AcOH-HCl or H_2SO_4
iv) NH_2OH
v) $CaCl_2$, MW, 5 min
vi) I_2, DMSO, heat
vii) DMSO, heat
viii) Br_2

Scheme 11

2.5 From furan derivatives

Irradiation of the 5-(2-acetoxy-substituted phenyl)-3*H*-furan-2-one **22** in benzene and/or ethanol led to the formation of 2-methylchromones **2** (R=CH_3, CH_2COOEt) (Scheme 12).[59]



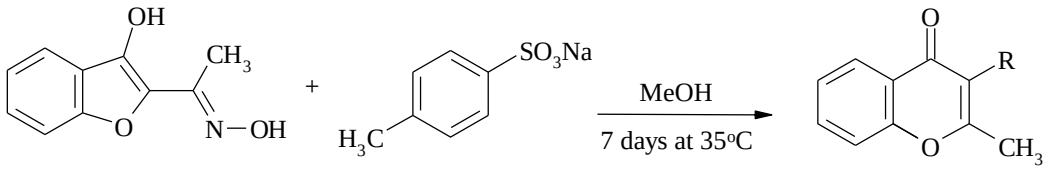
22

2, R=CH_3

2, R=CH_2COOEt

Scheme 12

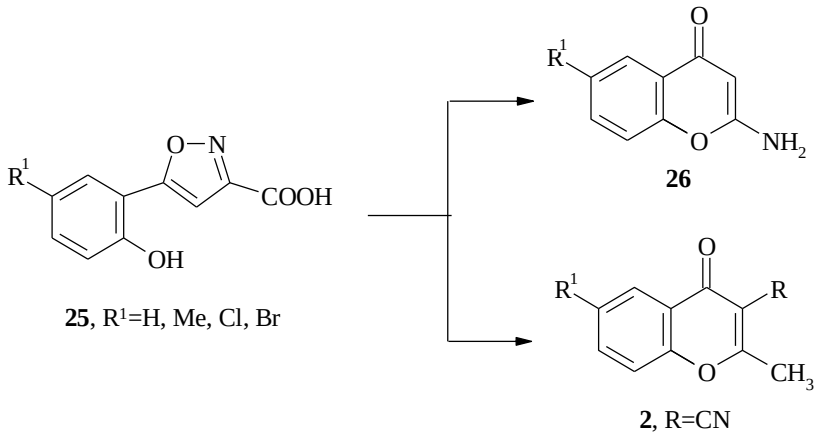
When 2-acetylbenzofuran oxime **23** and sodium *p*-toluenesulfonate **24** were kept in methanol for 7 days at 35 ºC, 2-methylchromone **2** (R=OH) was obtained (Scheme 13).[60]



Scheme 13

2.6 From isoxazole derivatives

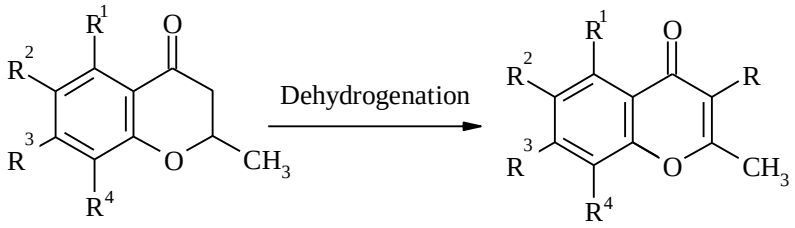
5-(2-Hydroxy substituted phenyl)-3-isoxazole-carboxylic acids **25** underwent transformation into the corresponding 2-aminochromones **26** and 2-methylchromones **2** (R=CN) (Scheme 14).[61]



Scheme 14

2.7 From chromone derivatives

2.7.1 From 2-methylchromanones. Dehydrogenation of chroman-4-ones **27** by using I_2-DMSO-H_2SO_4,[62,63] and isoamyl nitrite-HCl[64] systems yielded 2-methylchromones **2** (Scheme 15).

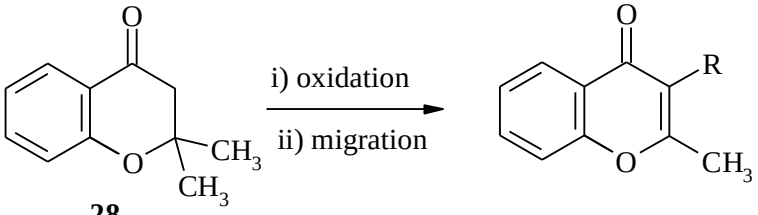


27, R^1=H, Me R^2=H, Me, Et, Cl, Br
R^3=H, R^4=H, MeO

2, R=H

Scheme 15

Oxidation of 2,2-dimethylchromanone **28** with thallium-*p*-tosylate followed by 2,3-alkyl migration gave 2-methychromone **2** (R=CH_3) in high yields (Scheme 16).[65]

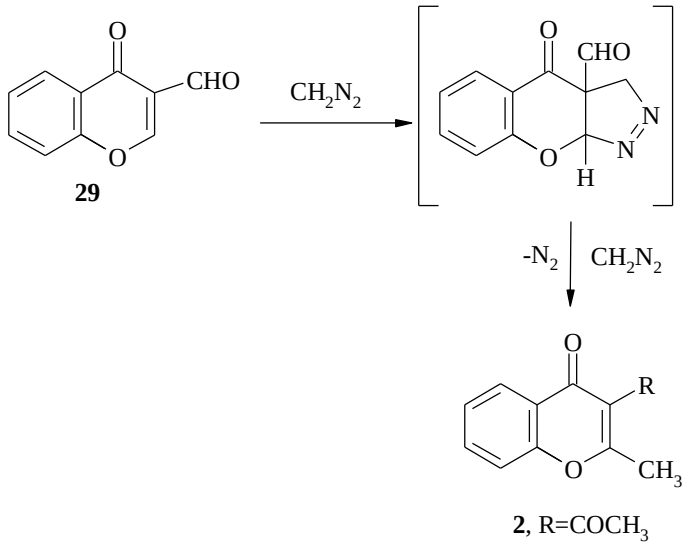


28

2, R=CH_3

Scheme 16

2.7.2 From 3-formylchromone. Diazomethane underwent *cis* addition to 2,3-olefinic bond of 3-formyl chromone **29** to give 1-pyrazoline derivatives as nonisolable intermediate which underwent, in the presence of excess of diazomethane, further transformation to 2-methylchromone **2** (R=$COCH_3$) (Scheme 17).[66]

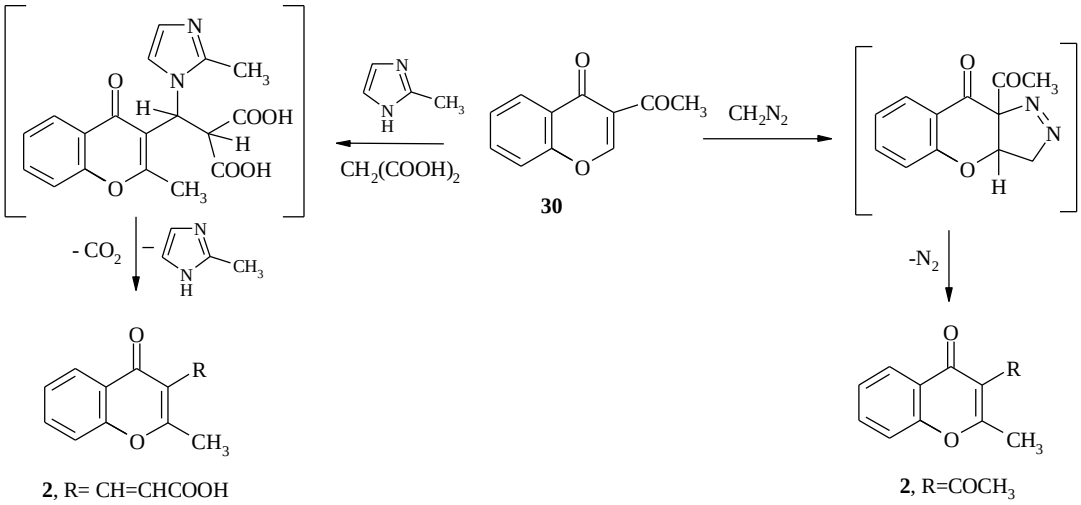


29

2, R=$COCH_3$

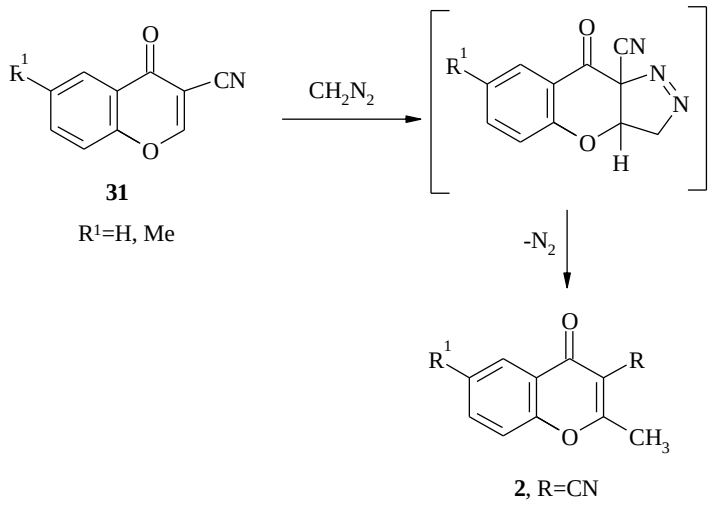
Scheme 17

2.7.3 From 3-acetylchromone. 1,3-Dipolar cycloaddition of diazomethane to 3-acetylchromone **30** as an activated olefin furnished 2-methylchromone **2** (R=$COCH_3$).[67] Also, its reaction with malonic acid in the presence of 2-methylimidazole afforded 3-(2-methylchromon-3-yl)acrylic acid **2** (R= CH=CH-COOH) (Scheme 18).[68]



Scheme 18

2.7.4. From 3-cyanochromone. Diazomethane underwent [3+2] cycloaddition to 2,3-olefinic bond of 3-cyanochromones **31** giving the 1-pyrazoline intermediate that by a concerted electrocyclic elimination of nitrogen and migration of hydrogen yielded 2-methylchromone **2** (R=CN) (Scheme 19).[69,70]

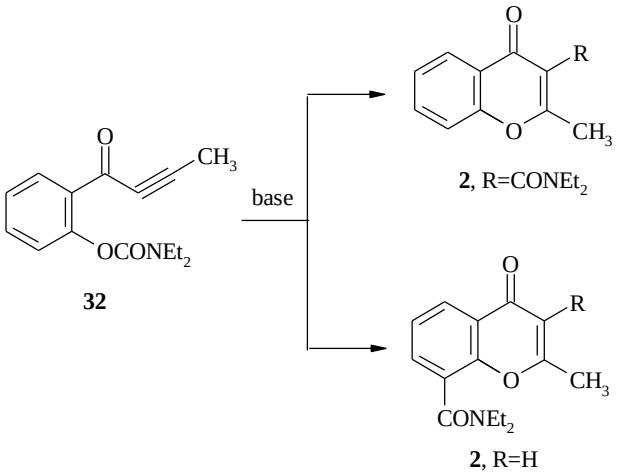


Scheme 19

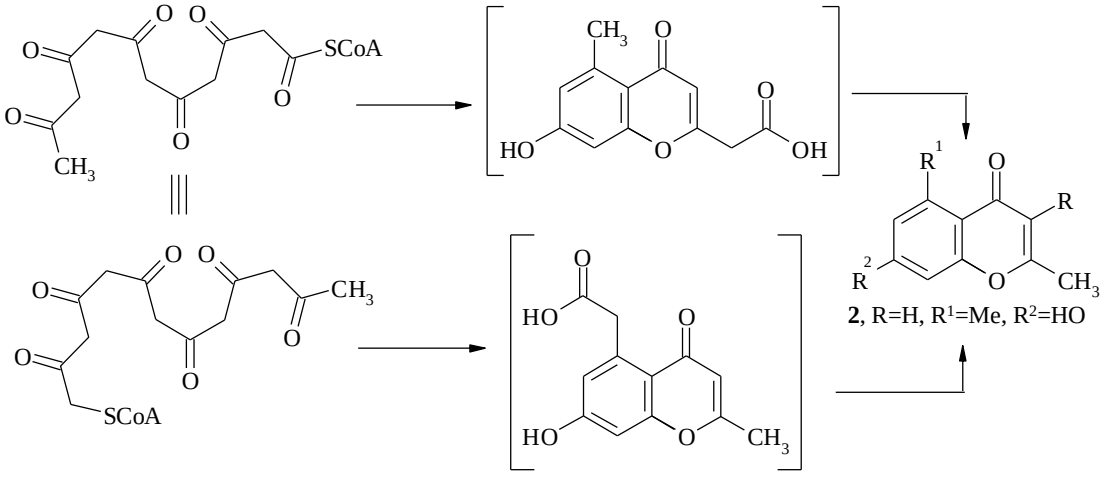
2.8 Miscellaneous methods

Treatment of but-2-ynoylaryl *O*-carbamate **32** with base gave either 2-methyl-chromone-3-/8-carboxamide **2** (R=CONEt$_2$, H) as published by Macklin *et al*[71] (Scheme 20).

One molecule of acetyl-CoA condensed with five molecules of malonyl-CoA to give a polyhexanone **33**, which on cyclization gave different chromone intermediates, bearing an acetoxy at C-2 or C-5, respectively. These intermediates underwent decarboxylation to give 2-methylchromones **2** (R=H) (Scheme 21).[72]



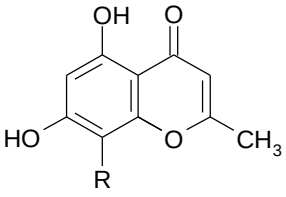
Scheme 20



Scheme 21

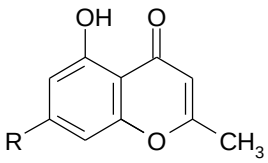
2.9 Extraction from plants

5,7-Dihydroxy-2-methylchromone β-D-glucopyranoside **2A** was isolated from and ethanolic extraction of cloves (*Eugenia caryophyllata*).[73] Also, 5-hydroxy-2-methylchromones **2B** were isolated from the root of *Adina rubella hance*.[74]



2A

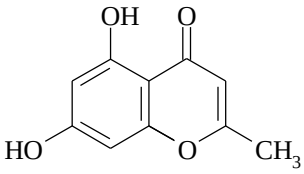
R= β-D-glucopyranoside



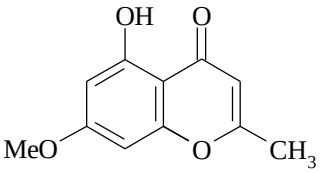
2B

R=O-β-xylopyranosyl
β-glycopyranoside
O-β-apiofuranosyl

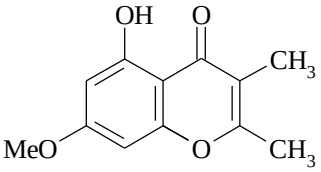
5,7-Dihydroxy-2-methylchromone **2C** and 5-hydroxy-7-methoxy-2-methyl-chromone **2D** were isolated from the bulbs of *P. maritimum*.[75] Also, **2E** was isolated from the cultures of spore derived mycobionts of lichen *Graphis scripta*.[76]



2C

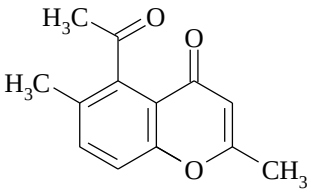


2D

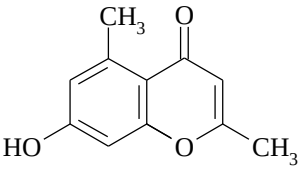


2E

5-Carboxymethyl-7-hydroxy-2-methylchromone (**2F**) was isolated from the antibiotic and anti-inflammatory active site of *Polygonum cuspidatum sieb*[77] while the over sephadex LH-20 column eluted with chloroform-methanol (50:50) furnished compound **2G**.[72]

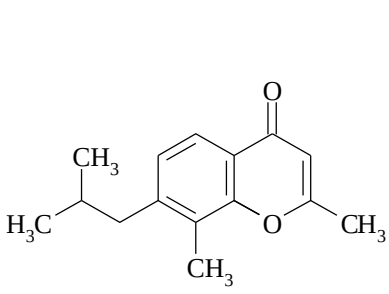


2F

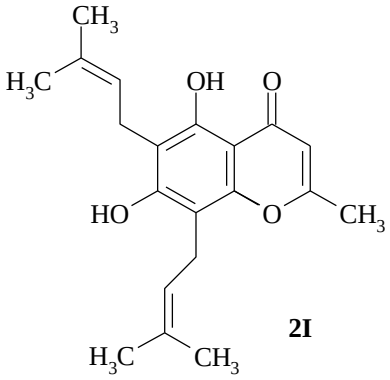


2G

2-Methylchromones **2H** and **2I** were isolated from *Leucas inflata* and *Neochamaclea puluervlenta*, respectively.[78,79]

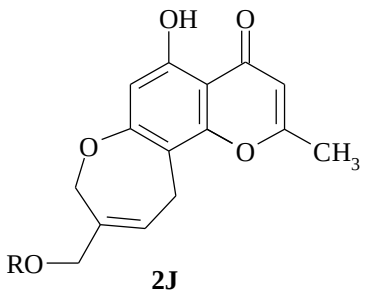


2H



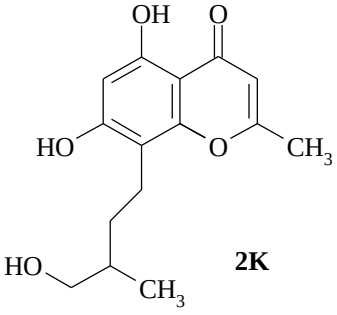
2I

9-(*O*-β-D-glucopyranosyl-D-glucopyranosyl)oxyl]methyl-8,11-dihydro-5-hydroxy-2-methy)-4*H*-pyrano[2.3.9][1]benzoxepin-4-one **2J** and 7-dihydroxy-8-[(2e)-4-hydroxy-3-methylbut-2-enyl] -2-methyl-4*H*-chromone **2K** were isolated from the tubers of *Eranthis cilicica*.[80]



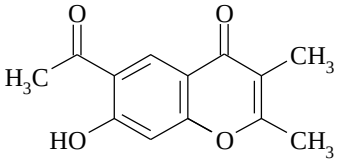
2J

R=Glu (1 ► 6) Glu

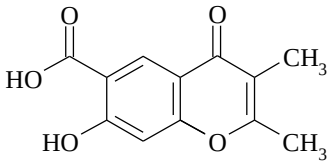


2K

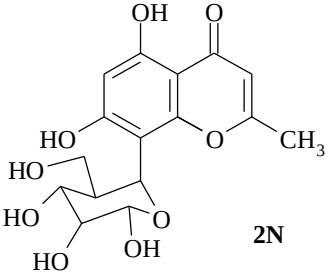
6-Acetyl-7-hydroxy-2,3-dimethylchromone **2L** and 6-carboxy-7-hydroxy-2,3-dimethylchromone **2M** were isolated from *Tussilago farfara*.[81] Also, 2-methyl-chromone derivative **2N** was isolated from the gel of *Aloe vera* leaves.[82]



2L

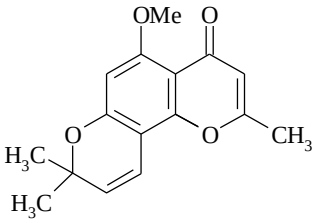


2M

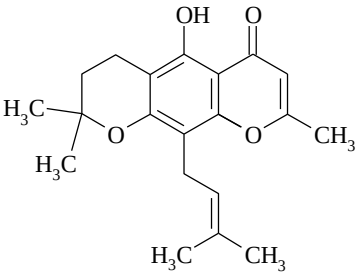


2N

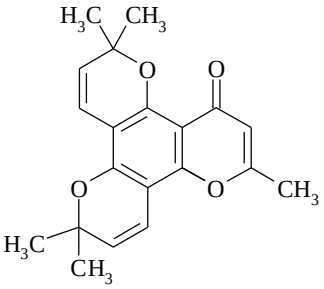
Compound **2O** was isolated from a Nigerian sample of *H. abyssini*,[83,84] while 3,3-dimethylallyl patheliachromene **2P** and spatheliabischromene **2Q** were isolated from the leaves of *Cneorum triciocuum*.[85-87]



2O



2P



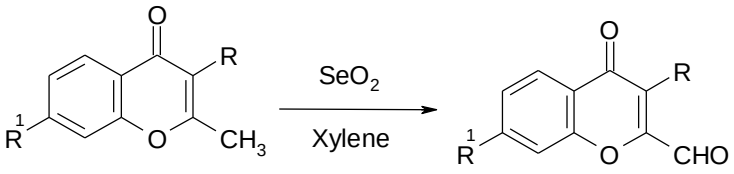
2Q

3. Reactivity of 2-Methylchromones

The reactivity of methyl group at position 2 of chromone moiety has special character due to the low electron density at C-2 which is caused by oxygen atom and α,β-unsaturated ketone system.

3.1 Oxidation reactions

3.1.1 Oxidation with SeO_2. Oxidation of 2-methylchromones **2** (R=H) by selenium dioxide in refluxing xylene yielded chromone-2-carboxaldehydes **34** (Scheme 22).[88-90]

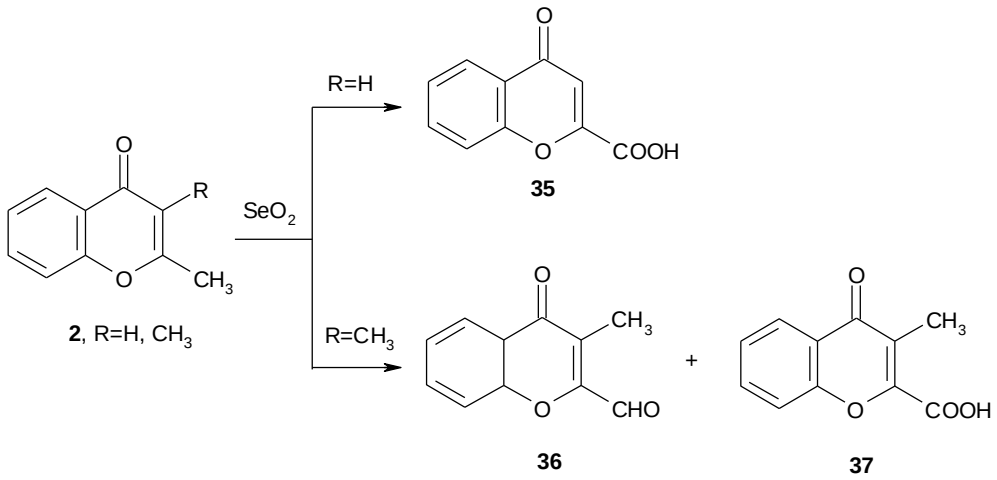


2, R=H
R^1= H, CH_3, Cl, Br

34

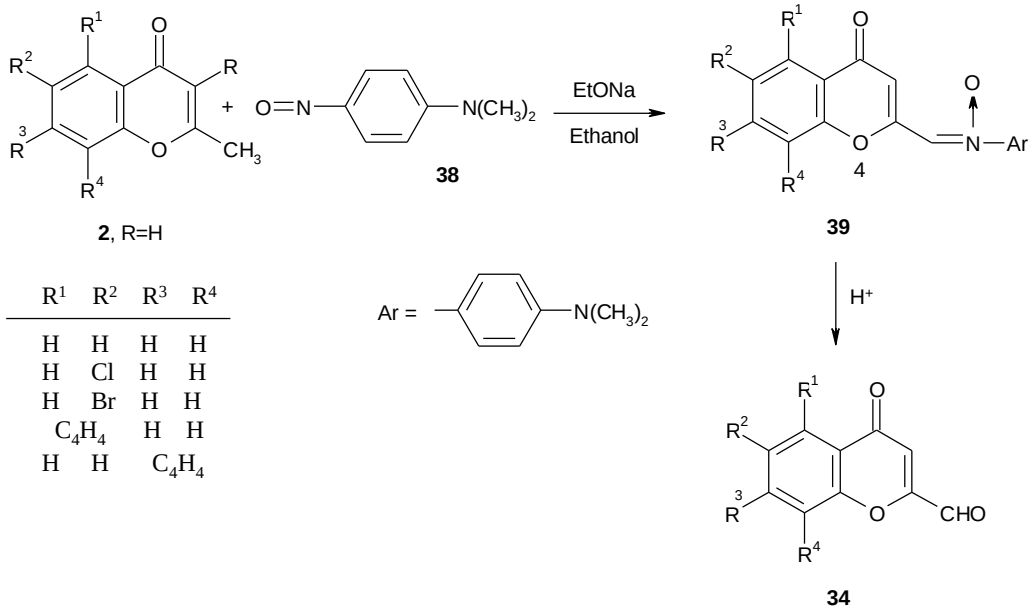
Scheme 22

On the other hand, oxidation of **2** (R=H) with selenium dioxide give chromone-2-carboxylic acid **35**, but 2,3-dimethylchromone on oxidation with SeO_2 gave a mixture of 3-methylchromone-2-carboxaldehyde **36** and 3-methylchromone-2-carboxylic acid **37** (Scheme 23).[91]



Scheme 23

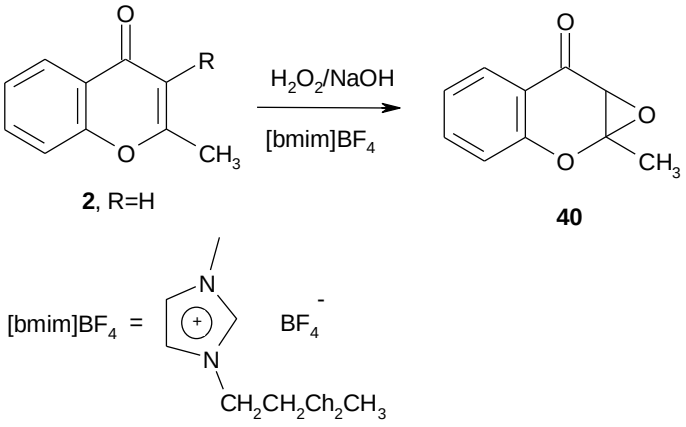
3.1.2 Oxidation by reaction with *p*-nitroso-*N*,*N*-dimethylaniline. Condensation of substituted-2-methylchromones **2** with 4-nitroso-*N*,*N*-dimethylaniline **38**, in the presence of sodium ethoxide or sodium hydroxide, afforded *N*-(*p*-dimethylamino- phenyl)-α-(chromon-2-yl)nitrones **39** that on hydrolysis with dilute acid gave the corresponding 2-formylchromone derivatives **34** (Scheme 24).[92,93]



R1	R2	R3	R4
H	H	H	H
H	Cl	H	H
H	Br	H	H
C4H4		H	H
H	H	C4H4	

Scheme 24

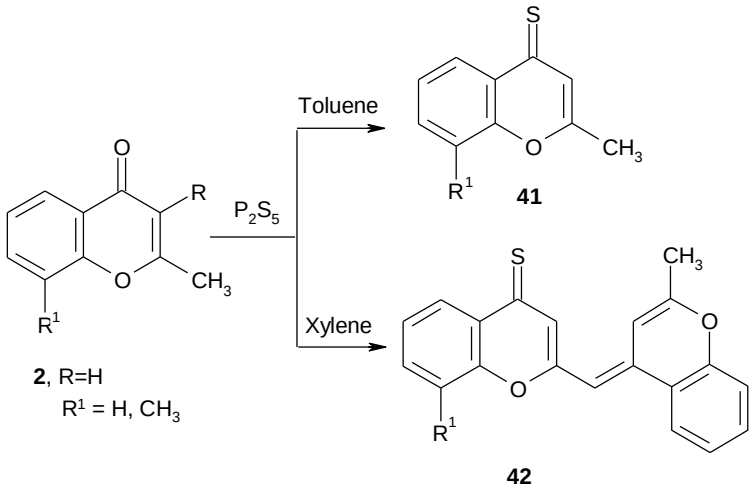
3.1.3 Oxidation with H_2O_2. 2-Methylchromone **2** (R=H) in the presence of alkaline hydrogen peroxide as an oxidant in 1-butyl-3-methylimidazoliumtetrafluoroborate [bmim]BF_4 as a solvent afforded 2-methylchromone epoxide **40** (Scheme 25).[94]



Scheme 25

3.2 Thiation

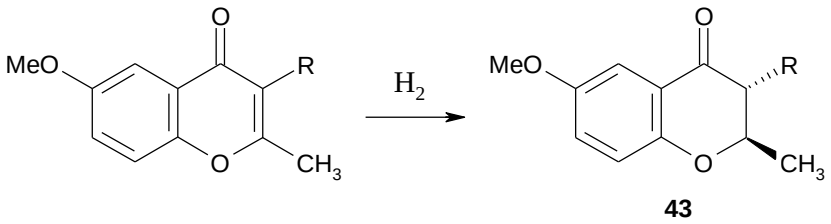
Treatment of 2-methylchromone **2** (R=H) with phosphorus pentasulfide in toluene afforded 2-methyl-4-thiochromone **41**.[95] The same reaction afforded 2-[2-methyl-4-benzopyranylidene)methyl]benzopyran-4-thione **42** when carried out in refluxing xylene.[96] Also, Simonis and Rosenberg[97] prepared 2,8-dimethyl-4-thiochromone **41** by direct fusion of **2** (R=H, R^1=CH_3) with phosphorus pentasulfide (Scheme 26).



Scheme 26

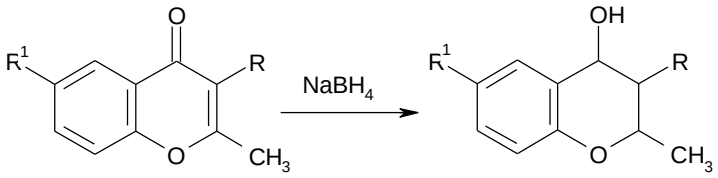
3.3 Hydrogenation

Reduction of 2-methylchromones **2** produced *trans*-2,3-disubstituted-4-chromanones **43**.[34] Also, Reduction of chromones **2** (R=*N*-methylimidazol-2-yl) with sodium borohydride afforded the corresponding chromanols **44** in good yields[98] (Scheme 27).

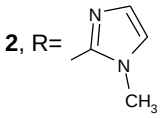


43

2, R= *m*-$CH_3OOCC_6H_4$, *m*-$CH_3CONHC_6H_4$



44

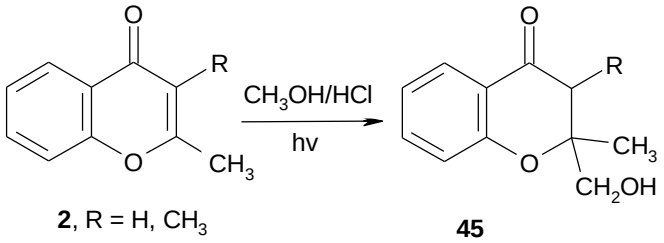


R^1 = H, Cl, Br, OCH_3

Scheme 27

3.4 Photolysis

Irradiation of 2-methylchromones **2** in CH_3OH-HCl induced the homolytic addition of CH_3OH to the double bond in the pyrone ring to give 2-hydroxymethyl- chromanones (**45**) (Scheme 28).[99]

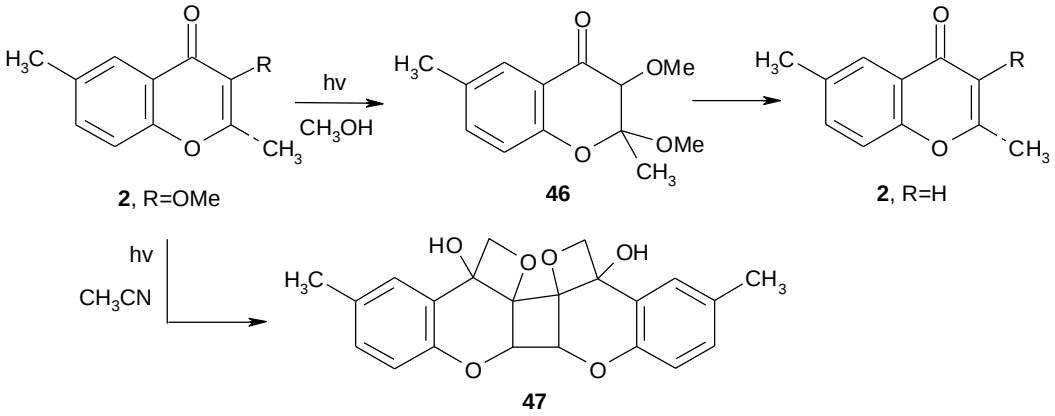


2, R = H, CH_3 **45**

Scheme 28

Photolysis of 2-methylchromone **2** (R=OMe) in methanol afforded chromanone **2** (R=H) through extrusion of a methoxy function, the reaction proceed through a conjugate addition of

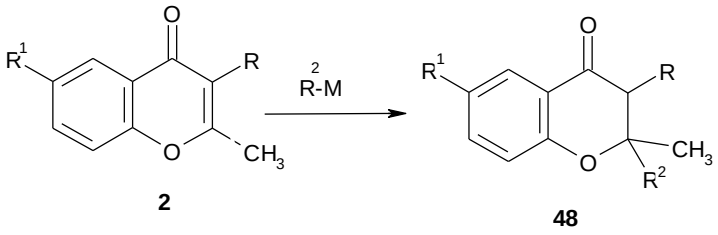
methanol to give **46**, followed by double methoxy elimination. When photolysis took place in non nucleophilic solvent such as benzene or acetonitrile the dimer **47** was obtained in good yield (Scheme 29).[100]



Scheme 29

3.5 Reactions with organometallic reagents

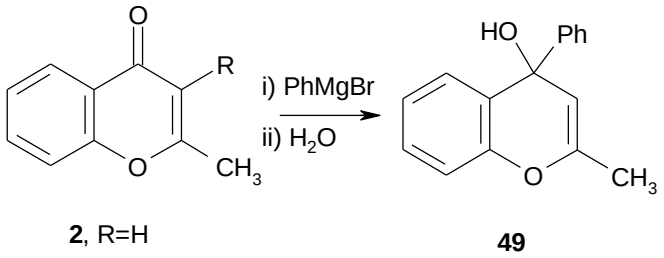
Reaction of 2-methylchromones **2** with organocopper reagents (alkylcopper-BF_3, lithium dimethylcuparate or lithium di-*n*-butylcuparate) provided 2,2-dimethyl-chromanone derivatives **48** *via* conjugate addition to the double bond in the γ-pyrone system (Scheme 30).[101,102]



R	R^1	R^2
H	H	CH_3
H	CH_3	CH_3
$COCH_3$	CH_3	CH_3, Bu^n
$COOCH_3$	OCH_3	CH_3, Bu^n
$COCH_3$	H	CH_3
$COOCH_3$	H	CH_3

Scheme 30

Reaction of 2-methylchromone **2** (R=H) with phenyl magnesium bromide gave after treatment with water 2-methyl-4-phenylchromen-4-ol **49** (Scheme 31).[103]



2, R=H **49**

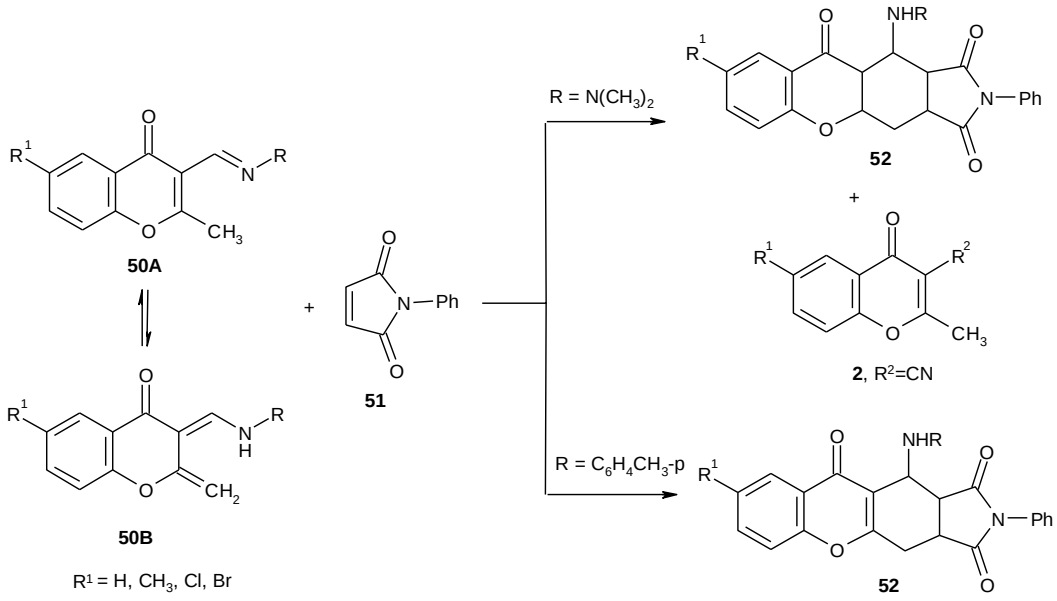
Scheme 31

3.6 Diels Alder reactions

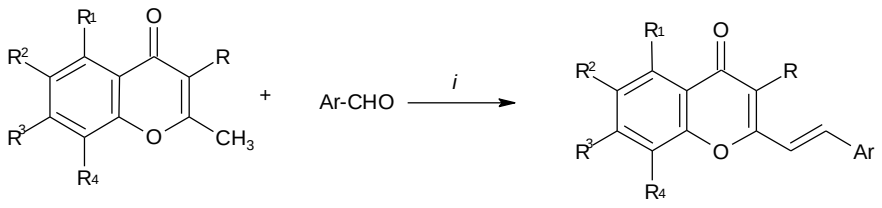
N,*N*-Dimethylhydrazones **50A** on treatment with *N*-phenylmaleimide **51** gave tetrahydroxanthone **52** together with a little amount (~10%) of 3-cyano-2-methylchromone **2** (R^2=CN). Reaction of anil **50** (R=4-$CH_3C_6H_4$) with **51** gave cycloadduct **52** through its imine tautomer **50B** (Scheme 32).[104,105]

3.7 Condensation reactions

3.7.1 Reactions with carbonyl compounds. Treatment of 2-methylchromones **2** (R=H, NO_2) with aromatic aldehydes under different basic conditions afforded the corresponding 2-styrylchromones **53** (Scheme 33).[50,91,106-117]



Scheme 32



2, R=H, NO_2
R^1=H, OMe,
R^2=H, Cl, Ph, PhCO
R^3=H, OH, OMe, $OCH_2C_6H_4$-OMe-*p*
R^2R^3=-OCH=CH-
R^4=H, OMe, $CH_2N(CH_2C_6H_4$-OMe-*p*$)(CH_2CH_2C_6H_5)$

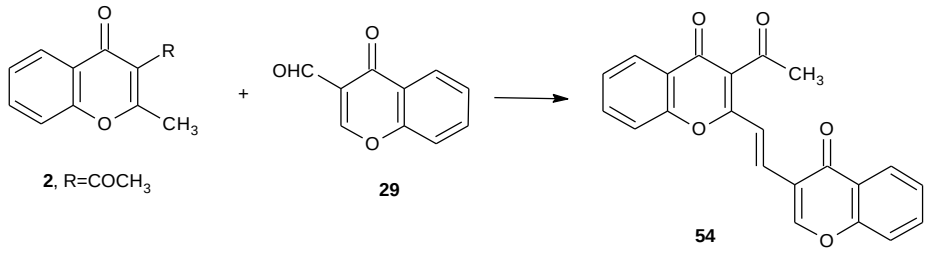
53

Ar= Ph, 2-$Et_2NCOC_6H_4$, 2-$HOOCC_6H_4$, 4-$CH_3OC_6H_4$, 4-ClC_6H_4, 4-$O_2NC_6H_4$, 2-furyl, 4-$CH_3NC_6H_4$, PhCH=CH, benzo[1,3]dioxol-5-yl, 3,4-$(CH_3O)_2C_6H_3$, 3-BrC_6H_4, 2-pyridinyl, 2-thienyl

i) EtONa-$Mg(OCH_3)_2$ or piperidine or EtOH-KOH, EtOH-EtONa

Scheme 33

Aldol condensation of 2-methylchromone **2** (R=$COCH_3$) with 3-formyl-chromone **29** gave the condensed product **54** *via* the condensation of the formyl group with the active methyl group at position 2 due to the methyl group more active than acetyl group in position 3 (Scheme 34).[118]



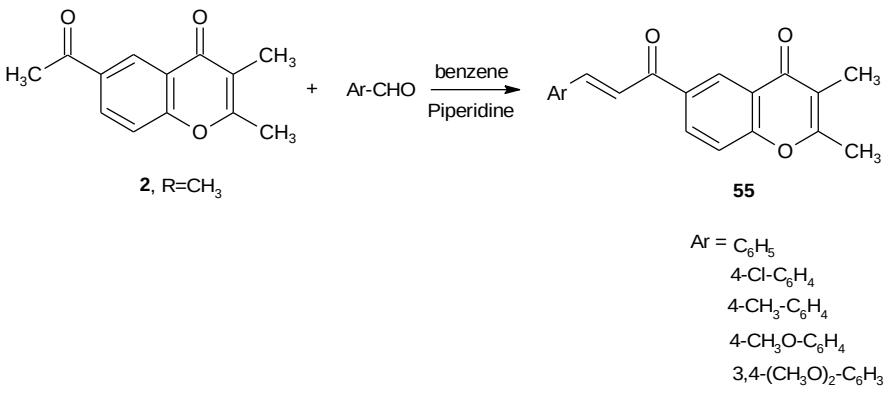
2, R=$COCH_3$

29

54

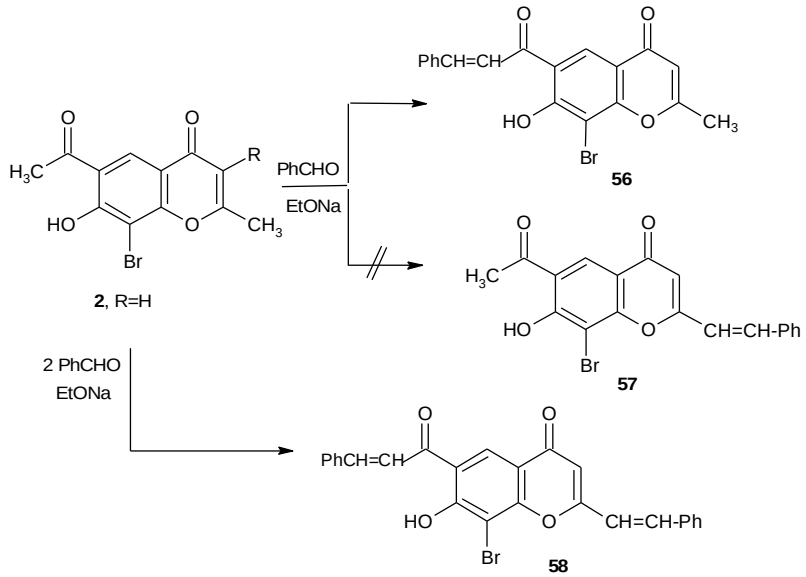
Scheme 34

On the other hand, 6-cinnamoyl-2,3-dimethylchromones **55** were obtained from the condensation of 2-methylchromones **2** (R=CH_3) with appropriate aldehydes in dry benzene in the presence of piperidine (Scheme 35).[119]



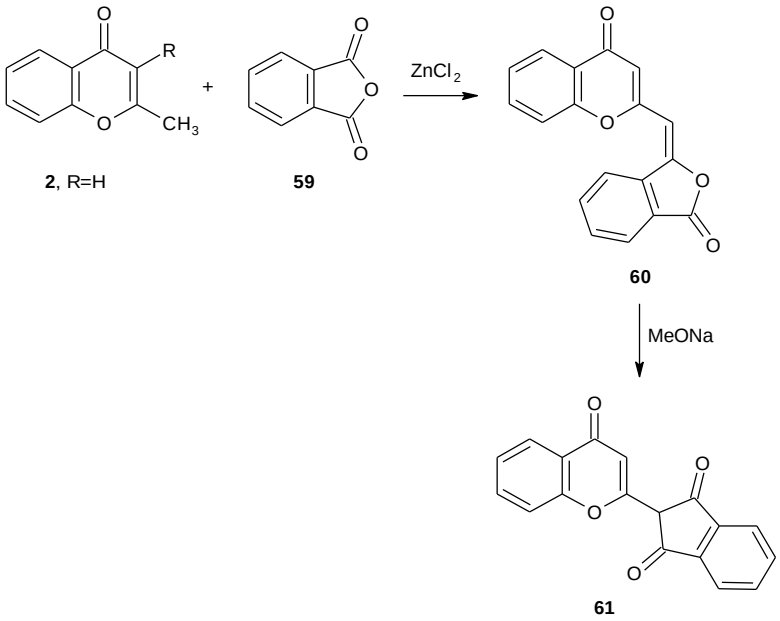
Scheme 35

Also, the reactivity of the two methyl groups in compound **2** towards aromatic aldehydes was tested, reaction of equimolar ratio of **2** (R=H) with benzaldehyde in the presence of piperidine as a basic catalyst led to the formation of the corresponding 6-cinnamoyl derivative **56** not the 2-styryl derivative **57**. With two moles of benzaldehyde in ethanolic sodium ethoxide solution compound **2** gave the 2-styryl-6-cinnamoylchromone derivative **58** (Scheme 36).[46]



Scheme 36

Condensation of 2-methylchromone **2** (R=H) with phthalic anhydride **59** in the presence of zinc chloride gave phthalide **60** which was rearranged by sodium methoxide to 1,3-indandione derivative **61** (Scheme 37).[120]

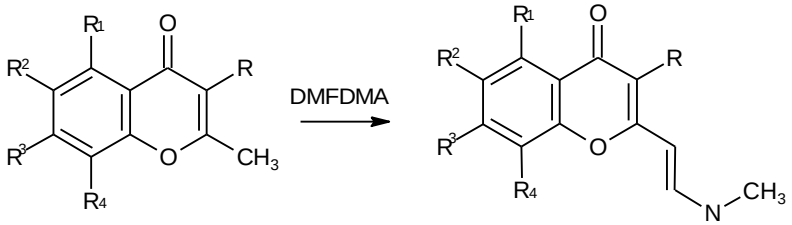


2, R=H **59** **60** **61**

Scheme 37

3.7.2 Reactions with DMFDMA

Reaction of 2-methylchromones **2** with DMFDMA afforded the dienamine **62**.[43,121-124] The *E*-geometry around the exocyclic olefinic bond in compounds **62** was established from their ^{1}H NMR spectra (Scheme 38).



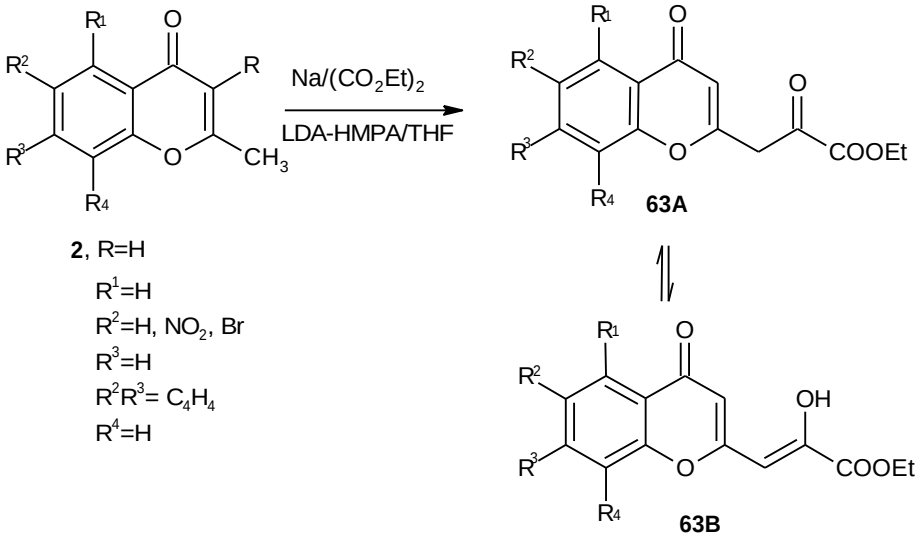
2, R=H, $COCH_3$, PhCO, CH_2SCH_3
R^1=H, OMe
R^2=CH_3, Cl
R^3=H
R^2R^3= -OCH=CH-
R^4=H, OMe

62

Scheme 38

3.7.3 Reaction with diethyl oxalate. Condensation of 2-methylchromones **2** (R=H) with diethyl oxalate in the presence of sodium metal gave the corresponding pyruvate esters **63**.[125] Also, esters **63** were obtained from **2** using lithium di-isopropylamide in hexamethylphosphoramide

(1 equiv.) and tetrahydrofuran at -30 °C followed by addition of diethyl oxalate at 0-20 °C (Scheme 39).[110]

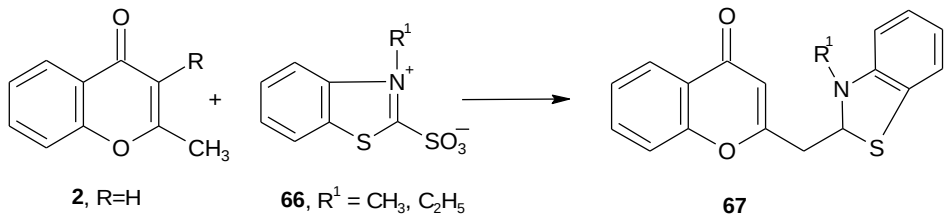


Scheme 39

3.7.4 Intramolecular cyclization. Refluxing 3-acetoacetyl-2-methylchromone **64** in 48% HBr under Wessely-Moser rearrangement conditions produced 3-methyl-1*H*-xanthene-1,9(4*H*)-dione **65** (Scheme 40).[126]

Scheme 40

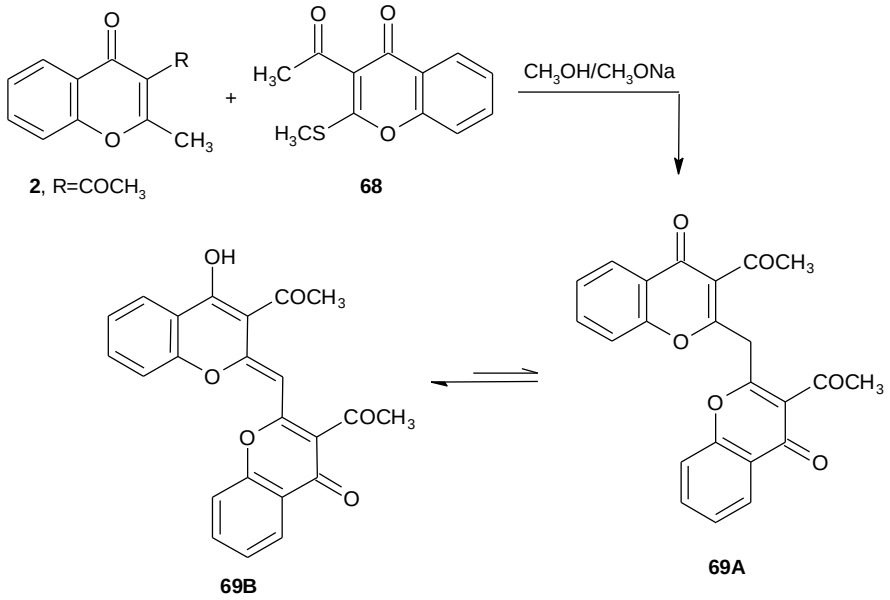
3.7.5 Reaction with benzothiazole-2-sulfobetaine. Heating of 2-methychromone **2** (R=H) with 3-ethyl/methylbenzothiazole-2- sulfobetaine **66** at 150 °C followed by treatment with aqueous NH_4OH gave 2-(3-ethyl/methyl benzothiazolin-2-yl)methyl)chromone **67** (Scheme 41).[96,127]



2, R=H **66**, R^1 = CH_3, C_2H_5 **67**

Scheme 41

3.7.6 Reaction with 3-acetyl-2-methylthiochromone. Treatment of 2-methylchromone **2** (R=$COCH_3$) with 3-acetyl-2-methylthiochromone **68** in sodium methoxide gave **69A** that exists exclusively in the tautomeric form **69B** due to its formation strong hydrogen bond (Scheme 42).[128]

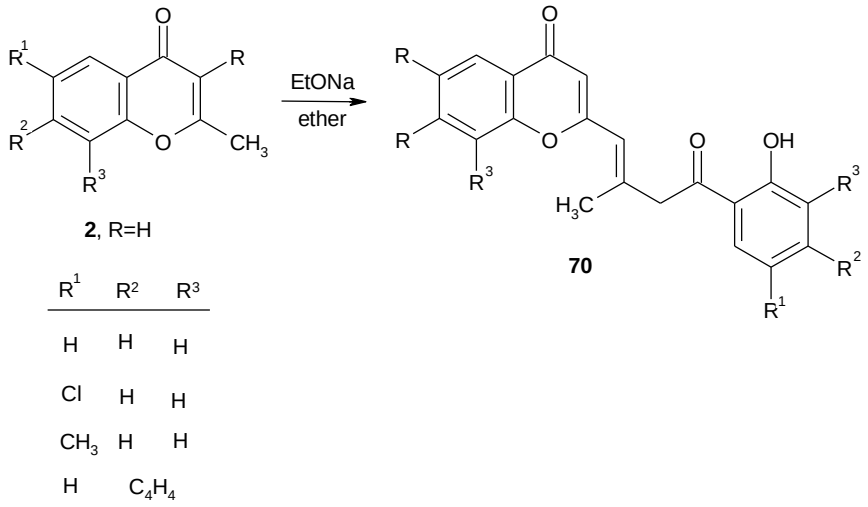


2, R=$COCH_3$ **68** **69B** **69A**

Scheme 42

3.8 Dimerization reactions

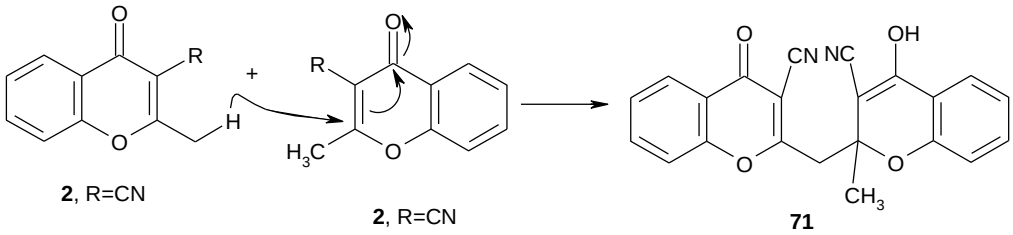
When 2-methylchromones **2** were treated with sodium ethoxide in dry ether, the dimeric products **70** were obtained. The formation of **70** may be attributed to ring opening of the pyrone nucleus of one molecule by the action of an active methyl group of another molecule of **2** (Scheme 43).[129,130]



R^1	R^2	R^3
H	H	H
Cl	H	H
CH_3	H	H
H	C_4H_4	

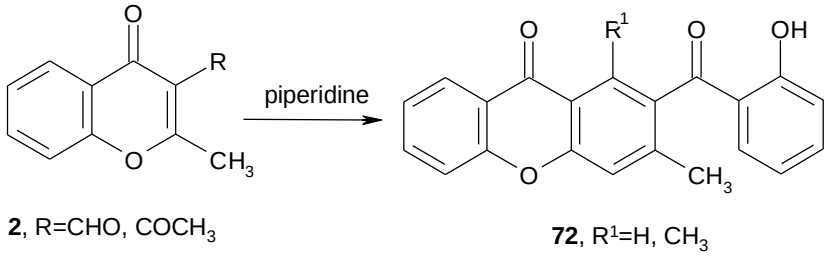
Scheme 43

Base catalyzed Michael addition of 2-methylchromone **2** (R=CN) to the α,β-unsaturated ketone function of a second molecule gave the dimeric product **71** (Scheme 44).[70]



Scheme 44

Also, base catalyzed self condensation of 2-methylchromones **2** (R=CHO, $COCH_3$) gave 2-salicyloyl-3-methylxanthone **72** (R=H, CH_3) (Scheme 45).[128]

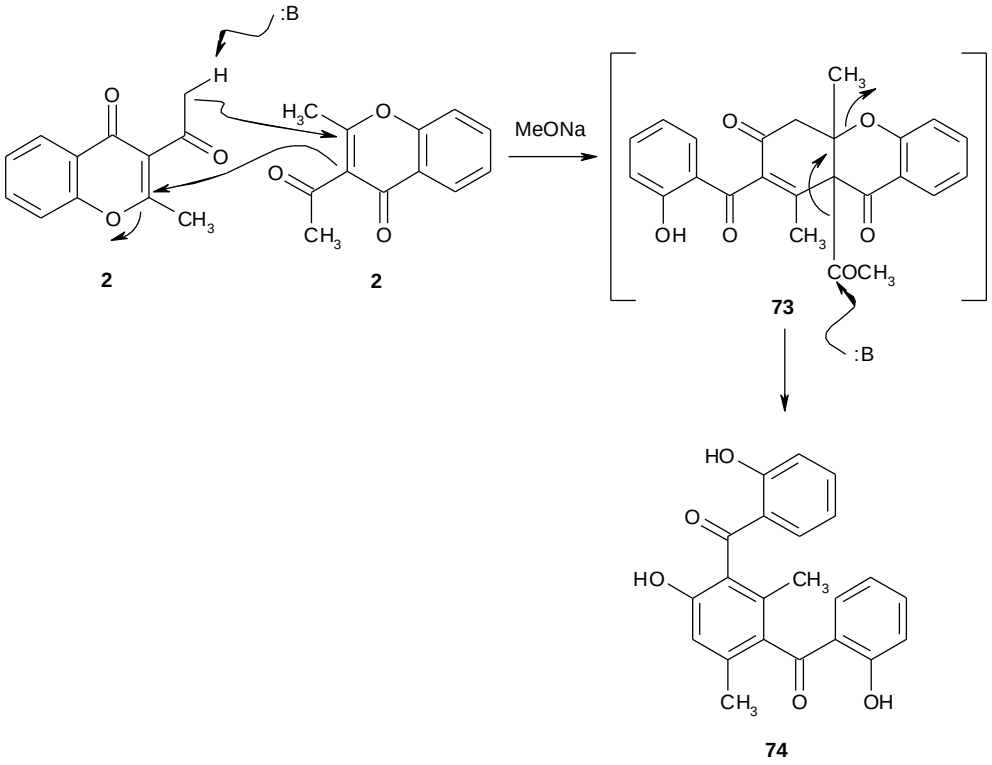


Scheme 45

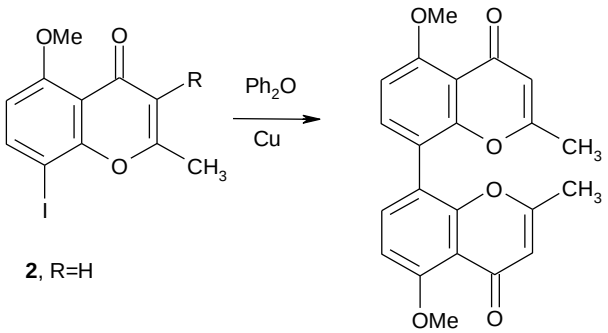
Surprisingly, boiling of chromone **2** (R=$COCH_3$) in methanol containing sodium methoxide yielded 2,4-disalicyloylphenol derivative **74**. The intramolecular reaction is initiated by the attack of the carbanion generated from the acetyl group at 3-position of a second molecule of **2**, the resultant intermediate **73** underwent base catalyzed deacylative pyran ring opening leading to **74** (Scheme 46).[128]

Refluxing 8-iodo-5-methoxy-2-methylchromone **2** (R=H) in diphenyl ether containing copper powder yielded 5,5`-dimethoxy-2,2`-dimethyl-8,8`-bichromonyl **75** (Scheme 47).[131]

Heating 2-methylchromone **2** (R=H) and 2-$O_2NC_6H_4SO_3Me$ **76** in toluene gave violet 2-[(2-methyl-4-benzopyranylidene)methyl]-4-methoxy-benzopyrylium-*o*-nitrobenzene sulfonate **77** (Scheme 48).[96]

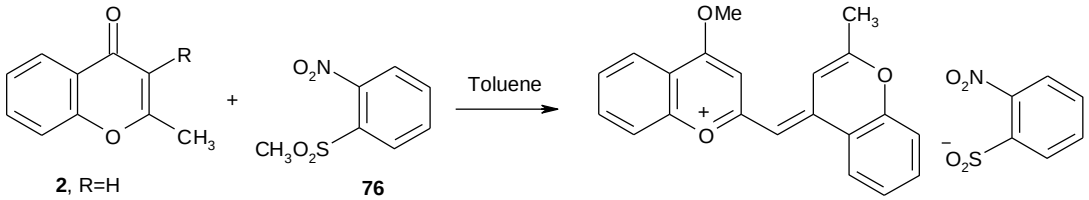


Scheme 46



2, R=H **75**

Scheme 47

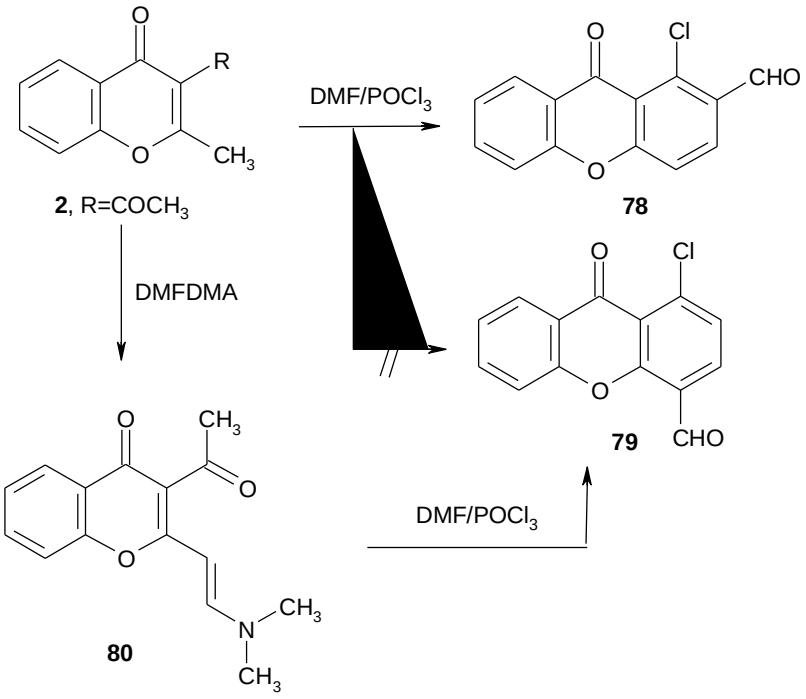


2, R=H **76** **77**

Scheme 48

3.9. Vilsmeier-Haack reaction

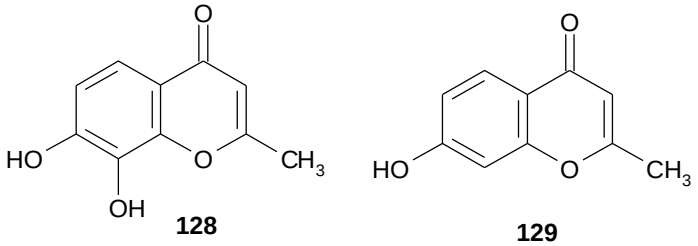
Reaction of 2-methylchromone **2** (R=$COCH_3$) with $POCl_3$/DMF gave the formylxanthone derivative **78**. The other isomer **79** was obtained by reacting enamine **80**, derived from **2** and DMFDMA, with phosphorus oxychloride and dimethylformamide (Vilsmeier-Haack reagent) (Scheme 49).[128]



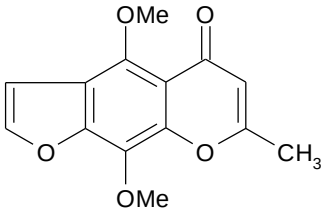
Scheme 49

5. Biological significance of 2-methylchromones

The significant antipyretic activity of 2-methychromones has been recognized fifteen years ago. They have the same antipyretic effect as paracetamol and analgesic effect as Novalgin.[195]
Also, 2-methylchromones **128** and **129** play vital role in the replication cycle of AIDS virus and thus act as HIV-1 protease inhibitors.[196]

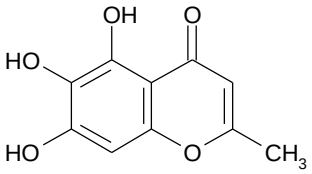


Also, khellins **130** is the principal constituent of Ammi visnaga L. It is 2-methylchromone with a linearly fused furan ring system and has been found to be a potent coronary vasodilator in bronchial action on bronchial muscle, gall bladder and bileduct. Additionally, it has been used as showed antispasmodic.[197-201]



130

5,6,7-Trihydroxy-2-methylchromone **131** showed a high inhibition activity towards α-glucosidase (the α-glucosidase enzyme catalyses the final step in the digestive process of carbohydrate) hence, α-glucosidase inhibitors can retard the decomposition and absorption of dietary carbohydrates to suppress postprandial hyperglycemia.[202]



131

Some of 2-methylchromones displayed inhibitory activity similar to that of Sorbinil but are more selective than Quercetin and Sorbinil with respect to the closely related enzyme, aldehyde reductase, and also possess antioxidant activity.[203]

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