

Synthesis and chemical reactivity of 2-methylchromones

Magdy A. Ibrahim,* Tarik E. Ali, Youssef A. Alnamer, and Yassin A. Gabr

*Department of Chemistry, Faculty of Education, Ain Shams University,
Roxy, 11711, Cairo, Egypt*

E-mail: magdy_ahmed1977@yahoo.com

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

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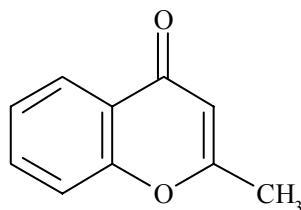
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1. Introduction

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 antispasmodic, estrogenic⁴ 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

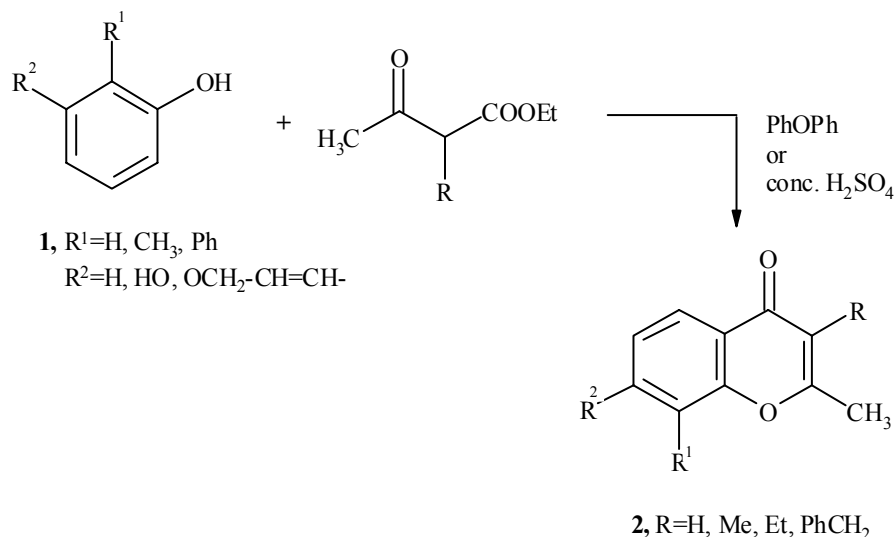
2-Methylchromones are one of the scarcest classes of natural chromones. Although 2-methylchromones constitute a small family of naturally occurring compounds, their synthesis should be extensively studied. To our knowledge, there is not any review summarizing the literature on the synthesis and chemistry 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

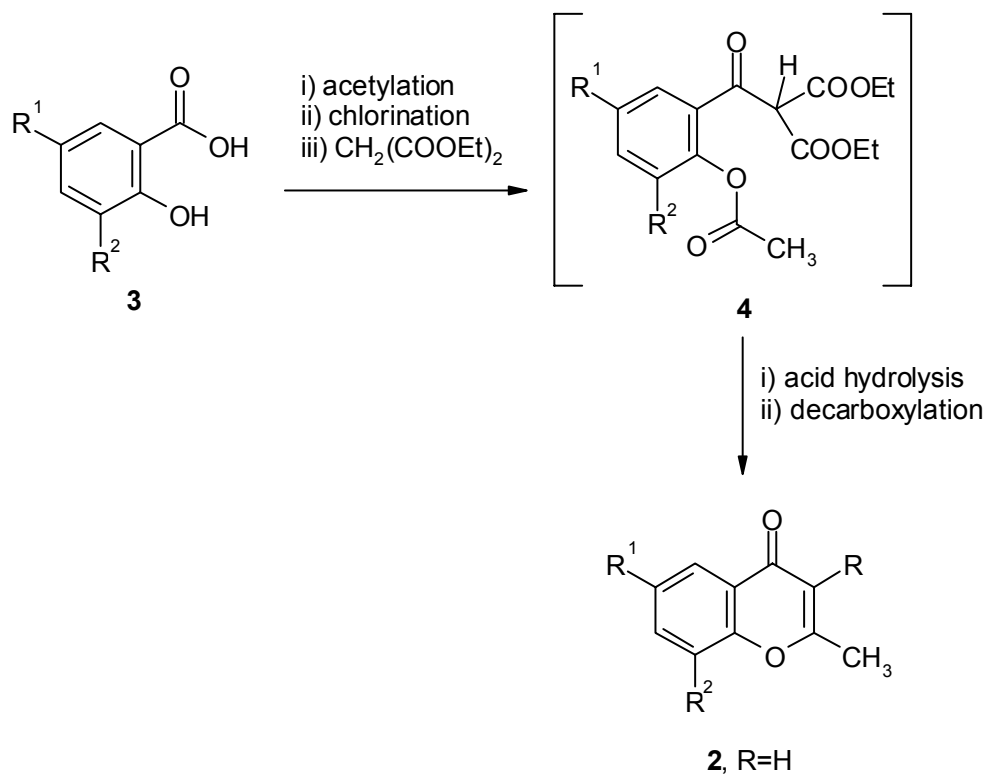
The Simonies reaction involved the reaction of phenols **1** with β -ketoester in the presence of diphenyl ether or concentrated H_2SO_4 to form 2-methylchromones **2** by losing ethanol and water molecules (Scheme 1).⁷⁻¹⁰



Scheme 1

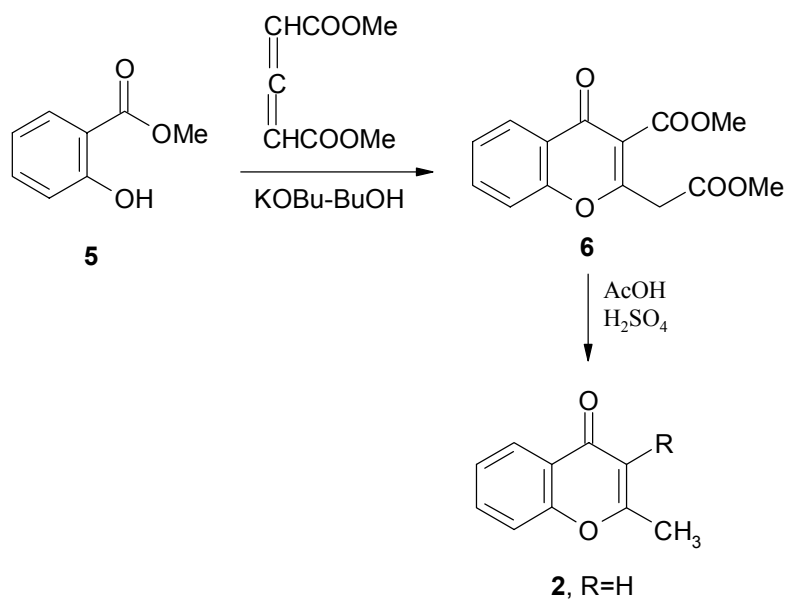
2.2 From salicylic acids

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



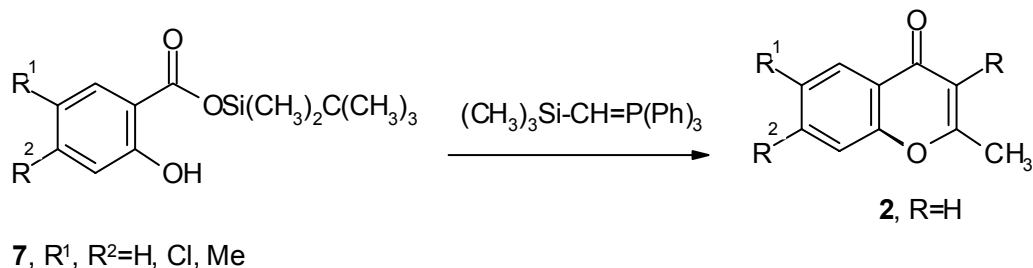
Scheme 2

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

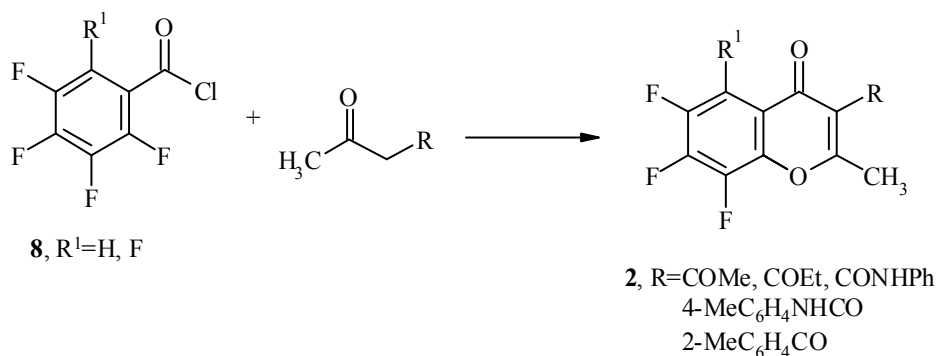
O-Acetylsalicylic acid *tert*-butyldimethylsilyl esters **7** underwent condensation with (trimethylsilyl)methylenetriphenylphosphorane followed by an intramolecular Wittig olefination to give substituted 2-methylchromones **2** (Scheme 4).¹³



Scheme 4

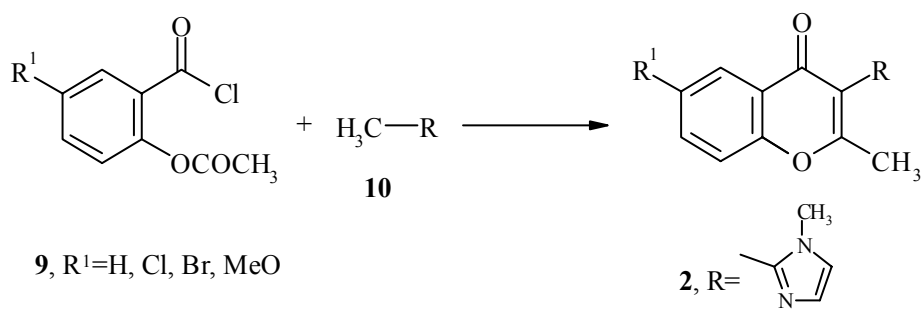
2.3 From benzoyl chlorides

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



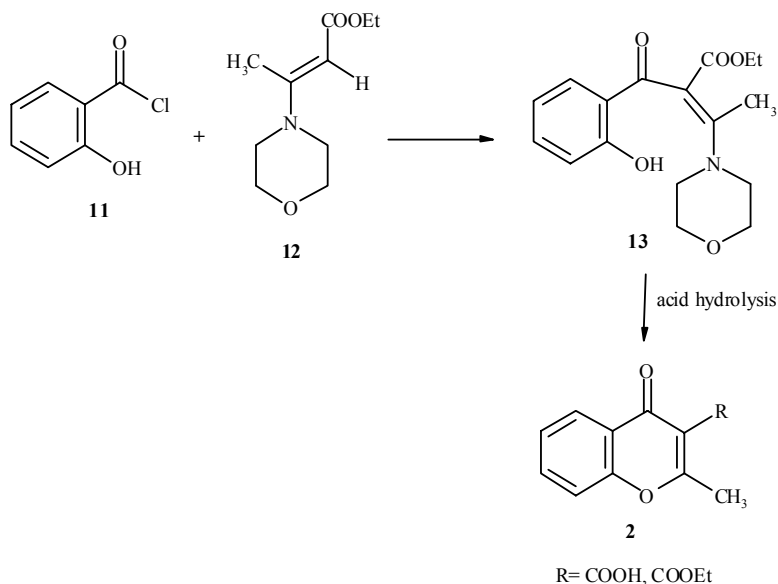
Scheme 5

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



Scheme 6

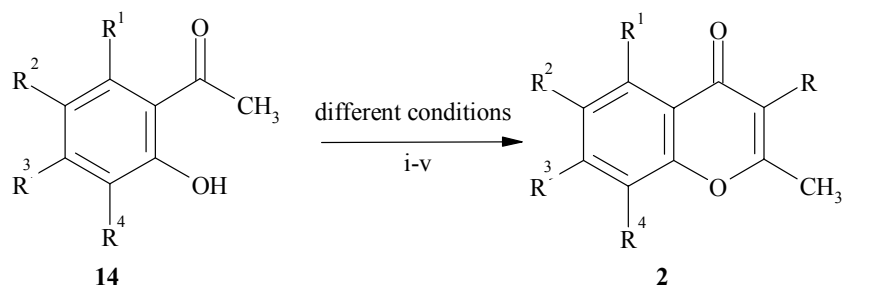
The direct condensation of salicyloyl chloride **11** with enamine **12** gave quantitative yield of morpholine derivative **13**, which was converted to 3-carboxy/carboethoxy-2-methylchromone **2** under acid hydrolysis (Scheme 7).^{18,19}



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



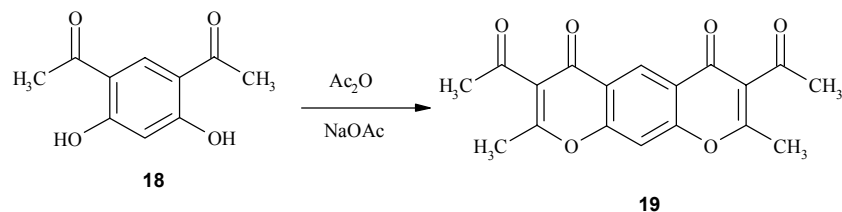
R=H, HO, COCH₃, P(O)(OCH₃)₂, CHO

- i) Ac₂O-NaOAc
- ii) AcCl-DBU-pyridine
- iii) a. LiCH₂CO₂C(CH₃)₃
b. acid hydrolysis
- iv) a. AcCl-NaOCH₃
b. Br₂-CCl₄
c. P(OCH₃)₃
- v) a. DMFDMA
b. Ac₂O

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

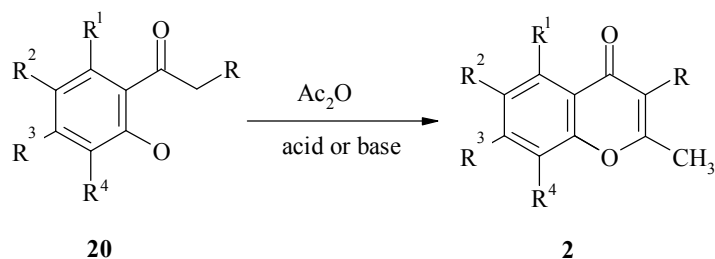
Scheme 8

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




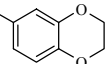
Scheme 9

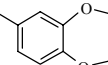
The ring closure of α -substituted-2-hydroxyacetophenones **20** was performed by acetic anhydride in the presence of a trace amount concentrated sulfuric acid or pyridine or triethylamine to give 2-methylchromones **2** (Scheme 10).³¹⁻³⁸




R=H, R¹=H, R²=Me, R³=R⁴=H
 R=Me, R¹=H, R²=H, COCH=CH-Ar, R³=R⁴=H
 R=NO₂, R¹=R²=R³=R⁴=H

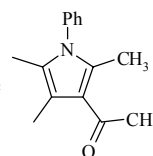
R=  R¹=H, R²=OMe, R³=R⁴=H
 X=CO₂Me, NHCOMe

R=  R¹=H, R²=H, Et, Pr, R³=OH, R⁴=H

R=  R¹=H, R²=OH, OMe, R³=H, OH, R⁴=H

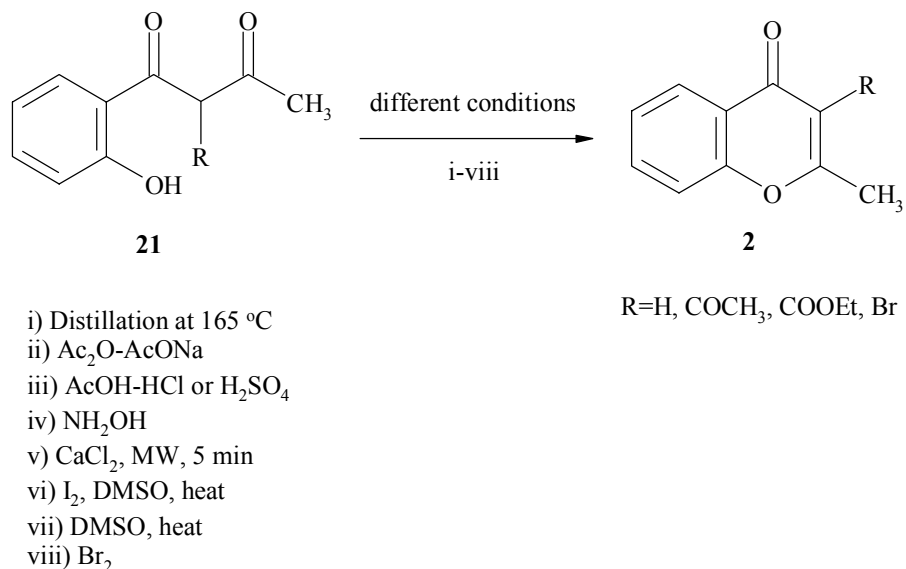
R=  R¹=R²=R³=R⁴=H

R=COCH=CHPh R¹=R²=H, R³ R⁴=



Scheme 10

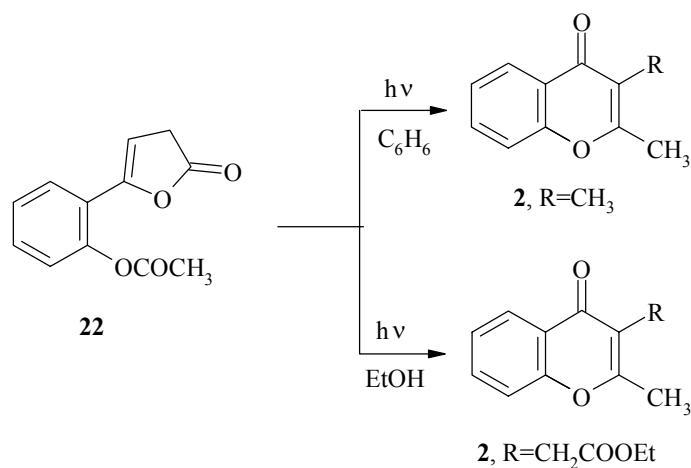
Cyclization of β -diketones **21** under certain conditions such as distillation,³⁹ acetic anhydride,^{19,24,40-44} acidic,⁴⁵⁻⁵³ basic media,⁵⁴ microwave,⁵⁵ iodine-DMSO,⁵⁶ DMSO-heat⁵⁷ and bromine⁵⁸ gave 2-methylchromones **2** (Scheme 11).



Scheme 11

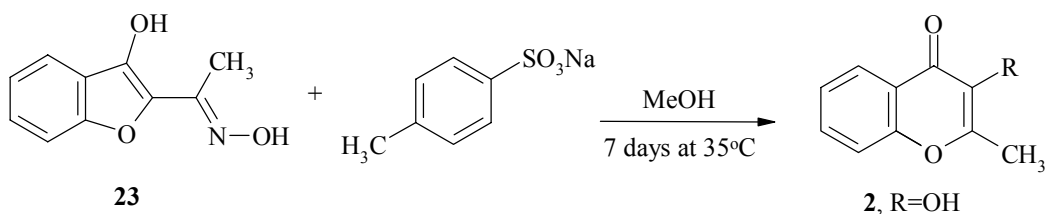
2.5 From furan derivatives

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=CH₃, CH₂COOEt) (Scheme 12).⁵⁹



Scheme 12

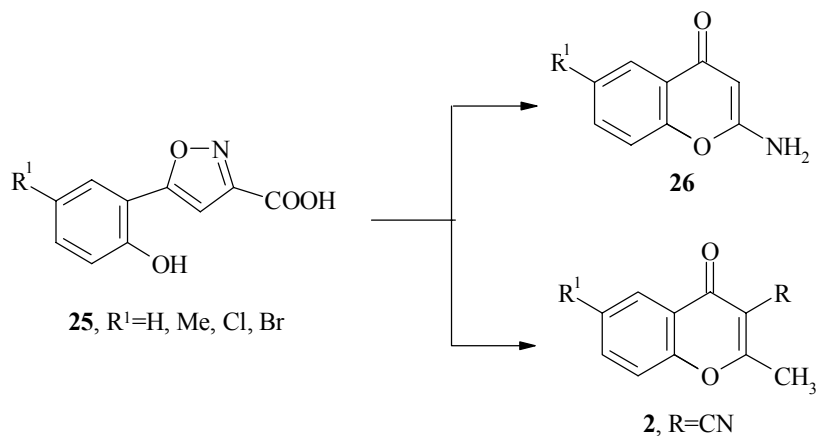
When 2-acetylbenzofuran oxime **23** and sodium *p*-toluenesulfonate **24** were kept in methanol for 7 days at 35 °C, 2-methylchromone **2** (R=OH) was obtained (Scheme 13).⁶⁰



Scheme 13

2.6 From isoxazole derivatives

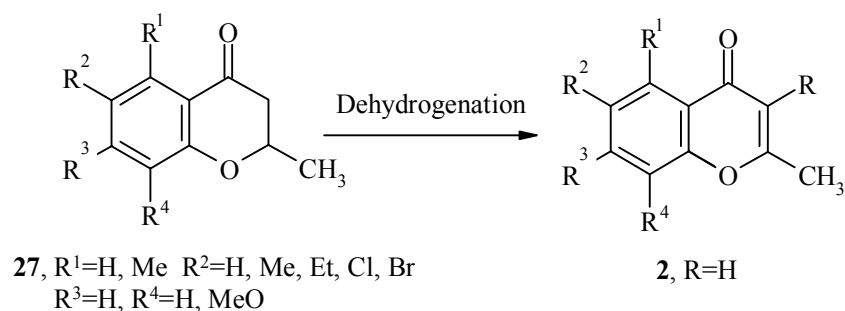
5-(2-Hydroxy substituted phenyl)-3-isoxazole-carboxylic acids **25** underwent transformation into the corresponding 2-aminochromones **26** and 2-methylchromones **2** (R=CN) (Scheme 14).⁶¹



Scheme 14

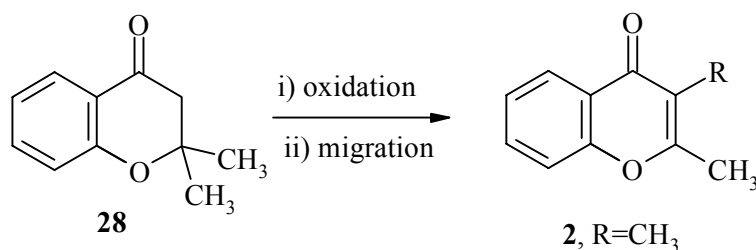
2.7 From chromone derivatives

2.7.1 From 2-methylchromanones. Dehydrogenation of chroman-4-ones **27** by using I₂-DMSO-H₂SO₄,^{62,63} and isoamyl nitrite-HCl⁶⁴ systems yielded 2-methylchromones **2** (Scheme 15).



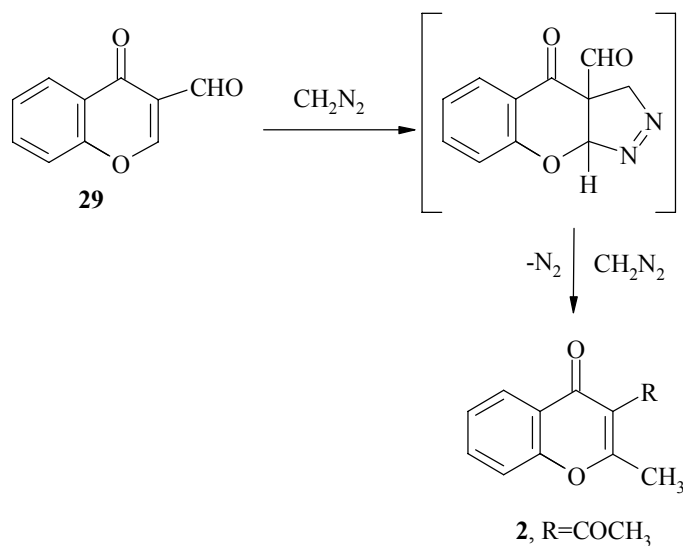
Scheme 15

Oxidation of 2,2-dimethylchromanone **28** with thallium-*p*-tosylate followed by 2,3-alkyl migration gave 2-methylchromone **2** (R=CH₃) in high yields (Scheme 16).⁶⁵



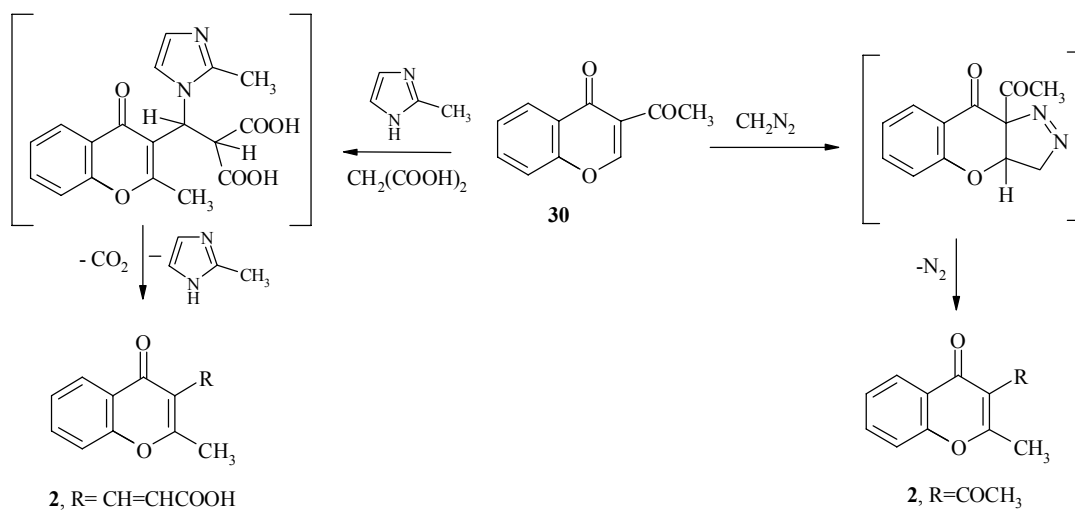
Scheme 16

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=COCH₃) (Scheme 17).⁶⁶



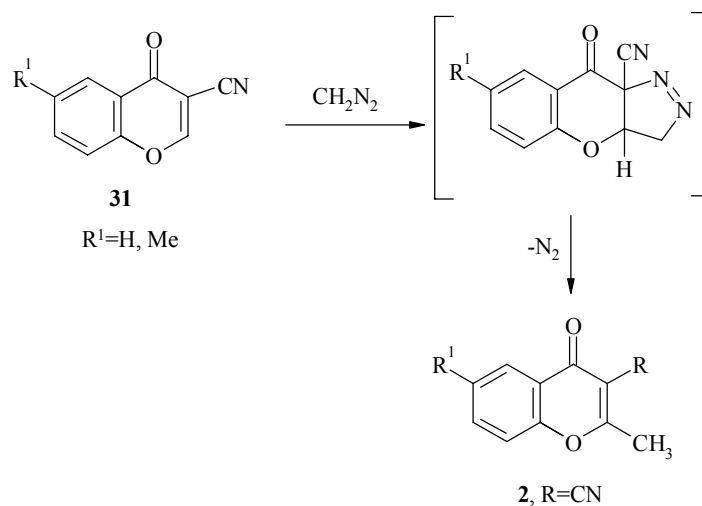
Scheme 17

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=COCH₃).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}

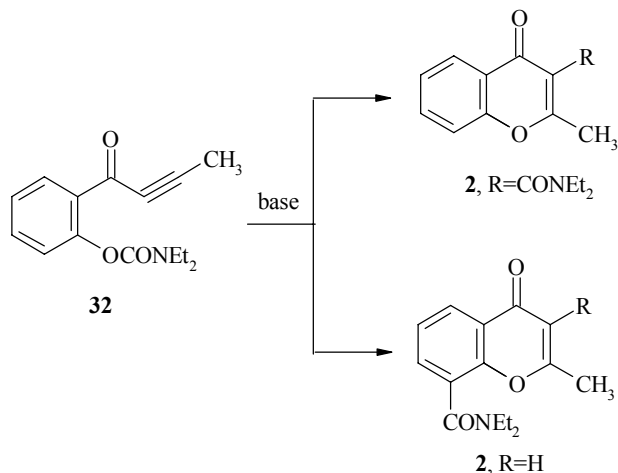


Scheme 19

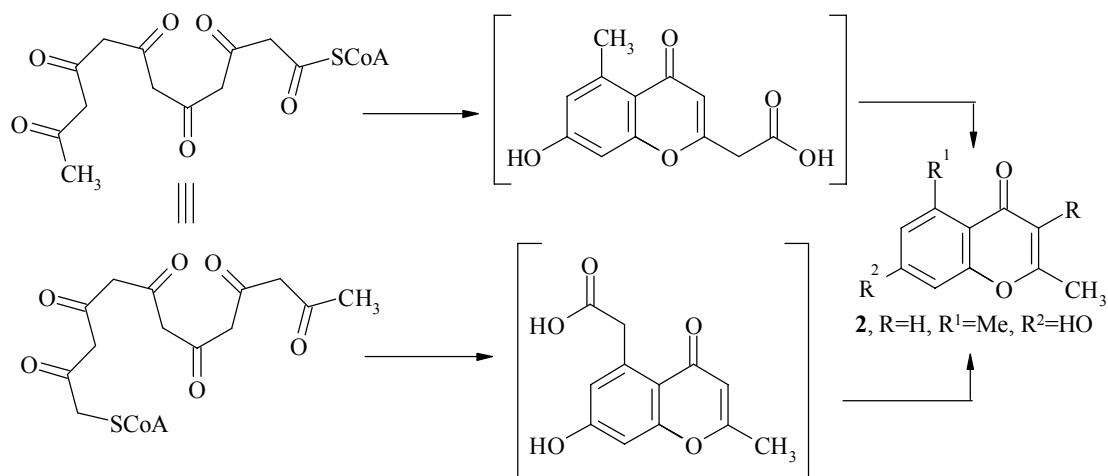
2.8 Miscellaneous methods

Treatment of but-2-ynoylaryl *O*-carbamate **32** with base gave either 2-methyl-chromone-3-/8-carboxamide **2** (R=CONEt₂, 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



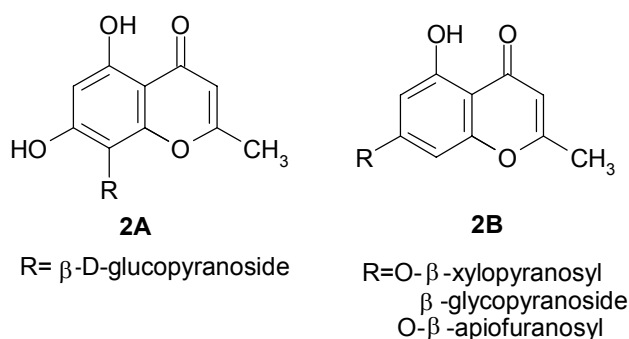
Scheme 20



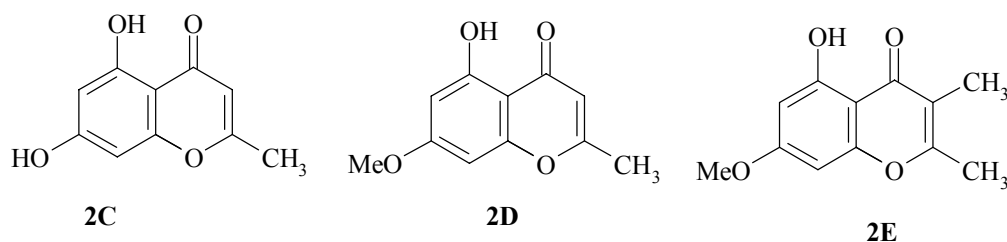
Scheme 21

2.9 Extraction from plants

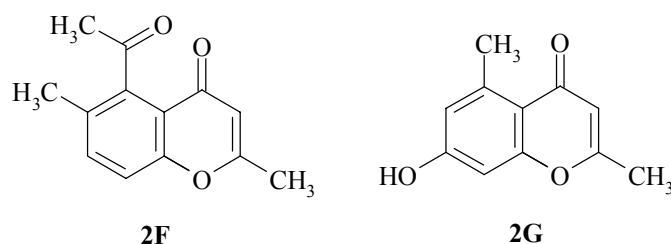
5,7-Dihydroxy-2-methylchromone β -D-glucopyranoside **2A** was isolated from an ethanolic extraction of cloves (*Eugenia caryophyllata*).⁷³ Also, 5-hydroxy-2-methylchromones **2B** were isolated from the root of *Adina rubella hance*.⁷⁴



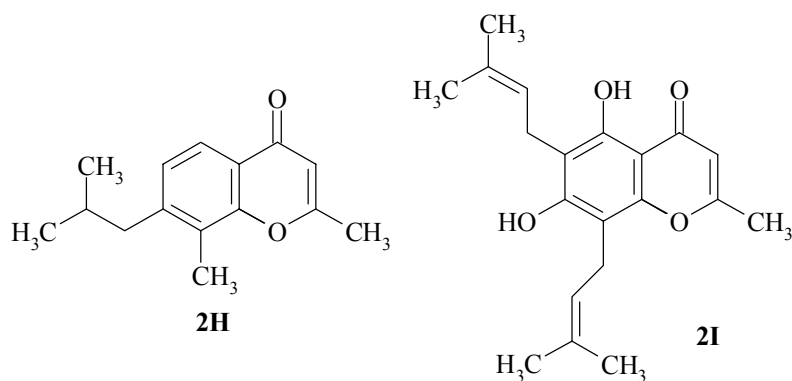
5,7-Dihydroxy-2-methylchromone **2C** and 5-hydroxy-7-methoxy-2-methylchromone **2D** were isolated from the bulbs of *P. maritimum*.⁷⁵ Also, **2E** was isolated from the cultures of spore derived mycobionts of lichen *Graphis scripta*.⁷⁶



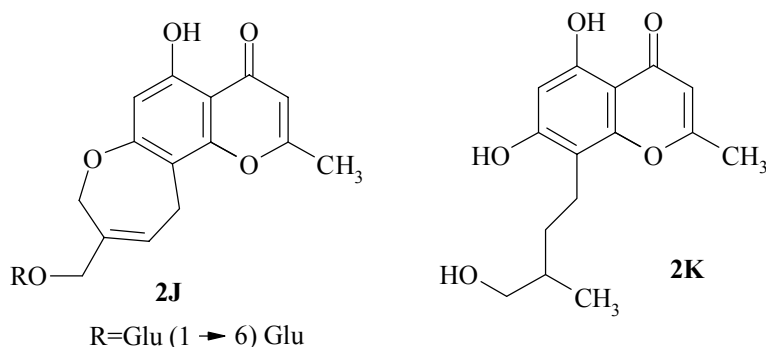
5-Carboxymethyl-7-hydroxy-2-methylchromone (**2F**) was isolated from the antibiotic and anti-inflammatory active site of *Polygonum cuspidatum sieb*⁷⁷ while the over sephadex LH-20 column eluted with chloroform-methanol (50:50) furnished compound **2G**.⁷²



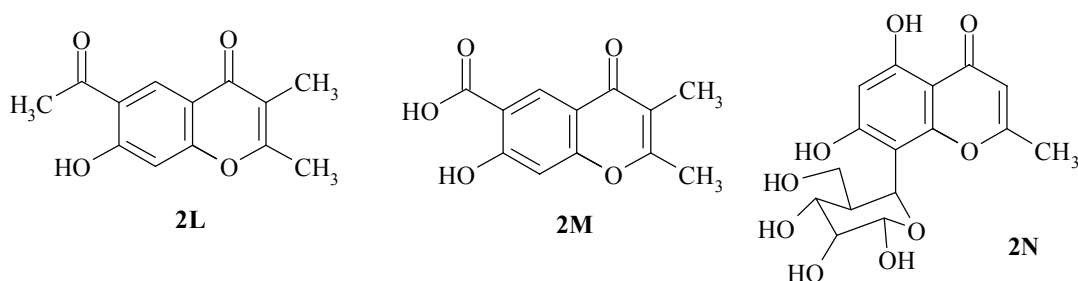
2-Methylchromones **2H** and **2I** were isolated from *Leucas inflata* and *Neochamaeclea puluervlenta*, respectively.^{78,79}



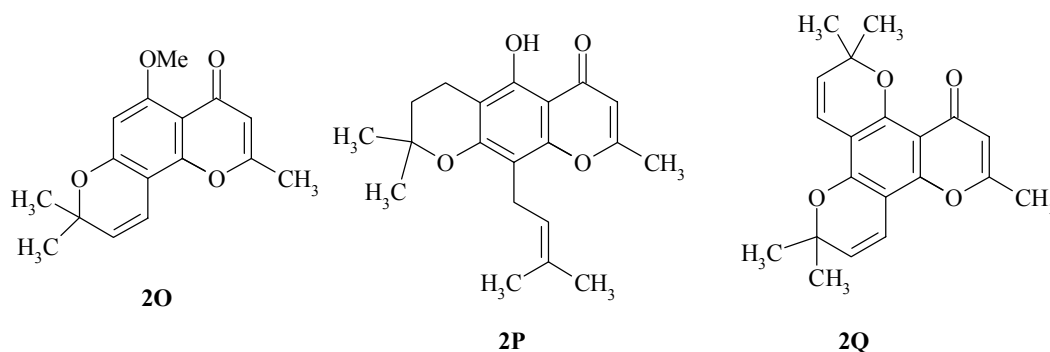
9-(*O*- β -D-glucopyranosyl-D-glucopyranosyl)oxyl]methyl-8,11-dihydro-5-hydroxy-2-methyl-4*H*-pyrano[2.3.9][1]benzoxepin-4-one **2J** and 7-dihydroxy-8-[(2*e*)-4-hydroxy-3-methylbut-2-enyl] -2-methyl-4*H*-chromone **2K** were isolated from the tubers of *Eranthis cilicica*.⁸⁰



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



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

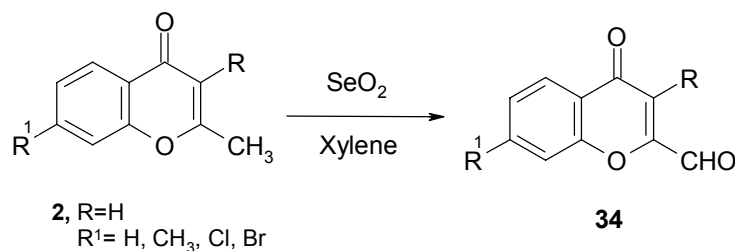


3. Reactivity of 2-Methylchromones

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.

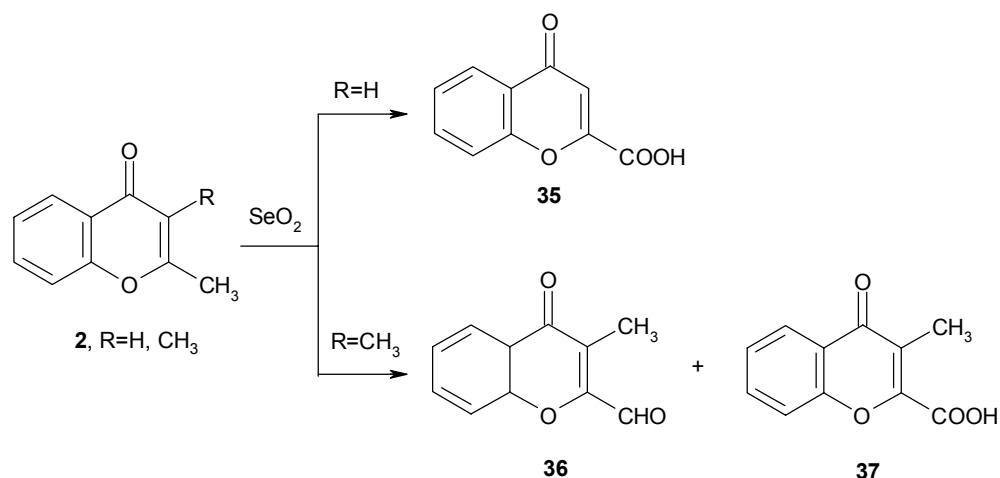
3.1 Oxidation reactions

3.1.1 Oxidation with SeO_2 . Oxidation of 2-methylchromones **2** ($\text{R}=\text{H}$) by selenium dioxide in refluxing xylene yielded chromone-2-carboxaldehydes **34** (Scheme 22).⁸⁸⁻⁹⁰



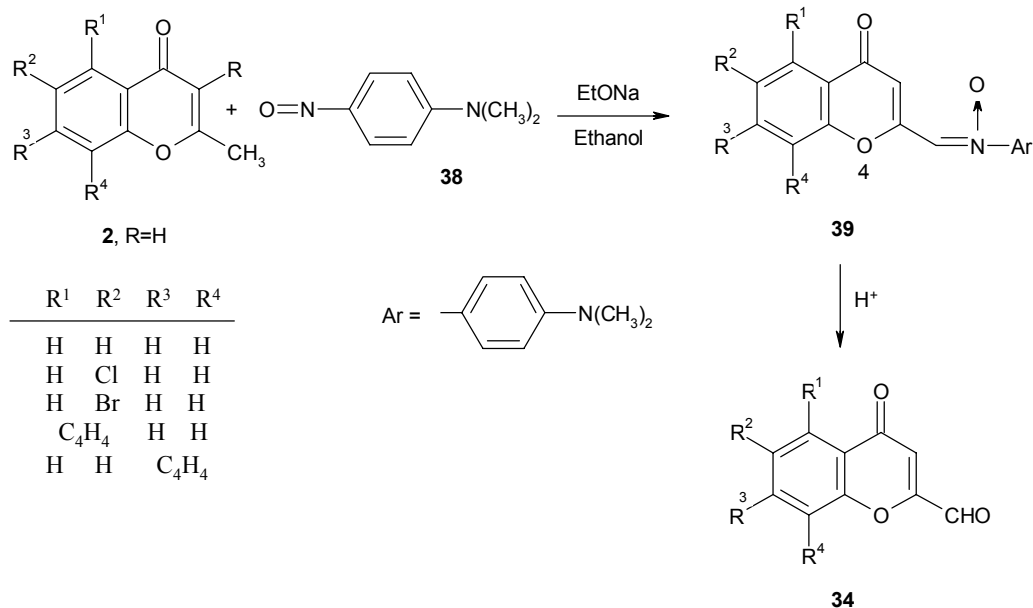
Scheme 22

On the other hand, oxidation of **2** ($\text{R}=\text{H}$) 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



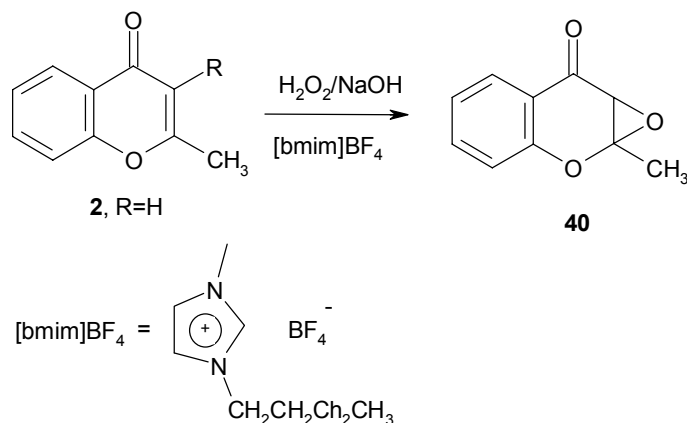
Scheme 23

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}



Scheme 24

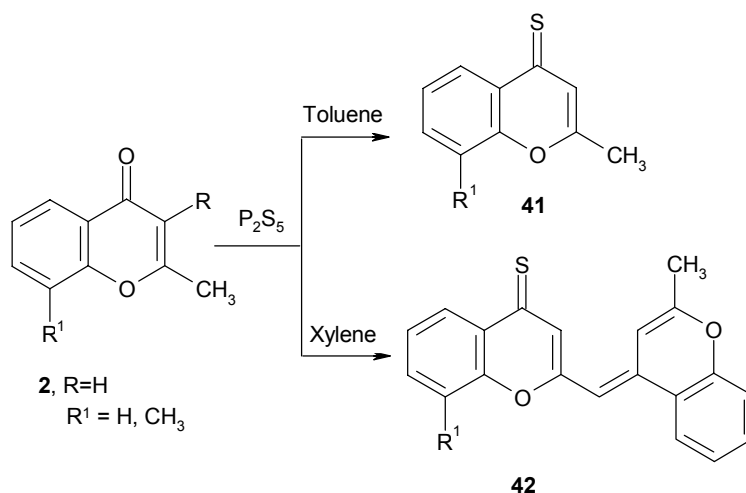
3.1.3 Oxidation with H₂O₂. 2-Methylchromone **2** (R=H) in the presence of alkaline hydrogen peroxide as an oxidant in 1-butyl-3-methylimidazoliumtetrafluoroborate [bmim]BF₄ as a solvent afforded 2-methylchromone epoxide **40** (Scheme 25).⁹⁴



Scheme 25

3.2 Thiation

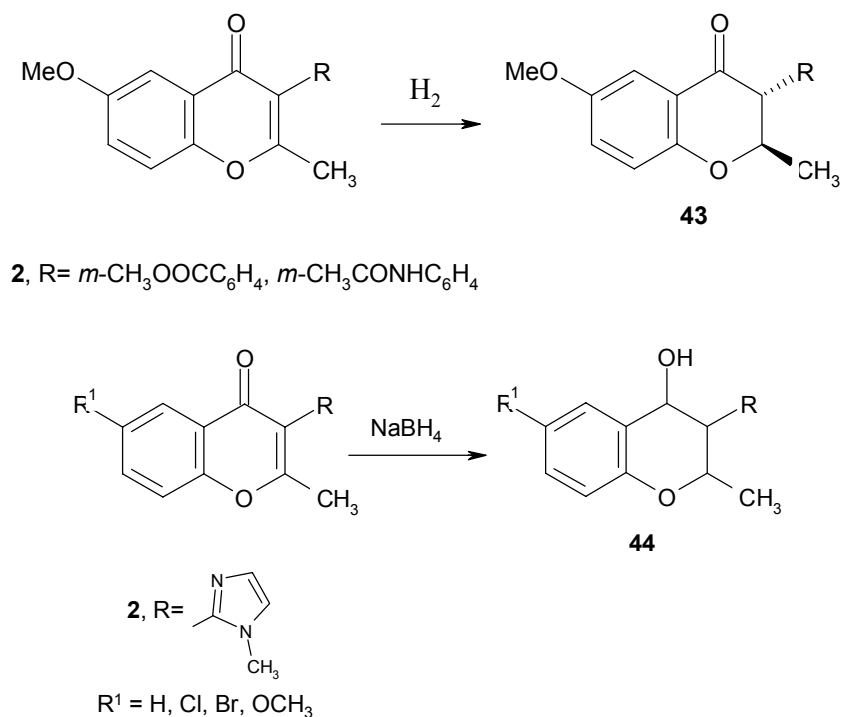
Treatment of 2-methylchromone **2** (R=H) with phosphorus pentasulfide in toluene afforded 2-methyl-4-thiochromone **41**.⁹⁵ The same reaction afforded 2-[2-methyl-4-benzopyranylidene)methyl]benzopyran-4-thione **42** when carried out in refluxing xylene.⁹⁶ Also, Simonis and Rosenberg⁹⁷ prepared 2,8-dimethyl-4-thiochromone **41** by direct fusion of **2** (R=H, R¹=CH₃) with phosphorus pentasulfide (Scheme 26).



Scheme 26

3.3 Hydrogenation

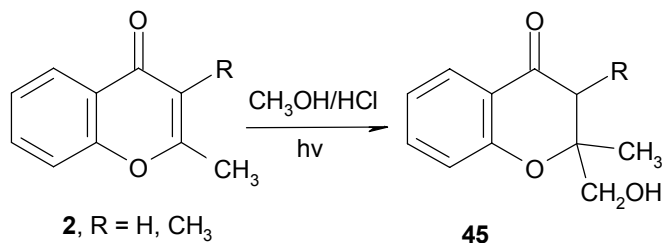
Reduction of 2-methylchromones **2** produced *trans*-2,3-disubstituted-4-chromanones **43**.³⁴ Also, Reduction of chromones **2** (R=*N*-methylimidazol-2-yl) with sodium borohydride afforded the corresponding chromanols **44** in good yields⁹⁸ (Scheme 27).



Scheme 27

3.4 Photolysis

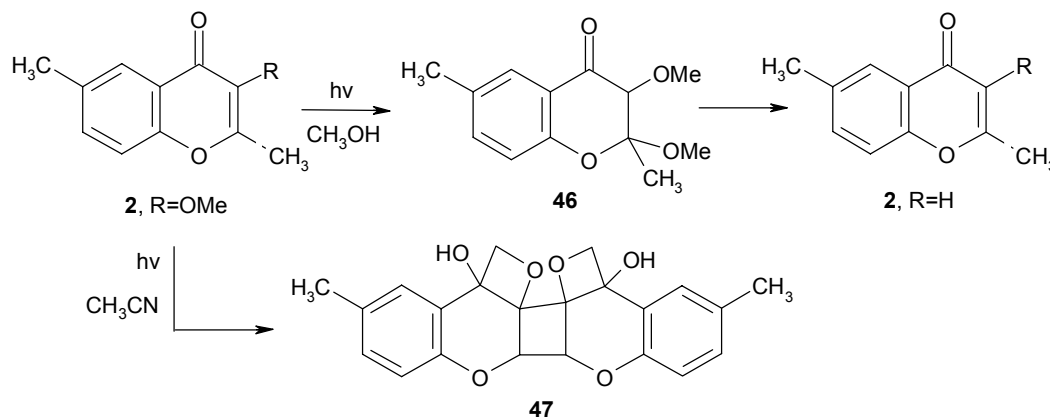
Irradiation of 2-methylchromones **2** in CH₃OH-HCl induced the homolytic addition of CH₃OH to the double bond in the pyrone ring to give 2-hydroxymethyl-chromanones (**45**) (Scheme 28).⁹⁹



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

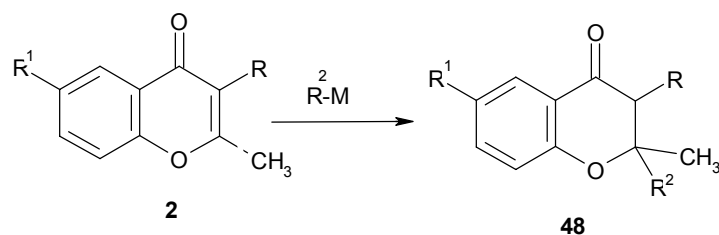
methanol to give **46**, followed by double methoxy elimination. When photolysis took place in non nucleophilic solvent such as benzene or acetonitrile the dimer **47** was obtained in good yield (Scheme 29).¹⁰⁰



Scheme 29

3.5 Reactions with organometallic reagents

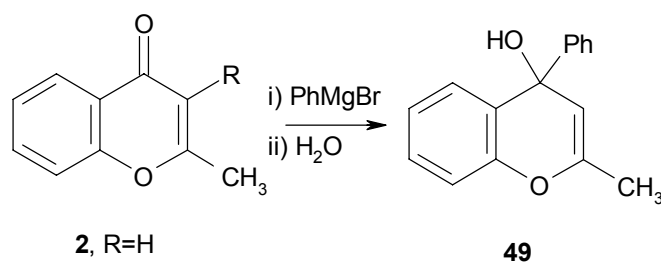
Reaction of 2-methylchromones **2** with organocopper reagents (alkylcopper-BF₃, lithium dimethylcuparate or lithium di-*n*-butylcuparate) provided 2,2-dimethyl-chromanone derivatives **48** via conjugate addition to the double bond in the γ -pyrone system (Scheme 30).^{101,102}



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



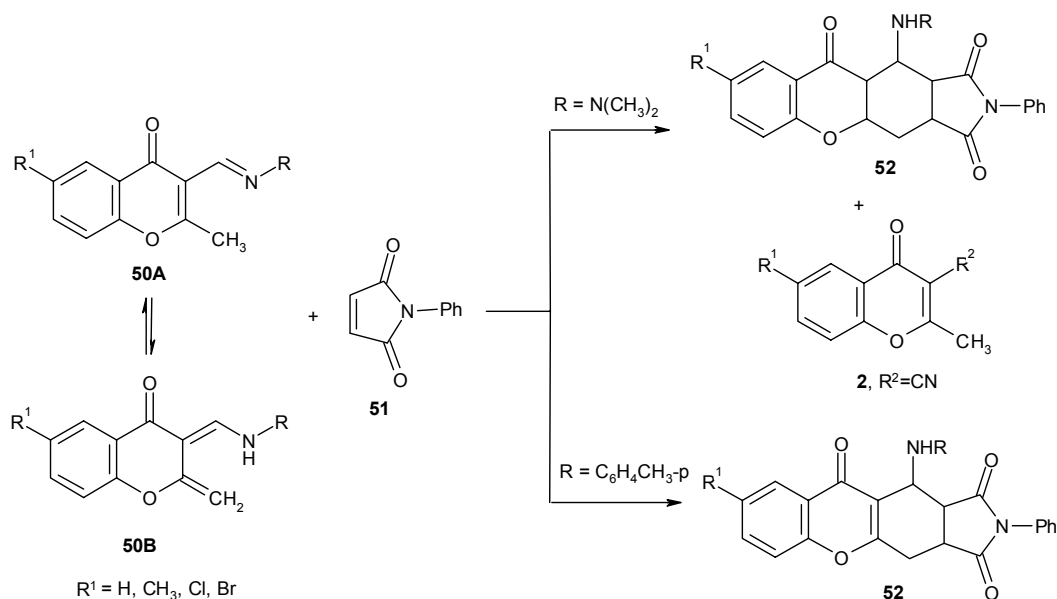
Scheme 31

3.6 Diels Alder reactions

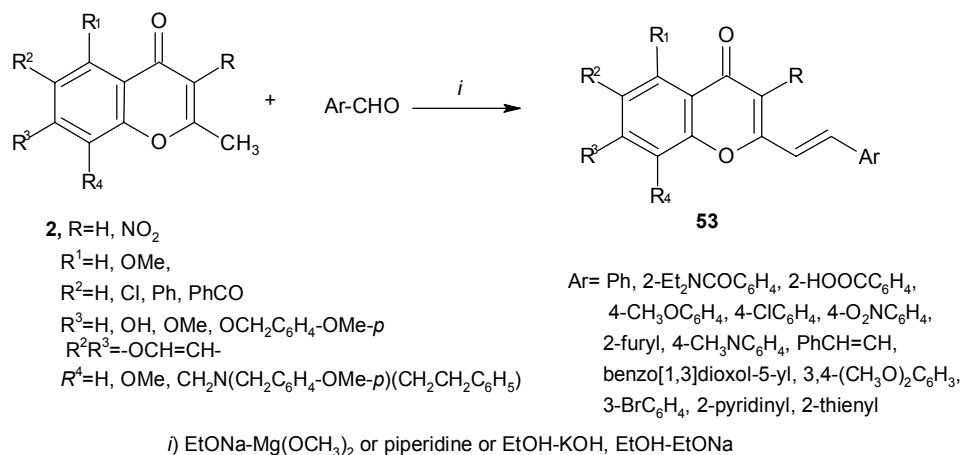
N,N-Dimethylhydrazones **50A** on treatment with *N*-phenylmaleimide **51** gave tetrahydroxanthone **52** together with a little amount (~10%) of 3-cyano-2-methylchromone **2** (R²=CN). Reaction of anil (*R*=4-CH₃C₆H₄) with **51** gave cycloadduct **52** through its imine tautomer **50B** (Scheme 32).^{104,105}

3.7 Condensation reactions

3.7.1 Reactions with carbonyl compounds. Treatment of 2-methylchromones **2** (R=H, NO₂) with aromatic aldehydes under different basic conditions afforded the corresponding 2-styrylchromones **53** (Scheme 33).^{50,91,106-117}

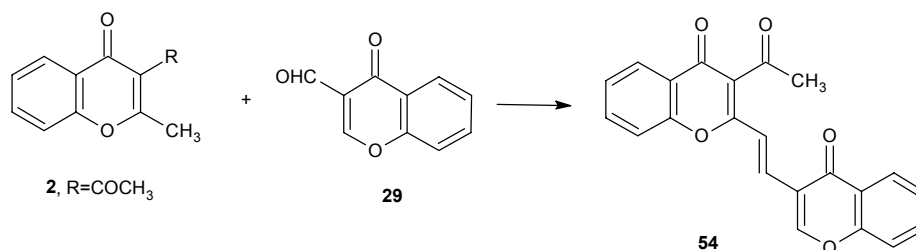


Scheme 32



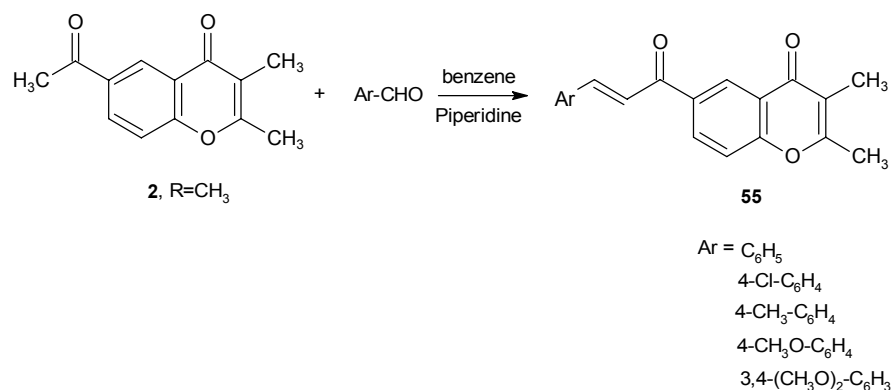
Scheme 33

Aldol condensation of 2-methylchromone **2** (R=COCH₃) 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



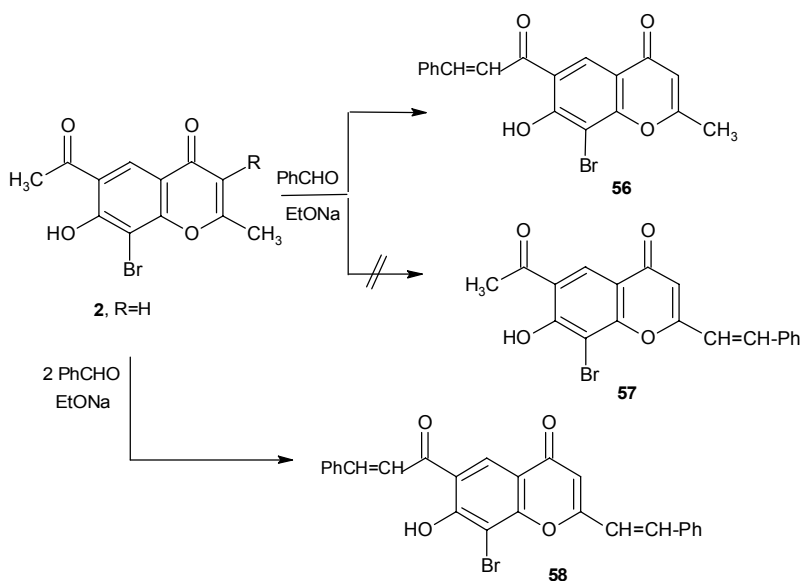
Scheme 34

On the other hand, 6-cinnamoyl-2,3-dimethylchromones **55** were obtained from the condensation of 2-methylchromones **2** (R=CH₃) with appropriate aldehydes in dry benzene in the presence of piperidine (Scheme 35).¹¹⁹



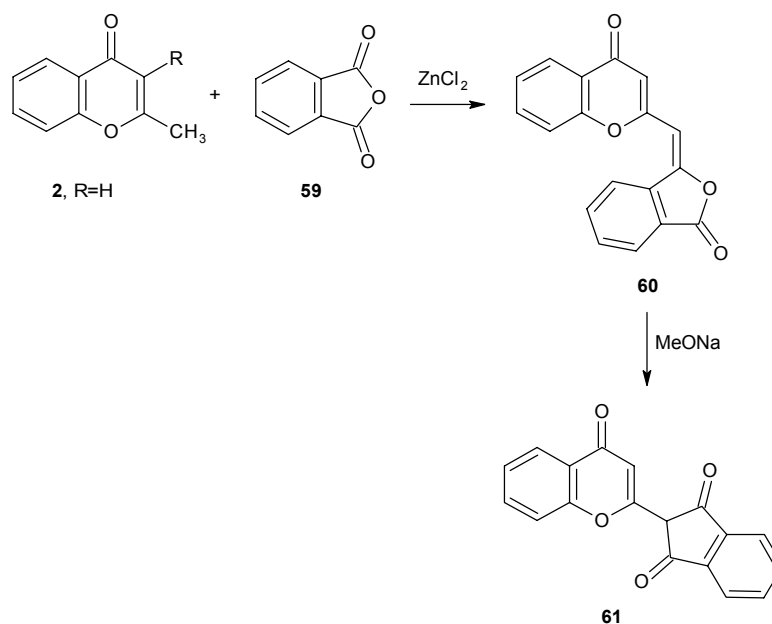
Scheme 35

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

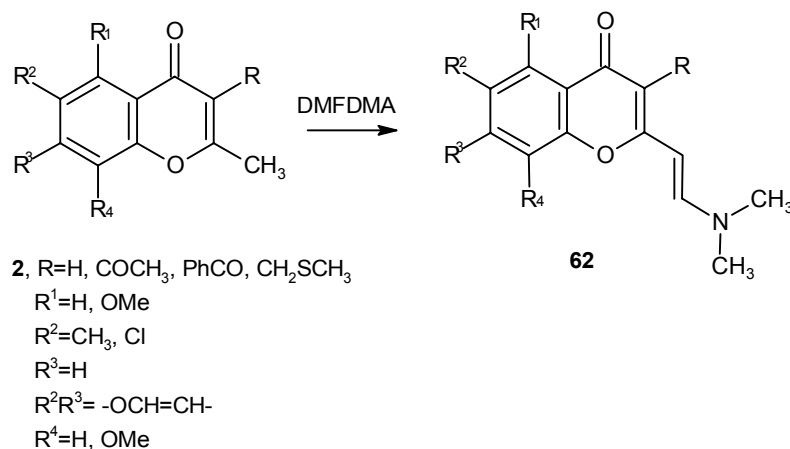
Condensation of 2-methylchromone **2** (R=H) with phthalic anhydride **59** in the presence of zinc chloride gave phthalide **60** which was rearranged by sodium methoxide to 1,3-indandione derivative **61** (Scheme 37).¹²⁰



Scheme 37

3.7.2 Reactions with DMFDMA

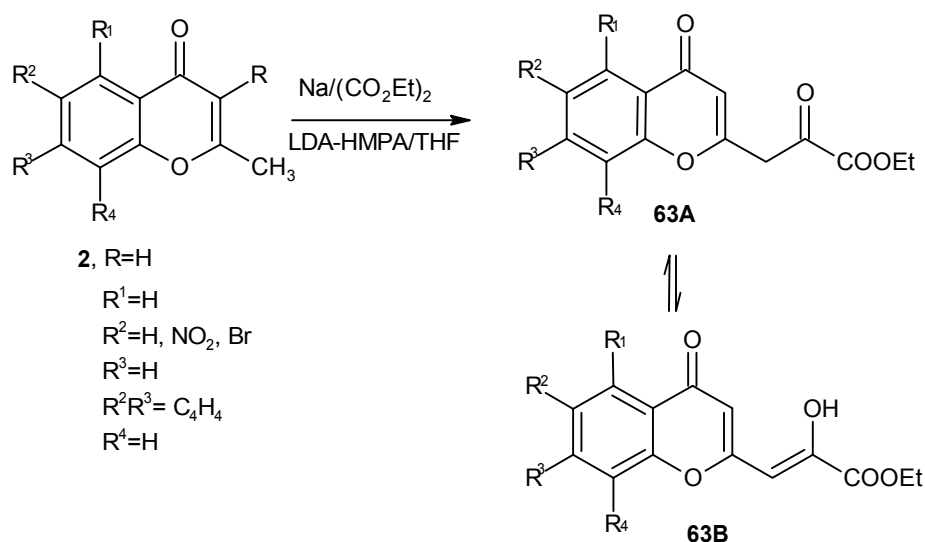
Reaction of 2-methylchromones **2** with DMFDMA afforded the dienamine **62**.^{43,121-124} The *E*-geometry around the exocyclic olefinic bond in compounds **62** was established from their ¹H NMR spectra (Scheme 38).



Scheme 38

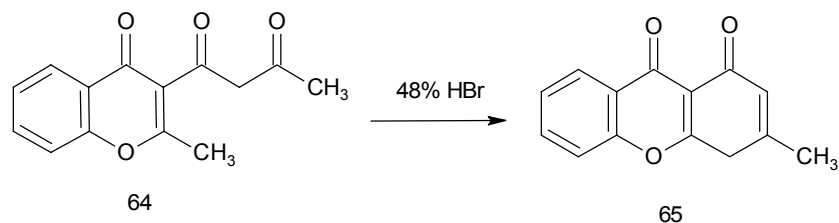
3.7.3 Reaction with diethyl oxalate. Condensation of 2-methylchromones **2** (R=H) with diethyl oxalate in the presence of sodium metal gave the corresponding pyruvate esters **63**.¹²⁵ Also, esters **63** were obtained from **2** using lithium di-isopropylamide in hexamethylphosphoramide

(1 equiv.) and tetrahydrofuran at $-30\text{ }^{\circ}\text{C}$ followed by addition of diethyl oxalate at $0\text{-}20\text{ }^{\circ}\text{C}$ (Scheme 39).¹¹⁰



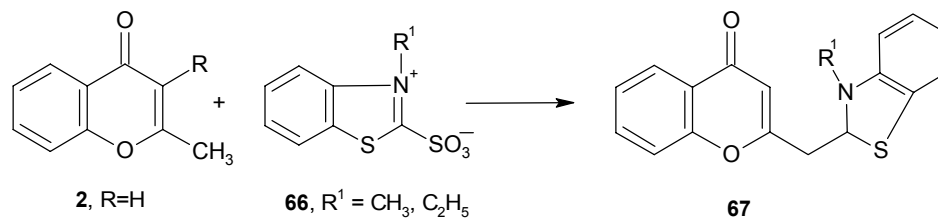
Scheme 39

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



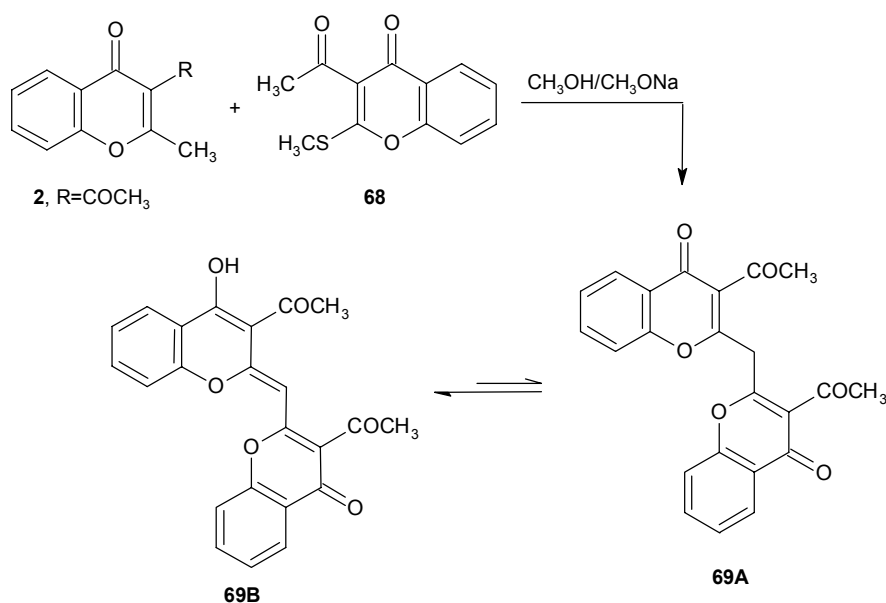
Scheme 40

3.7.5 Reaction with benzothiazole-2-sulfobetaine. Heating of 2-methylchromone **2** ($\text{R}=\text{H}$) with 3-ethyl/methylbenzothiazole-2-sulfobetaine **66** at $150\text{ }^{\circ}\text{C}$ followed by treatment with aqueous NH_4OH gave 2-(3-ethyl/methyl benzothiazolin-2-yl)methylchromone **67** (Scheme 41).^{96,127}



Scheme 41

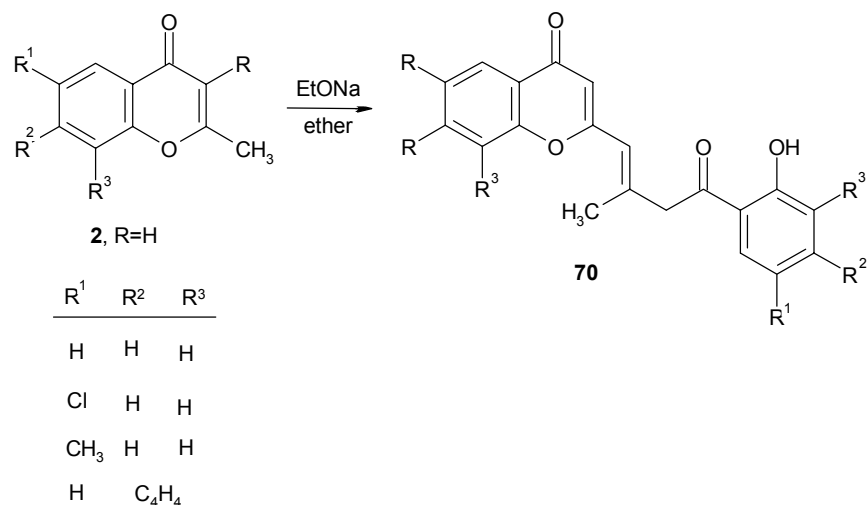
3.7.6 Reaction with 3-acetyl-2-methylthiochromone. Treatment of 2-methylchromone **2** (R=COCH₃) with 3-acetyl-2-methylthiochromone **68** in sodium methoxide gave **69A** that exists exclusively in the tautomeric form **69B** due to its formation strong hydrogen bond (Scheme 42).¹²⁸



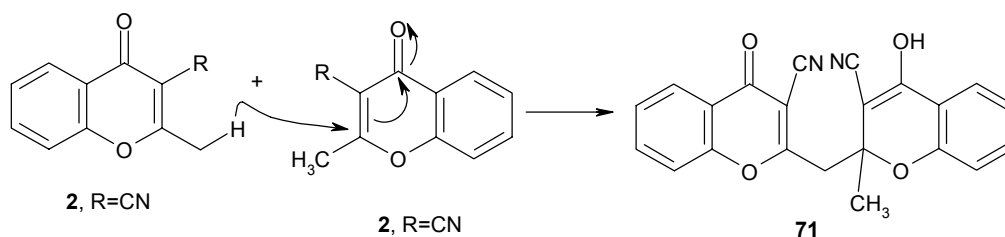
Scheme 42

3.8 Dimerization reactions

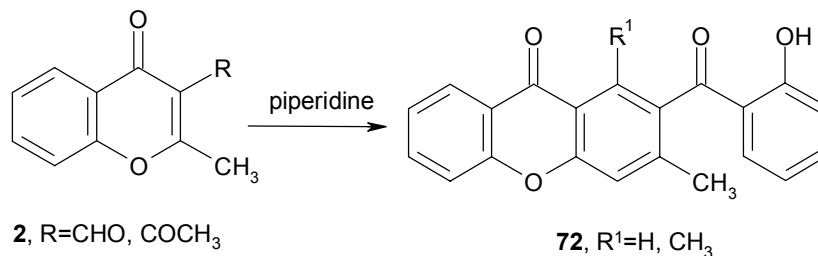
When 2-methylchromones **2** were treated with sodium ethoxide in dry ether, the dimeric products **70** were obtained. The formation of **70** may be attributed to ring opening of the pyrone nucleus of one molecule by the action of an active methyl group of another molecule of **2** (Scheme 43).^{129,130}

**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**

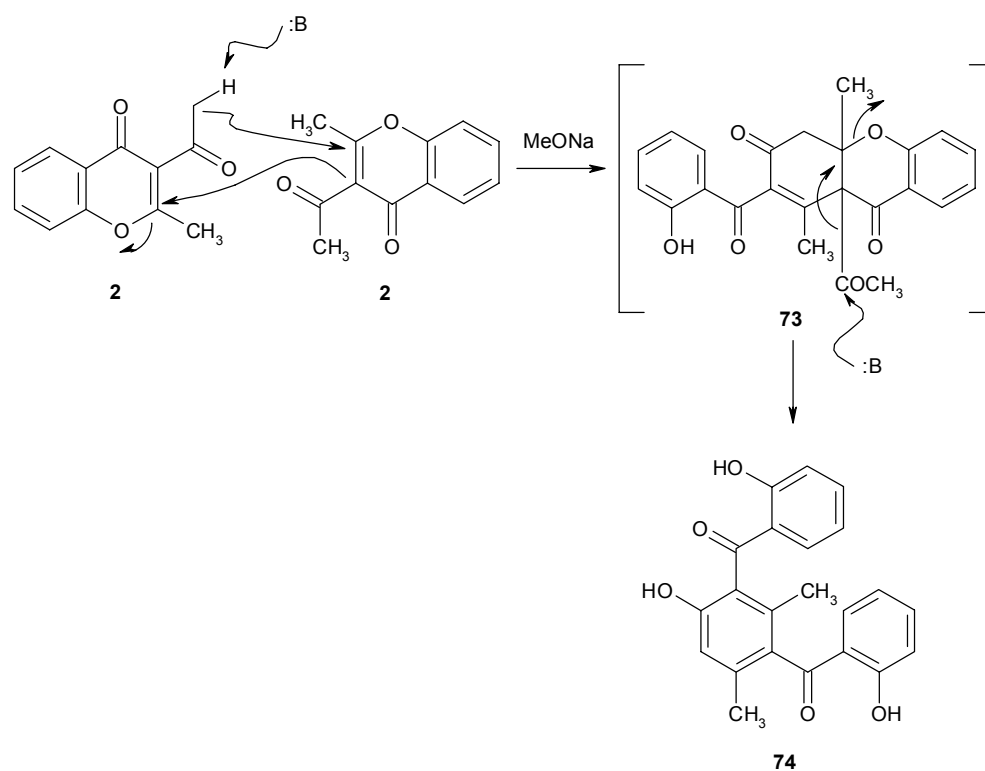
Also, base catalyzed self condensation of 2-methylchromones **2** (R=CHO, COCH₃) gave 2-salicyloyl-3-methylxanthone **72** (R=H, CH₃) (Scheme 45).¹²⁸

**Scheme 45**

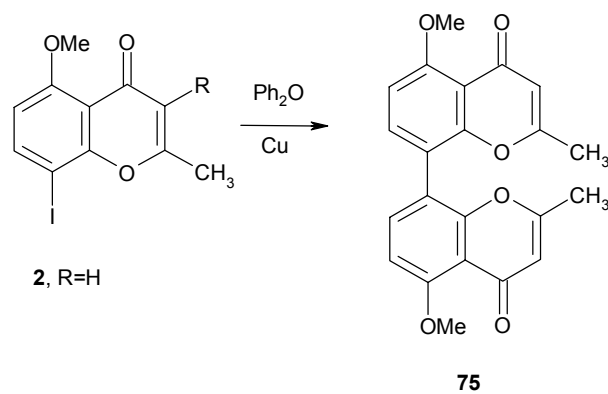
Surprisingly, boiling of chromone **2** ($R=\text{COCH}_3$) in methanol containing sodium methoxide yielded 2,4-disalicyloylphenol derivative **74**. The intramolecular reaction is initiated by the attack of the carbanion generated from the acetyl group at 3-position of a second molecule of **2**, the resultant intermediate **73** underwent base catalyzed deacylative pyran ring opening leading to **74** (Scheme 46).¹²⁸

Refluxing 8-iodo-5-methoxy-2-methylchromone **2** ($R=\text{H}$) in diphenyl ether containing copper powder yielded 5,5'-dimethoxy-2,2'-dimethyl-8,8'-bichromonyl **75** (Scheme 47).¹³¹

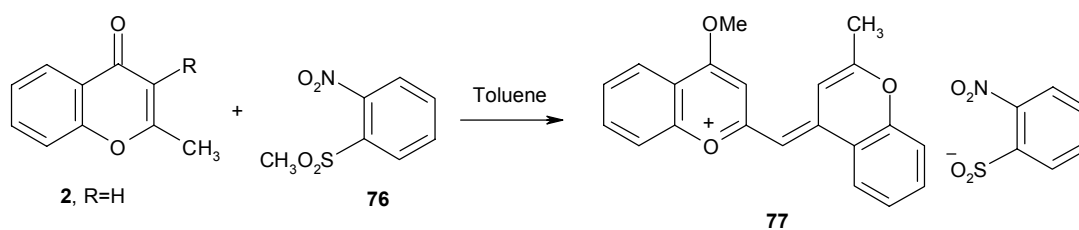
Heating 2-methylchromone **2** ($R=\text{H}$) and 2- $\text{O}_2\text{NC}_6\text{H}_4\text{SO}_3\text{Me}$ **76** in toluene gave violet 2-[(2-methyl-4-benzopyranylidene)methyl]-4-methoxy-benzopyrylium-*o*-nitrobenzene sulfonate **77** (Scheme 48).⁹⁶



Scheme 46



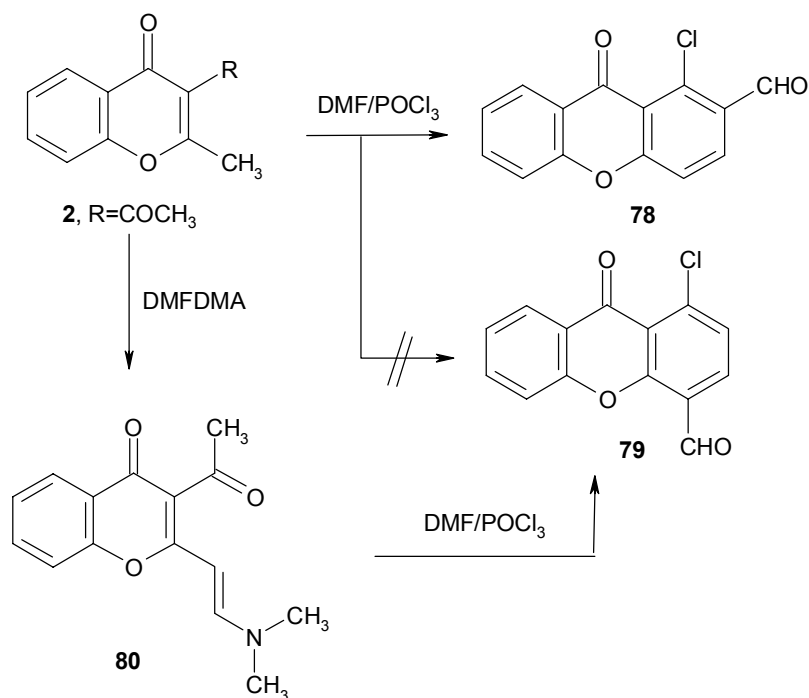
Scheme 47



Scheme 48

3.9. Vilsmeier-Haack reaction

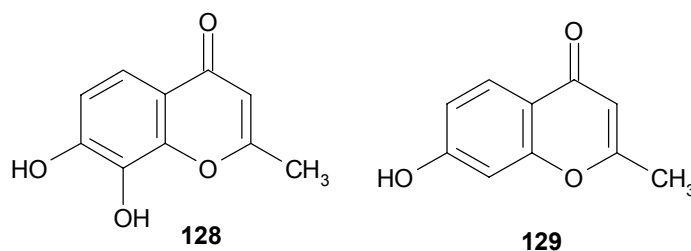
Reaction of 2-methylchromone **2** ($\text{R}=\text{COCH}_3$) with POCl_3/DMF gave the formylxanthone derivative **78**. The other isomer **79** was obtained by reacting enamine **80**, derived from **2** and DMFDMA, with phosphorus oxychloride and dimethylformamide (Vilsmeier-Haack reagent) (Scheme 49).¹²⁸



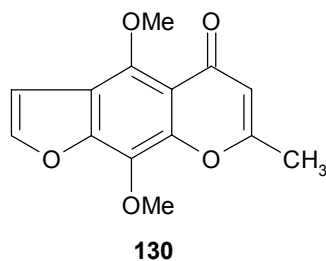
Scheme 49

5. Biological significance of 2-methylchromones

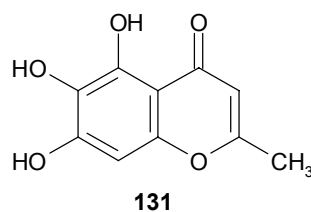
The significant antipyretic activity of 2-methylchromones has been recognized fifteen years ago. They have the same antipyretic effect as paracetamol and analgesic effect as Novalgin.¹⁹⁵ Also, 2-methylchromones **128** and **129** play vital role in the replication cycle of AIDS virus and thus act as 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 bile duct. Additionally, it has been used as showed antispasmodic.¹⁹⁷⁻²⁰¹



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



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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Authors' biography data



Magdy Ahmed Mohamed Ibrahim was born in Cairo, Egypt, in 1977. He received his B.Sc. in physics and chemistry (1999) and his M.Sc. in organic chemistry (2004). Also, he received his Ph.D. (2007) from the organic division, Department of Chemistry, Faculty of Education, Ain Shams University. His research is focused on the synthesis of heterocyclic compounds containing chromone, pyridine and 1,2,4-triazine with biological activity.



Tarik El-Sayed Ali was born in Cairo, Egypt, in 1975. He received his B.Sc. in physics and chemistry (1997) and his M.Sc. in organic chemistry (2001). Also, he received his Ph.D. (2005) from the organic division, Department of Chemistry, Faculty of Education, Ain Shams University. Awarded a post doctoral scientific grant for supporting young researchers (2007) from the Ministry of High Education and Scientific Research (Egypt) in organophosphorus laboratory, Institute of Polymers, Bulgarian Academy of Science, Sofia, Bulgaria. His research is

focused on the synthesis of heterocyclic compounds containing chromone, 1,2,4-triazine and α -aminophosphonate molecules with biological activity.



Yassin Abdallah Gabr was born in Cairo, Egypt, in 1951. He received his B.Sc. in physics and chemistry (1974) and his M.Sc. in organic chemistry (1978). Also, he received his Ph.D. (1988) from the organic division, Faculty of Chemistry, Moscow University. His research is focused on the polymer chemistry and synthesis of heterocyclic compounds.