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

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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, 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$_2$SO$_4$ to form 2-methylchromones 2 by losing ethanol and water molecules (Scheme 1).$^{7-10}$

![Scheme 1](image)

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).$^{11}$
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 2

Scheme 3
O-Acetylsalicylic acid tert-butyl(dimethyl)silyl esters 7 underwent condensation with (trimethylsilyl)methylenetriphenylphosphorane followed by an intramolecular Wittig olefination to give substituted 2-methylchromones 2 (Scheme 4).\(^{13}\)

![Scheme 4](image)

**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](image)

**Scheme 5**

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

![Scheme 6](image)

**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).\(^{20-29}\)

![Scheme 8]

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>R''</th>
<th>R'''</th>
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<tr>
<td>H</td>
<td>H</td>
<td>O</td>
<td>allyl</td>
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</table>
The action of acetic anhydride and sodium acetate on 4,6-diacylresorcinol 18 yielded unpurified 3,7-diacyl-8-dimethyl-4,6-dione 19 as reported by Gulati and Venkataraman (Scheme 9).  

![Scheme 9](image)

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).  

![Scheme 10](image)
Cyclization of $\beta$-diketones 21 under certain conditions such as distillation,\textsuperscript{39} acetic anhydride,\textsuperscript{19,24,40-44} acidic,\textsuperscript{45-53} basic media,\textsuperscript{54} microwave,\textsuperscript{55} iodine-DMSO,\textsuperscript{56} DMSO-heat\textsuperscript{57} and bromine\textsuperscript{58} gave 2-methylchromones 2 (Scheme 11).

\begin{align*}
\hline
\text{i) Distillation at } 165 \, ^\circ\text{C} \\
\text{ii) } \text{Ac}_2\text{O}-\text{AcONa} \\
\text{iii) } \text{AcOH-HCl or H}_2\text{SO}_4 \\
\text{iv) } \text{NH}_2\text{OH} \\
\text{v) CaCl}_2, \text{MW, 5 min} \\
\text{vi) I}_2, \text{DMSO, heat} \\
\text{vii) DMSO, heat} \\
\text{viii) Br}_2 \\
\end{align*}

\(21 \rightarrow 2\)

\(R=\text{H, COCH}_3, \text{COOEt, Br}\)

**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\(_2\)COOEt) (Scheme 12).\textsuperscript{59}

\begin{align*}
\hline
\text{22} \\
\text{hv} \\
\text{C}_6\text{H}_6 \\
\end{align*}

\(2, \text{R=CH}_3\)

\(2, \text{R=CH}_2\text{COOEt}\)

**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).

\[
\begin{align*}
\text{Scheme 13} \\

2.6 \text{ 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).

\[
\begin{align*}
\text{Scheme 14} \\

2.7 \text{ From chromone derivatives} \\
2.7.1 \text{ From 2-methylchromanones.} \text{ Dehydrogenation of chroman-4-ones 27 by using I}_2-\text{DMSO-H}_2\text{SO}_4,\text{ and isoamyl nitrite-HCl systems yielded 2-methylchromones 2 (Scheme 15).}
\end{align*}
\]

Scheme 15

Oxidation of 2,2-dimethylchromanone 28 with thallium-p-tosylate followed by 2,3-alkyl migration gave 2-methychromone 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
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). 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).

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).

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.¹¹ (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*). Also, 5-hydroxy-2-methylchromones 2B were isolated from the root of *Adina rubella hance*. 5,7-Dihydroxy-2-methylchromone 2C and 5-hydroxy-7-methoxy-2-methyl-chromone 2D were isolated from the bulbs of *P. maritimum*. Also, 2E was isolated from the cultures of spore derived mycobionts of lichen *Graphis scripta*. 5-Carboxymethyl-7-hydroxy-2-methylchromone (2F) was isolated from the antibiotic and anti-inflammatory active site of *Polygonum cuspidatum sieb* while the over sephadex LH-20 column eluted with chloroform-methanol (50:50) furnished compound 2G.

2-Methylchromones 2H and 2I were isolated from *Leucas inflata* and *Neochamaclea puluervlenta*, respectively.
9-(β-D-glucopyranosyl-D-glucopyranosyl)oxyl]methyl-8,11-dihydro-5-hydroxy-2-methyl-4H-pyran[2.3.9][1]benzoepin-4-one \( 2J \) and 7-dihydroxy-8-[2e)-4-hydroxy-3-methylbut-2-enyl] -2-methyl-4H-chromone \( 2K \) were isolated from the tubers of \textit{Eranthis ciliicica}.\(^\text{80}\)

6-Acetyl-7-hydroxy-2,3-dimethylchromone \( 2L \) and 6-carboxy-7-hydroxy-2,3-dimethylchromone \( 2M \) were isolated from \textit{Tussilago farfara}.\(^\text{81}\) Also, 2-methyl-chromone derivative \( 2N \) was isolated from the gel of \textit{Aloe vera} leaves.\(^\text{82}\)

Compound \( 2O \) was isolated from a Nigerian sample of \textit{H. abyssini},\(^\text{83,84}\) while 3,3-dimethylallyl patheliachromene \( 2P \) and patheliabischromene \( 2Q \) were isolated from the leaves of \textit{Cneorum triciocum}.\(^\text{85-87}\)
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 $\alpha,\beta$-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).

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).
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)-\( \alpha \)-(chromon-2-yl)nitrones 39 that on hydrolysis with dilute acid gave the corresponding 2-formylchromone derivatives 34 (Scheme 24).92,93
3.1.3 Oxidation with \( \text{H}_2\text{O}_2 \). 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](image)

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-[(1-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](image)
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).

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).

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).

\[
2, \text{R=H} \quad \xrightarrow{i) \text{PhMgBr}} \quad 49
\]

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 (\(R^2=\text{CN}\)). Reaction of anil 50 (R=4-CH\(_3\)C\(_6\)H\(_4\)) with 51 gave cycloadduct 52 through its imine tautomer 50B (Scheme 32).

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).

\[
\begin{align*}
2, \text{R}^2=\text{CN} & \quad \xrightarrow{R = \text{N(CH}_3)_2} \quad 52 \\
2, \text{R}^2=\text{CN} & \quad \xrightarrow{R = \text{C}_6\text{H}_4\text{CH}_3-p} \quad 52
\end{align*}
\]

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
3.7.2 Reactions with DMFDMA
Reaction of 2-methylchromones 2 with DMFDMA afforded the dienamine 62. The E-geometry around the exocyclic olefinic bond in compounds 62 was established from their $^1$H NMR spectra (Scheme 38).

Scheme 37

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. 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).\textsuperscript{110}

\textbf{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\textit{H}-xanthene-1,9(4\textit{H})-dione 65 (Scheme 40).\textsuperscript{126}

\textbf{Scheme 40}

3.7.5 Reaction with benzothiazole-2-sulfobetaine. Heating of 2-methylchromone 2 (R=H) with 3-ethyl/methylbenzothiazole-2- sulfobetaine 66 at 150 °C followed by treatment with aqueous \(\text{NH}_3\text{OH}\) gave 2-(3-ethyl/methyl benzothiazolin-2-yl)methyl)chromone 67 (Scheme 41).\textsuperscript{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
Surprisingly, boiling of chromone 2 (R=COCH₃) 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-O₂NC₆H₄SO₃Me 76 in toluene gave violet 2-[[(2-methyl-4-benzopyrylidyne)methyl]-4-methoxy-benzopyrylium-o-nitrobenzene sulfonate 77 (Scheme 48).⁹⁶

![Scheme 46]
3.9. Vilsmeier-Haack reaction

Reaction of 2-methylchromone 2 (R=COCH₃) with POCl₃/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).\textsuperscript{128}
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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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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.