CHEMICAL TRANSFORMATION OF CHROMONES INTO COUMARINS

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Abstract – The essential focus of the present review is to collect the chemical reactions of chromone derivatives involving their transformation into coumarin derivatives. A diversity of coumarins was efficiently synthesized from the reactions of chromones with some nucleophilic reagents. This review includes the reactions of chromone derivatives with nitrogen and carbon nucleophiles, (acyclic and cyclic) leading to coumarins.

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1. INTRODUCTION

The benzopyran chemical class, formed by fusion of a benzene ring and a pyran ring with various levels of saturation and oxidation, appears in many natural products. Benzopyran skeletons including coumarins and chromones are important scaffolds in many drugs and bioactive natural products.\textsuperscript{1-3} Chromones (4\textit{H}-chromen-4-one derivatives) belong to one of the most common natural heterocyclic systems.\textsuperscript{4} They exhibit various types of biological activities such as antitumor,\textsuperscript{5-7} neuroprotective,\textsuperscript{8} HIV-inhibitory,\textsuperscript{9} antioxidant,\textsuperscript{10} anti-inflammatory,\textsuperscript{11,12} antispasmodic,\textsuperscript{13} estrogenic\textsuperscript{14} and antibacterial activities.\textsuperscript{15} Also, coumarins (2\textit{H}-chromen-2-one derivatives) possess many biological activities including anticoagulant,\textsuperscript{16} anticancer,\textsuperscript{17} vasorelaxant,\textsuperscript{18} antimicrobial,\textsuperscript{19} antioxidant,\textsuperscript{20} anti-inflammatory,\textsuperscript{21} and anti-HIV activities.\textsuperscript{22} In addition to the biological activity, coumarins have used in food additives,\textsuperscript{23} cosmetics,\textsuperscript{24} fluorescent and laser dyes.\textsuperscript{25} The current review article summarizes the synthetic transformations used for construction of substituted coumarins from substituted chromones.

2. SYNTHETIC METHODS FOR COUMARIN DERIVATIVES FROM CHROMONE DERIVATIVES

2.1. From chromones

Cascade reactions of chromone derivatives 1 with ethyl mercaptoacetate, in dioxane containing DBU under nitrogen atmosphere produced thieno[2,3-\textit{c}]coumarins 2 in good-to-excellent yields, through intermediate I-1. This cascade reaction involved a \textit{Michael} addition–Knoevenagel condensation–intramolecular cyclization (Scheme 1).\textsuperscript{26}

\begin{center}
\begin{tikzpicture}

% TikZ code for the scheme

\end{tikzpicture}
\end{center}

Scheme 1
2.2. From 2-substituted chromones

2.2.1. From 2-trihalomethylchromones

Chemical transformations of 2-trichloromethylchromones 3 with a methanolic KOH solution, upon reflux for 0.5 h, produced 4-hydroxycoumarins 4, in 45-74% yields, via 2-hydroxychromones I-2 as non-isolable intermediates (Scheme 2).

![Scheme 2](image)

Reactions of 2-(trifluoromethyl)chromones 5 with three equivalents of ethyl mercaptoacetate at 80 °C in the presence of Et₃N as a catalyst, afforded dihydrothienocoumarins 6, through intermediates I-3 and I-4 (Scheme 3).

![Scheme 3](image)

Reactions of 2-(trifluoromethyl)chromones 5 with diethyl malonate, by using molar ratio 1:2, gave ethyl coumarine-3-carboxylates 7 (Scheme 4). This reaction proceeds through a domino reaction including
nucleophilic attack at position 2 giving intermediate \( \text{I-5} \) followed by cyclocondensation producing intermediate \( \text{I-6} \) which loses ethanol and ethoxycarbonyl group giving the final product \( 7 \).\textsuperscript{28-31}

![Scheme 4](image)

Alkyl 7-hydroxy-6-oxo-6\( H \)-benzo[c]chromene-8-carboxylates \( 10 \) were isolated, in 27–84% yields, from reaction of chromones \( 8 \) with dialkyl 1,3-acetonedicarboxylates \( 9 \), under various reaction conditions (Scheme 5).\textsuperscript{30,32-35}

<table>
<thead>
<tr>
<th>( R )</th>
<th>( R^1 )</th>
<th>( R^2 )</th>
<th>( R^3 )</th>
<th>Reaction conditions</th>
<th>Yield</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>CF(_3)</td>
<td>Et</td>
<td>EtOH/ EtONa/ reflux/ 12 h</td>
<td>57%</td>
<td>30</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Et</td>
<td>EtOH/ EtONa/ reflux/ 12 h</td>
<td>39%</td>
<td>30</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>THF/ DBU/ stir/ rt/ 2-3 h</td>
<td>56%</td>
<td>32</td>
</tr>
<tr>
<td>H</td>
<td>NO(_2)</td>
<td>H</td>
<td>Et</td>
<td>Py/ reflux/ stir/ rt/ 2 h</td>
<td>40%</td>
<td>34, 35</td>
</tr>
</tbody>
</table>
2.2.2. From 2-aminochromones

2-Aminochromones 11 reacted with 3-bromochromones 12, in refluxing acetic acid in the presence of Cs$_2$CO$_3$ as inorganic catalyst, producing furo[3,2-c]chromen-4-ones 13, in moderate yields (Scheme 6).\textsuperscript{33}

<table>
<thead>
<tr>
<th>H</th>
<th>NO$_2$</th>
<th>H</th>
<th>Et</th>
<th>EtOH/ Py/ reflux/ stir/ rt/ 2 h</th>
<th>40%</th>
<th>32, 33</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>2-NO$_2$PhCO</td>
<td>H</td>
<td>Me</td>
<td>dioxane/ DBU/ stir/ rt/ 10-12 h</td>
<td>72%</td>
<td>32</td>
</tr>
<tr>
<td>6-Me</td>
<td>2-NO$_2$PhCO</td>
<td>H</td>
<td>Me</td>
<td>dioxane/ DBU/ stir/ rt/ 10-12 h</td>
<td>84%</td>
<td>32</td>
</tr>
<tr>
<td>7-OMe</td>
<td>2-NO$_2$PhCO</td>
<td>H</td>
<td>Me</td>
<td>dioxane/ DBU/ stir/ rt/ 10-12 h</td>
<td>73%</td>
<td>32</td>
</tr>
<tr>
<td>H</td>
<td>PhCO</td>
<td>H</td>
<td>Me</td>
<td>dioxane/ DBU/ stir/ rt/ 10-12 h</td>
<td>27%</td>
<td>32</td>
</tr>
<tr>
<td>H</td>
<td>2-F-PhCO</td>
<td>H</td>
<td>Me</td>
<td>dioxane/ DBU/ stir/ rt/ 10-12 h</td>
<td>46%</td>
<td>32</td>
</tr>
</tbody>
</table>

Scheme 5

2.3. From 3-substituted chromones

2.3.1. From 3-alkynylchromone

3-Alkynylchromones 14 underwent transformations with H$_2$O in the presence of 20% CuCl as Lewis acid under an air atmosphere to yield 2-substituted-4H-furo[3,2-c]chromen-4-ones 15 (Scheme 7).\textsuperscript{36,37} The reaction proceeds through a cascade reaction involving addition, cyclization and oxidation.
Meanwhile, the previous reaction in the presence of 10% CuBr and excess CuCl\textsubscript{2} as an oxidant afforded 3-chloro-4\textit{H}-furo[3,2-\textit{c}]chromen-4-ones 16, through \textit{Michael} addition (intermediate I-7) followed by cyclization with concomitant chlorination producing intermediate I-8 which oxidized to the final product (Scheme 8).\textsuperscript{36,37}

\[ \text{Scheme 7} \]

2.3.2. From C-(chromen-3-yl)-N-phenylnitrones

Hamdi and his coworkers, postulated the formation of 3-(arylaninomethylene)chromane-2,4-dione 18 from boiling nitrones 17 in non-polar solvents (toluene or xylene) for varying times (Scheme 9).\textsuperscript{38}

\[ \text{Scheme 8} \]
In the previous reaction, using benzene or chloroform as a solvent, C-(chromen-3-yl)-N-phenyliminonitrones 17 rearranged yielding a mixture of 3-(phenyliminomethylene)chroman-2,4-diones 19 (25%) and 2-(N-phenylamino)chromone-3-carboxaldehydes 20 (70%) (Scheme 10).³⁹,⁴⁰

2.3.3. From chromone-3-carboxaldehydes
The conversions of some 3-substituted chromones into substituted coumarins were studied. Treating a suspension of 3-formylchromone (21) in CCl₄ with N-bromosuccinimide (NBS) under UV-irradiation afforded, after quenching with ammonia at 40 °C, chromane-2,4-dione (22), via intermediate I-9. Stirring compound 22 with aqueous NaOH solution followed by acidification produced 3-formyl-4-hydroxycoumarin (23), through intermediate I-10 (Scheme 11).⁴¹-⁴²
Stirring chromone-3-carboxaldehyde (21) with chromone-3-carboxylic acid (24), in dichloromethane containing alumina at room temperature, gave 4-hydroxy-3-(chromon-3-yl)methylcoumarin 25, in 30% yields (Scheme 12).43

Condensation of chromone-3-carboxaldehyde (21) with some primary amines, under different reaction conditions, afforded the Schiff bases of 4-hydroxycoumarin-3-carboxaldehyde 26 (Scheme 13).44,45
2.3.4. From chromone-3-carboxaldehyde oximes

Rearrangement of chromone-3-carboxaldehyde oximes 27 with alkaline hydroxylamine gave 3-aminoisoxazolocoumarins 28, via the non-isolable intermediates I-11—I-17 as illustrated in Scheme 14. Further reaction of compound 28 with alkaline hydroxylamine afforded chromane-2,4-diones 29 (Scheme 14).

---

**Scheme 13**

<table>
<thead>
<tr>
<th>R</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Reaction Conditions</th>
<th>Yield</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Ph</td>
<td>dry benzene/K-10 montmorillonite/reflux/2 h</td>
<td>45%</td>
<td>45</td>
</tr>
<tr>
<td>H</td>
<td>4-MePh</td>
<td>dry benzene/K-10 montmorillonite/reflux/2 h</td>
<td>40%</td>
<td>45</td>
</tr>
<tr>
<td>H</td>
<td>4-MeOPh</td>
<td>dry benzene/K-10 montmorillonite/reflux/2 h</td>
<td>46%</td>
<td>45</td>
</tr>
<tr>
<td>Me</td>
<td>Ph</td>
<td>dry benzene/K-10 montmorillonite/reflux/2 h</td>
<td>42%</td>
<td>45</td>
</tr>
<tr>
<td>Me</td>
<td>4-MePh</td>
<td>dry benzene/K-10 montmorillonite/reflux/2 h</td>
<td>35%</td>
<td>45</td>
</tr>
<tr>
<td>Me</td>
<td>8-quinolinyl</td>
<td>MeOH/stir/60 °C/3 h</td>
<td>76%</td>
<td>44</td>
</tr>
</tbody>
</table>

**Scheme 14**
2.3.5. From chromone-3-carbonitriles

Treatment of chromone-3-carbonitrile (30) active methylene compounds 31 in ethanol containing triethylamine afforded dibenzo[b,d]pyran-6-ones 32 (Scheme 15).\(^{49}\)

\[
\begin{align*}
\text{30} & \quad \text{31} \\
\text{32} & \quad \text{R}^1 = \text{Me, Et, } n-\text{Pr, } n-\text{Bu} \\
\text{R}^2 = \text{Me, Et} \\
\end{align*}
\]

Scheme 15

Reaction of chromone-3-carbonitriles 30 with chloroacetone, in methylene chloride and aluminum oxide, afforded 4-hydroxycoumarin 33 which upon cyclocondensation afforded 2-acetylfurocoumarins 34 (Scheme 16).\(^{50}\)

\[
\begin{align*}
\text{30} & \quad \text{AcCl} \\
\text{AcOH/ reflux} & \quad 8 \text{ h} \\
\text{33} & \quad \text{Ac} \\
\text{34} & \quad \text{R} \\
\end{align*}
\]

Scheme 16

On the other hand, ring opening/ring closure reactions of chromone-3-carbonitriles 30 with methylhydrazine, in acetic acid under reflux, afforded chromeno[4,3-c]pyrazol-4(2H)-ones 35, in 70-92\% yields (Scheme 17).\(^{51,52}\)

\[
\begin{align*}
\text{30} & \quad \text{NH}_2\text{NH-Me} \\
\text{AcOH/ reflux} & \quad 5 \text{ h/ } 70-92\% \\
\text{35} & \quad \text{R} \\
\end{align*}
\]

Scheme 17
Treating chromone-3-carbonitriles 30 with some hydrazine hydrate, phenylhydrazine, S-benzyl dithiocarbazate and nicotinic acid hydrazide, under various reaction conditions, led to chromeno[4,3-c]pyrazol-4(1H)-ones 36 (Scheme 18).  

![Reaction conditions](image)

<table>
<thead>
<tr>
<th>R</th>
<th>R¹</th>
<th>Reaction Conditions</th>
<th>Yield</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Ph</td>
<td>AcOH/ reflux/ 4 h</td>
<td>55%</td>
<td>51, 52, 53</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>AcOH/ reflux/ 2 h</td>
<td>57%</td>
<td>51, 54</td>
</tr>
<tr>
<td>Me</td>
<td>4-COPy</td>
<td>AcOH/ reflux/ 4 h</td>
<td>45%</td>
<td>54</td>
</tr>
<tr>
<td>Me</td>
<td>SCSCH₂Ph</td>
<td>AcOH/ reflux/ 4 h</td>
<td>48%</td>
<td>54</td>
</tr>
</tbody>
</table>

Scheme 18

The conversion of 6-methylchromone-3-carbonitrile (30) into 9-methyl-5H-chromeno[4,3-d]pyrimidin-5-ones 37 was achieved from its reactions with guanidine hydrochloride and cyanoguanidine, in absolute ethanol and aqueous potassium hydroxide solution (Scheme 19).  

![Reaction conditions](image)

Scheme 19

Chemical transformations of chromone-3-carbonitriles 30 with acetamidine hydrochloride under weakly acidic conditions (AcONa), in refluxing DMF for 15 min, afforded a mixture of 2,9-dimethyl-4-(trifluoromethyl)-5H-chromeno[4,3-d]pyrimidine derivatives 38 (X = O, NH). When this mixture was treated with aqueous acetic acid, coumarins 38 (X = O) were obtained in good yields (Scheme 20).  

51-54

53

55
Scheme 20

The chemical transformations of chromone-3-carbonitriles 30 were investigated towards malononitrile dimer (2-aminoprop-1-ene-1,1,3-tricarbonitrile) by Ibrahim and his coworkers.\textsuperscript{55-58} Ring conversion of 6-methylchromone-3-carbonitrile (30) with malononitrile dimer, in absolute ethanol containing DBU as a catalyst, led to (3-cyano-5-oxo-1,5-dihydro-2\textit{H}-chromeno[4,3-\textit{b}]pyridin-2-ylidene)propanedinitriles 39 (Scheme 21).\textsuperscript{54,56}

Scheme 21

While, reaction of carbonitrile 30 with malononitrile dimer, in boiling ethanol containing piperidine, produced a mixture of products identified as (3-cyano-5-oxo-1,5-dihydro-2\textit{H}-chromeno[4,3-\textit{b}]pyridin-2-ylidene)propanedinitrile (39) and 2,4-diamino-6-oxo-6\textit{H}-chromeno[2,3-\textit{b}]naphthyridine-3-carbonitrile (40) as depicted in Scheme 22.\textsuperscript{57} Compounds 39 and 40 formed through intermediate I-18 which formed from nucleophilic attack at position 2. Rotation of intermediate I-18 into intermediate I-19 followed by dehydration and cycloaddition gave intermediate I-20 which hydrolyzed to product 39. While, rotation of intermediate I-18 into intermediate I-21 followed by consecutive cycloaddition afforded product 40 as shown in Scheme 22.
Further, the previous reaction in case of 6,8-dimethylchromone-3-carbonitrile (21) produced a mixture of products identified as, (3-cyano-7,9-dimethyl-5-oxo-1,5-dihydro-2H-chromeno[4,3-b]pyridin-2-ylidene)propanedinitrile (39) and (3Z)-2-amino-4-(2-amino-6,8-dimethylchromon-3-yl)buta-1,3-diene-1,1,3-tricarbonitrile (41) as depicted in Scheme 23.^[38]
Further, 2-aminochremeno[4,3-b]pyridine-3-carboxylates 43 were synthesized via a cascade reactions of chromone-3-carbonitriles 30 with carbamimidoyl-acetic acid ethyl ester in aqueous medium. This cascade reaction involves a chemoselective nucleophilic attack at C-2 position with ring opening followed by free rotation around the single bonds giving intermediate I-26, which underwent cycloaddition and cyclocondensation producing intermediate I-27 that hydrolyzed to the final product 43 (Scheme 24).
Ibrahim et al.\textsuperscript{53-58} prepared 3-hydroxychromeno[4,3-\textit{b}]pyrazolo[4,3-\textit{e}]pyridin-5(1\textit{H})-ones \textbf{44} from chemical transformations of chromone-3-carbonitriles \textbf{30} with cyanoacetohydrazide, in boiling acetic acid (Scheme 25). These domino reactions occurred through $\gamma$-pyrone ring opening (intermediate \textbf{I-28}) with two consecutive cycloadditions (intermediate \textbf{I-29}) followed by dehydration giving intermediate \textbf{I-30} which hydrolyzed to the final product \textbf{44} as depicted in Scheme 25.
2.3.6. From chromone-3-carboxamides

Chromone-3-carboxamide (45) represents an excellent source for building coumarin derivatives. Stirring chromone-3-carboxamide (45) with NaOH solution at room temperature followed by acidification produced 3-formyl-4-hydroxycoumarin-3-carboxaldehyde (23) (Scheme 26).41-42

Reaction of chromone-3-carboxamide (45) with acetophenone, in ethanolic potassium hydroxide solution, afforded 4-hydroxycoumarin derivative 46 (Scheme 27).60
Substituted chromone-3-carboxamides 47 reacted with malononitrile, in the presence of potassium acetate in acetonitrile, through Michael reaction followed by retro-Michael and heterocyclization, giving chromeno[4,3-b]pyridine-3-carbonitriles 48 (Scheme 28).\(^{51}\)

Condensation of chromone-3-carboxamide (45) with thiobarbituric acid, in ethanolic sodium hydroxide, afforded 5-[(4-hydroxycoumarin-3-yl)methylidene]-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (49) (Scheme 29).\(^{60}\)
Treating chromone-3-carboxamide (45) with some primary aliphatic and aromatic amines namely, \(n\)-propylamine, benzylamine and \(p\)-bromoaniline, under various reaction conditions, afforded chromane-2,4-diones 18 which were isolated as stereoisomeric mixtures of \(Z\) and \(E\) isomers (Scheme 30).

\[
\begin{align*}
\text{Scheme 30}
\end{align*}
\]

Also, (3\(Z\))-3-(methyl-/ethylaminomethylene)chromane-2,4-diones 18 were prepared by refluxing an ethanolic solution of carboxamide 45 with methyl or ethylamine for 15 min (Scheme 31).

\[
\begin{align*}
\text{Scheme 31}
\end{align*}
\]

Ring transformations of carboxamide 45 with hydrazine hydrate and phenylhydrazine, in refluxing ethanol for 2 h, achieved chromeno[4,3-\(c\)]pyrazol-4(1\(H\))-ones 33 (Scheme 32).

\[
\begin{align*}
\text{Scheme 32}
\end{align*}
\]
Reacting chromone-3-carboxamide (45) with 7-chloro-4-hydrazinoquinoline (50), in refluxing ethanol for 15 min, afforded the rearranged product, 3-\{[2-(7-chloroquinolin-4-yl)hydrazinylidene]methyl\}-4-hydroxycoumarin 51 (Scheme 33). 60

\[ \text{45} \stackrel{\text{EtOH/ reflux} \ 15 \text{ min / 56\%}}{\longrightarrow} \text{51} \]

Scheme 33

Also, rearrangement of chromone-3-carboxamide (45) with hydroxylamine hydrochloride, in refluxing dimethylformamide (DMF) for 2 h, produced chromeno[3,4-d]isoxazol-4(4H)-one (52) (Scheme 34). 60

\[ \text{45} \stackrel{\text{DMF/ reflux} \ 2 \text{ h/ 66\%}}{\longrightarrow} \text{52} \]

Scheme 34

Chromone-3-carboxamide (45) reacted with some 1,3-binucleophiles such as guanidine hydrochloride, cyanoguanidine and thiourea, in ethanolic potassium hydroxide solution, produced chromeno[4,3-d]pyrimidines 53 (Scheme 35). 53

\[ \text{45} \stackrel{\text{EtOH/ KOH reflux/ 2 h} \ 46-66\%}{\longrightarrow} \text{53} \]

Scheme 35
Condensation of chromone-3-carboxamides 45 with cyanothioacetamide in ethanolic sodium ethoxide solution afforded chromeno[4,3-b]pyridine-3-carbonitriles 54, via intermediate I-31 followed by cyclization (Scheme 36).  

![Scheme 36](image)

Chromone-3-carboxamides 45 rearranged with cyanoacetohydrazide, in ethanolic sodium ethoxide solution, giving chromeno[4,3-b]pyridine-3-carbonitriles 55, via intermediate I-32 followed by cyclization with loss of water and ammonia molecules (Scheme 37).

![Scheme 37](image)

*Bis-*chromane-2,4(3H)-dione 56 was synthesized by reaction of chromone-3-carboxamide (45) with ethylenediamine, in boiling ethanol for 30 min (Scheme 38).
Rearrangement of chromone-3-carboxamide (45) with some 1,4-dinucleophiles namely \(o\)-phenylenediamine and \(o\)-aminophenol in refluxing DMF afforded (3Z)-3-{[(2-amino/2-hydroxyphenyl)amino]methylidene}chromane-2,4(3\(H\))-dione (57) (Scheme 39).\(^6^0\)

\[
\begin{array}{c}
\text{O} \quad \text{O} \\
\text{NH} \\
\text{O} \quad \text{O} \quad \text{O} \\
\text{N} \\
\text{H} \\
XH \\
\text{N} \\
\text{H} \\
\text{2} \quad \text{H} \quad \text{4} \\
\text{O} \quad \text{O} \\
\text{O} \quad \text{O} \\
\text{N} \\
\text{H} \\

45 \quad \text{DMF/ reflux} \\
2 h/ 42-46\%
\end{array}
\]

Scheme 39

Different to the previous behavior, ring transformation of chromone-3-carboxamide (45) with \(o\)-aminothiophenol, in refluxing DMF, furnished 3-benzothiazolyl-4-hydroxycoumarin 58 (Scheme 40).\(^6^0\)

\[
\begin{array}{c}
\text{O} \quad \text{O} \\
\text{NH} \\
\text{S} \quad \text{H} \\
\text{N} \\
\text{H} \\
\text{2} \\
\text{O} \quad \text{O} \\
\text{O} \\
\text{CONH} \\
\text{2} \\
\text{EtOH/ 25% NH}_3 \\
\text{NaOH/ reflux} \\
3 h/ 21\%
\end{array}
\]

Scheme 40

On the other hand, 2-aminochromone-3-carboxamide (59) was also utilized for construction of coumarin derivatives. 4-Hydroxycoumarin-3-carboxamide (60) was efficiently synthesized from hydrolysis of 2-aminochromone-3-carboxamide (59) using ammonia and NaOH, in boiling ethanol for 3 h (Scheme 41).\(^4^2\)

\[
\begin{array}{c}
\text{O} \\
\text{CONH}_2 \\
\text{EtOH/ 25% NH}_3 \\
\text{NaOH/ reflux} \\
3 h/ 21\%
\end{array}
\]

Scheme 41
Reaction of 2-aminochromone-3-carboxamide (59) with hydrazine hydrate, in boiling ethanol in the presence of NaOH for 3 h, produced 3-aminochromeno[4,3-c]pyrazolones 61a,b (Scheme 42). The product formed as a mixture of two tautomers in the ratio 88:12, according to the $^1$H NMR spectroscopic data.\textsuperscript{48,49}

![Scheme 42](image)

On the other hand, reaction of 2-aminochromone-3-carboxamide (59) with methylhydrazine, in ethanolic sodium hydroxide solution, afforded 2-methylchromeno[4,3-c]pyrazol-4(2H)-one 62, in 35% yield (Scheme 43).\textsuperscript{47}

![Scheme 43](image)

Carboxamides 59 were transformed with alkaline hydroxylamine to afford chromanediones 29 (Scheme 44).\textsuperscript{41,46-48}

![Scheme 44](image)
2.3.7. From chromone-3-carboxalic acids

Treating chromone-3-carboxylic acid (24) with some primary aliphatic and aromatic amines namely, n-propylamine and phenylamine, under various reaction conditions, afforded chromane-2,4-diones 18 which were isolated as stereoisomeric mixtures of Z and E isomers (Scheme 45).64

![Scheme 45](image)

Interaction of chromone-3-carboxylic acid (x) with aromatic amines, in mixture of DMF and dichloromethane in the presence of such activating reagent as phosphonium salt (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) gave chromanediones 18 (Scheme 46).65

![Scheme 46](image)

Reaction of fluorinated chromone-3-carboxylic acids 24 with hydrazine hydrate, under different reaction conditions, led to fluorinated coumarinopyrazole derivatives 36 (Scheme 47).66,67

![Scheme 47](image)
Condensation of chromone-3-carboxylic acids 24 with some hydrazines such as hydrazine hydrate, cyanoacetohydrazide, phenylhydrazine, 7-chloro-4-hyrazinoquinoline, under various reaction conditions, provided chromeno[4,3-c]pyrazoles 36 (Scheme 48).

<table>
<thead>
<tr>
<th>R</th>
<th>R¹</th>
<th>R²</th>
<th>Reaction Conditions</th>
<th>Yield</th>
<th>Ref.</th>
</tr>
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<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>AcOH/ reflux/ 2 h</td>
<td>46%</td>
<td>64</td>
</tr>
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<td>H</td>
<td>-COCH₂CN</td>
<td>AcOH/ reflux/ 2 h</td>
<td>48%</td>
<td>64</td>
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<tr>
<td>H</td>
<td>H</td>
<td>7-chloroquinolinyl</td>
<td>AcOH/ reflux/ 1 h</td>
<td>32%</td>
<td>64</td>
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<tr>
<td>H</td>
<td>H</td>
<td>Ph</td>
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<td>80%</td>
<td>68</td>
</tr>
<tr>
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<td>Me</td>
<td>Ph</td>
<td>AcOH/ reflux/ 4 h</td>
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<td>68</td>
</tr>
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<td>EtOH/ reflux/ 1 h</td>
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<td>H</td>
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<td>AcOH/ reflux/ 2 h</td>
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<td>69</td>
</tr>
<tr>
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<td>H</td>
<td>Ph</td>
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<td>H</td>
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</tr>
<tr>
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<td>Ph</td>
<td>AcOH/ reflux/ 2 h</td>
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<td>54</td>
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<tr>
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<td>H</td>
<td>Ph</td>
<td>AcOH/ reflux/ 2 h</td>
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</tbody>
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Scheme 48
Reaction of fluorinated chromone-3-carboxylic acid 24 with hydroxylamine, under different reaction conditions, afforded chromeno[3,4-d]isoxazole 52, through γ-pyrone ring opening (intermediate I-33) followed by cyclodehydration (Scheme 49).\(^{66}\)

![Scheme 49](image)

Interaction of chromone-3-carboxylic acids 24 with guanidine carbonate, in boiling ethanol, led to chromeno[4,3-d]pyrimidine 37, in moderate yields (Scheme 50).\(^{69}\)

![Scheme 50](image)

Interaction of chromone-3-carboxylic acid (24) with push-pull enamines 63, in boiling DMF, produced pyrido[3,2-c]coumarins 64, through intermediate I-34 (Scheme 51).\(^{69}\)

![Scheme 51](image)
Bis-chromane-2,4(3H)-diones 65 were synthesized, as a stereoisomeric mixture of (E)- and (Z)-isomers from reaction of chromone-3-carboxylic acid (24) with aliphatic diamines, in DMF by using carbonyldiimidazole (CDI) as the activating agent (Scheme 52).^{20}

\[
\begin{align*}
\text{CO}_2\text{H} & \quad \text{H}_2\text{N}^{\text{Z}}\text{NH}_2
\end{align*}
\]

\[\text{DMF/ CDI/ stir.} \quad \text{rt/ 1 h/ 60-97\%} \]

\[
\begin{align*}
\text{65 (Z)} & \quad +
\end{align*}
\]

\[
\begin{align*}
\text{65 (E)}
\end{align*}
\]

\[
\begin{align*}
\text{Z} & = \text{CH}_2(\text{CH}_2)_2\text{N}-\text{Me}, \quad \text{CH}_2(\text{CH}_2)_2\text{O}\text{-[(CH}_2\text{CH}_2)_2\text{N-CH}_2(\text{CH}_2)_2\text{CH}_2}
\end{align*}
\]

Scheme 52

2.3.8. From alkyl chromone-3-carboxylates

Basic rearrangement of ethyl chromone-3-carboxylates 66, in aqueous sodium hydroxide solution at room temperature, produced 3-substituted-4-hydroxycoumarins 23, in good yields (78-86\%) (Scheme 53).^{55}

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{NaOH/ stir.} \\
\text{rt/ 15 min/ 78-86\%} & \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{23}
\end{align*}
\]

Scheme 53

Treatment of ethyl chromone-3-carboxylate 66 with excess chloroacetone, in dichloromethane in the presence of Brockman neutral alumina, afforded 2-acetylfurocoumarin 34 (Scheme 54).^{50}
Reaction of methyl chromone-3-carboxylate (66) with triacetic acid lactone 67, in boiling toluene in the presence of pyridine for 4 h, afforded pyranob[4,3-b]coumarin 68 in 36% yield (Scheme 55).^{21}

While, conversions of ethyl chromone-3-carboxylates 66 into chromane-2,4(3H)-diones 69, were achieved by heating with ammonium chloride or ammonium hydroxide under different reaction conditions (Scheme 56).^{28,55,67,72,73}
Rearrangement of chromone-3-carboxylate derivative 66 with equimolar amount of methylamine sulfate, by heating in ethanol for 72 h, led to chromane-2,4-diones 70 and 71 (Scheme 57). Repeating the previous reaction using excess of methylamine salt under the same reaction conditions produced a single product 71, in 94% yield.\textsuperscript{66,74}

![Scheme 57](image)

Polyfluorochromone-3-carboxylates 66 reacted with a variety of primary amines, under different reaction conditions, producing chromane-2,4(3\textit{H})-diones 72 (Scheme 58).\textsuperscript{66-68,72,24,25}

![Scheme 58](image)

Reaction of ethyl chromone-3-carboxylate 66 with hydrazine hydrate, under different reaction conditions, afforded pyrazoles 36 (Scheme 59).\textsuperscript{28-66,67}
Reaction of methyl 2-methylchromone-3-carboxylate (66) with one equivalent of N-methylhydrazine, in methanol for 2 h, gave a mixture of products 73 (64%), 74 (16%) and 75 (20%) (Scheme 60).88,76

Reaction of fluorinated ethyl chromone-3-carboxylate 66 with hydroxylamine, under various reaction conditions, afforded chromenoisoxazole 52 (Scheme 61).66,67
2-Aminochromeno[4,3-b]pyridine-3-carboxylate 43 was synthesized via an intramolecular cyclization of methyl chromone-3-carboxylate 66 with carbamimidoyl-acetic acid ethyl ester (42) in aqueous medium (Scheme 62).

![Scheme 62](image)

Methyl chromone-3-carboxylate 66 reacted with some active methylene amides 76, in the presence of 4-dimethylaminopyridine (DMAP) and MeCN, giving chromeno[4,3-b]pyridine-2,5-diones 77 bearing the enaminone moiety (Scheme 63).

![Scheme 63](image)

### 2.3.9. From chromonylacrylonitrile

Recently, Cai et al. reported an efficient, convenient, and safe route to functionalized 3-acyl-4-arylcoumarins 79 using a mild base-promoted (Cs$_2$CO$_3$) reaction between electron deficient chromones 78 and $\beta$-keto esters via benzannulation and transesterification. The reaction mechanism involves Michael addition, 1,5-shift and transesterification (Scheme 64).
2.4. From annulated chromones

Boiling annulated furochromone 80 in 50% sulphuric acid for 8 h, furnished the annulated furocoumarin 81, in 87% yield (Scheme 65).  

3. CONCLUSION

In conclusion, variable synthetic methods were utilized to synthesize a variety of coumarins and annulated coumarins from chromone derivatives. Reactions of substituted chromones especially bearing electron withdrawing group at position 3 are valuable synthon for substituted coumarins. Chemical transformations of chromone derivatives with some mono- and bi-functional nucleophiles afforded a diversity of coumarins and fused coumarins.

REFERENCES

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Aya Ahmed Hamed Shahat was born in Cairo, Egypt, in 1994. She received his B.Sc. degree in chemistry (2017) Department of Chemistry, Faculty of Education, Ain Shams University. Her research is focuse on synthesis of new heterocyclic compounds containing chromone nuclus.

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