3-Formylchromones as diverse building blocks in heterocycles synthesis

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1. Introduction

Chromone derivatives are widely known as an important class of biologically active compounds. The chemical reactivity of 3-substituted chromones is widely different depending on the nature of the functional group present at the position 3 and the reaction conditions. Among the 3-functionalized chromones, their 3-formyl derivatives are widely used in heterocyclic synthesis. 3-Formylchromones are also known as 4-oxo-4H-1-benzoazepan-3-carboxaldehydes, 4-oxo-4H-chromene-3-carboxaldehydes and chromone-3-carboxaldehydes. Although many methods are known for the synthesis of 3-formylchromones, Vilsmeier-Haack reaction on substituted 2-hydroxycacetophenones is the most suitable among them [1-17]. In Vilsmeier-Haack reaction, the reaction takes place via double formulation of o-hydroxycacetophenones followed by cycloaddition with concomitant dehydration (Scheme 1). DMF·POCl3 plays a dual role of a reagent as well as a solvent. A variety of substituted 3-formylchromones 1a-z were prepared under traditional and microwave irradiation using Vilsmeier-Haack reagent and are reported herein.

2. Chemical reactivity of 3-formylchromones

3-Formylchromones, 1a-z, are a versatile syntheses for the synthesis of a variety of novel heterocyclic systems possessing diverse biological activities. From a synthetic view point, 3-formylchromones, 1a-z, occupy an important position in the synthesis of various heterocyclic systems, due to the availability of three electron deficient sites, the aldehydes carbon, C-2 carbon, and the C-4 carbon of the carbonyl group. Also, 3-formylchromones are able to serve as a heterodiene as well as a dieneophile or a Michael acceptor. Moreover, a variety of fused heterocycles were prepared directly from the reaction of compounds 1a-z with some bifunctional nucleophiles. The present review aims to study the chemical reactivity of 3-formylchromones towards a variety of carbon and nitrogen nucleophiles under different reaction conditions.

2.1. Chemical reactivity of 3-formylchromones towards active methyl and methylene compounds

Condensation reactions of 3-formylchromone 1a-c, h with substituted acetophenone 2 in freshly distilled pyridine or glacial acetic acid containing perchloric acid afforded substituted 3-(3-oxo-3-arylprop-1-enyl)chromones, 3 [Scheme 2] [18-21].

4-Hydroxy-1-alkyl-3-[3-(4-oxo-4H-chromen-3-yl)quinolin-2(1H)-ones (5) were smoothly obtained via a Knoevenagel condensation of 3-formylchromone (1a) with 3-acetyl-4-hydroxy-1-alkylquinolin-2(1H)-one (4) in ethanol containing piperidine as basic catalyst [Scheme 3] [22,23].

Interaction of equimolar amount of 3-formyl-6-chlorochromone (1c) with 4-acetyl-5,6-diphenylpyridazin-3(2H)-one (6) in sodium ethoxide afforded 4-[3-{6-chloro-4-oxochromen-3-yl}prop-2-enoyl]-5,6-diphenylpyridazin-3(2H)-one (7) in 87% yield. When this reaction was carried out in ethanol containing few drops of piperidine, 7-[6-chloro-4-oxochromen-3-yl]-3,4-diphenyl-6,7-dihydropyrazolo[2,3-c]-pyridazin-5-one (8) was obtained in 55% yield via intramolecular cycloaddition reaction in compound 7 [Scheme 4] [24].

Treating 3-formylchromones 1a-c with 5-acyethylbarbituric acid (9a) and 5-acyethylthio barbituric acid (9b), in ethanol containing pyridine or water-Zn(L-proline), gave the corresponding αβ-unsaturated ketones, 10a,b [Scheme 5] [25].

Similarly, treating 3-formylchromones 1a,b with 5-acyethyl-1,3-dimethylbarbituric acid (11) under the same reaction conditions afforded 1-(1,3-dimethyl-2,4,6-pyrimidinetrione-5-yl)-3-(4-oxo-4H-chromen-3-yl)-2-propen-1-one (12a) and...
1-[(1,3-dimethyl-2,4,6-pyrimidinetrione-5-yl)-3-(6-methyl-4-oxo-4H-chromen-3-yl)-2-propen-1-one (12b), respectively (Scheme 6) [26].

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Scheme 1

1-(1,3-dimethyl-2,4,6-pyrimidinetrione-5-yl)-3-(6-methyl-4-oxo-4H-chromen-3-yl)-2-propen-1-one (12b), respectively (Scheme 6) [26].

Condensation of 3-formylchromones 1a-c with dehydroacetic acid (13) in ethanol containing pyridine or water-Zn(L-proline); gave α,β-unsaturated ketones 14 in high yields (87-92%) (Scheme 7) [26].

Refluxing 3-formylchromones 1a-c with 3-acetyl-4-hydroxycoumarin (17) in ethanol containing pyridine as a basic catalyst gave 1-(4-hydroxychromen-2-one-3-yl)-3-(chromen-4-one-3-yl)-2-propen-1-ones (18) in 65-92% yields (Scheme 8) [26,27].
Reaction of 6,8-dichloro-3-formylchromone (1q) with 4-methyl-2-oxo-2H-chromone-3-carbonitrile (19) gave the addition product 20 as recently reported by El-Shaaer [28]. While Melikyan et al. [29] isolate the condensation products 21 on the reaction of 1a-d with compound 19 in refluxing toluene (Scheme 9).

Condensation of 3-formylchromone (1a) with 2-methyl-3-acyclochromones 22 in acetic anhydride-potassium acetate led to bis-chromonylethylene 23 (Scheme 10). This reaction occurred only at 2-methyl group [30].

2-(4-Oxo-4H-chromen-3-yl)vinylthiazoline (24) was synthesized by condensation of 3-formylchromone 1a with 2-methylthiazoline in glacial acetic acid containing sodium acetate (Scheme 11) [31].

Condensation of 3-formylchromone (1a) with 4,5,5-trimethyl-2,5-dihydrofuran-2-ones 25 and 4,6,6-trimethyl-5,6-dihydropyran-2-ones 26 in acetic anhydride yielded the condensation products 27 and 28, respectively (Scheme 12) [29].

3-Formylchromones 1h-c reacted with 2-methylbenzimidazole 29a and 2-methylbenzothiazole 29b in dry DMSO and boric acid to give the addition products 30a,b when the reaction took place at 60 °C, but when the reaction took place at 120 °C afforded the condensation products 31a,b (Scheme 13) [32].

Condensation of aldehydes 1a,b with 2-methylbenzothiazolium halides 32 in boiling acetonitrile gave chromenylbenzothiazolium derivatives 33 (Scheme 14) [33].

Treatment of 3-formylchromone 1a with 3-aryl-2-methyl-4(3H)-quinazolinones (34) in glacial acetic acid containing fused sodium acetate led to the condensed product 35 (Scheme 15) [33].

As a result of the above reactions, a variety of chromone derivatives bearing various heterocyclic systems were obtained from the condensation of 3-formylchromones with some active methyl compounds either under acidic or basic conditions.

2.1.2. Condensation reactions with acyclic active methylene compounds

3-Styrylchromone 37, which is associated with important biological activities, was obtained by the condensation of 4-nitrotoluene or 4-nitrophenyacetic acid 36 with 3-formylchromone 1a in dry pyridine (Scheme 16) [34,35].

Synthesis of trans-β-(chromon-3-yl)acrylic acids 38 were made by simple Knoevenagel condensation of 3-formyl-
chromones 1a b k with malonic acid in dry pyridine under reflux (Scheme 17) [17,36-38].

\[
\begin{align*}
\text{Scheme 17} \\
\end{align*}
\]

6,8-Dimethylcoumarin-4-acetic acid (39) gave 3-styrylchromones 40 when reacted with 3-formylchromones 1a b in boiling pyridine, via condensation followed by decarboxylation under the reaction conditions (Scheme 18) [39].

\[
\begin{align*}
\text{Scheme 18} \\
\end{align*}
\]

In the same manner, 3-formylchromones 1a c reacted with benzo[d]isoxazol-3-yiacetic acid (41) in dry pyridine under reflux to give 3-[2-benzo[d]isoxazol-3-ylnyl]-chromon-4-ones 42 in 51-62% yields (Scheme 19) [40].

\[
\begin{align*}
\text{Scheme 19} \\
\end{align*}
\]

Heating equimolar quantities of 3-formylchromones 1a b and phenylacetic acids 43 in acetic anhydride containing catalytic amounts of sodium acetate or potassium carbonate gave methyl 2-oxo-2H,5H-pyran[3,2-c]chromen-5-yl acetates 44 in 48-85% yields (Scheme 20). Shingare et al. [44] reported the formation of compounds 45 in 47-66% yields in acetic anhydride containing piperidine as a catalyst, the spectral data showed the presence of acetyl instead of the carboxy group, which could be explained by decarboxylation followed by acetylation in situ (Scheme 20).

\[
\begin{align*}
\text{Scheme 20} \\
\end{align*}
\]

Condensation of 3-formylchromones 1a c g with 3- or 4-coumarinylacetic acids in acetic anhydride in the presence of potassium acetate either by heating at 90-100 °C or by microwave irradiation produced compounds 46 and 47, respectively (Scheme 21) [41].

\[
\begin{align*}
\text{Scheme 21} \\
\end{align*}
\]

Reactions of 3-formylchromones 1a c with 4-substituted phenylselenylacetic acids 48 in acetic anhydride containing potassium acetate yielded 3-(phenylselenyl)-2-oxo-2H,5H-pyran[3,2-c]chromen-5-yl acetates 49 and not the other expected products 50 (Scheme 22) [45].

\[
\begin{align*}
\text{Scheme 22} \\
\end{align*}
\]

Synthesis of trans-β-[4-oxo-4H-chromen-3-yl]acrylonitrile 51 was made by simple condensation of 3-formylchromones 1a b with cyanoacetic acid in dry pyridine under reflux (Scheme 23) [46,47].

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

Condensation of 3-formylchromones 1a b d with p-nitrobenzyl cyanide and 1-naphthyl-acetonitrile in the presence of Ac2O/AcOK or Ac2O/AcONa afforded the corresponding condensation products 52 and 53, respectively (Scheme 24) [48].

\[
\begin{align*}
\text{Scheme 24} \\
\end{align*}
\]
Similarly, condensation of 3-formylchromones 1a, with tetracyclo-p-nitrotoluene (54) in dry pyridine gave 3-[2-(4-nitrophenyl)-2-[(1H-tetrazol-5-yl)vinyl]-4H-chromen-4-one (55) [Scheme 25] [49].

3-Formylchromones 1a-c condensed with 1-{2,4-difluorophenyl-2-[[1,2,4]triazol-4-yl]ethane (56) in acetic anhydride containing anhydrous sodium acetate to afford 3-{3-[2,4-difluorophenyl]-3-oxo-2-[[1,2,4]triazol-4-yl]propenyl] chromon-4-ones (57) [Scheme 26] [50].

Knoevenagel condensation of 3-formyl-7-methoxy chromone 11 with ethyl 3-(6-methoxy-1,3-benzodioxol-5-yl) propanoate 58 gave ethyl ester 59 [Scheme 27] [51].

Condensation of 3-formylchromones 1a,b,d,j with phenacyl aryl sulfoxide 60, in glacial acetic acid and acetic anhydride in the presence of benzylamine as catalyst, yielded 1-arylyl-1-(arylthionyl)-2-[4-oxo-4H-chromen-3-yl]ethanes 61 [Scheme 28] [52].

When 3-formylchromone (1a) was treated with 5-nitro furl chlormethyl sulfone (62), in glacial acetic acid in the presence of ammonium acetate and piperidine, gave the condensation product 63 [Scheme 29] [52].

Condensation product 64 was synthesized by reaction of 3-formylchromones 1a,b,c,g and 2,4-pentanediene in acetic anhydride containing sodium acetate. While, acid catalyzed 1,4-addition of the enol form of 2,4-pentanediene to 3-formyl chromones 1a,b,c,g followed by ring opening and enolization afforded 5-benzoyl-2-hydroxyacetophenones 65 [Scheme 30] [53,54].

Treatment of 3-formylchromone (1a) with ethyl acetoacetate in acetic anhydride containing sodium acetate yielded 3-{4-oxo-4H-1-chromen-3-yl}-2-(1-oxoethyl)-2-propenoic acid ethyl ester (66) in 62% yield. However, when the reaction was carried out with a (1:2) excess of the reagent using piperidine in ethanol, 5-(2-hydroxybenzoyl)-2-methylbenzene-1,3-dicarboxylic acid diethyl ester (67) was isolated in 80% yield [Scheme 31] [54,55].

Knoevenagel condensation of 3-formylchromones 1a-c with malononitrile, cyanoacetic acid and cyanoacetamide were carried out in various solvents such as water, ethanol, methanol, DMF, DMSO and toluene [Scheme 32]. Among these solvents, water was found to be the best solvent for the reaction to produce ylideneenitrites 68 in excellent yields [56].

Reaction of aldehyde 1a-c with chloroacetone in basic medium gave a mixture of aryline 69 [22-32%] and o-hydroxyphenyl furl ketone 70 [Scheme 33] [57].
Condensation of 3-formylchromones 1a-c with diethyl malonate in acetic anhydride containing sodium acetate gave diethyl acrylate ester 71 in 74-80% yield (Scheme 34) [58].

\[
\text{R} = \text{H, Me, Cl} \\
\text{CHO} + \text{CO}_2\text{Et} + \text{AcO} \quad \overset{74-80\%}{\text{AcOEt,One}} \quad \text{71}
\]

**Scheme 34**

Treatment of 3-formylchromone (1a) with 3(4,5-dihydro-4′-oxo-1′-phenylpyrazolo[3,4-d]pyrimidin-5′-yl)-3-oxopropionic acid ethyl ester (72) in ethanol containing piperidine afforded 3-[(4-oxo-4H-chromen-3-yl)-2(4,5-dihydro-4-oxo-1-phenylpyrazolo[3,4-d]pyrimidine-5′-carbonyl)acrylic acid ethyl ester (73) (Scheme 35) [59].

\[
\text{CHO} + \text{CO}_2\text{Et} + \text{Ph} \quad \overset{74-80\%}{\text{AcOEt,HCl,MeCN}} \quad \text{73}
\]

**Scheme 35**

3-Formylchromone (1a) reacted with acetalides 74 in dry pyridine to afford a mixture of chromenopyridones 75 and pyridone derivatives 76 (Scheme 36) [60, 61].

\[
\text{CHO} + \text{CONH}_2 \quad \overset{74\%}{\text{Pyridine}} \quad \text{75, 76}
\]

**Scheme 36**

3-Formylchromone 1a condensed with allyl acetoacetate or its acid in the presence of ammonia to give the pyridine derivatives 77 (46-50%). While, aldehyde 1a condensed with acetoacetamide to produce the 2-pyridone derivative 78 (Scheme 37). The reaction involves ring opening of pyrone moiety at C2 [62-64].

\[
\text{CHO} + \text{MeCOCH}_2\text{CO}_2\text{R} \quad \overset{74\%}{\text{Ammonia, R=H, Me}} \quad \text{77, 78}
\]

**Scheme 37**

When 3-formylchromones 1a-c,g were allowed to react with equimolar amounts of tosylmethyl isocyanide (TOSMIC) in THF in the presence of mild base as 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) at room temperature, the 2-tosyl-5-[2-hydroxybenzoyl]pyroles 79 were isolated in good yields (Scheme 38) [65].

\[
\text{CHO} + \text{Me}_{2}\text{SCONH}_2 \quad \overset{74-80\%}{\text{DBU, THF}} \quad \text{79, 80}
\]

**Scheme 38**

Condensation of 3-formylchromones 1a-d with 1H-benzimidazole-2-acetonitrile (80) in ethanol at room temperature gave the benzotriazole derivative 81 in 96%. When the reaction was carried out with in boiling ethylene glycol, 4-cyano-2-(2-hydroxybenzoyl)pyrid[1,2-a]benzimidazoles 82 were obtained in 70-81% yields (Scheme 39) [66, 67].

\[
\text{CHO} + \text{Ph}_2\text{CN} \quad \overset{80-96\%}{\text{PhH,120°C}} \quad \text{81}
\]

**Scheme 39**

Refluxing 1a with pyrazolinyltriazinylacetonitrile (83) in ethanol containing few drops of piperidine gave the condensation product 84 in 95% yield, as antitumor agent (Scheme 40) [68].

\[
\text{CHO} + \text{Ph}_2\text{CN} \quad \overset{95\%}{\text{Piperidine}} \quad \text{84}
\]

**Scheme 40**

Condensation of 1a with imidazole derivative 85 in MeSOCl/DMF produced the imidazo[1,2-a]pyridine 86 in 75% yield (Scheme 41) [69].

\[
\text{CHO} + \text{Ph}_2\text{CN} \quad \overset{75\%}{\text{MeSOCl,DMF}} \quad \text{86}
\]

**Scheme 41**

Oxazolones 87 were readily obtained from the reaction of 3-formylchromones 1a,b and N-acetyl/benzoylglycine in acetic anhydride containing freshly fused sodium acetate (Scheme 42) [17, 70, 71].

\[
\text{CHO} + \text{CH}_2\text{CO}_2\text{NHCH}_2\text{CO}_2\text{R} \quad \overset{60-70\%}{\text{AcOEt,AcO}} \quad \text{87}
\]

**Scheme 42**

On the other hand, the isoxazolone derivatives 88 were obtained in good yields (81-89%) from the Knoevenagel condensation of 3-formylchromones 1a-d with 3-methyl (or
condensation products or a variety of products depending on the active methylene compounds produced. When the reaction carried out in molar ratio 2:1 (3-formylchromone: amines), the fused chromonopyrrolone and pyrazolone derivatives were obtained in 54-64% yields (Scheme 44) [73].

Cyclocondensation of 3-formylchromone 1a with glycine derivatives 92 in the presence of Me2SiCl (4 equivalents) afforded pyrrole derivatives 93 in moderate yield (Scheme 45) [73].

A high yield of the novel pyrrolo[2,1-a]isoquinoline derivative 94 was prepared from the reaction of 3-formyl chromone 1a with isoquinoline and phenyl bromide in aqueous medium containing DBU as a catalyst as reported by Naskar et al. (Scheme 46) [74].

Therefore, condensation of 3-formylchromones with acyclic active methylene compounds produced the corresponding condensation products or a variety of products depending on the reagent used and the reaction conditions.

2.1.3. Condensation reactions with cyclic active methylene compounds

Condensation of 3-formylchromones 1a-d.g with 1,3-indandione 95 in glacial acetic acid containing piperidine afforded the condensation products 96 in 61-92% yields (Scheme 47) [75].

Treatment of 3-formylchromone 1a with 3-oxo-2,3-dihydrobenzo[b]thiophene-1,1-dioxide 97a and oxindole (indolone) 97b in dry pyridine afforded the corresponding condensation products 98 (Scheme 48) [76].

Simple condensation of aldehyde 1a with indolone 99a.b in the presence of sodium bicarbonate under microwave irradiation yielded (1H)-3-[4-oxo-4H-chromen-3-yl]methylene] indol-2-one (100a) and 1-[2,6-dichlorophenyl]-3-[4-oxo-4H-chromen-3-yl]methylene] indol-2-one (100b), respectively (Scheme 49) [76,77].

Condensation reaction of 1a and pyrazolone derivatives 101a,b in 1:1 molar ratio, under classical method or microwave irradiation, afforded 1-aryl-3-methyl-4-[4-oxo-4H-chromen-3-yl]methylene]pyrazol-5(4H)-ones (102a,b). [77,78] while using 1:2 molar ratio afforded the new 1-(chromon-3-yl)-1,1-bis[4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl]methylene 103 (Scheme 50) [79].

Condensation of 3-formylchromone (1a) with 1-phenylpyrazolidine-3,5-dione (104) in glacial acetic acid containing freshly fused sodium acetate, gave 4-[4-oxo-4H-
4,5-dihydro-1-acetate gave 5{4-[(4-oxo-4-isoxazolinone containing sodium acetate afforded chromenylpyrazolinone pyrazol-3-ylquinoline derivative substituted 4-oxo-4 using boric acid as a catalyst yielded 2-(trifluoromethyl)-1H-pyrazol-5(4H)-ones 107 in 70% yield (Scheme 52) [81].

Condensation of 1a with pyrazolinone 108a and isoxazolino 108b in acetic acid containing fused sodium acetate gave 5{4-[(4-oxo-4H-chromen-3-yl)methylene-5-oxo-4,5-dihydro-1H-pyrazol-3-yl)]-1-phenyl[pyrazol[3,4-d] pyrimidin-4-one 109a and 5-{4-[(4-oxo-4H-chromen-3-yl)methylene-5-oxo-4,5-dihydroisoxazol-3-yl)]]-1-phenyl pyrazol[3,4-d]pyrimidin-4-one 109b, respectively (Scheme 53) [59].

Similarly, condensation of 3-formylchromone (1a) with pyrazol-3-ylquinoline derivative 110 in glacial acetic acid containing sodium acetate afforded chromenylpyrazolinone 111 (Scheme 54) [82].

Also, condensation of 1a-d,f,g with creatinine 112 in DMSO using boric acid as a catalyst yielded 2-imino-1-methyl-5-[(6-substituted 4-oxo-4H-chromen-3-yl)methylen]imidazolin-4-one (113). While, 2-acetamido-1-methyl-5-[(6-substituted 4-oxo-chromen-3-yl) methylen] 4,5-dihydropyrimidazol-4-one 114 was obtained when the reaction took place in acetic anhydride and potassium acetate (Scheme 55) [83].

3-Formylchromones 1a-d,f,g condensed with thiobenzonitrile 115 in acetic anhydride in the presence of potassium acetate under both irradiation and classical condition yielded 2-thioxo-5-{[(6-substituted 4-oxo-chromen-3-yl)methylidyne]imidazolidine-4-ones (116) (Scheme 56) [83].

Reaction of 3-formylchromone (1a) with [1,3]thiazolo[3,2-a]benzimidazol-3(2H)-one (123) in glacial acetic acid containing fused sodium acetate afforded the condensation product 124 in high yield (68-97%) [87]. Similarly, treating 1a with 2-methyl[1,3]thiazolo[1,2,4](triazol-5(6H)-one (125) in acetic anhydride/sodium acetate yielded the condensation product 126 in 68-91% yields (Scheme 60) [88].

Knoevenagel products 128 were obtained in low yields (15-43%) by heating 3-formylchromones 1a-c with 2H-1,4-benzothiazin-3(4H)-one (127) in acetic anhydride/potassium acetate medium for 6-10 h. Using microwave the yields were increased (33-62%) in short time (7-20 min) (Scheme 61) [87].
Reaction of 6-bromo-3-formylchromone 1d with 2-aryl-4-hydroxy-6H-1,3-thiazin-6-ones 129a,b in DMSO or pyridine gave 8-bromo-3,10-dioxo-N-(arylcyanobenzothioyl)-4a-4,4a-dihydro-3H,10H-pyran[4,3-b]-chromene-4-carboxamides 130a.b in 60-70% yields [Scheme 62] [89].

Also, condensation of 3-formylchromone 1a with dinedone (5,5-dimethylcyclohexane-1,3-dione) in acetic anhydride containing sodium acetate yielded the condensation products 131 in 54-64% [87]. When the reaction took place in aqueous ethanol containing pyridine or aqueous pyridine by molar ratio (1:2) afforded the adduct 132 which dehydrated to form xanthone 133 in 73% yield (Scheme 63) [60,76,90].

Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) undergoes Knoevenagel condensation with 3-formylchromone 1a-c.e producing the corresponding condensation product derivatives 134 in 90-95% yields [Scheme 64] [91-93].

Reaction of 3-formylchromones 1a.c with 4-chromanone 135 in ethanol containing triethylamine gave benzopyrano-2,3-dihydrobenzopyranones 136 in 67-80% yields [Scheme 65] [94].

Treatment of 3-formylchromone 1a] with barbituric acid 137a, thiobarbituric acids 137b and 1,3-dimethylbarbituric acid 138 gave 5-[(4-oxo-4H-chromen-3-yl)methylene] pyrimidine derivatives 139 and 140 respectively (Scheme 66) [76,77].

\( N \)-Methylpyrrole reacted with 3-formylchromones 1a.c.d.g under solvent-free conditions exclusively via 1,4-addition followed by recyclication to form 2-hydroxy-3-(1-methylpyrrol-2-yl)methylene]chroman-4-ones 141 in good yield (Scheme 67) [95].

A similar reaction of 6,8-dibromo-3-formylchromone 1r with indole proceeded exclusively via 1,4-addition followed by recyclication to form a mixture of \( E \)-isomer 142 (91%) and \( Z \)-isomer 142 (9%) (Scheme 68) [95].
Reaction of 3-formyl-6-nitrochrome (1g) with N-methylindole afforded a mixture of E-2-hydroxy-6-nitro-3-(1-methyindol-3-yl)methenechroman-4-one (143) and the bis-adduct 144 (Scheme 69) [95].

On the other hand, 3-formylchromones 1a-c,g,i reacted without solvent with excess indole, 1-methyl or 2-methylindoles (2 equivalents) to give (chromon-3-yl)-bis-(indol-3-yl)methanes 145 (Scheme 70) [95].

Also, 3-formylchromones 1a reacted with triacetic acid lactone and 4-hydroxycoumarin derivatives (2 equivalents), under conventional and solvent free methods, to give (chromon-3-yl)-bis-(hetaryl)methanes 146 and 147, respectively (Scheme 71) [79].

Under acidic conditions, p-cresol underwent 1,2-addition through C-2 atom to the aldehyde function of 3-formylchrome (1a) to produce intermediate 150 which, converted to 2,14-dimethyl-10aH,15aH-tribenzo[1,6,7]trioxaphenalene (151) (Scheme 74) [97].

Condensation of 3-formylchromones 1a,b with alkyl isocyanides in dry dichloromethane at room temperature afforded (1Z)-3-(alkylmino)-1-[(chromon-3-yl)methylene]-1,3-dihydro-9H-furo[3,4-b]chromen-9-ones 148 in good yields (77-90%) (Scheme 72) [96].

The reaction of 3-formylchrome 1a with 3,4-dihydroquinolin-2(1H)-ones gave 2-(2-hydroxy-benzoyl) pyrrolo[1,2-c]quinazolin-4(5H)-ones 149 in 52-58% yields, respectively (Scheme 73) [73].

Under acidic conditions, p-cresol underwent 1,2-addition through C-2 atom to the aldehyde function of 3-formylchrome (1a) to produce intermediate 150 which, converted to 2,14-dimethyl-10aH,15aH-tribenzo[1,6,7]trioxaphenalene (151) (Scheme 74) [97].

Treating carboxaldehyde 1a with β-ketoacid 152, [98] in glacial acetic acid containing freshly fused sodium acetate, yielded the Knoevenagel condensation products 153 which underwent dehydration by stirring in concentrated H2SO4 at room temperature to afford 3-chromonylmethylenepyran[3,2-c]quinoline derivatives 154. Moreover, compound 153 was obtained authentically from condensation reaction of pyrano[3,2-c]quinoline 155 with 1a (Scheme 75) [99].
Thus, a large number of chromone derivatives linked a variety of heterocyclic systems were prepared from the direct condensation of 3-formylchromones with heterocyclic compounds containing active methylene groups.

2.2. Chemical reactivity of 3-formylchromones towards nitrogen nucleophiles

2.2.1. Reactions with primary amines

A large group of 3-(aryl/heteroaryliminomethyl)chromone derivatives 156 were prepared from condensation reactions of 3-formylchromones 1a-d with a variety of aryl/heteroarylamines in non-polar solvents such as benzene, toluene or xylene under reflux, in the presence of p-toluenesulfonic acid as a catalyst (Scheme 76) [100-108].

On the other hand, reaction of 3-formylchromones 1a-c with equimolar ratio of aryl/heteroarylamines 157 in boiling ethanol gave 3-(aryl/heteroaryliminomethylene)-2-(ethoxy)chromones 158, but when the reaction took place with two moles of 157 in dry toluene, the 1,4-adducts 159 were obtained (Scheme 77) [105-115].

Reaction of 3-formylchromone 1a with various amines in the presence of Me3SiCl/DMF led to either 3-[2-hydroxybenzoyl]quinolines 160 or 7H-chromeno[3,2-c]quinolin-7-ones 161 (Scheme 78), depending on the structure of the starting amine. Substituents in the amine molecule that withdraw electrons favored the formation of 161; on the contrary, electron-rich amines gave only 160 [116,117].

Condensation of 3-formylchromone (1a) with aniline and 6-amino-1,4-benzodioxane in methanol gave 3-(anilinemethylene)-2-methoxychroman-4-one (162) and 3-(1,4-benzodioxane-6-aminomethylene)-2-methoxychroman-4-one (163), respectively (Scheme 79) [118].

Also, reaction of 6-substituted 3-formylchromone 1a-cj with aromatic amino carboxylic acid 164 in benzene or toluene yielded only 3-(arylaminomethylene)-2-hydroxychroman-4-ones 165 at room temperature or under reflux (Scheme 80) [113].

Treatment of 3-formylchromone 1a with ethyl 2-aminopropanoate yielded pyrrole derivative 166 in high yield (Scheme 81) [119].

Chromenopyridines 168 were prepared by treating 3-formylchromone 1a with enaminoitriles, enamino ketones or β-aminoesters 167 (Scheme 82) [63,64,76,120].
Interaction of 3-formylchromones 1a-c,g with ethyl glycinate in boiling toluene in the presence of p-toluenesulfonic acid gave a mixture of ethyl 4-(2-hydroxybenzoyl)-6-[4-oxochromen-3-yl]-pyridine-2-carboxylates 169 and ethyl 4-[2-hydroxybenzoyl]pyrrole-2-carboxylates 170 (Scheme 83) [62,65,76,121].

Also, the reaction of 3-formylchromone 1a with equimolar amount of aminopyrazoles 171 in absolute ethanol afforded 6-[2-hydroxybenzoyl]pyrazolo[1,5-d]pyrimidines 172, via iminomethyl derivative (Scheme 84) [122].

Treatment of 3-formylchromones 1a,b,e with 5-amino pyrazoles 173 in boiling ethanol containing p-toluenesulfonic acid gave 2-hydroxybenzoylpyrazolo[3,4-b]pyridines 174. While, when this reaction was carried out at lower temperature (-10 °C), the enamine-adducts 175 were isolated. Enamine-adducts rearrange into pyrazolo[3,4-b]pyridines 174 after prolonged refluxing (Scheme 85) [123].

Reaction of 3-formylchromone 1a with ethyl 2-aminopyrimidine carboxylates 176 in ethanol gave ethyl 7-[2-hydroxybenzoyl]-2-H-[4]pyrimido[1,2-a]pyrimidine-3-carboxylate 177 (Scheme 86) [124].

On the other hand, aminopyrimidines 178 reacted with aldehyde 1a in refluxing ethanol to afford the unexpected pyrido[2,3-d]pyrimidines 179 but not the predicted pyridopyrimidines 180 (Scheme 87) [125].

Acetic acid catalyzed condensation of aldehyde 1a with 1-(2-amino phenyl)pyrrole 181 led to the pyrrolo[1,2-a] quinoxaline derivative 182 (Scheme 88) [126].

2-[4H-4-Chromen-3-yl]-3-aryl-1,2-dihydropyridazine-4(3H)-ones 184 are the final products from the reaction of carboxaldehyde 1a and amino amides 183 in both ethanolic and nonpolar medium (Scheme 89) [127].
Reaction of 3-formylchromone 1a with enamine derivatives 185-189 in pyridine or glacial acetic acid led to fused pyridine derivatives 190-194 in one step, respectively (46-82% yields) (Scheme 90) [76].

Reaction of 3-formylchromone 1a with 4-amino-3-mercapto-5-phenyl-1,2,4-triazole (195) under phase transfer condition yielded ring-opened thiadiazepine 196 (Scheme 91) [128].

Condensation of 1a-c with 4-phenyl-1H-imidazole-1-aminines 197 in the presence of Me3SiCl/DMF gave imidazo[1,5-b]pyridazines 198 in 81-96% yields (Scheme 92) [129].

Diaminomethane reacted with 3-formylchromone 1a to yield pyrimidine derivative 199. The reaction initially takes place on the formyl group and is followed by an intramolecular attack of the second amine function on the C-2 atom of the pyrone ring followed by the ring opening (Scheme 93) [130].

Condensation of equimolar amounts of 1a-c with ethylenediamine in benzene gave the 1,2-bis(chromon-3-yl)methyleneaminoethane 200, using excess of ethylenediamine afforded poor yield of 1:1 condensation product (Scheme 94) [130].

Reaction of aldehyde 1a with o-phenylenediamine in boiling ethanol gave 7,16-bis(2-hydroxybenzoyl)-5,14-dihydrodibenzo[6,7][1,4,8,11]tetraazacyclotetradecine (201), which then oxidized to 3-(2-benzimidazolyl)chromone 202, while in boiling benzene, benzodiazepinochromone 204 was obtained during dehydrogenation of the initially formed dihydro analogous 203, through air oxidation or boiling in nitrobenzene (Scheme 95) [130-141].

On the other hand, cyclocondensation of 6-chloro-3-formylchromone (1c) with diaminopyridine derivative 205 in DMF under reflux containing few drops of piperidine afforded the 1,2,3,5-tetrahydro[1,2,4]triazolo[1,5-c]pyridine derivative 206 (Scheme 96) [142].

Condensation reaction of 6-chloro-3-formylchromone (1c) with p-phenylenediamine in dry benzene containing p-toluenesulfonic acid in 1:1 and 2:1 molar ratio gave 3-[[4-aminophenyldimino]methyl]-6-chloro-4-oxo-4H-chromene (207) and the bis compound 208, respectively (Scheme 97) [143].

On the other hand, condensation reaction of 3-formylchromone (1a) with 2-aminophenol and 2-aminothiophenol in ethanol afforded compound 209 via the formation of the simple condensation product followed by 1,4-addition of ethanol molecules (Scheme 98) [132].

Consequently, the products obtained from the reaction of 3-formylchromones with primary amines depend mainly on the type of amine, molar ratio and the solvent used. Also, a diverse number of heterocyclic systems were obtained from the condensation of 3-formylchromones with bifunctional nucleophiles.
2.2.2. Reactions with secondary amines

When 3-formylchromone 1a treated with secondary amine like piperidine, an unstable 1,4-adduct 210 is formed, this adduct undergoes base catalyst deformylation to give the enamino ketone 211 in 55% yield [151]. Further, 3-formylchromones 1a when heated with N-methylpiperazine in ethanol furnished 1-(2-hydroxyphenyl)-3-(4-methylpiperazin-1-yl)propenone (212) [41]. Similarly, 1-(2-hydroxyaryl)-3-(pyrrolidin-1-yl)prop-2-en-1-one (213) was synthesized by the reaction of 3-formylchromones 1a with pyrrolidine in dry ethanol (Scheme 99) [145,146].

Treatment of 3-formylchromone (1a) with N-methylglycine in boiling toluene in the presence of p-toluenesulfonic acid
produces N-methyl-3-salicyloyl pyrrole 214 in high yield (Scheme 100) [119].

Condensation of 3-formylchromone 1a with N,N-dimethyl glycaminide (215) and L-pyrrolinamide 216 afforded chromonylimidazolinone 217 (79% yield) and pyrroloimidazolinone 218 (84% yield), respectively, these reactions proceed via [4+1] recyliclization (Scheme 101) [73,147].

As a result, a variety of products were obtained from the reaction of 3-formylchromones with secondary amines depending on the nucleophile used.

2.2.3. Reactions with tertiary amines

The acid-catalyzed condensation of 3-formylchromone (1a) with a range of tertiary aromatic amines gave the 3-[bis(4-aminophenyl)methyl]chromones 219 in moderate yield (Scheme 102) [148].

2.2.4. Reactions with hydrazines

The reaction of 3-formylchromones 1a-d with hydrazines gave initially hydrazones 220 which then reacted further at the C-2 position to give 4-(2-hydroxybenzoyl)pyrazoles 212 (Scheme 103) [149-151].

Treatment of 3-formylchromone 1a with substituted hydrazines 222a-c in absolute ethanol or toluene afforded the corresponding hydrazones 223a-c (Scheme 104) [152,153].

2.2.5. Reactions with hydroxylamine

The reaction of 3-formylchromone (1a) with hydroxylamine hydrochloride (1:2 molar ratio) afforded a mixture of pyrazole 224 and chromone 225 (Scheme 105) [154,155].

Treatment of 3-formylchromones (1a-d) with hydroxylamine hydrochloride in ethanol gave the corresponding oximes 226 which on dehydration by acetic anhydride gave chromone-3-carbonitriles 227. When the reaction of 1a-d with hydroxylamine hydrochloride took place in the presence of sodium formate containing HCl, the carbonitriles 227 were obtained directly. On the other hand, Oximation of 1a and its oxime 225 using hydroxylamine in sodium hydroxide led to 2-aminochromone-3-carboxamide (228) and 3-amino-4H-chromeno[3,4-d] isoxazol-4-one (229), respectively (Scheme 106) [156-158].

Nitrones 230 were prepared from the reaction of aldehydes 1a-c with hydroxylamine in ethanol. Nitrones 230 rearranged to 2-amino-3-formylchromones 231 in ethanol containing few drops of acetic acid in the presence of zinc (Scheme 107) [159,160].

Hence, hydroxylamine on reactions with 3-formylchromones gave diverse types of products depending on the reaction conditions.
2.2.6. Reactions with amidines

Reaction of 3-formylchromone 1a with formamidine gave a mixture of 5-(2-hydroxybenzoyl) pyrimidine 232 (R=H, 13%) and 5-hydroxy-5-H-chromeno[3,4-d]pyrimidine 233 (R=H, 31%) as reported by Loewe [161]. While, reaction of 1a with several C-substituted formamidines (R=alkyl, aryl, heteroaryl, NH2, NHCN, SH, SMe, OH, OMe, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholino) gave only chromeno-pyrimidines 233 in 26-90% yields [Scheme108] [161-166].

Thus, 3-formylchromones are a good precursors for the synthesis of pyrimidine derivatives via treatment with amide derivatives as 1,3-bifunctional nucleophiles.

2.2.7. Reactions with hyrazides

3-Formylchromones 1a-d reacted with semicarbazide and thiosemicarbazide in ethanol to give the corresponding semicarbazones 234a (X=O) and thiosemicarbazone 234b (X=S), respectively [Scheme109] [150,167,168].

The reaction of 3-formylchromone 1a-d with arylhydrazines gave the corresponding arylhydrazone 235 [Scheme110] [169-172].

3-Formylchromone 1c condensed with equimolar amount of hydrazine carbodithioic acid and thiocarbohydrazide in ethanol to give the corresponding hydrazone 236 and 237, respectively. Also, condensation of 1c with two equivalents of thiocarbohydrazide gave thiocarbohydrazide derivative 238 [Scheme111] [173].

Phosphorohydrazone of chromone 239 was obtained from stirring 3-formylchromone 1a with diethoxyphosphorylhydrazide in ethanol [Scheme112] [159].

3. Conclusion

In the present work, the chemical reactivity of 3-formylchromones was evaluated and summarized towards all types of carbon and nitrogen nucleophiles under different reaction conditions. 3-Formylchromones are very active toward the nucleophilic reagents, due to the availability of three electron deficient sites, the aldehydes carbon, C-2 carbon, and the C-4 carbon of the carbonyl group. A variety of fused heterocyclic systems were prepared directly from the reaction of 3-formylchromones with some bifunctional nucleophiles, these reactions mainly proceed via condensation with the aldehydic function followed by nucleophilic attack at C-2 position of the chromone moiety.

References