3-Acyl(aroyl)coumarins as synthon in heterocyclic synthesis

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Abstract: This review presents a systematic and comprehensive survey of the chemical reactivity of 3-acyl(aroyl) coumarins. The target compounds are important intermediates for the synthesis of a variety of synthetically useful and novel heterocyclic systems with different ring sizes such as isoxazole, pyrazole, 3H-triazolium salts, pyrimidine, pyridine, quinolone, benzoxocin, benzoxonin and benzoxepin.

Keywords: Coumarins; pyrazoles; thiazole; pyridine; heterocyclic; reduction. ©2019 ACG Publication. All right reserved.

1. Introduction

Coumarins (II) are the simple compounds (I-V) belonging to a large class of molecules known as benzopyrones.1 Furthermore, coumarins and their derivatives form an elite class of compounds, occupying an important place in the realm of natural products and synthetic organic chemistry.1

They are widely used as additives in food, perfumes, cosmetics,2 pharmaceuticals, optical brighteners3 (e.g. 7-diethylamino-4-methylcoumarin),4 dispersed fluorescent laser dyes,5 antithrombotic and anticoagulants6 (e.g. acenocoumarol),4 and in treatment of bronchial asthma (e.g. intal)4 and cancer.7 Also, coumarin derivatives are novel lipid-lowering agents, possessing moderate triglyceride lowering activity.8 Many coumarin derivatives can scavenge reactive oxygen species such as hydroxyl free radicals, superoxide radicals or hypochlorous acid to prevent free radical injury.9 While certain coumarin derivatives function as human immunodeficiency virus integrase inhibitors and are used in treatment of
HIV infection, the others are used as anti-invasive compounds against some serine proteases and matrix metalloproteases (MMPs). Moreover, 6-nitro-7-hydroxycoumarin acts as a selective anti-proliferative agent. Two naturally occurring coumarins have been isolated and shown to inhibit the polymerization of tubulin and arrest cells in mitotic phase by inhibiting microtubule formation. These coumarins act synergistically in inhibiting KB (human epidermoid carcinoma) cell proliferation.

![Figure 1. Skeleton of benzopyrones I-V](image1)

Coumarin derivatives usually occur as secondary metabolites in seeds, roots and leaves of many plant species via shikimate pathway. Their function includes waste products, plant growth regulators, fungstats and bacteriostats. Anthocyanins and flavones, grouped together, are known as flavonoids, and make up many flower pigments. Also, flavone and coumarin derivatives have marked toxic and other physiological properties in animals, though they have no part in normal metabolism of animals. The isomeric 2-benzopyrylium system is not naturally occurring; only a few isocoumarin derivatives occurs as natural products and, therefore, much less work on these has been described.

Our review deals with the effective use of 3-acyl(aroyl)coumarin derivatives in the synthesis of different polyfunctional heterocyclic compounds.

2. Reactivity

3-Acyl(aroyl)coumarins are difunctional compounds possessing electrophilic and nucleophilic properties. Typical nucleophilic position is C10. Furthermore, C9 of C=O and C4 could act as an electrophile. These chemical properties have been used to design different heterocyclic moieties with different ring sizes such as oxazole, pyrazole, thiophene, thiazole, pyridine, diazepine, benzoxocin, benzoxonin, benzoxepin and pyrimidine (Figure 2).

![Figure 2. Reactivity of 3-acyl(aroyl)coumarins.](image2)
2.1. Bromination

Halogenation of 1 with bromine in chloroform afforded 3-bromoacetyl coumarin derivatives 2 (Scheme 1).\textsuperscript{22,23}

\[
\text{R} \quad \text{O} \quad \text{CH}_3 \\
\begin{array}{c}
\text{O} \\
\text{Br}
\end{array} \\
\text{R} \quad \text{O} \\
\text{CH}_3
\]

\[
\begin{array}{c}
\text{R} \quad \text{O} \\
\text{Br}
\end{array} \\
\text{R} \quad \text{O} \\
\text{CH}_3
\]

\textbf{Scheme 1.} Synthesis of 3-bromoacetylcoumarin derivatives 2

Separately, La Pietra et al. prepared 3-bromoacetylcoumarin derivatives 2 via treating compound 1 with CuBr\textsubscript{2} in CHCl\textsubscript{3}/CH\textsubscript{3}COOEt mixture. The reaction of 3-bromoacetylcoumarin derivatives 2 with the appropriate arylamine 3 (aniline, 3-aminobenzoic acid, ethyl 3-aminobenzoate) in ethanol in the presence of NaHCO\textsubscript{3} yielded compounds 4. Derivatives 5a-h were then obtained by treatment of compounds 4 with a large excess of ammonium thiocyanate in acetic acid (Scheme 2).\textsuperscript{24,25}

\[
\begin{array}{c}
\text{R}_2 \quad \text{O} \\
\text{CH}_3
\end{array} \\
\text{R}_1=\text{R}_2=\text{H}; \text{R}_1=\text{OH}, \text{R}_2=\text{H}; \\
\text{R}_1=\text{OCH}_3, \text{R}_2=\text{H}; \text{R}_1=\text{H}, \text{R}_2=\text{Cl}; \\
\text{R}_1=\text{H}, \text{R}_2=\text{OCH}_3; \text{R}_1=\text{OCH}_3, \text{R}_2=\text{Cl}; \\
\text{R}_1=\text{OCH}_3, \text{R}_2=\text{CH}_2\text{CH}==\text{CH}_2
\]

\[
\begin{array}{c}
\text{R}_2 \quad \text{O} \\
\text{Br}
\end{array} \\
\text{R}_1=\text{R}_2=\text{H}; \text{R}_1=\text{OH}, \text{R}_2=\text{H}; \text{R}_1=\text{OCH}_3, \text{R}_2=\text{H}; \\
\text{R}_1=\text{H}, \text{R}_2=\text{Cl}; \text{R}_1=\text{H}, \text{R}_2=\text{OCH}_3; \text{R}_1=\text{OCH}_3, \text{R}_2=\text{Cl}; \\
\text{R}_1=\text{OCH}_3, \text{R}_2=\text{CH}_2\text{CH}==\text{CH}_2
\]

\[
\text{H}_2\text{N} \quad \text{X} \\
\text{NaHCO}_3 \quad \text{EtOH}
\]

\[
\begin{array}{c}
\text{R}_2 \quad \text{O} \\
\text{NH}_2\text{SCN}
\end{array} \\
\text{R}_1=\text{H}, \text{R}_2=\text{H}, \text{X}=\text{H}
\]

\[
\begin{array}{c}
\text{R}_2 \quad \text{O} \\
\text{NH}_2\text{SCN}
\end{array} \\
\text{R}_1=\text{H}, \text{R}_2=\text{H}, \text{X}=\text{COOH}
\]

\[
\begin{array}{c}
\text{R}_2 \quad \text{O} \\
\text{NH}_2\text{SCN}
\end{array} \\
\text{R}_1=\text{H}, \text{R}_2=\text{Cl}, \text{X}=\text{COOH}
\]

\[
\begin{array}{c}
\text{R}_2 \quad \text{O} \\
\text{NH}_2\text{SCN}
\end{array} \\
\text{R}_1=\text{OCH}_3, \text{R}_2=\text{Cl}, \text{X}=\text{COOH}
\]

\[
\begin{array}{c}
\text{R}_2 \quad \text{O} \\
\text{NH}_2\text{SCN}
\end{array} \\
\text{R}_1=\text{OCH}_3, \text{R}_2=\text{CH}_2\text{CH}=\text{CH}_2, \text{X}=\text{COOH}
\]

\textbf{Scheme 2.} Synthesis of imidazoline derivatives 5
Kurt, B. Z. et al.,\textsuperscript{26} carried out the reaction of 3-(bromoacetyl)-2H-chromen-2-one 2 in the presence of ethanol with thiourea 6, which yielded 3-(2-aminoo-1,3-thiazol-4-yl)-2H-chromen-2-one 7. This was reacted with sodium cyanate 8 in the presence of glacial acetic acid to produce N-[4-(2-oxo-2H-chromen-3-yl)-1,3-thiazol-2-yl]urea 9. Treatment of compound 9 with hydrazine hydrate 10 produced N-[4-(2-oxo-2H-chromen-3-yl)-1,3-thiazol-2-yl]hydrazinecarboxamide 11, which was condensed with different aromatic/heteroaromatic aldehydes and ketones 12 to form (1E)-1-arylalkane-1-one-N-[4-(2-oxo-2H-chromen-2-yl)-1,3-thiazol-2-yl]semicarbazones 13a-w (Scheme 3).\textsuperscript{26}

\textbf{Scheme 3.} Synthesis of (1E)-1-arylalkane-1-one-N-[4-(2-oxo-2H-chromen-2-yl)-1,3-thiazol-2-yl]semicarbazones 13a-w.

A series of coumarylthiazole derivatives containing arylurea/thiourea groups 17 and 18, respectively, were obtained by the reactions of 2 with thiourea 6, which was followed by treatment of the formed aminothiazole 7 with arylisocyanates 14 in THF and arylisothiocyanates 15 in DMF, respectively (Scheme 4).\textsuperscript{27}
Razi, et. al. prepared several thiazolylamine derivatives 19 by treating of compound 7 with the corresponding 2-hydroxy-3-methoxybenzaldehyde 18 in a basic ethanol solution. The Pd(II) and Pt(II) complexes 20 were synthesized by complexation of thiazolylamine derivatives 19 with Pd(II) and Pt(II), respectively (Scheme 5).28

Scheme 4. Synthesis of new urea/thiourea substituted coumarylthiazole derivatives

Scheme 5. Synthesis of Pd(II) and Pt(II) complexes 20
Sahu, S. K. et al prepared a series from thiourea derivatives 6a-d via the reaction of aniline derivatives 21 with ammonium thiocynate 22 under acidic condition. They were further reacted with compound 2 to obtain the aminothiazolyacoumarins 7a-e. Reacting the derivatives 7a with salicylaldehyde gave the probe 24, which showed good optical behavior in acetonitrile and, upon interaction with different metal ions and anions, displayed strong fluorescence quenching (∼87%; switch-off) with Cu²⁺. Moreover, 24-Cu²⁺(25), when tested toward different anions, only fluoride (F⁻) gave copper displacement (as CuF₂) and demonstrated a fluorescence enhancement (switched-on) (Scheme 6).²⁹

Diazotization of aminothiazole 7 gave the 2-chloro derivative 26, which was undergone alkaline hydrolysis in the presence of dimethyl sulfate to give the corresponding (E)-2-(2-chlorothiazol-5-yl)-3-(2-methoxyphenyl)acrylic acid 27. Also, aminothiazole 7 was reacted with phenylisothiocyanate¹⁵ to afford the unsymmetrical thiourea 1-(5-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)-3-phenylthiourea 17, which was cyclized with chloroacetic acid to give (Z)-2-(5-(2-oxo-2H-chromen-3-yl)thiazol-2-ylimino)3-phenyl thiazolidin-4-one 28. The reaction of 28 with different aromatic aldehydes gave the corresponding arylidene derivatives 29.³⁰ Furthermore, aminothiazole 7 was obtained via condensation of 3-acetylcoumarin 1 with formamidine disulfide dihydrobromide 30 (Scheme 7).³¹
Scheme 7. Synthesis of arylidene derivatives 29

Cyclocondensation of 3-bromoacetylcoumarin 2 with R₃NHC (SH): NN: CHR 31 in CHCl₃-EtOH gave the thiazolone derivatives 32 in 64-100% yield.32 Furthermore, the reaction of 3-(α-bromoacetyl)coumarins 2 (R₁=H or Br) with potassium salts of dithiocarbamic acids 33 in ethanol afforded 3-[(N,N-disubstitutedthiocarbamoilthio)acetyl]coumarin derivatives 34a-n (Scheme 8).33
Scheme 8. Synthesis of 3-[(N,N-disubstitutedthiocarbamoilthio)acetyl]coumarin derivatives 34a-n

3-Bromoacetylcoumarin 2 was reacted with 2-mercaptobenimidazole to give the corresponding 3-(2-1H-benzo[d]imidazol-2-ylthio)acetyl)-2H-chromen-2-one 35, which was subjected to cyclization in polyphosphoric acid to give 3-(benzo[d]thiazolo[3,2-a]imidazol-2-yl)-2H-chromen-2-one 36 (Scheme 9).

Moreover, 3-bromoacetylcoumarin 2 was condensed with 2-aminothiazole 37a, 2-amino-4-phenylthiazole 37b, 2-aminobenzothiazole, 2-amino-1,3,4-thiadiazole 38a, 3-amino-4H-1,2,4-triazole 38b and 2-amino-1,3,4-oxadiazole 38c in DMF to give the corresponding 2H-chromen-2-ones 39-41, respectively. On the other hand, the reaction of 3-bromoacetylcoumarin 2 with 3-substituted-5-mercapto-5-triazole 42a,b gave 3-(2-phenylthiazolo[3,2-b](1,2,4)triazol-5-yl)-2H-chromen-2-one 43a,b (Scheme 9).
Rajeswar Rao, V. et al. prepared a new series from 3-(2-alkylthiazolo[3,2-b][1,2,4]triazol-5-yl)-2H-chromen-2-one 46 by treating 3-bromoacetylcoumarin 2 (R= H, OCH₃, Br, R₂= H, Br, Cl, CH₃) with 3-alkyl-mercaptoptriazole 44 in polyphosphoric acid. Also, the reaction of 2 (R= H, OCH₃, Br, R₂= H, Br, Cl, CH₃) with acetyl/propanoylthiosemicarbazide 48 gave 2-acetyl or propanoylhydrazinethiazolylcoumarins 49, which, on treatment with phosphoryl trichloride, afforded 43 (Scheme 10).
Scheme 10. Synthesis of 2-acetyl or propanoyl hydrazinethiazolylcoumarins 49

Cyclocondensation of 3-bromoacetylcoumarin 2 with 2-amino-5-methyl-1,3,4-thiadiazole gave 3-(2-methylimidazo[2,1-b](1,3,4) thiadiazol-6-yl)-2H-chromen-2-one 50, while its reaction with 1-amino-2-mercapto-5-methyl-1,3,4-triazole produced 3-(3-methyl-3,7-dihydro-2H-[1,2,4] triazolo[3,4-b][1,3,4]thiadiazin-6-yl)-2H-chromen-2-one 51 (Scheme 11). Moreover, bromoacetylcoumarin 2 was reacted with phenylthiosemicarbazide 52 in the presence of pyridine to give 3-(2-phenylamino)-6H-1,3,4-thiadiazin-5-yl)-2H-chromen-2-one 53 (Scheme 11). The exocyclic N in compound 53 was acetylated by acetic anhydride to obtain the corresponding N-(5-(2-oxo-2H-chromen-3-yl)-6H-1,3,4-thiadiazin-2-yl)-N-phenylacetamide 54. Furthermore, one-pot condensation of bromoacetylcoumarin 2, pyridine, dimedone 55, aromatic aldehydes 56 and triethylamine afforded the benzofuran derivatives 57 (Scheme 11).
Scheme 11. Synthesis of imidazole 50, 1,3,4-thiadiazine 51, 54 and benzofurans 57

Multiple component reactions of 3-acetylcoumarin derivatives 1 with bromine in the presence of Ln(III) catalyst and o-aminothiophenol 58 gave 3-(2H-1,4-benothiazin-3-yl)-2H-1-benzopyran-2-ones 60 (Scheme 12).
Sinnur, K. H. et al., developed a short and efficient synthesis for dichloroacetamidomethyl-3-coumarinylketone. 3-Bromoacetylcoumarin 2 was reacted with hexamethylenetetramine 61 in concentrated alcoholic hydrochloric acid to produce the corresponding aminomethyl-3-coumarinyl ketone hydrochloride 62. Treatment of 62 with dichloroacetyl chloride 63 gave the corresponding dichloroacetamidomethyl-3-coumarinyl ketone 64 (Scheme 13). 30

3-Bromoacetyl coumarin 2, following Bischler's procedure, was reacted with primary aromatic amines, i.e. aniline 65 in ethanol for 15-45 minutes to yield 3-(2-(phenylamino)acetyl)-2H-chromen-2-one 66 40, which was condensed with the respective primary aromatic amine in the presence of catalytic amounts of the amine hydrobromide to give 3-(1H-indol-3-yl)-2H-chromen-2-one 67 (Scheme 13). 30 On the other hand, refluxing 2 with primary aromatic amines 68 for 5-8 hours gave the corresponding imino derivatives 69 (scheme 13). In a separate study, 3-bromoacetyl coumarin 2 was treated with pyridine to give the quaternary salt 70, which, upon condensation with chalcone 71 in the presence of acetic acid and ammonium acetate, gave the corresponding 3-(4,6-diphenylpyridin-2-yl)-2H-chromen-2-one 72 (Scheme 13). 41

Scheme 13. Reaction of 3-bromoacetyl coumarin 2 with amines

3-Bromoacetyl coumarin 2 was reacted with triphenylphosphine 73 in benzene to give (2-oxo-2-(oxo-2H-chromen-3-yl)ethyl)triphenylphosphonium 74 in 97.3%, which was treated with aq. K₂CO₃ in ethanol to obtain 75. When it was reacted with various aromatic aldehydes 76 in toluene yielded only the trans isomer 77. Moreover, 2 was transformed to 2-oxophosphonates 79 via Arbuzov reaction conditions (Scheme 14). 42-44 Also, 3-bromoacetyl coumarin transformation into the epoxypophonate derivatives 81 proceeded via Michaelis-Becker reaction conditions (Scheme 14). 45-47 Furthermore, 3-bromoacetyl coumarin was reacted with trialkylphosphites 82 in acetic acid to give enolphosphate 83 (Scheme 14).
Enolphosphate 83 was reacted withtrialkylphosphites 82 in refluxing toluene in the presence of p-toluenesulfonic acid (TsOH) to give the 1,4-adducts 84/85. Separately, 83 was obtained in 40-80% yield through the reaction of 3-acetylcoumarin 1 with dialkyl- and trialkylphosphites upon refluxing for 8-10 h. (Scheme 15).\textsuperscript{48-51} Also, when enol phosphate 83 was reacted withtrialkylphosphites 82 in the presence of p-toluenesulfonic acid and NBS, it gave the corresponding 86/87 (Scheme 15).\textsuperscript{52}
Scheme 15. Reaction of enolphosphate 83 with trialkyl phosphites 82

The reaction of 2 with P(OR)₃ in refluxing toluene in the presence of p-toluene sulfonic acid was completely different to that of acetic acid, giving new 1,4-addition products 90 along with the expected enol phosphates 83. Furthermore, when 3-bromoacetylcoumarin 2 was reacted with dialkylphosphites in refluxing toluene, a complicated reaction mixture was obtained, i.e. 3-acetylcoumarin 1 (2-5%), enol phosphates 83 (~ 20%) and 84, which are the products of 1,4-additions of dialkylphosphites to 3-acetylcoumarin 1. Compound 90 formed via the following mechanism (Scheme 16).

Scheme 16. Synthesis of 4-dialkylphosphono-2-oxocoumarin derivatives 90
2.2. Reactions of trialkylphosphites

Reactions of trialkylphosphites 82 with 3-acetylcoumarin 1 as well as with 3-benzoylcoumarin 91 and 3-ethoxycarbonylcoumarin 92, in the presence of p-toluenesulfonic acid under ultrasound irradiation gave the corresponding 4-dialkylphosphono-2-oxocoumarin derivatives 84/85, 93/94 and 95, respectively, in 60 to 95% yields (Scheme 17).\(^{53}\)

![Scheme 17. Synthesis of 4-dialkylphosphono-2-oxocoumarin derivatives 84, 85, 93, 94 and 95](image1)

2.3. Chlorosulfonation

3-Acetyl-8-methoxycoumarin 1 was subjected to chlorosulfonation reaction using excess chlorosulfonic acid 96 to give the corresponding 8-hydroxy-2-oxo-2H-chromen-3,5,7-trisulfonamide 97 (Scheme 18).\(^{54}\)

![Scheme 18. Synthesis of 8-hydroxy-2-oxo-2H-chromen-3,5,7-trisulfonamide 97](image2)

2.4. Reduction

3-Acetylcoumarin 1 was agitated with palladium-charcoal and hydrogen at 60 lbs./sq. at room temperature to give an excellent yield of 3-acetyl-3,4-dihydrocoumarin as a keto-enol mixture 98. The keto form was isolated giving a negative ferric reaction, while the enol form was obtained as a sole product via acetylation of the mixture 98 to give the acetate 99. Acetylation of 3-acetylcoumarin 1 with acetic acid and acetic anhydride produced the corresponding 3-acetylcoumarin derivative 100 (Scheme 19).\(^{55}\)

Liu et al. reported the selective reduction of endocyclic double bond of the 3-substituted coumarin derivatives 1 by using Hantzsch 1,4-dihydropyridine (HEH) 101 as a reducing agent, which yielded 3,4-dihydrocoumarin derivatives 102 (Scheme 19).\(^{56}\) Chemo-selective reduction of the endocyclic double bond in 3-substituted coumarin derivatives 1 took place by o-phenylenediamine and benzaldehyde to generate in situ 2-phenyl benzimidazolone.\(^{57}\) Reduction of 3-acetyl and 3-benzoyl coumarin derivatives 1
occurred with sodium borohydride in alcohol to give the corresponding ethyl-2-(2-hydroxy benzyl)-3-oxo(butanoate) and 3-phenyl propanoate 105 (Scheme 19).  

[Diagram showing chemical structures and reactions]

Scheme 19. Reduction of 3-acetylcoumarin derivatives 1

2.5. Photoreduction

Photo reduction of 3-acetyl coumarin 1 in i-propyl alcohol 106 gave the dihydro dimer 3,3′-diacetyl-4,4′-bichroman-2,2′-dione 107. Cyclobutanes 109 were formed by [2+2] cycloaddition of cyclohexene 108 with 3-acetyl coumarin 1 upon UV irradiation in benzene (Scheme 20).  

Furthermore, photo [2+2] cycloaddition of olefins 110 with 3-acetyl coumarin 1 gave 1-exo-substituted 1,2,2a,8b-tetrahydro-3H-benzo[b]cyclobuta[d]pyran-3-one derivatives 111. Endo-substituted 1,2,2a,8b-tetrahydro-3H-benzo[b]cyclobuta[d]pyran-3-one derivatives 114 were prepared by photo [2+2] cycloaddition of 3-acetyl coumarin 1 with acetylenes 112, which was followed by hydrogenation of the formed 2a,8b-dihydro-3H-benzo[b]cyclobuta[d]pyran-3-one derivatives 113 over Pd-C (Scheme 20).  

Treatment of 3-acetyl coumarin 1 with dimethylformamide in the presence of phosphorus oxychloride or HClO₄ yielded chloropropeninium salts 115 and aldehydes 116, respectively (Scheme 20).
Scheme 20. Photo and Vilsmier reaction of 3-acetylcoumarin derivatives 1

2.6. Mannich reaction

Mannich base 119 of 3-acetylcoumarin 1 was prepared via condensation of the corresponding acetylcoumarin 1 with paraformaldehyde 117 and dimethylamine 118 in the presence of conc. HCl (Scheme 21). The reaction of 119 with substituted phenacylpyridiniumbromide salts 120 in the presence of ammonium acetate in refluxing acetic acid gave the corresponding 3-(6-arylpyridin-2-yl) 121 in moderate to good yields (scheme 21).

Scheme 21. Mannich reaction of 3-acetylcoumarin derivatives 1
2.7. Reaction with hydrazine hydrate and its derivatives

It was reported that the reaction of hydrazine hydrate 10 with 3-acetylcoumarin 1 led to fission of the coumarin ring giving salicaldazine 122 (Scheme 22). On the other hand, refluxing of 3-acetylcoumarin 1 with phenylhydrazine 123a or (2,4,6-trichlorophenyl)hydrazine 123b in ethanol gave the corresponding hydrazones 124 and 125, respectively. Oxidation of 125 with tertbutylhypochlorite yielded chloroalkylazo 126. When 126 was treated with antimonypentachloride at 60 °C in dichloromethane, an orange precipitate 127 was formed. On addition of acetonitrile at room temperature 1H-triazolium salt 131 was afforded in 71% yield. The formation of 131 is assumed to take place via the formation of non-isolable acyclic intermediate 129, followed by cyclization to afford the non-isolable tiazole 130. This underwent Wagner-Meerwein type [1,2] shift of a methyl group to furnish the 1H-triazolium salts 131 (Scheme 22).

![Scheme 22. Reaction of 3-acetylcoumarin derivatives 1 with hydrazine derivatives](image)

Microwave irradiation of 3-hydrazinylquinoxalin-2(1H)-one 132 and 6-substituted acetylcoumarin 1 in dry DMF at 400 W for 1 min afforded the corresponding hydrazones 133. Furthermore, treatment of substituted acetylcoumarins 1 with phenylhydrazine 124a gave the hydrazone 134. Fischer indole synthesis of 134 in the presence of Eaton’s reagent produced substituted 3-(1H-Indol-2-yl)chromen-2-ones 136. Compounds 136 were allowed to undergo benzylation with beznyl...
chloride 137 and Vilsmeier–Haack formylation to yield substituted 3-(1-benzyl-1H-indol-2-yl)-2H-chromen-2-ones 138 and 2-(2-oxo-2H-chromen-3-yl)-1H-indole-3-carbaldehydes 139. Oxidation of 139 in the presence of potassium permanganate afforded 2-(2-oxo-2H-chromen-3-yl)-1H-indole-3-carboxylic acids 140 (Scheme 23).^{77}

**Scheme 23.** Synthesis of substituted indolecoumarin derivatives 138

Sixteen novel fluoro-substituted coumarin hydrazones were synthesized from a series of ethyl 2-hydroxy-2-(trifluoromethyl)-2H-chromene-3-carboxylates, using supported acid catalyst under microwave-assisted one-pot and solvent free conditions. The reaction was carried out in two steps under solid acid and microwave conditions. In step 1, fluoro-substituted coumarin esters 139 were transformed into fluoro-substituted coumarin ketones 140. Then, the ketones, 140, which were not isolated from the mixture, were directly reacted with arylhydrazine to give the hydrazones 142 (Scheme 24).^{78}
142a; R₁ = H, R₂ = H, 142b; R₁ = 6-Cl, R₂ = H, 142c; R₁ = 8-Dichloro, R₂ = H, 142d; R₁ = 6, 8-Dibromo, R₂ = H, 142e; R₁ = 8-CH₃, R₂ = OH, 142f; R₁ = 8-CH₃CH₂, R₂ = OH, 142g; R₁ = H, R₂ = 4-F, 142h; R₁ = H, R₂ = 4-Cl, 142i; R₁ = H, R₂ = 4-Br, 142j; R₁ = H, R₂ = 3-NO₂, 142k; R₁ = H, R₂ = 3, 5-Dichloro, 142l; R₁ = H, R₂ = 4-CH₃O, 142m; R₁ = H R₂ = 4-CH₃, 142n; R₁ = H R₂ = 4-CF₃, 142o; R₁ = H, R₂ = 2, 4-Dimethyl, 142p, R₁ = 6-Br; R₂ = H.

**Scheme 24.** Synthesis of fluorosubstituted coumarin hydrazones 142

3-[(1E)-2-aza-1-methyl-2-[(methylthiothioxomethyl)[vinyl]-2H-chromen-2-one 144, which prepared through the reaction of 3-acetylcoumarin 1 with methyl hydrazinecarbodithioate 143 in 2-propenol, was reacted with 145 to afford ethyl 2-[(2Z)-1,2-diaza-3-(2-oxo(2H-chromen-3-yl)but-2-enylidene]-3-phenyl-1,3,4-tbadiazolino-5-carboxylate 146 (Scheme 25).

**Scheme 25.** Synthesis of ethyl 2-[(2Z)-1,2-diaza-3-(2-oxo(2H-chromen-3-yl)but-2-enylidene]-3-phenyl 1,3,4-tbadiazolino-5-carboxylate 146

2.8. **Reaction with acid hydrazides and its derivatives**

Aminobenzoylhydrazone 149 was synthesized via condensation of 3-acetylcoumarin 1 with o-aminobenzoylhydrazone 148. Also, the reaction of 148 with Ln(NO₃)₃ gave the corresponding complexes of the composition [Ln(ACAB)x(NO₃)y(H₂O)z]·NO₃·H₂O 150, where Ln = La(III), Pr(III), Nd(III), Sm(III), Eu(III), Gd(III), Tb(III), Dy(III) and Y(III)⁴¹. Moreover, Hunoor et. al. synthesized Co(II), Ni(II), Cu(II) and Zn(II) complexes 153 and 154, using a new heterocyclic Schiff base 152, derived by condensation of isonicotinoylhydrazone 151 and 3-acetylcoumarin 1 in ethanol (Scheme 26).³²
Scheme 26. Synthesis of Co(II), Ni(II), Cu(II) and Zn(II) complexes 153 and 154

3-Substituted coumarin derivatives 1 were reacted with cyanoacetylhydrazine 155 and its N-acetyl and N-isopropylidene derivatives in the presence of piperidine at room temperature to give 3-cyano coumarin derivatives 156 (Scheme 27).
The reaction of 3-substituted coumarin derivatives 1 with hydrazide of p-nitrophenylacetic acid 157 in ethanol at 18-20 °C in the presence of catalytic amounts of piperidine gave the corresponding 3-(p-nitrophenyl)coumarin derivatives 158 (Scheme 28). Furthermore, interaction of 3-substituted coumarin derivatives 1 with malonic acid dihydrazide 159 under Michael reaction conditions showed the conversion of 1 into coumarin-3-carboxylic acid hydrazide 160 (Scheme 28). When the resulting hydrazide 160 was reacted with 3-substituted coumarin derivatives 1, coumarin-3-carboxylic acid hydrazone derivatives 161 were obtained (Scheme 28).
Scheme 28. Interaction of 1 with p-nitrophenylacetic acid and malonic acid hydrazide 157 and 159
2.9. Reaction with thiosemicarbazide and semicarbazide

Condensation of 3-acetyl coumarin 1 with thiosemicarbazide or semicarbazide derivatives 162 in acetic acid or ethanol gave the corresponding hydrazone derivatives 163. Acetylation of 163 with Ac₂O/ ZnCl₂ formed 5-substituted-3-acetyl-2-(coumarinyl)-methyl-1,3,4-oxa(thia)diazoline derivatives 164 (Scheme 29). Moreover, 3-acetyl coumarin 1 was reacted with semicarbazide hydrochloride 162 in the presence of sodium acetate to give the semicarbazone hydrochloride 163, which was subjected to oxidative cyclization using selenium dioxide in acetic acid to give 3-(1,2,3-selenadiazol-1,4-yl)coumarin 165. Oxidative cyclization of the semicarbazone 163 with thionyl chloride produced the corresponding 3-(1,2,3-thiadiazol-4-yl)coumarin 166 (Scheme 29). The bis-Schiff base 168 was prepared via refluxing of 3-acetyl coumarin 1 with thiocarbohydrazide 167 in ethanol/acetic acid (Scheme 29).

Scheme 29. Reaction of 1 thiosemicarbazide, semicarbazide 162 and thiocarbohydrazide 167

Treatment of thiosemicarbazone 163 with acetic anhydride, benzoyl chloride 169, ethyl chloroacetate 170, ω-bromomethylketones 171 and dicarbonyl compounds 172 and 173 afforded the corresponding diacetyle 174 and dibenzoyl-thiosemicarbazone 175, 3-(coumarin-3-ylethylidene)amino-2-thioxo-imidazolidin-4-one 176, 5-aryl-2-[(coumarin-3-ylethylidene)-hydrazino]thiazole 177 and 1-(coumarin-3-ylethylidene)amino-2-thioxopyrimidine derivatives 178 and 179, respectively. Acetylation of 176 with acetic anhydride gave 1-acetyl-2-thioxo-imidazolidin-4-one 180 (Scheme 30).
Scheme 30. Reaction of thiosemicarbazone 163 with acetic anhydride, benzoyl chloride 169, ethyl chloroacetate 170, ω-bromomethylketones 171 and dicarbonyl compounds 172 and 173

Reactions of hydrated lanthanide (III) chlorides; Ln = Nd, Sm and Gd, with the sodium salt of carbazone 163 in methanol in a microwave oven for 5–6 min. gave the corresponding complexes 181 (Scheme 31).94

Scheme 31. Reactions of hydrated lanthanide (III) chlorides; Ln = Nd, Sm and Gd, with the sodium salt of carbazone 163
2.10. Reaction with chiral Formaldehyde N,N-dialkylhydrazones

Michael addition of chiral formaldehyde N,N-dialkylhydrazone derivatives 182 to 3-acetyl coumarin 1 gave a 1.3:1 diastereoisomeric ratio of (1S)-trans/(1R)-trans 183 and 184 (Scheme 32).\(^{35}\)

\[ \text{Scheme 32. Reaction of 1 with chiral formaldehyde N,N-dialkylhydrazones} \]

2.11. Reaction with active methylene components

Condensation of 3-acetyl coumarin 1 with malononitrile 185 in boiling benzene containing ammonium acetate and acetic acid afforded 3-(2,2-dicyano-1-methylvinyl)coumarin 186 (Scheme 33).\(^{36}\) The reaction of compound 186 with phenylhydrazine 187 in boiling ethanol gave the imino compound 189, while the pyrazoline derivatives 188 did not form.\(^{97}\) The suggested structure for 188 was confirmed by its independent synthesis from 1, i.e. refluxing it with phenylhydrazine 187 in boiling ethanol (Scheme 33)\(^{64}\). Also, interaction of 186 with primary aromatic amines 190 in boiling ethanol gave 3-(2,2-dicyano-1-arylamino-1-methylethyl)coumarin derivatives 191 by initial attack of the nucleophile at C-β of the olefinic bond of the dicyano derivatives. Furthermore, the reaction of 186 with sulfur in a Gewald reaction\(^{98}\) produced 3-(5-amino-4-cyano-3-thienyl)coumarin 192. In addition, the interaction of 192 with maleic anhydride 193 through a Diels-Alder reaction gave 194, while its acetylation yielded the corresponding acylated compound 195. Passing hydrogen sulfide gas into a solution of 186 in ethanol containing a few drops of triethylamine gave 3-(2-cyano-1-methyl-2-thiocarboxamidovinyl)coumarin 196 (Scheme 33).\(^{96}\)
Scheme 33. Condensation of 3-acetylcoumarin 1 with malononitrile 185

Condensation of compound 186 with substituted α-cyanocinnamonic acid derivatives 197 in boiling ethanol, containing a few drops of piperidine, gave coumarin derivatives 199 through the intermediate 198 (Scheme 34).26
Scheme 34. Reaction of 186 with substituted α-cyanocinnaminitrile derivatives 197

Knoevenagel condensation reaction of 1 (R=6-OMe-H) with malononitrile 185 in ethanol, containing a catalytic amount of piperidine, afforded compound 186 (R=6-OMe-H) as the main product. However, the product obtained from the reaction of 3-acetyl-5-bromocoumarin (R=5-Br) with malononitrile 185 is the benzopyran derivative 201b. The corresponding mechanism for benzopyran derivatives involves the sequence of 186 → 200 → 201a → 202b (Scheme 35).\textsuperscript{99}

Mohareb et al. reported that condensation of 3-acetylcoumarin 1 with malononitrile 185 in dimethylformamide, containing a catalytic amount of piperidine, gave a mixture of pyrano[3,4-c]coumarin derivatives 202 and 186.\textsuperscript{100} Coupling of 202 with benzenediazonium chloride 203\textsuperscript{100} gave the corresponding (coumarin-3-yl)-6-imino-1-phenyl-1,6-dihydropyridazin-5-carbonitrile 204, not the compound 205 or 206 (Scheme 36).\textsuperscript{100}
Scheme 36. Synthesis of (coumarin-3-yl)-6-imino-1-phenyl-1,6-dihydro-pyridazin-5-carbonitrile 204

3-Acetylcoumarin 1 was reacted with 2-amino-1,1,3-tricyanopropene 207 in the presence of piperidine at room temperature to give the benzopyrano[3,4-c] pyridine derivative 209. The reaction proceeded via Michael addition of the active methylene group to the activated double bond to form the acyclic Michael intermediate 208, which was cyclized to give 209 (Scheme 37). Furthermore, the reaction of 3-acetylcoumarin 1 with different active methylene heterocyclic derivatives such as pyrazolone 210 and thiazolone 211a,b yielded coumarinopyranopyrazole derivatives 212, thiazolyl coumarinopyridine 213a and coumarinopyranone 213b, respectively (Scheme 37).

Scheme 37. Synthesis coumarinopyranopyrazole derivatives 212, thiazolyl coumarin pyridine 213a and coumarinopyranone 213b
Benzopyronopyridine, pyrazolo[3,4-\textit{d}]-pyridine, isoxazolo[5,4-\textit{b}]-pyridine, pyrido[2,3-\textit{d}]-pyrimidine and pyrrolylcoumarin derivatives 218-221 were synthesized through the reaction of 3-acetylcoumarin 1 with the corresponding active methylene compounds (e.g., 2-cyanoacetamide 214, 2-cyanoethanethioamide 215, 4,5-dihydro isoazole-3,5-diamine 216a, 4,5-dihydroisothiazole -3,5-diamine 216b, 6-amino-5,6-dihydro pyrimidine-2(1H)-one 217a or 6-amino-5,6-dihydro pyrimidine-2(1H)-thione 217b (Scheme 38).

Scheme 38. Synthesis Benzopyronopyridine, pyrazolo[3,4-\textit{d}]-pyridine, isoxazolo-[5,4-\textit{b}]-pyridine, pyrido[2,3-\textit{d}]-pyrimidine, and pyrrolylcoumarin derivatives 218-221

Facile and environmentally benign synthesis of some 2-(2-oxo-2\textit{H}-chromen-3-yl)-4-aryl-indeno[1,2-\textit{b}]pyridine-5-one derivatives 227 through the reaction of aromatic aldehydes 224, 3-acetylcoumarin 226, 1,3-indandione 225 and ammonium acetate using phthalimide-\textit{N}-sulfonic acid (PISA) 223 as a catalyst is described in Scheme 39. The present method has some important features such as mild reaction conditions, short reaction time, less catalyst dosage and high yields with the green aspects by avoiding toxic catalysts and solvents. Furthermore, the catalyst can be reused for four times without any noticeable decrease in the catalytic activity (Scheme 39).

Scheme 39. Synthesis of 2-(2-oxo-2\textit{H}-chromen-3-yl)-4-aryl-indeno[1,2-\textit{b}]pyridine-5-one derivatives 227
2.12. Reaction with hydrazonoyl halide derivatives

Cycloaddition reaction of \(N\)-phenyl nitrileimine derivatives 228 with 3-substituted coumarin 1 in benzene in the presence of triethylamine gave the benzopyrano[3,4-c]pyrazole derivatives 229, reflux of which in toluene in the presence of KOH led to decylation, debenzoylation and dehydrogenation to give the corresponding pyrazole derivative 230 (Scheme 40).\(^{105-108}\) Methylation of 230 afforded the substituted pyrazole 232. Saponification of compound 232 produced the acid 233, which was decarboxylated to yield 4-orthomethoxyphenyl-1,3-diphenylpyrazole 234 (Scheme 40).\(^{106}\)

\[\text{Scheme 40. Cycloaddition of 1 with nitrileimine 228}\]

Cycloaddition reaction of 3-substituted coumarin 1 with hydrazonoyl bromide derivatives 235 in benzene in the presence of triethylamine gave the 1,3-dipolar cycloadducts 1-aryl-3-(4-nitrophenyl)-3a,9b-dihydrochromeno[3,4-c]pyrazole-4(3H)-one derivatives 236, which was aromatized by heating in aqueous potassium hydroxide in toluene to give the corresponding chromeno[3,4-c]pyrazol-4(3H)one derivatives 237 (Scheme 41).\(^{109-111}\)

\[\text{Scheme 41. Cycloaddition reaction of 1 with hydrazonoyl bromide derivatives 235}\]
2.13. Reaction with phenacyl bromide

3-Substituted coumarin derivatives 1 were reacted with phenacyl bromide 171 in the presence of a base (e.g. EtONA, NaH, NaOH and DUB) to yield the cyclopropane derivatives 238 and 239 in moderate yields, which were improved by using catalyst such as Aliquat 336 or TPB under phase transfer conditions. These reactions have steric selectivity (Scheme 42).\textsuperscript{112}

\begin{scheme}
\begin{center}
\includegraphics[width=\textwidth]{Scheme42}
\end{center}
\caption{Cycloaddition reaction of 1 with phenacyl bromide 171.}
\end{scheme}

2.14. Acylation

The reaction of 3-substituted coumarin 1 with acid anhydride derivatives (e.g. acetic, propionic, butyric and isobutyric acid anhydrides) 240 in the form of \((\text{R}_1\text{R}_2\text{CHO})_2\text{O}\) in the presence of sodium acetate or triethylamine or potassium fluoride afforded dihydrolactones 241 (Scheme 43).\textsuperscript{113}

\begin{scheme}
\begin{center}
\includegraphics[width=\textwidth]{Scheme43}
\end{center}
\caption{Reaction of 1 with acid anhydride 240 and diazomethane 242}
\end{scheme}

2.15. Reaction with diazo derivatives

Alkylation of 3-acetylcoumarin 1 with diazomethane 242 gave the 4-methylcoumarin 243 (Scheme 43). On the other hand, the substituents at the 5-position were interfered during the methylation process that 3-acetyl-5,7-dimethylcoumarin 1 rather than 244 gave a pyrazoline derivative 245, which was then converted by methanol into the oxepin lactone derivative 246. It tautomerises rapidly to its isomer 247, which is more stable due to the extend conjugation (Scheme 44).\textsuperscript{114,115}
In 3-acetyl-5,6-benzocoumarin 1, as methine group is smaller than a methyl group, a simple 4-methylation did not take place to obtain the compound 248. The expected pyrazoline 249 was not detected as it rapidly collapsed to give the unsaturated lactone 250, which was added to a second molecule of the reagent to produce the pyrazoline 251 (Scheme 45).\(^ {114} \)

Diazoethane alkylation of 3-acetylcoumarin 1 gave the corresponding 3-acetyl-4-ethylcoumarin 253 and expanded the lactone ring 254, which reacted with a second molecule of diazoethane 252 to form the benzoxepinopyrazoline derivative 255. It underwent a second ring expansion to form the benzoxocin derivative 256. When the compound 255 was treated with diazoethane, a ring expansion took place giving the benzoxonin derivative 257 (Scheme 46).\(^ {116} \) Furthermore, 3-acetylcoumarin 1 underwent ring

Scheme 44. Synthesis of oxepin lactone 247

Scheme 45. Synthesis of pyrazoline 251
expansion upon treatment with 2-diazopropane 258, which was followed by inverse cycloaddition of diazoalkane leading to a 3-acetyltetramethyl-4H-(1)benzoxepino[4,3-c]pyrazol-4-one derivative 260 (Scheme 46).\textsuperscript{116}

\begin{center}
\textbf{Scheme 46. Synthesis of benzoxocin, benzoxonin and benzoxepin derivatives 256, 257 and 260}
\end{center}

Similarly, the reaction of 3-benzoylcoumarin 1 with dimethyldiazomethane 258 gave the lactone 262 along with a small amount of cyclopropane derivative 261. The compound 262 underwent AgNO\textsubscript{3}-alumina induced ring contraction to yield the benzofuran derivative 263. Also, diazopentane 264 converted 3-substituted coumarin 1 into 265 (Scheme 47).\textsuperscript{117}

\begin{center}
\textbf{Scheme 47. Reaction of 1 with dimethyldiazomethane 258 and diazopentane 264}
\end{center}
Cycloaddition reaction of ethyldiazoacetate 266 with 3-substituted coumarin 1 in benzene at room temperature or in silica gel gave a mixture of 267, 268, 269, 270 and 271. This is in agreement with the other analogous 1,3-dicycloadDITION of diazo compounds to 3- or 4-substituted coumarin derivatives, where the terminal nitrogen of diazo moiety binds to the carbon atom of the benzopyran 3,4-double bond bearing the electronegative substituent (Scheme 48).\textsuperscript{114,116-122}

![Scheme 48. Reaction of 1 with ethyldiazoacetate 266](image)

2.16. Reaction with enaminooesters and ethyl malonamate

Addition of the enaminooesters of 3-amino-3-ethoxy-acrylic acid ethyl ester 272 and 3,3-diamino-acrylic acid ethyl ester 273 to 3-substituted coumarin 1, gave the adducts 3-amino-3-ethoxyacrylic acid ethyl ester derivatives 275, 276. However, the adduct, produced from 3-substituted coumarin 1 and ethyl-1-amino-1-methylpropenoate 274, was benzopyran[3,4-c]pyridine derivative 277 (Scheme 49).\textsuperscript{123}

![Scheme 49. Reaction of 1 with enaminooesters 272-274](image)

Raev et al. studied the addition of 3-aminopropenoate derivatives 278-280 to 3-substituted coumarin 1 to obtain the coumarinenaminooester adducts 284, 287 and 288 via the intermediates 281, 282, 283, 285 and 286, respectively (Scheme 50).\textsuperscript{124}
Michael addition of ethyl malonate 289 to 3-acetylcoumarin 1 in the presence of triethylamine gave Michael adduct derivatives 290, which underwent spontaneous intramolecular cyclization to yield the product 291 (Scheme 51).  

**Scheme 50. Reaction of 1 with enaminoesters 278-280**

**Scheme 51. Michael addition of ethyl malonate 289 to 3-acetylcoumarin 1**
2.17. Reaction with sodium cyanide and isocyanide

3-Acetylcoumarin 1 was reacted with sodium cyanide to give 3-acetyl-4-cyanocoumarin 292, which was brominated to give benzopyrano[4,3-c]pyridine derivative 293 (Scheme 52). Furthermore, 3-acetylcoumarin 1 was reacted with isocyanide 294 in toluene under microwave irradiation to furnish 2-aminofuran 295. This combined very rapidly with triplet oxygen to afford hydroperoxide 296, in addition the ketoamide 297 as well as the 5-hydroxy-pyrrolidone 298 was formed when the same reaction in refluxing ethanol was repeated (Scheme 52).127

Scheme 52. Reaction of 1 with sodium cyanide and isocyanide

2.18. Alkylation

Alkylation of 3-acetylcoumarin 1 with allyl silane 299 in the presence of fluoride ion, titanium chloride128 or trimethylallylsilane in the presence of titanium chloride129 gave 300. Also, interaction of 3-acetylcoumarin 1 with allyl iodide 301 in dimethylformamide or tetrahydrofuran in the presence of indium/indium trichloride (In/InCl₃) gave 1,2-addition product 302 in a high yield (Scheme 46)130 (Scheme 53).

Scheme 53. Reaction of 1 with allyl silane and allyl iodide
2.19. Reaction with aldehydes and ketones

3-Acetylcoumarin 1 reacted with aldehydes 303 in ethanol in the presence of piperidin, potassium hydroxide\textsuperscript{135} or piperidine under solvent free condition to give the corresponding 3-cinnamoyl coumarin derivatives 304a-o. Michael addition of 304 a-g with 2-amino-1,1,3-tricyanopropene 305, cyanoethanoic acid hydrazide 306, 3-aminopyrozol-5-one 307, 3-amino-N-methylpyrazol-5-one 308 or cyanoacetamide 214 in the presence of piperidine gave 5-amino-3-aryl-4,6,6-tricyano-1-[2-(H)-oxo-1-benzopyran-3-yl]hex-5-en-1-one derivatives 309, 4-aryl-3,3a,4,5-tetrahydro-6-[2(H)-oxo-1-benzopyran-3yl]-2-H methylpyrazolo-[3,4-b]pyridines 310 and 311 and 3-aryl-5-carboxamido-4-cyano 1-[2(H)-oxo-1-benzopyran-3-yl]pentan-1-one derivatives 312 (Scheme 54)\textsuperscript{132}. Furthermore, a new efficient and eco-friendly methodology was developed for the synthesis of 4-aryl-2,6-dicoumarinyl pyridine derivatives 314 from coumarin chalcones 304 and urea 313, using Bi(III) nitrate-Al\textsubscript{2}O\textsubscript{3} as a catalyst (Scheme 54)\textsuperscript{135}.

Moreover, Seidel et al prepare a series from novel inhibitors of human histone deacetylases 316a-d, 316h and 316e-g, via condensation of coumarin derivatives 1 with bezaldehyde derivatives 315a-d, 315h and cinnamaldehyde derivatives 315e-g in ethanol in the presence of pyrrolidine (Scheme 55)\textsuperscript{136}.

**Scheme 54.** Reaction of 1 with aldehydes
Molaverdi et al. prepared 320a-s via the routes illustrated in Scheme 56. Initially, commercial hydroxysalicylaldehyde 317 was converted to 6- or 7-hydroxy-3-acetylcoumarins 1 using ethyl acetoacetate 318 in the presence of catalytic amount of piperidine. In the next step, 3-acetylcoumarins 1 were condensed with several aldehydes 319 in refluxing ethanol and in the presence of piperidine as a catalyst to afford the compounds 320a-h. On the other hand, O-benzylation of hydroxysalicylaldehyde 317 in dry acetonitrile produced benzyloxysalicylaldehydes 322. The reaction of 322 with ethyl acetoacetate 318 yielded the corresponding 3-acetylcoumarins 323, which were subsequently condensed with appropriate aldehydes 319 to afford the final compounds 320i-s.

When the compound 304 was reacted with various 1-(aryl)pyridinium bromide derivatives 324 in acetic acid in the presence of ammonium acetate, 3-(2-pyridyl)coumarin derivatives 325 were obtained. Condensation of 304 with malononitrile or ethyl cyanoacetate 326 in the presence of ammonium acetate afforded cyanopyridine derivatives 327. An alternative route for the synthesis of 327 by condensation of 3-acetylcoumarin with malononitrile or ethyl cyanoacetate and aromatic aldehydes in the presence of ammonium acetate was also reported (Scheme 57).

Furthermore, a facile procedure for the synthesis of 3-(2-amino-3-cyano-4-arylpyrid-6-yl) coumarins 327 (R=NH2, R1= C6H5, 4-ClC6H4, 4-NO2C6H4, 4-CH3C6H4, 4-OCH3C6H4, 3-NO2C6H4, 3,4-(OCH2OC6H4)) were reported, starting from 3-acetylcoumarin, aromatic aldehydes and malononitrile. The reactions were carried out on microwave irradiation in good yields with shorter time and easy work-up (Scheme 57).
Scheme 56. Synthesis of substituted cinnamoylcoumarins 320a-s

A series of 5-substituted aryl-3-(3-coumarinyl)-1-phenyl-2-pyrazoline derivatives 329a-c were synthesized by reacting 304a-c with hydrazine derivatives 328 in the presence of hot pyridine$^{140}$ or acetic acid$^{142}$. These compounds were screened for in vivo anti-inflammatory and analgesic activities at a dose of 200 mg/kg b.w.$^{141}$ Also, condensation of 3-acetyl-coumarin 1 with substituted benzaldehydes by using novel solvent-free method involving aheterogeneous catalyst, silica sulfuric acid, gave the corresponding chalcone 304 (R=3,4,5-triCH$_3$O-C$_6$H$_2$; 3- CH$_3$OC$_6$H$_4$; 3,4-diCH$_3$O-C$_6$H$_2$; 4-CH$_3$O-C$_6$H$_4$; 2,5-diCH$_3$O-C$_6$H$_3$; 2,3,5-triCH$_3$OC$_6$H$_2$; 2,4,5-triCH$_3$OC$_6$H$_2$; 2-CH$_3$OC$_6$H$_4$; 2-CiC$_6$H$_4$; 2,5-diCH$_3$OC$_6$H$_4$). Treatment of 304 (R=3,4-diCH$_3$O-C$_6$H$_3$) with hydrazine hydrate and phenyl hydrazine in the presence of acetic acid afforded pyrazolines 329 (R=3,4,5-triCH$_3$O-C$_6$H$_3$, R$_1$=COCH$_3$ or C$_6$H$_5$) (Scheme 57).$^{143}$ Condensation of 304 with hydroxylamine hydrochloride 330 in ethanol gave the substituted isoxazolinocoumarin derivatives 331.$^{144}$ Epoxidation of compound 304 using hydrogen peroxide in alkaline medium gave epoxy proprnoyl derivatives 332 (Scheme 57).$^{89}$
Furthermore, compound 304 was reacted with 2-aminobenzethiol 333 in ethanol in the presence of piperidine to yield 2-aryl-4-[2H-2-oxo-[1]benzopyran-2-one-3-yl]-2,5-dihydro-1,5-benzothiazepine derivatives 334. When the same reaction was repeated in the presence of acetic acid instead of piperidine, 2-aryl-4-[2H]-2-oxo-[1]benzopyran-3-yl]-2,3-dihydro-1,5-benzothiazepine derivatives 335 were produced. They were subjected to reduction with either sodium borohydride or o-aminothiophenol (o-ATP), contaminated with a little amount of di-O-aminophenyl disulphide in ethanol containing an acid (HCl or HBr) to give the tetrahydrobenzothiazepine derivatives 338, through the intermediate 336 and 337 (Scheme 58).145
Scheme 58. Synthesis of tetrahydrobenzothiazepine derivatives 338

Friedlander condensation of the 3-substituted coumarin derivatives 1 with 2-aminonicotinaldehyde 339 in the presence of glacial acetic acid containing a catalytic amount of conc. H$_2$SO$_4$ gave 3-(1, 8-naphthyridin-2-yl)-2H-1-benzopyran-2-one derivatives 340 (Scheme 59).$^{146}$

![Scheme 58](image_url)

Scheme 59. Synthesis of 3-(1, 8-naphthyridin-2-yl)-2H-1-benzopyran-2-one derivatives 340

3-Acetylcoumarin 1, refluxed in ethanol in the presence of piperidine, gave compound 341, not 342.$^{147}$ Moreover, the reaction of 3-acetylcoumarin 1 with ninhydrin 343 in ethanol in the presence of piperidine produced 2-hydroxy-2-[2-oxo-2-(2-oxo-2H-chromen-3-yl)-ethyl]indan-1,3-dione derivatives 344, to which in-situ addition of hydrazine hydrate gave the corresponding 3-(2-oxo-2H-chromen-3-yl)-inden0[2,1-c]pyridazin-9-one derivatives 345 (Scheme 60).$^{148}$

The reaction of 3-substituted coumarin derivatives 1 with isatin 346 in ethanol in presence of piperidine afforded the corresponding 3-[3'-hydroxy-2'-(oxo)indolo]acetylcoumarin derivatives 347, which, on
dehydration in HCl/AcOH, gave the corresponding α,β-unsaturated ketone derivatives 348. Cyclocondensation reaction of compound 348 with substituted o-phenylenediamine derivatives 349 in ethanol in the presence of acetic acid afforded the novel 3-coumarinylspiro[indolo-1,5-benzodiazepine] derivatives 350 (Scheme 60). Furthermore, the reaction of 3-acetylcoumarin 1 with alloxan monohydrate 351 in acetic acid, followed by treatment with hydrazine hydrate, afforded 3-(2-oxo-2H-chromen-3-yl)-6H, 8H-pyrimido[4,5-c]pyridazine-5,7-dione derivative 352 (Scheme 60).

3-Acetylcoumarin 1 was reacted with acetone 353 in the presence of cyanoacetamide, liprating ammonia which was reacted with 3-acetylcoumarin 1, primary aliphatic amines 354 (e.g. methyl amine), primary aromatic amines 86 (e.g. aniline), aqueous ammonia or ammonium acetate to obtain the corresponding 2,4-dimethyl-5H-chromeno[3,4-c]pyridine-5-one 355, 9-bromo-2,3,4-trimethyl-2,3-dihydro-1H-chromeno[3,4-c]pyridin-5(10bH)-one 356, aminobenzocoumarin derivatives 357 and 258, tricyclic derivatives 359 or enamine derivative 360, respectively (Scheme 61).
Condensation of 3-substituted coumarin derivatives 1 with ammonium acetate afforded a chemoselective high yield of the corresponding (oxobenzopyranyl)benzopyranopyridinone derivatives 361 in boiling acetic acid or gave methanobenzoxazocine derivative 362 in boiling pyridine (Scheme 62).\textsuperscript{153}
3-Acetyl coumarin 1 was reacted with 2-amino-3-cyano-1,8-naphthopyridine 363 in glacial acetic acid in the presence of a catalytic amount of concentrated sulfuric acid to give 2-(3-coumaryl)-(1H)-anthryridinone derivatives 364. Moreover, condensation of 3-acetyl coumarin 1 with N-amino-3-cyano-4, 6-dimethyl-2-(1H)-pyridone 365 in dimethylformamide in the presence of anhydrous zinc chloride afforded the pyrazolo[1,5-a]pyridine derivatives 366. Furthermore, the reaction of 1 with 3-amino-1H-pyrazol-5(4H)-one 367 in acetic acid gave a comparable yield of poly heterocycle 368 (Scheme 63).

Scheme 63. Reaction of 1 with heterocyclic amines 363, 365 and 367

2.20. Reaction with thiourea derivatives

3-Substituted coumarin derivatives 1 were reacted with substituted thiourea derivatives 369 in the presence of iodine to give the substituted 3-(2-arylamino-4-thiazolyl)-2-1-benzopyran-2-one derivatives 370, which were then converted into their acetyl derivatives 371(Scheme 64).
Scheme 64. Reaction of 1 with thioureas 369, enamines 372 and 1,3-diarylhexachlorocyclo-
diphosphazane 375

2.21. Reaction with enamineone

Cyclocondensation reaction of 3-acetyl coumarin 1 with the enamine of methyl acetoacetate 372 afforded only benzopyranopyridine derivative 373a, while using ethyl acetoacetate instead of methyl acetoacetate afforded 373b together with tricyclic derivative 374 (scheme 64).158

2.22. Reaction with diphosphazane derivative and triaminophosphate

Condensation of 3-acetyl coumarin 1 with 1,3-diarylhexachlorocyclo-diphosphazane derivatives 375 yielded the corresponding carbonyl methylene derivative 376 (Scheme 64).159 3-Substituted coumarin 1 was reacted with triaminophosphine 377 in methylene chloride at 5 °C to give the corresponding trisdimethylamino-2-acetyl(3H)naphth[a2,1-b][1H-3-oxo-pyrana-1-yl]phosphorane 380 through the intermediate 378. Treatment of 380 with water resulted in its conversion to the reduced form 381. On heating the amino-ylide derivatives 380 above their melting points under reduced pressure, the starting material 1 was produced (Scheme 65).50
Scheme 65. Synthesis of dihydro-3-aceylcoumarins 381

2.23. Reaction with lithium tetramethyl thallium

Condensation of 3-acetylcoumarin 1 with lithium tetramethyl thallium 382 at 40 °C gave the conjugated (1,4) addition product 4-methyl-3-acetyl coumarin 243 (Scheme 66).160

2.23.1. Reaction with NaBH₄/CeCl₃

Reduction of 3-acetylcoumarin 1 under Luche's condition (NaBH₄, CeCl₃) afforded the secondary alcohol 383, which was brominated with PBr₃ to give the corresponding bromocoumarin derivative 384. N-alkylation of 384 with 1,4,7,10-tetraazacyclododecane yielded the monosubstituted cyclen derivative 385 (Scheme 66).161

2.24. Reaction with dimethylsulfoxonium methylide

When 3-acetylcoumarin 1 was treated with 2.4 equivalent of dimethylsulfoxonium methylide 386 at room temperature in dimethylformamide or DMSO, novel (3α R*, 8α S*)-2-acetyl-3a,8b-dihydro-1H-cyclopenta-[b]benzofuran-3-ol 389 was obtained through 338 (Scheme 66).162
Scheme 66. Reaction of 1 with lithium tetramethyl thallium 382, CeCl₃ and dimethylsulfoxonium 386

2.25. Reaction with dimethylformamide dimethylacetal

Enaminone 391 was obtained by reacting 3-acetylcoumarin 1 with dimethylformamide dimethylacetal (DMFDMA) 390 in a microwave oven (390 W). The yield was found to be much higher than heating in a solvent. It was reported in the literature that enaminone 391, when refluxed in acetic acid in the presence of ammonium acetate, gave the pyridine derivative 392, but the same reaction when occurred in a microwave oven (390 W) instead of refluxing, produced a compound with a molecular formula of C₂₂H₁₃NO₄, for which a structure, 394, was suggested, through a Nenitzescu like cyclization and decarboxylation products, respectively. Furthermore, the reaction of compound 391 with enaminone 395 in a microwave oven (390 W) gave a mixture of 396 and 392 (Scheme 67).
Furthermore, enaminone 391 was reacted with nitrogen nucleophiles in a microwave oven (390 W) such as 3(5)1,2,4-aminotriazole 397, ethyl 2-amino tetrahydrobenzo-[b]thiophene-3-carboxylate 398, hydrazine hydrate 10 and guanidine hydrochloride 399 to afford the corresponding 5-(coumarin-3-yl)-1,2,4-triazolo[4,3-a]pyrimidine 400, 2-[3-oxo-3-(2-oxo-2H-chromen-3-yl)-propenyl-amino]-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxylic acid ethyl ester 401, 3-(coumarin-3-yl)-pyrazole 402 and 2-amino-4-(coumarin-3-yl)pyrimidine 403, respectively (Scheme 68).
Scheme 68. Reaction of enaminone 391 with nitrogen nucleophiles 10, 397-399

The reaction of enaminone 391 with nitrile oxide 404 gave the isoxazole derivative 405, rather than the potential isomeric product 406. The isoxazole 405 was reacted with hydrazine hydrate to give the coumarinyl isoxazolopyridazine 407 (Scheme 69).\textsuperscript{166}

Scheme 69. Reaction of enaminone 391 with nitrile oxide 404
2.26. Reaction with dichloro phenyl phosphine

Addition of dichloro phenyl phosphine (PhPCl₂ 408) to 3-acetylcoumarin 1 in the presence of acetic anhydride afforded coumarino[3,4-c]-3H-10-methyl-2-oxo-2-phenyl-1,2-oxaphosphole 409A, which underwent an allylic rearrangement to give the isomeric coumarino[3,4-c]-9H-9-methyl-2-oxo-2-phenyl-1,2-oxaphosphole 409B (Scheme 70).167

2.27. Reaction with 4-methyl-2-phenyl-1,3-oxazol-5(4H)-one

Strirring of 3-acetyl coumarin 1 with 4-methyl-2-phenyl-1,3-oxazol-5(4H)-one (MPO 410) under reflux in toluene afforded 3-acetyl[3,4-c]pyrrolecoumarin acid 411. Furthermore, 411 was prepared in another route via triturating the same reactants together in a mortar rapidly and then reacting in a sealed vial in a bath set at 100 °C for 15–20 min. Stirring of 411 with fresh ethereal diazomethane solution in dioxane/THF at room temperature afforded the methyl ester 412 (Scheme 70).168

Scheme 70. Reaction of 1 with dichloro phenyl phosphine 408 and 4-methyl-2-phenyl-1,3-oxazol-5(4H)-one 410

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