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Ethyl coumarin-3-carboxylate: Synthesis and chemical properties

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Abstract – Ethyl coumarin-3-carboxylate occupies an important position in the organic synthesis and is used in production of biologically active compounds. Thus, the data published over the last few years on the methods of synthesis and chemical properties of ethyl coumarin-3-carboxylate are reviewed here for the first time. The reactions were classified as coumarin ring reactions and ester group reactions, and some of these reactions have been applied successfully to the synthesis of biologically and industrially important compounds.

Keywords: Ethyl coumarin-3-carboxylate; synthesis; chemistry.

1. Introduction

Coumarins, an old class of compounds, are a family of naturally occurring compounds.[1, 2] These compounds are involved in the actions of plant growth hormones and growth regulators, the control of respiration, photosynthesis, as well as defense against infection.[3] Also, they have important effects in plant biochemistry and physiology, acting as antioxidants, enzyme inhibitors and precursors of toxic substances [3]. Coumarins and their derivatives are used in the fields of biology, medicine and polymer science. They are also present or used in perfumes and cosmetics, [4-8] cigarettes, [5-8] alcoholic beverages [9] and laser dyes. [10] In addition, coumarins have been found to be connected with a number of cases of homicide and suicide in Korea. [11] Coumarins were first synthesized *via* the Perkin reaction in 1868, and many simple coumarins are still prepared through this method. In the early 1900s, the Knoevenagel reaction emerged as an important synthetic method to synthesize coumarin derivatives with carboxyl group at the 3-position. [12, 13] Many other synthetic methods for coumarins have been reported, including the Pechmann, [14] Reformatsky [15] and Wittig reactions. [16, 17] The review is not exhaustive; it is intended to acquaint the reader with interesting group of synthetic organic compounds. It is the objective of this review to summarize the synthesis and the chemical reactions of

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ethyl coumarin-3-carboxylate, which known as 3-carboethoxy(coumarin) and as ethyl 2-oxo-2*H*-chromene-3-carboxylate or ethyl 2*H*-1-benzopyran-3-carboxylate in IUPAC system, till the end of 2009 and provides useful and up-to-date data for organic chemists.

2. Synthesis

2.1. Knoevenagel Reaction

The Knoevenagel condensation of 2-hydroxybenzaldehyde with diethyl malonate was catalyzed with different catalysts to give ethyl coumarin-3-carboxylate **1** (Figure 1). Various catalysts were used in this reaction, such as piperidine,[18-20] molecular sieves/piperidine catalyst,[21] Magnesium aluminophosphate (MAPO-5) and ion-exchanged MAPO-5,[22] alumina/KSF/K10 montmorillonites,[23,24] liquid-functionalized SiO_2 at 100°C,[25] L-Proline,[26] sodium methoxide,[27] 1-*n*-butyl-3-methylimidazolium bromide/potassium carbonate,[28] 1-butyl-3-methylimidazolium hydroxide ([bmim]OH),[29] aluminum phosphate-aluminum oxide,[30] zinc chloride,[31] calcined Mg-Al hydrotalcite,[32] *N*,*N*-dimethyl(dichlorophosphoryloxymethylene)ammonium chloride, [33] mixed oxide catalysts obtained from calcined Mg-Al double hydroxides, Mg-Al + Ln (Ln = Dy, Gd) and Li-Al hydrotalcites.[34]

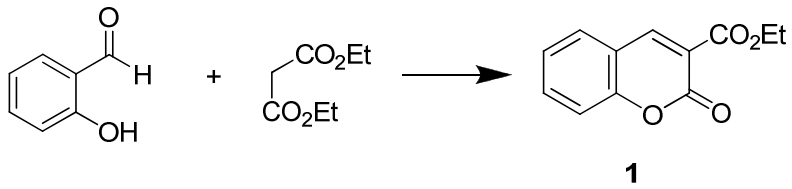


Figure 1. Reaction of *o*-salicylaldehyde with diethyl malonate

The synthesis of ethyl coumarin-3-carboxylate **1** under microwave irradiation conditions was also reported. The title compound was obtained from the reaction of *o*-salicylaldehyde and diethyl malonate under microwave irradiation with 86% yield.[35]

The Knoevenagel reaction of *o*-salicylaldehyde with ethyl cyanoacetate using sodium bicarbonate followed by hydrolysis of carbonitrile group with hydrochloric acid in ethanol afforded ethyl coumarin-3-carboxylate **1** in 87% yield. [36]

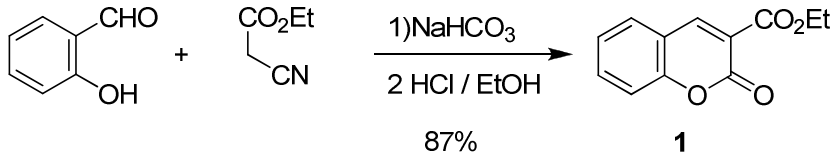


Figure 2. Reaction of *o*-salicylaldehyde with ethyl cyanoacetate

Also, treating salicylaldehyde with ethyl cyanoacetate in the presence of sodium ethoxide or potassium hydroxide at room temperature for 40-80 h gave **1** in 35% yield. [37]

2.2. Miscellaneous Methods

Ethyl coumarin-3-carboxylate can be also obtained through copper(II)-catalyzed C-C bond forming reactions. The reaction of ketene dithioacetal with salicylaldehyde was catalyzed with copper(II) bromide to afford **1** (Figure 3).[38]

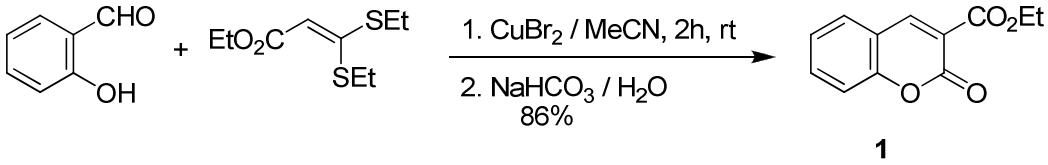


Figure 3. Reaction of ketene dithioacetal with salicylaldehyde

Tetrabutylammonium fluoride also catalyzes the cyclization of diethyl ester **2** to afford ethyl coumarins-3-ester **1** (Figure 4).[39]

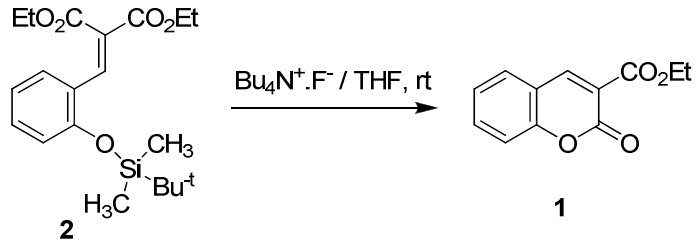


Figure 4. Cyclization of diethyl ester **2** to ethyl coumarins-3-ester **1**

(*E*)-Ethyl 2-bromo-3-[2-(methoxymethoxy)phenyl]acrylate **3** was converted into ethyl coumarin-3-carboxylate **1** via two steps. Firstly by treatment with hydrochloric acid in ethanol and secondly cyclization by Pd-catalyzed cross-coupling reaction (Figure 5).[40]

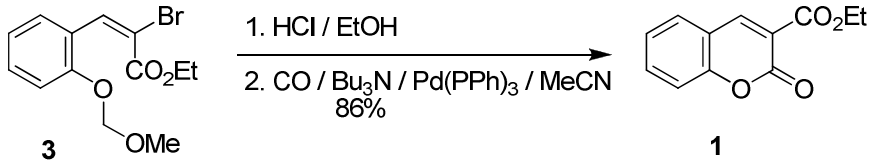


Figure 5. cyclization of acrylate **3** to ethyl coumarins-3-ester **1**

Condensation of the 2,4-dihydroxybenzaldehyde with Meldrum´s acid **4** using catalytic amount of ammonium acetate gives compound **5** that was *O*-alkylated to obtain coumarins **6** (Figure 6).[41]

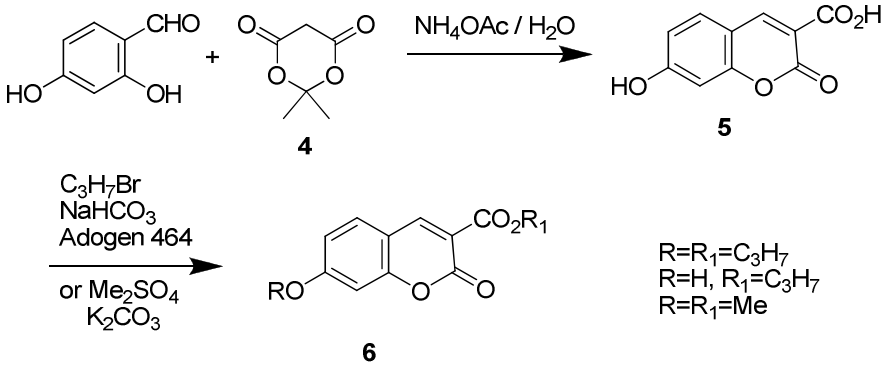


Figure 6. Reaction of 2,4-dihydroxybenzaldehyde with Meldrum´s acid **4**.

3. Chemical Properties

3.1. Ring Reactions

3.1.1. Ring Cleavage

Reaction of ethyl coumarin-3-carboxylate **1** with amines in a 1:4 molar ratio results in ring cleavage, hence salicylaldehyde and ammonium salts **7** were obtained (Figure 7).[42]

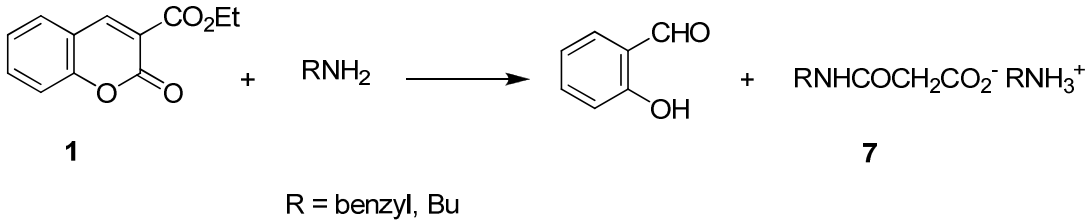


Figure 7. Reaction of ethyl coumarin-3-carboxylate **1** with amines

Malonate esters **9** were obtained by sodium borohydride reduction of the corresponding coumarins **8** in alcohols (Figure 8).[43]

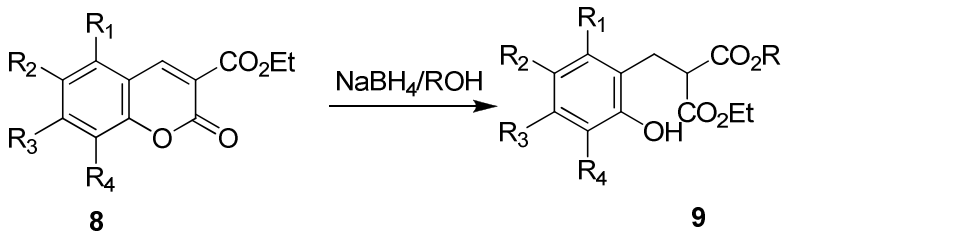


Figure 8. Reduction of coumarins **8**

Coumarin-3-carboxamides **10** was cleaved by hydrazine hydrate to yield carbohydrazide **11** and (*E*)-2-(hydrazonomethyl)phenol **12**. Also the reaction of **11** with ethylenediamine gave diamides **13** in addition to compound **12** (Figure 9). [44]

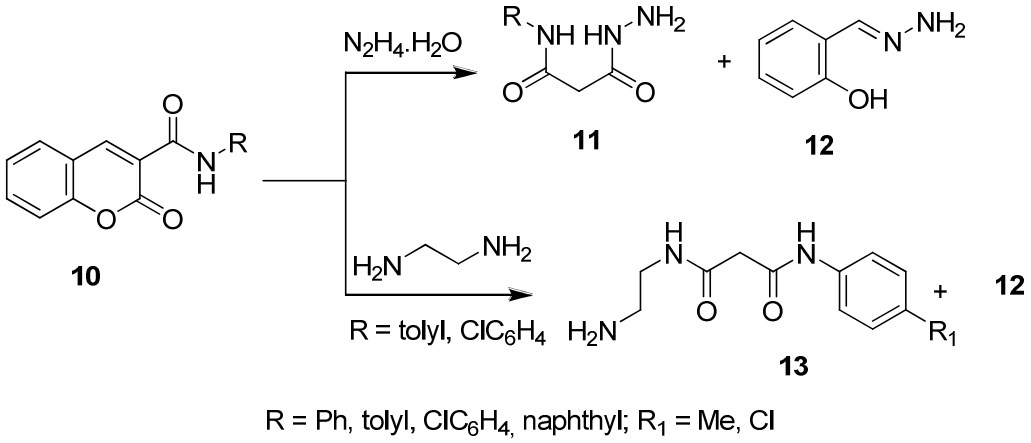


Figure 9. Cleavage of Coumarin-3-carboxamides with hydrazine hydrate and ethylenediamine

Cycloaddition of diphenylnitrilimine **14** to ethyl coumarin-3-carboxylate **1** in sodium ethoxide, yieldes the diazo-ether derivative **15** (Figure 10).[45]

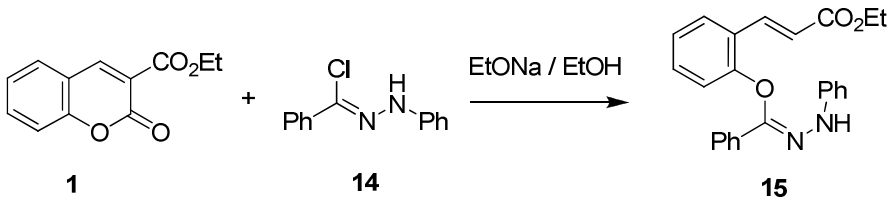


Figure 10. Cycloaddition of diphenylnitrilimine **14** to ethyl coumarin-3-carboxylate **1**

The reaction of **1** with trichloroacetic acid and nitromethane was studied. Thus, oxochromane **16**, cyclopropane **17** and the corresponding **18** were obtained by reaction of **1** with trichloroacetic acid, while the reaction of **1** with nitro methane gives the diesters **19** (Figure 11).[46, 47]

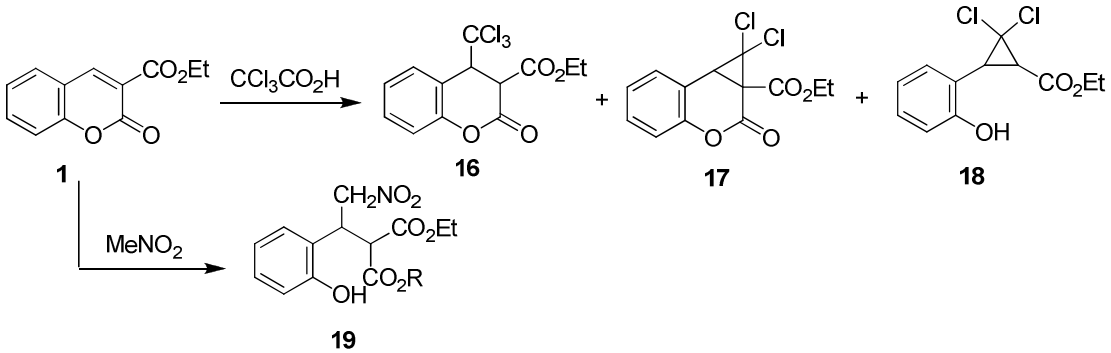


Figure 11. Reaction of **1** with trichloroacetic acid and nitromethane

3.1.2. Reduction

Reduction of coumarin-3-carboxylate with boranes has been studied. Thus, reduction of methyl coumarin-3-carboxylate with borane, BH_3-SMe_2, 9-borabicyclo[3.3.1]nonane and bis(tert-butylthio)ethane-diborane gives 57% dihydrocoumarin **20** (Figure 12).[48]

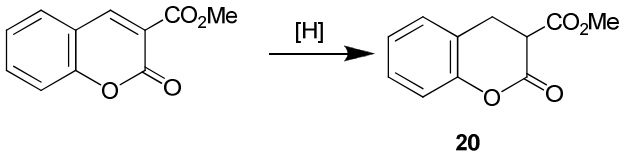


Figure 12. Reduction coumarin-3-carboxylate

The selective reduction of the endocyclic double bond of coumarins-3-carboxylates by Hantzsch 1,4-dihydropyridine was studied. Hantzsch 1,4-dihydropyridine catalyzes the chemoselective reduction of the 3,4-double bond in **1** to give 3,4-dihydrocoumarin-3-carboxylate **21** (Figure 13).[49]

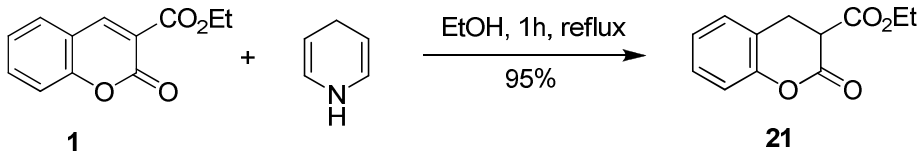
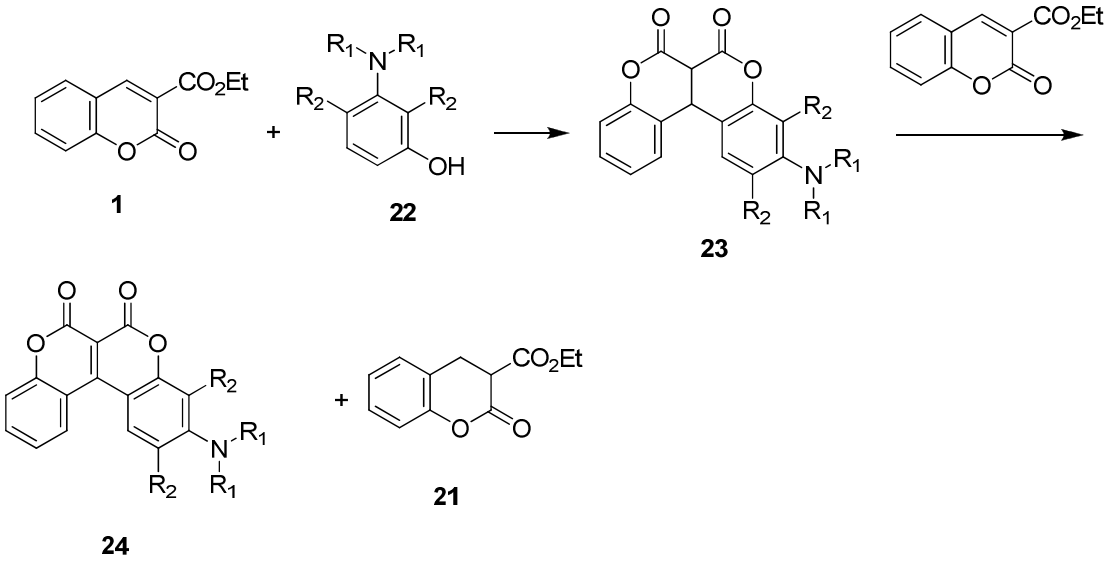


Figure 13. Selective reduction of the endocyclic double bond of coumarin-3-carboxylate

6*H*,7*H*-3-Diethylamino[1]benzopyrano[3,4-*c*][1]benzopyran-6,7-dione **23** and (6*H*,7*H*-[1]benzopyrano[3,4-*c*][1]benzopyran-6,7-dione)[2,3,4-i,j]2,3,4,6,7,8-hexahydroquinolizine **24**, were prepared in 74 and 86% yield, respectively, by condensation (140°C, 1.5 h) of **1** (2 equiv.) with 3-(*N*,*N*-dialkylamino)phenols **22** (where alkyl = Et or triethylene chains) closing rings to the 2- and 4-positions of the arene ring (1 equiv.). Excess **1** acts obviously as oxidant (ethyl 3,4-dihydrocoumarin-3-carboxylate **21** was found in the reaction mixture) and hence the products contain the double bond [3,4-*c*] in place of the expected single bond (Figure 14).[50]



a. R_1=Et, R_2=H; b. R_1R_2= $CH_2CH_2CH_3$

Figure 14. Reaction of coumarin-3-carboxylate **1** with 3-(*N*,*N*-dialkylamino)phenols **22**

3.1.3. Rearrangement

Reduction of **1** with sodium borohydride and then aminolyzing the products with triethylenetetramine, without isolation of intermediate, leads to dioxotetramine ligand **25** (Figure 15).[51, 52]

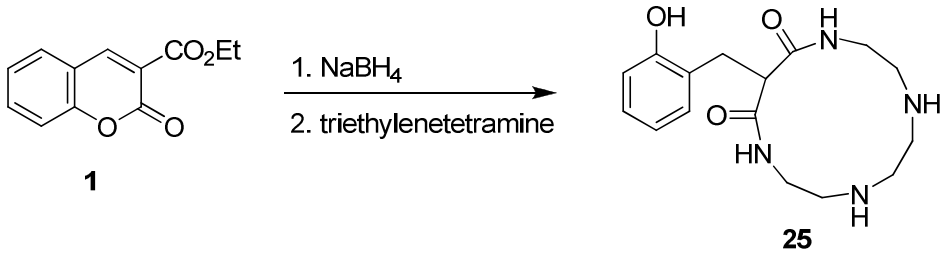


Figure 15. Formation of dioxotetramine ligand **25**

The treatment of **1** with 2.4 equiv of dimethylsulfoxonium methylide in DMF or DMSO at room temperature gave tricyclic product, ethyl 3-hydroxycyclopenta[*b*]benzofuran-2-carboxylate **26** in 64%, instead of the desired oxobenzo[*b*]cyclopropa[*d*]pyrancarboxylate **27** (Figure 16).[53]

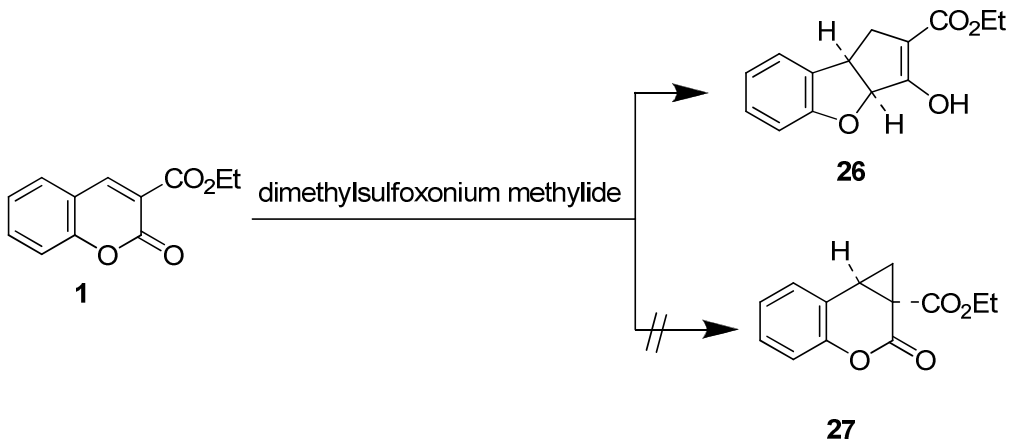


Figure 16. Formation of ethyl 3-hydroxycyclopenta[*b*]benzofuran-2-carboxylate **26**

Activating groups for the ring expansion of coumarin by diazoethane was studied. When coumarins-3-ester **1** reacted with diazoethane, 4-alkylated product **28** was isolated (Figure 17).[44]

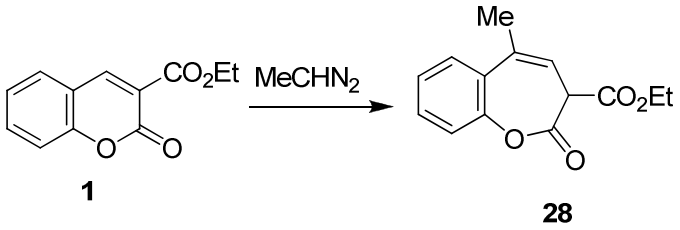


Figure 17. Reaction of coumarins-3-ester **1** with diazoethane

Rearrangement of ethyl coumarin-3-carboxylate **1** with 3-methylbutanoic anhydride **29** in the presence of triethylamine gave ethyl 2-(3,3-dimethyl-2-oxochroman-4-yl)acetate **30** in a good yield (Figure 18).[54]

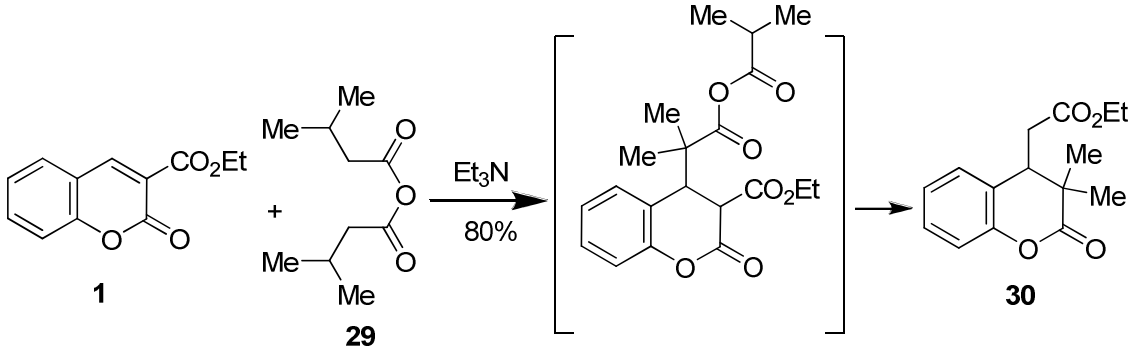
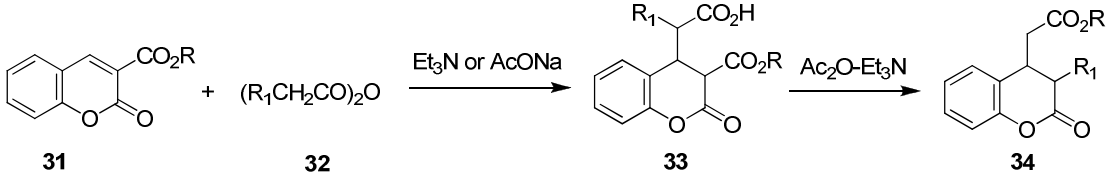


Figure 18. Formation of ethyl 2-(3,3-dimethyl-2-oxochroman-4-yl)acetate **30**

Esters of coumarin-3-carboxylic acids **31** were heated with carboxylic anhydrides **32** in the presence of triethylamine or sodium acetate to give **33**, which rearranged in the presence of Ac_2O-Et_3N to give **34** (Figure 19).[55]



R = Me, Et, Me_2CH, Me_3C, Ph; R_1 = H, Me, Et, Ph, CH:CH_2

Figure 19. Reaction of coumarin-3-carboxylates with carboxylic anhydrides

3.1.4. Cycloaddition Reactions

3.1.4.1. Stereoselective Cyclopropanation

The cycloaddition of ethyl diazoacetate to **1** gave the tetrahydro cyclopropa [c] chromene derivative **35** (Figure 20). Ethyl diazoacetate was added to the 3,4-double bond of **1** regio- and stereoselectively giving the endo-form of the initial cycloadduct, which, being unstable, is then transformed mainly to the above mentioned compound.[56]

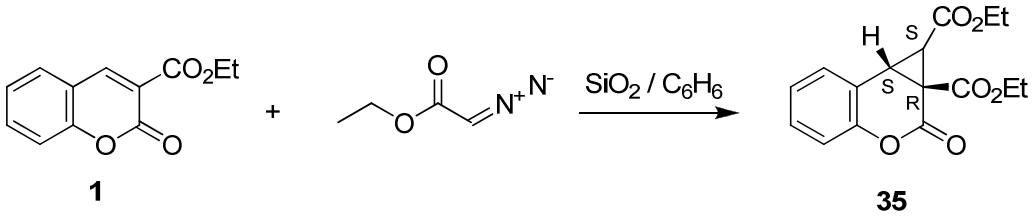


Figure 20. Cycloaddition of ethyl diazoacetate to coumarin-3-carboxylate

The high stereoselective cyclopropanation reaction of 3-acylcoumarins with α-bromo ketones at room temperature has been reported. Ethyl coumarin-3-carboxylate **1** reacted with phenacyl bromide in the presence of a base to give the cyclopropane derivative **36** in moderate yield (Figure 21).[57, 58]

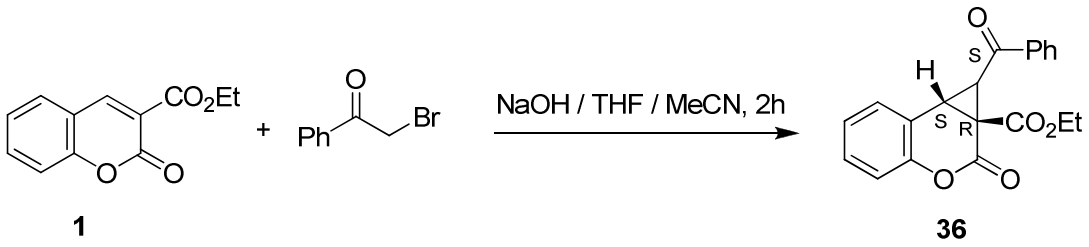
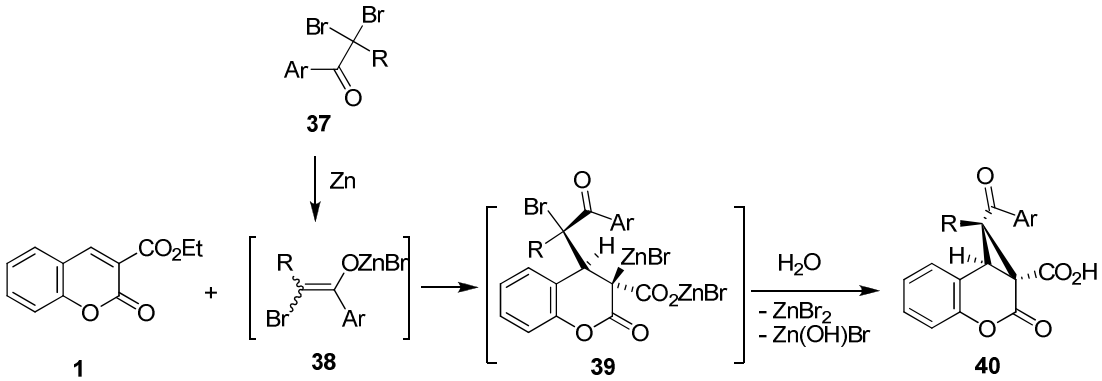


Figure 21. Reaction of coumarin-3-carboxylate with phenacylbromides

Cyclopropanation of ethyl coumarin-3-carboxylates with bromine-containing zinc enolates has been reported. Thus zinc enolates **38** derived from 1-aryl-2,2-dibromoalkanones **37** reacted with **1** to give 1-alkyl-1-aroyl-2-oxo-1a,7b-dihydrocyclopropa[*c*]chromene-1a-carboxylic acids **40** as a single geometric isomer (Figure 22).[59]



R= Me, Ar = 4-Br-C_6H_4, Ar= 4-F-C_6H_4; R = Et, Ar = 4-F-C_6H_4

Figure 22. Reaction of coumarin-3-carboxylate with 1-aryl-2,2-dibromoalkanones **37**

Zinc enolate **42** obtained from 2,2-dibromo-1-indanone **41** reacted with **1** giving the corresponding derivative of 2,1'-dioxo-spiro(1a,7b-dihydrocyclopropa[*c*]chromen-1,2'-indan) **44** in the form of a single geometric isomer (**Figure 23**).[60]

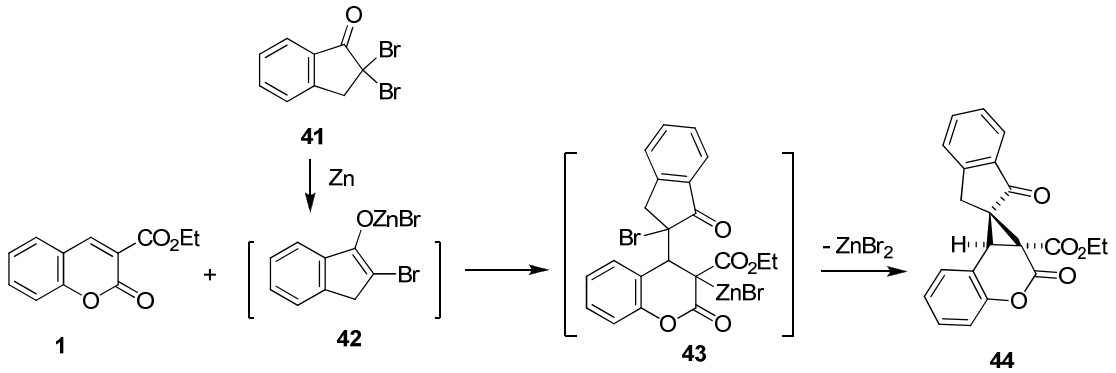


Figure 23. Reaction of coumarin-3-carboxylate with 2,2-dibromo-1-indanone

3.1.4.2. [2+2] Cycloaddition

The photo [2+2] cycloaddition of styrene **45** to **1** gave a mixture of equal two stereoisomers **46** and **47** respectively (Figure 24).[61]

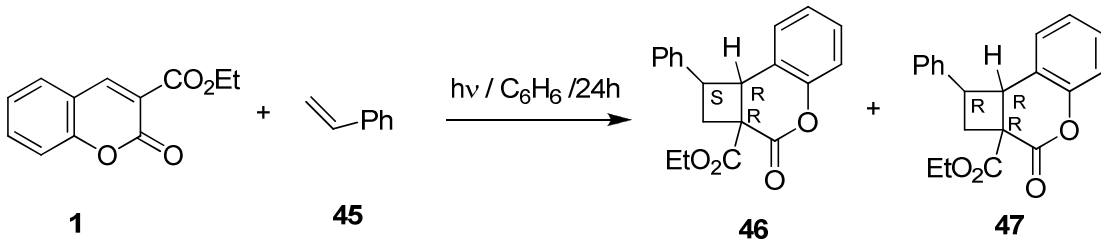


Figure 24. [2+2] cycloaddition of styrene to coumarin-3-carboxylate

2a,8b-Dihydro-3*H*-benzo[*b*]cyclobuta[*d*]pyran-3-one **49** was obtained by photo [2+2] cycloaddition of **1** to phenylacetylene **48** (Figure 25).[62]

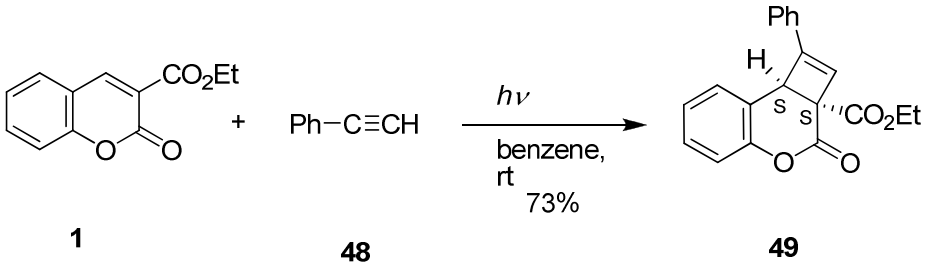


Figure 25. [2+2]cycloaddition of coumarin-3-carboxylate to phenylacetylene

3.1.4.3. [3+2] Cycloaddition

Regiochemistry of the cycloaddition of diphenylnitrilimine to coumarin-3-ester has been reported. The cycloaddition reaction of diphenylnitrilimine **50** to **1** gave regioisomeric pyrazole derivative **52** not the benzopyranopyrazole derivative **53**, due to the electron-withdrawing properties of ester reversed the regiochemistrty of the reaction (Figure 26).[45,63]

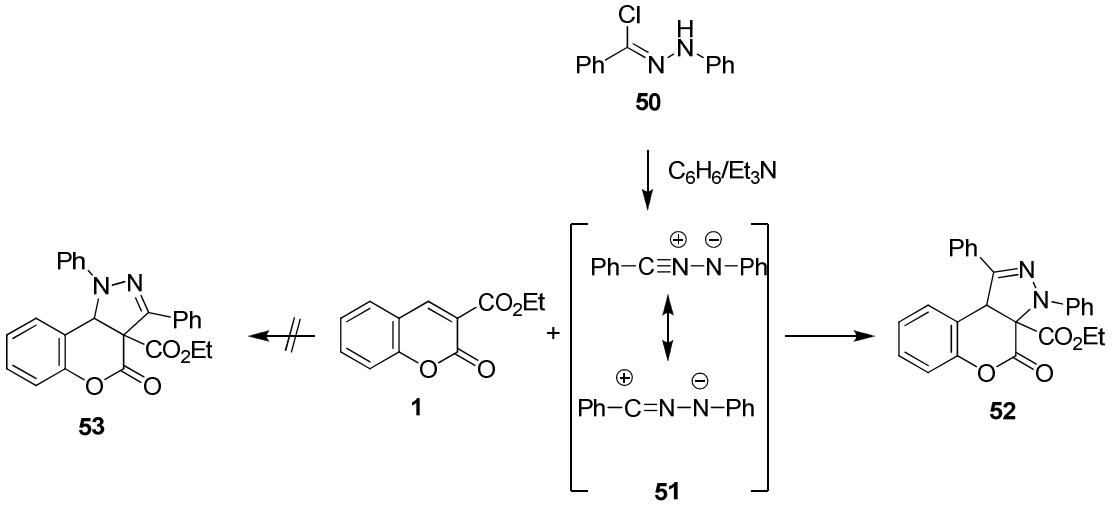


Figure 26. [3+2] cycloaddition reaction of diphenylnitrilimine to coumarin-3-carboxylate

3.1.4.4. [4+2] Cycloaddition

Diels-Alder reaction of 2-[(trialkylsilyl)oxy]pyrylium cations of 2*H*-1-benzopyran-2-one derivatives was reported. Thus, **1** reacted with diene derivative **53** in the presence of *tert*-butyldimethyl[(trifluoromethylthio)trioxidanyl]silane to give tetrahydrobenzo[*c*]chromen-6-one derivative **54** (**Figure 27**).[64]

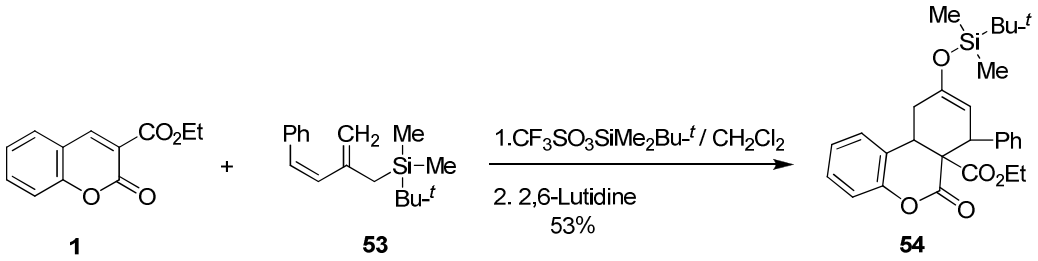


Figure 27. Diels-Alder reaction with diene derivative **53**

A Diels-Alder reaction of 3-substituted coumarins in water and under high-pressure condition was considered as an uncatalyzed route to tetrahydro-6*H*-benzo[*c*]chromen-6-ones. Thus, Diels-Alder reactions of coumarins-3-ester **1** with 1,3-dimethyl-1,3-butadiene **55** carried out in dichloromethane and under 9 kbar pressure to afford tetrahydro-6*H*-benzo[*c*]chromen-6-one derivative **56** in excellent yield (Scheme 29). [65] Also, hafnium chloride-THF complex is an efficient catalyst for the Diels-Alder cycloaddition of **1** and 1,3-butadiene **57** under solvent-free conditions furnishing the corresponding cycloadduct **58** (Figure 28).[66]

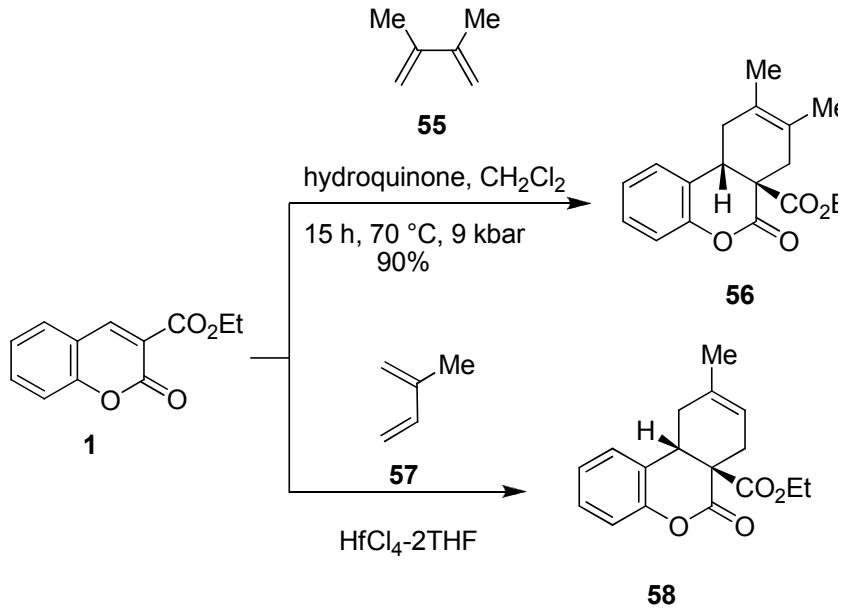


Figure 28. Diels-Alder reaction with 1,3-dimethyl-1,3-butadiene **55** and 1,3-butadiene **57**

3.1.5. Alkylation

3.1.5.1. With Organometallic Reagents

3.1.5.1.1. Grignard Reagents

Reaction of ethyl coumarin-3-carboxylate **1** with *tert*-butylmagnesium chloride gave ethyl 4-*tert*-butyl-3,4-dihydrocoumarin-3-carboxylate **59**, 4-*tert*-butyl-3-pivaloyl-3,4-dihydrocoumarin **60**, and diethyl 2,2'-dioxo-4,4'-bichroman-3,3'-dicarboxylate **61** (Figure 29).[67]

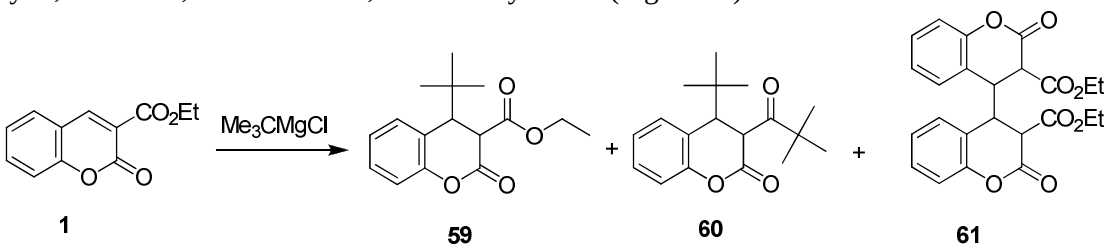


Figure 29. Reaction of ethyl coumarin-3-carboxylate with *tert*-butylmagnesium chloride

Grignard addition of alkylmagnesium halides to **1** in the presence of CuBr followed by hydrolysis, decarboxylation and dehydrogenation of the resulting dihydrocoumarins afforded 4-alkylcoumarins **62** (Figure 30).[68]

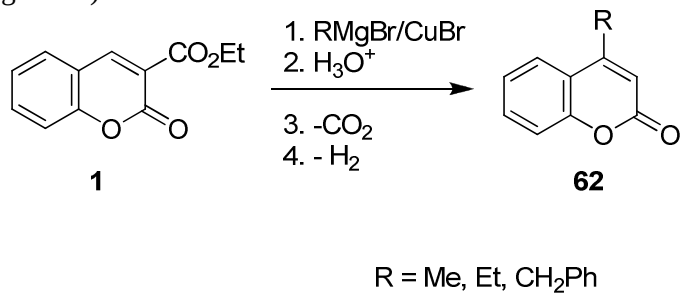


Figure 30. Grignard addition of alkylmagnesium halides to ethyl coumarin-3-carboxylate

The reaction of 2-methylphenylmagnesium bromide with ethyl coumarin-3-carboxylate **1** has been reported to give **64** in 25% yield via the formation of **63**. Further addition of 2-methylphenylmagnesium bromide to **63** gave **65** which eliminate the elements of EtOMgBr to give **66**. 1,4-Addition of RMgBr to **66** gives **67** which on hydrolysis gives **68** in a reverse aldol condensation. Hydrolysis of **63** gives **68** (Figure 31). [69]

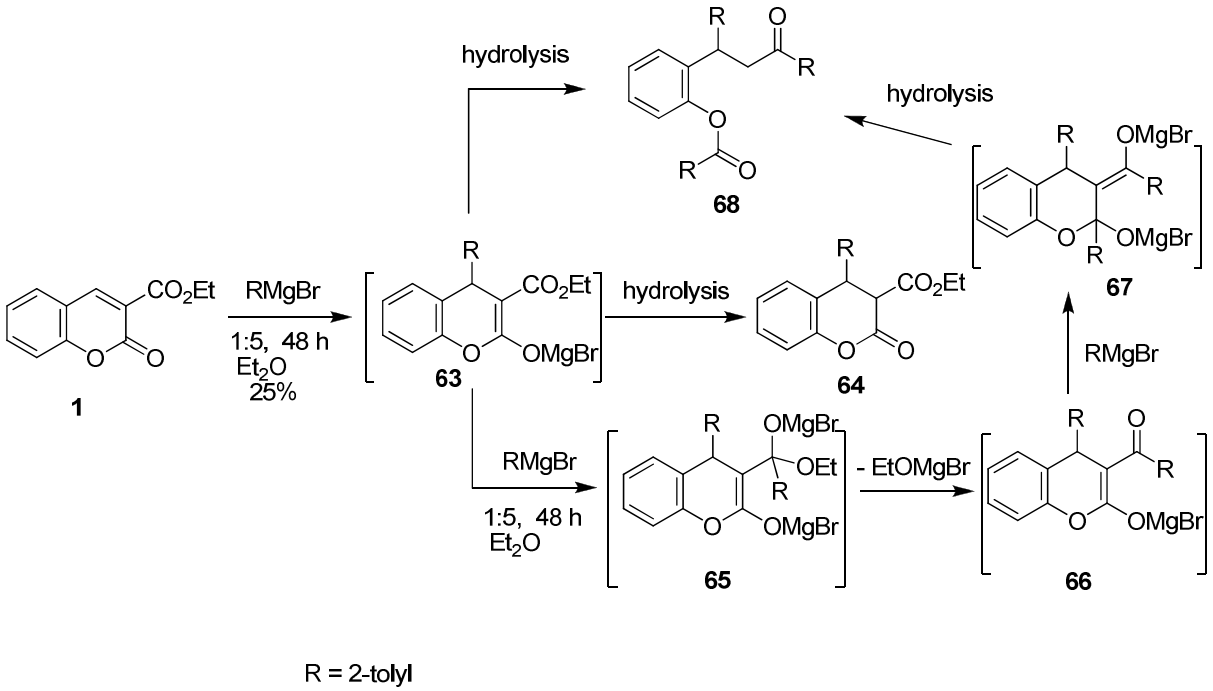


Figure 31. Reaction of 2-methylphenylmagnesium bromide with ethyl coumarin-3-carboxylate

3.1.5.1.2. Organolithium

Conjugate addition of (*Z*)-2-ethoxyvinyl anion to α,β-unsaturated lactones is best affected via Noyori-type organocopper reagents. The copper reagent, lithium (*Z*)-2-ethoxyethenylbis(tributylphosphine)cuprate **70**, was prepared in situ from *cis*-1-bromo-2-ethoxyethene **69**, *tert*-butyllithium, copper iodide (CuI), and tributylphosphine. Addition of this reagent to coumarin-3-ester **1** gave vinyl ether **71** in 89% yield (Figure 32).[70]

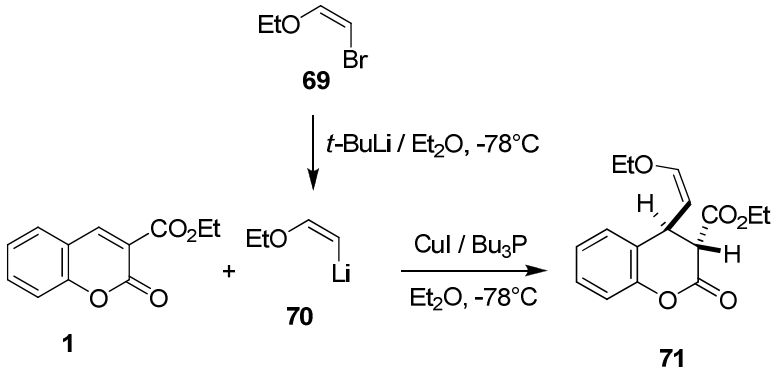


Figure 32. Reaction of *cis*-1-bromo-2-ethoxyethene with ethyl coumarin-3-carboxylate

3.1.5.1.3. Zinc Enolates

Zinc enolates **73** derived from 1-aryl-2-bromo-2-phenylethanone **72** react with alkyl coumarin-3-carboxylates **31** to give alkyl 4-(2-aryl-2-oxo-1-phenylethyl)-coumarin-3-carboxylates **75** as a single diastereomer (Figure 33).[71]

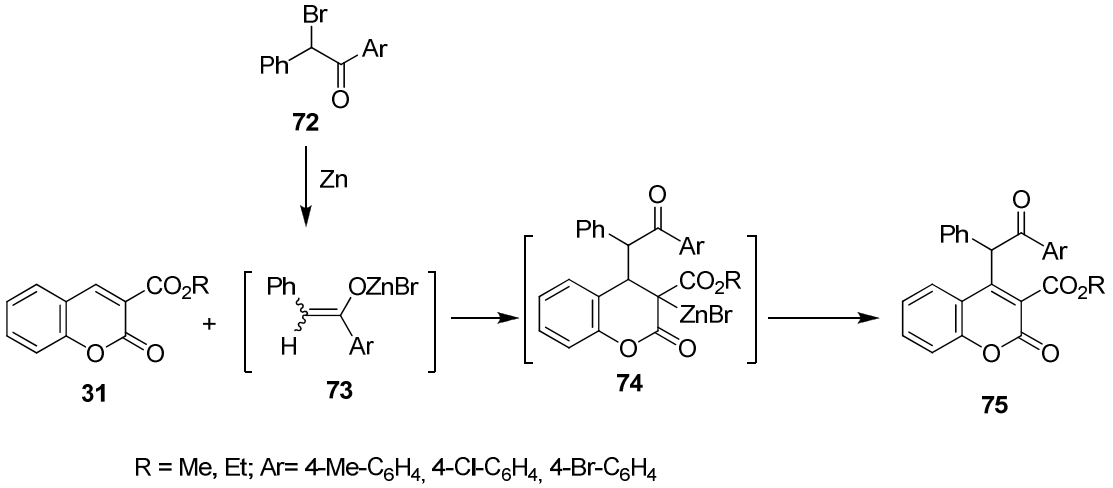


Figure 33. Formation of alkyl 4-(2-aryl-2-oxo-1-phenylethyl)-coumarin-3-carboxylates **75**

Also, zinc enolate **77** derived from 2-bromo-1-indanone **76** reacted with ethyl coumarin-3-carboxylate **1** to give ethyl 2-oxo-4-(1-oxo-2-indanyl)chroman-3-carboxylate **78** as a single diastereomer (Figure 34).[71]

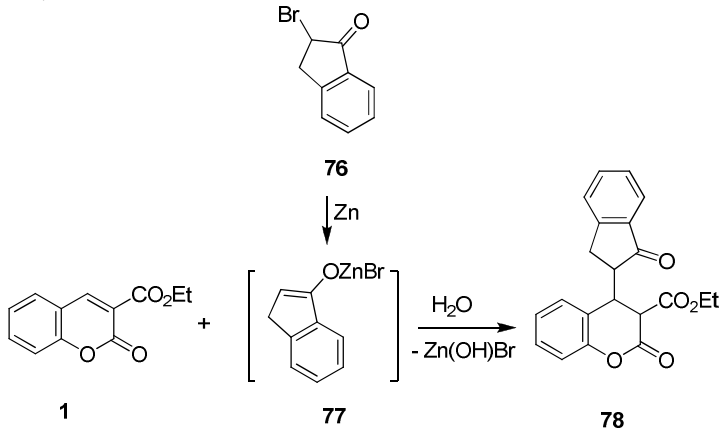
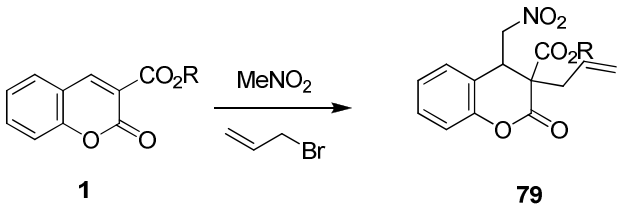


Figure 34. Formation of ethyl 2-oxo-4-(1-oxo-2-indanyl)chroman-3-carboxylate **78**

3.1.5.2. Miscellaneous Reagents

Allylation-assisted addition of nitromethane to ethyl coumarin-3-carboxylates has been reported. Thus, the addition of nitromethane to **31** using 1,8-diazabicyclo[5.4.0]undec-7-ene as basic catalyst proceeds in the presence of allyl bromide to give benzopyrans **79** (Figure 35).[72]



R = Me, Et, CMe_3, $CH_2C_6H_4NO_{2-4}$, Ph

Figure 35. Reaction of allyl bromide and nitromethane with coumarin-3-carboxylates

The addition of some enamino esters to 3-substituted coumarins has been reported. Thus, **1** reacted with enamino esters **80** to give coumarins **81**-**83** in good yields (Figure 36).[73]

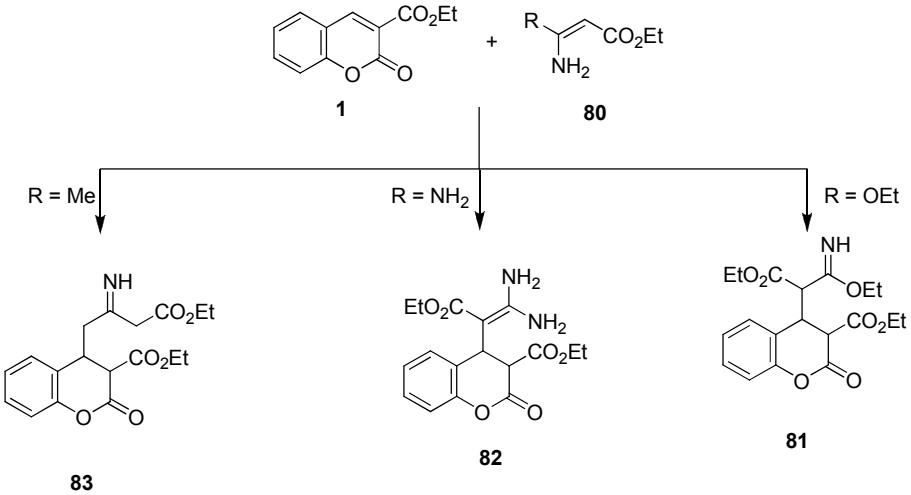


Figure 36. Addition of some enamino esters to 3-substituted coumarins

In the same sense, Ivanov et al. reported the addition of methyl 3-amino-3-ethoxyacrylate **84** to **1** to give 67% *trans*-adduct **85** (Figure 37).[74]

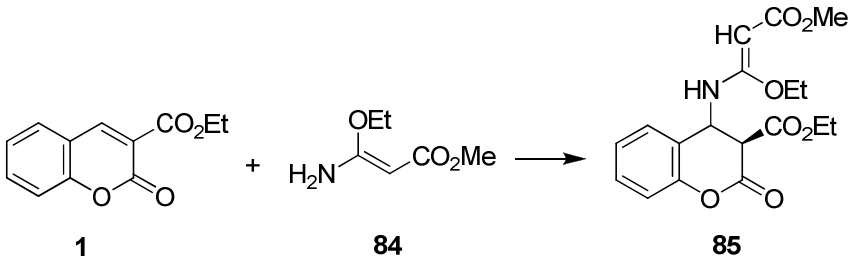
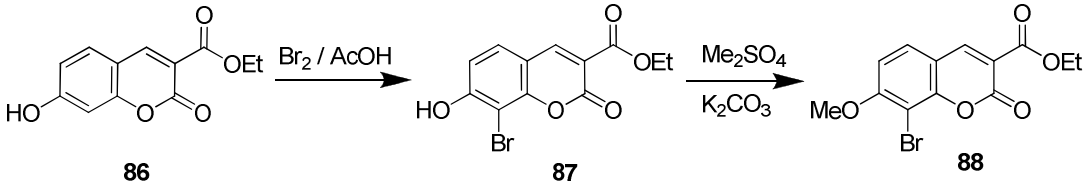


Figure 37. Addition of methyl 3-amino-3-ethoxyacrylate to coumarin-3-carboxylates

3.1.6. Bromination

Treatment of **86** with bromine in acetic acid gave the brominated compound **87**, that was *O*-alkylated to furnish compound **88** (Figure 38).[41]



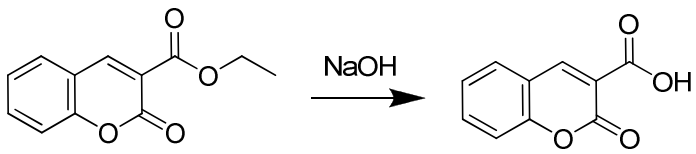
86 **87** **88**

Figure 38. Bromination of coumarin-3-carboxylates

3.2. Ester Group Reaction

3.2.1. Hydrolysis

Hydrolysis of ethyl coumarin-3-carboxylate **1** with sodium hydroxide gave coumarin-3-carboxylic acid **89** (Figure 39).[75]

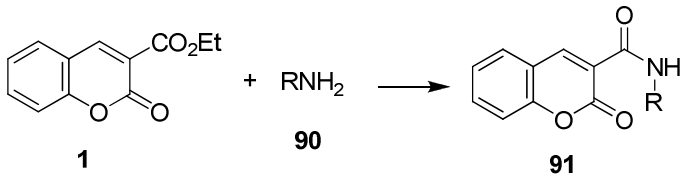


1 **89**

Figure 39. Hydrolysis of ethyl coumarin-3-carboxylate

3.2.2. Reaction With Amines

Amidation of ethyl coumarin-3-carboxylate **1** with primary amines **90** gave coumarin-3-carboxamides **91** (Figure 40).[42, 76, 77]



1 **90** **91**

R = Bu, $PhCH_2$, 4-$MeOC_6H_4$

Figure 40. Amidation of ethyl coumarin-3-carboxylate

Nitration of ethyl coumarin-3-carboxylate **1** gave the corresponding nitro derivative **92** which was converted into amide **93** on treatment with benzylamine, which then reacted with phosphorus pentasulfide to give *N*-benzyl-6-nitrocoumarin-3-carbothioamide **94** (Figure 41).[78]

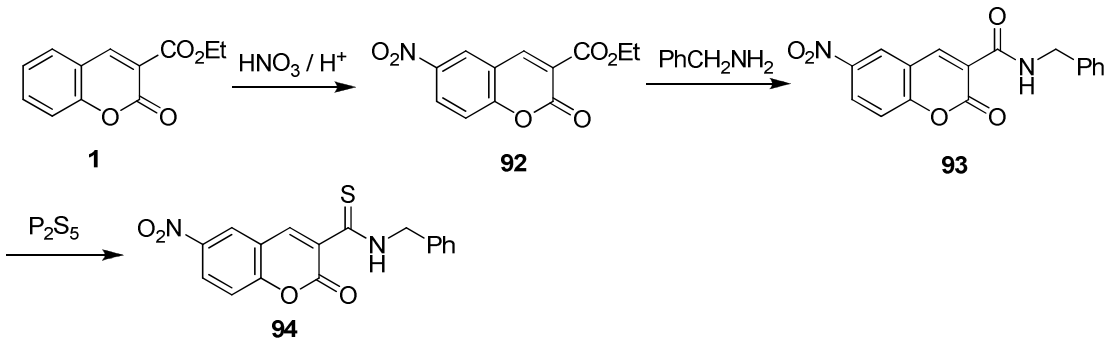
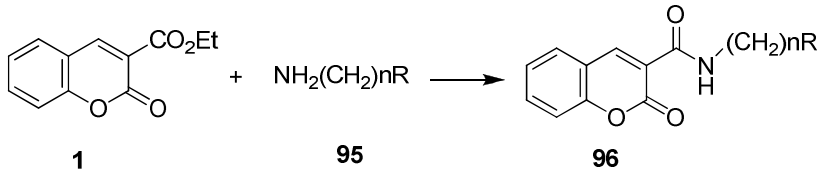


Figure 41. Nitration of ethyl coumarin-3-carboxylate

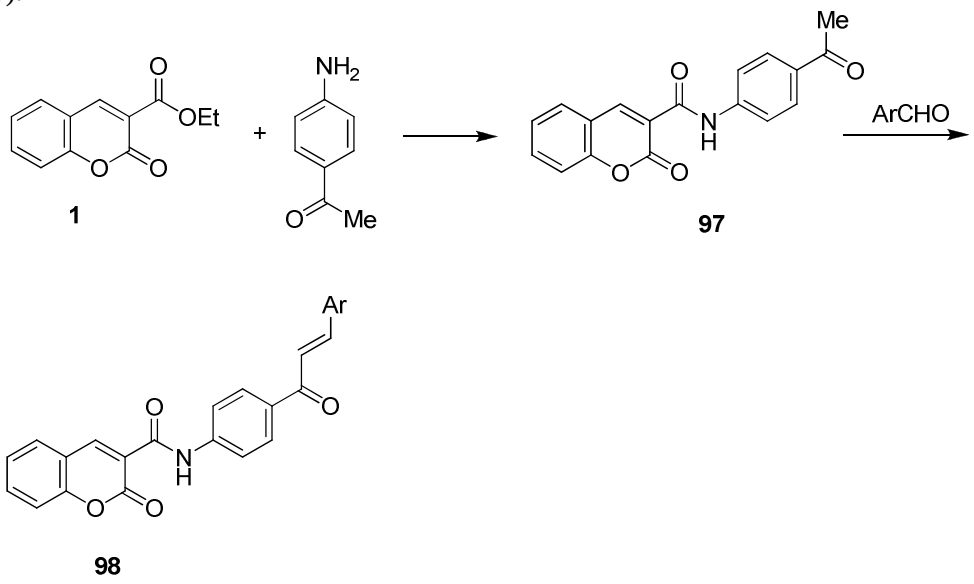
N-Substituted coumarin-3-carboxamides with antimicrobial and insecticidal activities have been prepared. Thus, coumarin carboxamides **96** were prepared from **1** with amines **95** (Figure 42).[79]



n= 2, R= OH; n=2, R= Cl; n= 2; R = NMe_2

Figure 42. Formation of coumarincarboxamides **96**

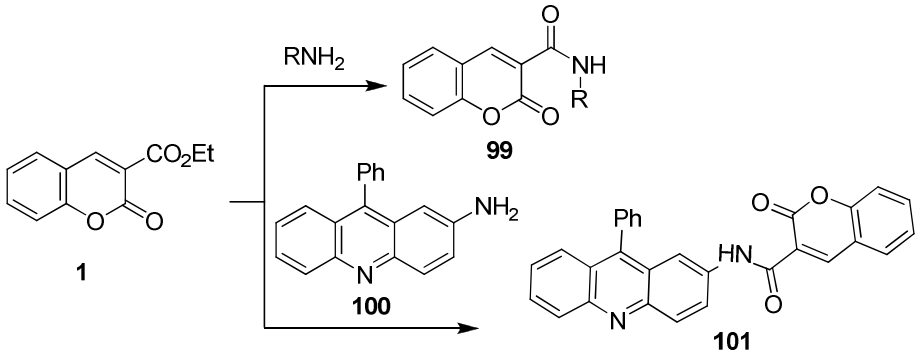
Additionally, condensation of **1** with *p*-aminoacetophenone gave the corresponding intermediate **97** which reacted with a number of aromatic aldehydes to yield the chalcone analogs **98** (Figure 43). [80]



Ar = Ph, 4-ClC_6H_4, 3-$O_2NH_6H_4$, 2-$MeOC_6H_4$, 2,4-$(MeO)_2C_6H_3$

Figure 43. Formation of chalcone analogs **98**

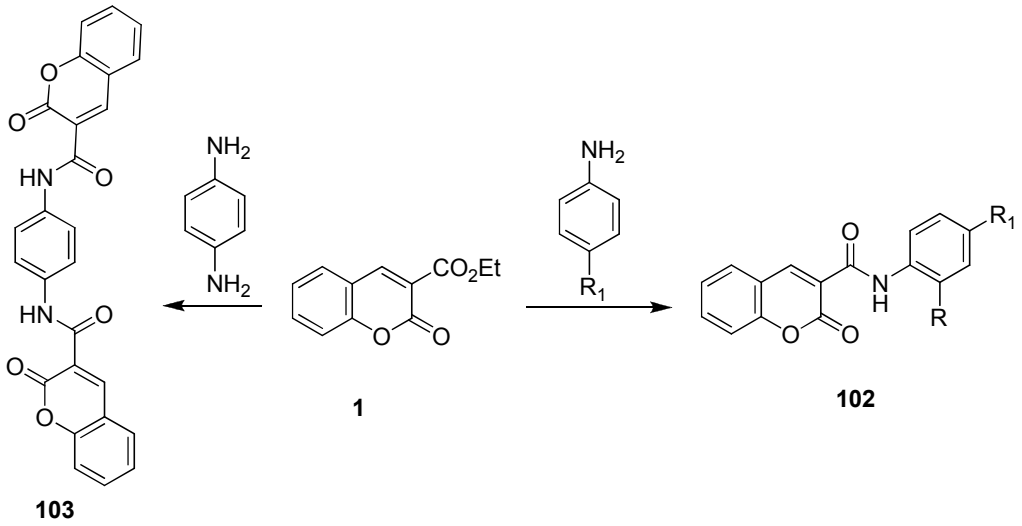
Various *N*-bromoaryl coumarin-3-carboxamides **99** were prepared by amidation of **1** with bromoarylamines. Some acridinyl derivatives, e.g. **101**, were prepared (Figure 44.).[81]



R = 4-BrC_6H_4, 4,2-, 4,3-, or 2,4-$BrMeC_6H_3$, 4,2- or 2,4-$BrClC_6H_3$, 4-bromo-, and 4,7-dibromonaphthyl

Figure 44. Formation of *N*-bromoaryl coumarin-3-carboxamides **99** and **101**

Coumarin-3-carboxanilides, **102** and **103**, reported as bactericidal and fungicidal activities, were prepared by amidation of **1** with anilines (Figure 45).[82]



R_1 = H, Me, CO_2Et, CH_2CO_2H, $CONHCH_2CO_2H$, $CONHC_6H_4Me$-4, $CONHCH_2CO_2Me$

Figure 45. Reaction of ethyl coumarin-3-carboxylate with anilines and *p*-phenylene diamine

Amidation of **1** and sulfa drugs **103** gave amide **104** (Figure 46).[83]

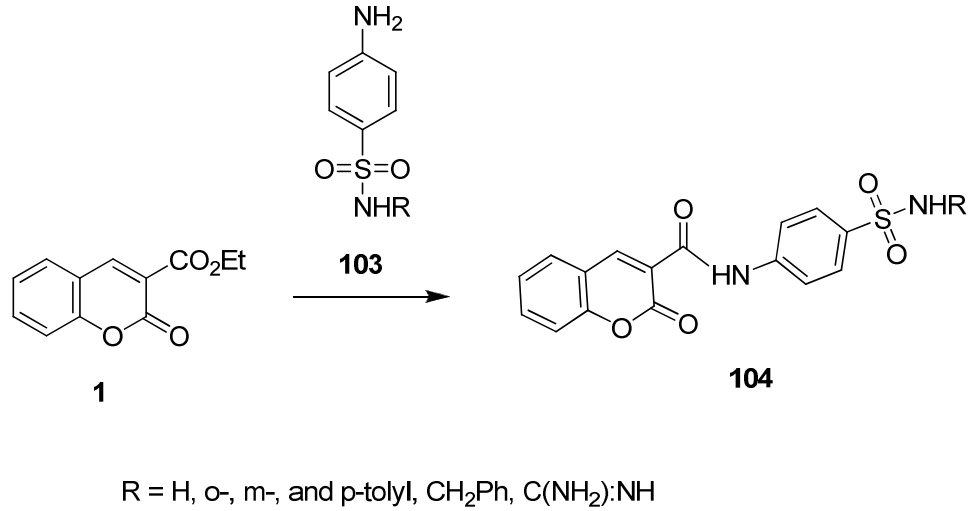


Figure 46. Reaction of coumarin-3-carboxylate with sulfa drugs **103**

N,*N*′-bis[2-oxo-2*H*-1-benzopyran]-3-carboxamide derivatives **106** have been synthesized by the reaction of **1** with diamines **105** in different yields ranging from 11% to 30%. Some of the synthesized compounds show good selective inhibitory activity against the monoamine oxidase (MAO-A) isoform (Figure 47).[84]

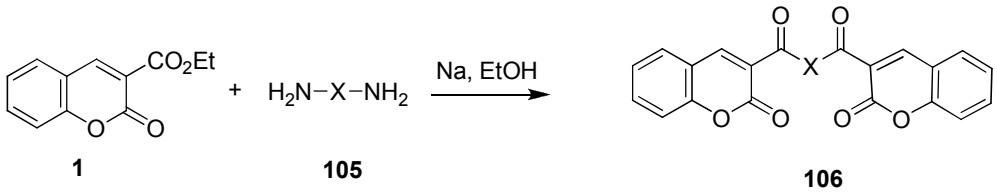


Figure 47. Reaction of coumarin-3-carboxylate with diamines **105**

Coumarin-3-carboxylic acid **89** was treated with thionylchloride to give the key intermediate **107**. At last, **107** reacted with corresponding *N*-substituted piperazine, **108** and the target compounds **109** were obtained, that have acetylcholinesterase inhibitory activity (Figure 48).[85]

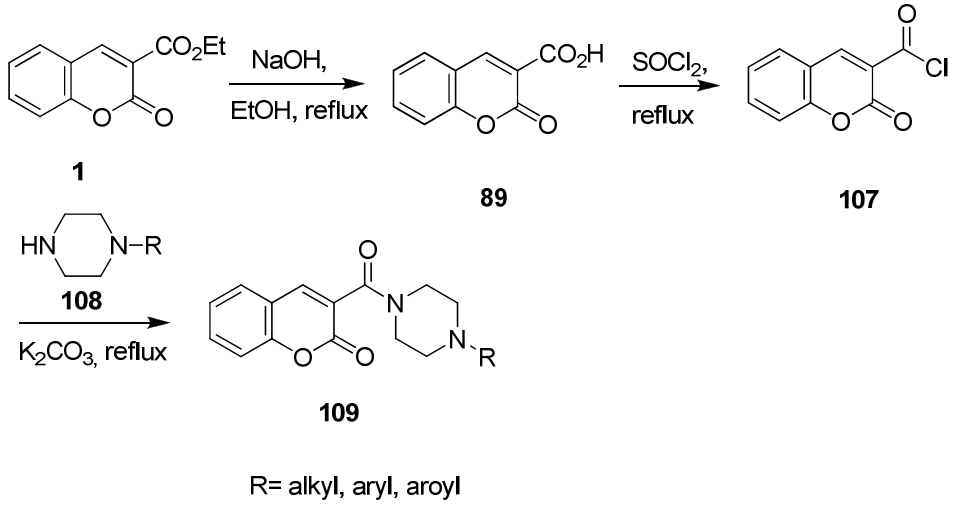


Figure 48. Reaction of coumarin-3-carboxylate with *N*-substituted piperazine, **108**

Conjugate reduction of **1** with Pd/C-NEt_3 to *N*-ethyl coumarin-3-carboxamide **110** in 44% yield was reported (Figure 49).[86]

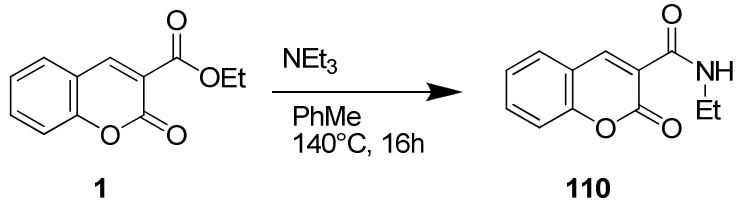


Figure 49. Formation of *N*-ethyl coumarin-3-carboxamide **110**

3.2.3. Formation of Carbohydrazides

Coumarin incorporated Schiff bases of 1,3,4-oxadiazoles bearing coumarin have anticonvulsant activities. Thus, **1** was reacted with hydrazine hydrate in ethanol to give coumarin-3-carbohydrazide **111**. 3-(5-amino-1,3,4-oxadiazol-2-yl)coumarin **112** was prepared by reaction of the hydrazide **111** with cyanogens bromide. 3-[5-((1*E*)-Arylmethyleneamineamino)]-1,3,4-oxadiazol-2-yl]coumarin **113** was prepared by reaction of 3-(5-amino-1,3,4-oxadiazol-2-yl)coumarin **112** with 3-nitrobenzaldehyde in glacial acetic acid and 1,4-dioxane (Figure 50).[87]

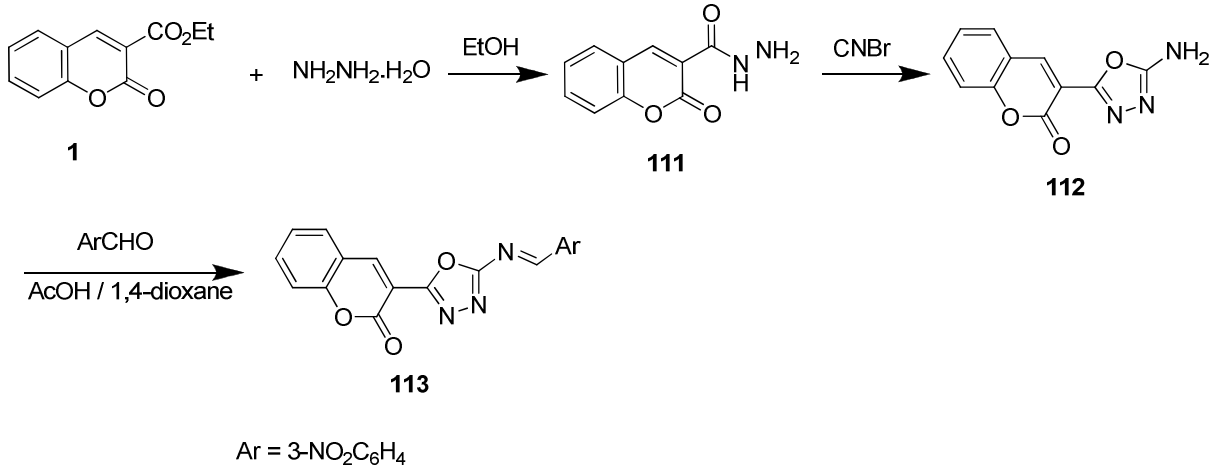


Figure 50. Reaction of coumarin-3-carboxylate with hydrazine hydrate

Thiosemicarbazide derivatives of coumarins **115**, as potential anticonvulsant and analgesic agents, were synthesized by reaction of carbohydrazide **111** with aryl isothiocyanates **114** (Figure 51).[88]

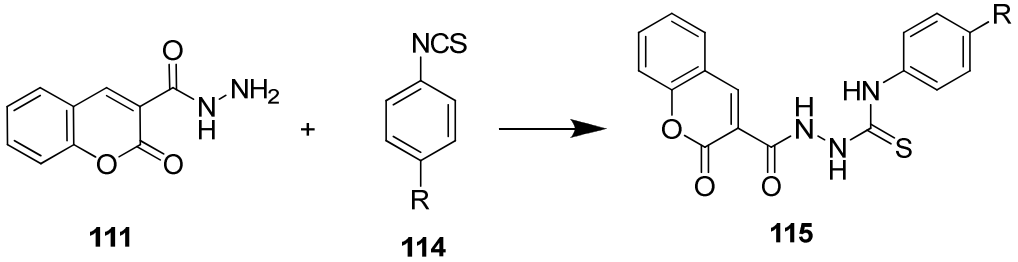


Figure 51. Formation of thiosemicarbazide derivatives of coumarins **115**

Imran et al. have reported the synthesis of 1-arylaminomethyl-3-(coumarin-3-yl carbohydrazino) isatins **117** as potential anticonvulsants. Thus, the condensation of the carbohydrazide **111** with isatin followed by reaction with formaldehyde and different aromatic amines resulted in the formation of **117** (Figure 52.).[89]

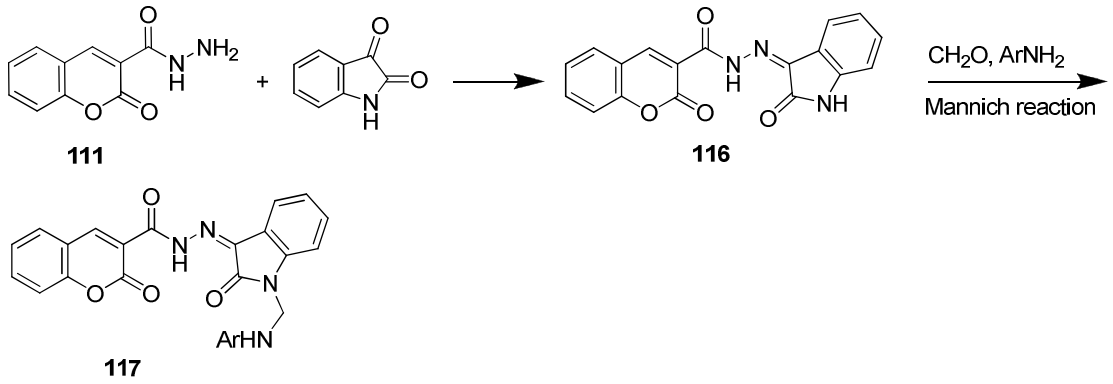
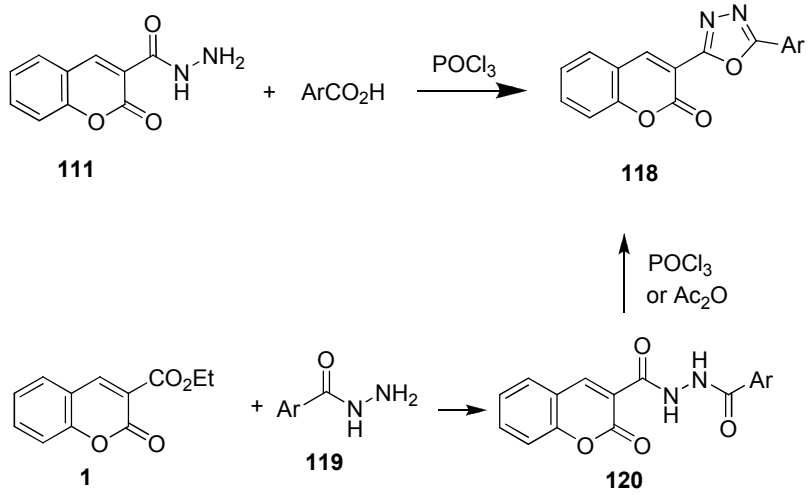


Figure 52. Formation of 1-arylaminomethyl-3-(coumarin-3-yl-carbohydrazino) isatins **117**

2-(Coumarin-3-yl)-5-aryl-1,3,4-oxadiazoles **118** were synthesized by reacting the carbohydrazide **111** with various aromatic acids in presence of phosphorus oxychloride (Figure 53).[90]



Ar = Ph, 2-ClC_6H_4, 4-ClC_6H_4, 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$, 3,5-$(O_2N)_2C_6H_3$, 4-$AcNHC_6H_4$, 3-pyridyl, 4-pyridyl, 2-HOC_6H_4, 3-$AcOC_6H_4$

Figure 53. Formation of 2-(coumarin-3-yl)-5-aryl-1,3,4-oxadiazoles **118**

The alternative synthesis of a series of 3-(1,3,4-oxadiazolyl)coumarins **118** have been described by treatment of **1** with several aryl carbohydrazides **119** afforded the corresponding *N*-acyl coumarin-3-carboxhydrazides which undergo cyclization in presence of phosphorus oxychloride or acetic anhydride (Figure 53).[79]

Coumarin-3-carbohydrazide **111** reacted with different aldehydes and ketones **121** to form the Schiff bases **122** which on cyclization by refluxing in excess acetic anhydride for 1 h resulted in 3-(4-acetyl-5*H*-aryl-4,5-dihydro-1,3,4-oxadiazol-2-yl)coumarins **123**, and these compounds were less neurotoxic as compared with the standared drug phenytoin (Figure 54).[91]

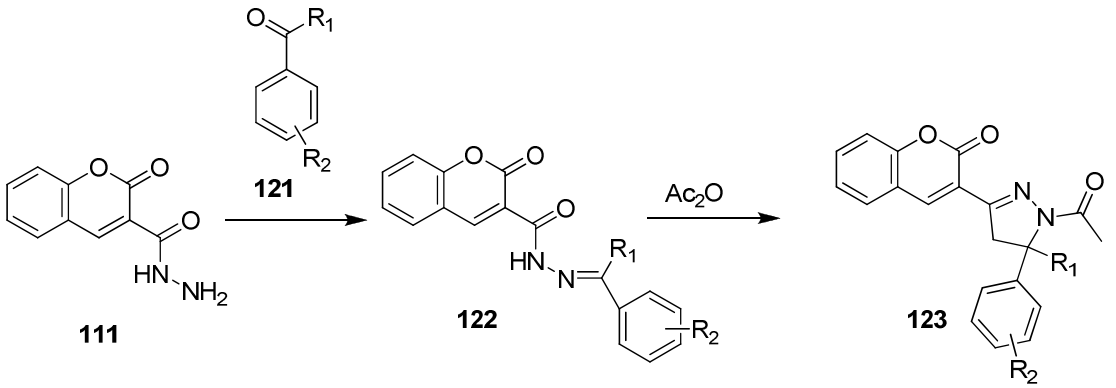


Figure 54. Reaction of coumarin-3-carbohydrazide with different aldehydes and ketones

Amidation of **1** with the hydrazine **124** gave the corresponding acetamide **125** which was converted to **126** by reaction with benzaldehyde after hydrolysis (Figure 55).[82]

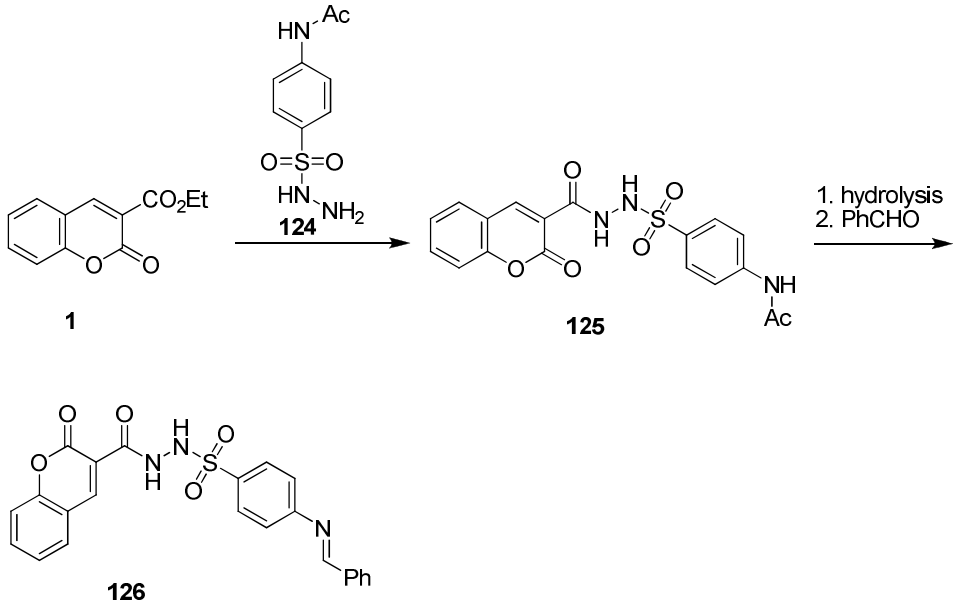


Figure 55. Amidation of coumarin-3-carboxylate with the hydrazine **124**

The reaction of **1** with the *N*,*N*'-diisopropylidene **127** and *N*,*N*'-diacetyl derivatives **128** of malonic acid dihydrazide under the conditions of the Michael reaction lead to the formation of *N*'-isopropylidene **129** and *N*'-acetyl **130** derivatives of coumarin-3-carbohydrazide (Figure 56).[92]

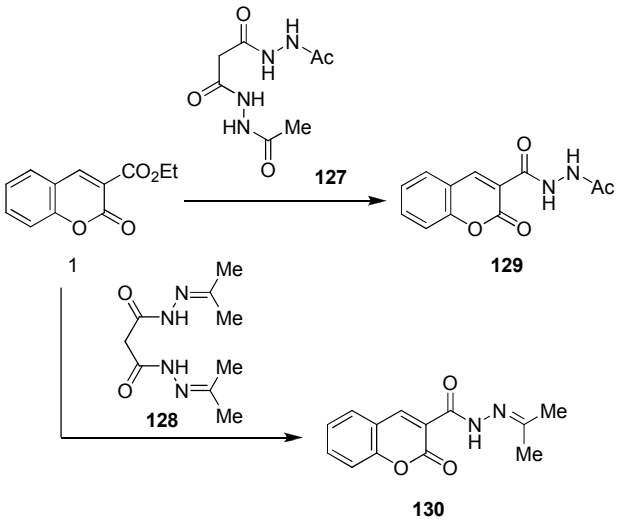


Figure 56. formation of *N*'-isopropylidene **129** and *N*'-acetyl **130**

3.3. Reaction With Acetylacetone

Ethyl coumarin-3-carboxylate **1** reacted with pentane-2,4-dione in the presence of sodium ethoxide to form 10-acetyl-7,9-dihydroxy-6*H*-benzo[*c*]chromen-6-one **131** in 67% yield (Scheme 58). [93] Bakeer has reported, the same reaction in sodium ethoxide to afford **131** as main product in addition to ethyl 4-(2,4-dioxopentan-3-yl)coumarin-3-carboxylate **132** as a side product (Figure 57).[94]

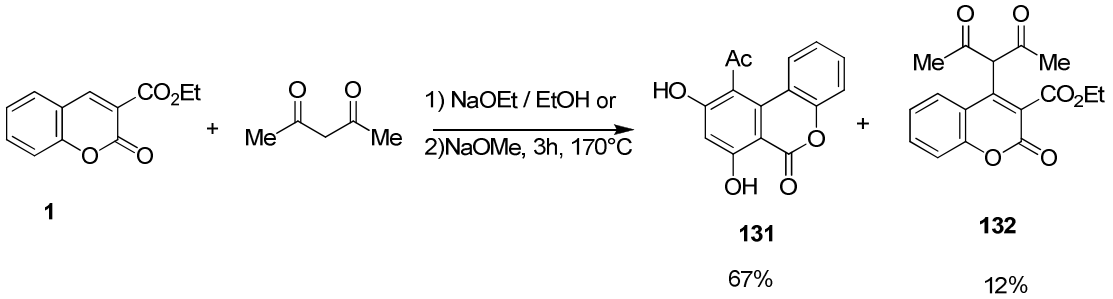


Figure 57. Reaction of coumarin-3-carboxylate with pentane-2,4-dione

3.4. Miscellaneous Reactions

2-Mercapto-4-hydroxypyrimidine[3,4-*b*]coumarins **133** was prepared by the condensation of 3-(ethoxycarbonyl)coumarin **1** with thiourea. Alkylation of **133** with alkyl halides yielded the corresponding 2-alkylthio compound **134** (Figure 58).[95]

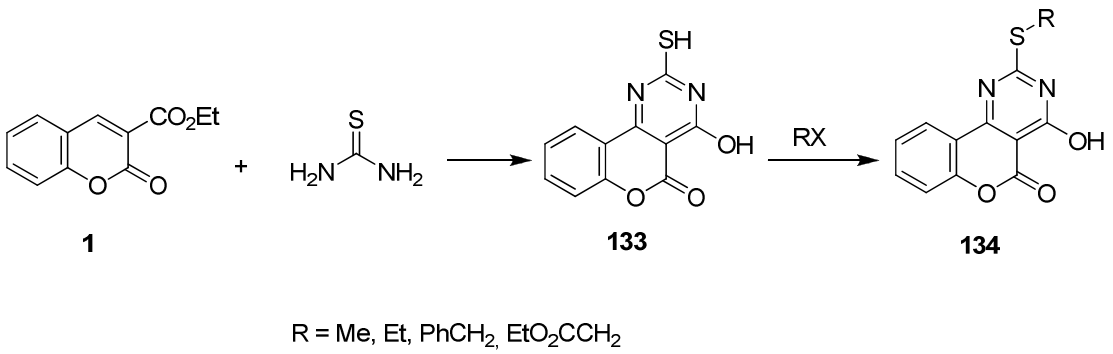


Figure 58. Formation of 2-mercapto-4-hydroxypyrimidine[3,4-*b*]coumarins **133**

Ethyl coumarin-3-carboxylate **1** reacted with cyanoaceteohydrazide in the presence of piperidine to give dihydrocoumarin **135**, which converted into pyrazolopyridone **136** (Figure 59).[96]

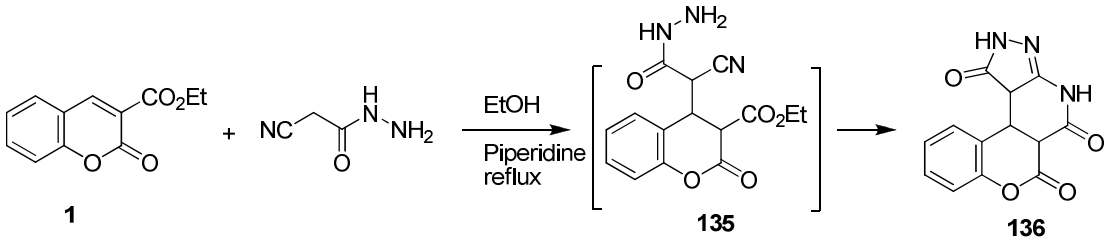


Figure 59. Reaction of coumarin-3-carboxylate with cyanoaceteohydrazide

References

[1] Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G. Q.; Barluenga, S.; Mitchell, H. J. Natural product-linked combinatorial libraries based on privileged structure I: general principles and solid phase synthesis of benzopyrans. *J. Am. Chem. Soc.* **2000**, *122*, 9939-9953.

[2] Kazuo, M.; Kazuya, O.; Hironobu, H. Mukai, K.; Okabe, K.; Hosose, H.; Synthesis and stopped-flow investigation of antioxidant activity of tocopherols. Finding of new tocopherol derivatives having the highest antioxidant activity among phenolic antioxidants. *J. Org. Chem*. **1989**, *54*, 557-560.

[3] Kostova, I. Synthetic and Natural Coumarins as Cytotoxic Agents. *Curr. Med. Chem.* **2005**, *5*, 29-46.

[4] Yourick, J. J.; Bronaugh, R. L. . Percutaneous absorption and mechanism of coumarin in human and rat skin. *J. Appl. Toxicol*. **1997**, *17*, 153-158.

[5] O'Kennedy R.; Thornes, R. D. Coumarins: Biology, Applications, and Mode of Action, John Wiley & Sons, New York, **1997**.

[6] Nielson, B. E. Heywood in the Biology and Chemistry of the Umbelliferae, Academic Press, London, **1971**.

[7] Murray, R. D. H.; Mendez, J.; Brown, S. A. The Natural Coumarins, Occurrence, Chemistry and Biochemistry, John Wiely & Sons, New York, **1982**.

[8] Yamazaki, H.; Tanaka, M.; Shimada, T. Highly sensitive high-performance liquid chromatographic assay for coumarin 7-hydroxylation O-deethylation by human liver cytochrome P450 enzymes. *J. Chromatogr.* B, **1999**, *721*, 13-19.

[9] Izquierdo, M. E. F.; Granados, J. Q.; Mir, V. M.; Martinez, M. C. L. Comparison of methods for determining coumarins in distilled beverages. *Food Chem.* **2000**, *70*, 251-258.

[10] Trenor, S. R.; Shultz, A. R.; Love, B. J.; Long, T. E. Coumarins in polymers: from light harvesting to photo-cross-linkable tissue scaffolds. *Chem.Rev*. **2004**, *104*, 3059-3078.

[11] Park, S. W.; Seo, B. S.; Kim, E.H.; Kim, D.H.; Paeng, K. J. Purification and determination procedure of coumarin derivatives. *J. Forensic Sci*. **1996**, *41*, 685-688.

[12] Knoevenagel, E. About the condensirende effect of organic bases. Chem. Ber. **1904**, 37, 4461-4463.

[13] Song, A. M.; Wang, X. B.; Lam, K.S. First total synthesis of a new sesquiterpenoid natural product, (±)-3-(2,4-dihydroxybenzoyl)-4,5-dimethyl-5-(4,8-dimethyl)-3(E),7(E)-nonadien-1-yl)tetrahydro-2-furanone. *Tetrahedron Lett*. **2003**, *41*, 1775-1777.

[14] Pechmann, H.; Duisberg, C. Novel synthesis of coumarins. *Chem. Ber*. **1884**, *17*, 929-936.

[15] Shriner, R. L. Reformatsky reaction. *Org. React*. **1942**, *1*, 1-37.

[16] Narasimahan, N.S.; Mali, R.S.; Barve, M.V. Synthetic Application of lithiation reactions; Part XIII. Synthesis of 3-phenylcoumarins and their benzo derivatives. *Synthesis*, **1979**, 906-909.

[17] Yavari, I.; Hekmat-Shoar, A. Z. A new and efficient route to 4-carboxymethylcoumarins mediated by vinyltriphenylphosphonium salt. *Tetrahedron Lett*. **1998**, *39*, 2391-2392.

[18] Li, J.; Jia, X. Synthesis of coumarin-3-carboxylic acid ethyl ester under room-temperature and solvent-free conditions. *Huaxue Shiji* **2008**, *30*, 228.

[19] Bogdal, D. Institute of Organic Chemistry, Politechnika Krakowska, Krakow, Pol. Editor(s): Rzepa, Henry S.; Kappe, C. Oliver; Leach, Christopher Coumarins - fast synthesis by the Knoevenagel condensation under microwave irradiation. Electronic Conference on Heterocyclic Chemistry, June 29-July 24, **1998** (1998), 383-386 (*Chem. Abstr*. **1999**, *132*, 107850).

[20] Bogdal, D. Coumarins: Fast Synthesis by Knoevenagel Condensation under Microwave Irradiation. *J. Chem. Res. (S)*, **1998**, *8*, 468-469
[21] Chen, X. Synthesis of coumarin-3-carboxylic acid ethyl ester. *Huagong Shikan*, **2005**, *19*, 11-12.
[22] Gopalakrishnan, S.; Viswanathan, K. R.; Priya, S. V.; Mabel, J. H.; Palanichamy, M.; Murugesan, V. Lewis acid metal ion-exchanged MAPO-5 molecular sieves for solvent free synthesis of coumarin derivative. *Catal. Commun.* **2008**, *10*, 23-28.
[23] Moussaoui, Y.; Ben, S. R. Catalyzed Knoevenagel reactions on inorganic solid supports: Application to the synthesis of coumarin compounds. *Comptes Rendus Chimie* **2007**, *10*, 1162-1169.
[24] Bigi, F.; Chesini, L.; Maggi, R.; Sartori, G. Montmorillonite KSF as an Inorganic, Water Stable, and Reusable Catalyst for the Knoevenagel Synthesis of Coumarin-3-carboxylic Acids. *J. Org. Chem.* **1999**, *64*, 1033.
[25] Li, J.Y.; Peng, J.J.; Qiu, H.Y.; Jiang, J.X.; Wu, J.R.; Ni, Y.; Lia, G.Q. Knoevenagel condensation reaction catalyzed by ionic liquid-functionalized silica. *Youji Huaxue* **2007**, *27*, 483-487.
[26] Karade, N. N.; Gampawar, S. V.; Shinde, S. V.; Jadhav, W. N. L-proline-catalyzed solvent-free Knoevenagel condensation for the synthesis of 3-substituted coumarins. *Chin. J. Chem.* **2007**, *25*, 1686-1689.
[27] Valizadeh, H.; Vaghefi, S. One-pot Wittig and Knoevenagel reactions in ionic liquid as convenient methods for the synthesis of coumarin derivatives. *Synth. Commun.* **2009**, *39*, 1666-1678.
[28] Valizadeh, H.; Shockravi, A.; Gholipur, H. Microwave assisted synthesis of coumarins via potassium carbonate catalyzed Knoevenagel condensation in 1-n-butyl-3-methylimidazolium bromide ionic liquid. *J. Heterocycl. Chem.* **2007**, *44*, 867-870.
[29] Ranu, B. C.; Jana, R. Ionic liquid as catalyst and reaction medium - a simple, efficient and Green procedure for Knoevenagel condensation of aliphatic and aromatic carbonyl compounds using a task-specific basic ionic liquid. *Eur. J. Org. Chem.* **2006**, *16*, 3767-3770.
[30] Cabello, J. A.; Campelo, J. M.; Garcia, A.; Luna, D.; Marinas, J. M. Knoevenagel condensation in the heterogeneous phase using aluminum phosphate-aluminum oxide as a new catalyst. *J. Org. Chem.* **1984**, *49*, 5195-5197.
[31] Rao, P. S.; Srinivas, K.; Krishna, K. L.; Sivaprasad, A. A process for the preparation of 2-oxo(2H)-1-benzopyrans (coumarins). IN 184895 (2000) (*Chem. Abstr*. **2004**, *141*, 314154).
[32] Ramani, A.; Chanda, B. M.; Velu, S.; Sivasanker, S. One-pot synthesis of coumarins. *Green Chem.* **1999**, *1*, 163-165.
[33] Awasthi, A. K.; Tewari, R. S. A novel and convenient synthesis of substituted coumarins. *Synthesis* **1986**,*12*, 1061-1062.
[34] Angelescu, E.; Pavel, O. D.; Birjega, R.; Zavoianu, R.; Costentin, G.; Che, M. Solid base catalysts obtained from hydrotalcite precursors, for Knoevenagel synthesis of cinnamic acid and coumarin derivatives. *Appl. Catal.* **2006**, *308*, 13-18.
[35] He, B.; Lin, Z. Synthesis of 2-oxo-2*H*-1-benzopyran-3-carboxylic acid ethyl ester under microwave irradiation conditions. *Huaxue Gongchengshi* **2007**, *21*, 9-10.
[36] Brufola, G.; Fringuelli, F.; Piermatti, O.; Pizzo, F. Simple and efficient one-pot preparation of 3-substituted coumarins in water. *Heterocycles*, **1996**, *43*, 1257-1266.
[37] Avetisyan, A. A.; Vanyan, Z. V.; Dangyan, M. T. Synthesis of functionally substituted coumarins. 42. *Khim. Geterotsikl. Soedin.* **1979**, *9*, 1181-1182.
[38] Yuan, H.J.; Wang, M.; Liu, Y. J.; Liu, Q. Copper (II)-catalyzed C-C bond-forming reactions of α-electron-withdrawing group-substituted ketene S,S-acetals with carbonyl compounds and a facile synthesis of coumarins. *Adv. Syn. Cat.* **2009**, *351*, 112-116.
[39] Kim, T.H.; Kim, I.; Yoo, M.; Swager, T. M. Development of Highly Selective Fluorescent Chemosensors for Fluoride Ion *J. Korean Chem. Soc*. **2007**, 51, 258-264.
[40] Rossi, R.; Bellina, F.; Carpita, A.; Gori, R. Alkyl (E)- and (Z)-2,3-dibromopropenoates as precursors to 3-substituted alkyl (E)- and (Z)-2-bromopropenoates, 2,3-disubstituted alkyl (Z)- and (E)-propenoates and some heterocyclic compounds. *Gazz. Chim. Ital.* **1995**, *125*, 381-392.
[41] Alvim, J.; Dias, R. L. A.;Castilho, M. S.; Oliva, G.; Correa, A. G. Preparation and evaluation of a coumarin library towards the inhibitory activity of the enzyme gGAPDH from Trypanosoma cruzi. *J. Braz. Chem. Soc*. **2005**, *16*, 763-373.
[42] Avetisyan, A. A.; Vanyan, E. V.; Boyadzhyan, Z. G.; Dangyan, M. T. Studies of unsaturated lactones. LII. Reaction of functionally substituted coumarins with certain nucleophilic agents. *Armyanskii Khim. Zh.* **1981**, *34*, 876-879.
[43] Kirkiacharian, B. S.; Brion, J. D.; Billet, D. Hydride reduction of coumarin derivatives: new method of synthesis of 2'-hydroxybenzylmalonic esters. Comptes Rendus des Seances de l'Academie des Sciences, Serie 2: Mecanique-Physique, Chimie, Sciences de l'Univers, Sciences de la Terre. *Comptes Rendus* **1982,** *294*, 181-184.

[44] Islam, A. M.; Aly, F. M.; El-Sharief, A. M. S.; Bedair, A. H.; El-Masry, F. M. Some reactions of coumarins with hydrazine and ethylenediamine. *Egypt. J. Chem.* **1983**, *26*, 233-239.
[45] Shawali, A. S.; Elanadouli, B. E.; Albar, H. A. Cycloaddition of diphenylnitrilimine to coumarins. The synthesis of 3a,9b-dihydro-4-oxo-1H-benzopyrano[4,3-c]pyrazole derivatives. *Tetrahedron* **1985**, *41*, 1877-1884.
[46] Bozhilova, A. Interaction of trichloroacetic acid with some 3-substituted 2*H*-1-benzopyran-2-ones. *Synth. Commun.* **1990,** *20*, 1967-1976.
[47] Bodzhilova, A.; Kostadinova, T.; Ivanov, C. Interaction of nitromethane with esters and amides of 2-oxo-2H-1-benzopyran-3-carboxylic acid. *Synth. Commun.* **1989**, *19*, 2963-2975.
[48] Kirkiacharian, B. S.; Danan, A. Reductions via boranes. A new, convenient method for the preparation of 3-substituted esters and thio esters of 3,4-dihydrocoumarin. *Synthesis*, **1986**, *5*, 383-385.
[49] Liu, Z.; Liu, Q.; Zhang, W.; Mu, R.; Yang, L.; Liu, Z. L.; Yu, W. Selective reduction of the endocyclic double bond of 3-substituted coumarins by Hantzsch 1,4-dihydropyridine. *Synthesis* **2006**, *5*, 771-774.
[50] Poronik, E. M.; Shandura, M. P.; Kovtun, Y. P. Synthesis of 6*H*,7*H*-[1]benzopyrano[3,4-c][1]benzopyran-6,7-diones. *Chem. Heterocycl. Compds.* **2006**, *42*, 410-411.
[51] Shourong, Z.; Huakuan, L.; Chunchen, L.; Fuping, K.; Yun-Ti, C. A convenient method for the synthesis of macrocyclic dioxotetramine ligands bearing pendant coordinating groups and the properties of their copper (II) complexes. *Inorg. Chim. Acta* **1995**, *228*, 225-232.
[52] Zhu, S. R.; Xian, J. C.; Bu, X. H.; Lin, H. K.; Chen, R. T. A convenient way for synthesis of C-functionalized macrocyclic dioxotetramine. *Chin. Chem. Lett.* **1993**, *4*, 669-672.
[53] Yamashita, M.; Okuyama, K.; Kawasaki, I.; Ohta, S. One-step synthesis of 2-substituted cyclopenta[b]benzofuran-3-ol derivatives from 3-substituted coumarins. *Tetrahedron Lett.* **1995**, *36*, 5603-5606.
[54] Bojilova, A.; Ivanov, C. Synthesis of the nitrile and some esters of 3,3-dimethyl-2-oxochroman-4-acetic acid. *Synthesis* **1986**, *5*, 415-416.
[55] Ivanov, K.; Bozhilova, A. Conversion of the esters of 2-oxo-2*H*-1-benzopyran-3-carboxylic acids into esters of 2-oxo-4-chromanacetic acid- a new rearrangement. *Chem. Ber.* **1978**, *111*, 3755-3763.
[56] Bojilova, A.; Videnova, I.; Ivanov, C.; Rodios, N. A.; Terzis, A.; Raptopoulou, C. P. Regio- and stereoselective 1,3-dipolar cycloaddition reactions of ethyl diazoacetate to 3-substituted 2H-1-benzopyran-2-ones. *Tetrahedron* **1994**, *50*, 13023-13036.
[57] Bojilova, A.; Trendafilova, A.; Ivanov, C.; Rodios, N. A. Cyclopropanation reaction of 3-acyl-2H-1-benzopyran-2-ones with phenacyl bromide in phase transfer systems. *Tetrahedron* **1993**, *49*, 2275-2286.
[58] Zhao, Q.; Chen, M.; Hui, H. H.; She, D. B.; Yang, M. Y.; Huang, G. S. High stereoselective cyclopropanation reaction of 3-acylcoumarins with α-bromo ketones at room temperature. *J. Chem. Sci.* **2008**, *120*, 391-394.
[59] Shchepin, V. V.; Silaichev, P. S.; Stepanyan, Y. G.; Kalyuzhnyi, M. M.; Russkikh, N. Y.; Kodess, M. I. Cyclopropanation of N-substituted 3-aryl-2-cyano-2-propenamides and derivatives of 5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carboxylic acid and 2-oxochromene-3-carboxylic acid with bromine-containing zinc enolates. *Russ. J. Org. Chem.* **2006**, *42*, 973-980.
[60] Shchepin, V. V.; Silaichev, P. S.; Kodess, M. I. Reaction of zinc enolates prepared from 2,2-dibromoindan-1-one or 2,2-dibromo-1-tetralone and zinc with 2-oxochromene-3-carboxylic acid derivatives. *Russ. J. Org. Chem.* **2007**, *43*, 1441-1445.
[61] Yamashita, M.; Inaba, T.; Nagahama, M.; Shimizu, T.; Kosaka, S.; Kawasaki, I.; Ohta, S. Novel stereoconvergent transformation of 1,2a-disubstituted 1,2,2a,8b-tetrahydro-3H-benzo[b]cyclobuta[d]pyran-3-ones to 1,3-disubstituted 1,2,4a,9b-tetrahydrodibenzofuran-4-ols and its application to the second-generation synthesis of (±)-linderol. *Org. Biomol. Chem.* **2005**, *3*, 2296-2304.
[62] Yamashita, M.; Dnyanoba, Y. N.; Nagahama, M.; Inaba, T.; Nishino, Y.; Miura, K.; Kosaka, S.; Fukao, J.; Kawasaki, I.; Ohta, S. Synthesis and Unambiguous Stereochemical Determination of 1-exo- and 1-endo-1-Aryl-1,2,2a,8b-tetrahydro-3*H*-benzo[*b*]cyclobuta[*d*]pyran-3-ones. *Heterocycles* **2005**, 65, 2411-2430.
[63] Fathi, T.; Nguyen, D. A.; Schmitt, G.; Cerutti, E.; Laude, B. Regiochemistry of the cycloadditions of diphenylnitrilimine to coumarin, 3-(ethoxycarbonyl)- and 3-acetylcoumarins. A reinvestigation. *Tetrahedron*, **1988**, *44*, 4527-4536.
[64] Ohkata, K.; Lee, Y. G.; Utsumi, Y.; Ishimaru, K.; Akiba, K. Diels-Alder reactions of 2-[(trialkylsilyl)oxy]pyrylium cations of 2*H*-pyran-2-one and 2*H*-1-benzopyran-2-one derivatives. *J. Org. Chem.* **1991**, *56*, 5052-5059.
[65] Girotti, R.; Marrocchi, A.; Minuti, L.; Piermatti, O.; Pizzo, F.; Vaccaro, L. Diels-Alder Reactions of 3-Substituted Coumarins in Water and under High-Pressure Condition. An Uncatalyzed Route to Tetrahydro-6*H*-benzo[c]chromen-6-ones. *J. Org. Chem.* **2006**, *71*, 70-74.

[66] Fringuelli, F.; Girotti, R.; Pizzo, F.; Zunino, E.; Vaccaro, L. Hafnium chloride-tetrahydrofuran complex-catalyzed Diels-Alder cycloadditions of 3-(ethoxycarbonyl)coumarins with 1,3-dienes under solvent-free conditions. *Adv. Syn. Catal.* **2006**, *348*, 297
[67] Gustafsson, B. Case of radical formation in the reactions between ethyl 3-coumarincarboxylate and Grignard reagents. *Finnish Chem. Lett.* **1975**, *2*, 49-50.
[68] Patra, A.; Misra, S. K. Synthesis of 4-alkylcoumarins. *Indian J. Chem.* **1988**, *27B*, 272-3
[69] Gustafsson, B.; Ostman, K. The reaction of 2-methylphenylmagnesium bromide with ethyl 3-coumarincarboxylate. Addition of three reagent molecules followed by a ring opening. *Acta Chem. Scand.* **1977**, *B31*, 425-6.
[70] Bennabi, S.; Narkunan, K.; Rousset, L.; Bouchu, D.;Ciufolini, M. A. Conjugate propargylation of α,β-unsaturated lactones: a solution via 1,4-addition of (Z)-2-ethoxyvinyl anion. *Tetrahedron Lett.* **2000**, *41*, 8873-8876.
[71] Shchepin, V. V.; Korzun, A. E.; Vakhrin, M. I.; Silaichev, P. S.; Ezhikova, M. A.; Kodess, M. I. I. Reactions of zinc enolates derived from 1-aryl-2-bromo-2-phenylethanone and 2-bromo-1-indanone with alkyl 2-oxochromene-and 6-bromo-2-oxochromene-3-carboxylates. *Russ. J. Gen. Chem.* **2006**, *76*, 777-780.
[72] Bozhilova, A.; Kostadinova, T.; Ivanov, K. Allylation-assisted addition of nitromethane to 2*H*-1-benzopyran-2-ones substituted in position 3. *Liebigs Ann. Chem.* **1989**, *10*, 1041-1043.
[73] Ivanov, I.; Raev, L. Addition of some enamino esters to 3-substituted coumarins. *Synth. Commun*. **1986**, *16*, 1679-1691.
[74] Ivanov, I.; Raev, L.; Sulai, P. Some new properties of ethyl 3-amino-3-ethoxypropenoate and ethyl 3,3-diaminopropenoate. *Farmatsiya* **1984**, *34*, 14-21.
[75] Liu, X.; Li, L.; Wang, G. Studies on synthesis of coumarin-3-carboxylic acid and its ester. *Huaxue Shiji* **2007**, *29*, 43-45.
[76] El-Farargy, A. F.; Soliman, A. Y.; El-Mobayed, M.; El-Esser, S. Synthesis and studies of 3-N-arylcarbamidocoumarins. *Rev. Roum. Chim.* **1987**, *32*, 435-441.
[77] El-Farargy, A. F.; Soliman, A. Y.; El-Mobayed, M.; El-Esser, S. Some reactions of 3-(arylcarbamoyl)coumarins and 4-methyl-5,6-benzocoumarin. *Egypt. J. Chem.* **1987**, *30*, 497-505.
[78] Avetisyan, A. A.; Vanyan, E. V.; Dangyan, M. T. Studies of unsaturated lactones. LI. Some chemical transformations of functionally substituted coumarins. *Armyanskii Khim. Zh.* **1982,** *35*, 319-322.
[79] El-Agrody, A. M.; Abdul-Ghany, A. R.; Bedair, A. H.; Ghazal, S. A. Coumarin-3-N-substituted carboxamides with antimicrobial and insecticidal activities. *Afinidad* **1988**, *45*, 447-450.
[80] Badran, M. M.; El-Gendy, A. A.; Soliman, L. N.; El-Assi, H. R. Synthesis of certain novel 3-substituted coumarins. *Bull. Fac. Pharm.* **1990**, *28*, 39-42.
[81] Islam, A. M.; Bedair, A. H.; Aly, F. M.; El-Sharief, A. M.; El-Masry, F. M. Synthesis and reactions of coumarin-3-N-bromoarylcarboxamides. *Indian J. Chem.* **1980**, *19B*, 224-227.
[82] Bedair, A. H. Synthesis of biologically active *N*-substituted 3-coumarincarboxamides. *J. Prakt. Chem.* **1987**, *329*, 359-364.
[83] Bedair, A. H.; Aly, F. M.; El-Assy, R. K. M. Biologically active sulfonamides derived from α-pyrones. *Indian J. Chem.* **1987**, *26B*, 91-94.
[84] Chimenti, F.; Secci, D.; Bolasco, A.; Chimenti, P.; Granese, A.; Carradori, S.; Befani, O.; Turini, P.; Alcaro, S.; Ortuso, F. Synthesis, molecular modeling studies, and selective inhibitory activity against monoamine oxidase of N,N'-bis[2-oxo-2H-benzopyran]-3-carboxamides. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4135-4140.
[85] Zhou, X.; Wang, X. B.; Wang, T.; Kong, L. Y. Design, synthesis, and acetylcholinesterase inhibitory activity of novel coumarin analogues. *Bioorg. Med. Chem.* **2008**, *16*, 8011-8021.
[86] Coquerel, Y.; Rodriguez, J. Catalytic properties of the Pd/C - triethylamine system. *ARKIVOC* **2008**, *11*, 227-237.
[87] Siddiqui, N.; Bhat, M. A.; Khan, S. A.; Ahsan, W.; Alam, M. S. Synthesis and in vivo anticonvulsant screening of coumarin incorporated Schiff bases of 1,3,4-oxadiazoles. *J. Chin. Chem. Soc.* **2008**, *55*, 1326-1331.
[88] Bhat, M. A.; Siddiqui, N.; Khan, S. A. Synthesis of novel thioureido derivatives of sulfonamides and thiosemicarbazido derivatives of coumarin as potential anticonvulsant and analgesic agents. *Indian J. Pharm. Sci.* **2006**, *68*, 120-124.
[89] Imran, M.; Alam, O.; Kaushik, D.; Khan, S. A. Synthesis of 1-(substituted-phenylaminomethyl)-3-(coumarin-3-yl carbohydrazino) isatins as potential anticonvulsants. *Indian J. Heterocycl. Chem.* **2007**, *16*, 251-254.
[90] Alam, O.; Gupta, S. K.; Imran, M.; Khan, S. A. Synthesis and biological activity of some 2,5-disubstituted 1,3,4-oxadiazoles. *Asian J. Chem.* **2005**, *17*, 1281-1286.

[91] Bhat, M. A.; Siddiqui, N.; Khan, S. A. Synthesis of novel 3-(4-acetyl-5H/methyl-5-substituted phenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2*H*-chromen-2-ones as potential anticonvulsant agents. *Acta Poloniae Pharmaceut.* **2008**, *65*, 235-239.
[92] Nemeryuk, M. P.; Dimitrova, V. D.; Anisimova, O. S.;Sedov, A. L.; Solov'eva, N. P.; Traven, V. F. D. I. Conversions of coumarins accompanied by intermediate opening and recyclization of the lactone ring. 2. Study of the interaction of malonic acid hydrazide and amide derivatives with 3-acyl(3-cyano, 3-ethoxycarbonyl)coumarins. *Chem. Heterocycl. Compds.* **2005**, *41*, 1255-1266.
[93] Mahmoud, M. R.; El-Bassiouny, F. A.; Azab, M. E.; El-Kady, M. Y.; Rashed, H. M. Heteroannulation of chromene derivatives. Synthesis of chromeno[4,3-e]indazolone, chromeno[4,3-f]quinazoline and pyrano[3,2-c]chromene derivatives. *J. Chem. Res.* **2009**, *1*, 41-45.
[94] Bakeer, H. M. Studies on 3-substituted coumarin derivatives toward different electrophiles and nucleophiles. *Int. J. Chem.* **2007**, *17*, 197-204.
[95] El-Deen, I. M.; Ibrahim, H. K. Synthesis and some reactions of 2-mercapto-4-hydroxypyrimidine[3,4-b]coumarin. *Phosp. Sul. Sil. Relat. Elem.* **2000**, *160*, 241-250.
[96] Gohar, A. M. N.; Abdel-Latif, F. F.; El-Ktatny, M. S. Synthesis and biological activity of some 5-substituted 1,2,5a,6,11b,11c-hexahydro[1]benzopyrano[4,3-d]pyrazolo[3,4-b]pyridine-1,6-diones and 5H-4a,10b-dihydrobenzopyrano[3,4-c]pyridine derivatives. *Ind. J. Chem.* **1986**, *25B*, 404-406.