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RECENT APPLICATION OF 4-HYDROXYCOUMARIN IN MULTI-COMPONENT REACTIONS

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Abstract - 4-Hydroxycoumarin has been utilized in many heterocyclic preparations such as indole-containing compounds, furo- and pyran-annulated, and spiro-compounds. In addition, significant places of its derivatives as pharmaceutical compounds cause it more important. There are a diversity of multi-component reactions of this useful reagent which we highlight the recent reports of them in this review. Also, herein some asymmetric syntheses via 4-hydroxycoumarin is discussed.

CONTENTS

1. INTRODUCTION

Substituted coumarin analogues have a lot of significant properties as they constitute valuable building blocks for potential pharmaceuticals such as anticoagulants,[1-3] antifungal,[4] pharmaceuticals including antimicrobial activity,[5] and inhibiting clotting factor synthesis by interrupting the vitamin K_1 epoxide cycle.[6] They are also widely exist in plants, including edible vegetables and fruits[7] and are used in drug discovery.[8,9] Therefore, synthetic strategies involving multicomponent reactions (MCRs) attract many attentions as a powerful tool for the rapid introduction and expansive of molecular diversity.[10-12]

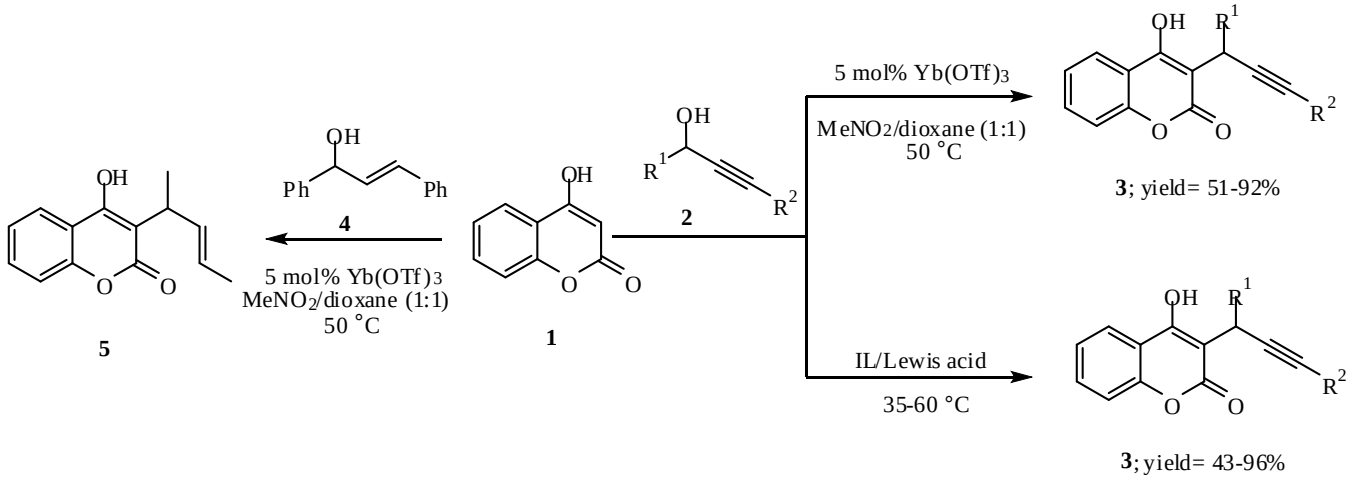
Thus, we decided to study the role of 4-hydroxycoumarin **1** in multi-component reactions and asymmetric syntheses.

2. TWO-COMPONENT REACTION OF 4-HYDROXYCOUMARIN

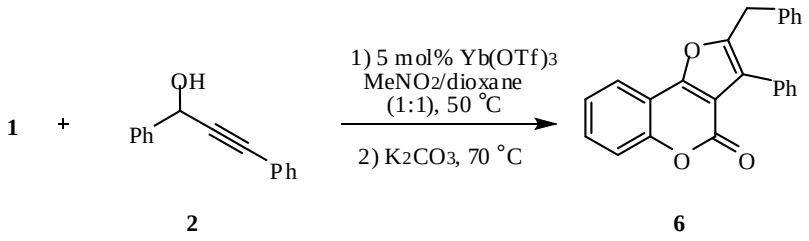
2.1 TWO-COMPONENT BENZYLATION AND PROPARGYLATION OF 4-HYDROXYCOUMARIN

Herein, Lewis acid-catalyzed propargylation of 1,3-dicarbonyl compounds such as **1** with propargylic alcohols **2** is demonstrated. Huang and co-workers obtained selective propargylation or allylation products **3** and **5** on the nature of propargylic alcohols using catalytic quantities of $Yb(OTf)_3$ in a mixture of CH_3NO_2:dioxane (**Scheme 1**). This reaction is also a key step for the synthesis of multi-substituted furocoumarin **6** followed by addition of K_2CO_3 in a one-pot procedure (**Scheme 2**).[13]

Lewis or Brønsted acidic ionic liquid systems was studied in propargylation of 4-hydroxycoumarin **1** by Aridoss and co-workers (**Scheme 1**). Metallic triflates [in particular $Sc(OTf)_3$ and $Ln(OTf)_3$] and bismuth nitrate in imidazolium ionic liquid (ILs) such as $[BMIM][PF_6]/Bi(NO_3)_3•5H_2O$ and $[BMIM][PF_6]/Sc(OTf)_3$ were the most effective system.[14]

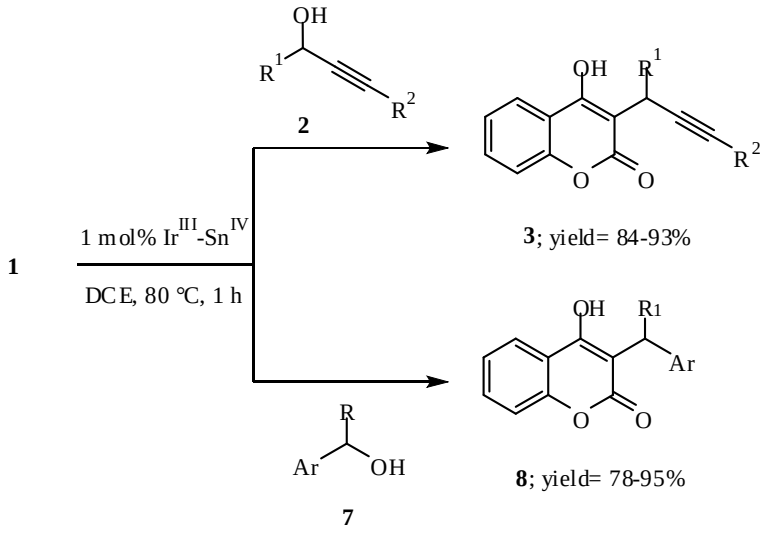


Scheme 1



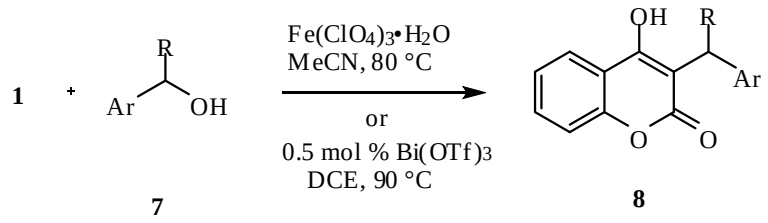
Scheme 2

Benzylation and propargylation of 4-hydroxycoumarin **1** was also carried out in the presence of $[Ir(COD)(SnCl_3)Cl(\mu\text{-}Cl)]_2$ as Ir-Sn bimetallic catalyst in 1,2-dichloroethane (DCE). Nucleophilic substitution of propargylic alcohols with 1,3-dicarbonyl compounds was employed as the key step for the synthesis of substituted furans and pyrroles (**Scheme 3**).[15]



Scheme 3

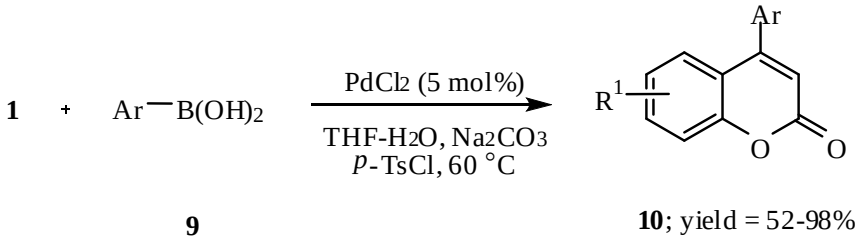
Two other efficient methods for benzylation of 4-hydroxycoumarin **1** using benzylic alcohols **7** were demonstrated in the **Scheme 4**. Compound **1** in the presence of $Fe(ClO_4)_3$•H_2O in MeCN or $Bi(OTf)_3$ in DCE were applied to synthesis anticoagulant compounds such as 4-hydroxy-3-(1,2,3,4-tetrahydronaphthalen-1-yl)-2*H*-chromen-2-one (Coumatetralyl (B))[16] and numerous differently substituted warfarin derivatives. Two widely used anticoagulants phenprocoumon and coumatetralyl were synthesized by applying the latter method.[17]



Scheme 4

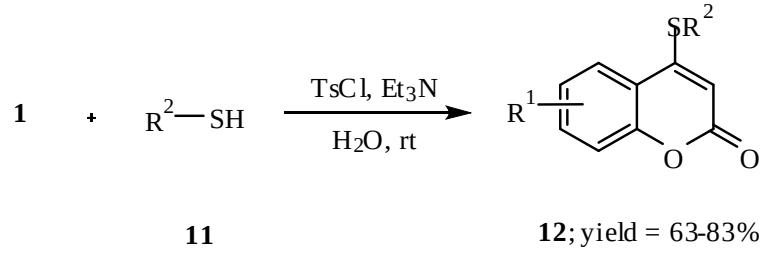
2.2 TWO-COMPONENT ARYLATION AND SULFANYLATION OF 4-HYDROXY-COUMARIN

Direct arylation of 4-hydroxycoumarins **1** with arylboronic acids **9** via C-OH bond activation was catalyzed by $PdCl_2$ to provide 4-arylcouamrins **10** in good to excellent yields (**Scheme 5**).[18]



Scheme 5

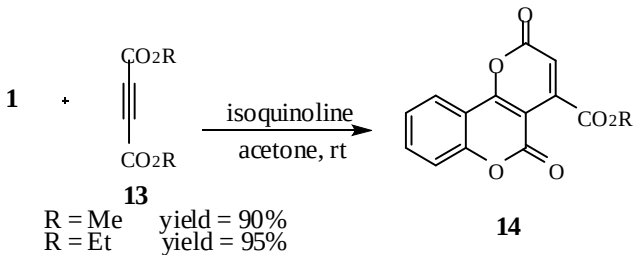
Direct sulfanylation of 4-hydroxycoumarins **1** with thiols **11** was performed via C-OH bond activation in the presense of Et_3N in H_2O at room temperature to provide 4-sulfanylcoumarins **12** (**Scheme 6**).[19]



Scheme 6

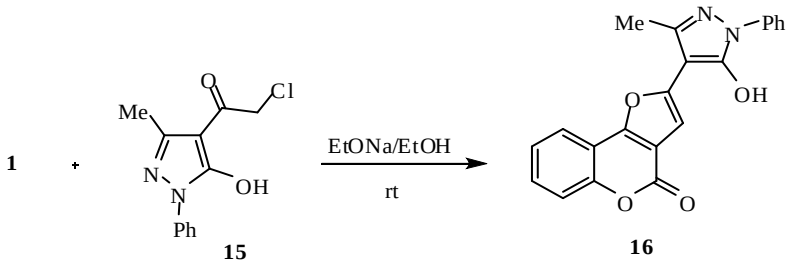
2.3 TWO-COMPONENT CYCLIZATION REACTIONS OF 4-HYDROXYCOUMARIN

The reaction between dialkyl acetylenedicarboxylates **13** and 4-hydroxycoumarin **1** in the presence of isoquinoline was reported by Anary-Abbasinejad and co-workers to produce new fused coumarin derivatives **14** in excellent yield (**Scheme 7**).[20] In this additional reaction between acetylene derivative and enolic system followed by *δ*-lactonization, isoquinoline was used as catalyst.



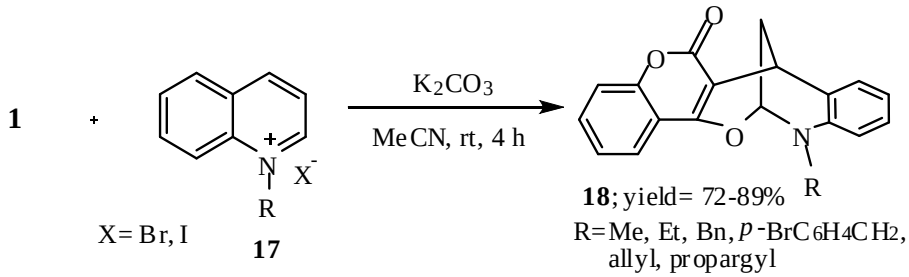
Scheme 7

As demonstrated in **Scheme 8**, after stirring an ethanolic solution of NaOEt and 4-hydroxycoumarin **1** at room temperature, compound **15** was added and stirred for 24 h to produce new functionalized antimicrobial active furo[2,3-*c*]pyrazoles **16**.[21]



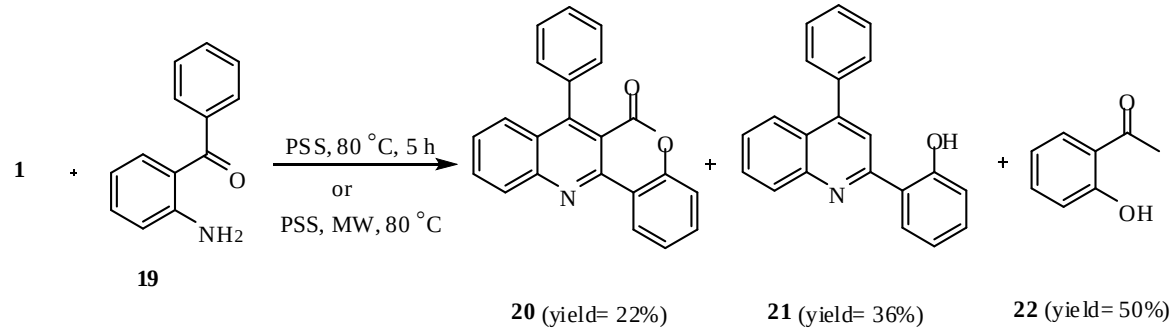
Scheme 8

A new one-pot synthesis of polycyclic structures containing nitrogen and oxygen related to eight-membered hydroquinolines **18** via tandem *C*-alkylation and intramolecular *O*-alkylation of 4-hydroxycoumarin **1** with quinolinium salts **17** (71–89%) was reported. The products were produced in excellent yields using K_2CO_3 at room temperature (**Scheme 9**).[22]



Scheme 9

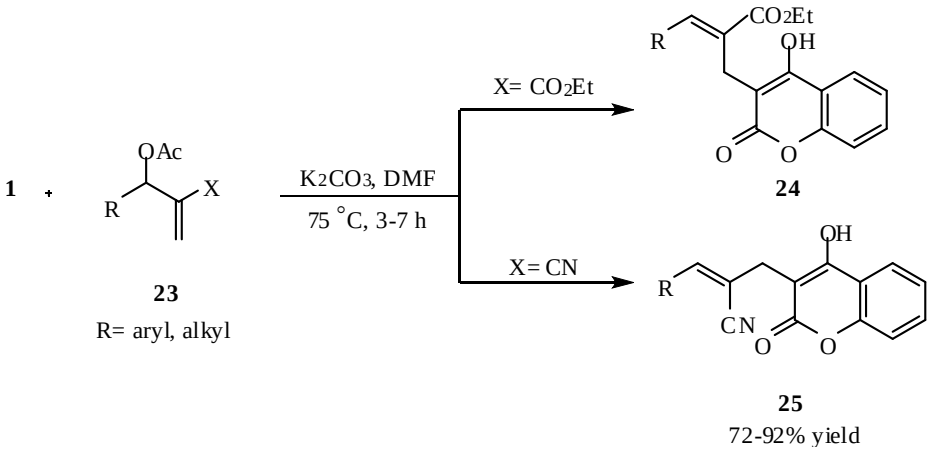
Propylsulfonic silica (PSS) as a reusable solid catalyst was used in a solvent-free method for the synthesis of substituted quinoline **20**, **21** derivatives via Friedländer cyclization (**Scheme 10**). The reaction of 4-hydroxycoumarin **1**, a masked β-ketoester, and *o*-aminobenzophenone **19** afforded tetracyclic derivative **20**, the product of lactone hydrolysis-decarboxylation **21**, and *o*-hydroxyacetophenone **22** as the main product (about 50%). [23]



Scheme 10

2.4 TWO-COMPONENT NUCLEOPHILIC ADDITION OF 4-HYDROXYCOUMARIN

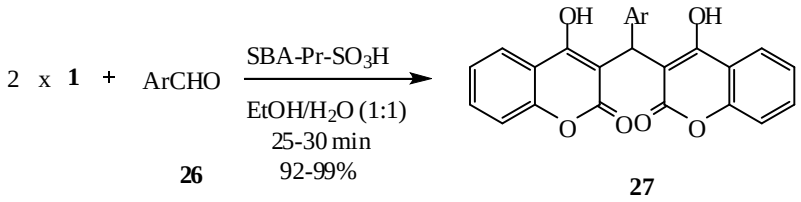
Nucleophilic addition of 4-hydroxycoumarin **1** to Baylis–Hillman (BH) acetate adducts **23** in the presence of K_2CO_3 as base afforded the corresponding 3-substituted 4-hydroxycoumarins **24** and **25** in good yields (**Scheme 11**).[24] In addition, 2D NMR studies showed that the reactions of adducts with ester group gave the *E*-isomers selectively while the BH acetate adduct with nitrile group produced *Z*-isomer predominantly.



Scheme 11

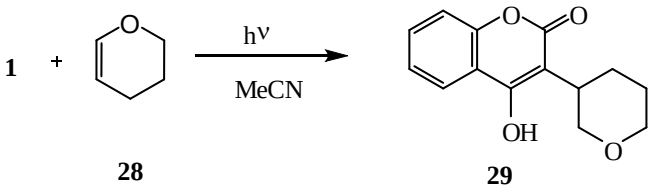
Reaction of 4-hydroxycoumarin **1** with aromatic aldehydes **26** using sulfonic acid functionalized nanoporous silica (SBA-Pr-SO_3H) in EtOH/H_2O was performed to prepare the α,α-bis(4-hydroxycoumarin-3-yl)toluene derivatives **27** in excellent yields (**Scheme 12**).[25] Also catalyst-free

reaction with similar procedure in aqueous media under microwave irradiation was performed by Gong and co-workers to produce the desired product **27** in high yields.[26]



Scheme 12

Photochemical reaction of 4-hydroxycoumarin **1** with 3,4-dihydro-2*H*-pyran **28** was performed to afford 4-hydroxy-3-(oxan-3-yl)coumarin **29** whose formation was explained by considering a hydrogen shift and keto-enol isomerization from a head-tail biradical intermediate (**Scheme 13**).[27]

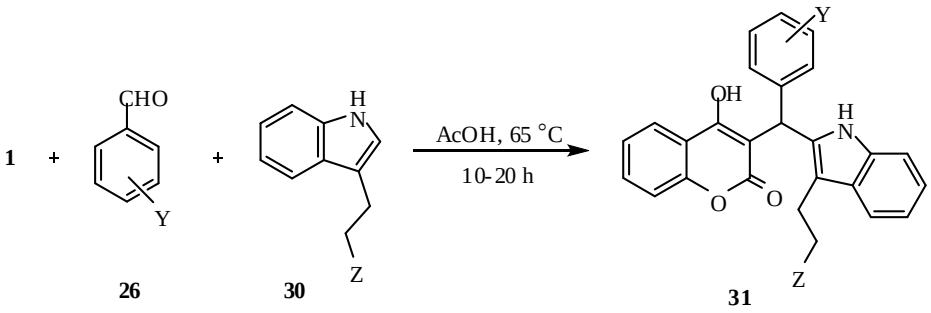


Scheme 13

3. THREE-COMPONENT REACTION OF 4-HYDROXYCOUMARIN

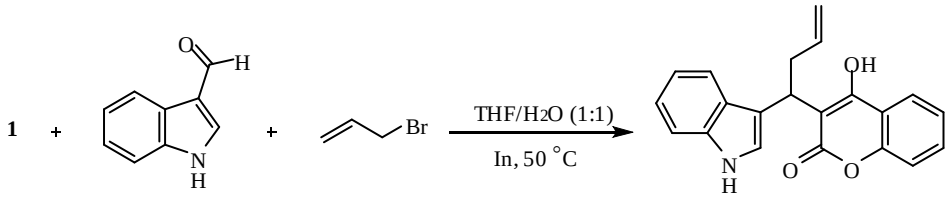
3.1 SYNTHESIS OF INDOLE-CONTAINING COMPOUNDS

4-Hydroxycoumarin, indole, and various aliphatic and aromatic aldehydes representative of various electronic and steric conditions were employed. Thus, a new class of indole-containing antibacterial agents **31** was prepared by Yamamoto and co-workers to reveal their *in vitro* antibacterial activities (MIC) against *Staphylococcus aureus* and *Enterococcus faecium* including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) (**Scheme 14**).[28] Two years later, Appendino and co-workers modified the reaction condition to produce the desired product **31** as follow: (1) $CHCl_3$ at room temperature for 6 h, and (2) in $CHCl_3$:H_2O 1:1 at 40 ºC overnight.[29]



Scheme 14

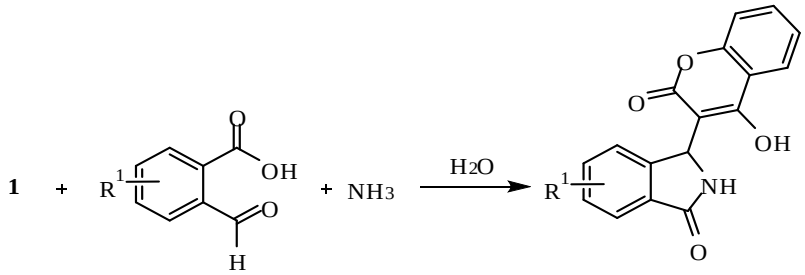
A three-component domino allylation reaction of 1*H*-indole-3-carbaldehyde **32** with the stabilized C-nucleophiles such as 4-hydroxycoumarin **1** as electron-rich (hetero)arenes and allylbromide **33** was reported to prepare variously functionalized indolylbutenes **34** using indium powder (**Scheme 15**).[30]



32 **33** **34**; yield= 91%

Scheme 15

Three-component reaction of 2-formyl benzoic acid **35**, ammonia and 4-hydroxycoumarin **1** or indole in aqueous medium was reported by Lin and co-workers to produce a series of isoindolinone derivatives **36** in good to excellent yields (**Scheme 16**).[31]

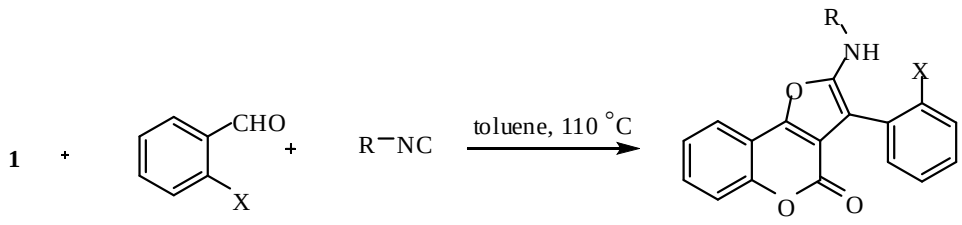


35 **36**

Scheme 16

3.2 SYNTHESIS OF FURO-ANNULATED HETEROCYCLIC COMPOUNDS

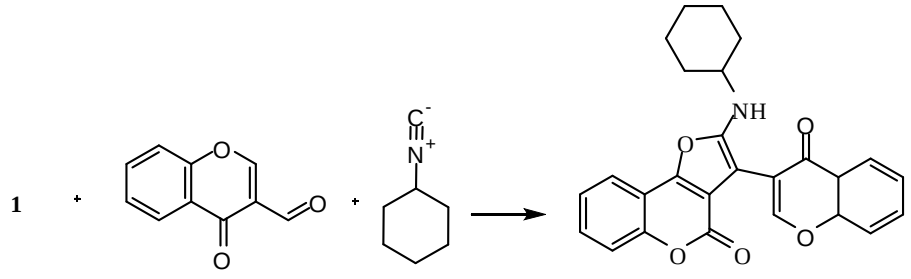
The isocyanide-based multicomponent reaction (I-MCRs) of 4-hydroxycoumarin **1**, 2-halobenzaldehyde **37**, and isocyanide **38** was reported by Xu and co-workers as a key step toward furo[2,3-*b*]indole scaffold synthesis of compound **39** in moderate to good yields (**Scheme 17**).[32]



37 **38** **39**; yield= 73%

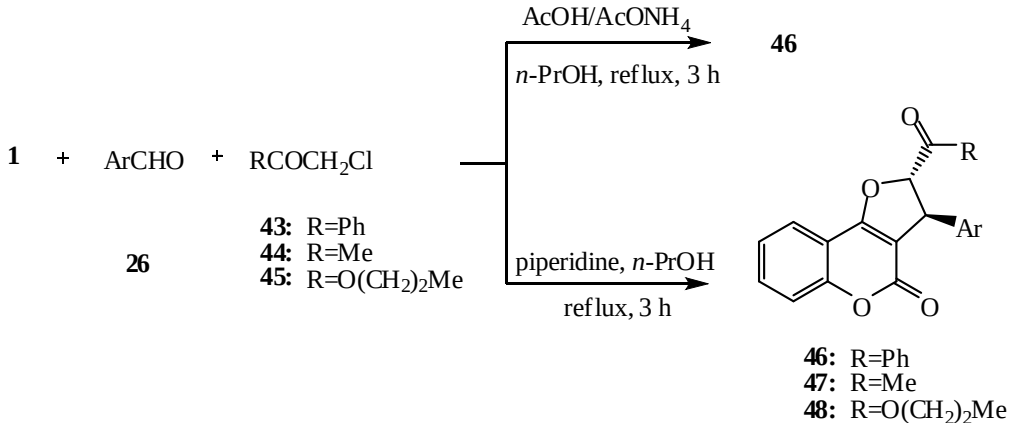
Scheme 17

Three-component reaction of chromone-3-carbaldehyde **40**, 4-hydroxycoumarin **1** and cyclohexyl isocyanide **41** was performed to produce furocoumarin derivatives **42**. Cyclohexyl isocyanide was found to act as a masked source of cyclohexylamine in this procedure (**Scheme 18**).[33]



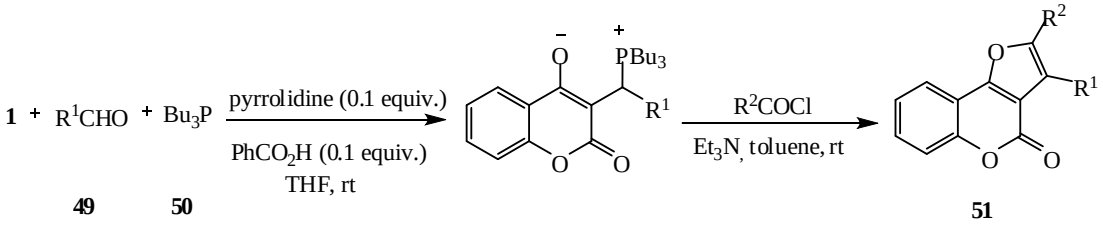
Scheme 18

Regio and diastereoselective synthesis of functionalized 2,3-dihydrofuro[3,2-*c*]coumarins (**46**-**48**) was achieved via a one-pot three-component condensation of aromatic aldehydes **26**, 4-hydroxycoumarin **1**, and α-chloromethyl ketones (**43**-**45**) in refluxing *n*-PrOH (**Scheme 19**). The reaction proceeded using pyridine or a mixture of AcOH and $AcONH_4$ as a basic catalyst.[34]



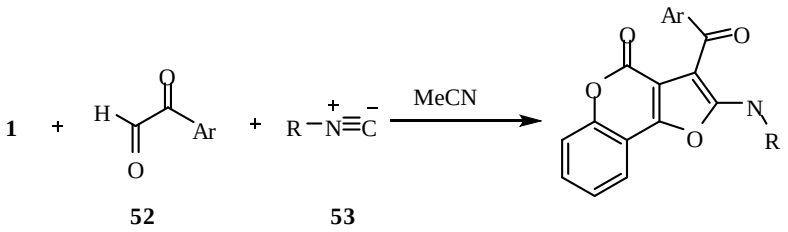
Scheme 19

Functionalized phosphorus zwitterions were prepared by the reaction of 4-hydroxycoumarin **1**, aldehydes **49**, and tributylphosphine **50** in dry THF under nitrogen to synthesis polysubstituted furo[3,2-*c*]coumarins **51** in good to excellent yields via a tandem three-component reaction (**Scheme 20**).[35]



Scheme 20

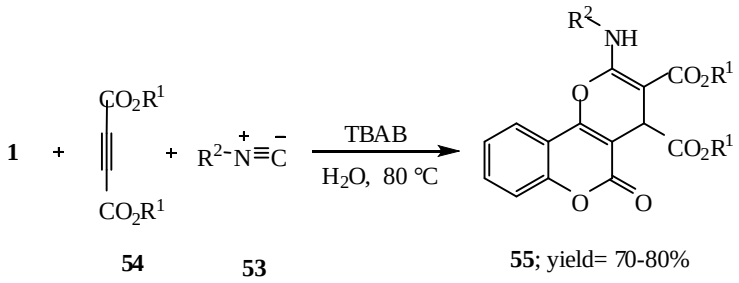
In addition M. H. Mosslemin reported a three-component reaction between 4-hydroxycoumarin **1**, or 5,5-dimethyl-1,3-cyclohexandione, arylglyoxals **52**, and alkyl isocyanides **53** in refluxing MeCN to afford furocoumarin or benzofuran derivatives in high yields (**Scheme 21**).[36]



Scheme 21

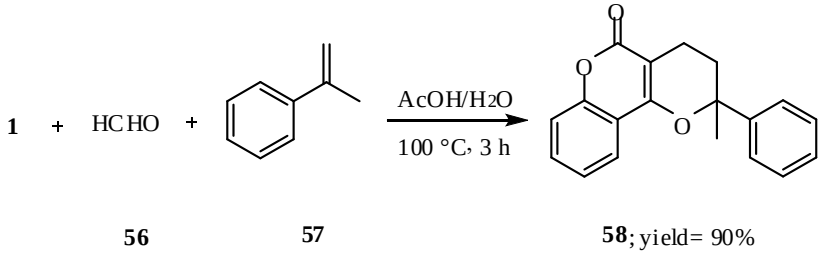
3.3 SYNTHESIS OF PYRAN-ANNULATED HETEROCYCLIC COMPOUNDS

Synthesis of some pyrano[3,2-*c*]coumarin derivatives **55** in aqueous medium was reported by Sarma and co-workers via a three-component reaction of an isocyanide **53**, dialkyl acetylenedicarboxylate **54**, and 4-hydroxycoumarin **1** using a phase-transfer catalyst (PTCs) of tetrabutylammonium bromide (TBAB) as catalyst to provide pyrano[3,2-*c*]coumarins **55** in good yields (**Scheme 22**).[37]



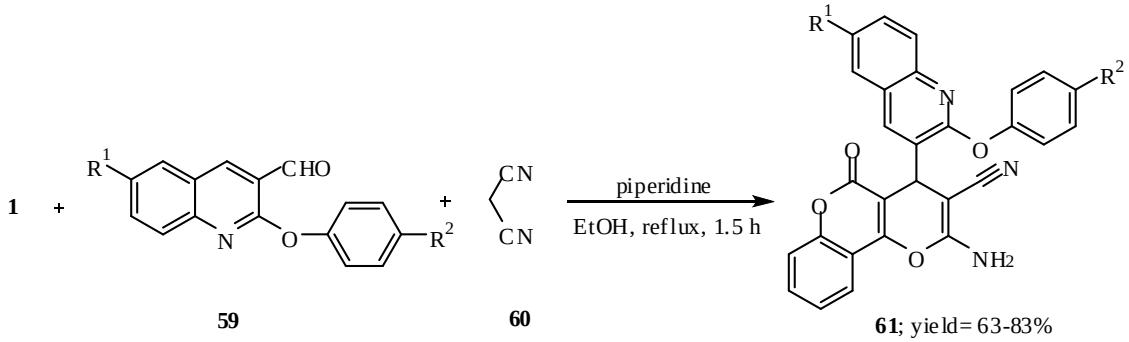
Scheme 22

In the following protocol, a selective multicomponent reaction of 4-hydroxycoumarin **1**, formaldehyde **56**, and α-methylstyrene **57** is illustrated in **Scheme 23**. Formaldehyde **56** is able to methylenate a large variety of electron-rich carbons, such as 4-hydroxycoumarin **1** which was then trapped by means of a hetero-Diels-Alder reaction with alkene **57** to produce the desired product in excellent yields.[38]



Scheme 23

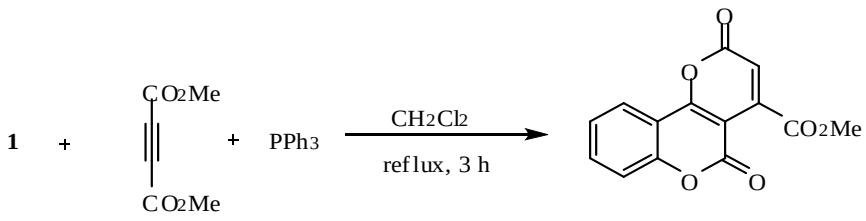
Synthesis and identification of pyrano[3,2-*c*]chromene derivatives **61** as a new class of antimicrobial and antituberculosis agents was described (**Scheme 24**). In this protocol β-aryloxyquinoline-3-carbaldehyde **59**, malononitrile **60**, 4-hydroxycoumarin **1**, and a catalytic amount of piperidine in EtOH were heated under reflux to produce product **61**.[39]



59 **60** **61**; yield= 63-83%

Scheme 24

The reaction of 4-hydroxycoumarin **1**, DMAD **53**, and triphenylphosphite **62** afforded compound **63** (**Scheme 25**). This reaction proceeds by an initial addition of the 4-hydroxycoumarin conjugate base to the vinyl triphenylphosphonium salt leads to the formation of the corresponding ylide which affords compound **63** as a desirable product via a 1,2-H shift transformation by PPh_3 elimination and lactonization.[40] Recently the similar protocol in multicomponent reactions of dialkyl acetylenedicarboxylate with 4-hydroxycoumarin **1** in the presence of trimethyl or triphenyl phosphate (PPh_3O_4) was reported by Rostami-Charati and co-workers in H_2O.[41]

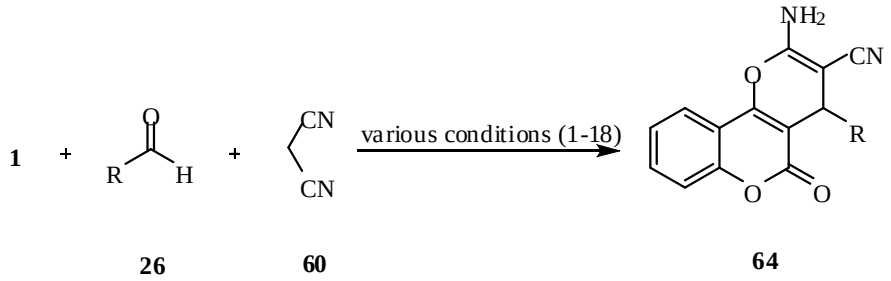


53 **62** **63**

Scheme 25

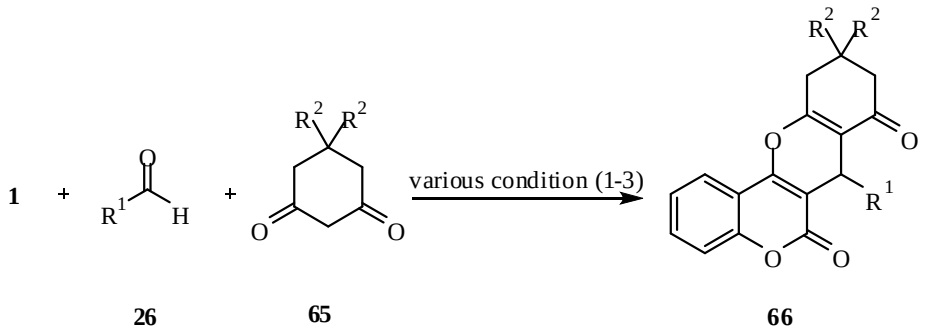
Recently, 3,4-dihydropyrano[*c*]chromene derivatives **64** were synthesized by the reaction of 4-hydroxycoumarin **1**, malononitrile **60**, and aromatic aldehydes **26** in various conditions such as: (1) using microwave irradiation in aqueous K_2CO_3,[42] (2) heating in H_2O at 80 ºC without any catalyst,[43] (3) heating in H_2O or solvent-free neat condition at 100 ºC using tetrabutylammonium bromide (TBAB) as catalyst,[44] (4) refluxing in H_2O using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as catalyst,[45] (5) refluxing in EtOH using catalytic amount of 4-(dimethylamino)pyridine (DMAP),[46] (6) using silica gel in EtOH at room

temperature,[47] (7) refluxing in H_2O using morpholine as catalyst,[48] (8) refluxing in anhydrous EtOH using morpholine as catalyst,[49] (9) refluxing in aqueous EtOH in the presence of trisodium citrate,[50] (10) refluxing in EtOH in the presence of a catalytic amount of hexamethylenetetramine,[51] (11) heating in H_2O/EtOH in the presence of potassium sodium tartrate,[52] (12) under ultrasound conditions in H_2O using catalytic amount of sodium acetate,[53] (13) catalyzed by 3-hydroxypropanaminium acetate (HPAA) as an ionic liquid at room temperature,[54] (14) refluxing in aqueous EtOH (1:1 v/v) using silica-bonded *N*-propylpiperazine sodium *n*-propionate (SBPPSP) as a basic catalyst,[55] (16) using catalytic amounts of sodium dodecyl sulfate (SDS) in aqueous medium,[56] (17) in the presence of low loading of potassium phthalimide-*N*-oxyl (POPINO), as a new organocatalyst, in aqueous media,[57] and (18) in the presence of catalytic amounts of ruthenium complexes ($RuBr_2(PPh_3)_4$) (**Scheme 26**).[58]



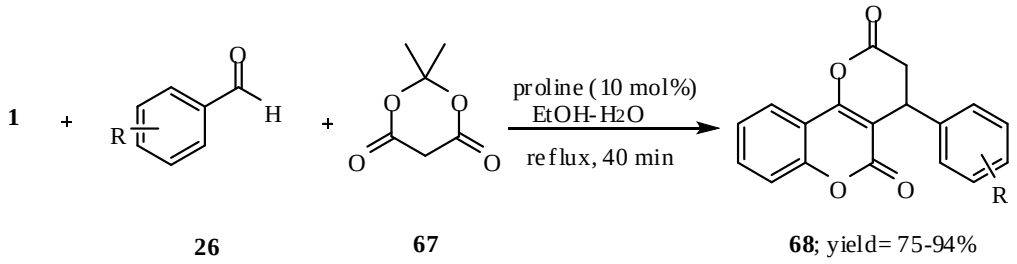
Scheme 26

Also 10,11-dihydrochromeno[4,3-*b*]chromene-6,8(7*H*,9*H*)-dione derivatives **66** was produced in good yields via a one-pot condensation of 4-hydroxycoumarin **1**, aromatic aldehydes **26**, and 5,5-dimethylcyclohexane-1,3-dione **65** in different conditions such as: (1) refluxing in H_2O using sulfonic acid functionalized ionic liquids 1,3-dimethyl-2-oxo-1,3-bis(4-sulfobutyl)imidazolidine-1,3-diium hydrogen sulfate ([DMDBSI]•$2HSO_4$),[59] (2) refluxing and microwave irradiation in AcOH using molecular iodine as a catalyst,[60] and (3) refluxing in EtOH using catalytic amount of heteropolyacids (HPAs) (**Scheme 27**).[61]



Scheme 27

The reaction of 4-hydroxycoumarin **1** with Meldrum's acid **67** and aromatic aldehydes **26** in aqueous EtOH in the presence of proline (10 mol%) as catalyst afforded 4-aryl-3,4-dihydro-2*H*,5*H*-pyrano[3,2-*c*]-chromene-2,5-diones **68** in good yields (**Scheme 28**).[62]

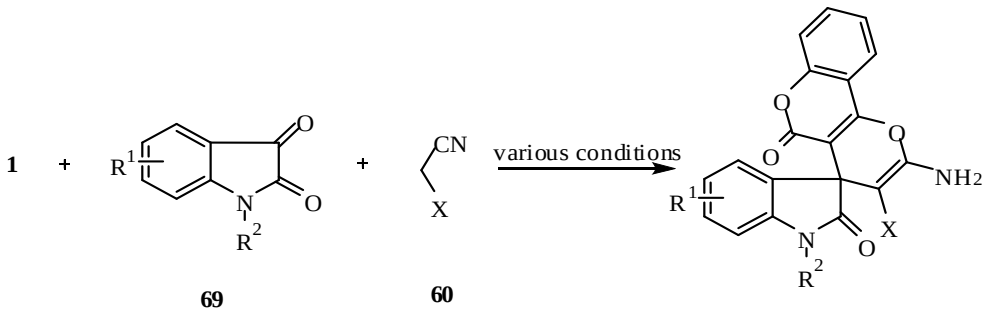


26 **67** **68**; yield= 75-94%

Scheme 28

3.4 SYNTHESIS OF SPIRO-COMPOUNDS

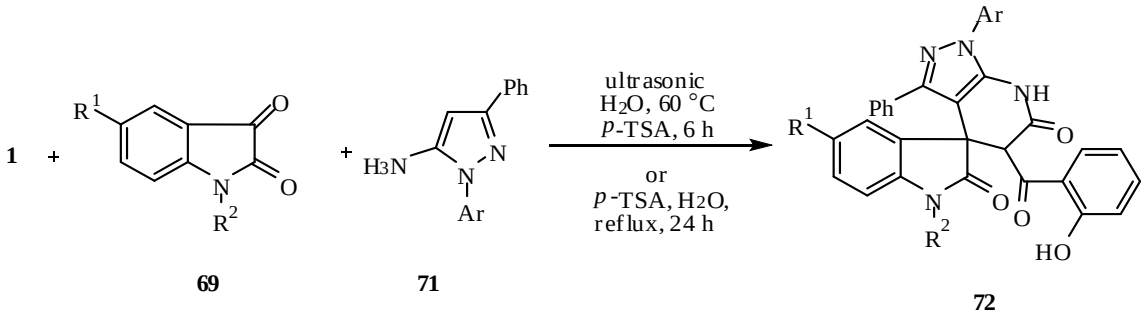
In recent years, a series of three-component procedure was performed to prepare spirooxindoles scaffold **70** by the reaction of 4-hydroxycoumarin **1** with isatin **69** and activated methylene reagent **60** in different conditions such as: (1) in the presence of a catalytic amount of triethylbenzylammonium chloride (TEBA) in H_2O at 60 ºC,[63] (2) polyethylene glycol (PEG) was utilized as an efficient and convenient medium,[64] (3) alum [$KAl(SO_4)_2$•$12H_2O$] was used as catalyst to afforded spirooxindoles in H_2O or aqueous EtOH at rt or 60 ºC,[65] (4) under microwave conditions using basic alumina as solid support,[66] (5) using sulfonic acid functionalized SBA-15 (SBA-Pr-SO_3H) as a nanoporous solid acid catalyst in H_2O,[67] and (6) in H_2O using alum as catalyst at 25 or 60 °C (**Scheme 29**).[68]



69 **60** **70**

Scheme 29

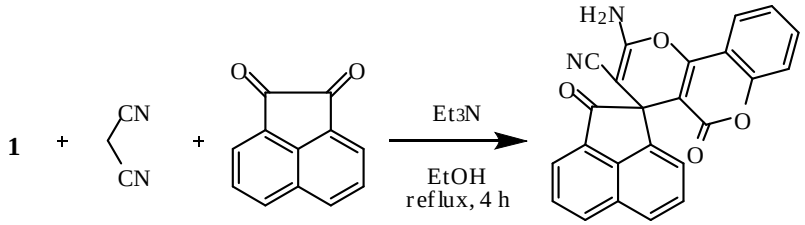
Two procedure was described for the synthesis of spiro[indoline-3,4′-pyrazolo[3,4-*b*]pyridine]-2,6′(1′*H*)-diones **72** by a three-component reaction of 4-hydroxycumarin **1**, isatins **69** and 1*H*-pyrazol-5-amines **71** as follow: (1) in the presense of *p*-TSA in H_2O under ultrasonic irradiation,[69] (2) refluxing of the reaction mixture and *p*-TSA in H_2O for 24 h (**Scheme 30**).[70]



69 **71** **72**

Scheme 30

4-Hydroxycumarin **1**, acenaphthequinone **73**, malononitrile **60** reacted in the presence of Et_3N as catalyst via a one-pot three component synthesis to form new spiroacenaphthylene derivatives **74** (**Scheme 31**).[71]

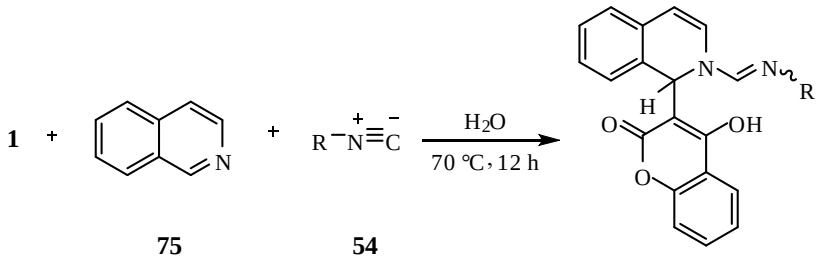


60 **73** **74**; yield= 60%

Scheme 31

3.5 MISCELLANEOUS

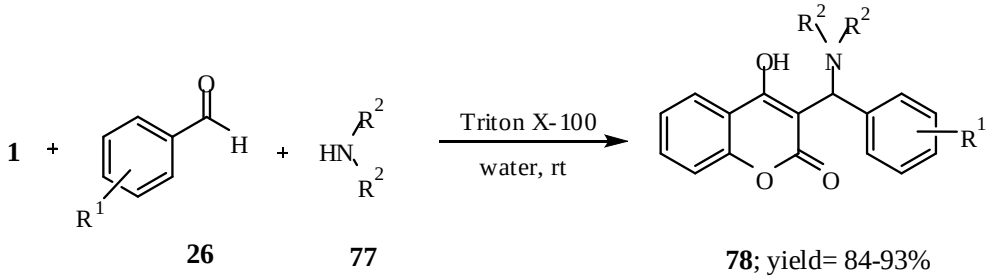
Synthesis of 1,2-dihydroisoquinoline derivatives **76** via the three-component reaction of isoquinoline **75**, isocyanides **54**, and strong CH-acids such as 4-hydroxycoumarin **1** in water was reported (**Scheme 32**).[72]



75 **54** **76**; yield= 59-99%

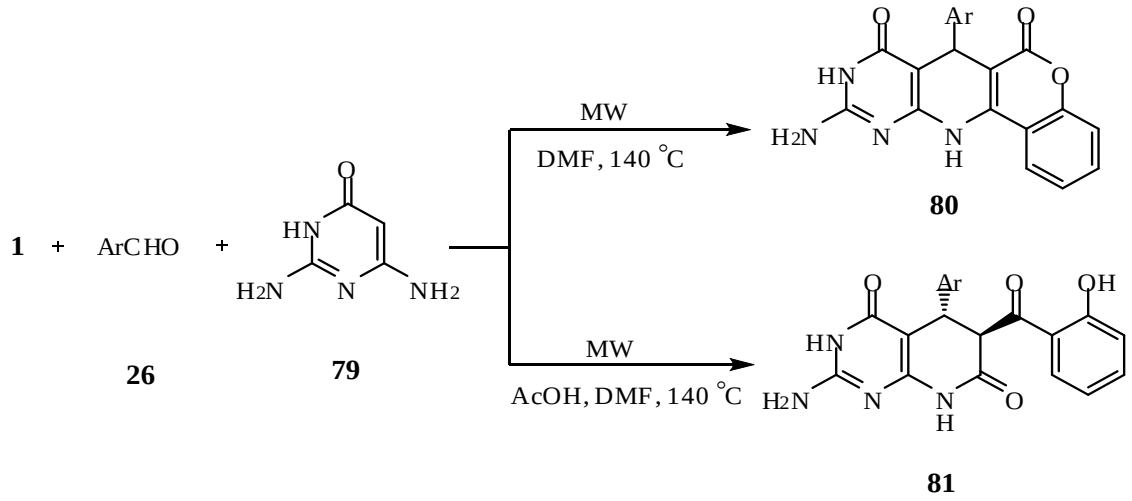
Scheme 32

Non-ionic surfactant catalyzed three-component synthesis of (benzylamino)coumarin derivative **78** was reported via Mannich type reaction in aqueous media without formation of any side product (**Scheme 33**). The mixture of secondary amines **77**, aromatic aldehyde **26**, and 4-hydroxycoumarin **1** were taken in water at room temperature using non-ionic surfactant triton X-100 ($C_{14}H_{22}O(C_2H_4O)_n$). Non-ionic surfactant (triton X-100) is a valuable surfactant to form a stable colloidal medium which stabilizes imine intermediate to increase the speed of reaction in water.[73]



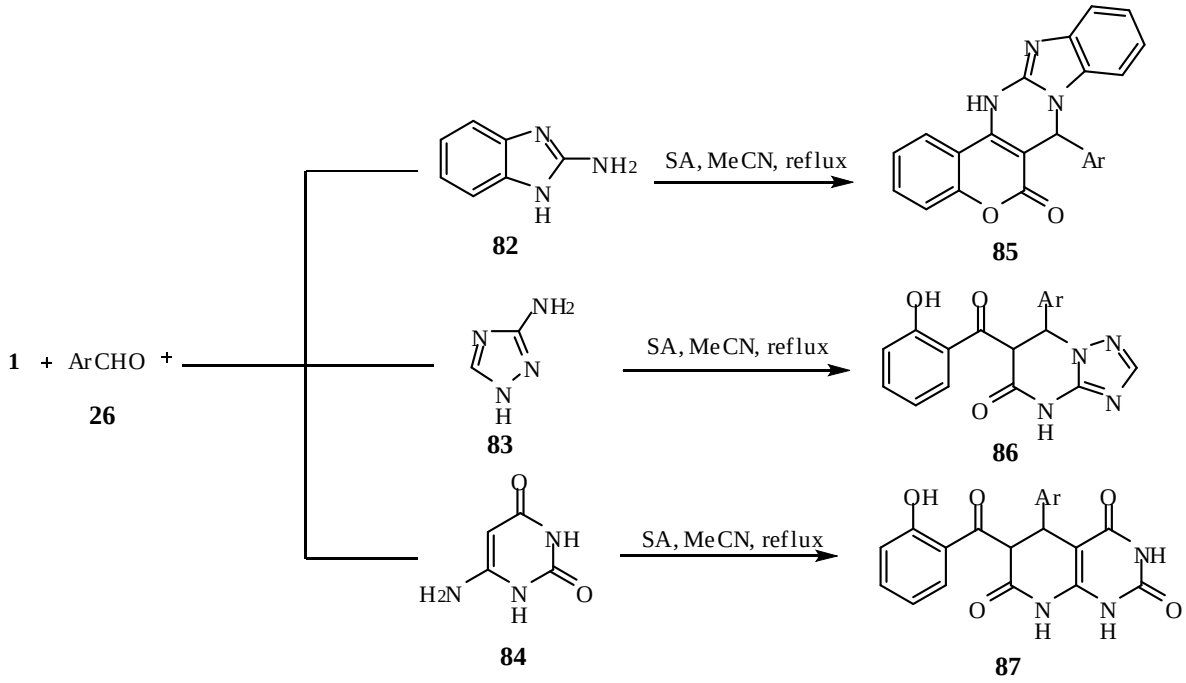
Scheme 33

A chemoselective synthesis of poly-substituted pyrido[2,3-*d*]pyrimidines **80** and **81** is accomplished via a microwave-assisted three-component reaction. Aldehyde **26**, 2,6-diaminopyrimidin-4(3*H*)-one **79**, and 4-hydroxycoumarin **1** were taken under microwave irradiation to show solvent nature on chemoselectivity such as: (1) in DMF at 140 °C to produce 10-amino-7-aryl-7,12-dihydro-6*H*-chromeno[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine-6,8(9*H*)-diones **80** and (2) in AcOH and DMF at 140 °C to produce 2-amino-5-aryl-6-(2-hydroxybenzoyl)-5,8-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,6*H*)-dione **81** (**Scheme 34**).[74]



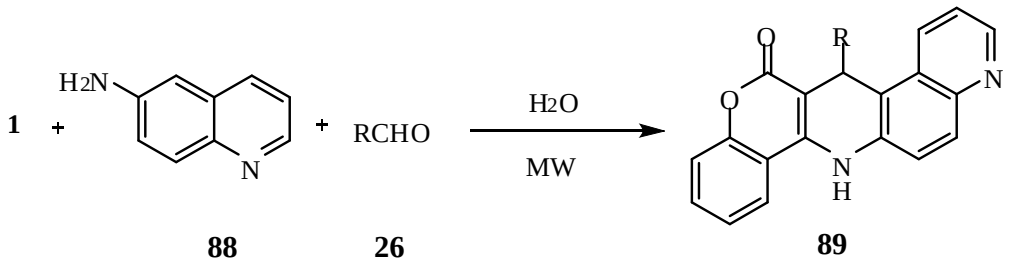
Scheme 34

One-pot reaction of 4-hydroxycoumarin **1** and aromatic aldehydes **26** with 2-aminobenzimidazole **82**, 3-amino-1*H*-1,2,4-triazole **83**, or 6-aminouracil **84** in MeCN using sulfamic acid as catalyst led to a chemoselective synthesis of chromeno[4,3-*d*]pyrimidine-6-one **85**, triazolo[1,5-*a*]pyrimidin-5-one **86**, and pyrido[2,3-*d*]pyrimidine-2,4,7-trione derivatives **87**, respectively, in good yields (**Scheme 35**).[75]



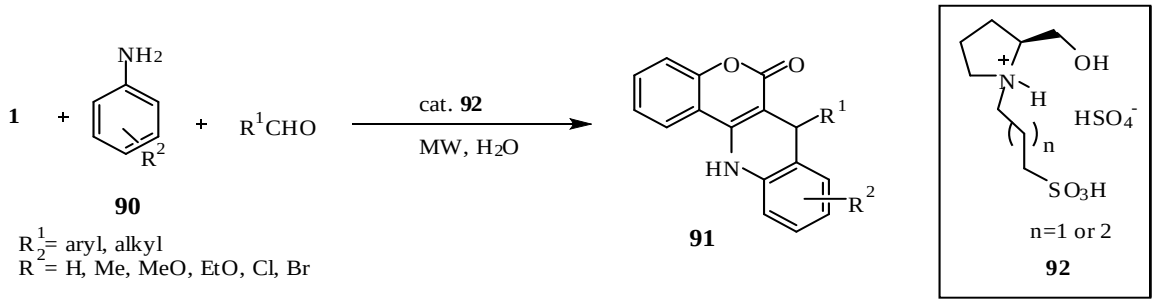
Scheme 35

As illustrated in the **Scheme 35**, three-component reaction of aromatic aldehyde **26**, 6-aminoquinoline **88** and 4-hydroxycoumarin **1** in H_2O, under microwave irradiation was achieved to synthesize chromeno[3,4-*b*][4,7]phenanthroline derivatives **89** (**Scheme 36**).[76]



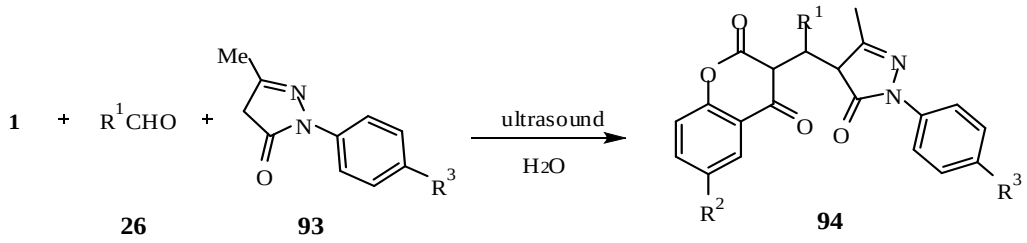
Scheme 36

Sulfonic acid functionalized ionic liquid L-2-(hydroxymethyl)-1-(4-sulfobutyl) pyrrolidinium hydrogen sulfate [HYSBPI]·HSO_4 catalyzed synthesis of coumarin derivatives **91** via a three-component condensation of 4-hydroxycoumarin **1**, aldehydes **26** and aromatic amines **90** in H_2O under microwave irradiation condition in excellent yields. The product **91** had weak-to-good antitumor activities and their IC_{50} ranged from 0.05 to more than 100 μmol·L^{-1} (**Scheme 37**).[77]



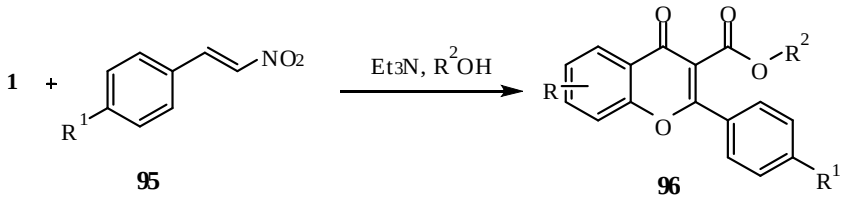
Scheme 37

Three-component reaction of aromatic aldehydes **26**, 4-hydroxycoumarins **1** and diverse pyrazolone derivatives **93** under ultrasonic irradiation in H_2O was described to produce 3-substituted chroman-2,4-diones **94** which found out to be an edaravone moiety represent an exploitable source of brand anticancer agents (**Scheme 38**).[78]



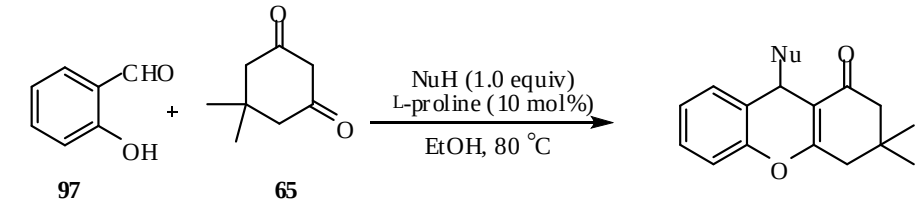
Scheme 38

The unusual formation of 4-oxo-2-aryl-4*H*-chromene-3-carboxylate (flavone-3-carboxylate) derivatives **96** was achieved from the treatment of 4-hydroxycoumarins **1**, β-nitroalkenes **95** in an alcoholic medium using Et_3N (**Scheme 39**). The transformation arises via the following processes: *in situ* Michael addition and then the alkoxide ion mediated rearrangement of the intermediate.[79]



Scheme 39

L-Proline was utilized as catalyst in the three-component reaction of salicylaldehyde **97**, 1,3-cyclohexanedione **65** and a sulfur, carbon, or nitrogen-based nucleophile (such as 4-hydroxycoumarin **1**, 2-hydroxy-1,4-naphthoquinone and barbituric acid) to generate various substituted 4*H*-chromene derivative **98** in good to excellent yields in ethanol under mild and metal-free condition (**Scheme 40**). Replacing L-proline with other acids or bases resulted in the formation of many side products.[80]



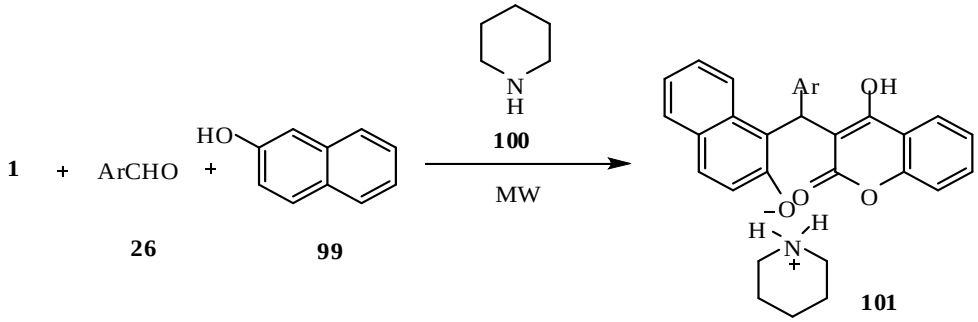
97 **65** **98**

NuH= **1** or 2-hydroxy-1,4-naphthoquinone or barbituric acid

yield= 50-99%

Scheme 40

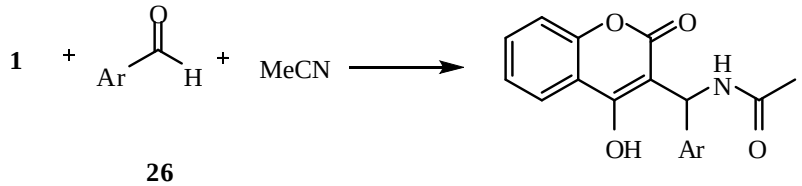
A three-component reaction of 4- hydroxycoumarin **1**, aldehydes **26** and naphthol **99** in the presence of piperidine **100** as catalyst under microwave irradiation is described by Mohammed and co-workers (**Scheme 41**).[81]



26 **99** **101**

Scheme 41

In addition aryl aldehydes, 4-hydroxycoumarin **1**, and acetonitrile as another reagent reacted to synthesize 3-[(acetylamino)(aryl)methyl]-4-hydroxycoumarins via two following procedures: (1) in the presence of chlorosulfonic acid,[82] and (2) using phosphorus pentoxide and hexamethyldisiloxane (P_2O_5-HMDS) (**Scheme 42**).[83]

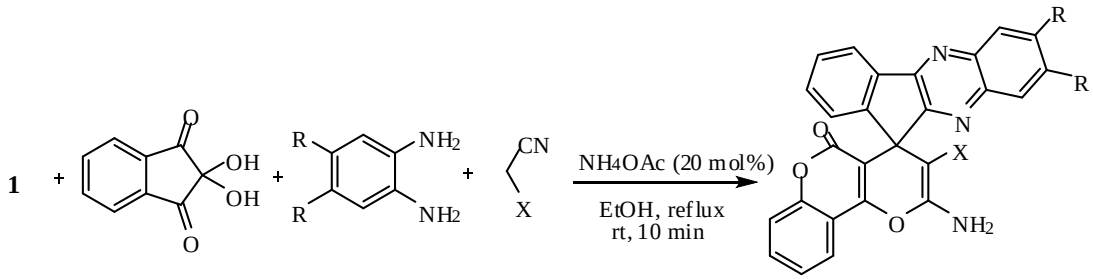


26

Scheme 42

4. FOUR-COMPONENT REACTION OF 4-HYDROXYCOUMARIN

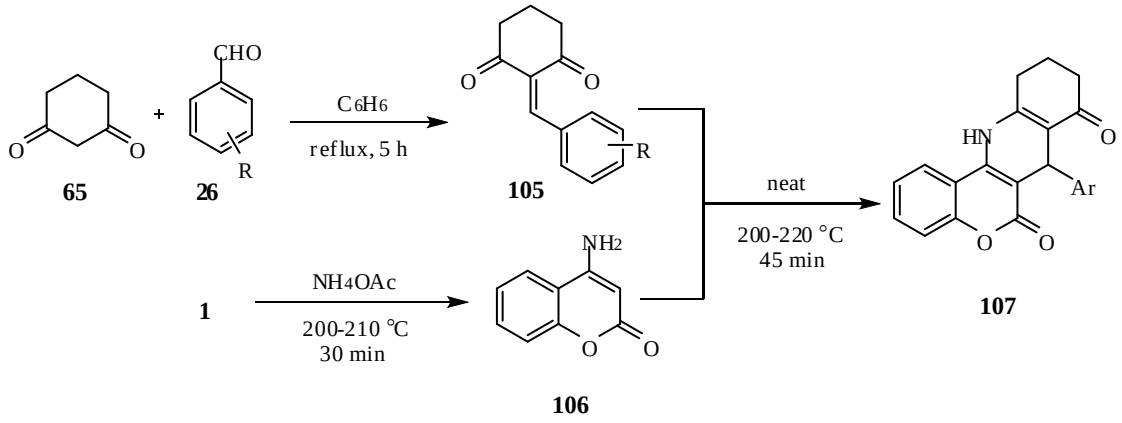
2′-Aminospiro[11*H*-indeno[1,2-*b*]quinoxaline-11,4′-[4*H*]pyran] derivatives **104** was synthesized in good yields in the presence of NH_4OAc as a neutral catalyst via a one-pot four-component reaction of ninhydrin **102**, benzene-1,2-diamine **103**, malono derivatives **60**, and α-methylenecarbonyl compounds **1** (**Scheme 43**).[84]



102 **103** **60** **104**; yield=91%

Scheme 43

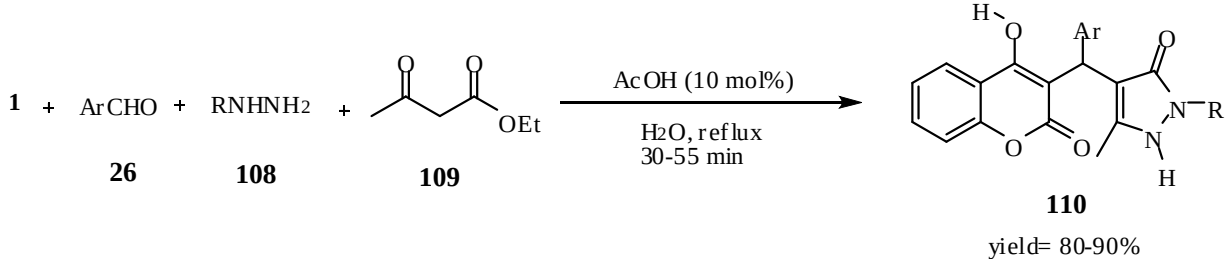
Miri and co-workers synthesized chromeno[4,3-*b*]quinoline derivatives **107** and tested their cytotoxic activity on human cancer cell lines. In this protocol 1,3-cyclohexadione **65** and aryl aldehydes **26** yield 2-benzylidene-cyclohexane-1,3-dione derivatives **105** (80-90%). In the other hand, a mixture of 4-hydroxycoumarin **1** and ammonium acetate were stirred at 200-210 ºC for 30 min to produce 4-aminocoumarin **106** which reacted with 2-benzylidene-cyclohexane-1,3-dione derivatives **105** to afford chromeno[4,3-*b*]quinoline derivatives **107** in 30-50% yield (**Scheme 44**).[85]



65 **26** **105** **1** **107** **106**

Scheme 44

One-pot four-component reaction of arylhydrazine/hydrazine hydrate **108**, ethyl acetoacetate **109**, aromatic aldehydes **26** and 4-hydroxycoumarin **1** in H_2O and glacial AcOH as catalyst was reported by Das and co-workers (**Scheme 45**).[86]

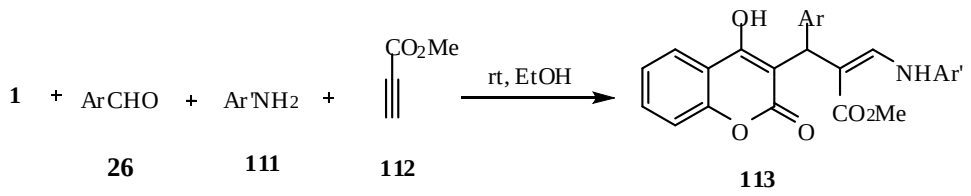


26 **108** **109** **110**

yield= 80-90%

Scheme 45

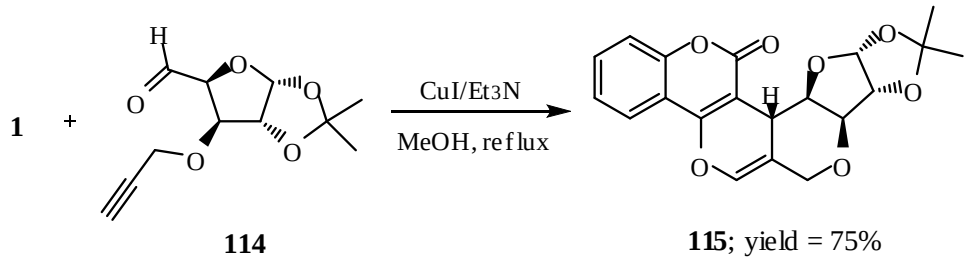
A synthetic method for the densely substituted 3-arylaminoacrylates **113** was developed via the one-pot reaction of arylamines **111**, methyl propiolate **112**, aromatic aldehydes **26**, and 4-hydroxycoumarin **1** (**Scheme 46**). The key step of the reaction involve the formation of α,β-enamino ester followed by a sequential Michael addition to prepare the arylidene dicarbonyl compound.[87]



Scheme 46

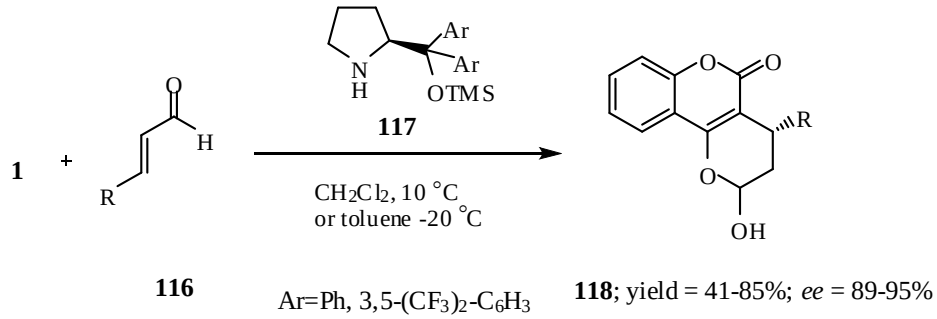
5. ASYMMETRIC SYNTHESIS VIA 4-HYDROXYCOUMARIN

Intramolecular domino Knoevenagel-hetero-Diels-Alder reaction of 1,3-diketones **1** and *O*-propargylated sugar aldehyde **114** in the presence of 0.3 equiv of CuI and a stoichiometric amount of triethylamine resulted in the formation of a stereoselective synthesis of sugar-annulated furo[3,2-*b*] pyrano[4,3-*d*]pyran derivatives **115** in good yields (**Scheme 47**).[88]



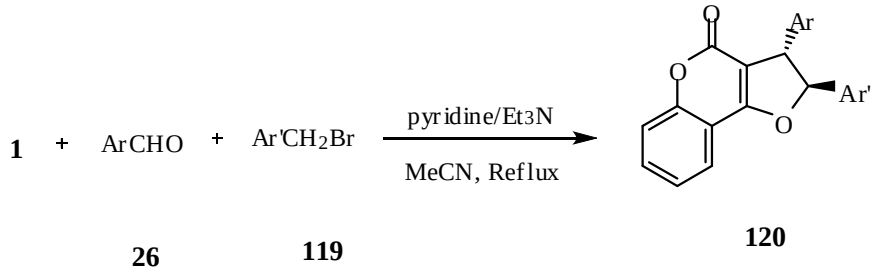
Scheme 47

Enantioselective organocatalytic reaction of 4-hydroxycoumarin **1** with α,β-unsaturated aldehydes **116** was performed by Rueping and co-workers (**Scheme 48**). Diarylprolinol ether **117** catalyzed Michael addition-acetalization of 4-hydroxycoumarin **1** with α,β-unsaturated aldehydes **116** led to chromenones **118** in good yields and high enantioselectivities.[89]



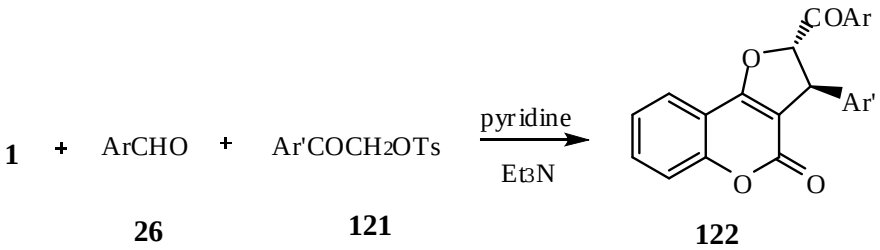
Scheme 48

A Diastereoselective sequential one-pot, two-step tandem reaction of aromatic aldehyde **26**, 4-hydroxycoumarin **1** and α-phenacyl bromide or *p*-nitrobenzyl bromide **119** with triethylamine and pyridine as catalyst was proceeded in boiling acetonitrile (**Scheme 49**). The reaction based on Michael addition and intramolecular cyclization of pyridinium ylide formed in situ. Diastereoselective formation of *trans*-2,3-dihydrofuran derivatives **120** due to steric hindnace in the cyclization step confirmed by the analysis of the vicinal coupling constant of the two methine protons and further confirmed by the X-ray analysis. 2,3-Dihydrofuro[3,2-*c*]chromen-4-ones is a natural product that have various biological activities.[90]



Scheme 49

A one-pot diastereoselective multi-comoponent reaction of aromatic aldehydes **26**, 4-hydroxycoumarin **1**, and α-tosyloxyacetophenones **121** in the presence of pyridine and triethylamine as catalysts was achieved to synthesize differently substituted *trans*-2,3-dihydrofuro[3,2-*c*]coumarins **122** (**Scheme 50**). In this protocol, α-tosyloxyacetophenones may be generated *in situ* from acetophenones and [hydroxyl(tosyloxy)iodo]benzene (HTIB, Koser's reagent), avoiding the use of α-haloacetophenones.[91]



Scheme 50

6. CONCLUSION

In summary, we gave an overview on two, three, and four-component reaction of 4-hydroxycoumarin as a useful skeletal motif. In addition, research on MCRs is an opportunity in the field of green organic reactions or green chemistry due to minimizing waste of cost and time. These are also valuable factors in the chemical and pharmaceutical industries. From the reported results it can be concluded that substituted coumarin analogues has a significant place due to their diversity of organic compounds synthesis.

7. ACKNOWLEGEMENTS

We gratefully acknowledge for financial support of Alzahra University Research Council.

8. REFERENCES AND NOTES

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