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The chemical reactivity of naphthols and their derivatives toward α-cyanocinnamonitriles and ethyl α-cyanocinnamates: A review of synthesis, reactions and applications of naphthopyrano derivatives

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Naphthopyranotriazolopyrimidine

ABSTRACT

This review deals with synthesis and reactions of some naphthopyrano derivatives and their applications. The main purpose of this review is to present a survey of literatures on the reactivity of naphthols and their derivatives toward α-cyanocinnamonitrile or ethyl α-cyanocinnamate derivatives and the reactions of β-enaminonitriles and β-enaminoesters with different electrophiles followed by nucleophilic reagents. Some of these reactions have been applied successfully to the synthesis of biologically important compounds.

1. Introduction

Naturally occurring naphthopyrans have a variety of interesting biological activities and physiological properties [1,2]. Among these, mollugin (**I**) and 3,4-dihydromollugin (**II**) were isolated from the medicinal plant *Rubia cordifolia* in China and India (Figure 1) [3]. The dried roots and rhizomes of this plant are used officially as herbal medicine in the Chinese Pharmacopeia for treating arthritis, dysmenorrhea hemostasis, and other diseases [4]. In India, this plant has been used for treatment of rheumatism, menstrual pain, and urinary disorders [5]. Mollugin (**I**) was also isolated from rhizome of *Galium mollugo*, which is found in many rubiaceous herbs in Europe and Africa [6]. Mollugin (**I**) and its analogue, 3,4-dihydromollugin (**II**), have biologically interesting properties such as antitumor [7], antimutagenic [8], antileukemia [9], anti-inflammatory [10], and antiallergic activities [10].

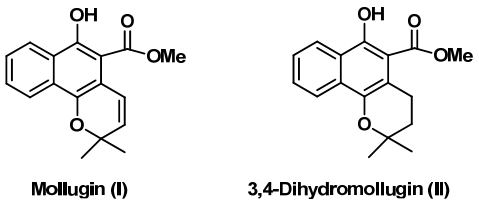
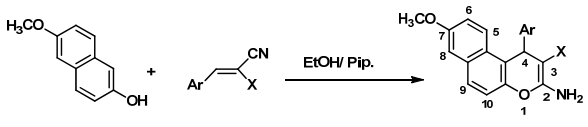


Figure 1. Structures of mollugin (**I**) and 3,4-dihydromollgin (**II**).

2. Synthesis of 4*H*-naphtho[2,1-*b*]pyrans

2.1. Synthesis from 6-methoxy-2-naphthol

Condensation of 6-methoxy-2-naphthol (**1**) with *α*-cyano cinnamonitriles, **2a-f** and/or ethyl *α*-cyanocinnamates, **2g-l**, afforded the corresponding 2-amino-4-aryl-7-methoxy-4*H*-naphtho[2,1-*b*]pyran-3-carbonitriles, **3a-f**, and ethyl-2-amino-4-aryl-7-methoxy-4*H*-naphtho[2,1-*b*]pyran-3-carboxy-lates, **3g-l**, respectively [11,12] (Scheme 1). A mechanism for the piperidine catalyzed formation of the naphtho[2,1-*b*]pyran derivatives **3** is outlined in Scheme 2.



a; Ar = *p*-Br-C_6H_4 X = CN
b; Ar = *p*-Cl-C_6H_4 X = CN
c; Ar = *p* F-C_6H_4 X = CN
d; Ar = C_6H_5 X = CN
e; Ar = *p*-CH_3-C_6H_4 X = CN
f; Ar = *p*-CH_3O-C_6H_4 X = CN
g; Ar = C_6H_5 X = COOEt
h; Ar = *p*-CH_3-C_6H_4 X = COOEt
i; Ar = *p*-CH_3O-C_6H_4 X = COOEt
g; Ar = *p* Br-C_6H_4 X = COOEt
h; Ar = *p* Cl-C_6H_4 X = COOEt
i; Ar = *p* F-C_6H_4 X = COOEt

Scheme 1

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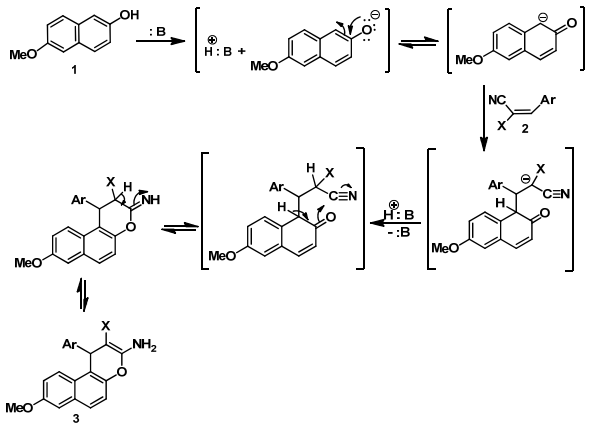
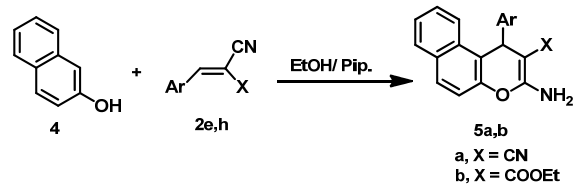


Scheme 2

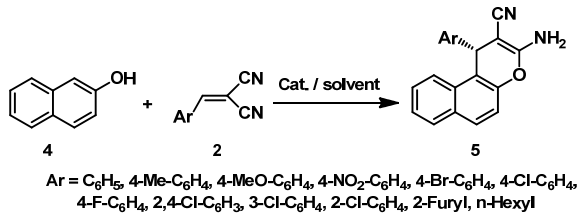
2.2. Synthesis from 2-naphthol

a) Condensation of *α*-cyano-*p*-methylcinnamonitrile (**2e**) or ethyl *α*-cyano-*p*-methylcinnamate (**2h**), with 2-naphthol (**4**) in ethanolic piperidine afforded 2-amino-4-(*p*-tolyl)-4*H*-naphtho[2,1-*b*]pyran-3-carbonitrile (**5a**) and ethyl 2-amino-4-(*p*-tolyl)-4*H*-naphtho[2,1-*b*]pyran-3-carboxylate (**5b**) (Scheme 3) [13].



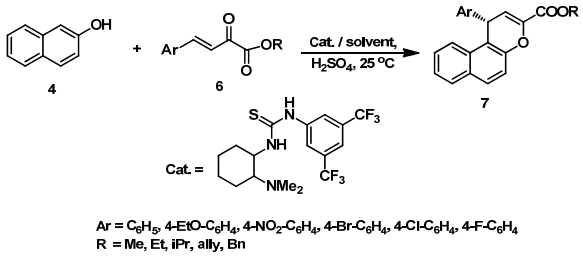
Scheme 3

b) An efficient bifunctional thiourea catalyzed addition-cyclization reaction of arylidenemalononitriles **2** with 2-naphthol (**4**) is realized under mild conditions to afford the corresponding 2-amino-3-cyano-4-aryl-4*H*-naphtho[2,1-*b*]pyrans (**5**), in high yields and moderate enantioselectivities (Scheme 4) [14].

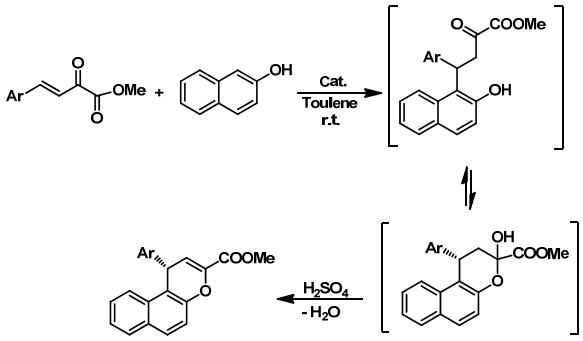


Scheme 4

c) A novel bifunctional thiourea–tertiary-amine-catalyzed enantioselective Friedel-Craft-type addition reaction of 2-naphthol (**4**) with β,γ-unsaturated α-keto ester, **6**, was developed. Subsequent dehydration of the reaction adducts with a catalytic amount of concentrated H_2SO_4 in a one-pot fashion readily afforded a series of new optically active naphthopyran derivatives **7** (Scheme 5), with moderate to good yields (up to 91%) and enantio selectivities (up to 90%) [15]. A mechanism for the bifunctional thiourea-tertiary-amino-catalyzed formation of the naphthopyran derivatives **7** is outlined in Scheme 6.



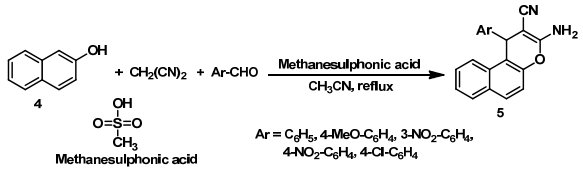
Scheme 5



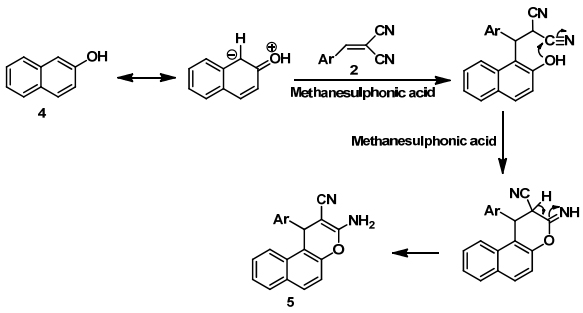
Scheme 6

2.3. Synthesis from multicomponent reactions

a) Methanesulfonic acid efficiently catalyzes the one-pot, three component reaction of an 2-naphthol (**4**), aromatic aldehyde and malononitrile to yield 2-amino-3-cyano-4-aryl-4*H*-naphtho[2,1-*b*]pyrans (**5**) in good yields (Scheme 7) [16]. A mechanism for the methanesulfonic acid catalyzed formation of the naphtho[2,1-*b*]pyran derivatives **5** is outlined in Scheme 8.

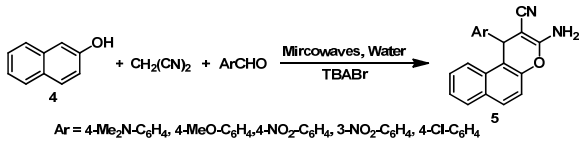


Scheme 7



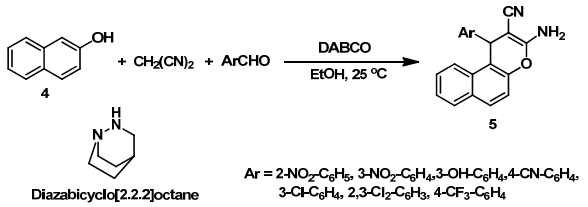
Scheme 8

b) Naphtho[2,1-*b*]pyran derivatives, **5**, have been synthesized involving a one pot three-component reaction of an aldehyde, malononitrile and 2-naphthol (**4**) using catalytic amounts *tetra*-butyl ammonium bromide (TBABr) under aqueous conditions (Scheme 9) [17].

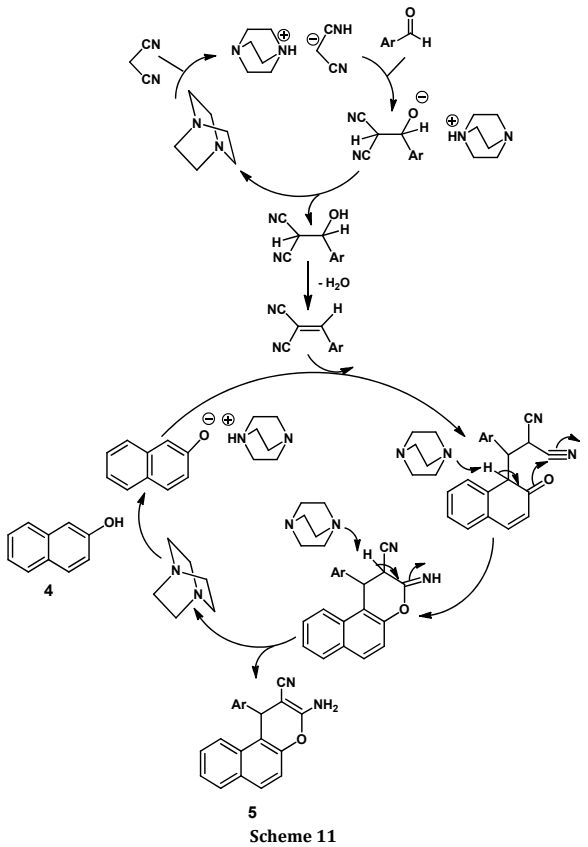


Scheme 9

c) Diazabicyclo[2.2.2]octane (DABCO) has been used as a mild and efficient catalyst for synthesis of 2-amino-3-cyano-4-aryl-4*H*-naphtho[2,1-*b*]pyrans (**5**) via a one-pot three-component reaction of aromatic aldehydes, 2-naphthol (**4**), and malononitrile at room temperature [18]. The short reaction times, easy workup, good to excellent yields, and mild reaction conditions make this domino Knoevenagel-Michael reaction both practical and attractive (Scheme 10). A mechanism for the DABCO catalyzed formation of the naphtho[2,1-*b*]pyran derivatives **5** is outlined in Scheme 11

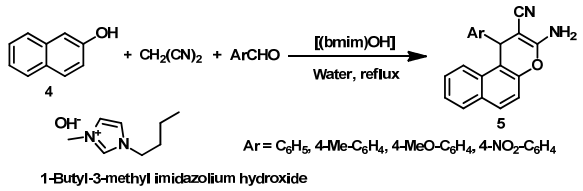


Scheme 10



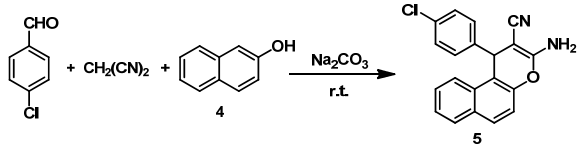
Scheme 11

d) A basic functionalized ionic liquid, 1-butyl-3-methyl imidazolium hydroxide ([bmim]OH), catalyzed three-component condensation reaction of aromatic aldehydes, malononitrile and 2-naphthol (**4**) proceeded rapidly in water at reflux to afford corresponding 2-amino-3-cyano-4-aryl-4*H*-naphtho[2,1-*b*]pyrans (**5**) in high yields [19]. The greener protocol was found to be fairly general and the aqueous reaction media was reused in subsequent reactions with consistent activity (Scheme 12).

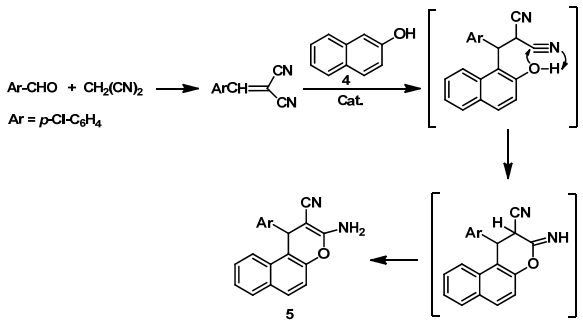


Scheme 12

e) The model reaction was carried out simply by mixing of 4-chlorobenzaldehyde, malononitrile and 2-naphthol (**4**) using Na_2CO_3 as catalyst afforded 2-amino-3-cyano-4-(*p*-chloro phenyl)-4*H*-naphtho[2,1-*b*]pyran (**5**). In the absence of catalyst no reaction was observed at room temperature (Scheme 13) [20]. A mechanism for the Na_2CO_3 catalyzed formation of the naphtho[2,1-*b*]pyrans **5** is outlined in Scheme 14.

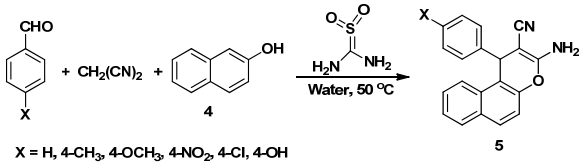


Scheme 13



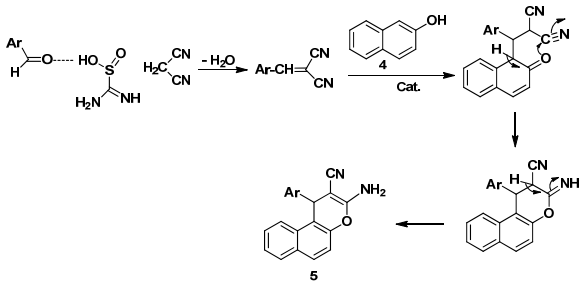
Scheme 14

f) An aqueous solution of thiourea dioxide (TUD) was used to catalyze a one-pot three-component coupling reaction of an aromatic aldehyde, malononitrile, and 2-naphthol (**4**) for the synthesis of various naphthopyran derivatives **5** in excellent yields (Scheme 15) [21]. A mechanism for the TUD catalyzed formation of the pyran derivatives **5** is outlined in Scheme 16.

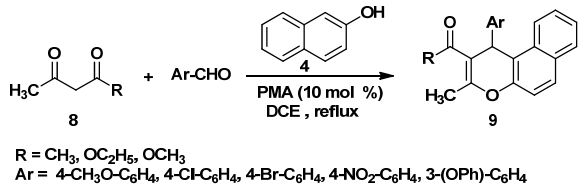


Scheme 15

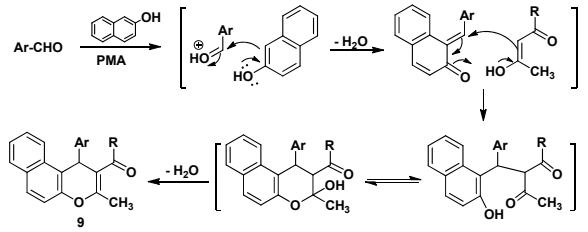
g) Naphthopyran derivatives **9** have been synthesized involving a one pot three-component reaction of an aldehyde, active methylene substrate **8**, and 2-naphthol (**4**) catalyzed by Bronsted acid molybdophosphoric acid [phosphomolybdic acid (PMA)] (Scheme 17) [22]. A mechanism for PMA catalyzed the formation of the pyran derivatives **9** is outlined in Scheme 18.



Scheme 16

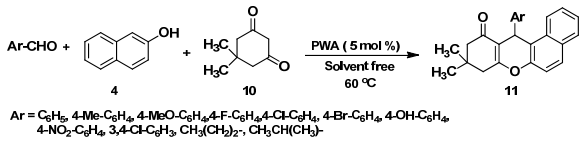


Scheme 17

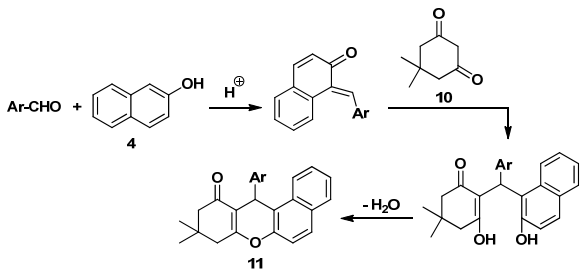


Scheme 18

h) The condensation of 2-naphthol (**4**), aromatic aldehde and 5,5-dimethyl-1,3-cyclohexanedione (**10**), the presence of a catalytic amount of tungstophosphoric acid [phosphotungstic acid (PWA)] (5 mol%) at 60 °C under solvent-free condition afforded 12-(4-chlorophenyl)-9,9-dimethyl-8,9,10,12-tetra-hydrobenzo-[*a*]xanthen-11-one (**12**) (Scheme 19) [23]. A mechanism for the PWA catalyzed formation of the pyran derivatives **12** is outlined in Scheme 20.

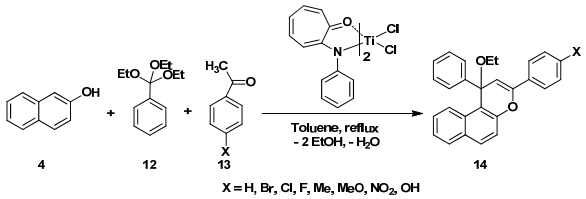


Scheme 19

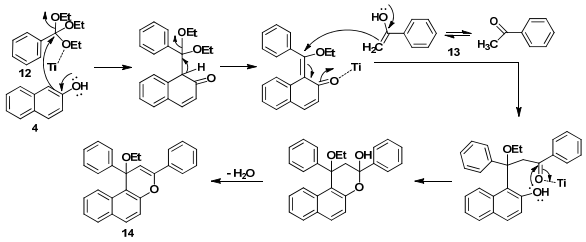


Scheme 20

i) Treatment of 2-naphthol (**4**), triethyl orthobenzoate (**12**) and acetophenone derivatives **13** and, in the presence of a catalytic amount of *bis*(2-anilinotropone) Ti complex afforded naphtho[2,1-*b*]pyrans **14** (Scheme 21) [24]. A mechanism for the *bis*(2-anilinotropone)Ti complex catalyzed formation of the naphthopyran derivatives **14** is outlined in Scheme 22.

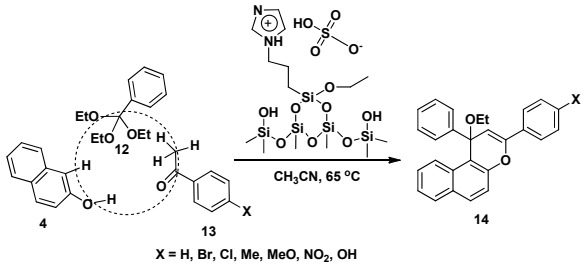


Scheme 21



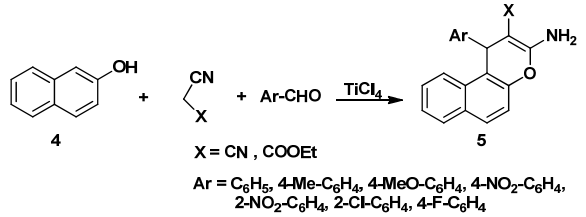
Scheme 22

j) A facile method for the synthesis of naphthopyran derivatives **14** is reported. The procedure involves a novel three-component reaction of 2-naphthol (**4**), triethyl ortho-benzoate (**12**) and acetophenone derivatives **13** in the presence of silica supported ionic liquid [pmim]HSO_4SiO_2 [silica supported 1-methyl-3-(triethoxysilyl-propyl)imidazolium hydrogensulfate] as an efficient catalyst (Scheme 23) [25].



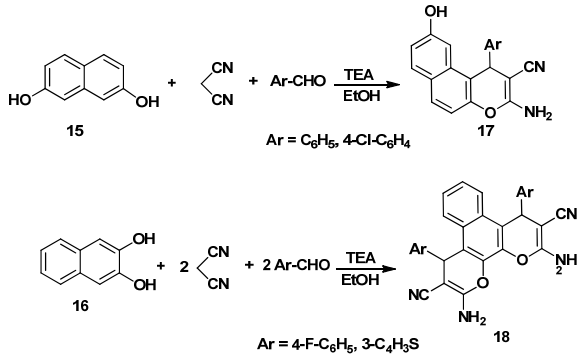
Scheme 23

k) A mixture of 2-naphthol (**4**), aromatic aldehyde, active methylene compound, (malononitrile or ethyl cyanoacetate), activated and $TiCl_4$ (10 mol %) was stirred at room temperature afforded naphthopyrans **5** (Scheme 24) [26].



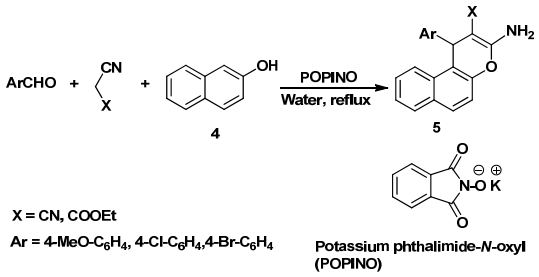
Scheme 24

l) A three component condensation aromatic aldehyde, malononitrile and 2,7-naphthalenediol (**15**), afforded only naphthopyran **17**, regardless of the reagent ratio (1:1:1), whereas three-component condensation with the use of 2,2-naphthalenediol (**16**), gave pyranonaphthopyran **18** regardless of the reagent ratio (2:2:1), respectively, (Scheme 25) [27].

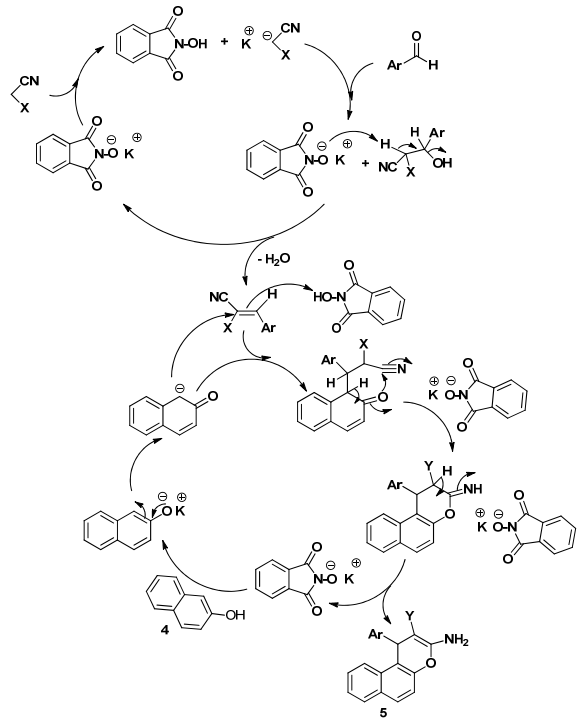


Scheme 25

m) A wide variety of 2-amino-4*H*-naphthopyran derivatives **5** prepared via one-pot, three-component reaction of an aromatic aldehyde, malononitrile (or ethyl cyanoacetate), and 2-naphthol (**4**), diverse enolizable C-H activated acidic compounds in the presence of low loading of potassium phthalimide-*N*-oxyl (POPINO), as a new organocatalyst (Scheme 26) [28]. A mechanism for the POPINO catalyzed formation of the naphthopyran derivatives **5** is outlined in Scheme 27.

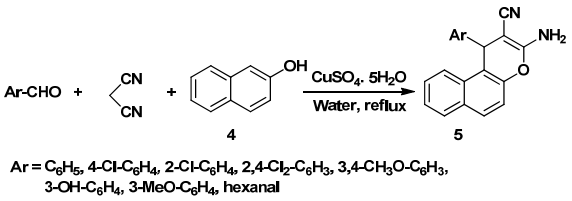


Scheme 26

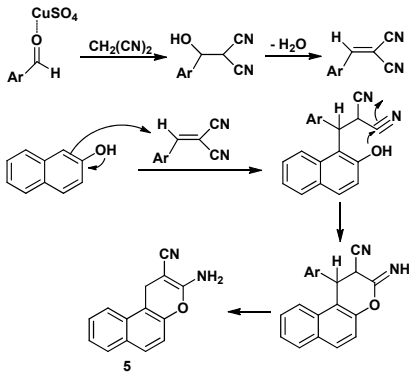


Scheme 27

n) A green chemistry method for synthesis of naphtho[2,1-*b*]pyran derivatives **5** is reported. The procedure involves three-component reaction of 2-naphthol (**4**), aromatic aldehyde, malononitrile in the presence of copper (II) sulfate pentahydrate, (Scheme 28) [29]. A mechanism for the $CuSO_4.5H_2O$ catalyzed formation of the naphtho[2,1-*b*]pyrans **5** is outlined in Scheme 29.



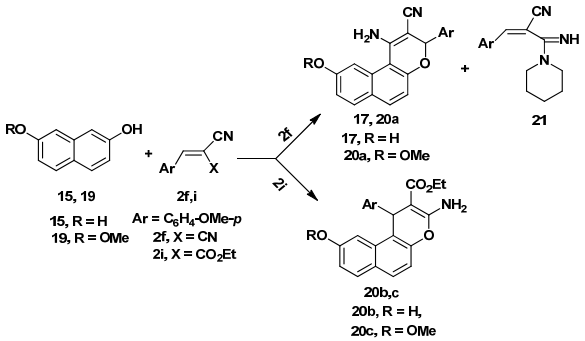
Scheme 28



Scheme 29

2.4. Synthesis from 7-substituted-2-naphthols

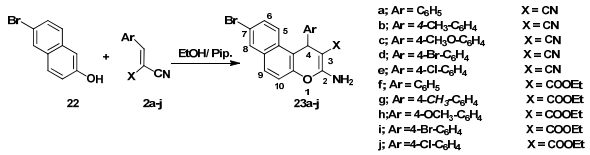
Thus, condensation of 2,7-naphthalenediol (**15**) or 7-methoxy-2-naphthol (**19**) with *α*-cyano-4-methoxycinnamo nitrile (**2f**) in ethanolic piperidine afforded the 1:1 adducts **17**,**20a** along with 2-(imino-piperidin-1-yl-methyl)-3-(4-methoxy phenyl)-acrylonitrile (**21**), while condensation of **15** and **19** with ethyl *α*-cyano-4-methoxycinnamate (**2i**) afforded **20b**,**c** as the only isolable products (Scheme 30) [30].



Scheme 30

2.5. Synthesis from 6-bromo-2-naphthol

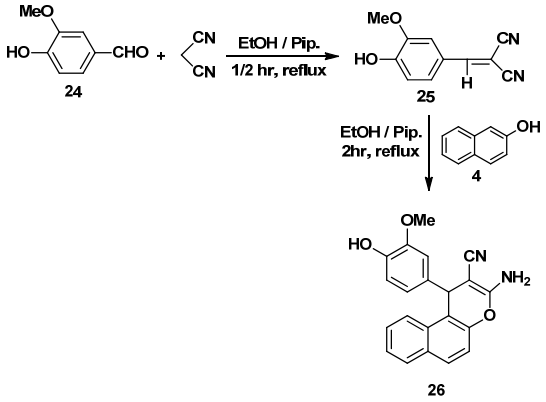
Condensation of various substituted α-cyanocinnamo nitriles (**2a**-**e**) ethyl 3-aryl 2-cyano acrylates (**2f**-**j**) with 6-bromo-2-naphthol (**22**) in ethanolic piperidine afforded naphthopyrano derivatives (**23a**-**j**) (Scheme 31) [31,32].



Scheme 31

2.6. Synthesis from 2-(4-hydroxy-3-methoxybenzylidene) malononitrile

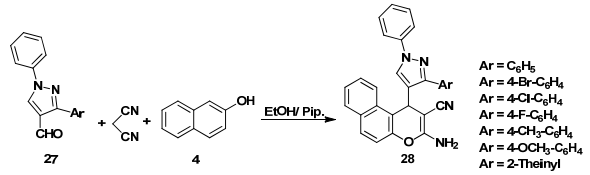
The 2-(4-hydroxy-3-methoxybenzylidene)malononitrile (**25**) [33] was prepared by reaction of molononitrile with 4-hydroxy-3-methoxy benzaldehyde (24), which upon condensation with 2-naphthol (**4**) to 2-amino-3-cyano-4-(4-hydroxy-3-methoxyphenyl)-4H-naphtho[2,1-b]pyran (26), respectively (Scheme 32) [34].



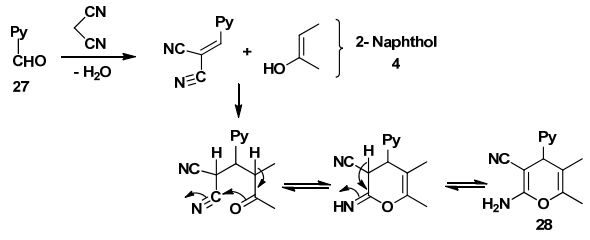
Scheme 32

2.7. Synthesis from 1-phenyl-3-aryl-pyrazole-4-carbaldehyde

Naphthopyran derivatives **28** have been synthesized by one-pot three-component cyclocondensation reaction of 1-phenyl-3-aryl-pyrazole-4-carbaldehyde (**27**), malononitrile and 2-naphthol (**4**), respectively [35], in the presence of piperidine as catalyst. The mixture refluxing under ethanol or acetonitrile gives moderate to good yield (50-76%) (Scheme 33). A mechanism for the piperidine catalyzed formation of the naphthopyran derivatives **28** is outlined in Scheme 34.



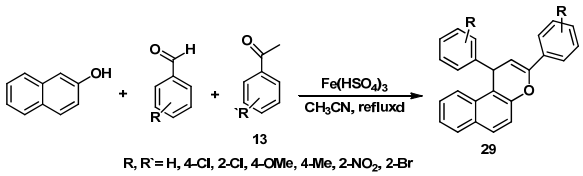
Scheme 33



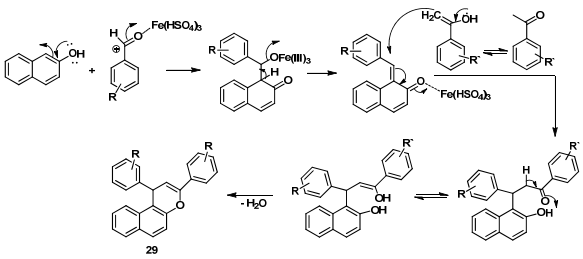
Scheme 34

2.8. Synthesis from 2-naphthol by [Fe(HSO4)3]

2,4-Diaryl-4*H*-naphtho[2,1-*b*]pyran (**29**) was synthesized by one-pot reaction from 2-naphthol (**4**), aromatic aldehydes and acetophenones (**13**) in acetonitrile in the presence of ferric hydrogensulfate. In the present study, the target products have been synthesized through new approach in good to excellent yields (Scheme 35) [36]. A mechanism for the $Fe(HSO_4)_3$ catalyzed formation of the naphthopyran derivatives **31** is outlined in Scheme 36.



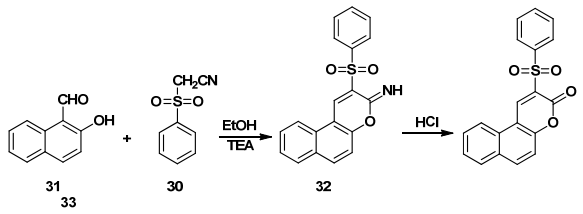
Scheme 35



Scheme 36

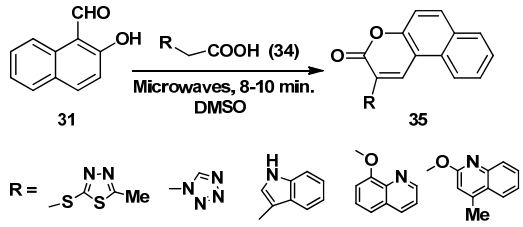
2.9. Synthesis from 2-hydroxy naphthaldehyde

a) Phenylsulfonylacetonitrile (**30**) reacts with 2-hydroxy naphthaldehyde (**31**) in refluxing ethanol in the presence of *triethylamine* TEA gave 2-imino-3-phenylsulfonyl-naphtho[2,1-*b*]pyran (**32**), which by acid hydrolysis gave 3-phenylsulfonyl-naphtho[2,1-*b*]pyran-2-one (**33**) (Scheme 37) [37].



Scheme 37

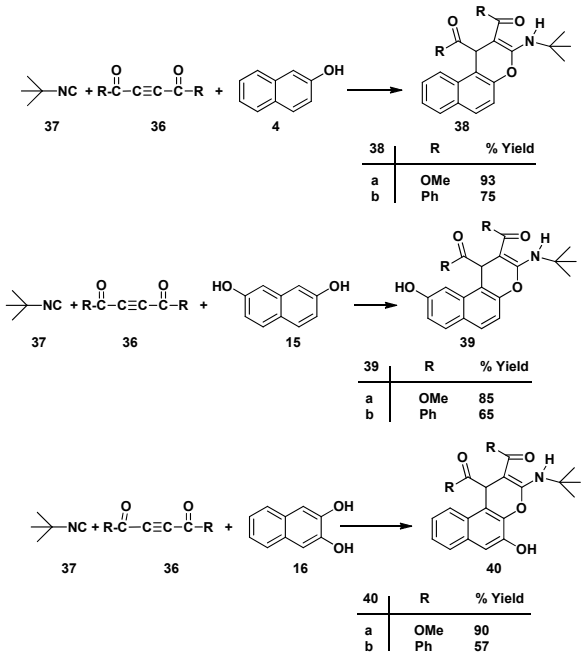
b) 2-Substituted naphtho[2,1-*b*]pyran-2-ones (**35**) have been synthesized by a novel one-pot method which involves cyclocondensation of 2-hydroxy-1-naphthaldehyde (**31**) with 5-methyl-1,3,4-thiadiazol-2-ylsulfanyl-, 1*H*-1,2,3,4-tetrazol-1-yl-, 1*H*-indol-3-yl-, quinolin-8-yloxy- and 4-methylquinolin-2-yloxy-acetic acids (**34**) in the presence of DCC–DMSO using microwaves as well as conventional heating (Scheme 38) [38].



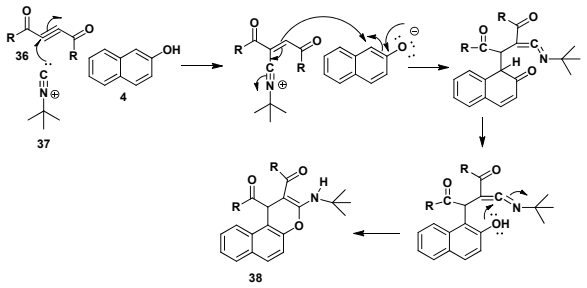
Scheme 38

2.10. Synthesis from of dimethyl acetylenedicarboxylate (DMAD) or dibenzoylacetylene

The reaction of dimethyl acetylene-dicarboxylate DMAD or dibenzoylacetylene (**36**) with tert-butyl isocyanide (**37**) in the presence of naphthols, proceeded spontaneously at room temperature in dichloromethane, and produced 2-tert-butylamino-4*H*- naphtho[2,1-*b*]pyrans **38**-**40** (Scheme 39) [39]. A mechanism for the formation of the pyran derivatives, **39**-**41**, is outlined in Scheme 40.



Scheme 39

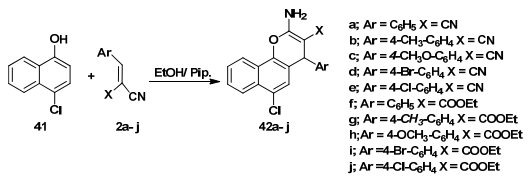


Scheme 40

3. Synthesis of 4*H*-naphtho[1,2-*b*]pyrans

3.1. Synthesis from 4-chloro-1-naphthol

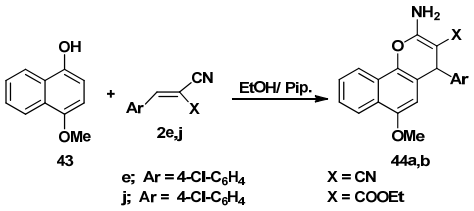
Thus, condensation of various substituted benzyliden malonitrile (**2a**-**e**) and ethyl 3-aryl 2-cyano acrylates (**2f**-**j**) with 4-chloro-1-naphthol (**41**) in the ethanolic piperidine afforded naphthopyran derivatives **42a**-**j** (Scheme 41) [40,41].



Scheme 41

3.2. Synthesis from 4-methoxy-1-naphthol

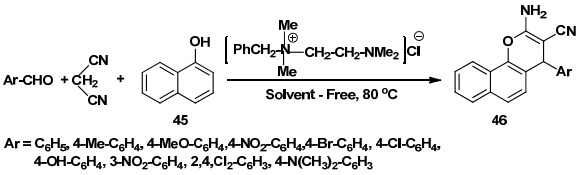
Reaction of 4-methoxy-1-naphthol (**43**) with α-cyano-*p*-chlorocinnamonitrile (**2e**) or ethyl *α*-cyano-*p*-chlorocinnamate (**2j**) in ethanolic piperidine afforded naphthopyrano derivatives **44a**,**b** (Scheme 42) [42].



Scheme 42

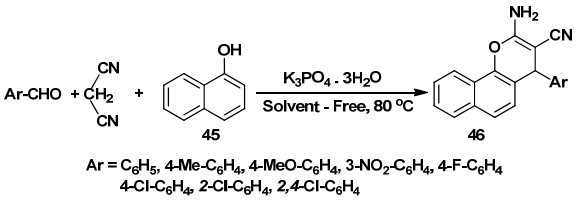
3.3. Synthesis from multicomponent reactions

a) Naphtho[1,2-*b*]pyrans (**46**) have been synthesized through the three-component reaction of aromatic aldehydes, malononitrile, and 1-naphthol (**45**) using a catalytic amount of *N*,*N*-dimethylaminoethylbenzyldimethylammonium chloride as catalyst under solvent-free condition (Scheme 43) [43].



Scheme 43

b) Using the reaction of 1-naphthol (**45**), malononitrile and aromatic aldehydes in the presence of 10% mol of potassium phosphate tribasic trihydrate under solvent-free conditions, afforded naphtho[1,2-*b*]pyrans **46** (Scheme 44) [44]. A mechanism for the $K_3PO_4.3H_2O$ catalyzed formation of the pyran derivatives **46** is outlined in Scheme 45.

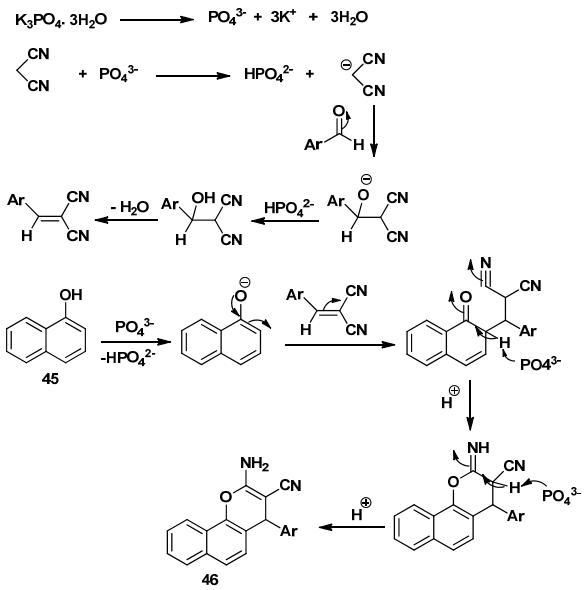


Scheme 44

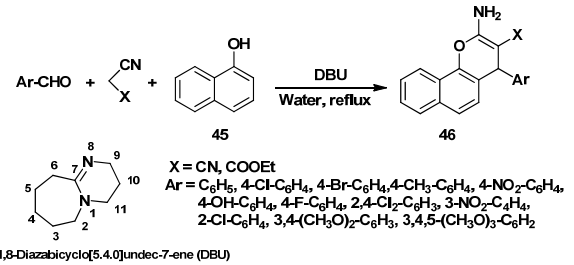
c) 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) has been used as a catalyst for synthesis of naphtho[1,2-*b*]pyran derivatives **46** via a one-pot three-component reaction of 1-naphthol (**45**), aromatic aldehydes and malononitrile/ethyl cyanocacetate in water under reflux (Scheme 46) [45]. A mechanism for the DBU catalyzed formation of the 4H-naphtho[1,2-*b*]pyrans 46 is outlined in Scheme 47.

d) Condensation of aromatic aldehyde, malononitrile and 1-naphthol (**45**) or 4-chloro-1-naphthol (**41**) using Na_2CO_3 as catalyst afforded naphtho[1,2-*b*]pyrans **46** and **42** (Scheme 48) [20].

e) One-pot, three components reaction of 1-naphthol (**45**), aromatic aldehyde and malonitrile in presences of methanesulfonic acid to yield 4*H*-naphtho[1,2-*b*]pyrans **46** in good yields (Scheme 49) [16] .



Scheme 45



Scheme 46

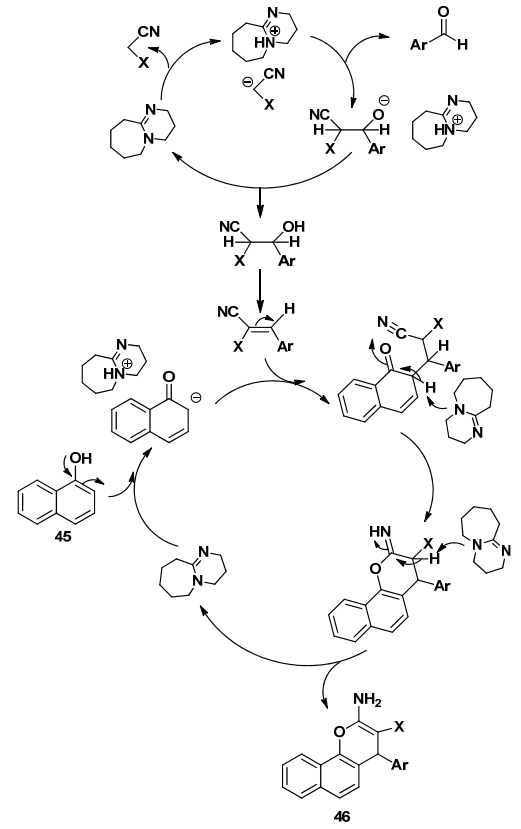
f) A basic functionalized ionic liquid, 1-butyl-3-methyl-imidazolium hydroxide ([bmim]OH), catalyzed three component condensation of aromatic aldehydes, malononitrile and 1-naphthol (**45**), proceeded rapidly in water at reflux to afford corresponding naphtho[1,2-*b*]pyrans **46** in high yields. (Scheme 50) [19].

g) An aqueous solution of thiourea dioxide was used to catalyze a one-pot three-component coupling reaction of an aromatic aldehyde, malononitrile, and 1-naphthol (**45**), for the synthesis of various naphthopyran derivatives **46** in excellent yields (Scheme 51) [21].

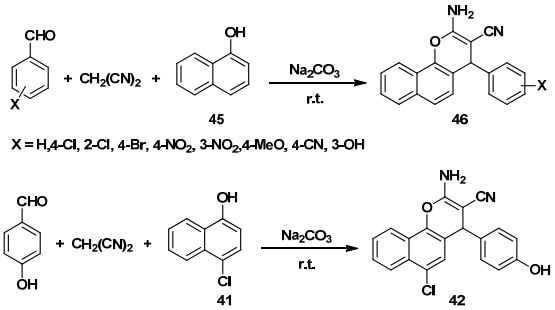
h) Diazabicyclo[2.2.2]octane (DABCO) has been used as a mild and efficient catalyst for synthesis of 2-amino-3-cyano naphthopyran derivatives (46) [18] via a one-pot three-component reaction of aromatic aldehydes, 1-naphthol (**45**), and malononitrile at room temperature. The short reaction times, easy workup, good to excellent yields (Scheme 52).

i) A green chemistry method for synthesis of naphtho[1,2-*b*]pyrans (**46**) is reported. The procedure invoves three-component reaction of 1-naphthol (**45**), aromatic aldehyde, malononitrile in the presence of copper(II)sulfate penta hydrate, (Scheme 53) [29].

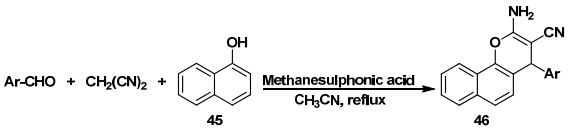
j) A wide variety of naphtho[1,2-*b*]pyrans **46** prepared via one-pot, three-component reaction of an aromatic aldehyde, malononitrile (or ethyl cyanoacetate), and 1-naphthol (**45**), in the presence of low loading of potassium phthalimide-*N*-oxyl (POPINO), as a new organocatalyst (Scheme 54) [28].



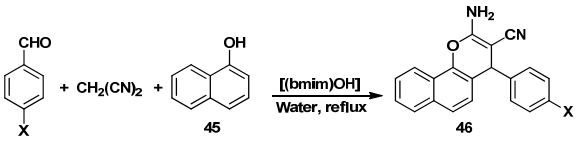
Scheme 47



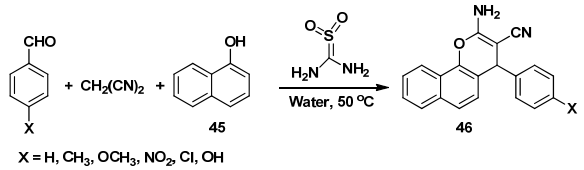
Scheme 48



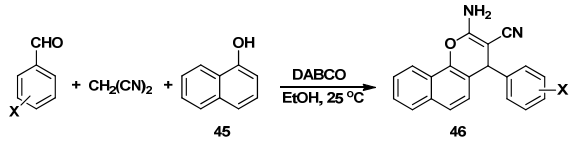
Scheme 49



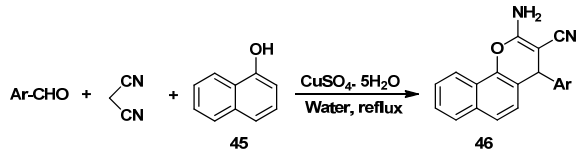
Scheme 50



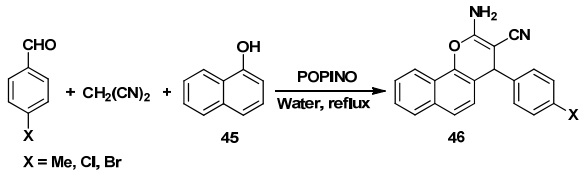
Scheme 51



Scheme 52

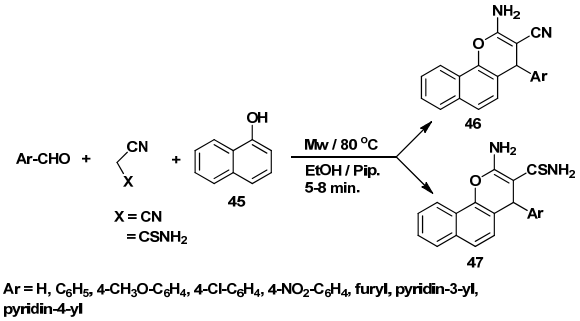


Scheme 53



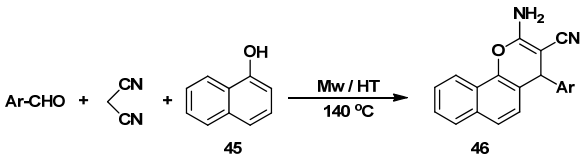
Scheme 54

k) A simple and efficient three component process for the synthesis of naphtho[1,2-*b*]pyrans **46** and **47** utilizing the reaction of aryl with active methylenes (malononitrile, 2-cyanoethyanethioamide) and 1-naphthol (**45**), in refluxing ethanol/piperidine under microwave-heating is described (Scheme 55) [46].



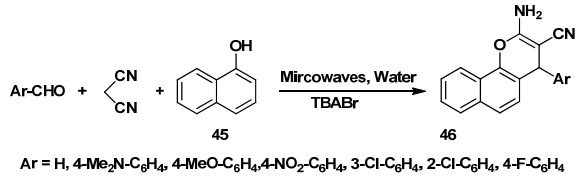
Scheme 55

l) Mg/Al hydrotalcite, a heterogeneous base catalyst, was found to be highly effective for the synthesis of naphtho[1,2-*b*]pyrans **46** via a multicomponent reaction of aromatic aldehydes, malononitrile and 1-naphthol (**45**) under microwaves. The reaction is rapid, clean and gives the products in high yields. The catalyst is reusable; however, there was reduction in the yield of the product (Scheme 56) [47].



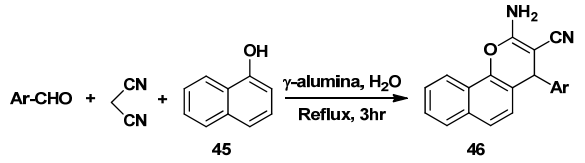
Scheme 56

m) One pot multicomponent, condensation reaction of 1-naphthol (**45**) aldehyde and malononitrile using catalytic amounts tetrabutyl ammonium bromide (TBABr) under microwaves aqueous conditions afforded naphthopyrans **46** (Scheme 57) [17].



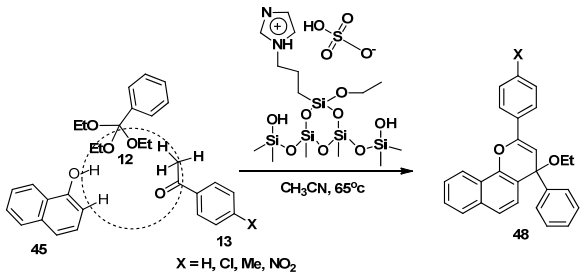
Scheme 57

n) Maggi *et al.* [48] have described the use of basic alumina as a heterogeneous and reusable catalyst for the three-component synthesis of substituted naphtho[1,2-*b*]pyrans **46**. The reaction is highly regioselective. This process is industrially viable due to the use of water as a solvent and *γ*-alumina as an inexpensive and reusable catalyst. However, one drawback of this methodology is 1-naphthol (**45**) can only be used as an activated phenol. The preparation of these compounds has also been reported by Wang *et al.* [49] using KF-alumina as a catalyst (Scheme 58).



Scheme 58

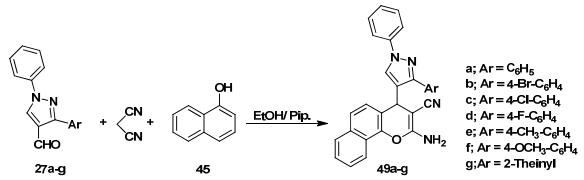
o) A facile method for the synthesis of naphtho[1,2-*b*]pyrans **48** is reported. The procedure involves a novel three-component reaction of 1-naphthol (**45**), triethyl ortho benzoate(**12**) and acetophenone derivatives **13**, in the presence of silica supported ionic liquid [pmim]HSO_4 SiO_2 [silica supported 1-methyl-3-(triethoxysilyl-propyl)imidazo lium hydrogen-sulfate] (Scheme 59) [25].



Scheme 59

3.4. Synthesis from 1-phenyl-3-aryl-pyrazole-4-carbaldehyde

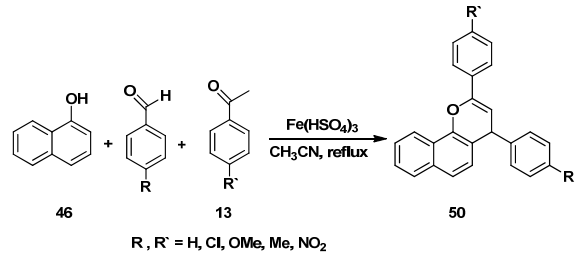
Naphthopyran derivatives **49a-g** has been synthesized by one-pot three-component cyclocondensation reaction of 1-phenyl-3-aryl-pyrazole-4-carbaldehyde (**27a-g**), malononitrile and 1-naphthol (**45**), respectively, in the presence of piperidine as catalyst (Scheme 60) [35].



Scheme 60

3.5. Synthesis from 1-naphthol by [Fe(HSO4)3]

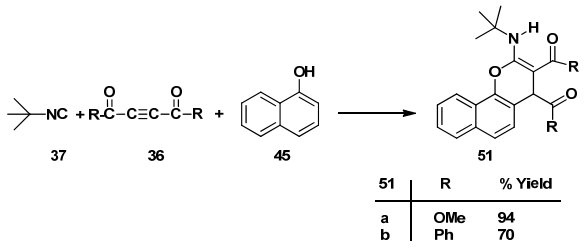
Synthesis of 2,4-diaryl-4*H*- naphtho[1,2-*b*]pyrans **50** by one-pot reaction from 1-naphthol (**45**) , aromatic aldehydes and acetophenone in acetonitrile in the presence of ferric hydrogen sulfate. In the present study, the target products have been synthesized through new approach in good to excellent yields (Scheme 61) [36].



Scheme 61

3.6. Synthesis from of dimethyl acetylenedicarboxylate DMAD or dibenzoylacetylene

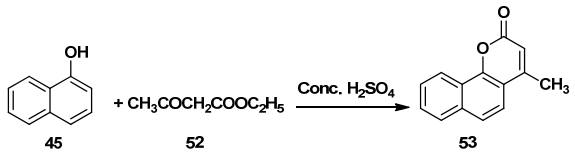
The reaction of dimethyl acetylenedicarboxylate DMAD or dibenzoylacetylene (**36**) with tert-butyl isocyanide (**37**) in the presence of 1-naphthol (**45**), proceeded spontaneously at room temperature in dichloromethane, and produced 2-tert-butylamino-4*H*-naphtho[1,2-*b*]pyrans **52** (Scheme 62) [39].



Scheme 62

3.7. Synthesis from ethylacetoacetate

Formation of 4-methyl-naphtho[1,2-*b*]pyran-2-one (**53**) takes place via cyclization reaction of 1-naphthol (**45**) and ethylacetoacetate (**52**) in presence of sulphuric acid. (Scheme 63) [50].



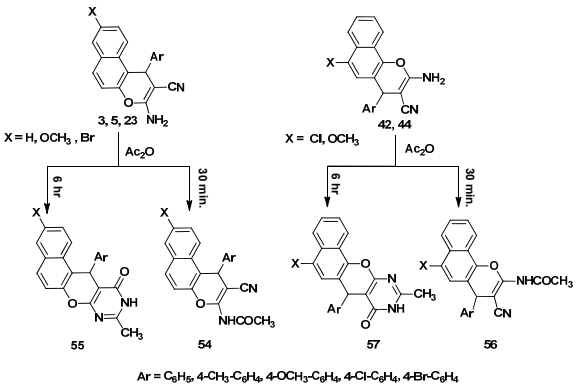
Scheme 63

4. Reactions of naphtho[2,1-*b*]pyrans and naphtha [1,2-*b*]pyrans with some electrophilic and nucleophilic reagents

4.1. Reactions of naphthopyranoaminonitriles

4.1.1. Acetic anhydride

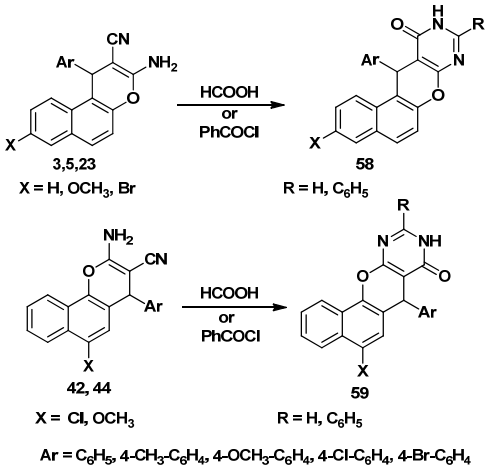
Treatment of naphtho[2,1-*b*]pyran **3**, **5** and **23** and or naphtho[1,2-*b*]-pyran **42** and **44** derivatives with Ac_2O gave two products dependening on the reaction time; one product was identified as 2-acetylamino-naphthopyrans derivatives **54** and **56** (30 min), while the other was identified as naphthopyranopyrimidine derivatives **55** and **57** (6 h) (Scheme 64) [11-13,30-33,40-42].



Scheme 64

4.1.2. Formic acid or benzoyl chloride

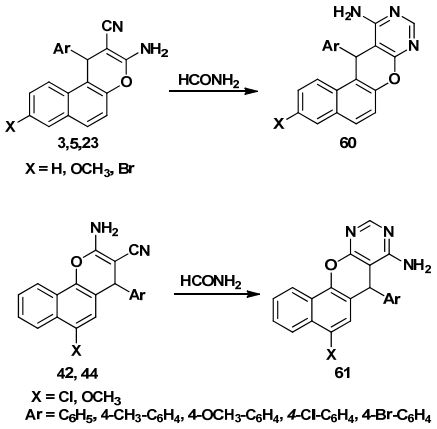
Reaction of naphtho[2,1-*b*]pyrans **3**, **5** and **23** and or naphtho[1,2-*b*]-pyran **42** and **44** derivatives with formic acid or benzoyl chloride to give naphthopyranopyrimidine and phenyl-naphthopyranopyrimidine derivatives **58** and **59** (6h), respectively (Scheme 65) [11-13,30-33,40-42].



Scheme 65

4.1.3. Formamide

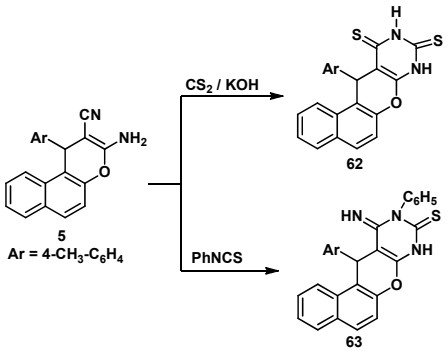
Reaction of naphtho[2,1-*b*]pyrans **3**, **5** and **23** and or naphtho[1,2-*b*]-pyran **42** and **44** derivatives with formamide to give aminonaphtho-pyranopyrimidine derivatives **60** and **61** (Scheme 66) [11-13,30-33,40-42].



Scheme 66

4.1.4. Carbon disulfide or phenyl isothiocyanate [13]

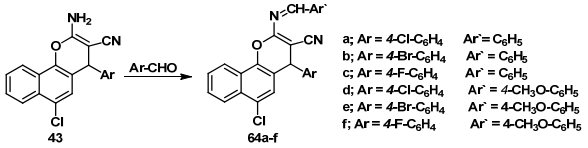
Treatment of compound **5** with carbon disulphide in alcoholic postassium hydroxide furnished 9,11-dithione derivative **62**, whereas treatment with phenyl isothiocyanate yielded the 9-thione derivative **63** (Scheme 67) [13].



Scheme 67

4.1.5. Aromatic aldehyde

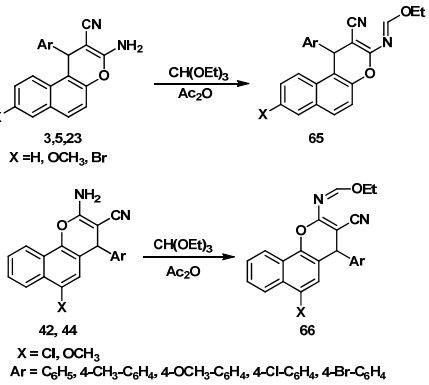
Condensation of compound **43** with benzaldehyde or 4-methyloxy-benzaldehyde in dioxin- piperidine solution under reflux afforded the corresponding arylmethyleneamino derivatives **64a-f** (Scheme 68) [41].



Scheme 68

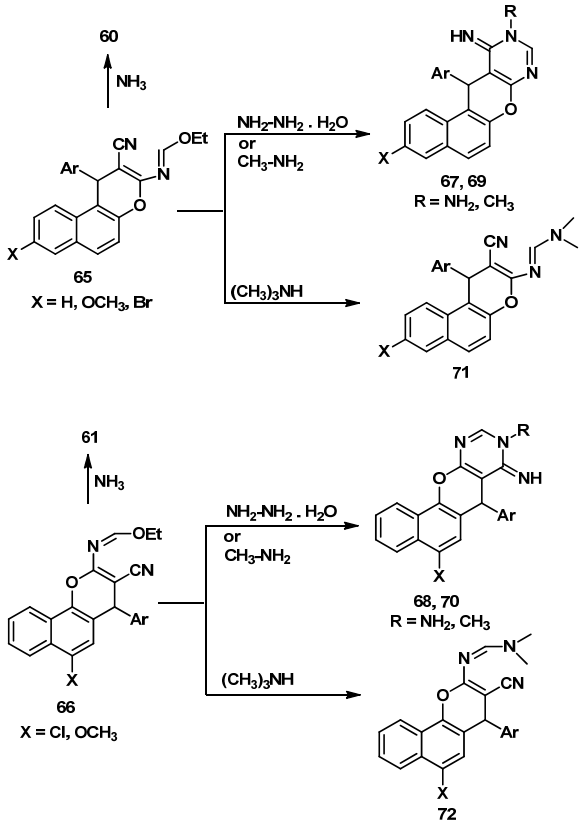
4.1.6. Triethyl orthoformate

Ethoxymethylene derivatives **65** and **66** was obtained by refluxing compounds naphthopyrano derivatives **3**, **5**, **22**, **42** and **44**, with triethyl orthoformate as electrophile in the presence of acetic anhydride (Scheme 69) [11-13,30-33,40-42].



Scheme 69

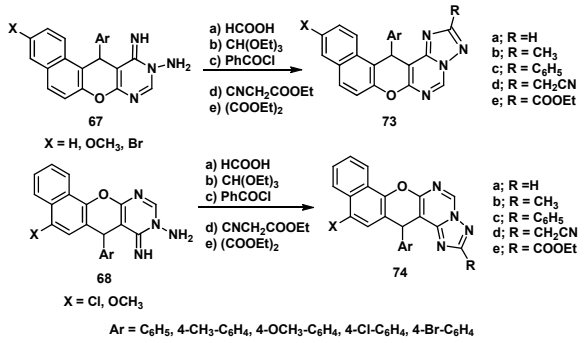
Treatment of **65** and **66** with hydrazine hydrate in ethanol, at room temperature furnished the novel naphthopyrano pyrimidine derivatives **67** and **69** in good yield. Also, compound **64** and **65** underwent aminolysis and cyclization with primary amine, while with dimethylamine the opene-chain product **68** and **70**. Ammonolysis of compound **64** and **65** in methanol at room temperature afforded amino-naphthopyranpyrimidine derivatives **60** and **61** (Scheme 70) [11-13,30-33,40-42].



Scheme 70

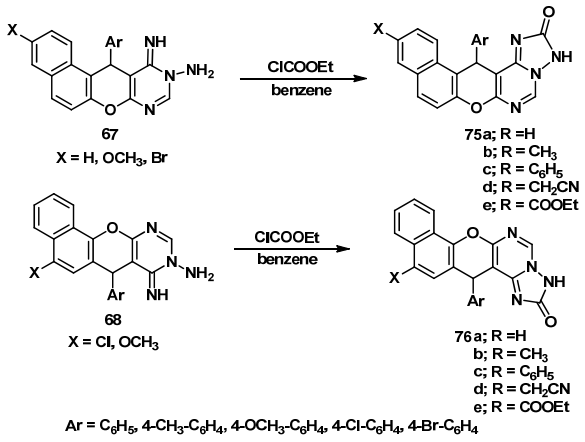
Reaction of naphthopyranpyrimidine derivatives **67** and **68** with formic acid or triethyl orthoformate, acetylchloride and benzoyl chloride, ethyl cyanoacetate and diethyl oxalate

afforded the corresponding triazolopyrimidine derivatives **73** and **74** (Scheme 71) [11-13,30-33,40-42].



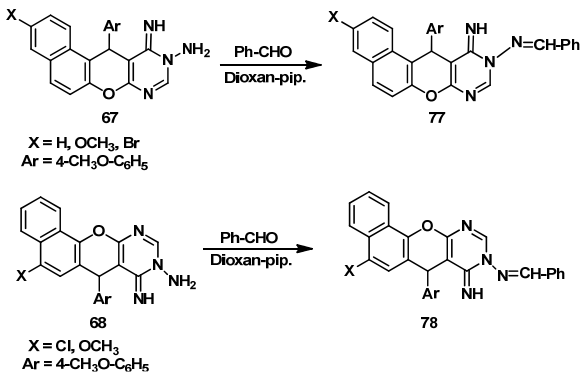
Scheme 71

Treatment of **67** and **68** with ethyl chloroformate in dry benzene afforded traizolo-2-one derivative **75** and **76** (Scheme 72) [11-13,30-33,40-42].



Scheme 72

Reaction of compound **67** and **68** with benzaldehyde gave 10-benzalamino-10,11-dihydro-11-imino-3-methoxy-12-(aryl)-12*H*-naphtho-[2,1-*b*]pyrano-[2,3-*d*]pyrimidine (**77** and **78**) instead of the expected triazolopyrimidine derivative **72** and **73** (Scheme 73) [11,13,30-33,40-42].



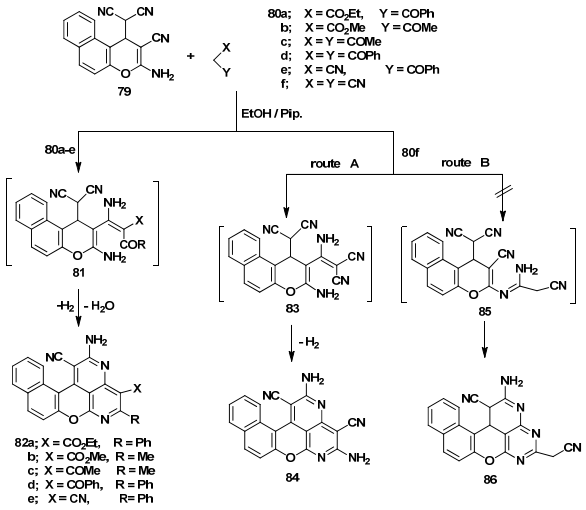
Scheme 73

4.1.7. Active methylene reagents

Compound 2-(3-amino-2-cyano-1*H*-benzo[*f*]chromen-1-yl)-malononitrile (**79**) was condensed with different active methylene reagents such as methyl 3-oxobutanoate (**80b**), 2,4-pentanedione (**80c**) and 1,3-diphenyl-1,3-propanedione (**80d**) to give the corresponding pentacyclic compounds **82b-d** (Scheme 74). According to the literature results [52,53-55] the heterocycles obtained in the reaction between aminonitriles and β-dicarbonyles is formed via the intermediate β-enaminodiones (**81**). These intermediates have never been isolated possibly due to their fast intramolecular cyclization to heterocyclic rings.

Therefore, the structure of compounds **82a-d** is rationalized in terms of the initial formation of the intermediate **81**, which on subsequent intramolecular cyclization followed by elimination of a water molecule and partial dehydrogenation under the reaction conditions affords the final product (Scheme 74) [51].

In a similar manner, compound **79** condensed with benzoylacetonitrile (**80e**) under the previous reaction conditions to yield a product formulated as **82e** (Scheme 74). Moreover, a mixture of equimolar amounts of compound **79** and malononitrile (**80f**) reacted in refluxing ethanol and in the presence of a catalytic amount of piperidine to yield a solid product naphthyridine **84** (route A) or pyridopyrimidine **86** (route B) (Scheme 74). Thus it appears that the dicyanomethyl anion attacks the cyano group of **79** yielding the intermediate **83** (route A) which by intra-molecular cyclization between amino and cyano groups with partial dehydrogenation under the reaction conditions gives compound **84** (Scheme 74) [51].



Scheme 74

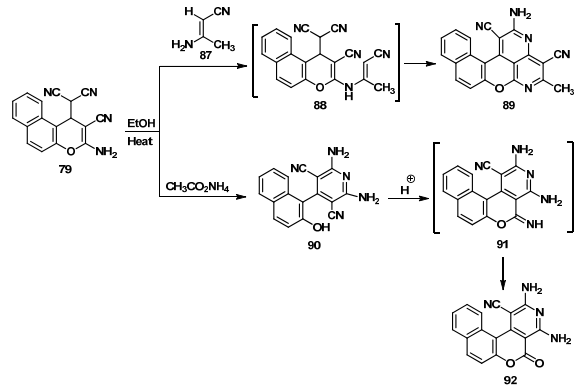
2-Amino-5-methyl-benzo[5,6]chromeno[4,3,2-*de*]1,6]napthyridine-1,4-dicarbonitrile (**89**) was obtained when **79** was heated under reflux with 3-amino-crotononitrile (**87**) in boiling ethanol. The formation of compound **89** can be described in terms of the initial formation of the intermediate **88** followed by its cyclization to the final product **89** (Scheme 75).

Trinitriles **79** reacted with ammonium acetate in molar ratio 1:2 to afford 2,6-diamino-4-(2-hydroxy-1-naphthyl)-3,5-pyridine-dicarbonitrile (**90**). Compound **90** was converted, in the presence of hydrochloric acid, into 2,4-diamino-5-oxo-5*H*-benzo[5,6]chromeno[3,4-c]pyridine-1-carbonitrile (**92**), presumeably the imino group in the postulated intermediate **91** is hydrolysed during formation of **92** (Scheme 75).

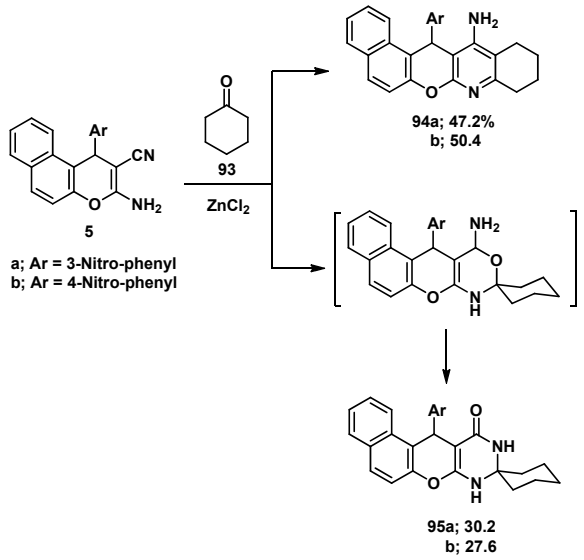
4.1.8. Cyclohexanone

The cyclocondensation of 2-amino-3-cyano-4*H*-4-aryl-naphthopyran derivatives **5** with cyclohexanone (**93**) in DMF in the presence of anhydrous zinc chloride under reflux gave two different skeletons compounds, one is quinolines **94**

(tacrineanalogues) from the famous Friendlander condensation, and another one is the spiro compound **95** from new annulation (Scheme 76). A plausible mechanism was proposed (Scheme 77) [56].



Scheme 75

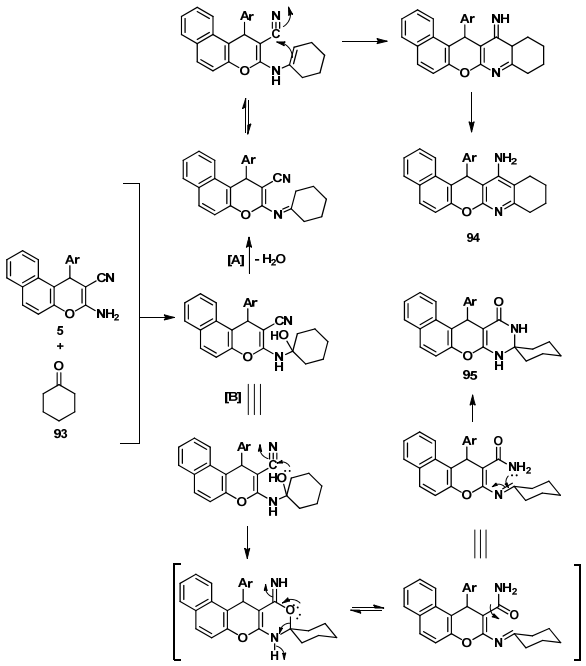


Scheme 76

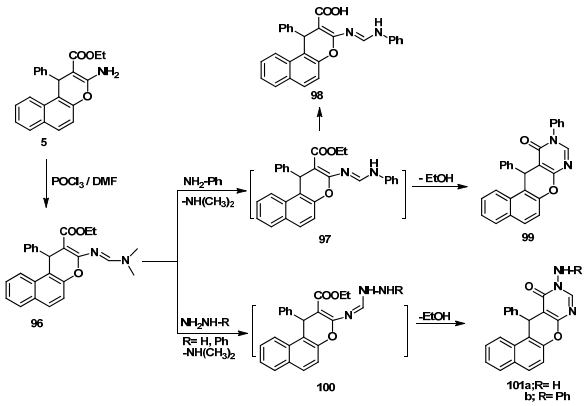
4.2. Reactions of naphthopyranoaminoester

4.2.1. Dimethyl formamide

Reaction of ethyl 2-amino-4-phenyl-4*H*-naphtho[2,1-*b*]pyran-2-carboxylate (**5**) with dimethyl formamide in presence of phosphorus oxychloride, afforded ethyl 2-(dimethylaminomethyleneamino)-4-phenyl-4*H*-naphtho[2,1-*b*]pyran -3-carboxylate (**96**) (Scheme 78). Thus, treatment of compound **96** with aromatic amine in refluxing ethanol afforded 2-(phenylaminomethyleneamino)-4-phenyl-4*H*-naphtho[2,1-*b*]pyran-3-carboxylic acid (**98**). So, it was assumed that the reaction proceeded via losing *N*-dimethylamine to give the intermediate **97** which underwent hydrolysis rather than cyclization via losing ethanol yielding what we expected as product **98**, (Scheme 78) [57]. While repeating this reaction in pyridine at reflux for five hours afforded the expected 10,12-diphenyl-12*H*- naphtho[2,1-*b*]pyrano[2,3-*d*]pyrimidine-11-one (**99**). Compound **96** formed via losing of *N*-dimethylamine to give the intermediate **97** which cyclized through releasing of ethanol. On the other hand, compound **96** reacted with substituted hydrazine to yield the corresponding naphtho[2,1-*b*]pyrano[2,3-*d*]pyrimidine derivatives **101a,b** via elimination of ethanol from the corresponding intermediate **100** which cyclized via release of ethanol [57].



Scheme 77



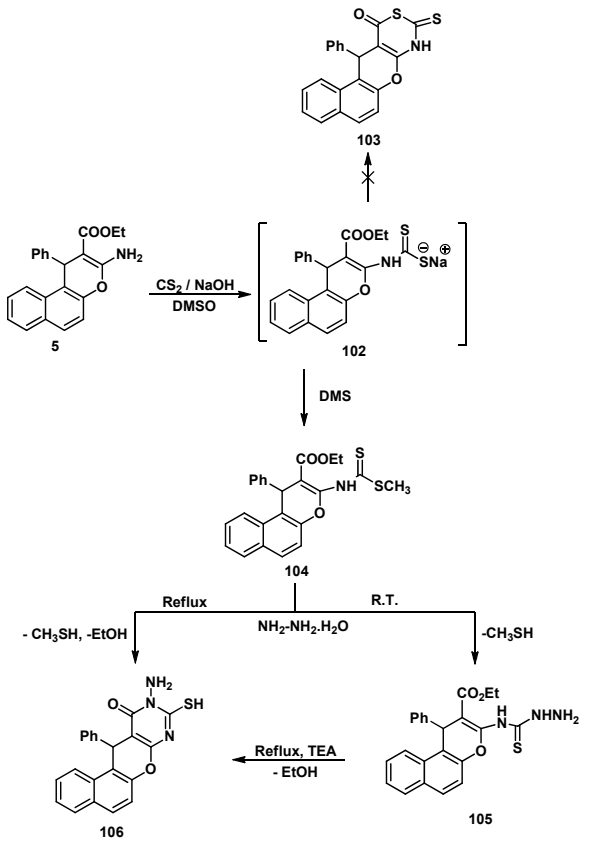
Scheme 78

4.2.2. With carbon disulfide

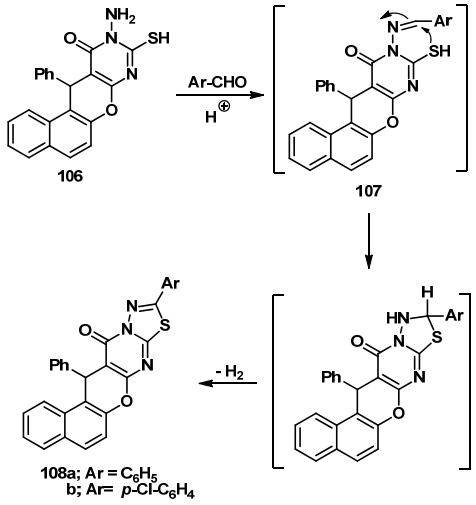
A solution of compound **5** in dimethyl sulfoxide was treated with carbon disulfide in presence of sodium hydroxide solution. The sodium salt of dithiocarbamic acid, **102**, was obtained in situ and then methylated with dimethyl sulfate to yield ethyl 2-(methylsulfanylthiocarbonylamino)-4-phenyl-4*H*-naphtho[2,1-*b*]pyran-3-carboxylate (**104**), but non-isolable compound **103**. The compound **104** when reacted with hydrazine hydrate in ethanol with stirring at room temperature yielded the open chain thiosemicarbazide derivative **105** via elimination of methylsulfane, while, under reflux in ethanol for 8 hours, it yielded the expected naphtho[2,1-*b*]pyrano[2,3-*d*]pyrimidine **106** via elimination of methylsulfane and ethanol. Boiling the thiosemicarbazide **105** in ethanol in presence of triethylamine yielded the same compound **106** (Scheme 79) [57].

Compound **106** was allowed to react with benzaldehyde and/or 4-chlorobenzaldehyde to give the corresponding expected Schiff's base **107**. However, the isolated compounds proved to be the new and unexpected compounds **108a**,**b**

formed via simultaneous nucleophilic attack of the sulfur atom on the hydrazone carbon with cyclization to the new thiadiazole derivatives **108a**,**b**, as shown in (Scheme 80) [57].

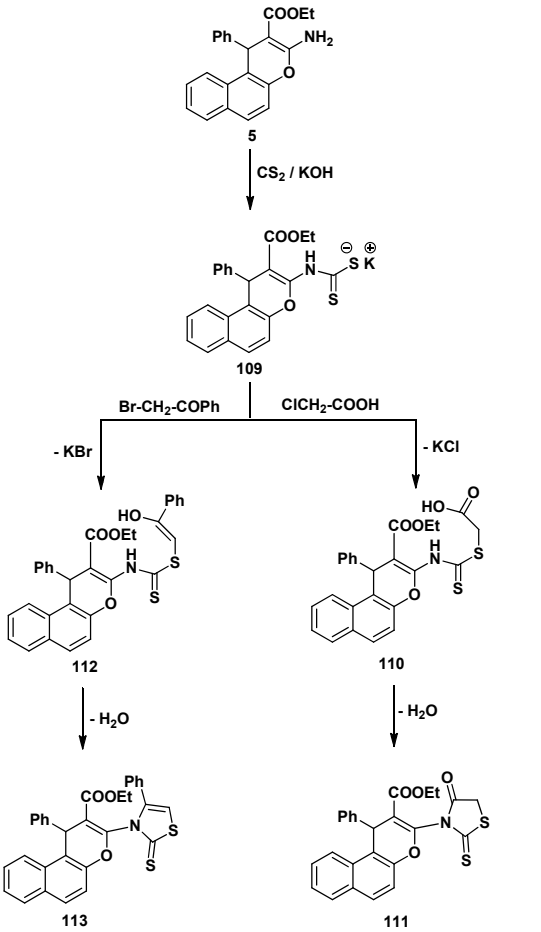


Scheme 79



Scheme 80

Furthermore compound **5**, when treated with carbon disulfide and potassium hydroxide solution, yielded the soluble potassium salt of dithiocarbamic acid, **109**, which was further treated in situ with chloroacetic acid and phenacylbromide, respectively, to afford ethyl 2-(4-oxo-2-thioxothiazolidin-3-yl) -4-phenyl-4*H*-naphtho[2,1-*b*]pyran-3-carboxylate (**111**) and 4-phenyl-2-(4-phenyl-2-thioxothiazol-3(2*H*)-yl)-4H-naphtha[2, 1-*b*]pyran -3-carboxylate (**113**) via release of water from the two corresponding intermediates **110** and **112**, respectively, (Scheme 81) [57].



Scheme 81

4.2.3. Acetic anhydride

Compound **5** was acylated with acetic anhydride yielding the acetyl derivative, **114**, which easily reacted with hydrazine hydrate to afford the new substituted 10-amino-9-methyl-12-phenyl-12*H*-naphtho[2,1-*b*]pyrano[2,3-*d*]-pyrimidi ne-11-one (**116**) via intermediate **115** which formed from **114** by displacement of ethanol rather than water as shown in (Scheme 82) [57].

5. Applications of naphthopyrans

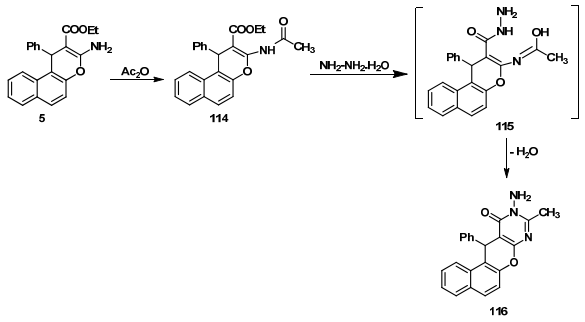
Naphtho[2,1-*b*]pyran derivatives **3**, **5** and **23** and naphtho[1,2-*b*]pyran derivatives **42** were found exhibited inhibition antibacterial activities (Scheme 83) [11-13,23-26,33].

4-Aryl-2-amino-5,6-dihydro-4*H*-naphtho[1,2-*b*]pyran-3-carbonitrile derivatives, **117**, have antiproliferative activities (Scheme 84) [58,59].

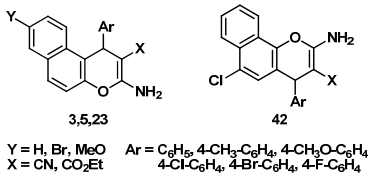
4-(Piperazin-1-yl)-4*H*-naphtho[2,1-b]pyran-2-one, 4-(piperazin-1-yl)-4*H*-naphtho[1,2-*b*]pyran-2-one, and 4-(piperazin-1-yl)-4*H*-naphtho[2,3-*b*]-pyran-2-one (118-120) have antiplatelet agents (Scheme 85) [60].

3,3-Dihydro-2,2-dimethyl-4*H*-naphtho[1,2-*b*]pyran-4-one (**121**) was hypotensive action (Scheme 86) [61].

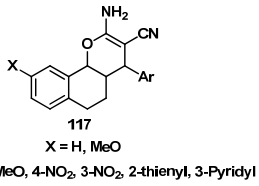
4-Methyl-7-hydroxy-4*H*-naphtho[1,2-*b*]pyran-2-one (**122**) as used fluorescence reagents (Scheme 87) [62].



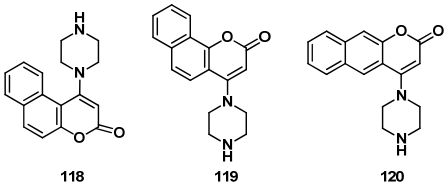
Scheme 82



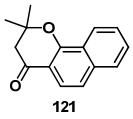
Scheme 83



Scheme 84

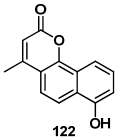


Scheme 85



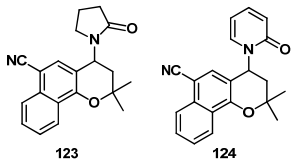
Scheme 86

3,4-Dihydro-2,2-dimethyl-4-(2-oxo-pyrrolidin-1-yl)-4*H*-naphtho[1,2-*b*]pyran-6-carbonitrile (**123**) and 3,4-dihydro-2,2-dimethyl-4-(2-oxo-pyridin-1-yl)-4*H*-naphtho[1,2-*b*]pyran-6-carbonitrile(124) were promised vasorelaxant activity (Scheme 88) [63].

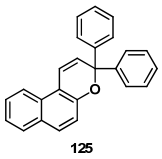


Scheme 87

The photochromic properties of naphthopyrans (**125**) have been extensively studied in the last decade due to the wide range of applications with prominence in the manufacture of ophthalmic plastic lenses and solar protection glasses (Scheme 89) [64-67].

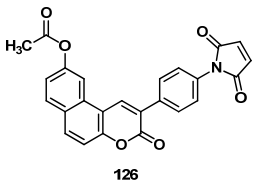


Scheme 88



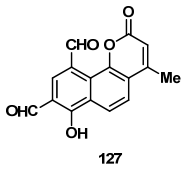
Scheme 89

6-Acetoxy-3-(4-(2,5-dihydro-2,5-dioxo-1*H*-pyrrol-1-yl) phenyl)-4*H*-naphtho[2,1-*b*]pyran-2-one (**126**) show have cytoxicity activities (Scheme 90) [68].



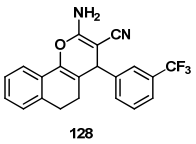
Scheme 90

7-Hydroxy-4-methyl-naphtho[1,2-*b*]pyran-2-one-8,10-di carbaldehyde (**127**) as potential antidyslipidemic and antioxidant agents (Scheme 91) [69].



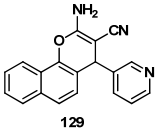
Scheme 91

2-Amino-4a,5,6,10b-tetrahydro-4-(3-(trifluoromethyl) phenyl)-4*H*-naphtho[1,2-*b*]pyran-3-carbonitrile (**128**) show have rheumatoid arthritis (Scheme 92) [70,71].



Scheme 92

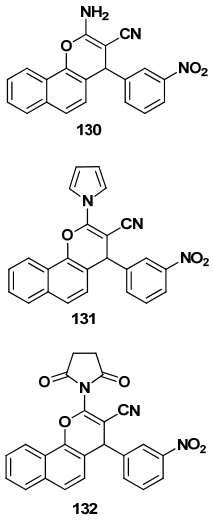
2-Amino-4-(pyridine-3-yl)-4*H*-naphtho[1,2-*b*]pyran-3-carbonitrile (**129**) show have restenosis (Scheme 93) [72-75].



Scheme 93

2-Amino-4-(3-nitrophenyl)-4*H*-naphtho[1,2-*b*]pyran-3-carbonitrile (**130**), 4-(3-nitrophenyl)-2-(1*H*-pyrrol-1-yl)-4*H*-naphtho[1,2-*b*]pyran-3-carbonitrile (131) and 4-(3-nitro

phenyl)-2-(2,5-dioxopyrrolidin-1-yl)-4*H*- naphtho[1,2-*b*]pyran-3-carbonitrile (**132**) show have diabetic complications (Scheme 94) [76,77].



Scheme 94

6. Conclusions

Naphthopyran derivatives have been reported in the literatures as a result of fusion of naphthalene moiety to the pyran ring and were synthesized either starting with naphthols and arylidene in presence catalyst. Also naphthopyran derivatives were prepared by multicomponent reactions (Aromatic aldehyde, naphthols, active methylene compounds) in presence catalyst. Naphthopyran derivatives described have been reported to furnish interesting biological properties.

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