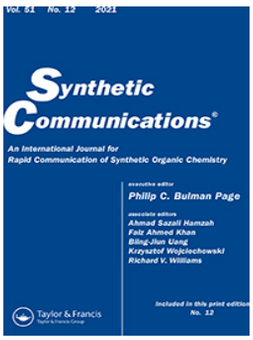

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Nucleophilic reactions with the novel condensation product derived from 3-formylchromone and 4-hydroxycoumarin

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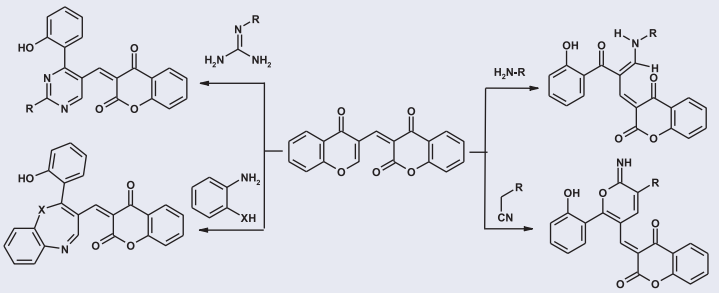
ABSTRACT

Condensation of 3-formylchromone and 4-hydroxycoumarin gave a novel 3-[(chromon-3-yl)methylidene]-2*H*-chromene-2,4(3*H*)-dione (**3**). The reactivity of the electrophilic centers within the synthesized substrate **3** was examined toward a variety of nucleophiles. Reaction of compound **3** with a diversity of primary amines yielded enaminones. Treatment of compound **3** with malononitrile and ethyl cyanoacetate produced pyran derivatives. Condensation of compound **3** with hydrazine hydrate afforded chromeno[4,3-*c*]pyrazole **13**. Boiling compound **3** with cyanoacetohydrazide in DMF gave pyrazole derivative **12**, while in boiling acetic acid gave pyrazolo[3,4-*b*]pyridine **15**. Ttreating compound **3** with phenylhydrazine and hydroxylamine hydrochloride furnished pyrazole **16** and isoxazole **17**, respectively. Reaction of compound **3** with guanidine and cyanoguanidine gave pyrimidine derivatives **18** and **19**. Reacting compound **3** with ethylenediamine in 1:1 and 1:2 molar ratio furnished diazepine **20** and chromeno[4,3-*e*][1,4]diazepine **21**. Finally, condensing compound **3** with *o*-phenylenediamine, *o*-aminophenol and *o*-aminothiophenol gave benzodiazepine **22**, benzoxazepine **23**, and benzothiazepine **24**, respectively

GRAPHICAL ABSTRACT



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KEYWORDS
3-Formylchromone; nucleophilic reactions; RORC; nitrogen heterocycles; spectral data

Introduction

The combination of a benzene ring with a pyrone ring construct two specific types benzopyrone rings. These rings are known as benzo-α-pyrones (coumarins) and benzo-

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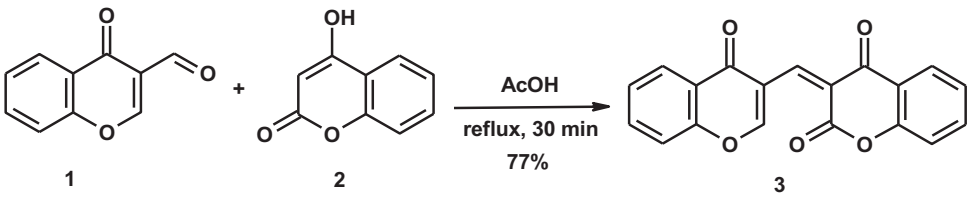
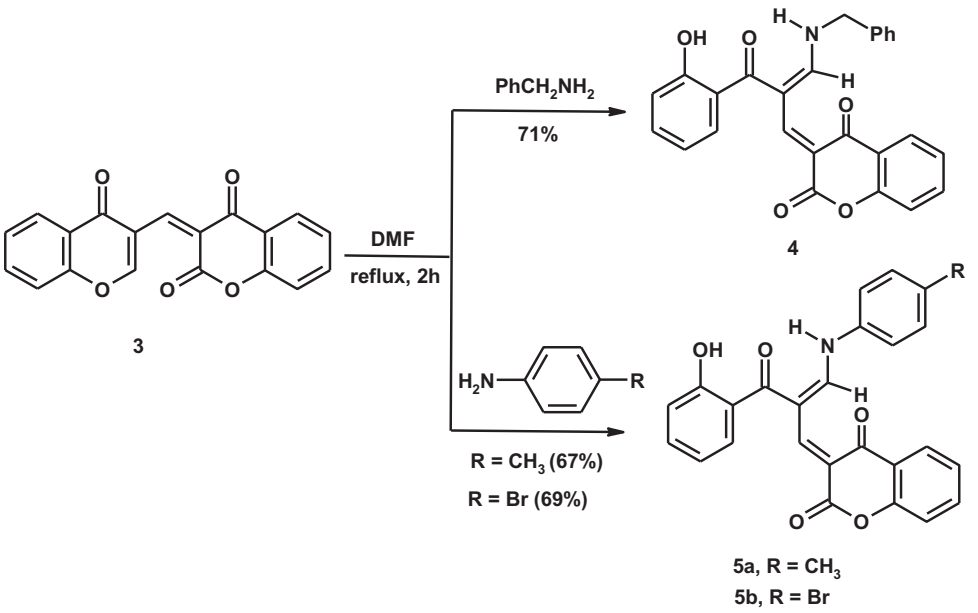


Scheme 1. Formation of the starting substrate **3.**

γ-pyrones (chromones).[1] Coumarins have been isolated from different families of plant kingdom like Clusiaceae, Umbelliferae and Rutaceae.[2] Various synthetic pathways have been utilized for building of coumarin derivatives including Knoevenagel condensation, Perkin condensation and Pechmann reaction.[3] Coumarin derivatives have potential applications in fluorescent chemosensors, fluorescent probes, laser dyes, and dye sensitized solar cells due to their unique electronic, optical and photophysical properties.[4–6] Density functional theory (DFT) computation was performed to understand the optimized structures, energy gaps and intramolecular charge transfer property for some coumarin derivatives.[7] Docking and molecular modeling studies were carried out to predict the binding modes between coumarins and enzymes to detect their inhibition actions.[8] Coumarins are known to possess a wide range bioactive properties such as antiviral,[9] antibacterial,[10] antimicrobial,[11] antioxidant,[12] anti-inflammatory,[13] anticancer,[14] antidiarrheal, antiulcerogenic,[15] antihaemolytic,[16] antidiabetic,[17] and inhibitors for Alzheimer's diseases.[18] Chromones are a large family of oxygen heterocyclic compounds exhibited numerous therapeutic and pharmacological applications including antimicrobial,[19] antioxidant,[20] anticancer,[21] anti-inflammatory,[22] neuroprotective,[23] anti-HIV,[24] antidiabetic,[25] antiproliferative,[26] and inhibitors for potential Alzheimer's disease.[27] 3-Formylchromone and its derivatives are widely used as chelating agents with different metal ions during complexes formation.[28–30] 3-Formylchromones are a highly reactive compounds which can serve as the starting material for the syntheses of a whole series of heterocycles due to the presence of three electrophilic centers which are C-2, C-4 and the aldehyde carbon at C-3.[31–36] The current work is designed to combine chromone and coumarin moieties in the same molecule, through condensation reaction of 3-formylchromone (**1**) and 4-hydroxycoumarin (**2**), and examine chemical behavior of the synthesized condensation product; 3-[(chromon-3-yl)methylidene]-2*H*-chromene-2,4(3*H*)-dione (**3**) toward some nucleophilic reagents.

Results and discussion

In the present work, condensation reaction of 3-formylchromone (**1**) and 4-hydroxycoumarin (**2**) in glacial acetic acid under reflux afforded the condensation product; 3-[(chromon-3-yl)methylidene]-2*H*-chromene-2,4(3*H*)-dione (**3**) in 77% yield (Scheme 1). The ^{1}H NMR spectrum of compound **3** displayed two characteristic singlets attributed to CH_{vinyl} and $H\text{-}2_{chromone}$ at δ 6.04 and 8.04 ppm, respectively. The mass spectrum recorded the parent ion peak at m/z 318 and support the identity of the structure.

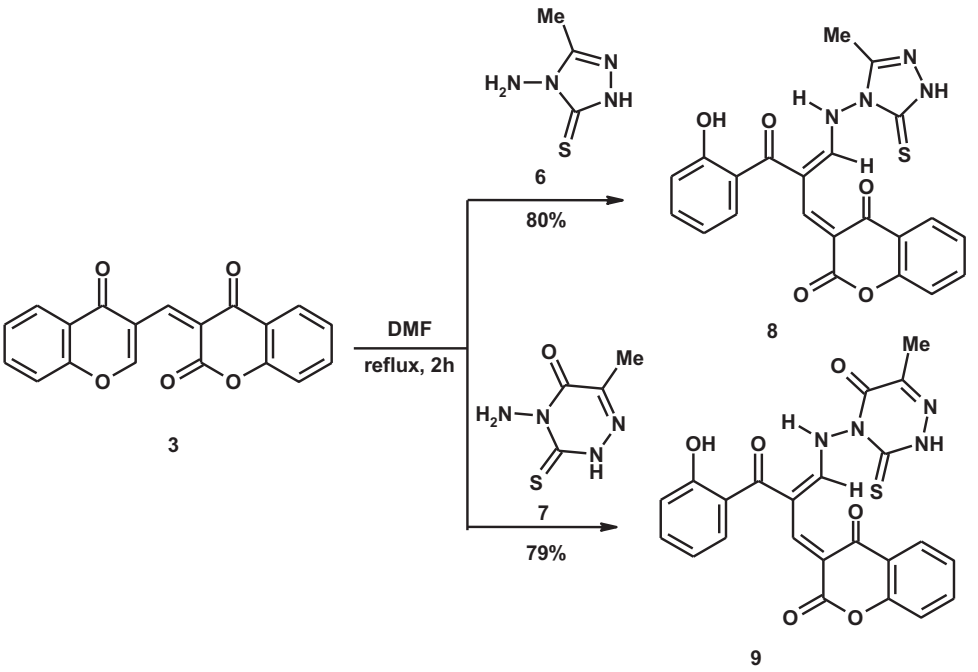


Scheme 2. Reaction of compound **3** with some primary amines.

Compound **3** possess variable electron deficient centers and may serve as active substrate toward nucleophilic reagents leading to some novel heterocyclic systems. The current study aimed to investigate the reactivity of the electron deficient centers in compound **3** toward a diversity of mono and bifunctional nucleophilic reagents.

Firstly, the chemical behavior of compound **3** was tested toward some primary amines. Thus, treatment of compound **3** with benzylamine, as aliphatic amine, in boiling DMF produced enaminone derivative **4** in 71% yield (Scheme 2).[37] This reaction occurs through nucleophilic attack at C-2 position of the chromone nucleus with concomitant γ-pyrone ring opening. Compound **4** gave dark red color with $FeCl_3$ solution, confirming the presence of free hydroxyl group. In addition, formation of enaminone **4** confirms that the C-2 position in chromone nucleus is the more electron deficient center in compound **3** and this may attribute to the electron withdrawing mesomeric effect of the three carbonyl groups that activate C-2 position toward nucleophilic reagents. The mass spectrum of compound **4** appeared the molecular ion peaks at m/z 425 which agrees well with the assigned molecular formula $C_{26}H_{19}NO_5$. The ^{1}H NMR spectrum of compound **4** showed two specific doublets with high coupling constant ($J = 13.8$ Hz) assignable to CH_{enone} and NH protons at δ 8.94 and 13.73 ppm. The doublet signal of the NH proton vanished by addition of D_2O with concomitant conversion of the doublet of CH_{enone} into singlet. The high coupling constant of the adjacent C*H*-N*H* protons confirms their *trans* configuration.

Similarly, reaction of substrate **3** with *p*-toluidine and 4-bromoaniline, as aromatic amines, in boiling DMF afforded enaminone derivatives **5a,b** (Scheme 2). The ^{1}H NMR spectra of compounds **5a,b** showed characteristic doublet singlets ($J = 13.8$ Hz) attributed to CH_{enone} and NH protons at δ 8.82/8.87 and 13.45/13.46 ppm, respectively. The doublet signals of the NH protons were disappeared in the presence of D_2O with



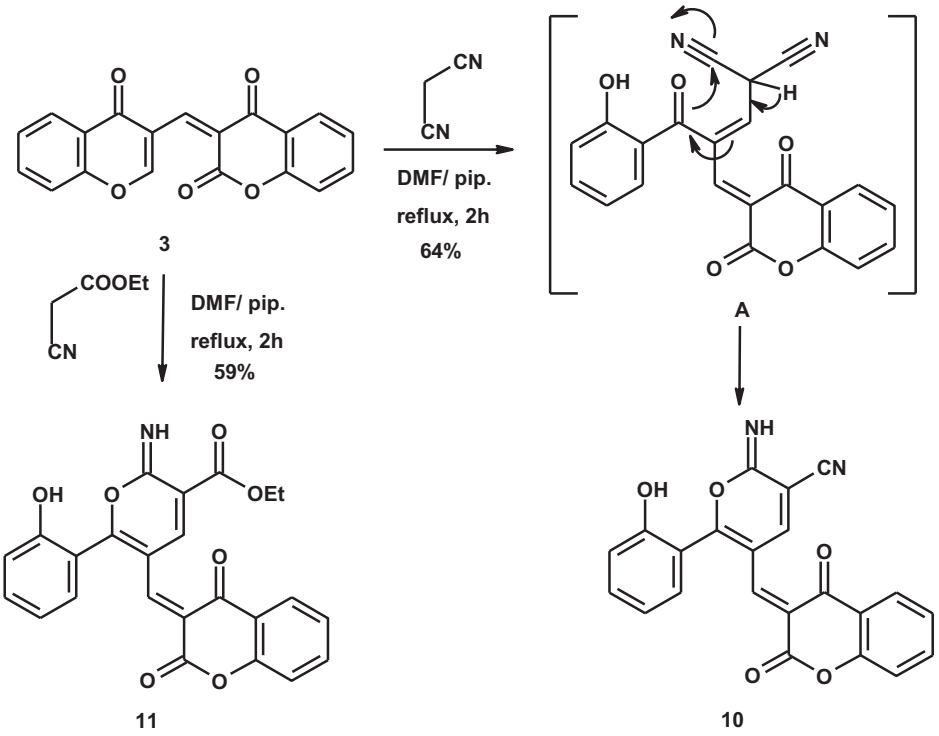
Scheme 3. Reaction of compound **3** with some heterocyclic amines.

concomitant conversion of the doublets of CH_{enone} into singlet. The exocyclic olefinic protons appeared as typical singlets at δ 8.89 and 8.97 ppm for compounds **5a** and **5 b**, respectively. The spectrum of compound **5a** showed distinctive singlet in the upfield region at δ 2.32 ppm attributed to the methyl protons.

Moreover, treatment of compound **3** with some heterocyclic amines namely 4-amino-5-methyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (**6**) and 4-amino-6-methyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one (**7**), in boiling DMF, afforded heterocyclic enaminones **8** and **9**, respectively (Scheme 3). Structures of compounds **8** and **9** were deduced from their mass spectra which appeared the molecular ion peaks at m/z 448 and 476 supporting the assigned structures.

On the other hand, the reactivity of active substrate **3** was examined toward some carbon nucleophiles. Reaction of compound **3** with malononitrile, in boiling DMF containing piperidine, afforded pyran-3-carbonitrile derivative **10**, through nucleophilic attack at C-2 position with ring opening giving intermediate **A** followed by cycloaddition into the nitrile function (Scheme 4). The ^{1}H NMR spectrum of compound **10** showed two specific singlet signals at δ 7.38 and 8.56 ppm attributed to H-4_{pyran} and $CH_{olefinic}$, respectively. The IR spectrum showed characteristic absorption band attributed to C≡N group at 2195 cm^{-1}. The mass spectrum of compound **10** recorded the parent ion peak at m/z 384 which agrees well with the suggested formula weight (384.34).

Under the previous conditions, pyran-3-carboxylate derivative **11** was efficiently synthesized from reaction of compound **3** with ethyl cyanoacetate (Scheme 4). The mass

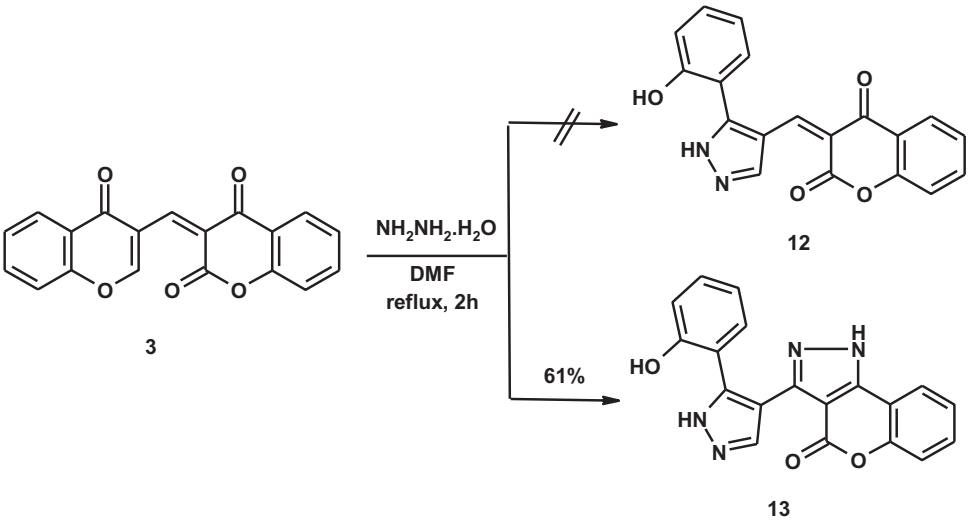


Scheme 4. Reaction of compound **3** with malononitrile and ethyl cyanoacetate.

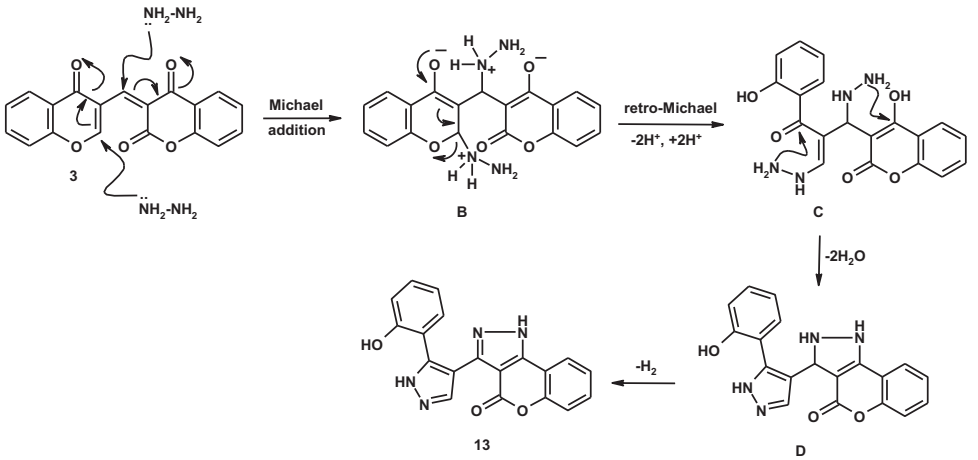
spectrum appeared the molecular ion peak at m/z 431 and confirms the proposed structure formula $C_{24}H_{17}NO_7$.

After that, the chemical reactivity of active substrate **3** was examined toward some binucleophilic reagents. Therefore, boiling compound **3** with hydrazine hydrate in DMF did not afford the expected pyrazole derivative **12**, but produced chromeno[4,3-*c*]pyrazole derivative **13** (Scheme 5). Due to the high nucleophilicity of hydrazine hydrate, the latter reaction occurs throughout reaction of hydrazine hydrate with compound **3** at 2:1 molar ratio. The suggested mechanism for formation of compound **13** is depicted in Scheme 6, where one molecule of hydrazine hydrate underwent *Michael* addition at C-2 position of chromone moiety and the other molecule underwent addition at the exocyclic double bond giving intermediate **B**. The latter intermediate underwent retro *Michael* addition with concomitant two protons transfer leading to intermediate **C** which underwent two pyrazoles ring closure generating intermediate **D** followed by dehydration producing the final product **13**. The mass spectrum of compound **13** showed the parent ion peak at m/z 344, while the base peak appeared at m/z 186 assignable to chromeno[4,3-*c*]pyrazole moiety and supports the assigned structure. In the ^{1}H NMR spectrum of compound **13**, the singlet signal of H-3_{pyrazole} appeared at δ 8.69 ppm.

Interestingly, treatment of compound **3** with cyanoacetohydrazide in boiling DMF gave pyrazole derivative **12**. The reaction proceeds through γ-pyrone ring opening giving intermediate **E** followed by pyrazole ring closure producing intermediate **F**, which



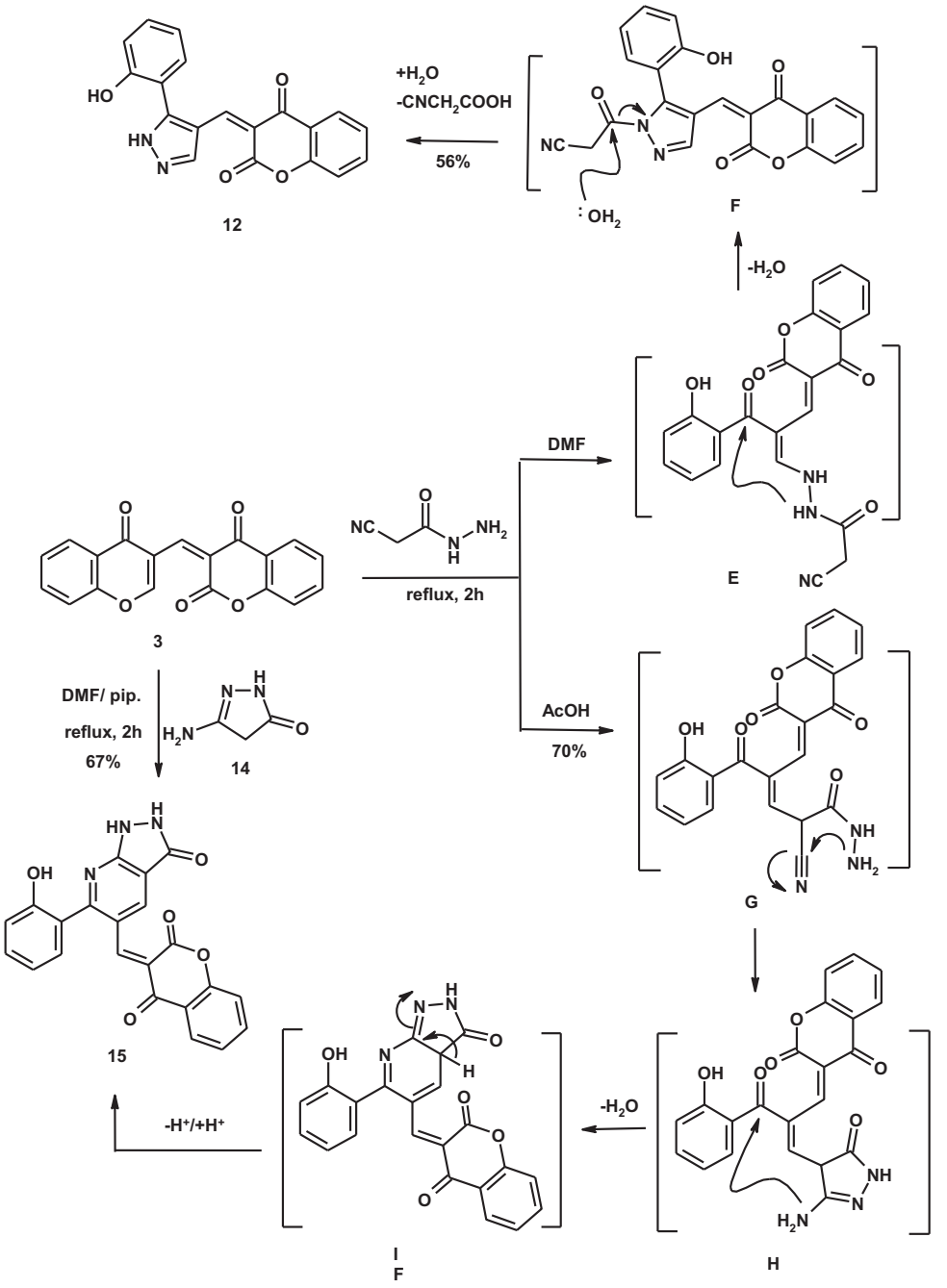
Scheme 5. Reaction of compound **3** with hydrazine hydrate.



Scheme 6. The suggested mechanism for formation of compound **13.**

underwent decyanoacetylation generating the final product **12** as illustrated in Scheme 7. The ^{1}H NMR spectrum of compound **12** showed two definite singlet signals attributed to H-3$_{pyrazole}$ and CH$_{olefinic}$ at δ 8.09 and 8.29 ppm, respectively. The structure **12** was further confirmed from its mass spectrum which recorded the molecular ion peak at m/z 332 which is coincident with the suggested molecular formula ($C_{19}H_{12}N_2O_4$).

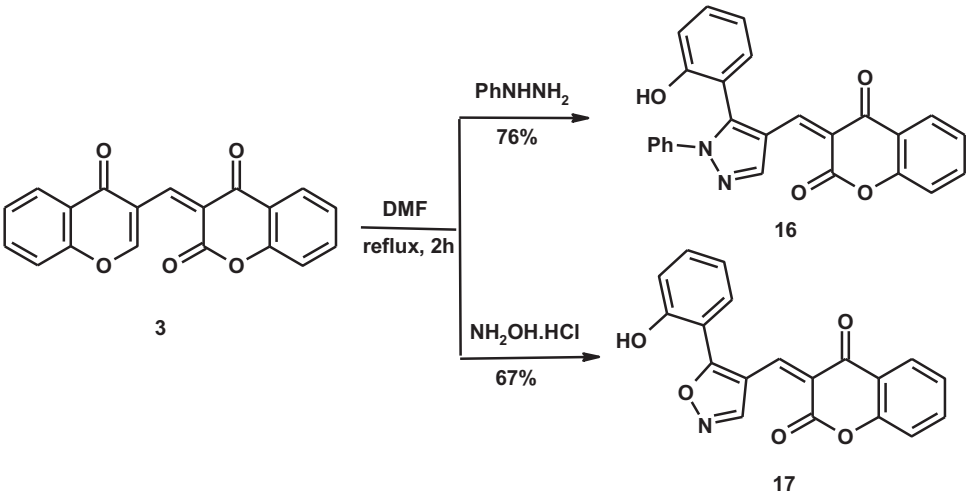
Further, when the reaction of compound **3** with cyanoacetohydrazide was performed in glacial acetic acid, pyrazolo[3,4-*b*]pyridine derivative **15** was formed.[38] In this reaction, cyanoacetohydrazide acted as carbon nucleophile and opened the γ-pyrone ring furnishing intermediate **G** followed by cycloaddition into the nitrile function giving intermediate **H** which underwent cyclodehydration (intermediate **I**) with proton transfer (Scheme 7). Compound **15** was also obtained authentically from reaction of compound **3** with 5-amino-2,4-dihydro-3*H*-pyrazol-3-one (**14**), in boiling DMF containing piperidine



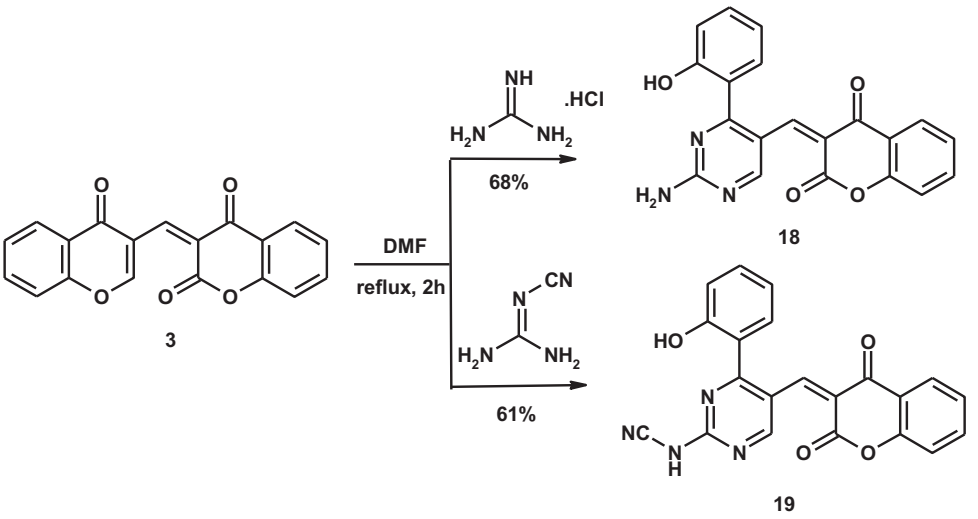
Scheme 7. Reaction of compound **3** with cyanoacetohydrazide under different reaction conditions.

(Scheme 7). Two characteristic singlet signals observed in ^{1}H NMR spectrum of compound **15** at δ 8.38 and 8.78 ppm; attributed to H-4$_{pyridine}$ and CH$_{olefinic}$, respectively.

Furthermore, reaction of compound **3** with phenylhydrazine and hydroxylamine hydrochloride, in boiling DMF, afforded pyrazole **16** and isoxazole **17**, respectively



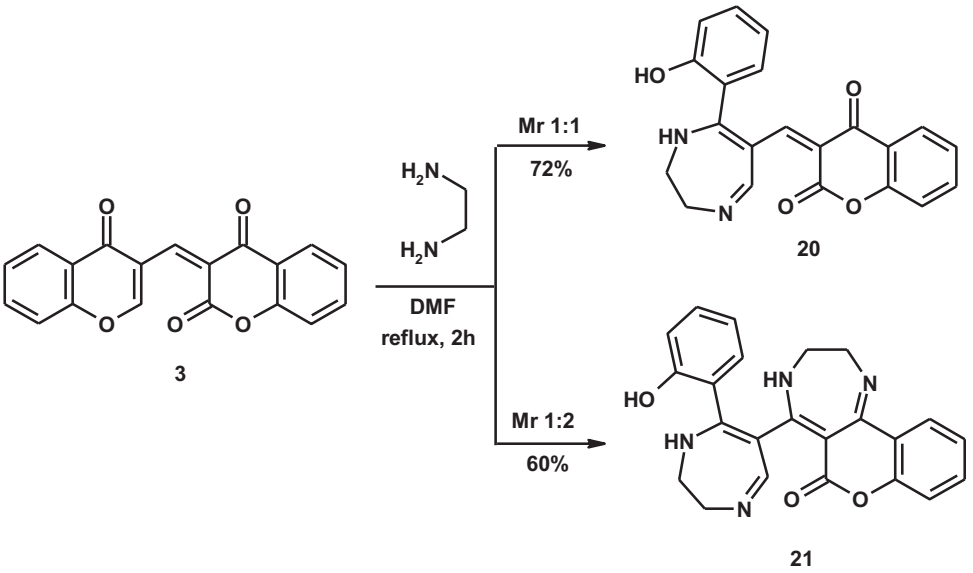
Scheme 8. Reaction of compound **3** with phenylhydrazine and hydroxylamine hydrochloride.



Scheme 9. Reaction of compound **3** with guanidine and cyanoguanidine.

(Scheme 8). The mass spectra of compounds **16** and **17** recorded their molecular ion peaks at m/z 408 and 333, respectively.

Reaction of compound **3** with guanidine hydrochloride and cyanoguanidine in boiling DMF produced pyrimidine derivatives **18** and **19**, respectively (Scheme 9).[39] The ^{1}H NMR spectra of compounds **18** and **19** showed two specific singlet signals attributed to H-4$_{\text{pyrimidine}}$ and CH$_{\text{olefinic}}$ at δ 8.40/7.86 and 8.75/8.19 ppm, respectively. The IR spectrum of compound **19** appeared characteristic absorption band attributed to C≡N function at 2191 cm^{-1}. The molecular ion peaks appeared in the mass spectra of compounds **18** and **19** at m/z 359 and 384; which are typical with the proposed formula weights.



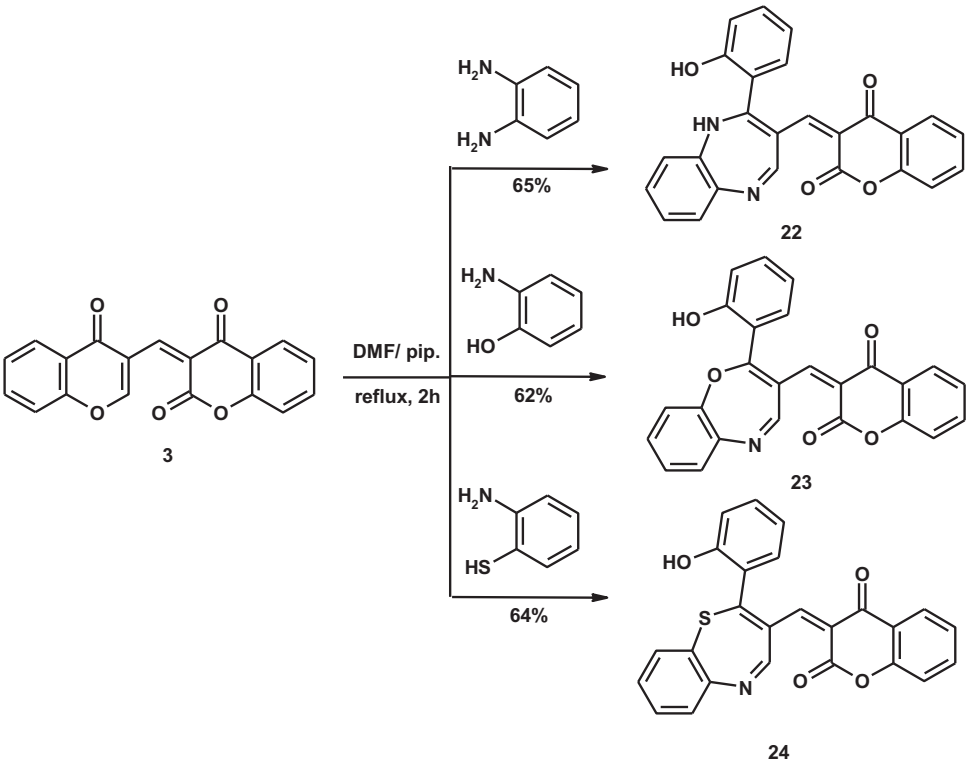
Scheme 10. Reaction of compound **3** with ethylenediamine at different molar ratio.

Next, the reactivity of compound **3** was studied toward some 1,4-bi nucleophilic reagents. Treatment of compound **3** with ethylenediamine in 1:1 and 1:2 afforded diazepine **20** and chromeno[4,3-*e*][1,4]diazepine **21**, respectively (Scheme 10). The molecular ion peaks of compound **20** and **21** appeared in their mass spectrum at m/z 360 and 400, respectively; and confirm the suggested structures.

Finally, reaction of compound **3** with *o*-phenylenediamine, *o*-aminophenol and *o*-aminothiophenol, in boiling DMF, afforded benzodiazepine **22**, benzoxazepine **23**, and benzothiazepine **24**, respectively (Scheme 11). The mass spectra of compounds **22**-**24** recorded their molecular ion peaks at m/z 408, 409 and 425, respectively. Their ^{1}H NMR spectra appeared the singlet signals attributed to $CH_{olefinic}$ at δ 9.24, 8.96 and 8.81 ppm. While, the singlet signals attributed to H-$4_{diazepine}$, H-$4_{oxazepine}$ and H-$4_{thiazepine}$ appeared at δ 8.06, 8.39 and 8.43 ppm, respectively.

Conclusions

The novel 3-[(chromon-3-yl)methylidene]-2*H*-chromene-2,4(3*H*)-dione (**3**) was efficiently synthesized from the direct condensation reaction of 3-formylchromone with 4-hydroxycoumarin. The starting substrate **3** has variable electron deficient centers and its chemical reactivity was investigated toward a variety of nucleophilic reagents hoping to deduce the reactivity of these electrophilic centers during nucleophilic reactions. C-2 position of the chromone moiety was found to be the most electron deficient center by the action of the electron withdrawing carbonyl groups and usually attacked by nucleophilic reagent leading to a diversity of products depending on the type of nucleophile used. Reaction of compound **3** with some primary amines afforded enaminones. While reaction of compound **3** with malononitrile and ethyl cyanoacetate produced pyran derivatives. The chemical reactivity of compound **3** was tested toward a diversity of



Scheme 11. Reaction of compound **3** with some 1,4-binucleophiles.

1,2-/1,3- and 1,4-bi nucleophilic reagents producing a variety of five, six and seven heterocyclic systems incorporating chromane-2,4-dione moiety.

Experimental

General information

Melting points were determined on a digital Stuart SMP3 apparatus. Infrared spectra were measured on FTIR Nicolet IS10 spectrophotometer (cm^{-1}), using KBr disks. ^{1}H NMR spectra were measured on Mercury-300/400BB (300 or 400 MHz), using DMSO-d_6 as a solvent and TMS (δ) as the internal standard. ^{13}C NMR spectra were measured on Mercury-300/400BB (75 or 100 MHz), using DMSO-d_6 as a solvent and TMS (δ) as the internal standard. Mass spectra were obtained using GC-2010 Shimadzu Gas chromatography instrument mass spectrometer (70 eV). Elemental microanalyses were performed on a Perkin–Elmer CHN-2400 analyzer. Chromone-3-carboxaldehyde (**1**) [40] was prepared according to literature.

3-[(Chromon-3-yl)methylidene]-2H-chromene-2,4(3H)-dione (3)

A mixture of 3-formylchromone **1** (1.74 g, 10 mmol) and 4-hydroxycoumarin (1.64 g, 10 mmol) in glacial acetic acid (20 mL) was heated under reflux for 30 min. The yellow

crystals obtained after cooling were filtered and crystallized from acetic acid to give compound **3**.

Synthesis of compounds 4, 5a,b, 8 and 9: General procedure for reaction of compound 3 with some amine primary derivatives

A mixture of compound **3** (0.63 g, 2 mmol) and benzylamine, *p*-toluidine, 4-bromoaniline, 4-amino-5-methyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (**6**) and 4-amino-6-methyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one (**7**) (2 mmol) in DMF (20 mL) was heated under reflux for 2 h. The crystals obtained after cooling were filtered and crystallized to give compounds **4**, **5a**,**b**, **8** and **9**, respectively.

Synthesis of compounds 10, 11 and 15: General procedure for reaction of compound 3 with active methylene compounds

A mixture of compound **3** (0.63 g, 2 mmol) and malononitrile, ethyl cyanoacetate and 5-amino-2,4-dihydro-3*H*-pyrazol-3-one (14) (2 mmol), in DMF (10 mL) containing piperidine (0.5 mL), was heated under reflux for 2 h. The crystals obtained were filtered and crystallized to give compounds **10**, **11** and **1**5, respectively.

Synthesis of compounds 12, 16 and 17

A mixture of compound **3** (0.63 g, 2 mmol) and cyanoacetohydrazide, phenylhydrazine and hydroxylamine hydrochloride (2 mmol) in DMF (10 mL) was heated under reflux for 2 h. The crystals obtained after cooling were filtered and crystallized to give compounds **12**, **16** and **17**, respectively.

Synthesis of compounds 18 and 19

A mixture of compound **3** (0.63 g, 2 mmol) and guanidine hydrochloride and cyanoguandine (2 mmol) in DMF (20 mL) containing TEA (0.1 mL) was heated under reflux for 2 h. The crystals obtained after cooling were filtered and crystallized to give compounds **18** and **19**, respectively.

Synthesis of compounds 13 and 21

A mixture of compound **3** (0.63 g, 2 mmol) and hydrazine hydrate and ethylenediamine (4 mmol) in DMF (10 mL) was heated under reflux for 2 h. The crystals obtained were filtered and crystallized to give compounds **13** and **21**, respectively.

Synthesis of compounds 20, 22, 23 and 24

A mixture of compound **3** (0.63 g, 2 mmol) and ethylenediamine, *o*-phenylenediamine, *o*-aminophenol, *o*-aminothiophenol (2 mmol) in DMF (20 mL) was heated under reflux

for 2 h. The crystals obtained were filtered and crystallized to give compounds **20, 22, 23** and **24**, respectively

Full characterization of the synthesized compounds and spectral data can be found via Supplementary Content section of this article's Web page.

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