Cairo University – Fayoum Branch
Faculty of Science
Chemistry Department

UTILITY OF COUMARINIC NITRILES IN HETEROCYCLIC SYNTHESIS

Thesis

Submitted in Partial Fulfillment of the Requirements of the Degree of Master of Science in Organic Chemistry

By

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The present thesis is submitted to the Faculty of Science, Fayoum-Branch, Cairo University in partial fulfillment for the requirements of Degree of Master of Science in Chemistry.

Besides the works carried out in this thesis, the candidate **Wael Abd El-Gayed Ahmed Arafa** has passed the following post graduate courses for one academic year:

1. Advanced Heterocyclic Chemistry.
2. Natural products.
3. Organometallic.
4. Spectroscopy.
5. Instrumental Analysis.
6. C-Nucleosides.
7. Chemotherapy.
8. Advanced Quantum Chemistry.
9. Inorganic Reactions Mechanism.
10. Organic Reactions Mechanism.
11. Advanced Physical Organic Chemistry.
12. Advanced Organic Synthesis.
13. Photochemistry.
14. Stereochemistry.
15. Polymer Chemistry.
16. Dyes.

He has successfully passed the final examination of these courses in October 1999.

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***Title*: Utility of Coumarinic Nitriles in Heterocyclic Synthesis**

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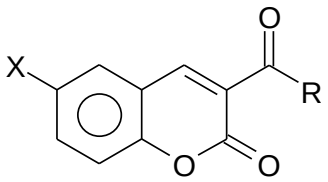
Summary

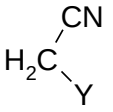
Part I

New Synthesis of Coumarin-3-yl Crotononitrile, Coumarin-3-yl Cinnamonitrile and Coumarinopyridine Derivatives

The reaction of 3-acetyl and/or 3-benzyl coumarin **1a-c** with activated nitrile reagents has been studied. In this reaction different conditions have been tried aiming to establish new routes for synthesis of new coumarinic nitriles and coumarinic heterocycles.



1a: R=CH_3, X=H
b: R=CH_3, X=Br
c: R=C_6H_5, X=Br



Y=CN
Y=$CH_3C(NH)$-

Thus, it has been found that **1a-c** reacts with malononitrile in dry benzene containing catalytic amounts of ammonium acetate and acetic acid to afford the Knoevenagel condensation products **2a-c** as main products and **3a, b** as minor products (scheme 1).
Structures of **2a-c** and **3a, b** have been confirmed from their elemental and spectral analyses.

When the reaction of **1a-c** with malononitrile was conducted in the presence of ammonium acetate, compounds **4a-c** were obtained. It seemed in this reaction that beside the condensation of the malononitrile with the ketonic group, ammonium acetate participate as a reactant through addition of NH_3 to the pyrone ring. Confirmation of **4a-c** is obtained from their elemental and spectral data. Further confirmation

for **4a-c** is obtained on their formation from heating equimolecular amounts of **2a-c** and ammonium acetate (Scheme 1).

The coumarinopyridine derivatives **5a-c** were obtained on heating **4a-c** in glacial acetic acid and identified from their elemental analyses and spectral data.

Similar to the reaction of **1a-c** with malononitrile, their reactions with 3-iminobutyronitrile **6** have been studied in different reaction conditions. Thus, when **1a-c** reacted with **6** in the presence of ammonium acetate, the pyridine derivatives **9a-c** were obtained. While conducting the same reaction in the presence of sodium ethoxide, it furnished the pyridine derivatives **10a, b** (Scheme 1). Formation of **9** and **10** was accompanied with traces from **3**. Structures of both **9** and **10** were established from inspecting the spectral data of the reaction products. Compounds **10a, b** could be converted into **9a, b** on heating utilizing Cope-Knoevenagle condition. The interconversion of **9** and **10** is considered as a further confirmation for both structures.

In contrast, to the behavior **1a, b** toward **6** in the presence of sodium ethoxide, the reaction of **1c** with **6** afforded compound **11** under the same reaction condition. Structure **11** was characterized from its elemental and spectral data. The difference in behavior between **1a, b** and **1c** toward **6** may be attributed to the electron affinity of the phenyl group in **1c** to enhance rapid addition of ethanol.

Part II

SOME REACTIONS OF COUMARIN-3-YL CROTONONITRILE DERIVATIVES

The reactivity of **2a, b** toward some electrophilic and nucleophilic reagents has been studied as shown in scheme 2.

Thus, compounds **2a, b** coupled with aryldiazonium salts to give colored products. The nature of the reaction products was found to depend on the applied reaction conditions. While conducting the reaction in ethanolic sodium acetate solution afforded the bis-coupling products as acyclic azohydrazones **13a-f**, the mono coupling products **16a-f** were obtained on conducting the reaction in acetic acid/sodium acetate. Compounds 13a**-f** and **16a-f** were identified from their elemental analyses and spectral data. The mass spectra of **13a** and **16a**, as an example revealed parent peaks at 444 and 340 respectively. Special confirmation is obtained from IR, which revealed two cyano functions as a prove of acyclic structures. Compounds **13a-f** could smoothly transformed to the arylazopyridazinone derivatives **15a-f** upon heating in aqueous acetic acid via intermediacy of **14a-f**. Similarly, the pyridazinones **18a-f** were obtained on heating **16a-f** in aqueous acetic acid and through the intermediates **17a-f** (scheme 2).

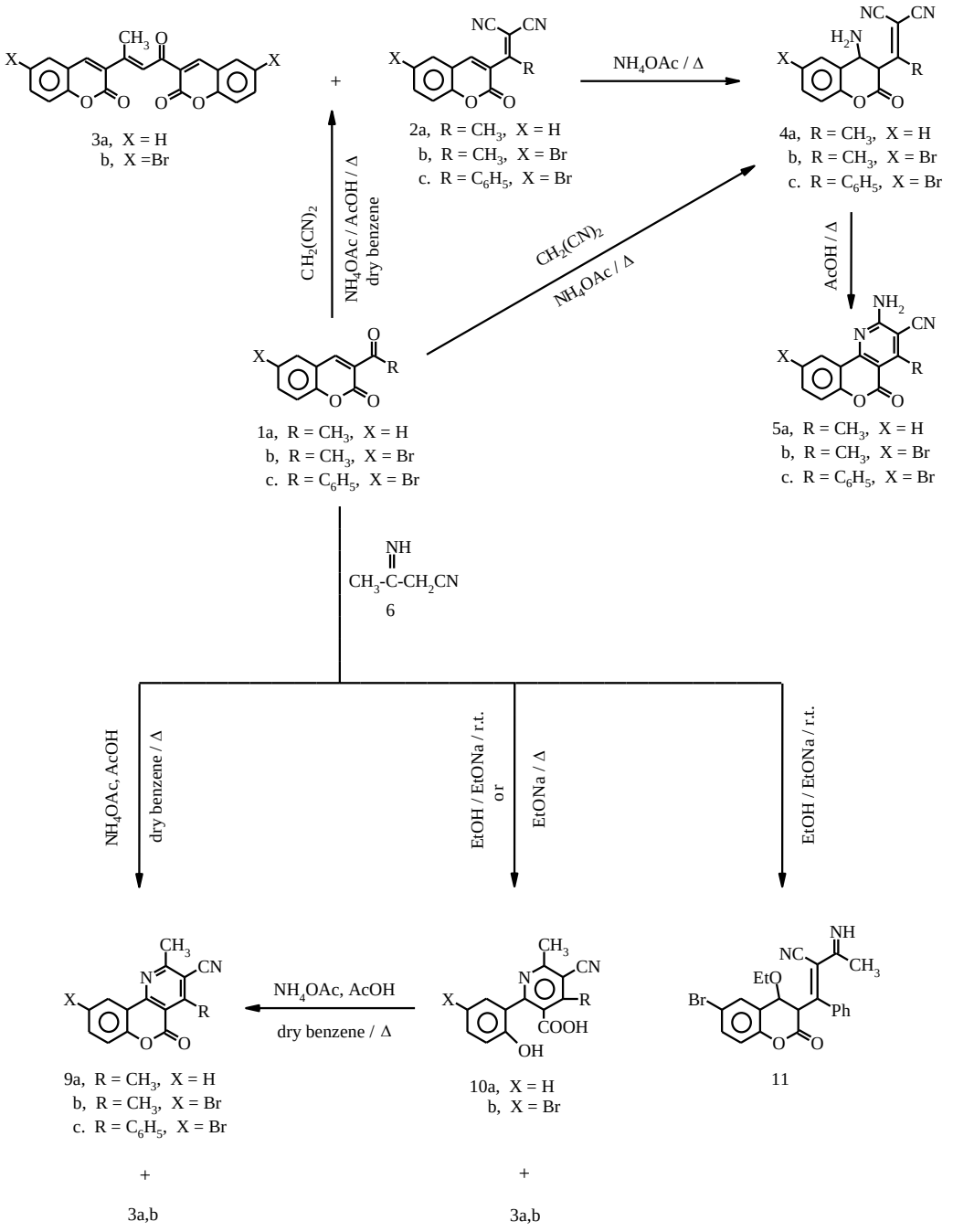
The coupling reaction of **2a** with diazotized anthranilic acid afforded directly the pyridazinoquinazoline derivatives **21** (scheme 2). Compound **21** is assumed to be formed via mono coupling reaction and through the fleeting intermediates hydrazone and iminopyridazine derivatives.

In a trial to condense the active methyl group in **2a, b** with aromatic aldehydes, in basic medium the reaction took a new route and the furan derivatives **25a,b** were obtained. The structure assignment of **25a,b** was based on their elemental analyses and spectral data. Compound **25** is assumed to be formed via tandem two nucleophilic

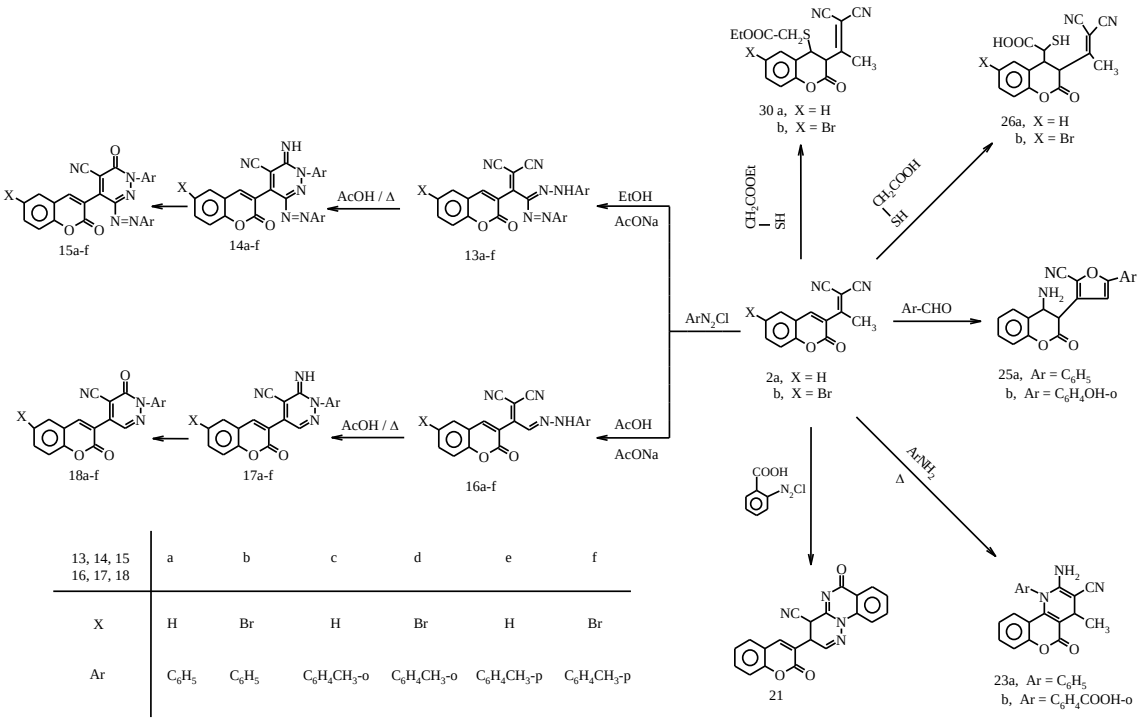
additions to give the tetrahydrofuran intermediate which readily aromatized via HCN and hydrogen elimination to afford the final isolable product, **25** (scheme 2).

In exploring the reactivity of **2a, b** toward nucleophilic reagents, it was found that the double bond C_3-C_4 of the pyran ring is the most active site.

Thus, treatment of **2a** with aromatic amines afforded the dihydropyridine derivatives **23a, b**. Similarly, compounds **2a, b** reacted with thioglycolic acid and ethyl thioglycolate to afford 4-mercapto-coumarine derivatives **26a, b** and **30a, b** respectively (Scheme 2). While, the reaction of **2** with ethyl thioglycolate takes place through SH group, its reaction with thioglycolic acid takes place through the active methylene of the addendum. Compounds **23**, **26** and **30** were identified from their elemental analysis and spectral data. Special confirmation for structures **26** and **30** is obtained from IR spectra which revealed a carbonyl function of saturated pyran.


3a, X = H
b, X =Br
+
2a, R = CH3, X = H
b, R = CH3, X = Br
c. R = C6H5, X = Br
NH4OAc / Δ
4a, R = CH3, X = H
b, R = CH3, X = Br
c. R = C6H5, X = Br
CH2(CN)2
NH4OAc / AcOH / Δ
dry benzene
CH2(CN)2
NH4OAc / Δ
AcOH / Δ
1a, R = CH3, X = H
b, R = CH3, X = Br
c. R = C6H5, X = Br
5a, R = CH3, X = H
b, R = CH3, X = Br
c. R = C6H5, X = Br
CH3-C-CH2CN
6
NH4OAc, AcOH
dry benzene / Δ
EtOH / EtONa / r.t.
or
EtONa / Δ
EtOH / EtONa / r.t.
NH4OAc, AcOH
dry benzene / Δ
9a, R = CH3, X = H
b, R = CH3, X = Br
c. R = C6H5, X = Br
+
3a,b
10a, X = H
b, X = Br
+
3a,b
11

Scheme 1



13, 14, 15 16, 17, 18	a	b	c	d	e	f
X	H	Br	H	Br	H	Br
Ar	C_6H_5	C_6H_5	$C_6H_4CH_3$-o	$C_6H_4CH_3$-o	$C_6H_4CH_3$-p	$C_6H_4CH_3$-p

Scheme 2