جامعة عين شمس

كلية العلوم

قسم الكيمياء

استخدام النيتريلات فى تحضير المركبات الحلقية غير المتجانسة

رسالة مقدمة من

آمنه شعبان على القبى

(مدرس مساعد)

كلية العلوم – جامعة مصراته – ليبيا

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Chemistry Department

Utility of nitriles in synthesis of heterocyclic compounds

A thesis submitted for the degree of Ph. D. of science in chemistry

By

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بخالص الحب والإحترام أهدي هذه الرسالة لأسرتي الحبيبة ، ثم أتوجه بجزيل الشكر والعرفان لأساتذتي المشرفين على هذه الرسالة وهم:

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ABSTRACT

In this study 3-amino-1-(2-chlorophenyl)-1*H*-benzo[*f*]chromene-2-carbonitrile has been utilized to design and synthesize a series of benzo[*f*]chromene-based heterocycles for biological evaluation as antimicrobial and anticancer agents.

Benzo[*f*]chromene-based heterocycles result from chemical transformation of enaminocarbonitrile, ethyl formimidate and cyanomethyl functionalities using various carbon electrophiles and nitrogen nucleophiles.

The newly synthesized compounds were evaluated for their *in vitro* antitumor effect against two human tumor cell lines namely; heptacelluar carcinoma (HePG2), and breast cancer (MCF-7) and the results revealed that compounds **3, 9, 25, 38** exhibited very strong cytotoxic activity for both cell lines.

Key words: enaminonitriles, 1*H*-benzo[*f*]chromenes, benzo[5,6]

chromeno[2,3-*d*]pyrimidines,benzo[5,6]chromeno[3,2-*e*] [1,2,4] triazolo [1,5-*c*]pyrimidines.

SUMMARY

In this study, 3-amino-1-(2-chlorophenyl)-1*H*-benzo[*f*] chromene-2-carbonitrile **1** has been utilized to design and synthesize a series of benzo[*f*]chromene-based heterocycles and investigate their antimicrobial and anticancer activities. The desired starting compound for this study was prepared *via* one pot-three component cyclocondensation reaction of malononitrile, 2-chlorobenzaldehyde, and *β*-naphthol in ethanol containing a catalytic amount of piperidine. Enaminonitrile derivative **1** was allowed to react with different carbon electrophiles. Thus, refluxing 3-amino-1-(2-chlorophenyl)-1*H*-benzo[*f*]chromene-2-carbonitrile **1** with formic acid yielded unexpected product which was identified as 10-(2-chlorophenyl)-8,10-dihydro-9*H*-benzo[5,6]chromeno[2,3-*b*]azet-9-one **2 (Scheme I**). The behavior of azetidinone derivative **2** towards different nitrogen nucleophiles was investigated. Hydrazinolysis of product **2** with hydrazine hydrate in ethanol yielded the corresponding benzo[*f*]chromene-2-carbohydrazide **3**. On the other hand, heating azetidinone derivative **2** with neat fomamide under reflux afforded, through ring expansion, compound **4** which was identified as 12-(2-chlorophenyl)-10,12-dihydro-11*H*-benzo[5,6] chromeno[2,3-*d*]pyrimidine-11-one.

However, the reactivity of azetidinone **2** towards bidentate nucleophiles was investigated. Thus, refluxing compound **2** and ethanolamine, ethylenediamine and/or *o*-phenylenediamine in dioxane yielded the benzo[5,6]chromeno[3,2-*f*][1,4]oxazepinone derivative **5** and benzo[5,6]chromeno[2,3-*e*][1,4]diazepinone derivatives **6** and **7**, respectively .

On the other hand, the behavior of enaminonitrile **1** towards acetic acid in the presence of fused sodium acetate was reinvestigated and the isolated product was identified to be 1-(2-chlorophenyl)-1,2-dihydro-3H-benzo[*f*]chromen-3-one **8 (Scheme II)**. Herein, the researcher reported an interesting heterocyclic ring transformation form benzo[*f*]chromenone to benzo[*f*]quinolone *via* reaction of **8** with different nitrogen nucleophiles. Thus, treatment of **8** with hydrazine hydrate afforded benzo[*f*]quinoline derivative **9**. However, when benzo[*f*]chromeneone **8** and ethylenediamine were heated under reflux in dioxane, 11-(2-chlorophenyl)-1,2,3,11-tetrahydrobenzo[*f*]imidazo[1,2-*a*]quinoline **10** was obtained. Furthermore, conducting enaminonitrile **1** with formamide afforded the desired aminopyrimidine derivative **11**. Supporting chemical evidence for the structure of compound **11** was forthcoming from treatment of **11** with freshly distilled acetic anhydride to isolate the corresponding diacetyl derivative **12** as a

sole product. Condensation of enaminonitrile **1** with *p*-nitrobenzaldehyde in glacial acetic acid furnished the corresponding Schiff base **13**.

Treatment of enaminonitrile **1** with freshly distilled acetic anhydride led to a mixture of diacetyl derivative **14** and benzo[5,6]chromeno[2,3-*d*]pyrimidine-11-one derivative **15** which were separated by fractional crystallization in yields 75%, and 20%, respectively (**Scheme III**). However, when the reaction was conducted in presence of pyridine, the yield of pyrimidinone derivative **15** increased to 84%. An attempt to chloroacetylate enaminonitrile **1** with chloroacetyl chloride in DMF containing KOH didn't led to chloroacetyl derivative. Instead an interesting heterocyclic transformation from benzo[*f*]chromene **1** to benzo[*f*]coumarin **17** occurred. On the other hand, 12-(2-chlorophenyl)-11-imino-10-phenyl-8,10,11,12-tetrahydro-9*H*-benzo [5,6]chromeno[2,3-*d*]pyrimidine-9-thione **18** was obtained from treatment of enaminonitrile **1** with phenyl isothiocyanate in neat conditions. Refluxing enaminonitrile **1** with triethyl orthoformate in acetic anhydride yielded ethyl formimidate derivative **19**.

Ethyl formimidate **19** was the key compound for the preparation of fused pyrimidine derivatives *via* reaction with various nitrogen nucleophiles. Thus, conducting ethyl formimidate

19 with either *p*-toluidine or 3-aminopyridine in boiling dioxane afforded formamidine derivatives **20** and **21**, respectively. On the other hand, aminolysis with aliphatic primary amine namely, cyclohexyl amine in refluxing pyridine gave iminopyrimidine derivative **22** (**Scheme IV**). Refluxing ethyl formimidate **19** with ethylenediamine in dioxane for six hours yielded imidazole derivative **23**. Interestingly, hydrazinolysis of **19** with hydrazine hydrate in ethanol at room temperature or reflux yielded enaminonitrile **1** instead of any of expected derivatives. When ethyl formimidate **19** was allowed to react with hydroxylamine hydrochloride in refluxing pyridine, 12-(2-chlorophenyl)-11-imino-11*H*-benzo[5,6]chromeno[2,3-*d*]

pyrimidin -10(12*H*)-ol **24** was obtained .

On the other hand, boiling ethyl formimidate **19** with thiosemicarbazide in dioxane afforded a white solid after thirty minutes and it was identified as thiosemicarbazide derivative **25**. However, on continuing heating, the formed solid dissolved and the reaction mixture was heated for further six hours until completeness and the final product was identified as iminopyrimidine derivative **26** which was formed from 1,6-exo-dig cyclization on the previously formed product **25**. Moreover, when ethyl formimidate **19** was allowed to react with semicarbazide

hydrochloride in boiling pyridine, iminopyrimidine derivative **27** was formed (**Scheme V**). Benzo[5,6]chromeno[2,3-*d*]pyrimidine derivative **28** was obtained from treatment of ethyl formimidate **19** with *p*-toluene sulphonohydrazide in refluxing pyridine. Treatment of ethyl formimidate **19** with ethyl carbazate in refluxing dioxane afforded ethyl 2-{[(1-(2-chlorophenyl)-2-cyano-1*H*-benzo[*f*]chromen-3-yl)-imino]methyl}hydrazine-1-carboxylate **29** as a sole product. However, when the reaction was conducted in pyridine, chromenotriazolo[1,5-*c*]pyrimidine derivative **30** was yielded as a sole product which is believed to form from two successive, 1,6-exo-dig followed by 1,5-exo-trig, cyclization on product **29**.

Compounds containing cyanomethyl functionality are important and widely used compounds in the construction of various heterocyclic compounds. Thus, chromenotriazolopyrimidine derivative **31** was isolated *via* interaction of ethyl formimidate **19** with 2-cyanoacetic acid hydrazide in refluxing dioxane (**Scheme VI**). The presence of cyanomethyl functionality in **31** was utilized to insert and construct new heterocyclic systems *via* reaction with electrophilic reagents, including aromatic aldehydes, phenyl isothiocyanate and carbon disulphide, in addition to mercaptoacetic acid as sulfur nucleophile. Thus, cyanomethyl

derivative **31** was subjected to react with *p*-nitrobenzaldehyde and/or salicylaldehyde in dixoane containing a catalytic amount of piperidine to obtain arylidene **32** and iminochromene derivatives**33**were obtained, respectively. However, when compound **31** was allowed to react with phenyl isothiocyanate and elemental sulfur in presence of a catalytic amount of triethylamine, thiazole-2-thione derivative **34** was obtained. Moreover, stirring cyanomethyl derivative**31**with carbon disulphide in ethanolic potassium hydroxide and N,N-dimethylformamide afforded the dipotassium disulphide salt **35** which reacted *in situ* with ethyl chloroacetate to give ethyl acetate derivative **37**. Moreover, under the same conditions treatment of dipotassium disulphide salt **35** with dimethyl sulfate yielded 2-{14-(2-chlorophenyl)-14*H*-benzo[5,6]chromeno[3,2-*e*][1,2,4]triazolo [1,5-*c*]pyrimidin-2-yl}-3,3-bis(methylthio)acrylonitrile **38**.

Refluxing compound **31** with thioglycolic acid in pyridine afforded thiazolidin-4-one derivative **39**. The structures of all the synthesized compounds were substantiated on the basis of correct analytical and spectroscopic data.

Some synthesized compounds were investigated for antimicrobial activity and the results showed that in general the tested compounds didn’t give promising results, however,