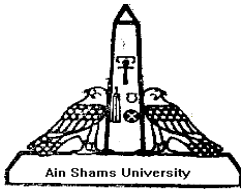

Faculty of Education
Chemistry Department

A THESIS
ENTITLED

Synthesis of Some New Heterocyclic Compounds of Expected Biological Activity

Submitted by

Osama Farouk Mohamed Ibrahim
B.Sc & Ed.

For the degree of

Master of Teacher's Preparation in Science
(Organic Chemistry)

Department of Chemistry
Faculty of Education
Ain Shams University
Cairo

2011

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Synthesis of Some New Heterocyclic Compounds of Expected Biological Activity

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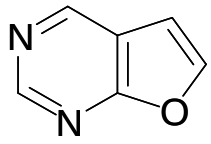
CONTENTS

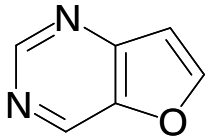
CHEMISTRY OF FUROPYRIMIDINES

INTRODUCTION:

There are three fundamental furopyrimidine systems. They are furo[2,3-*d*] pyrimidine (I), furo[3,2-*d*]pyrimidine (II) and furo[3,4-*d*]pyrimidine (III) according to the following presentation.



(I)



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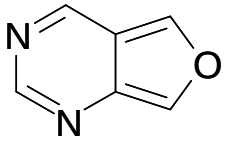


(III)

Furopyrimidines have been known for many years and have been thoroughly examined in the latter years.

SYNTHESIS OF FUROPYRIMIDINES

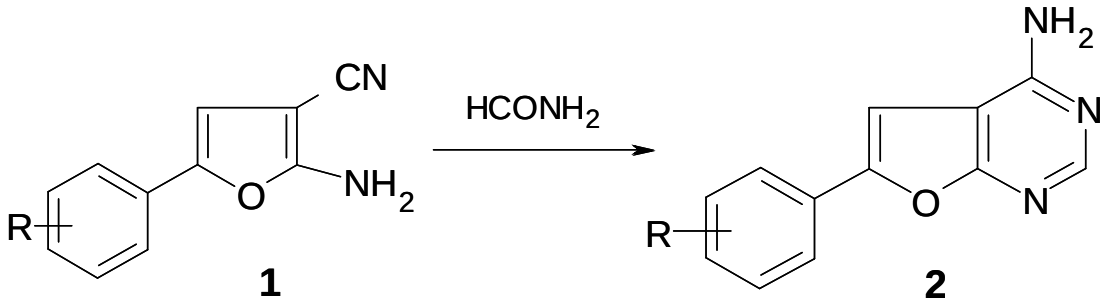
The building of furopyrimidine moiety has been achieved either by construction of pyrimidine nucleus on the parent furan ring or construction of furan nucleus on the parent pyrimidine ring.

1- From Furan derivatives

The simple approach to a new pyrimidine ring involves introducing a one-carbon fragment between two suitable and vicinal functional groups in furan rings.

1.1- With formamide

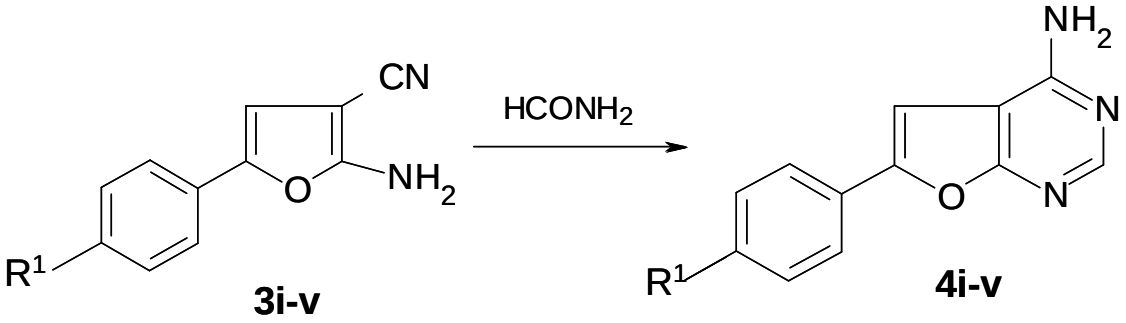
Formamide reacted with vicinal aminocyano, vicinal acylamino and vicinal aminoester furans to yield the target furopyrimidines. Therefore, treatment of 2-amino-5-arylfuran-3-carbonitrile derivatives (**1**) with formamide yielded 4-amino-6-arylfuro[2,3-*d*]pyrimidine derivatives (**2**)[1].



1 **2**

R = 3,4-Cl_2, 3-$CONH_2$, 3-$CONMe_2$,3-$NHSO_2Me$, 4-OMe

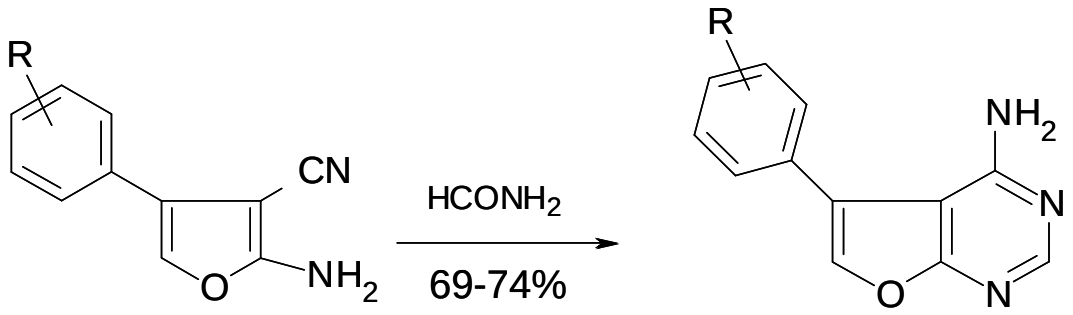
In similar manner, cyclization of 2-amino-5-substitutedfuran-3-carbonitrile derivatives (**3i-v**) with formamide gave 4-amino-6-substitutedfuro[2,3-*d*] pyrimidines (**4i-v**)[2].



3i-v **4i-v**

(i) $R^1 = OCH_3$; (ii) $R^1 = H$; (iii) $R^1 = Cl$
(iv) $R^1 = CH_3$; (v) $R^1 = F$

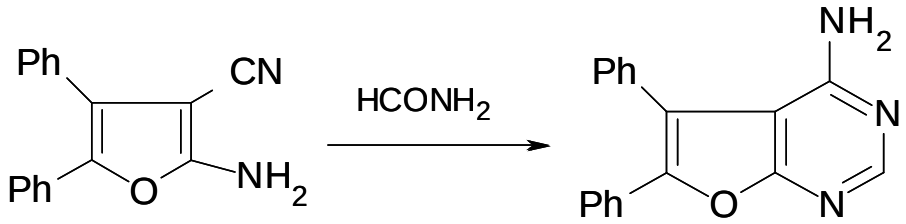
Also, cycloaddition of 2-amino-4-arylfuran-3-carbonitrile derivatives (**5)** with formamide led to the corresponding 4-amino-5-arylfuro[2,3-*d*] pyrimidine derivatives (**6**)[1].



5 **6**

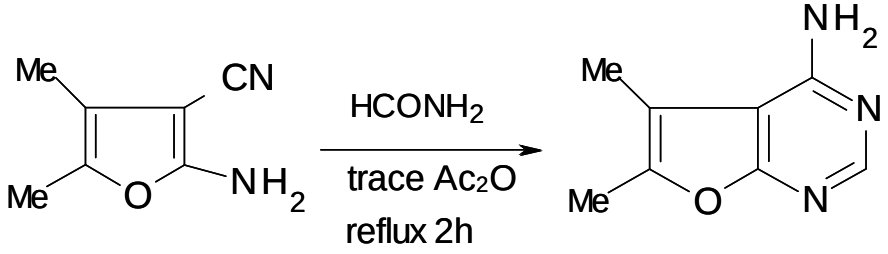
R = 4-OMe, 4-NMe_2, 4-phenyl and 3-NHAc

Also, reaction of 2-amino-4,5-diphenylfuran-3-carbonitrile (**7**)[3] with formamide gave 4-amino-5,6-diphenylfuro[2,3-*d*]pyrimidine (**8**)[4].



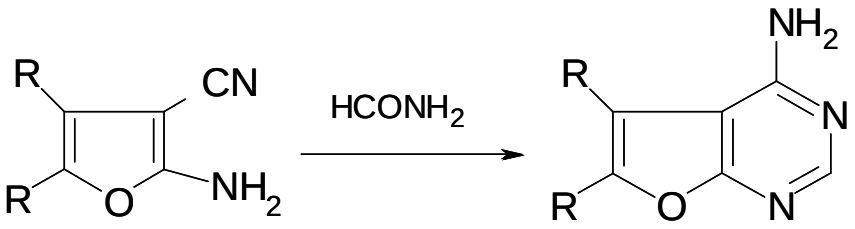
7 **8**

By analogy, the synthesis of other fused pyrimidines can be achieved by refluxing of 2-amino-4,5-dimethylfuran-3-carbonitrile (**9**) with formamide in the presence of acetic anhydride afforded 4-amino-5,6-dimethylfuro[2,3-*d*] pyrimidine (**10**)[5-7].



9 **10**

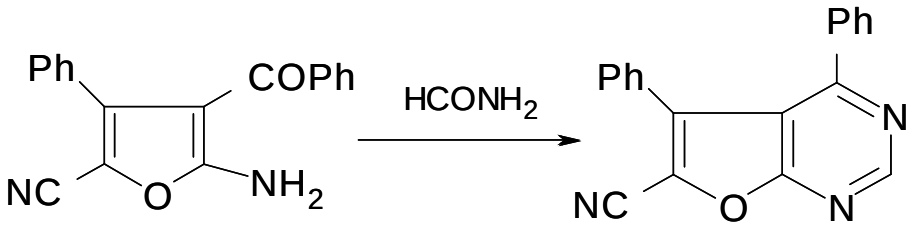
Treatment of 2-amino-4,5-disubstitutedfuran-3-carbonitrile (**11a,b**) with formamide yielded 4-amino-5,6-disubstitutedfuro[2,3-*d*]pyrimidines (**12a,b**)[8].



11a,b **12a,b**

a, R = 2-furyl
b, R = 2-thienyl

On the other hand, furopyrimidines can be obtained by reaction of vicinal acylamino and vicinal aminoester furans with formamide. Thus, treatment of 5-amino-4-benzoyl-3-phenylfuran-2-carbonitrile (**13**) and furan derivatives **15a,b** with formamide afforded 4,5-diphenylfuro[2,3-*d*]pyrimidine-6-carbonitrile (**14**)[9] and the corresponding furo[2,3-*d*]pyrimidine derivatives **16a,b**[10].



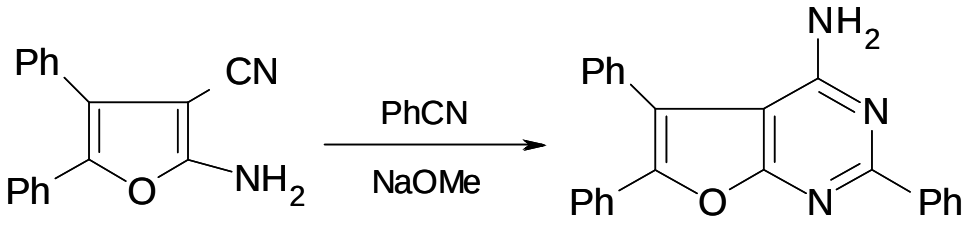
13 **14**

15a, 4-NO_2
b, 3-NO_2

16a, 4-NO_2
b, 3-NO_2

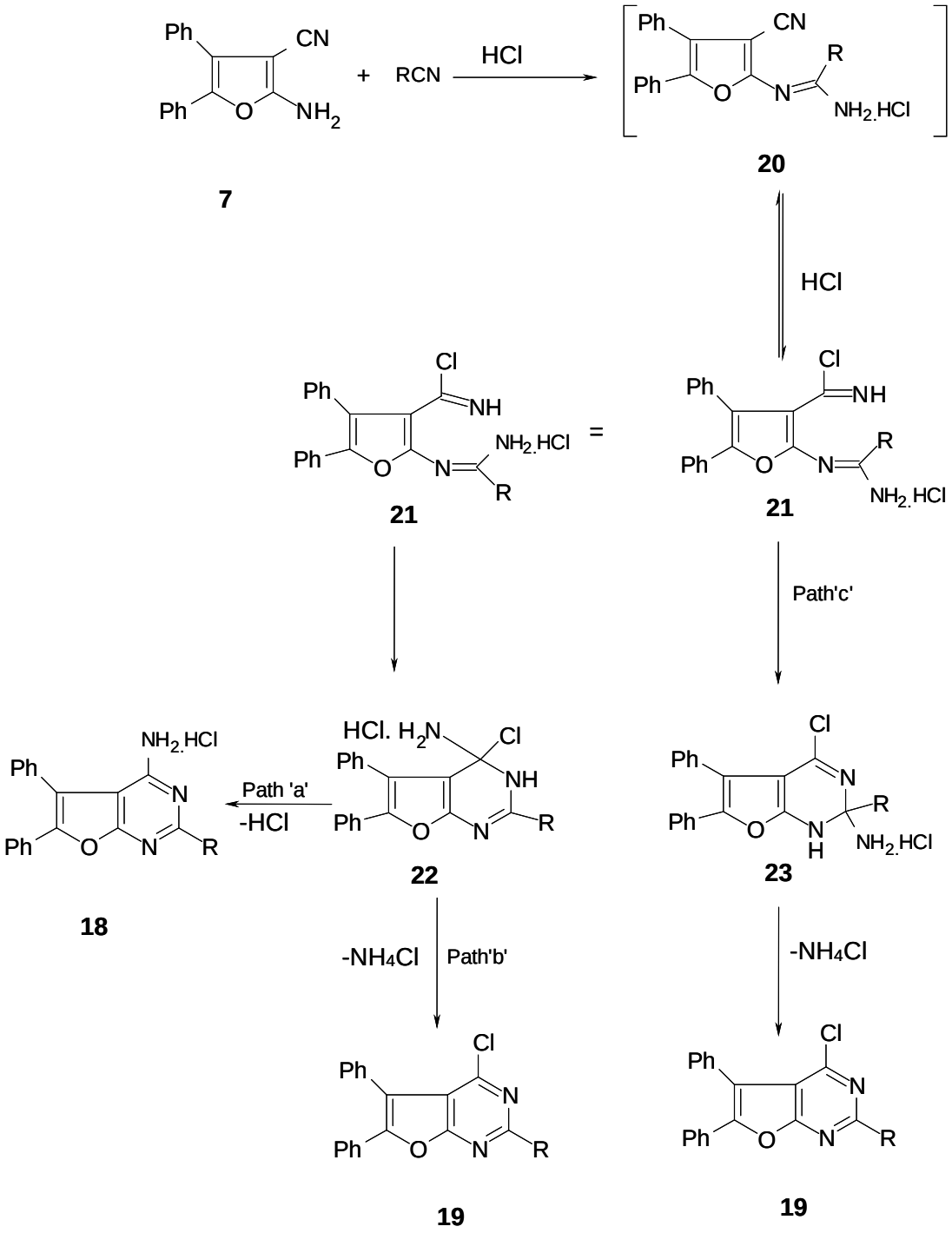
1. 2- With nitrile compounds

Nitriles reacted with vicinal aminocyano and vicinal acylamino furans to yield the target furopyrimidines. Thus, interaction of compound **7** with benzonitrile and sodium methoxide in refluxing 2-propanol afforded 4-amino-2,5,6-triphenylfuro[2,3-*d*]pyrimidine (**17**)[4].



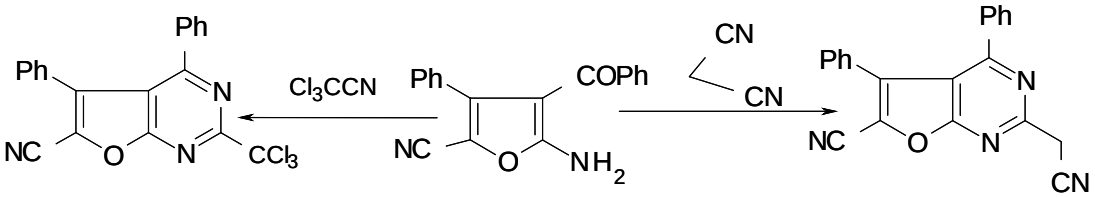
7 **17**

Also, the effect of acetonitrile on the compound **7** afforded exclusively fused 4-aminopyrimidines **18**, while chloroacetonitrile led to the formation of 4-chloropyrimidines **19**. These different products can be represented as shown in the following scheme[11].



R = CH_3, C_6H_5, $ClCH_2$, Cl_2CH,
$CH_2CO_2C_2H_5$, $CO_2C_2H_5$

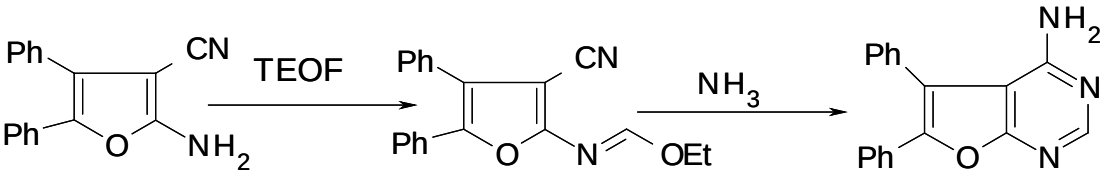
On the other hand, 2-cyanomethyl-4,5-diphenylfuro[2,3-*d*]pyrimidine-6-carbonitrile (**24**) and 4,5-diphenyl-2-trichloromethylfuro[2,3-*d*]pyrimidine-6-carbonitrile (**25**) can be obtained from reaction of vicinal acylamino furan **13** with malononitrile and trichloroacetonitrile, respectively[9].



25 **13** **24**

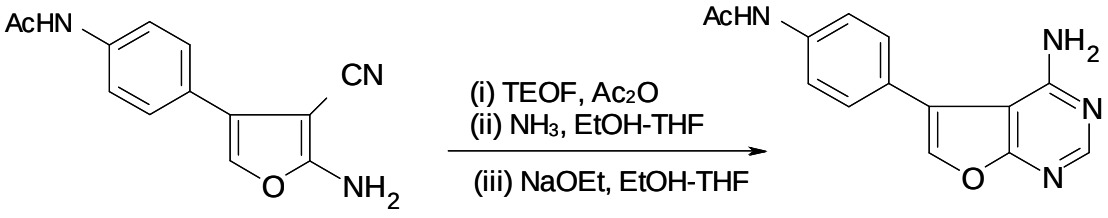
1.3- With orthoethers

Treating of compound **7** with triethylorthoformate (TEOF) yielded ethoxymethyleneimine derivative **26**, which can be cyclized by the action of ammonia giving compound **8**[12].



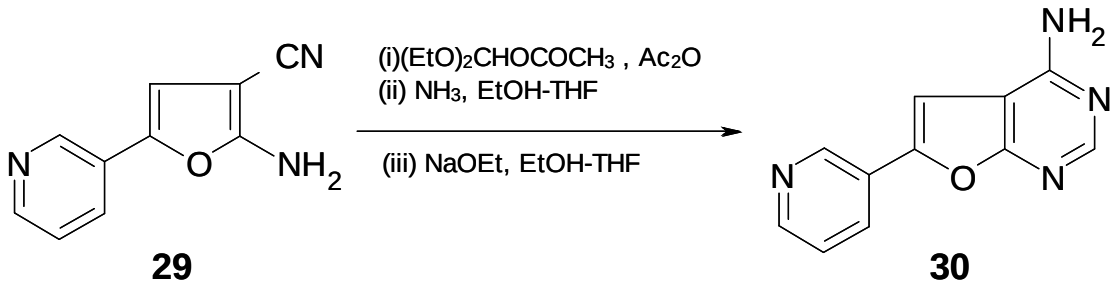
7 **26** **8**

Also, 4-acetamidophenyl-2-aminofuran-3-carbonitrile (**27**) was treated with TEOF followed by amination and cyclization in the presence of sodium ethoxide to give 5-(4-acetamidophenyl)-4-aminofuro[2,3-*d*]pyrimidine (**28**)[13].



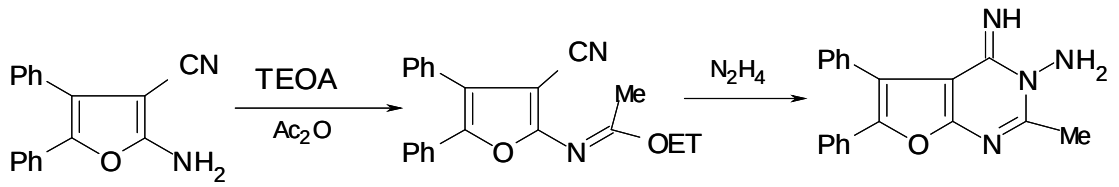
27 **28**

Similarly, treatment of 2-amino-5-(3-pyridyl)furan-3-carbonitrile (**29**) with diethoxymethineacetate afforded an ethoxyimino derivativewhich on treatment with ammonia followed by addition of sodium ethoxide gave 4-amino-6-(3-pyridyl)furo[2,3-*d*]pyrimidine (**30**)[2].



29 **30**

In addition to, 2-(*α*-ethoxyethylideneamino)-4,5-diphenylfuran-3-carbonitrile (**31**) was obtained by reaction of compound **7** with triethylorthoacetate (TEOA) in refluxing acetic anhydride. Furthermore, compound **31** was stirred with hydrazine hydrate yielding 3-amino-4-imino-2-methyl-5,6-diphenyl-3*H*,4*H*-furo[2,3-*d*]pyrimidine (**32**) in good yield[14].



7 **31** **32**

Also, 2-amino-4,5-di-(4-methoxyphenyl)furan-3-carbonitrile (**33**) reacted with TEOF or TEOA in acetic anhydride affording the corresponding imidates **34a,b**. The reaction of **34a,b** with semicarbazide hydrochloride gave 4-imino-5,6-di-(4-methoxyphenyl)-3-uriedofuro[2,3-*d*]pyrimidine **36a** and 4-imino-5,6-di-(4-methoxyphenyl)-2-methyl-3-uriedofuro[2,3-*d*] pyrimidine **36b**, respectively. The formation of compounds **36a,b** was rationalized in terms of the initial formation of the intermediate **35**. Also, hydrazinolysis of **34a** in ethanol yielded the 3-amino-4-imino-5,6-di(4-methoxyphenyl)-3*H*,4*H*-furo[2,3-*d*]pyrimidine (**37**)[15].