



**Faculty of Education
Chemistry Department**

**A THESIS
ENTITLED**

**Synthesis of Some New Heterocyclic Compounds of
Expected Biological Activity**

Submitted by

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B.Sc & Ed.

For the degree of

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

Department of Chemistry
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Ain Shams University
Cairo

2011



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Department of Chemistry

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Synthesis of Some New Heterocyclic Compounds of Expected Biological Activity

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B.Sc. 2005

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ACKNOWLEDGEMENT

I would like to express my deep gratitude to Prof. Dr. Magdy Hamed El-Metwally Seada, Prof. Dr. Mohamed Abdel-Megid Abdel-Hamid and Dr. Azza Mohamed Mohamed El-Kazak, Department of Chemistry, Faculty of Education, Ain Shams University, for the defining and directing this study and their supervision, encouragement and involvement assured significant conclusions.

I do much thanks to Prof. Dr. S. Labib, the pervious Head of Chemistry Department, Faculty of Education, Ain Shams University, for his kind valuable help during the course of research work.

I am particularly gratitude to Prof. Dr. S. Khalil, Head of Chemistry Department, Faculty of Education, Ain Shams University, for facilities provided and his valuable help during the course of research work.

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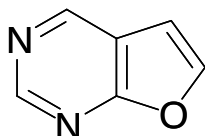
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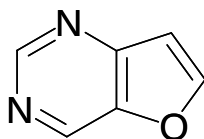
CHEMISTRY OF **FUROPYRIMIDINES**

INTRODUCTION:

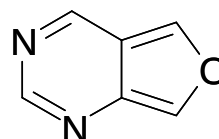
There are three fundamental furopyrimidine systems. They are furo[2,3-*d*]pyrimidine (I), furo[3,2-*d*]pyrimidine (II) and furo[3,4-*d*]pyrimidine (III) according to the following presentation.



(I)



(II)



(III)

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

SYNTHESIS OF **FUROPYRIMIDINES**

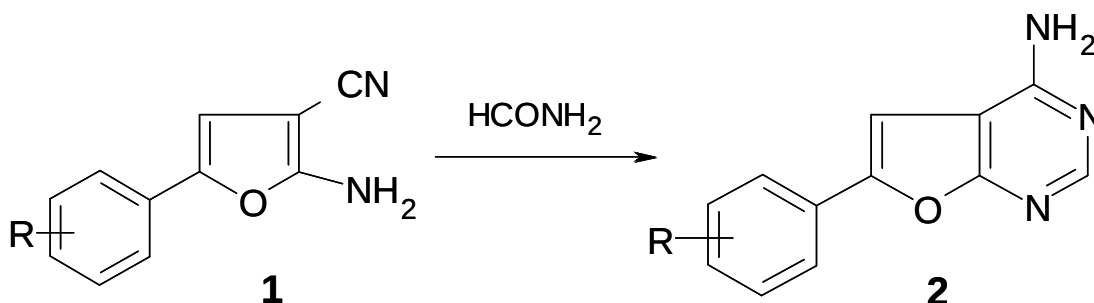
The building of furopyrimidine moiety has been achieved either by construction of pyrimidine nucleus on the parent furan ring or construction of furan nucleus on the parent pyrimidine ring.

1- From Furan derivatives

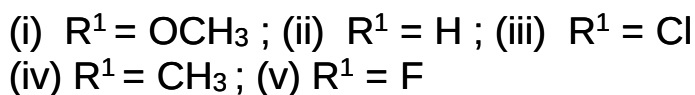
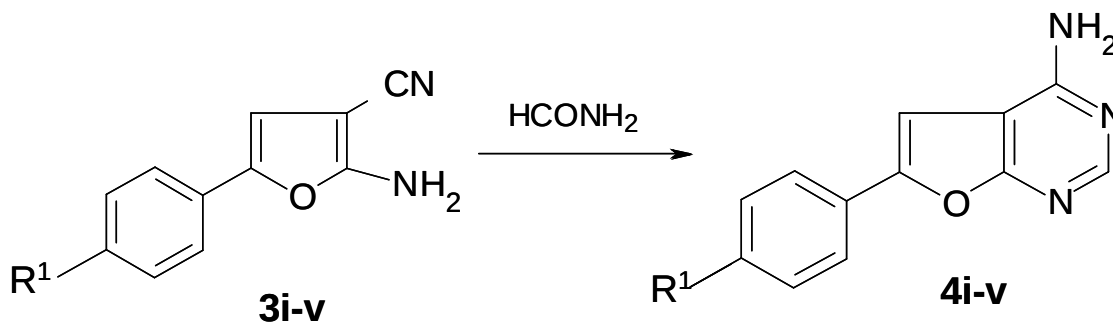
The simple approach to a new pyrimidine ring involves introducing a one-carbon fragment between two suitable and vicinal functional groups in furan rings.

1.1- With formamide

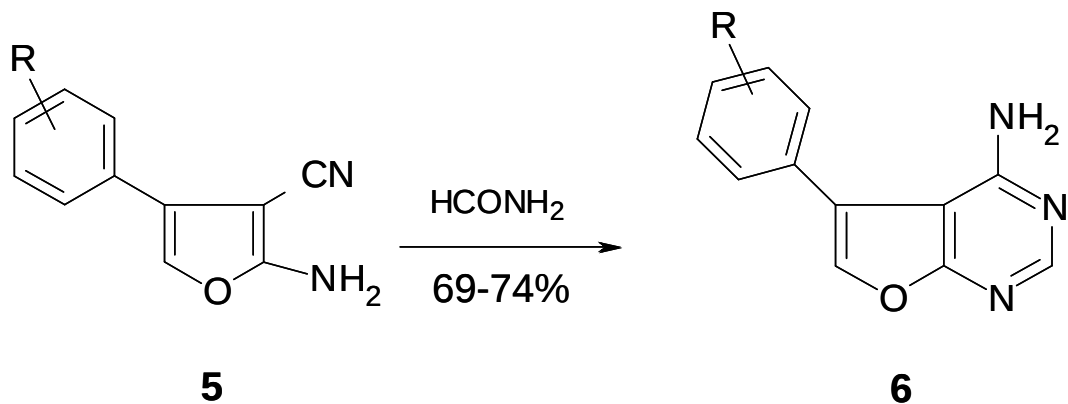
Formamide reacted with vicinal aminocyano, vicinal acylamino and vicinal aminoester furans to yield the target furopyrimidines. Therefore, treatment of 2-amino-5-aryl-3-furancarbonitrile derivatives (**1**) with formamide yielded 4-amino-6-aryl-2-furo[2,3-*d*]pyrimidine derivatives (**2**)¹.



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.

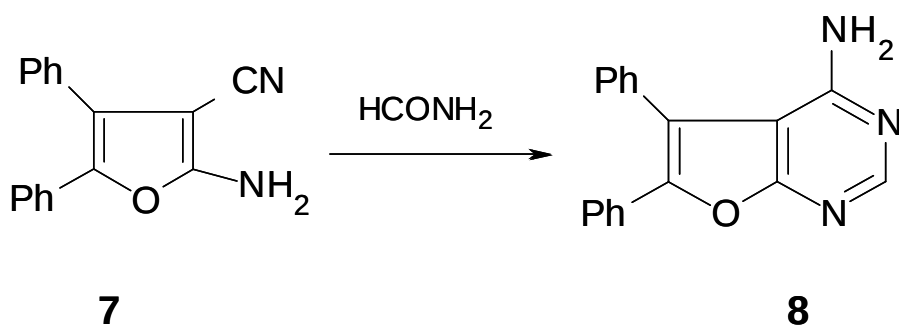


Also, cycloaddition of 2-amino-4-aryl-3-furancarbonitrile derivatives (**5**) with formamide led to the corresponding 4-amino-5-aryl-2-furo[2,3-*d*]pyrimidine derivatives (**6**)¹.

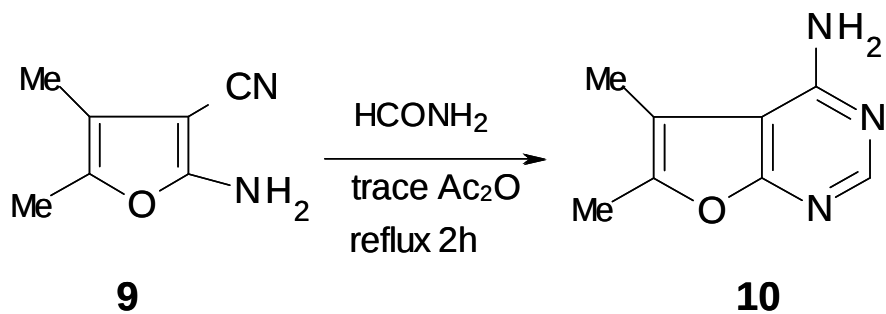


R = 4-OMe, 4-NMe₂, 4-phenyl and 3-NHAc

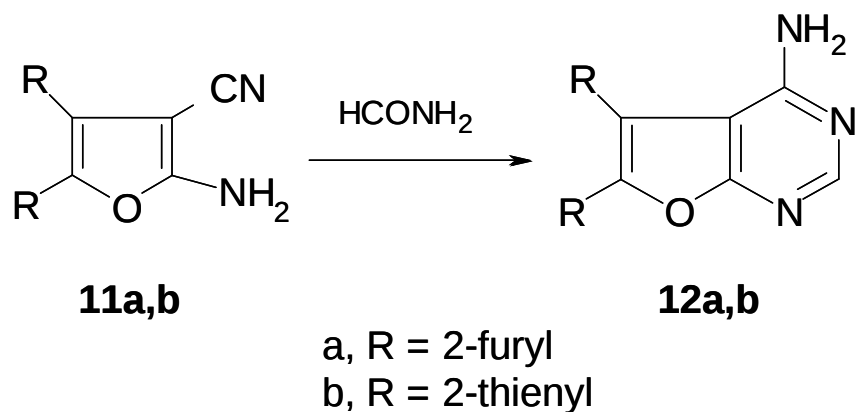
Also, reaction of 2-amino-4,5-diphenylfuran-3-carbonitrile (**7**)³ with formamide gave 4-amino-5,6-diphenylfuro[2,3-*d*]pyrimidine (**8**)⁴.



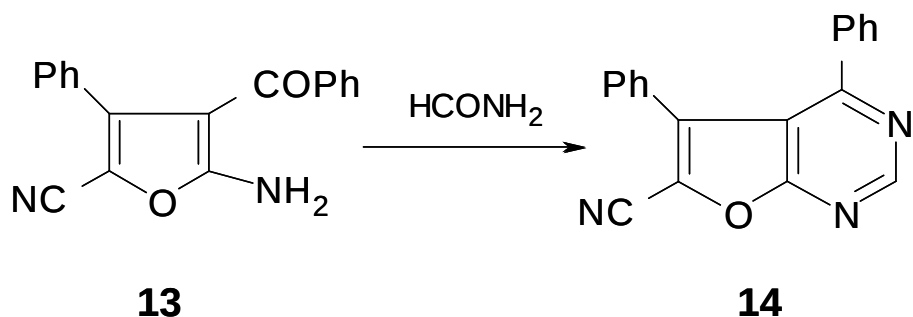
By analogy, the synthesis of other fused pyrimidines can be achieved by refluxing of 2-amino-4,5-dimethylfuran-3-carbonitrile (**9**) with formamide in the presence of acetic anhydride afforded 4-amino-5,6-dimethylfuro[2,3-*d*]pyrimidine (**10**)⁵⁻⁷.



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.



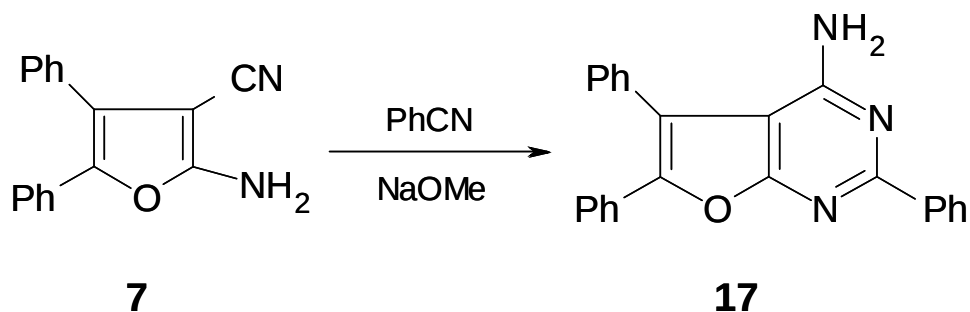
On the other hand, furopyrimidines can be obtained by reaction of vicinal acylamino and vicinal aminoester furans with formamide. Thus, treatment of 5-amino-4-benzoyl-3-phenylfuran-2-carbonitrile (**13**) and furan derivatives **15a,b** with formamide afforded 4,5-diphenylfuro[2,3-*d*]pyrimidine-6-carbonitrile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



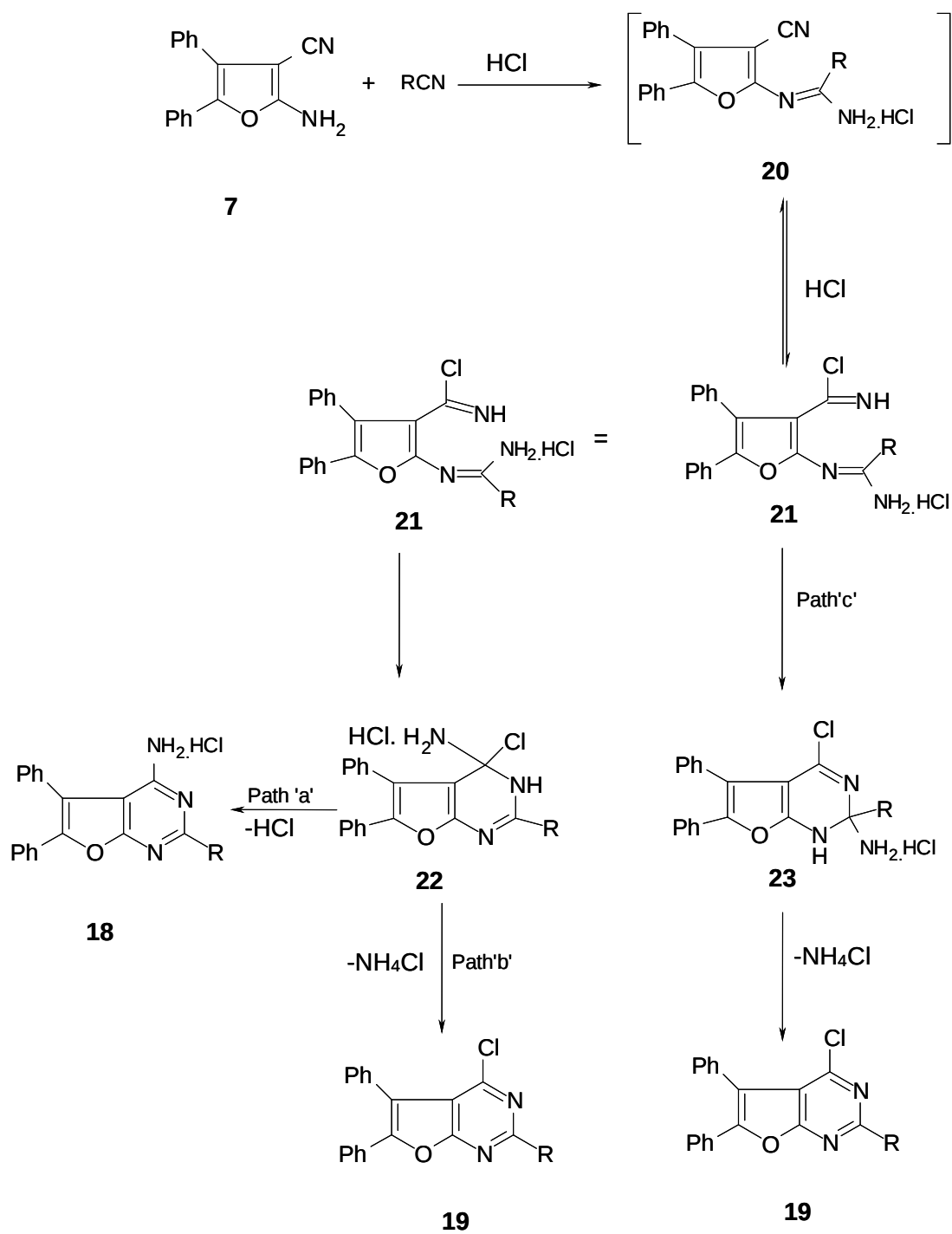


1. 2- With nitrile compounds

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.

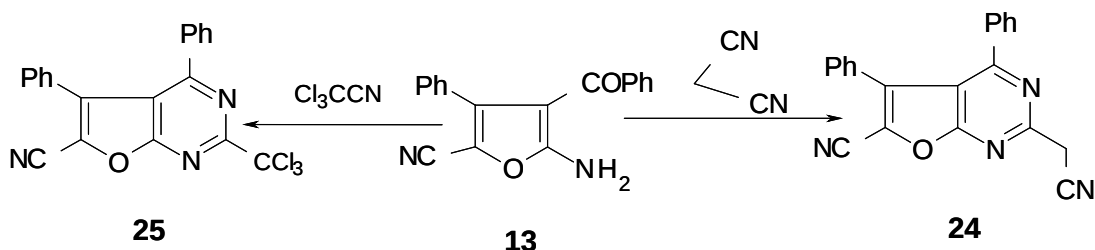


Also, the effect of acetonitrile on the compound **7** afforded exclusively fused 4-aminopyrimidines **18**, while chloroacetonitrile led to the formation of 4-chloropyrimidines **19**. These different products can be represented as shown in the following scheme¹¹.



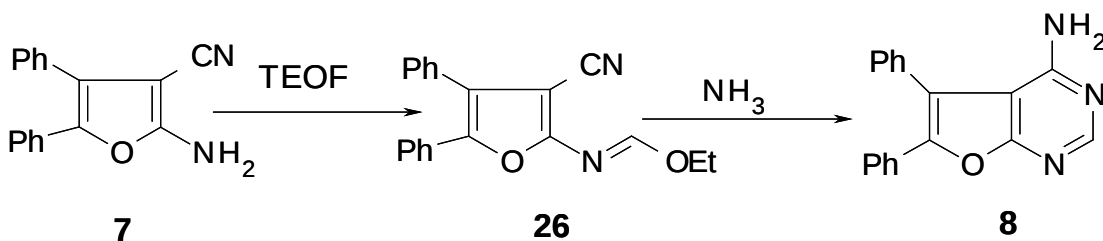
$\text{R} = \text{CH}_3, \text{C}_6\text{H}_5, \text{ClCH}_2, \text{Cl}_2\text{CH},$
 $\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5, \text{CO}_2\text{C}_2\text{H}_5$

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, respectively⁹.

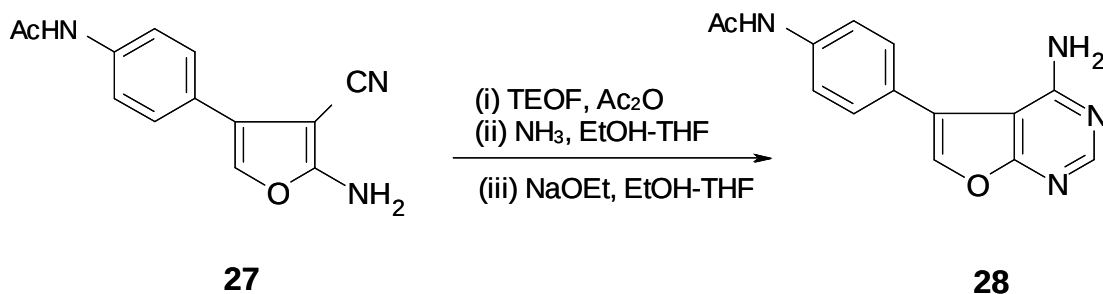


1.3- With orthoethers

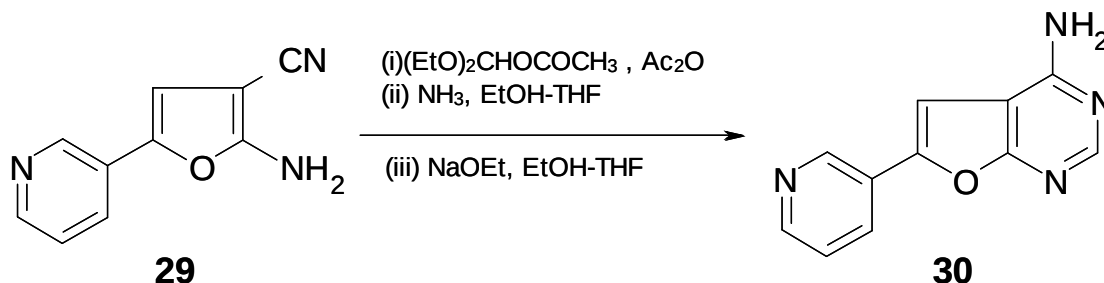
Treating of compound **7** with triethylorthoformate (TEOF) yielded ethoxymethyleneimine derivative **26**, which can be cyclized by the action of ammonia giving compound **8**¹².



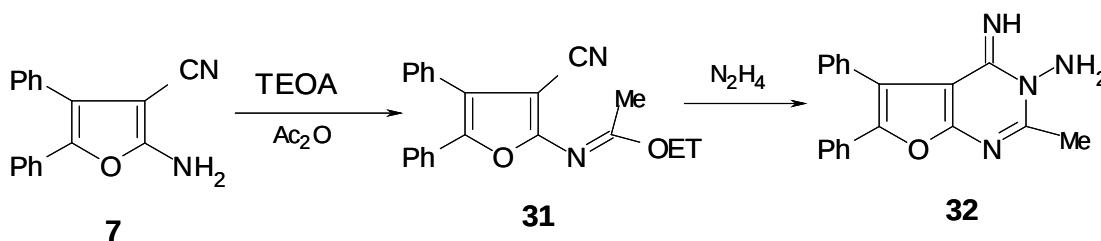
Also, 4-acetamidophenyl-2-aminofuran-3-carbonitrile (**27**) was treated with TEOF followed by amination and cyclization in the presence of sodium ethoxide to give 5-(4-acetamidophenyl)-4-aminofuro[2,3-*d*]pyrimidine (**28**)¹³.



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.



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 yield¹⁴.



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.