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SYNTHESIS OF PYRIMIDINES AND CONDENSED PYRIMIDINES THROUGH REACTIONS OF NITRILES WITH *o*-AMINOCARBONYL SUBSTRATES UNDER ACIDIC CONDITIONS

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Abstract - The single pot facile reaction of a host of nitriles with a variety of *o*-aminocarbonyl substrates of benzene, thiophene, benzothiophene, pyridothiophene, furan, pyrrole, pyridopyrazole, naphthopyran *etc.*, to form corresponding condensed pyrimidines functionalized at 2- and 4- positions has been reviewed and investigation into the reaction mechanisms and isolation of intermediates have been discussed. A new modification of this reaction under microwave condition has also been discussed. Further, a few applications of this novel reaction for the synthesis of API's are also presented.

CONTENTS

1. INTRODUCTION

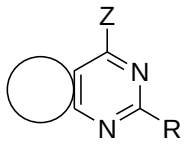
Pyrimidines and condensed pyrimidines have a long and distinguished history extending from the days of their discovery as important constituents of nucleic acids to their current use in the chemotherapy of

HIV/AIDS. The pyrimidine nucleus has a very wide biological and medicinal significance. For more details a comprehensive review[1] on this topic can be consulted.

The bioisosterism[2] between benzene and various heterocycles, namely thiophene, furan, pyrrole, pyridine *etc*., is known since long. Thus, various condensed pyrimidine systems like thienopyrimidines, furopyrimidines, pyrrolopyrimidines, pyrido-pyrimidines *etc*., are the logical bioisosters of the bioactive quinazolines (Figure 1).

2. SYNTHESIS OF CONDENSED PYRIMIDINES: GENERAL ASPECTS

Logically, medicinal chemistry research worldwide routinely involves the synthesis and evaluation of bioisosteric molecules of existing drugs. As many of the drug molecules have quinazoline as the basic nucleus, the synthesis of condensed pyrimidines (**1**), appropriately functionalised, especially at the 2- and 4-positions has attracted great attention of the medicinal chemists.



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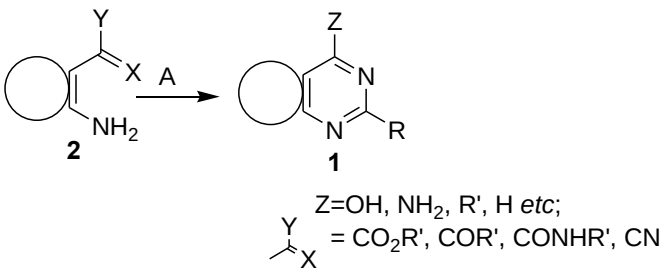
The synthesis of condensed pyrimidine systems is a very important process subject to improvement on various points and parameters. The regularly employed methods for synthesis of condensed pyrimidines involve essentially, two different approaches as mentioned below.

Approach A:

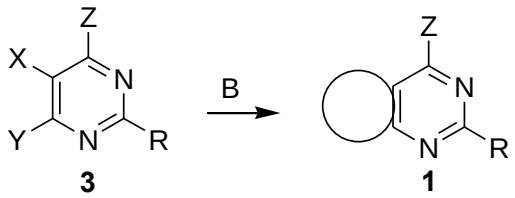
Annelation of the pyrimidine on an appropriately substituted heterocycle (**2**)[3] (Scheme 1).



Scheme 1

Approach B:

Annelation of a heterocycle on the appropriately substituted pyrimidine ring (**3**)[3] (Scheme 2).



3 **1**

Scheme 2

Approach A is the most widely used approach for the synthesis of condensed pyrimidines.[3] Under this approach, a variety of *o*-aminocarbonyl substrates of various heterocycles have been cyclocondensed with a host of reagents namely amides, thioamides, imidates, amidines *etc*., mostly under basic conditions, to afford various condensed pyrimidines, quinazolines, thienopyrimidines, pyrrolopyrimidines, triazolopyrimidines, pteridines, furopyrimidines, pyridopyrimidines and many more (Scheme 3).

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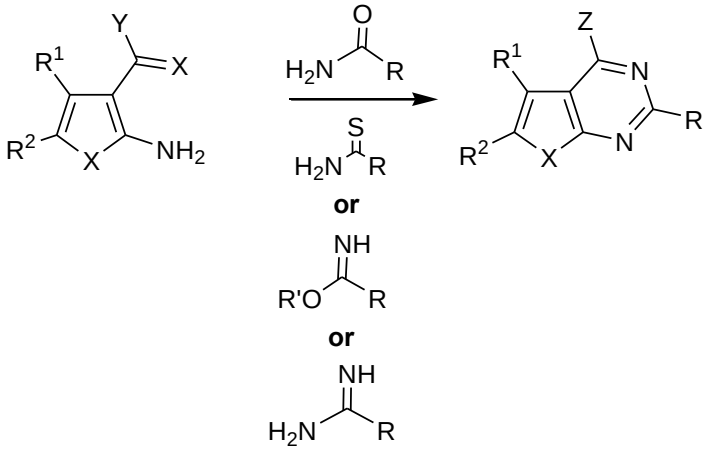
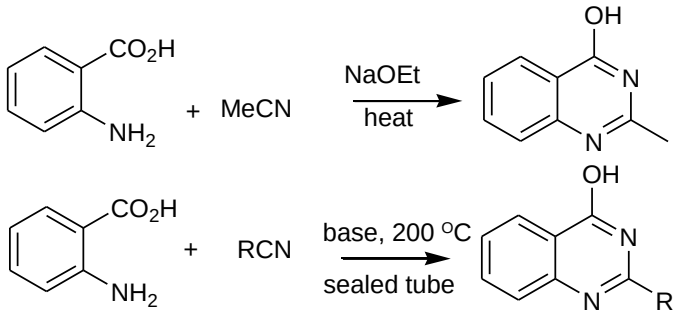


R^1, R^2 = H, alkyl, aryl, cycloalkyl, aloxy, carboxy, heterocycloalkyl *etc*;
X = HC=CH, NH, S, O, CH=N, N=NH, *etc*;
Y = CO_2H, CO_2R^3, $CONH_2$, COR^3, CHO,CN, *etc*;
Z =OH, NH_2;
R = alkyl, aryl,aralkyl, *etc*.
R^3 = Me, Et, alkyl, aryl

Scheme 3

However, the direct use of a nitrile (RCN) as a reagent to cyclocondense with *o*-amino carbonyl substrates to afford condensed pyrimidines has received only scant attention. There are a few reports[3-5] available in the literature on such reactions under basic conditions (Scheme 4). The major drawback of these reactions under basic conditions is poor product yields.

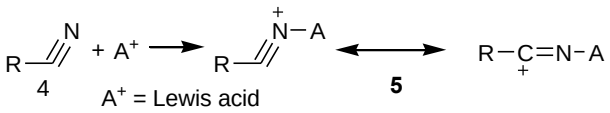


Scheme 4

3. REACTIONS OF NITRILES UNDER ACIDIC CONDITIONS

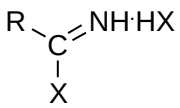
Nitriles have played a major role in the synthesis of a variety of open chain and heterocyclic compounds.[6] The polar C≡N group of the nitrile is prone to an electrophilic attack at the nitrogen and a nucleophilic attack at the carbon.

The enhanced electrophilicity of nitriles in the presence of halogen acids is known since long. The interaction of a nitrile (**4**) with an acid or its complexation with Lewis acids results in the formation of a species **5**, with enhanced electrophilicity (Scheme 5) and therefore, many of the reactions of nitriles with nucleophilic reagents are acid catalyzed. Halogen acids (HX) have been found to be particularly effective in promoting the reaction of nitriles with a variety of nucleophiles.



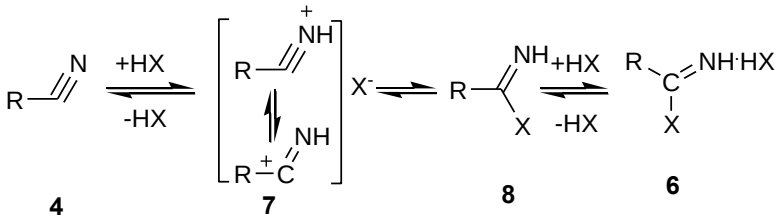
Scheme 5

In the absence of other nucleophilic species, nitriles react with halogen acids, to yield unstable adducts of different compositions. The nature of these adducts, as well as, the possible involvement of such nitrile-halogen acid adducts in the hydrogen halide catalyzed reactions of nitriles with nucleophiles has been the subject of considerable discussion.[6-16] These adducts are of compositions, such as RCN·HX, 2RCN·HX, 2RCN·nHX *etc.*, depending upon the nature of the nitriles and the reaction conditions employed. The unstable, hygroscopic adducts resulting from the reaction of a variety of aliphatic and aromatic nitriles with halogen acids, at low temperatures, have been found to be of the general composition RCN·2HX. The structure **6**, however, has been assigned to many of these adducts.[7,17-21]



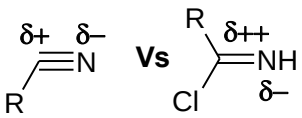
6

The sequence of reactions leading to the formation of imidoyl halide hydrohalide (**6**) from a nitrile (**4**) can be depicted as shown below. The protonation of the nitrile yields the nitrilium ion (**7**), which combines with a halide ion to form imidoyl halide (**8**). The imidoyl halide (**8**) thus formed, is sufficiently basic to react with another molecule of halogen acid to yield the imidoyl halide hydrohalide salt (**6**). In this reversible reaction, the formation of imidoyl halide hydrochloride salt (**6**), is frequently slow and is favoured by high concentrations of hydrogen halide (Scheme 6).[11,12]

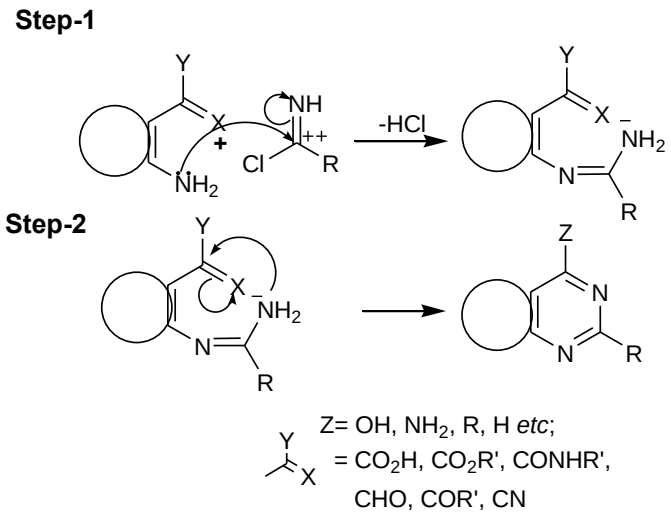


Scheme 6

This reactive intermediate, imidoyl halide (**8**), is formed *in situ* through the reaction of nitrile R-C≡N and halogen acid HX. The addition of HX is across the polar C≡N bond. The electron withdrawing group X (Cl) further makes the nitrile carbon more electrophilic or enhances its electrophilicity.

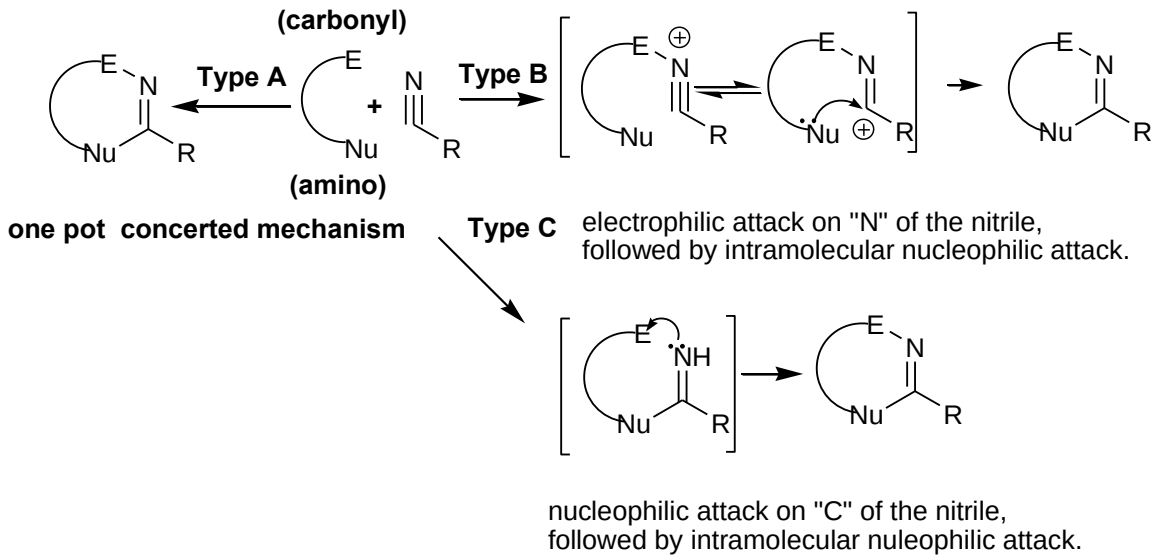


The imidoyl halide (**8**), when reacted with the *o*-aminocarbonyl substrate, attracts the electrons of the nucleophilic-NH_2 group of the substrate very readily as follows (Scheme 7).



Scheme 7

The reaction of a nitrile with an *o*-aminocarbonyl substrate possessing electrophilic and nucleophilic centers leads to the formation of an azaheterocycle through the incorporation of CN of the nitrile in the ring. The mechanism may be any of the following three, a concerted cycloaddition process (Type A), or by discreet steps, involving either the initial electrophilic attack on the nitrile nitrogen (Type B) or by the initial nucleophilic attack at the nitrile carbon (Type C), followed by ring closure[22] (Scheme 8).

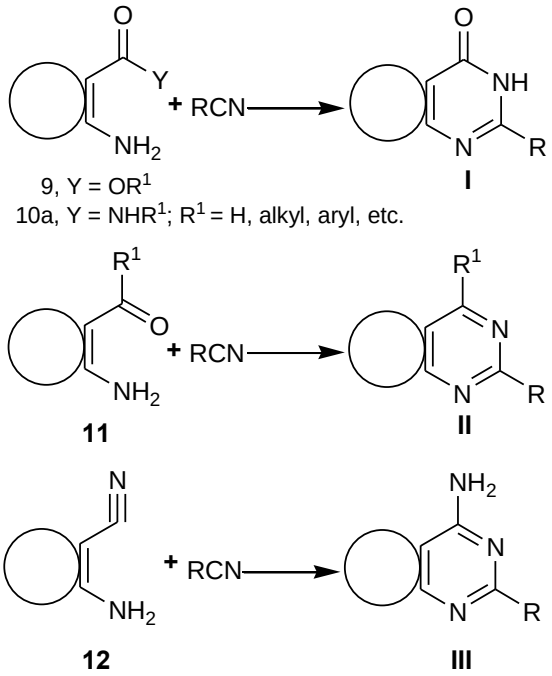


Scheme 8

Of the above three mechanisms the type C mechanism is the most favored mechanism and is widely reported.[22]

4. SYNTHESIS OF VARIOUS CONDENSED PYRIMIDINES UNDER THE INFLUENCE OF DRY HCl GAS

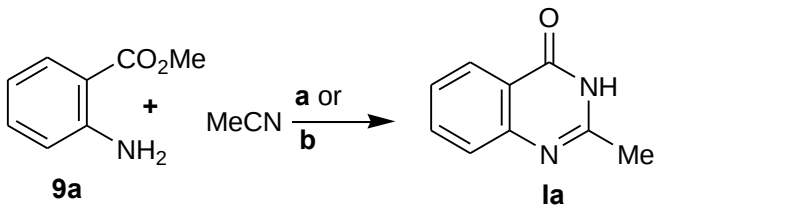
This enhanced reactivity of nitriles in the presence of acids has been particularly exploited for the synthesis of condensed pyrimidines. A host of nitriles have been reacted with various *o*-aminocarbonyl compounds to obtain a variety of condensed pyrimidines. This approach has led to the development of a facile, one pot synthesis of condensed 2-substituted functionalised pyrimidines of wide applicability.[23-30] Thus, a variety of *o*-aminocarbonyl compounds, such as *o*-aminoesters (**9**), *o*-aminoamides (**10**), *o*-aminoketones (**11**) and *o*-aminonitriles (**12**) have been reacted with nitriles to obtain the corresponding condensed 4-oxo (**I**), 4-aryl (**II**), and 4-aminopyrimidines (**III**) (Scheme 9).



Scheme 9

4.1. Synthesis of Condensed 4-Oxopyrimidines

The reaction essentially consists of bubbling a stream of dry hydrogen chloride gas through a mixture of an *o*-aminoester (**9**) or *o*-aminoamide (**10**) substrate and the nitrile in a suitable solvent like dioxane at ambient temperature for a few hours. On basification the condensed 4-oxopyrimidines (**I**) are isolated in good yields (60-80%). This is exemplified by the reaction between methyl anthranilate (**9a**) and acetonitrile which when conducted in the presence of dry hydrogen chloride gas has been found to give 2-methylquinazolin-4(3*H*)-one (**Ia**) in 75% yield. This is higher in yields, than that obtained under basic conditions[4] (Scheme 10).

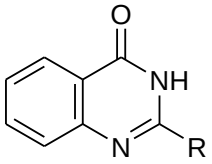


Scheme 10

A series of 2-substituted quinazolin-4(3*H*)-ones (**Ia**) (Table 1) has been synthesized through the reaction of methyl anthranilates (**9a**), with alkyl, aryl, aralkyl and heteroaryl nitriles under the influence of dry HCl gas. Further, the reaction has been found to be applicable to the condensation of a large variety of

active methylene nitriles to obtain the corresponding condensed 2-substituted-methylquinazolin-4(3*H*)-ones, which are otherwise inaccessible by the base catalyzed condensations.

Table 1. 2-Substituted quinazolin-4(3*H*)-ones



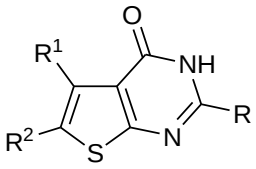
Ia

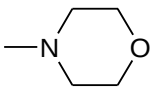
R	Nitrile used	R. Solv.	Yield (%)	Reference
Me	MeCN	E	75	28
C_6H_5-	C_6H_5CN	E- D	77	28
4-ClC_6H_4-	4-ClC_6H_4CN	E-D	70	28
$C_6H_5CH_2$-	$C_6H_5CH_2CN$	E-D	64	28
3-C_5H_4N	3-CNC_5H_4N	E-D	58	28
$EtCO_2CH_2$-	$EtCO_2CH_2CN$	E	69	23
$MeCO_2CH_2$-	$MeCO_2CH_2CN$	E	72	28
NH_2COCH_2-	NH_2COCH_2CN	E-C	68	28
$ClCH_2$-	$ClCH_2CN$	Di	72	28
4-$ClC_6H_4OCH_2$-	4-$ClC_6H_4OCH_2CN$	E-D	65	28
4-$ClC_6H_4SCH_2$-	4-$ClC_6H_4SCH_2CN$	E-D	79	28
$C_6H_5SO_2CH_2$-	$C_6H_5SO_2CH_2CN$	E-D	67	28

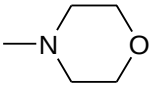
C= chloroform, D=dimethylformamide, Di= dioxane, E= ethanol

This method has been found to be equally applicable to the condensation of the *o*-amino esters and amides of a variety of substrates like thiophenes, with a host of alkyl, aryl, aralkyl, heteroaryl nitriles as well as a range of α-substituted acetonitriles to give the corresponding condensed 2-substituted pyrimidin-4(3*H*)-ones, namely, 2-substituted thieno[2,3-*d*]pyrimidin-4(3*H*)-ones[28] (Table 2), 2-substituted thieno[3,2-*d*]pyrimidin-4(3*H*)-ones (Scheme 11) and 2-substituted benzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones (Scheme 12)

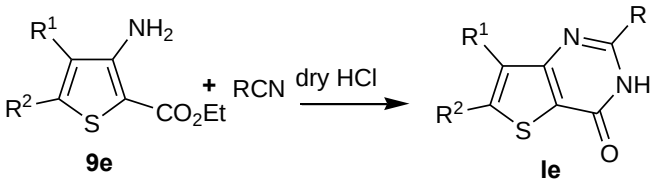
Table 2. 2-Substituted thieno[2,3-*d*]pyrimidin-4(3*H*)-ones



R^1	R^2	R	Yield (%)	R. Solv.	Reference
- $(CH_2)_4$-		Me	85	E-D	24
- $(CH_2)_4$-		-CH_2CO_2Et	72	E	28
- $(CH_2)_4$-		-CH_2CONH_2	46	E-D	28
- $(CH_2)_4$-		-$CHClCH_2Cl$	40	Di	28
- $(CH_2)_4$-		-CH_2Cl	81	E-C	25
- $(CH_2)_4$-		-$CH_2OC_6H_4Cl$-4	75	D	31
- $(CH_2)_4$-		-$CH_2SC_6H_4Me$ -4	75	E-C	31
- $(CH_2)_4$-		-$CH_2SO_2C_6H_4Me$-4	58	E-C	31
- $(CH_2)_4$-		-CH_2CO_2Me	66	E-C	31
- $(CH_2)_4$-		-$CH_2NHSO_2C_6H_5NH_2$-4	50	E	31
- $(CH_2)_4$-		-$CH_2NHSO_2C_6H_4NHCOMe$-4	58	E-C	31
- $(CH_2)_4$-		-$CH_2SO_2C_6H_4Cl$-4	50	D	31
- $(CH_2)_4$-		-$CH_2SC_6H_4Cl$-4	70	E-C	31
-$(CH_2)_4$-		-C_6H_5	80	E-D	24
- $(CH_2)_4$-		3-C_5H_4N	60	E-D	28
- $(CH_2)_4$-		-NHC_6H_5	57	E-D	26
- $(CH_2)_4$-		-NHC_6H_4Me-4	45	E-D	26
- $(CH_2)_4$-		-NHC_6H_4Cl-4	69	E-C	26
- $(CH_2)_4$-		-NHC_6H_4Cl-2	35	Di	26
- $(CH_2)_4$-		-NH_2	68	*n*-P	26
- $(CH_2)_4$-			62	E-C	26
- $(CH_2)_4$-		-$CH{=}CHC_6H_5$	50	E-C	23
- $(CH_2)_4$-		-SH	60	E-D	26
- $(CH_2)_3$-		Me	73	E-D	28
- $(CH_2)_3$-		-CO_2Et	65	E	28

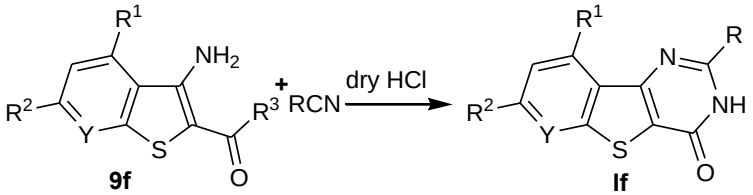
- $(CH_2)_3$-		$-CH_2CH_2Cl$	47	E-C	28
- $(CH_2)_3$-		$-CH_2CO_2Et$	68	E	28
- $(CH_2)_3$-		$-CH_2Cl$	70	Di	26
Me	Me	Me	85	E-C	24
Me	Me	3-C_5H_4N	66	Di	28
Me	Me	$-C_6H_5$	66	D-E	24
Me	Me	$-CH_2CO_2Et$	68	E	28
Me	Me	$-CH_2Cl$	78	E-C	26
Me	Me		57	Ch	26
Me	Me	$-CH_2SC_6H_4Cl$-4	59	E-C	26
C_6H_5-	H	Me	74	E-C	24
C_6H_5-	H	$-C_6H_5$	56	Di	24
C_6H_5-	H	$-CH_2C_6H_5$	50	E-C	24
C_6H_5-	H	$-CH_2CO_2Et$	70	E	28
C_6H_5-	H	$-CH_2Cl$	81	Ch	31
4-ClC_6H_4-	H	CH_2Cl	65	M-C	26
4-MeC_6H_4-	H	$-CH_2Cl$	86	E-C	32
H	Et	$-CH_2Cl$	98	Di	31
H	Et	$-C_6H_3(OMe)_2$-3,4	65	E-C	28
Me	CO_2Et	$-CH_2C_6H_5$	58	E-D	23
Me	CO_2Et	$-CH_2Cl$	87	Di	31
Me	CO_2Et	Me	80	D	23
Me	CO_2Et	$-C_6H_3(OMe)_2$-3,4	50	E-C	28
C_6H_5-	Me	$-CH_2Cl$	94	E-C	33
$-(CH_2)_2$-N-$(CH_2C_6H_5)CH_2$-		Me	77	D-P	28
$-(CH_2)_2$-N-$(CH_2C_6H_5)CH_2$-		$-CH_2Cl$	54	D	28
$-(CH_2)_2$-N-$(CH_2C_6H_5)CH_2$-		$-CH_2C_6H_5$	60	E-C	28
$-(CH_2)_2$-N-$(CH_2C_6H_5)CH_2$-		$-C_6H_5$	55	E-C	28
$-(CH_2)_2$-N-$(CH_2C_6H_5)CH_2$-		$-C_6H_3(OMe)_2$-3,4	50	E-C	28
$-(CH_2)_2$-N-$(MeCO)CH_2$-		3-C_5H_4N	57	E-D	28

C = chloroform, Ch = cyclohexane, D = dimethylformamide, Di = dioxane, E = ethanol, M = methanol, P = petroleum ether (60-80^{o}C), n-P = n-propanol.



Scheme 11

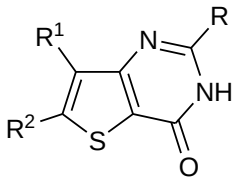
2-Substituted thieno[3,2-*d*]pyrimidin-4(3*H*)-ones (Table 3)



Scheme 12

2-Substituted benzothieno[3,2-*d*]pyrimidin-4(3*H*)-ones (Table 3)

Table 3. 2-Substituted thieno[3,2-*d*] / benzo(b)thieno[3,2-*d*]/pyridothieno[3,2-*d*]pyrimidin-4(3*H*)-ones

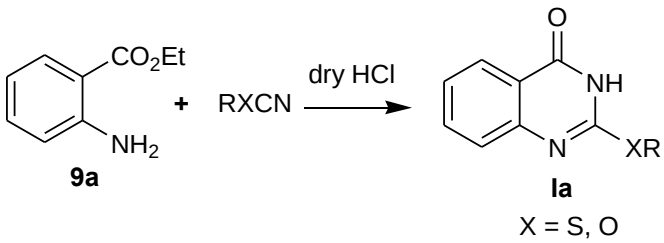


R_1	R_2	R	Yield (%)	R. Solv.	Reference
C_6H_5	H	Me	80	C	33
C_6H_5	H	$-CH_2Cl$	82	E	33
C_6H_5	H	$-CH_2CH_2Cl$	76	C	33
H	C_6H_5	Me	45	E-C	33
H	C_6H_5	$-CH_2Cl$	40	E-C	33
H	C_6H_5	$-CO_2Et$	25	E-C	33
H	C_6H_5	$-CH_2CO_2Et$	38	C-P	33
H	C_6H_5	$-CH_2CH_2Cl$	41	E-C	33
H	C_6H_5	$-C_6H_5$	35	E-C	33
H	C_6H_5	$-CH_2C_6H_5$	32	E-C	33
H	C_6H_5	$-CH_2C_6H_4Cl$-4	38	C-P	33
H	C_6H_5	$-CH_2C_6H_4NO_2$-4	52	C-P	33

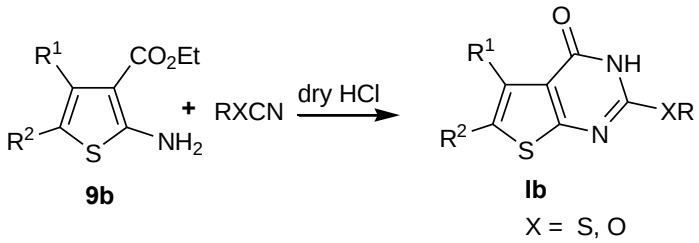
H	C_6H_5	$-CH_2=CH-C_6H_5$	55	E-C	33
-CH=CH-CH=CH-		Me	73	E-D	28, 34
-CH=CH-CH=CH-		$-CH_2C_6H_5$	69	E-D	28
-CH=CH-CH=CH-		$-CH_2Cl$	63	E-D	34
-C(OMe)=CH-CH=CH-		$-CH_2C_6H_5$	65	E-D	28
-C(Me)=CH-C(Me)=N-		Me	62	E-C	34
-C(Me)=CH-C(Me)=N-		$-CH_2Cl$	68	E	34

A = gl.acetic acid, C = chloroform, D = dimethylformamide, E = ethanol, M = methanol, P= petroleum ether (60-80^oC)

Heteronitriles, such as arylthioacetonitriles and aryloxyacetonitriles have been found to react with methyl anthranilate (**9a**) and thiophene 2-amino-3-carboxylates (**9b)** in the presence of dry hydrogen chloride to yield 2-arylthiomethyl- and 2-aryloxymethylthioquinazolin-4(3*H*)-ones (**Ia**) (Table 1), as well as, 2-arylthiomethyl- and 2-aryloxymethylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones (**Ib**) (Table 2) which are otherwise accessible only through two step syntheses.

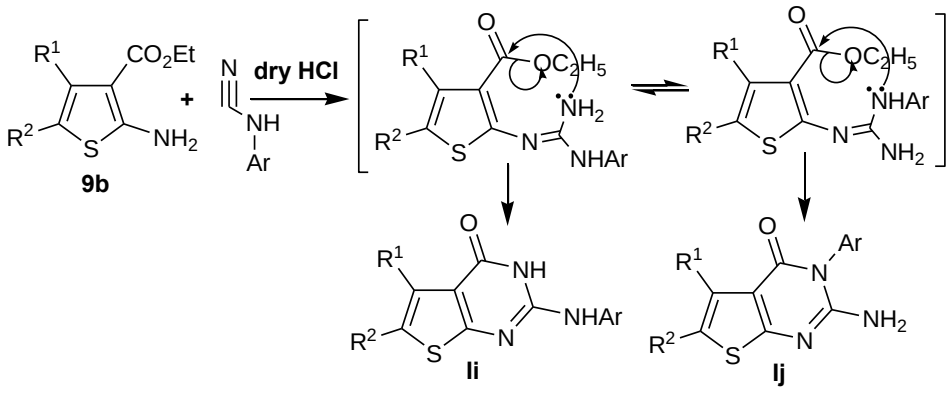


2-Arylthiomethyl- and 2-aryloxymethylquinazolin-4(3*H*)-ones (Table 1)



2-Arylthiomethyl- and 2-aryloxymethylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones (Table 2)

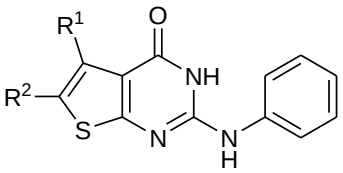
Similarly, simple cyanamide and dialkyl cyanamides yield 2-amino- and 2-dialkylaminothieno[2,3-*d*]-pyrimidin-4(3*H*)-ones, respectively (Table 2) under these reaction conditions. However, when *N*-monoaryl cyanamides were used two isomeric thienopyrimidin-4-ones (**Ii**) and (**Ij**) have been obtained as the condensation products of their dry HCl catalyzed reaction with thiophene *o*-aminoesters (**9b**). The reaction proceeds *via* the transient guanidine intermediate, which cyclizes through two alternate pathways to afford the isomeric 2-aminothieno[2,3-*d*]pyrimidin-4(3*H*)-ones. (Scheme 13) (Tables 4 and 5).[26]



$R^1 = R^2 = -(CH_2)_4$,-$(CH_2)_2$-N-$(CH_2C_6H_5)CH_2$-; $R^1 = R^2$ = Me, $R^1 = C_6H_5$, R^2 = H, Ar = C_6H_5, 4-MeC_6H_4, 4-MeOC_6H_4, 4-ClC_6H_4, 2-ClC_6H_4.

Scheme 13

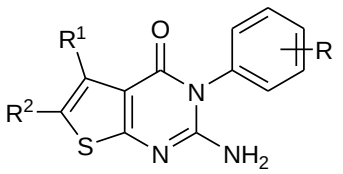
Table 4. 2-Arylaminothieno[2,3-*d*]pyrimidin-4(3*H*)-ones



R^1	R^2	R	Yield %	R. Solv	Reference
-$(CH_2)_4$-		H	57	E-D	26
-$(CH_2)_4$-		4-Me	45	E-D	26
-$(CH_2)_4$-		2-Cl	35	Di	26

D = dimethylformamide, C = chloroform, E = ethanol, Di = dioxane

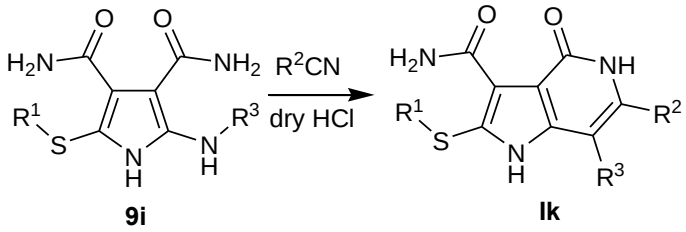
Table 5. 3-Substituted 2-aminoarylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones



R^1	R^2	R	Yield (%)	R. Solv.	Reference
-(-CH_2-)$_4$-		H	20	E-C	26
-(-CH_2-)$_4$-		4-Me	25	E	26
-(-CH_2-)$_4$-		2-Cl	30	E-C	26

B=benzene, C=chloroform, E = ethanol

Boehm *et al.*,[35] have reported the synthesis of 2-substituted pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-ones(**Ik**) by reacting the pyrrole *o*-aminoester (**9i**) with various nitriles in the presence of dry hydrogen chloride (Scheme 14).

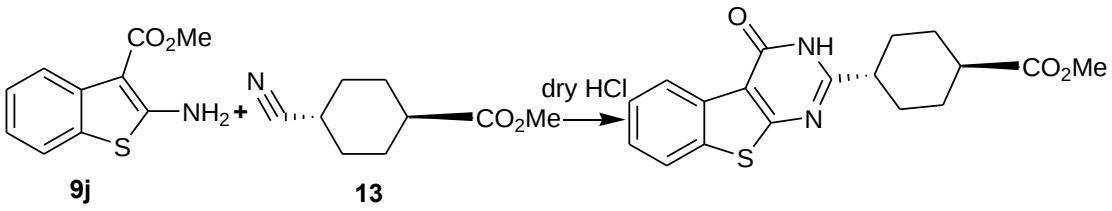


9i **Ik**

R^1 = alkyl, R^2 = alkyl, arylalkyl, carboxyalkyl, R^3 = H

Scheme 14

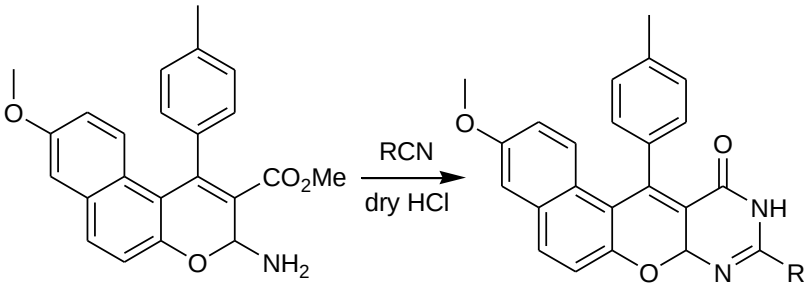
Recently, Juraszyk and coworkers[36] have utilized the same approach to synthesize methyl *trans*-4-(4-oxo-3,4-dihydro[1]benzothieno[2,3-*d*]pyrimidin-2-yl)cyclohexane carboxylate from 2-aminobenzothiophene-3-carboxylate (**9j**) and methyl *trans*-4-cynocyclohexane carboxylate (**13**) under the influence of dry HCl gas (Scheme 15).



9j **13**

Scheme 15

Similarly, Eid *et al.*[37] have synthesized novel naphtha[2,1-*b*]pyrano[2,3-*d*]pyrimidin-4-one derivatives from the corresponding *o*-amino ester **14** under the influence of dry HCl gas (Scheme 16).



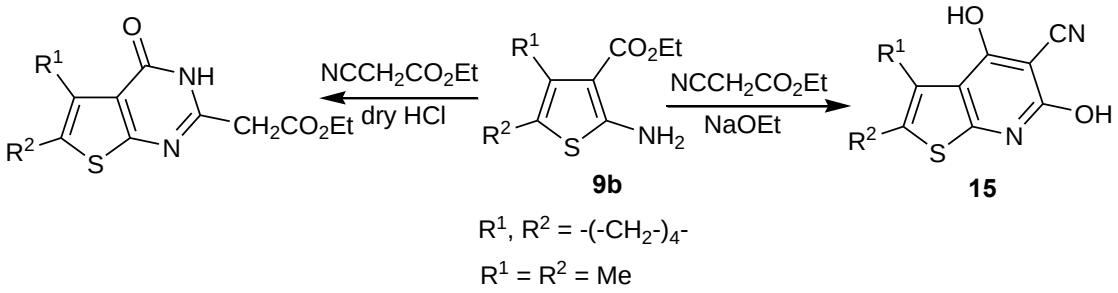
14

Scheme 16

4.1.1 Some interesting observations: Condensed 4-oxopyrimidines

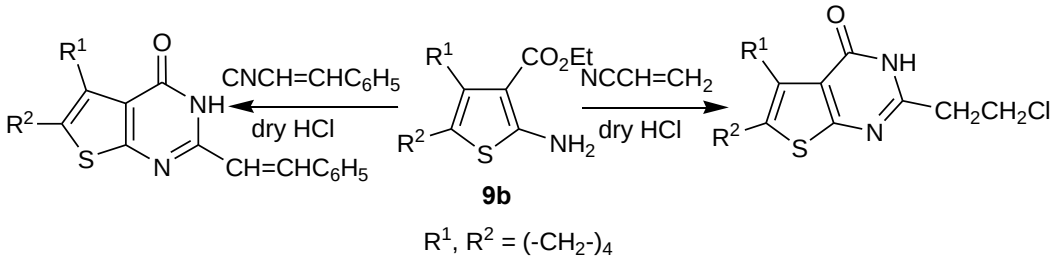
The condensation of thiophene *o*-aminoester (**9b**) with ethyl cyanoacetate, when effected in the presence of dry HCl gas yields the corresponding 2-ethoxycarbonyl-4-oxothienopyrimidine in 65% yields.[23,26] In contrast, the base catalyzed condensation, employing sodium ethoxide is reported to afford the 3-cyano-

2,4-dihydroxythienopyridine (**15**) (Scheme 17).



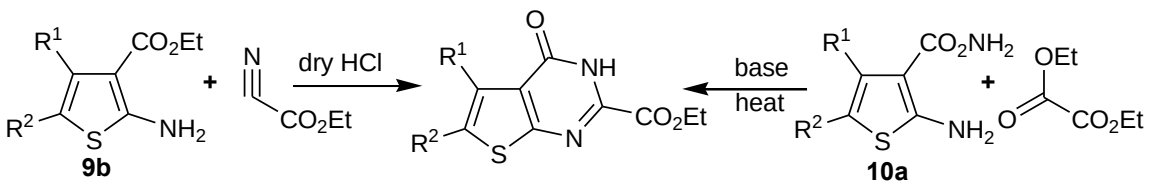
Scheme 17

While, the use of cinnamonitrile in this condensation with the thiophene *o*-aminoester (**9b**) has yielded the expected 2-styrylthienopyrimidin-4(3*H*)-ones, acrylonitrile when condensed with 2-amino-3-carbethoxythiophene, however, yields 2-chloroethylthienopyrimidin-4(3*H*)-ones as the only product of the reaction[23] (Scheme 18) (Table 2).



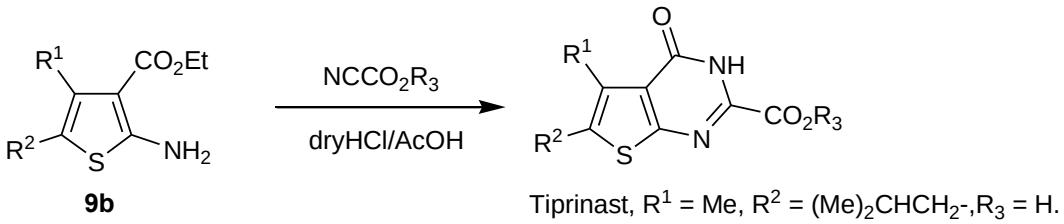
Scheme 18

The condensation of thiophene *o*-aminoesters with ethyl cyanoformate has yielded the 2-ethoxycarbonyl-4-oxothieno[2,3-*d*]pyrimidin-4(3*H*)-one, which otherwise is, accessible only by the condensation of the *o*-aminoamide with diethyl oxalate at elevated temperature[38] (Scheme 19).



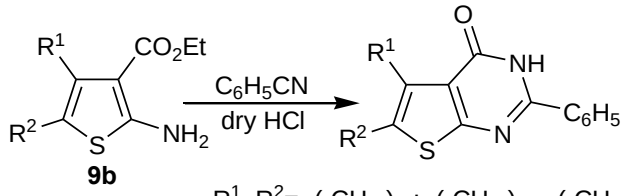
Scheme 19

On this basis Madding and co-workers[39] have reported the synthesis of 3,4-dihydro-4-oxothieno[2,3-*d*]-pyrimidine 2-carboxylates *via* the HCl catalyzed reactions of a mixture of the thiophene 3-carboxylates with activated nitriles. One of the derivatives, tiprinast, 3,4-dihydro-5-methyl-6-(2-methylpropyl)-4-oxothieno[2,3-*d*]pyrimidinecarboxylic acid is a proven orally active antiallergic and antiasthamatic drug (Scheme 20).



Scheme 20

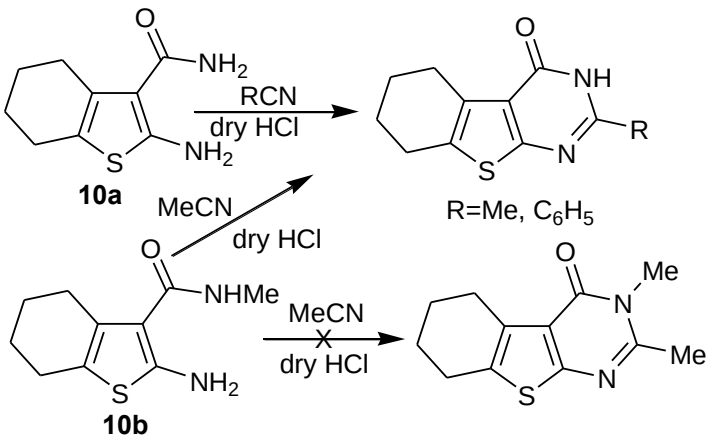
Some European workers[40] have synthesized a series of 3-phenylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones by the cyclization of 2-amino-3-ethoxycarbonylthiophenes with benzonitrile in the presence of dry HCl gas. These compounds have exhibited potent analgesic and anti-inflammatory activities (Scheme 21).



R^1, R^2= -(-CH_2-)$_3$-; -(-CH_2-)$_4$-, -(-CH_2-)$_5$-; -$CH(CH_3)$-(-CH_2-)$_3$-;
-(-CH_2-)$_2$-CH(Me)-CH_2-CH_2-CH(Me)-(-CH_2-)$_2$-;
R^1 = C_6H_5, R_2= H.

Scheme 21

The dry HCl gas catalysed reaction of 2-aminothiophene-3-carboxamide (**10a**) with acetonitrile and benzonitrile has yielded the corresponding 2-substituted 4-oxothienopyrimidines. Similar reaction of *N*-substituted 2-aminothiophene-3-caboxamide (**10b**) with acetonitrile could be expected to yield the 3-*N*-substituted 2-substituted thienopyrimidin-4(3*H*)-one. However, the reaction when actually conducted led to the formation of the 3-unsubstituted thienopyrimidin-4(3*H*)-one (R = Me), as the only product[23] (Scheme 22).

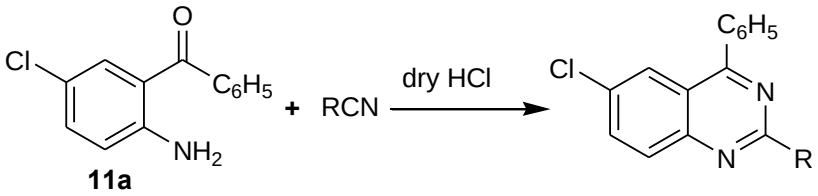


Scheme 22

The plausible explanation and proof for the reaction mechanism has been discussed in details in section **5** in the later part of this review.

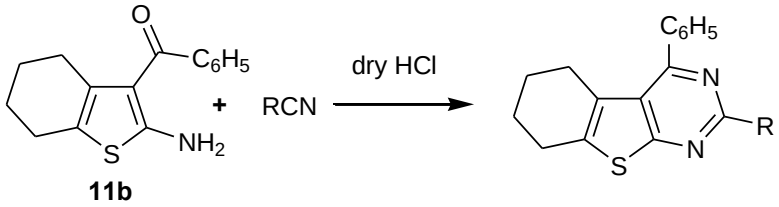
4.2. Synthesis of Condensed 4-Arylpyrimidines

The hydrogen chloride catalyzed condensation has been found applicable to the synthesis of certain fully aromatic condensed pyrimidines by the reaction of *ortho*-aminoketones with nitriles. Thus, 2-amino-5-chlorobenzophenone (**11a**) has been reacted with aliphatic and aromatic nitriles to obtain the corresponding 2-substituted 4-phenyl-6-chloroquinazolines[23] (Scheme 23).



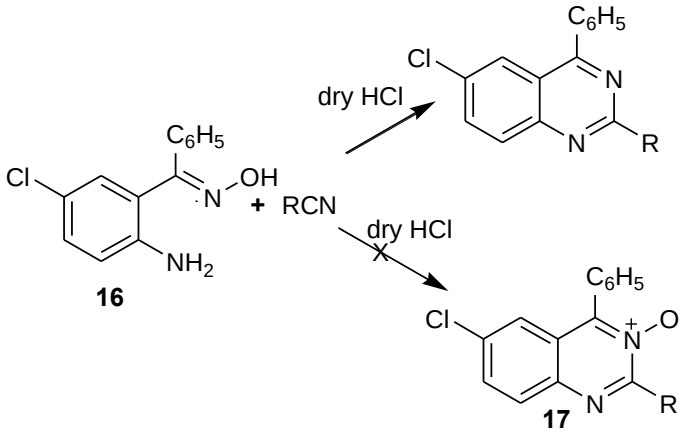
Scheme 23

Similarly, 4-phenylthienopyrimidines have been obtained through the reaction of 2-amino-3-benzoylthiophenes (**11b**) with various nitriles[23] (Scheme 24).



Scheme 24

The condensation of *o*-aminoketoxime (**16**) with nitriles was found to yield the condensed 4-arylpyrimidines *via* the elimination of hydroxylamine, rather than the expected condensed 4-arylpyrimidin-*N*-oxides (**17**)[23] (Scheme 25).

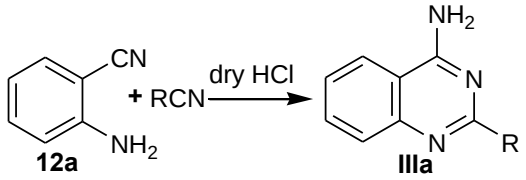


Scheme 25

4.3. Synthesis of Condensed 4-Aminopyrimidines

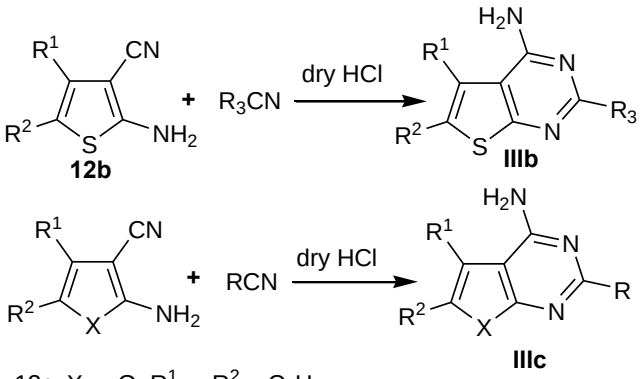
This facile, dry HCl gas catalyzed one-pot synthesis of condensed pyrimidin-4(3*H*)-ones has been further extended to obtain condensed 4-aminopyrimidines through the reaction of nitriles with a variety of

o-aminonitrile substrates. Thus, anthranilonitrile (**12a**) has been reacted with nitriles; acetonitrile, benzylcyanide and benzoylacetonitrile in presence of hydrogen chloride gas to give the corresponding 2-substituted 4-aminoquinazolines (**III**) in 40-65% yields[29,41] (Scheme 26) (Table 6).



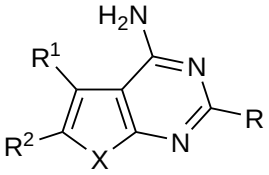
Scheme 26

A host of nitriles has been found to react smoothly to give condensed 4-aminopyrimidines in good yields. Thus, the HCl (g) catalyzed reaction of nitrile with *o*-aminonitriles, for the synthesis of condensed pyrimidines can be said to be quite general in its scope. This hydrogen chloride catalysed condensation of nitriles, especially acetonitrile, benzonitrile, phenylacetonitrile, as well as, heteronitriles like alkylthiocyanates, dialkyl and monoaryl cyanamides with thiophene *o*-aminonitriles, furan *o*-aminonitriles and pyrrole *o*-aminonitriles (**12b-d**) has been found to give the corresponding 2-substituted condensed 4-aminopyrimidines derivatives (Table 6) in good yields[29,31] (Scheme 27).

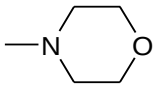
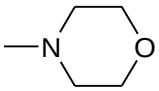


Scheme 27

Table 6. Condensed 2-substituted 4-amino[2,3-*d*]pyrimidines

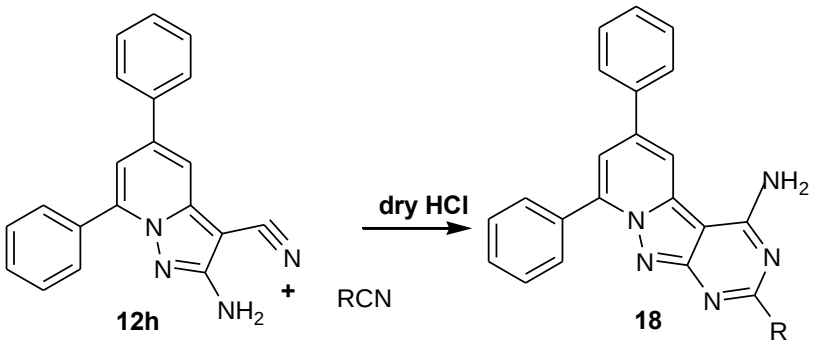


R^1	R^2	R	X	Yield (%)	R. Solv.	Reference
H	H	Me	-HC=CH-	63	Ea-Ch	29
H	H	$-CH_2C_6H_5$	-HC=CH-	40	Ea-Ch	29

H	H	$-CH_2OC_6H_5$	-HC=CH-	40	E	29
$-(CH_2)_4-$		Me	S	50	B	29
$-(CH_2)_4-$		$-CH_2C_6H_5$	S	43	B	29
$-(CH_2)_4-$		$-C_6H_5$	S	47	B	29
$-(CH_2)_4-$		-SMe	S	84	I	29
$-(CH_2)_4-$			S	40	C-H	29
$-(CH_2)_4-$		$2\text{-}C_5H_4N$	S	40	B-M	29
$-(CH_2)_4-$		$-NHC_6H_5$	S	33.8	E	31
$-(CH_2)_4-$		$-NHC_6H_4Me\text{-}2$	S	55.2	E-C	31
$-(CH_2)_4-$		$-NHC_6H_4Me\text{-}4$	S	41.8	E	31
$-(CH_2)_4-$		$-NHC_6H_4OMe\text{-}2$	S	61.3	E	31
$-(CH_2)_4-$		$-NHC_6H_4OMe\text{-}4$	S	61	E	31
$-(CH_2)_4-$		$-NHC_6H_4OEt\text{-}4$	S	58.8	E-C	31
$-(CH_2)_4-$		$-NHC_6H_4Cl\text{-}3$	S	40	E-C	31
$-(CH_2)_4-$		$-NHC_6H_4Cl\text{-}2$	S	51.5	E-C	31
$-(CH_2)_4-$		$-NHC_6H_4Br\text{-}4$	S	56.1	E-C	31
$-(CH_2)_4-$		-SEt	S	68	B-H	41
$-(CH_2)_4-$		$-SC_3H_7$	S	79	B-H	41
$-(CH_2)_4-$		$-SC_4H_9$	S	84	B	41
$-(CH_2)_4-$		$-SCH_2C_6H_5$	S	70	B	41
Me	Me	-SMe	S	66	I	29
Me	Me		S	35	B-H	29
Me	Me	$-SC_3H_7$	S	83	I	41
Me	Me	$-SC_4H_9$	S	72	I	41
Me	Me	$-SCH_2C_6H_5$	S	71	E-C	41
$-(CH_2)_5-$		$-SCH_2C_6H_5$	S	56	E-C	41
$-C_6H_5$	$-C_6H_5$	Me	O	68	B	29
$-C_6H_5$	$-C_6H_5$	$-C_6H_5$	O	47	B-M	29
$-C_6H_5$	$-C_6H_5$	$-CHCl_2$	O	55	B-H	29
$-C_6H_5$	$-C_6H_5$	$-CO_2Et$	O	35	B-H	29

B=benzene, C = chloroform, Ch =cyclohexane, D = dimethylformamide, E =ethanol, Ea =ethylacetate, H = hexane, I = isopropanol, M = methanol

Molina and co-workers[42] have reacted pyridopyrazole *o*-aminonitrile (**12h**) with aliphatic nitriles to yield the corresponding 2-substituted 4-aminopyrazolopyrimidines (**18**) (Scheme 28).

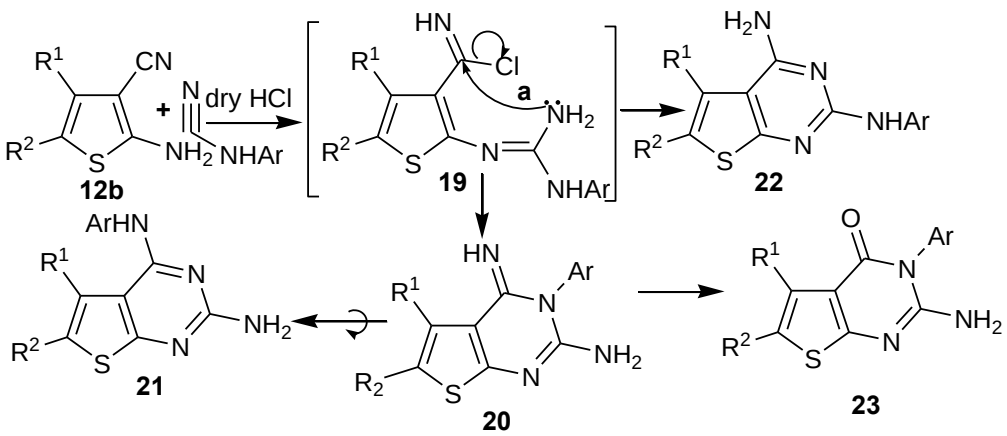


Scheme 28

Interestingly, when mono arylcyanamides were reacted with thiophene *o*-aminonitriles under the influence of dry HCl gas, a mixture of two products was obtained. The major product was 2-amino-3-aryl-4-iminothieno[2,3-*d*]pyrimidine (**20**), while the minor product was 2-amino-3-arylthieno[2,3-*d*]-pyrimidin-4(3*H*)-one (**23**) (Scheme 29).

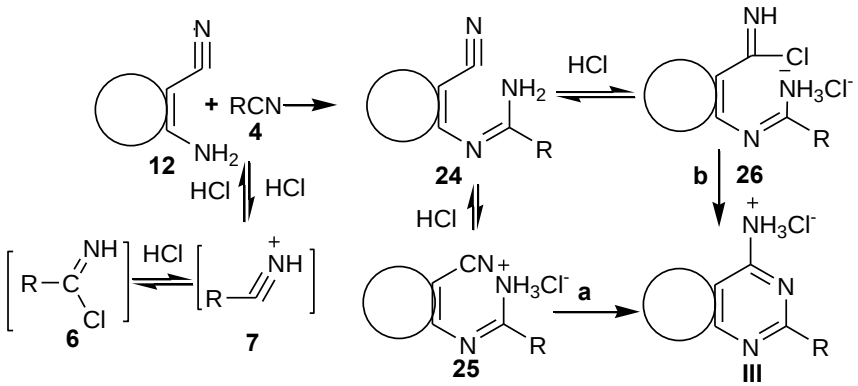
The proposed reaction mechanism envisages the possibility of the formation of three isomeric 2,4-diamoaminothieno[2,3-*d*]pyrimidines (**20**-**22**), of these **20** and **22** could be formed through the alternate modes of cyclization of the guanidine intermediate (**19**) and **21** through the Dimroth rearrangement of **23**. However, the structural proof to the actual products was given through the unequivocal synthesis of three isomeric 2,4-diamoaminothieno[2,3-*d*]pyrimidines (Table 6) as well as, the 2-amino-3-arylthieno-[2,3-*d*]pyrimidin-4(3*H*)-ones (Table 5).[30] Compound (**23**), is infact the artifact of the reaction, arising through the hydrolysis of (**20**), during the workup.

A plausible explanation[27,43] for the reaction mechanism involved in the condensation of an *o*-aminonitrile substrate (**12**) and a nitrile under the influence of dry HCl gas to yield a 2-substituted condensed 4-aminopyrimidine (**III**) is also discussed below.



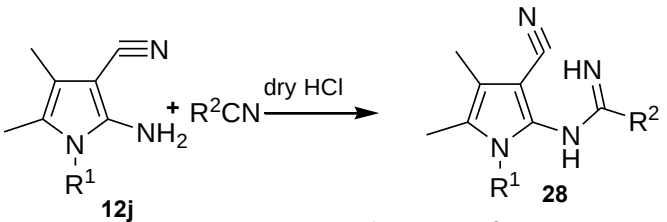
Scheme 29

These reactions, possibly, proceed through a *o*-cyanoamidine intermediate (**24**) formed by the nucleophilic attack of the amino nitrogen on the *N*-protonated nitrilium species **7**, as the imidoyl halide, hydrohalide (**6**). The *o*-cyanoamidine intermediate undergoes intra-molecular cyclization through the nucleophilic attack by the amidine nitrogen on the carbon to yield the condensed 4-aminopyridine (**III**) as the observed product (path 'a'). The intramolecular cyclisation of *o*-cyanoamidine (**24**) is facilitated by the protonation of the cyano function (**25**) under the reaction conditions employed. Such *ortho* functionalised amidines have been presumed to be the intermediates in a variety of condensed pyrimidine synthesis through the reaction of *o*-aminocarbonyl derivatives with imidoyl derivatives. In view of the known tendency of the nitriles to form imidoyl halides in the presence of halogen acids, an alternate pathway involving the formation of *o*-amidinoimidoyl chloride (**26**) and its intramolecular cyclisation to condensed 4-aminopyrimidines (**III**) also seems plausible (path 'b') (Scheme 30).



Scheme 30

Eger *et al*.[44] have also isolated such amidine intermediate **28** in reaction of trimethylpyrrole *o*-aminonitrile **12j** with cyanamide and acetonitrile (Scheme 31).

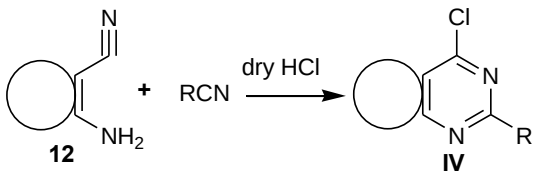


$R^1 = C_6H_5$, $R^2 = NH_2$
$R^1 = CH(Me)C_6H_5$, $R^2 = NH_2$
$R^1 = CH(Me)C_6H_5$, $R^2 = Me$

Scheme 31

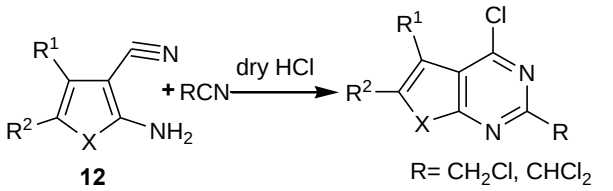
4.4. Synthesis of Condensed 4-Chloropyrimidines

In some of the reactions of *o*-aminonitriles with nitriles in presence of dry hydrogen chloride, interestingly condensed 4-chloropyrimidine (**IV**) has been found to be the sole product formed (Scheme 32).



Scheme 32

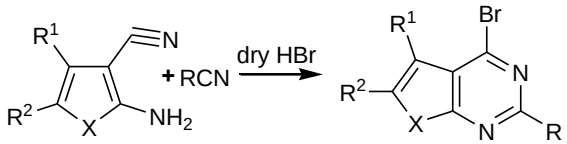
For example, the reaction of chloroacetonitrile and dichloroacetonitrile with **12a** in presence of excess of dry hydrogen chloride gas has been found to yield 4-chloro-2-chloromethylquinazolines in 85% yield. Surprisingly the expected 4-amino-2-chloromethylquinazoline was found to be totally absent.[29,43] Similarly, this hydrogen chloride catalysed condensation of active nitriles, especially, chloroacetonitrile and dichloroacetonitrile with thiophene *o*-aminonitriles (**12b**) and furan *o*-aminonitriles (**12c**) has been found to give the corresponding condensed 2-substituted 4-chloropyrimidines derivatives in good yields[29] (Scheme 33).



a, R^1 = R^2 = H, X = -CH=CH-;
b, R^1 = R^2 = Me, X = S; R^1, R^2 = -$(CH_2)_4$-, X = S;
c, R^1 = R^2 = C_6H_5, X = O

Scheme 33

Interestingly, when chloroacetonitrile and dichloroacetinitrile are reacted with anthranilonitrile (**12a**), thiophene *o*-aminonitriles (**12b**), furan *o*-amino nitrile (**12c**), as well as, 3-amino-2-cyanopyridothiophene (**12k**) in presence of dry HBr gas. The corresponding condensed 2-substituted 4-bromopyrimidine is the sole product[45] (Scheme 34).

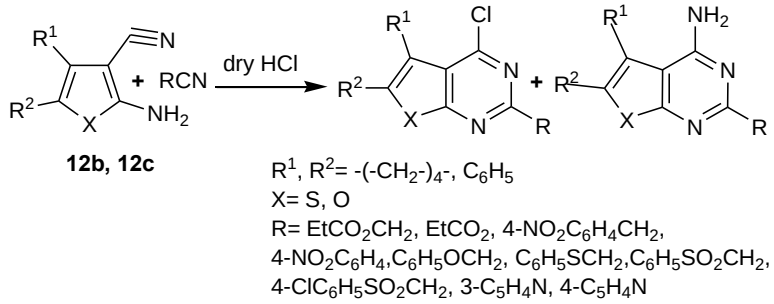


R^1 = R^2 = H, Me, C_6H_5, R^1, R^2 = -$(CH_2)_4$-,
X = -CH=CH-, S, O; R = CH_2Cl, $CHCl_2$

Scheme 34

In contrast to the exclusive formation of condensed 2-substituted 4-chloropyrimidines as seen particularly in the reactions of mono and dichloroacetonitriles with various *o*-aminonitrile substrates, the condensation of the nitriles bearing moderately electron withdrawing groups, such as ethyl cyanoacetate, ethyl cyanoformate, phenylthioacetonitrile, phenoxyacetonitrile, phenylsulphonylacetonitrile, 4-nitrobenzo-nitrile, 4-nitrobenzyl cyanide, 3-cyanopyridine and 4-cyanopyridine, with thiophene *o*-aminonitriles (**12b**)

and furan *o*-aminonitrile (**12c**) has been found to give a mixture of the corresponding condensed 2-substituted 4-amino- and 4-chloropyrimidines[29] (Scheme 35).

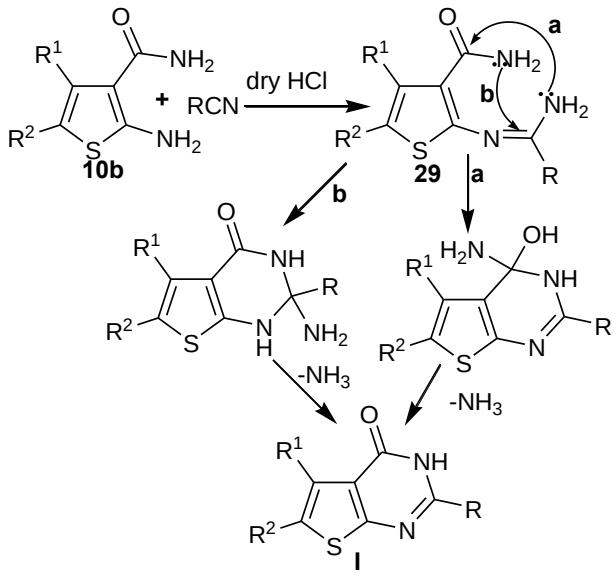


Scheme 35

5. INVESTIGATIONS INTO THE REACTION MECHANISMS FOR PRODUCT FORMATION, DISPROPORTIONATIONS, AS WELL AS, ISOLATION AND CYCLIZATIONS OF INTERMEDIATES INVOLVED

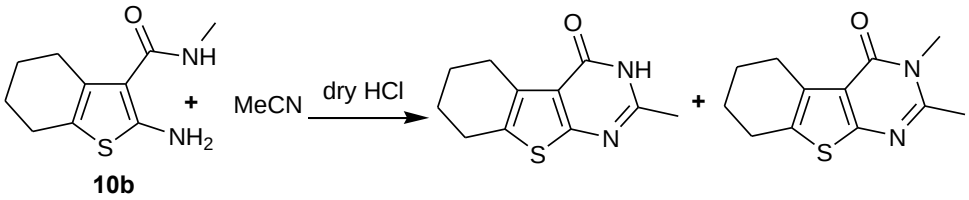
5.1. The isolation of Amidine Intermediates in the Synthesis of Condensed 4-Oxopyrimidines and their Dry HCl Gas Catalyzed Cyclization to Condensed 2,3-Disubstituted thieno[2,3-*d*]pyrimidin-4-ones and Condensed 3-Unsubstituted-thieno[2,3-*d*]pyrimidin-4(3*H*)-ones

The reaction of 2-aminothiophene-3-carboxamide (**10b**) with acetonitrile and benzonitrile in presence of dry HCl has been found to yield the corresponding 2-substituted thieno[2,3-*d*]pyrimidin-4(3*H*)-ones (**I**). These pyrimidines could conceivably arise by the loss of ammonia from the amidine intermediate (**29**), by either of the pathways involving the nucleophilic attack by the amidine nitrogen on the amide carbonyl group (path ‘a’) or through the nucleophilic attack of the amide nitrogen on the amidine carbon (path ‘b’) (Scheme 36).



Scheme 36

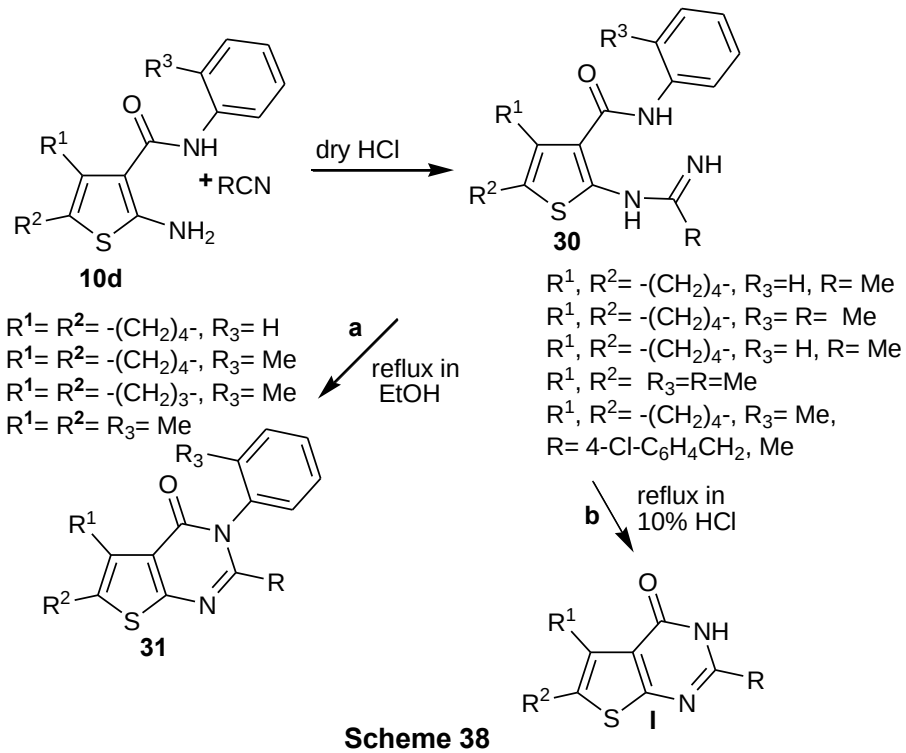
The fact that the reaction of *o*-amino *N*-methylcarboxamide (**10b**) with acetonitrile leads to the exclusive formation of 3-*N*-unsubstituted thienopyrimidin-4(3*H*)-one and not to 3-*N*-methyltheinopyrimidin-4(3*H*)-one indicates that the reaction with the amides, presumably proceeds by the pathway 'a' involving the loss of NH_3 from the amide function[28] (Scheme 37).



Scheme 37

The condensation reaction of *o*-aminocarbonyl substrate with nitriles, presumably, proceeds by the nucleophilic addition of the amino group of the substrate to the nitrile or to a reaction species derived from the nitriles to yield the *o*-functionalized amidine intermediate, which undergoes intramolecular cyclisation to yield the pyrimidine.

Generally, such intermediates are not isolated due to their unstable nature. However, isolation of such amidine intermediates (**30**), has been reported in the reaction of thiophene *o*-aminoanilides (**10d)** with nitriles under acidic conditions[28] (Scheme 38).



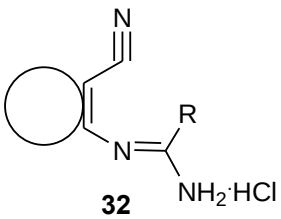
Scheme 38

These intermediate amidines (**30**) when heated in absolute ethanol (path 'a') have been found to give the 2,3-disubstituted thieno[2,3-*d*]pyrimidin-4(3*H*)-ones (**31**), while on heating in acidic media they have been found to yield the 3-unsubstituted thieno[2,3-*d*]pyrimidin-4(3*H*)-ones (**I**).[28]

5.2. The isolation of Amidine Intermediates and their Dry HCl Gas Catalyzed Cyclization to Mononuclear 4-Chloropyrimidines

A perusal of the comparative yields of the condensed 4-aminothienopyrimidines (**III**) and 4-chlorothienopyrimidines (**IV**) obtained in the reaction of various nitriles including acetonitrile and substituted acetonitriles etc. with thiophene *o*-aminonitrile indicates that 4-chlorothienopyrimidine formation can be observed in the reactions of thiophene-*o*-aminonitrile with nitriles possessing strong electron withdrawing substituent. Moreover, it appears that the yield of 4-chlorothienopyrimidine increases progressively with an increase in the –I effect of the substituent, reaching maximum with dichloroacetonitrile.

Thus, the product formation in these reactions appears to depend upon the reactivity of amidine carbon of the *o*-cyanoamidine intermediate (**32**) towards nucleophilic attack which in turn can be expected to depend upon the nature of the nitrile component employed in the condensed pyrimidine synthesis. The formation of condensed 4-chloropyrimidines (**IV**) in the reaction of nitriles, possessing electron withdrawing substituent with *o*-aminonitriles (**12**) can be attributed to a low electron density at the amidine carbon of the *o*-cyanoamidine (**32**) intermediate because of the electron withdrawing effect of the substituent, which makes amidine carbon prone to nucleophilic attack by the incipient imidoyl nitrogen.



32

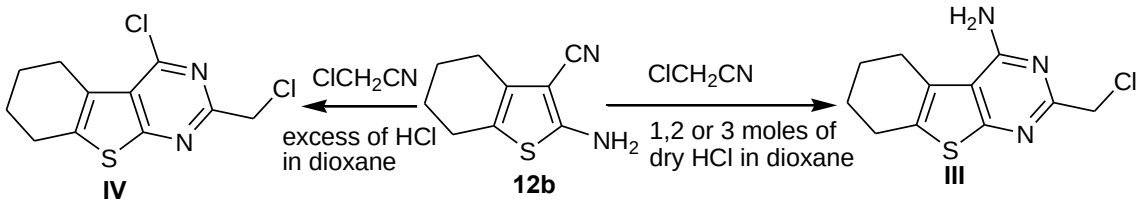
On the other hand, the nitriles, which do not possess an electron withdrawing substituent, lead to an amidine intermediate with a higher electron density at the amidine carbon, therefore an alternative pathway involving the nucleophilic attack of the amidine nitrogen on the cyano or imidoyl carbon predominates to yield the condensed 4-aminopyrimidine, (**III**).

It has been found that changes in reaction temperature and rate of flow of hydrogen chloride, do not affect either the nature of the product or its yield. Nor the solvent of the reaction has any influence on the product nature or disproportionation.

However, it has been observed that the amount of hydrogen chloride does play some role in influencing the nature of product formed. Thus, in a set of experiment the condensation of equimolar quantities of thiophene *o*-aminonitrile and chloroacetonitrile was affected by employing dry HCl in different molar quantities.

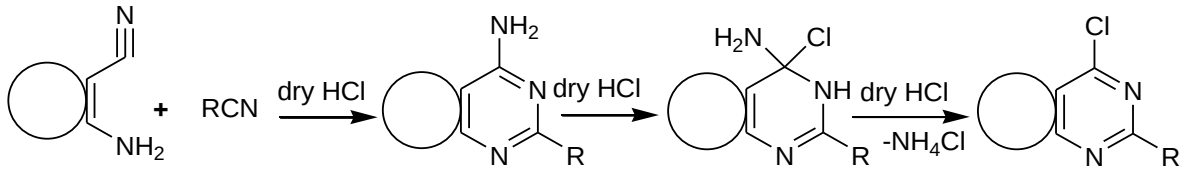
With 1, 2 and 3 molar equivalents of a solution of dry HCl in dioxane, the product of the reaction was not the 4-chlorothienopyrimidine, but instead, the 4-aminothienopyrimidine. Addition of further excess of dry

HCl, however, led to the formation the 4-chloropyrimidine (Scheme 39).



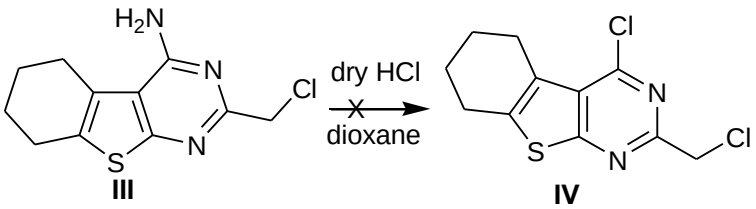
Scheme 39

The above observations indicated the possibility of the formation of 4-chloropyrimidine through the 4-aminopyrimidine in the presence of excess of dry HCl gas, by the addition-elimination of HCl and NH_4Cl (Scheme 40).



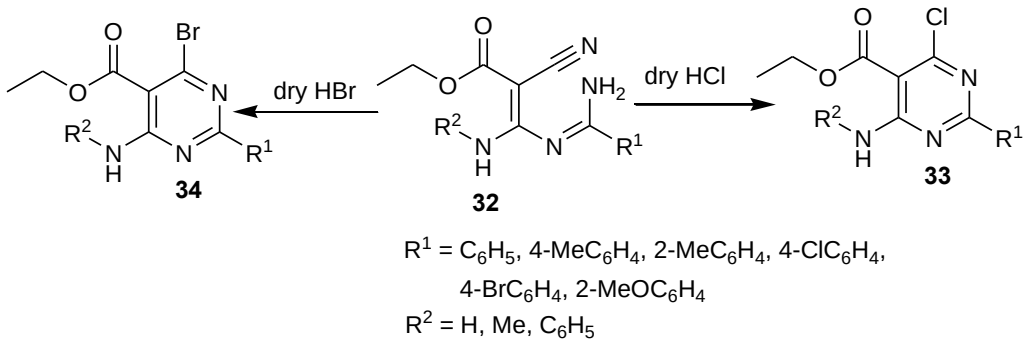
Scheme 40

However, the possibility of the 4-aminopyrimidine as an intermediate in the formation of 4-chloropyrimidine has been excluded experimentally by bubbling excess of dry HCl gas through the solution of the preformed 4-aminothienopyrimidine in dioxane, under same standard reaction conditions. The workup of the reaction mixture didn't yield the expected 4-chlorothienopyrimidine, instead the unchanged 4-aminopyrimidine was recovered (Scheme 41).



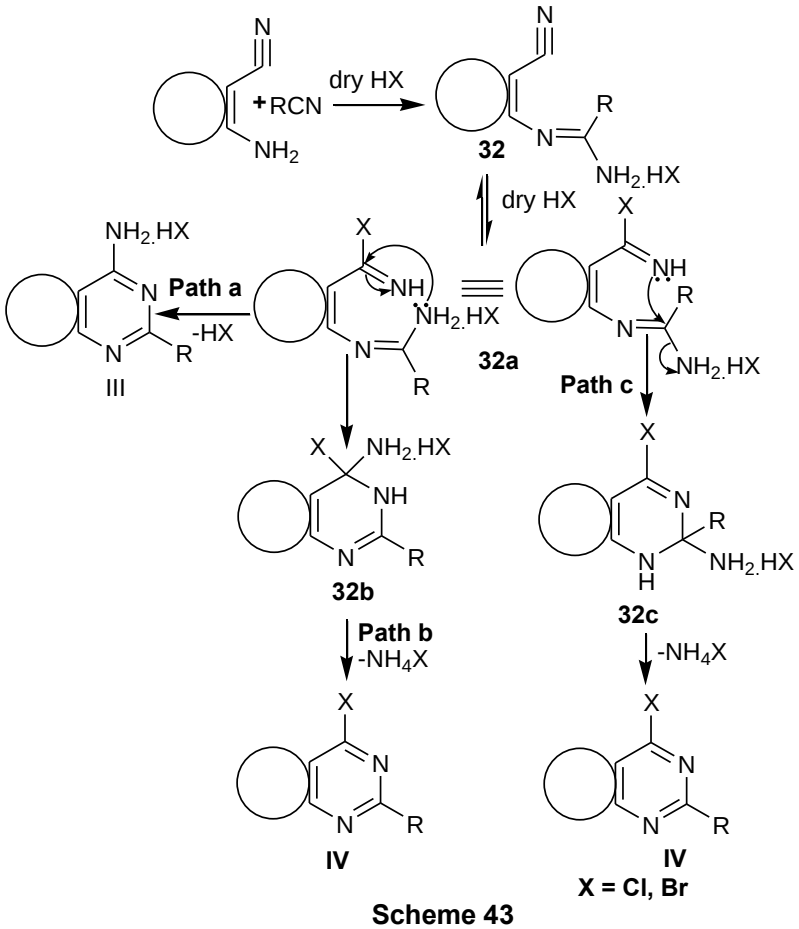
Scheme 41

This one-pot formation of 4-chloropyrimidines is indeed novel, especially, in view of the fact that 4-chloropyrimidines are normally prepared through multistep synthesis, involving the preparation of the corresponding 4-oxopyrimidine, followed by its chlorination with $POCl_3$. The formation of 4-chloropyrimidines presumably proceeds through the transient *o*-cyanoamidine intermediates, (**32**), especially in view of the demonstrated isolability and also the cyclization of acyclic analogs of *o*-cyanoamidines, namely the *N*-(cyanovinyl)amidines (**32**) to 4-chloropyrimidines (**33**) and 4-bromopyrimidines (**34**) in the presence of hydrogen chloride and hydrogen bromide, respectively, under essentially the same condition[45,46] (Scheme 42).



Scheme 42

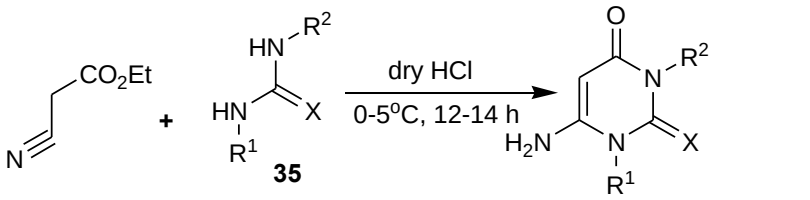
On these lines, a plausible mechanism has been proposed[29,45,46] for the formation of condensed functionalised 4-halopyrimidines (**33** or **34**) in these reactions under the influence of dry HCl or HBr gas. It appears reasonable to assume that under the reaction conditions employed, the CN groups of both, the substrate, *o*-aminonitrile and the nitrile are activated by protonation or by the formation of hydrogen halide adducts. The initial condensation between the two components or their activated forms can be expected to result in the formation of the amidine hydrohalide or its hydrohalide adduct. Assuming that the imidoyl halide derivatives is the common intermediate, the formation of 4-aminopyrimidines (**III**), can take place by **path a** from the cyclic adduct and that of the 4-halopyrimidines (**IV**) by the **path b** or **path c** (Scheme 43).



Scheme 43

6. SYNTHESIS OF VARIOUS MONONUCLEAR PYRIMIDINES UNDER INFLUENCE OF DRY HCl GAS

This novel reaction has been extended to the synthesis of monocyclic pyrimidines. Thus, ethyl cyanoacetate has been condensed with monoaryl and diaryl thioureas **35** to yield 6-amino-1-aryl and 6-amino-1, 3-diaryl thiouracils.[47,48] (Scheme 44)



R^1= H, 3-MeC_6H_4, 3-ClC_6H_4, C_6H_5, 4-MeC_6H_4, 2-MeC_6H_4, 4-ClC_6H_4, 2-ClC_6H_4, 4-$MeOC_6H_4$, 2-$MeOC_6H_4$

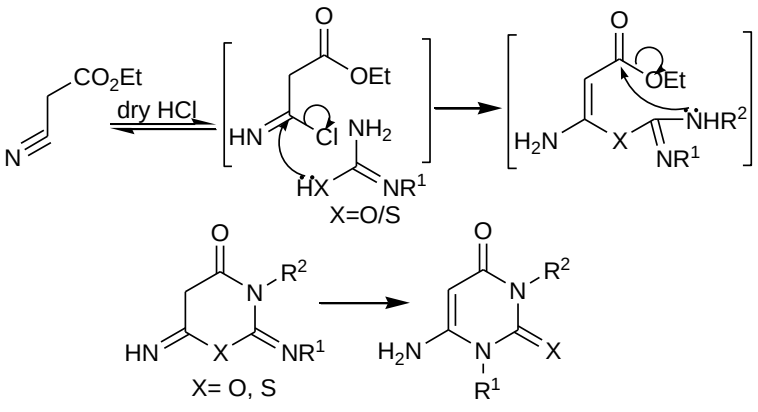
R^2= H, 3-MeC_6H_4, 3-ClC_6H_4

X= S, O

Scheme 44

Novel series of 6-amino-1,3-diaryl-2-thiouracils, 6-aminouracil, 6-amino-2-thiouracil, 6-amino-1-aryluracils and 6-amino-1-aryl-2-thiouracils were synthesized[47] through the dry HCl catalyzed cycolcondensation of ethyl cyanoacetate with *s*-diarylthioureas, urea, thiourea, monoarylureas and monoarylthioureas, respectively. The reaction involves the condensation of ethyl cyanoacetate with an appropriate urea or thiourea in the presence of dry HCl gas in dioxane at 0-5 °C for 12-14 hours. However, ethyl cyanoacetate failed to react with 1,3-diarylureas may be due to weaker nucleophilicity of the latter.

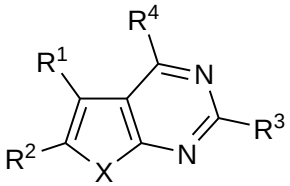
As an extension, on similar condensation benzoylacetonitrile with simple thiourea yielded 6-amino-4-phenyl-2-thioxopyrimidine.[47] Ethyl cyanoacetate reacts with ureas and thioureas presumably through the initial nucleophilic attack of the sulphur or oxygen atom of urea or thiourea on the protonated nitrile or imidoyl halide to yield imino oxide or sulphide intermediate, followed by its intramolecular cyclization through the corresponding oxazine or thiazine. The oxazine or thiazine intermediate may then under go a Dimroth rearrangement under the reaction condition to yield then corresponding 6-aminouracils or 6-amino-2-thiouracils[48] (Scheme 45).



Scheme 45

7. SYNTHESIS OF CONDENSED 4-OXOPYRIMIDINES BY NOVEL ACID CATALYZED MICROWAVE ASSISTED REACTION OF NITRILES WITH *O*-AMINOESTERS UNDER SOLVENT FREE CONDITIONS.

Encouraging results in the MWI based syntheses of thiophene *o*-aminoesters involving Gewald reaction,[49] as well as, thienopyrimidine bioisosteres of gefitinib[50] under microwave irradiation conditions, prompted us to exploit MWI to be extended to the one-pot cyclocondensation of the nitriles with various *o*-aminoester substrates under solvent free conditions for generating compound libraries of condensed pyrimidines (**36**).

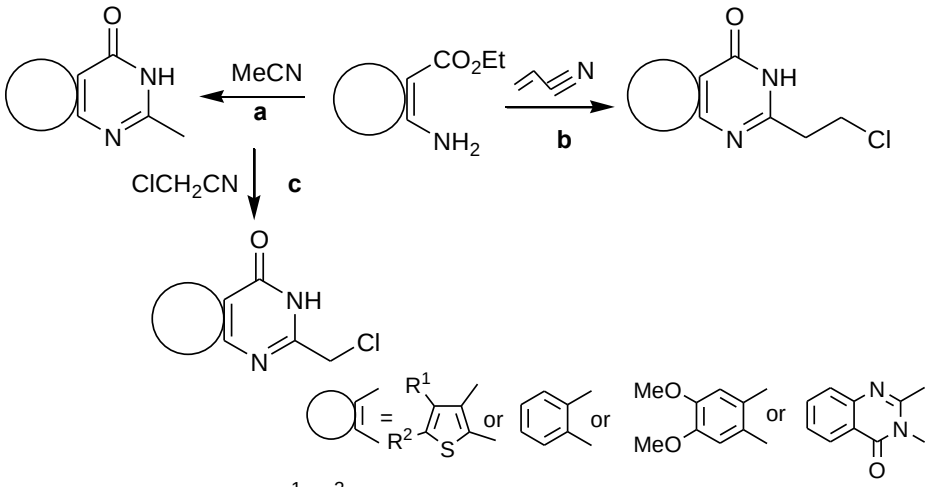


36

X = S, -CH=CH-
R^1, R^2 = H, alkyl, aryl, cycloalkyl,
carboalkoxy,carbocyclic, heterocyclic, *etc*

A novel microwave assisted green synthesis of the bioactive condensed 2-substituted pyrimidin-4(3*H*)-ones (**I**) under solvent free conditions has been reported for the first time.[51] The unusually rapid synthetic methodology involves the cyclocondensation of a variety of nitriles with *o*-aminoesters of benzene (**9a**), thiophene (**9b**), quinazolinone (**9g**) and dimethoxybenzene in the presence of catalytic amount of conc. HCl alone or with the Lewis acid, $AlCl_3$. This novel synthesis involving nitriles as the building blocks, under microwave irradiation for these condensed 2-substituted pyrimidin-4(3*H*)-ones requires only 10-75 min as compared to the conventional reaction protocols requiring 6-12 h, thereby showing a significant acceleration in reaction rates (Table 7 and 8) (Scheme 46). The reaction proceeds through the same activated electrophilic nitrile derivatives, the imidoyl halide intermediate & affords the products in yields superior to that by the conventional protocols. Coupled with simple workup procedures and superior yields the methodology is eminently suitable for the generation of diverse libraries of condensed 2-substituted pyrimidin-4(3*H*)-ones employing parallel synthesis procedures.

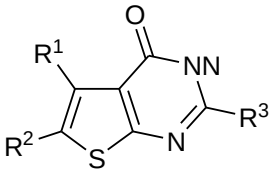
It is therefore really interesting, that this acid catalysed cyclocondensation reaction has been made adaptable to high throughput synthesis, for the generation of diverse libraries of condensed pyrimidines (**36**) with four diversity points for further functionalization, if necessary.



R^1, R^2 = -$(CH_2)_4$-; Me;
R^1, =4-Me-C_6H_4, R_2 = H;
R^1 = Me, R_2 = CO_2Et;
R^1 = C_6H_5, R_2 = H.
Reaction conditions;
a:under microwave irradiation; 350W, 20-75 min (60-94%),
b:under microwave irradiation; 350W, 20-50 min (83-99%),
c:under microwave irradiation; 350W, 10-40 min (66-95%).

Scheme 46

Table 7. 2-Substituted thieno[2,3-*d*]pyrimidin-4(3*H*)-ones

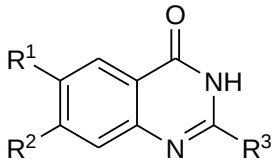


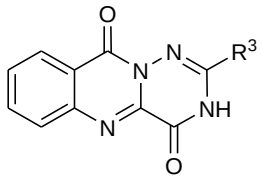
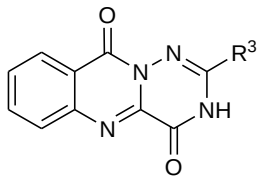
R^1	R^2	R^3	Conventional Method		Microwave-Assisted Method	
			Yield (%)	Time (h)	Yield (%)	Time (min.)
-$(CH_2)_4$-		Me	66	8-10	68	75
Me	Me	Me	76	10-12	89	60
4-MeC_6H_4	Me	Me	93	8-10	94	55
Me	Me	Me	71	8-10	85	40
C_6H_5	Me	Me	69	8-10	75	65
-$(CH_2)_4$-		CH_2CH_2Cl	84	8-10	96*	45
Me	Me	CH_2CH_2Cl	85	20-24	99	50
4-MeC_6H_4	H	CH_2CH_2Cl	91	10-12	92*	35
Me	CO_2Et	CH_2CH_2Cl	85	8-10	88	20
C_6H_5	H	CH_2CH_2Cl	94	8-10	96	45

-$(CH_2)_4$-		CH_2Cl	77	6-8	90	30
Me	Me	CH_2Cl	83	8-10	91	25
4-MeC_6H_4	H	CH_2Cl	88	6-8	93	40
Me	CO_2Et	CH_2Cl	86	6-8	95	10
C_6H_5	H	CH_2Cl	90	6-8	91	35

** Catalytic amount of anhydrous $AlCl_3$ was added to the reaction mixture*

Table 8. Other condensed 2-substituted pyrimidin-4(3*H*)-ones



R^1	**R^2**	**R^3**	**Conventional Method**		**Microwave-Assisted Method**	
			Yield (%)	**Time (h)**	**Yield (%)**	**Time (min.)**
H	H	Me	70	8-10	80	45
OMe	OMe	Me	62	8-10	70	45
		Me	52	8-10	71	20
H	H	CH_2CH_2Cl	80	8-10	83	30
H	H	CH_2Cl	90	6-8	94	30
OMe	OMe	CH_2Cl	65	6-8	70	25
		CH_2Cl	53	8-10	66	20

8. SCOPE AND LIMITATIONS

The synthesis of condensed 2-substituted pyrimidines is in general carried out by initially introducing the appropriate *o*-aminocarbonyl substrate and a nitrile into a suitable solvent like dry dioxane and then

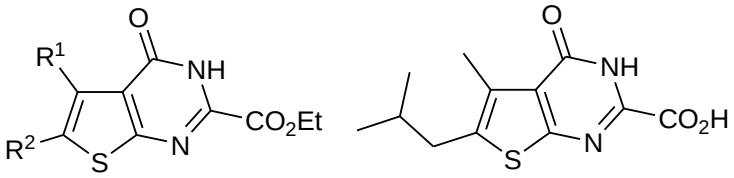
passing a stream of dry hydrogen chloride gas under ambient temperature through the reaction mixture. However, it is possible to significantly increase reaction yield and purity of reaction product and further to shorten the reaction time if initially an excess of acid is dissolved in the solvent, preferably the solvent is saturated with the acid.

An excess of acid is an amount of acid so large that after quantitative reaction of compounds subsequent precipitation as salt unbound acid still remains in this solution. This amount of acid is to be already present in the reaction mixture at the start of reaction. It has proved to be appropriate for the solvent to be selected from the group consisting of ethers, esters, alcohols, formamides, carboxylic acid, but particularly important and suitable solvent is dioxane.

The acids are suitably selected from the group consisting of Bronsted acids and Lewis acids in particular hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, particularly suitable are gaseous acids *e.g.*, hydrogen chloride.

The reaction is suitably carried out at temperature of from -10 ^{o}C to 100 ^{o}C, preferably 0 ^{o}C to 60 ^{o}C, in particular 10 ^{o}C to 50 ^{o}C. The addition of acid to the mixture is continued during the reaction. Thus, it is possible to achieve nearly quantitative precipitation of compound as salt of acid.

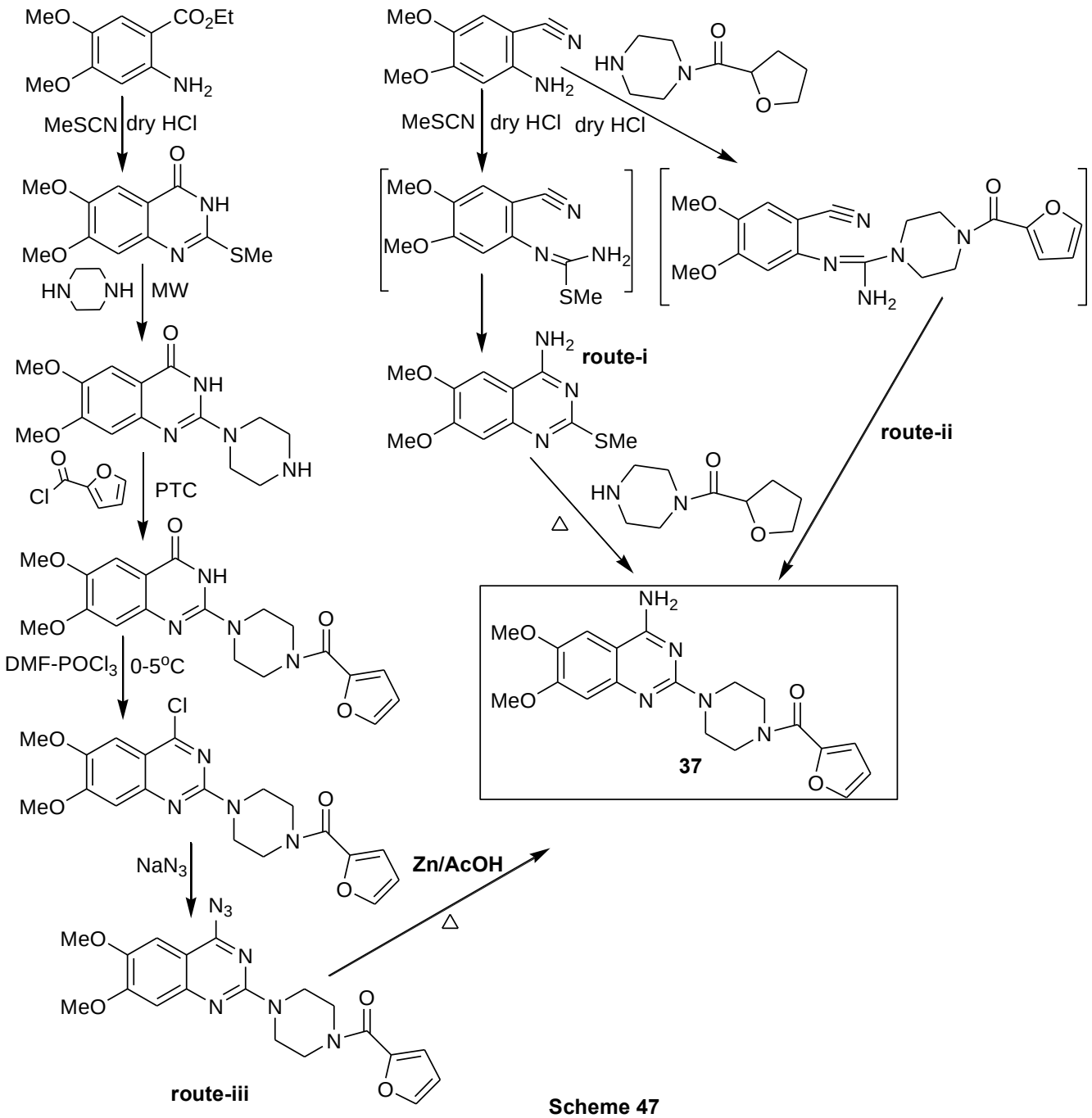
Madding & co-workers[39] have reported the synthesis of 3,4-dihydro-4-oxothieno[2,3-*d*]pyrimidine-2-carboxylates *via* the HCl catalysed reactions of thiophene-3-carboxylates with activated nitriles. One of the derivatives, Tiprinast, 3,4-dihydro-5-methyl-6-(2-methylpropyl)-4-oxothieno[2,3-*d*]pyrimidine-carboxylic acid is a proven orally active antiallergic and antiasthamatic drug.



tiprinast

There are three reported routes for the synthesis and manufacture of Prazosin (**37**) a selective α_1-adrenoreceptor antagonist antihypertensive drug. However, these presently used routes are having disadvantages[52,53] (Scheme 47) of very low overall yields of 8-10%, or use of thiophosgene, use of drastic reaction conditions as well as prolonged reaction times and lastly longer and multistep syntheses, which increases the overall cost of the product.

Many of the key steps in this synthesis have been modified and replaced with simpler reactants and drastic reaction conditions have been replaced by this novel nitrile reaction under acidic conditions.[54] Thus, many more uses of this novel reaction can be explored for the syntheses of Active Pharmaceutical Ingradients (API) and drug intermediates as well as specialty fine chemicals.

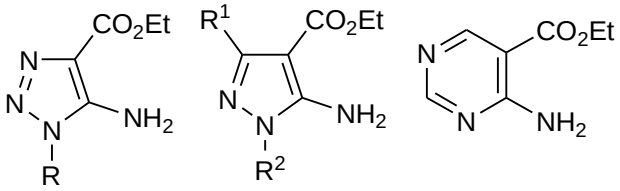


Scheme 47

The potential of this reaction for parallel synthesis by judiciously modifying the reaction conditions to generate novel libraries of NCE's of pyrimidine and condensed pyrimidines is also quite good. With the successful application of MWI in speeding up this reaction, the potential of this reaction for the parallel synthesis of NCE's is much more.

A few limitations to this reaction, especially its failure to proceed to completion with a few typical *o*-aminocarbonyl substrates are noted below.

This one-pot, hydrogen chloride catalyzed reaction has been found to fail with the *o*-amino carbonyl substrates of 1, 2, 3-triazole (**38**), pyrazole (**39**) and pyrimidine (**40**).[56]



38 39 40

9. CONCLUSIONS

Interestingly, this novel and interesting reaction can be explored to prepare a variety of drugs and drug intermediates, through almost one pot condensations and to afford products in good yields as well as purity.

Secondly, the reaction can also be modified suitably in its reaction conditions to be exploited and used for high throughput synthesis of compound libraries[55] for New Drug Discovery Research (N.D.D.R).

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