Current Chemistry Letters 11 (2022) 121–138

Contents lists available atGrowingScience

Current Chemistry Letters

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Synthesis, reactions, and applications of pyrimidine derivatives

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C H R O N I C L E

Article history:
Received June 2, 2021
Received in revised form
June 18, 2021
Accepted August 15, 2021
Available online
August 16, 2021

Keywords:
Pyrimidine
Survey
Synthesis
Derivatives

A B S T R A C T

Pyrimidine compounds continue to attract great interest in the field of organic synthesis due to their various chemical and biological applications observed, especially in recent times. As a result, this review covering some periods from 1957 to 2021 has been prepared to discuss some of the structural pathways of these compounds as well as some of their interactions and applications.

1. Introduction

Pyrimidines ("m-diazine") were known as the breakdown products of uric acid. The first pyrimidine derivative to be isolated was alloxan (5,5-dihydroxypyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione) (**Fig. 1**) in 1818 by Brugnatelli, oxidizing uric acid with nitric acid.[1] Pyrimidines (**Fig. 1**) are the heterocyclic aromatic compounds similar to benzene and pyridine containing two nitrogen atoms at positions 1 and 3 of the six-membered rings. Pyrimidine has one axis of symmetry about the 2-5 axis; it has three different pairs of bond lengths and four different bond angles. Accordingly, in ^{1}H and ^{13}CNMR spectra, the ^{1}H and ^{13}C nuclei are found at three different chemical shifts. Symmetry is lost by unequal substitution at the 4 or/and 6 position.[2] Heterocyclic containing pyrimidine moiety are of great interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activities and clinical applications.[3,4] Heterocyclic compounds containing pyrimidine moiety are gaining the focus in recent research due to their wide range of biological activities such as anti-inflammatory, antioxidant, antimicrobial, antitumor, antiviral, antidepressant, antiplatelet, antihypertensive and herbicidal. Additionally, thienopyrimidine-containing compounds are found in many pharmaceutical medications and as natural products.

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doi: 10.5267/j.ccl.2021.008.002

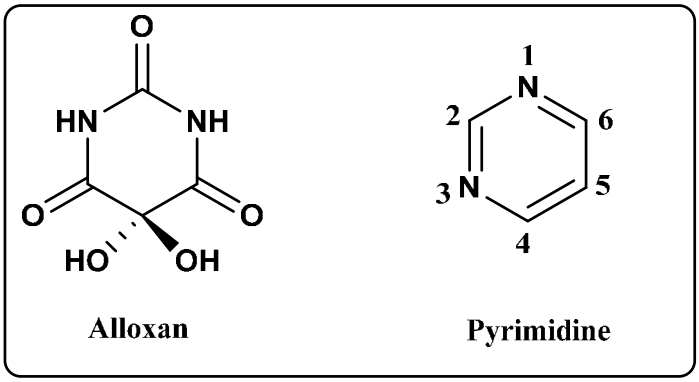
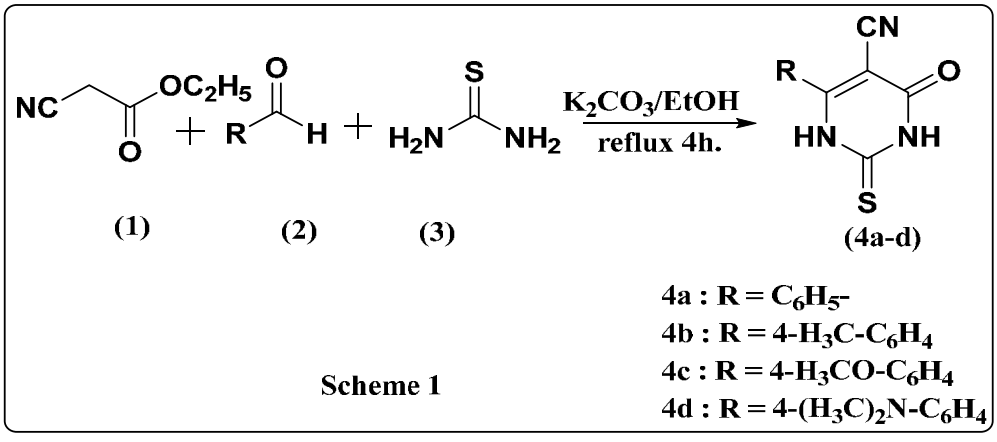


Fig. 1. Structures of alloxan and pyrimidine

2. Synthesis of pyrimidine and its compounds

2.1 From ethyl cyanoacetate.

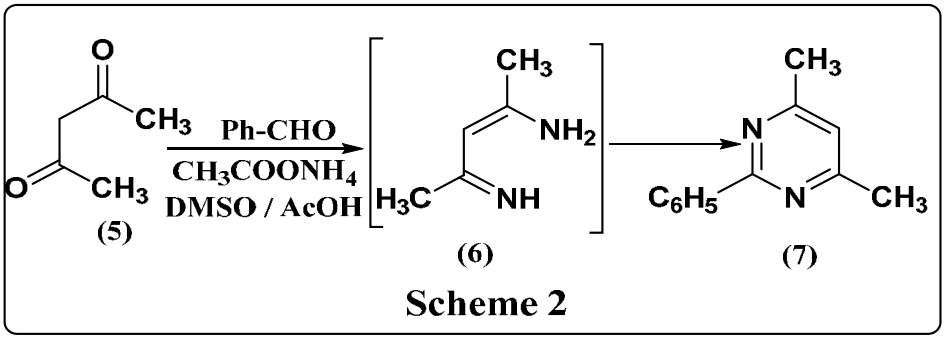
Kambe *et al.* synthesized 5-cyano-4-oxo-6-alkyl(aryl)-2-thioxo-1,2,3,4-tetra hydropyrimidine derivatives **(4a-d)** by the reaction of a mixture of ethyl cyanoacetate **(1)**, aldehyes **(2)** and thiourea **(3)** in the presence of potassium carbonate as a catalyst under condensation reaction (**Scheme 1**).[5]



Scheme 1. Synthesis of pyrimidine derivatives from ethyl cyano acetate

2.2 From acetyl acetone.

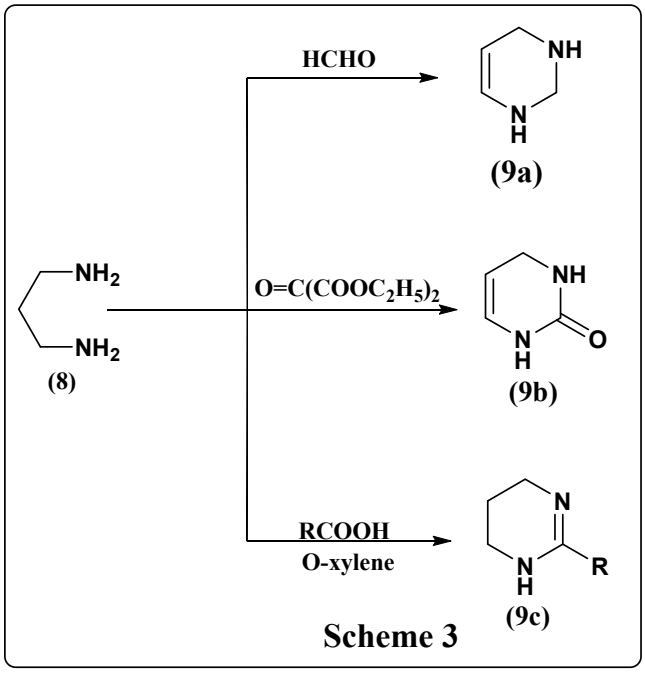
Lweis *et al.* synthesized the pyrimidine derivatives **(7)** by the reaction of acetyl acetone **(5)** and benzaldehyde in the presence of two eq. of ammonium acetate to afford *(Z)*-4-iminopent-2-en-2-amine intermediate **(6)**, then a process of dehydro genation occurs from the latter to afford the primidine derivative **(7)** (**Scheme 2**).[6]



Scheme 2. Synthesis of pyrimidine derivatives from acetyl acetone.

2.3 From 1,3-diaminopropane.

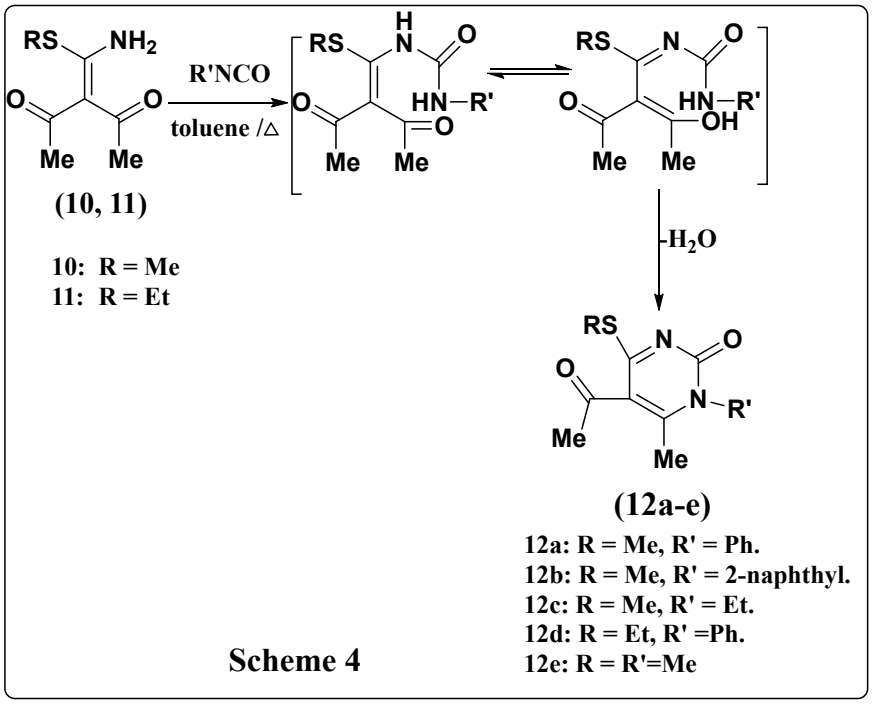
One of the most important methods to synthesize tetrahydro pyrimidine derivatives from 1,3-diaminopropane was reported by Fischer *et al.* and Developed by Grath *et al.* they reacted 1,3-diaminopropane **(8)** with formaldehyde, diethyl carbonate and carboxylic acid to afford the corresponding pyrimidine derivatives **(9a-c)** (**Scheme 3**).[7,8]



Scheme 3. Synthesis of pyrimidine derivatives from 1,3-diaminopropane

2.4 From diacetyl ketene.

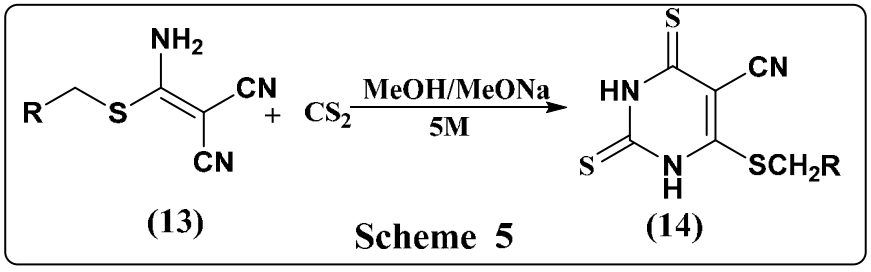
Gordeev *et al.* reported the synthesis of some pyrimidine derivatives from the reaction of 3-(amino(substituted thio)methylene)pentane-2,4-dione **(10, 11)** with isocyanates in the absence of bases to give 4-alkylthio-5-acetyl-l-alkyl(aryl)-6-methyl-1*H*-pyrimidin-2-ones **(12a-e)** in good yields (**Scheme 4**).[9]



Scheme 4. Synthesis of pyrimidine derivatives from diacetyl ketene

2.5 From enaminonitrile.

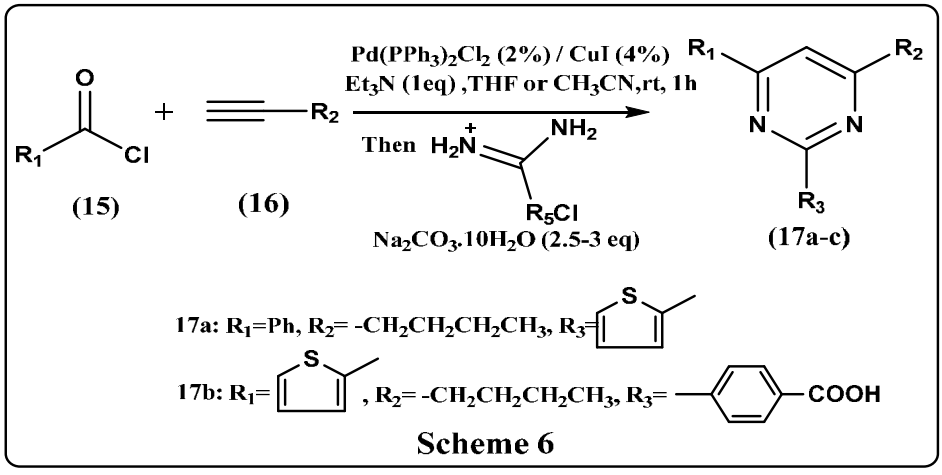
Synthesis of heterosystems containing pyrimidine moiety was reported by Briel *et al.* remains one of the most versatile methods. In their method, enaminonitrile **(13)** was treated with CS_2 in the presence of sodium methoxide to give pyrimidinethione derivative **(14)** (**Scheme 5**).[10]



Scheme 5. Synthesis of pyrimidine derivatives from enaminonitrile

2.6 From alkynes.

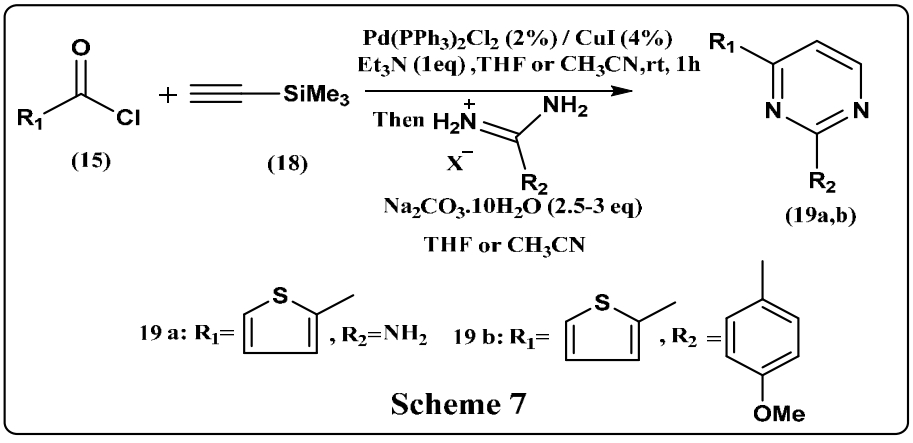
Müller's group developed a method to synthesize pyrimidines by the reaction of acid chlorides **(15)** and terminal alkynes **(16)** under Sonogashira conditions. It represented a straight forward one-pot three-components method to produce 2,4-di- and 2,4,6-trisubstituted pyrimidines **(17a,b)** in moderate to good yields (**Scheme 6**).[11]



Scheme 6. Synthesis of pyrimidine derivatives from alkynes

2.7 From (trimethylsilyl) acetylene.

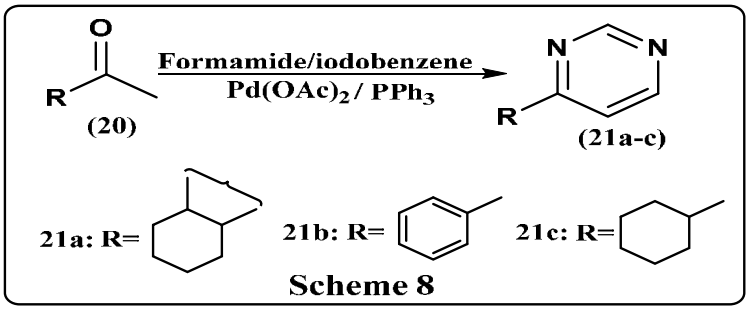
Müller *et al.* developed a method to synthesize 2,4-substituted pyrimidines. By the reaction of (hetero)aroyl chlorides **(15)** with (trimethylsilyl)-acetylene **(18)** in the presence of triethylamine, THF and methyl cyanide under Sonogashira coupling conditions to afford disubstitutedpyrimidines **(19a,b)** (**Scheme 7**).[12]



Scheme 7. Synthesis of pyrimidine derivatives from trimethylsilyl acetylene

2.8 From α-methyl or α-methylene ketones.

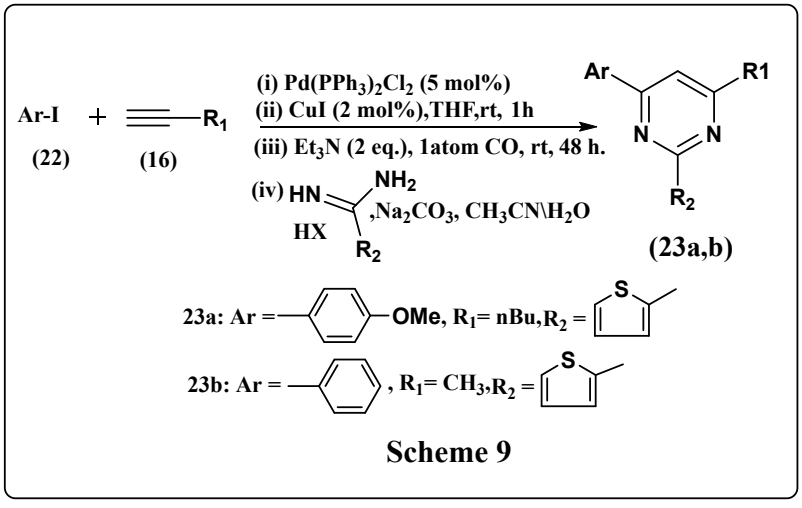
Lejon *et al.* developed a palladium-catalyzed synthesis of pyrimidines **(21a-c)** by the reaction of α-methyl or α-methylene ketones **(20)** with formamide in the presence of palladium (II) acetate and triphenylphosphine (**Scheme 8**).[13]



Scheme 8. Synthesis of pyrimidine derivatives from α-methyl or α-methylene ketones

2.9 From (hetero)aryl iodides

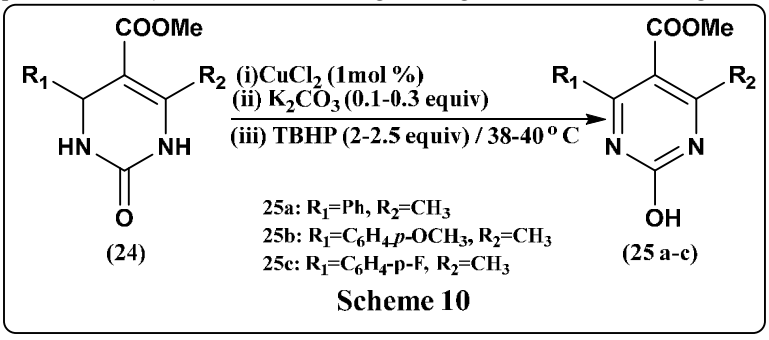
Müller and coworkers developed a method for synthesis of pyrimidine derivatives **(23a,b)**. By the reaction of (hetero) aryl iodides **(22)** and terminal alkynes **(16)** in THF at room temperature under 1 atom of carbon monoxide in the presence of 2 eq. of triethylamine and catalytic amounts of $[Pd(PPh_3)_2Cl_2]$ and CuI for 48 h followed by addition of the amidinium salts in the presence of 2.5 eq. of sodium carbonate in acetonitrile/water gave the 2,4,6-tri substituted pyrimidines **(23a,b)** (**Scheme 9**).[14]



Scheme 9. Synthesis of 2,4,6-tri substituted pyrimidines

2.10 From dihydropyrimidinones.

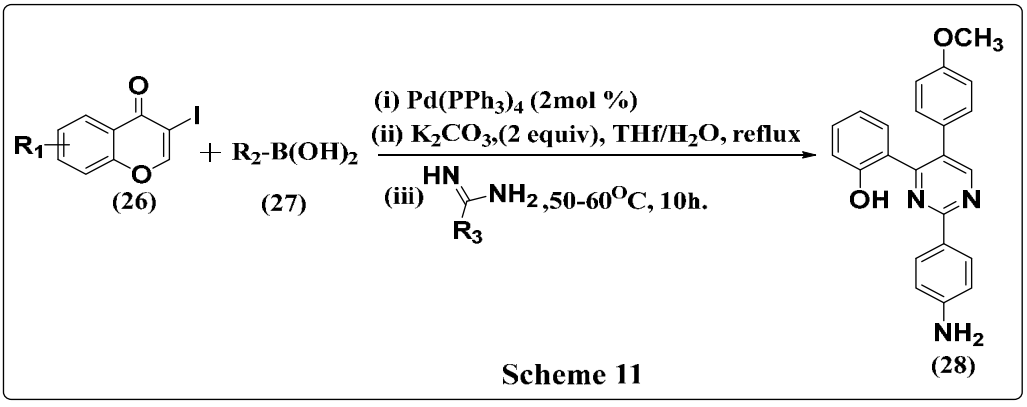
Pyrimidine derivatives **(25a-c)** were synthesized by Yamamoto *et al.* through the oxidation of dihydropyrimidinones **(24)** in the presence of $CuCl_2$, K_2CO_3 and CH_2Cl_2.The suspension was heated at 38 °C and treated with tert-butyl hydroperoxide (70% aqueous solution) over 120 min with vigorous agitation to afford the target compounds (**Scheme 10**).[15]



Scheme 10. Synthesis of pyrimidine derivatives from dihydropyrimidinones

2.11 From iodochromone.

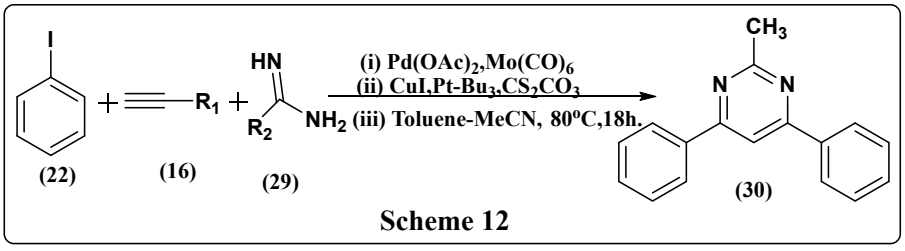
Langer's group reported on the synthesis of 2,4,6-trisubstitutedpyrimidine derivatives by ring transformation reactions of 2-alkylidene tetrahydrofurans with amidines. However, Hu *et al.* developed an efficient method to generate a diversified pyrimidine library *via* a sequential one-pot reaction of iodochromone **(26)**, arylboronic acid **(27)**, and amidine by Suzuki coupling and condensation to give the pyrimidine derivatives **(28)** (**Scheme 11**).[16,17]



Scheme 11. Synthesis of pyrimidine derivatives from iodochromone

2.12 From aryl halides.

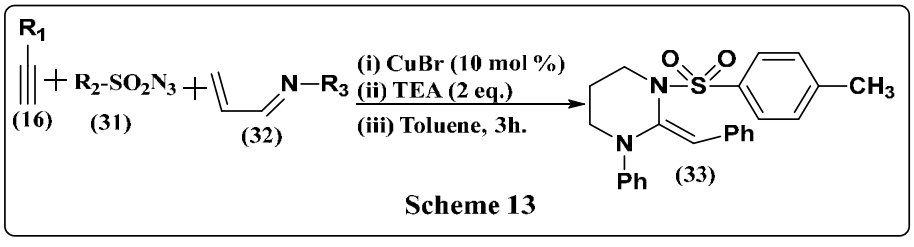
Stonehouse *et al.* described a palladium-catalyzed four-component reaction for the generation of pyrimidines, which was a one-pot process. In their reaction, a wide range of aryl halides **(22)**, terminal alkynes **(16)**, molybdenumhexa carbonyl and amidines **(29)** were shown to be an efficient method for the construction of highly substituted pyrimidines **(30)** (**Scheme 12**).[18]



Scheme 12. Synthesis of pyrimidine derivatives from aryl halides

2.13 From sulfonyl azides.

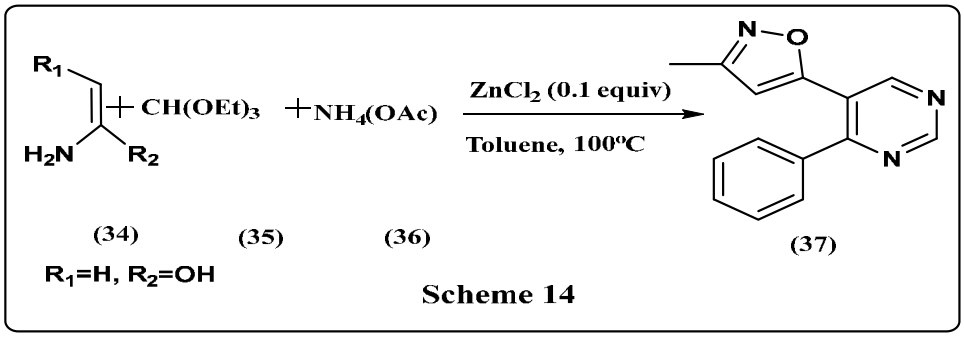
A one-pot synthesis of *N*-sulfonyl-2-alkylidene-1,2,3,4-tetrahydropyrimidines **(33)** *via* a highly selective and copper-catalyzed multi-components reaction of sulfonyl azides **(31)**, terminal alkynes **(16)**, and α,β-unsaturated imines **(32)** was developed by Wang *et al.* (**Scheme 13**).[19]



Scheme 13. Synthesis of pyrimidine derivatives from sulfonyl azides

2.14 From functionalized enamines.

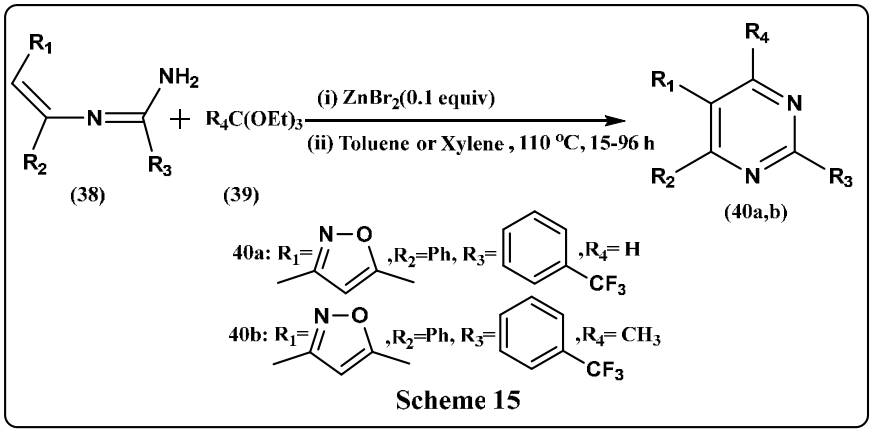
Konakahara *et al.* reported a $ZnCl_2$-catalyzed three-components coupling reaction involving a variety of functionalized enamines **(34)**, triethyl orthoformate **(35)**, and ammonium acetate **(36)**, which led to the production of 4,5-disubstituted pyrimidine derivatives **(37)** (**Scheme 14**).[20]



Scheme 14. Synthesis of pyrimidine derivatives from functionalized enamines

2.15 From orthoester

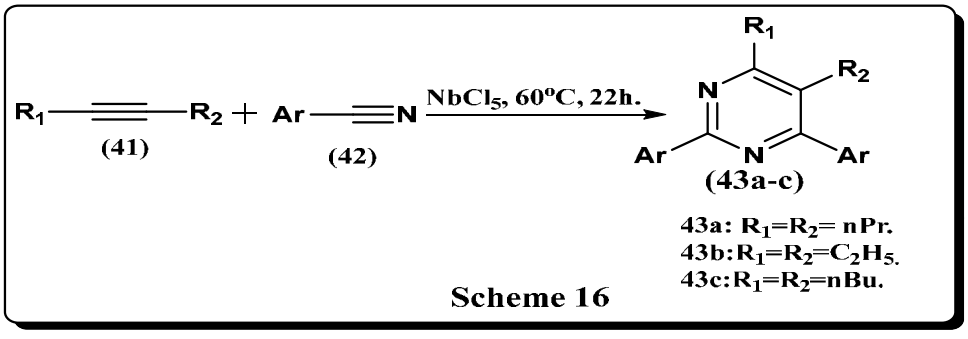
Sasada groups developed procedures for the synthesis of tri- and tetra substituted pyrimidine derivatives **(40a,b)** in good to excellent yields by the reaction of enamidine **(38)** with an orthoester **(39)** in toluene or xylene at 110 °C, for 15-96 h (**Scheme 15**).[21]



Scheme 15. Synthesis of pyrimidine derivatives from orthoester

2.16 From benzonitrile

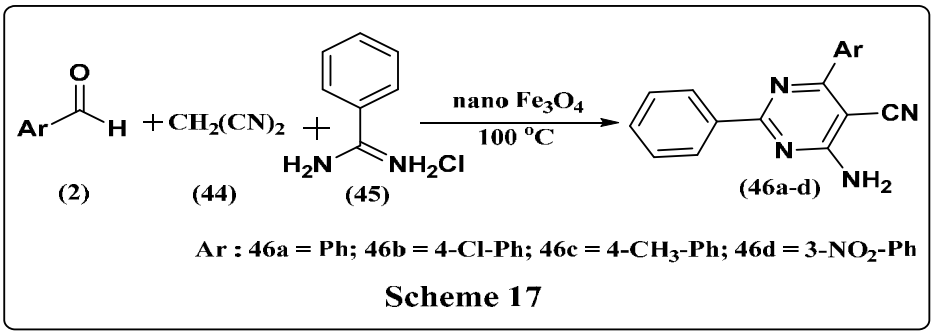
Obora *et al.* established a practical method for the preparation of poly substituted pyrimidine derivatives **(43a-e)**, which gave moderate to good yields. The reaction was successful using terminal alkynes with n-octyl, phenyl, and cyclohexyl groups **(41)** and benzonitrile **(42)**. In the presence of $NbCl_5$ as a catalyst at 60 °C for around 22 h (**Scheme 16**).[22]



Scheme 16. Synthesis of pyrimidine derivatives from benzonitrile

2.17 From malononitrile.

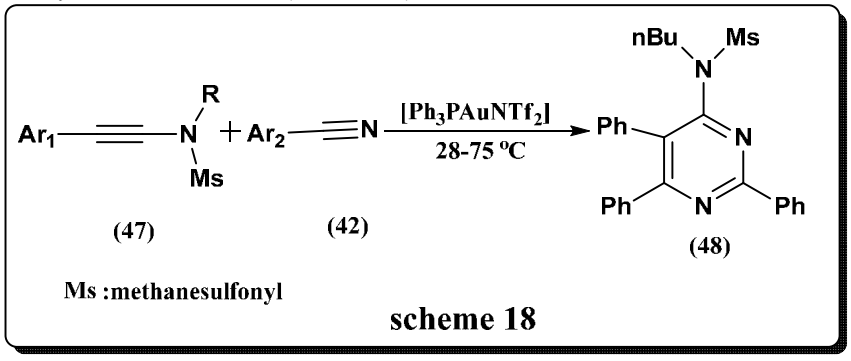
Rostamizadeh *et al.* reported a one-pot, three-component reaction to synthesize pyrimidine derivatives **(46a-d)**. By the reaction of aldehyde **(2)**, malononitrile **(44)**, and benzamidine hydrochloride **(45)** were synthesis transformed in the presence of magnetic nano Fe_3O_4 particles as the catalyst under solvent-free conditions. The pyrimidine-5-carbonitrile derivatives **(46a-d)** in their method were prepared in good yields (**Scheme 17**).[23]



Scheme 17. Synthesis of pyrimidine derivatives from malononitrile

2.18 From N-methyl-N-(phenylethynyl)methane sulfonamide.

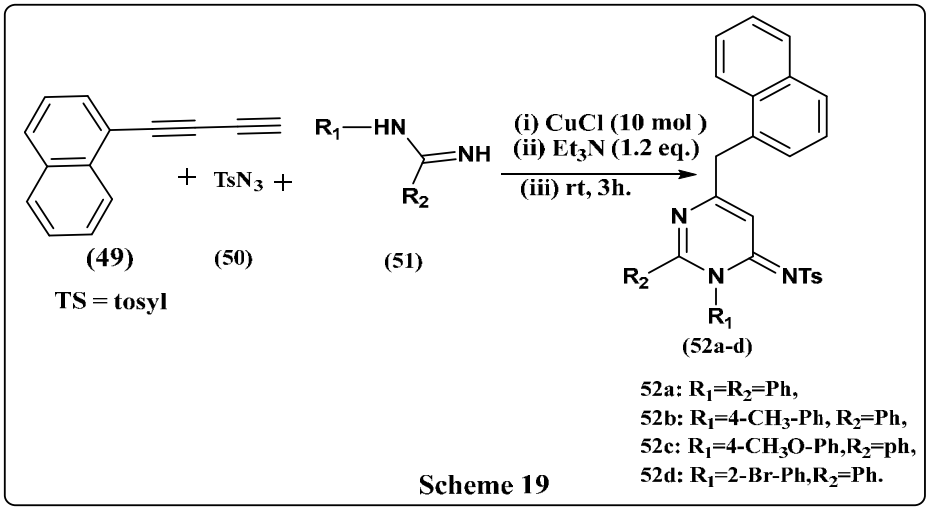
Karad *et al.* reported on gold-catalyzed cycloadditions reaction between *N*-methyl-*N*-(phenylethynyl)methanesulfonamid **(47)** and benzonitrile **(42)** to afford monomeric 4-aminopyrimidines **(48)**, which were commonly found in many bioactive molecules (**Scheme 18**).[24]



Scheme 18. Synthesis of monomeric 4-aminopyrimidines **(48)**

2.19 From 1-(naphthalene-1-yl)-1,3-butadiyne.

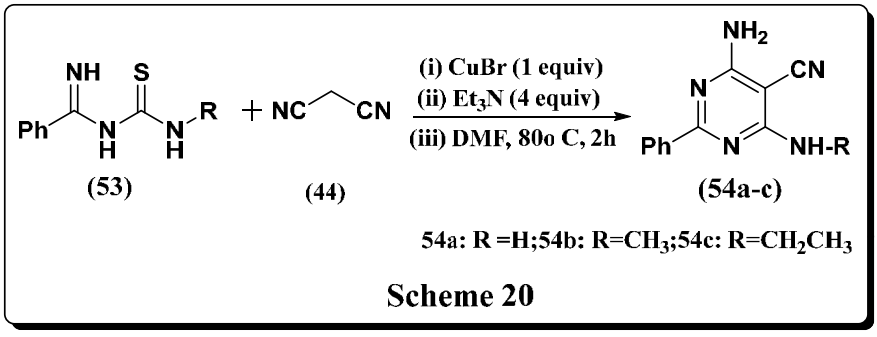
Xing *et al.* developed a facile and efficient synthesis of 4-iminopyrimidines **(52a-d)** *via* a copper-catalyzed three-component reaction. in that method a mixture of 1-(naphthalene-1-yl)-1,3-butadiyne **(49)**, tosylazide **(50)** and substituted imidamides **(51)** was stirred continually for 3 h at room temperature in the presence CuCl at room temperature under N_2 atmosphere and Et_3N (**Scheme 19**).[25]



Scheme 19. Synthesis of pyrimidine derivatives from naphthalene butadiyne

2.20 From N-(substituted carbamothioyl) benzimidamides.

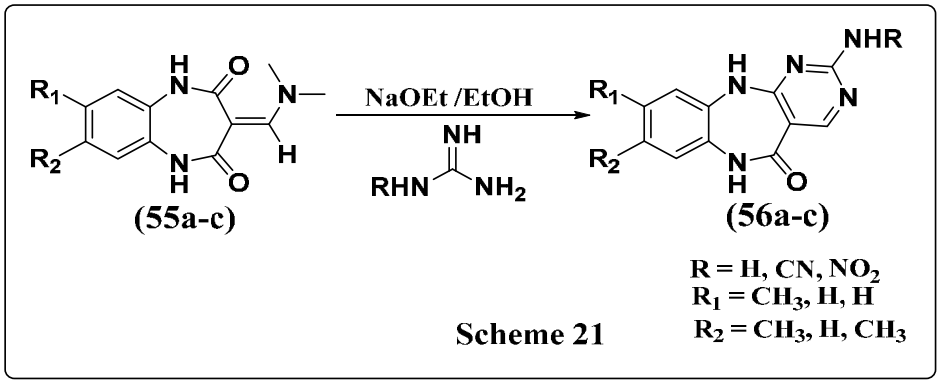
Shafiee and coworkers reported a simple procedure for the synthesis of a series of poly functionalized pyrimidines **(54a-c)**. In the presence of CuBr/Et_3N in DMF at 80 ºC *via* the reaction between *N*-(substitutedcarbamothioyl) benzimidamides **(53)** and malononitrile **(44)**, good yields of the desired products were observed (**Scheme 20**).[26-28]



Scheme 20. Synthesis of poly functionalized pyrimidines

2.21 From β-enaminonamide intermediates.

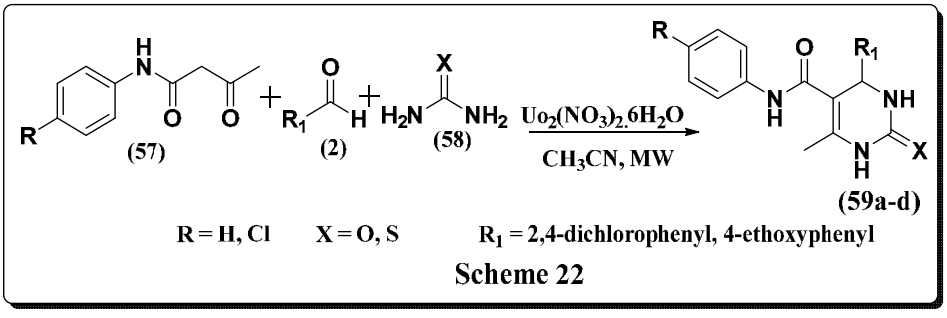
Qomi *et al.* reported that a method for the synthesis of some pyrimidines derivatives **(56a-c)** in good to excellent yields. In their method the intermediates **(55a-c)** were condensed with guanidine derivatives under reflux with ethanol in the presence of sodium ethoxide to form the corresponding tricyclic derivatives **(56a-c)** (**Scheme 21**).[29]



Scheme 21. Synthesis of pyrimidine derivatives from β-enaminonamid intermediates

2.22 From acetoaetanilide.

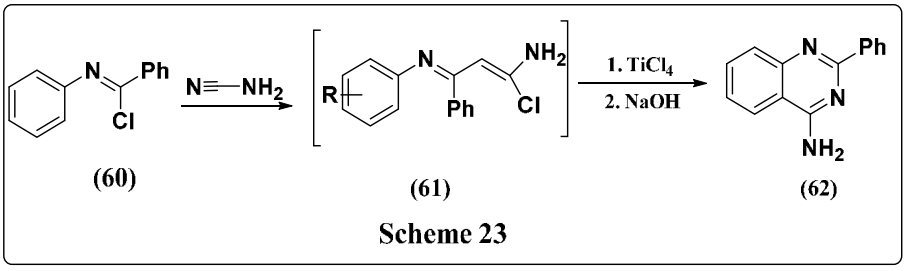
Venkatesan *et al.* reported that an efficient and simple method for the synthesis of pyrimidine-5-carboxamides **(59a-d)** using a mixture of substituted acetoaetanilide **(57)**, aldehyde **(2)**, urea or thiourea **(58)** and $Uo_2(NO_3)_2.6H_2O$ as a catalyst under conventional and microwave irradiation. The synthesis of dihydropyrimidine using uranyl nitrate had produced many advantages such as easy work up, short reaction time and high yields (**Scheme 22**).[30]



Scheme 22. Synthesis of pyrimidine derivatives from acetoaetanilide

2.23 From N-arylbenzimidoyl chlorides

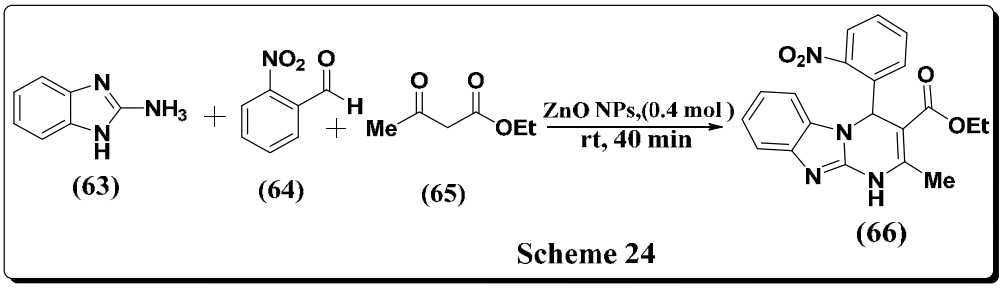
Zielin'ski *et al.* reported the synthesis of 2-phenylquinazolin-4-amine by the reaction of *N*-arylbenzimidoyl chlorides **(60)** with cyanamide at room temperature to afford the crossponding intermediates **(61)**. Finally, after several hours of heating in benzene in the presence of the Lewis acid catalyst $TiCl_4$. Compound **(61)** underwent cyclization gave the final product **(62)** (**Scheme 23**).[31]



Scheme 23. Synthesis of pyrimidine derivatives from *N*-arylbenzimidoyl chlorides

2.24 From 2-aminobenzimidazole

Sharma *et al.* reported the synthesis of ethyl 2-methyl-4-(2-nitrophenyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carboxylate **(66)** by the reaction of 2-aminobenzimidazole **(63)**, 2- nitrobenzaldehyde **(64)** and ethyl acetoacetate **(65)** in the presence of ZnONPs as catalyst for 40 min (**Scheme 24**).[32]



Scheme 24. Synthesis of pyrimidine derivatives from 2-aminobenzimidazole

3. Reactions of pyrimidine and its compounds

3.1 Electrophilic substitution's reaction.

Electrophilic substitutions like halogenation, Vilsmeier formylation, nitration and alkylation, were demonstrated in thieno[2,3-*d*]pyrimidines (**I**) and thieno [3,4-*d*]pyrimidines (**III**) involved position 6 and eq. position 7, respectively, which is typical of thiophene itself and suggested a weak influence of annulation with the pyrimidine ring. A different situation was observed for electrophilic substitution in thieno[3,2-*d*] pyrimidines (**II**), where the influence of annulation of the pyrimidine ring was stronger than the effect of orientation of the sulfur atom in the thiophene ring and, consequently, the attack occurred at position 7 (**Fig. 2**).

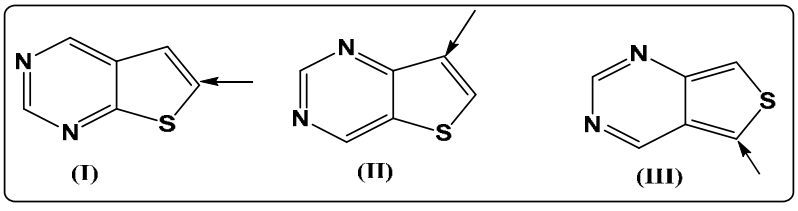
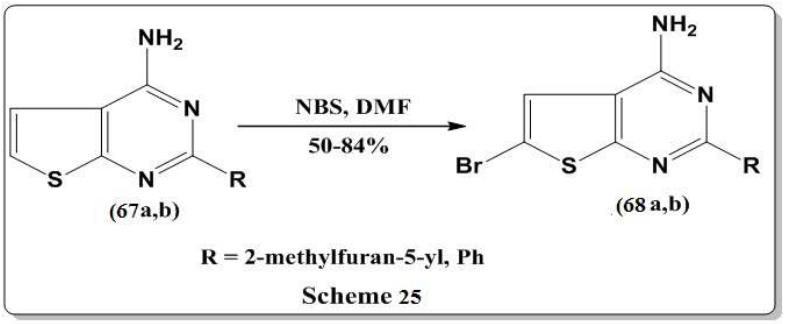


Fig. 2. The active positions for electrophilic substitutions in thienopyrimidines derivatives

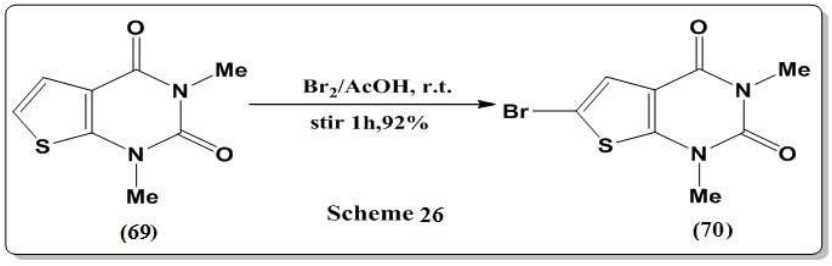
3.2 Halogenation

(a) Bromination of compounds **(67a,b)** with mild bromonating agent, (NBS), in DMF afforded 4-amino-6-bromo-2-subutitutedthieno[2,3-*d*]pyrimidines **(68a,b)** (**Scheme 25**).[33]



Scheme 25. Bromination of compound **(67a,b)**

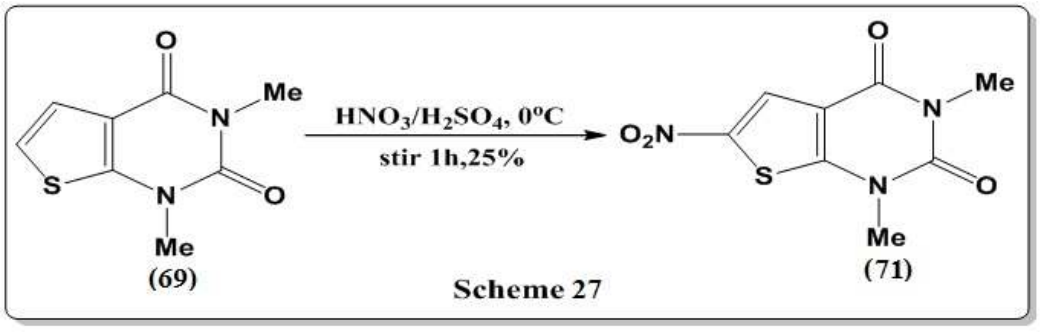
(b) 6-Bromo-1,3-dimethylthieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **(70)** was formed by the addition of a solution of bromine dissolved in acetic acid to thienopyrimidine **(69)** (**Scheme 26**).[34]



Scheme 26. Bromination of compound **(69)**

3.3 Nitration

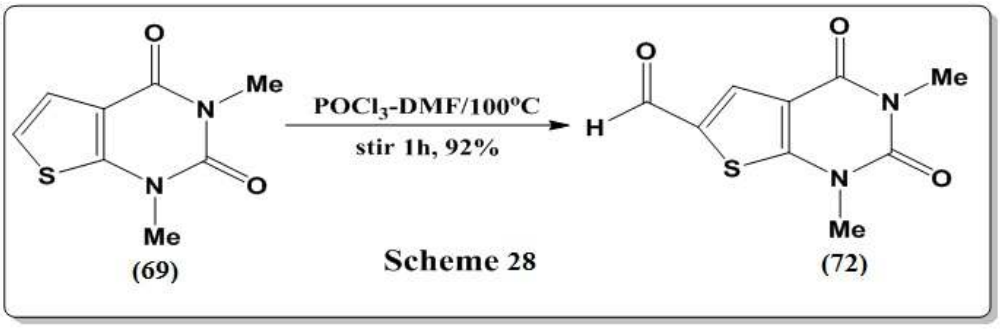
Thieno[2,3-*d*]pyrimidine **(69)** was reacted with a solution of fuming nitric acid in concentrated sulfuric acid to afford 6-nitro-1,3-dimethyl thieno[2,3-*d*] pyrimidine-2,4 (1*H*,3*H*)-dione **(71)** (**Scheme 27**).[34]



Scheme 27. Nitration of compound **(69)**

3.4 Vilsmeier-Haack reaction.

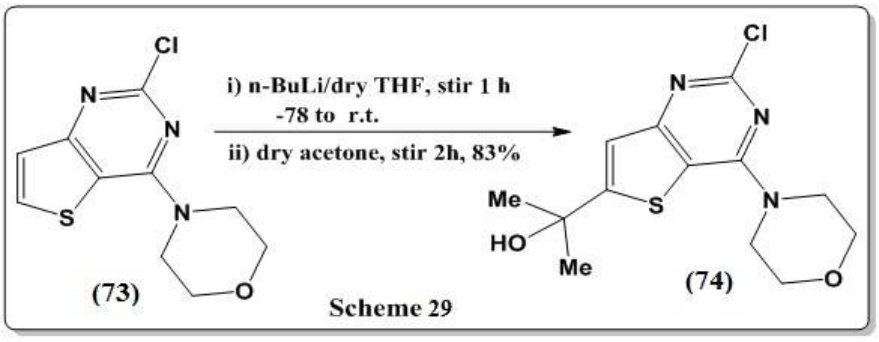
Reaction of compound **(69)** with phosphorus oxychloride and DMF under Vilsmeier-Haack condition gave 6-formyl-1,3-dimethylthieno[2,3-*d*]pyrimidine -2,4(1*H*,3*H*)-dione **(72)** (**Scheme 28**).[34]



Scheme 28. Vilsmeier-Haack reaction of compound **(69)**

3.5 Alkylation

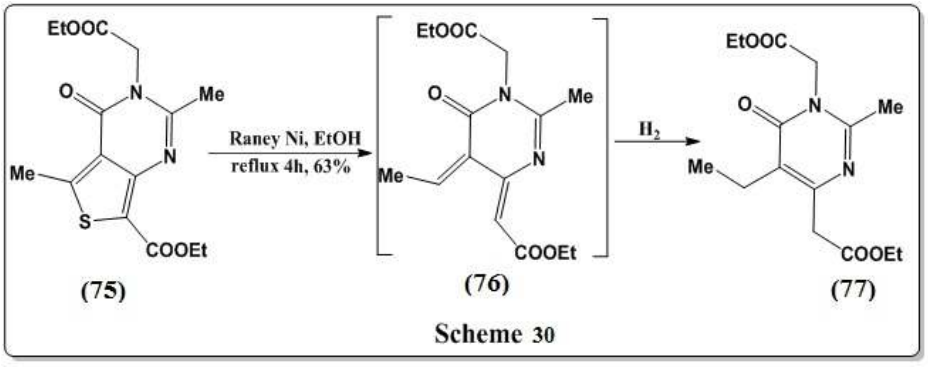
2-(2-Chloro-4-morpholinothieno[2,3-*d*]pyrimidin-6-yl)propan-2-ol **(74)** was obtained from treatment of (2-chloro-4-morphlin-4-yl)thieno[3,2-*d*]pyrimidine **(73)** with *n*-BuLi followed by addition of dry acetone (**Scheme 29**).[35]



Scheme 29. Alkylation reaction of compound **(73)**

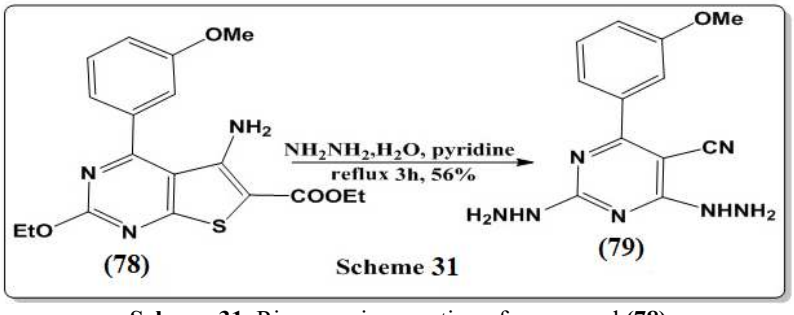
3.6 Ring opening of the thiophene ring

(a) Ethyl 3-(2-ethoxy-2-oxoethyl)-2,5-dimethyl-4-oxo-3,4-dihydrothieno[3,4-*d*] pyrimindine-7-carboxylate **(75)** was underwent desulfurization under the action of raney nickel to yield ethyl 4-(ethoxycarbonylmethyl)-5-ethyl-2-methyl-6-oxo-1,6-dihydropyrimidin -1-yl-acetate **(77)** (**Scheme 30**).[36]



Scheme 30. Ring opening reaction of compound **(75)**

(b) When compound **(78)** was allowed to react with hydrazine hydrate, gave unexpectedly a ring opened compound, 2,4-dihydrazino-6-(3-methoxy phenyl)-pyrimidine-5-carbonitrile **(79)** (**Scheme 31**).[37]

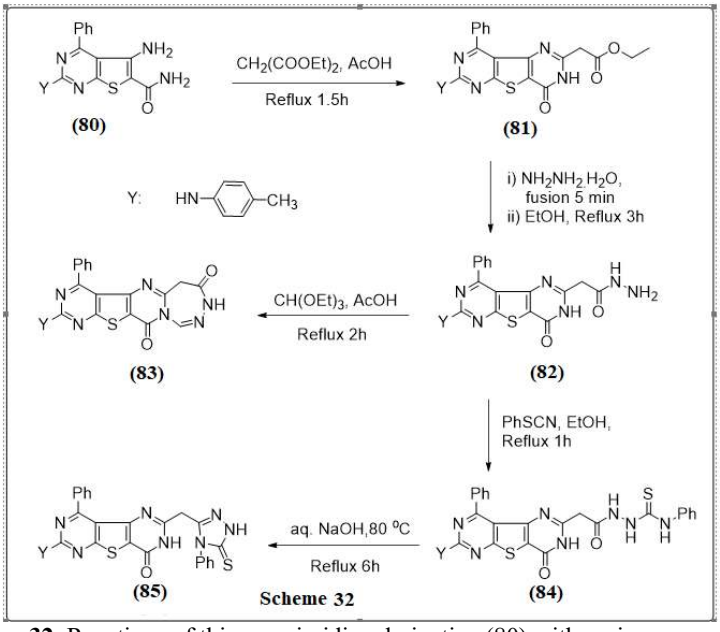


Scheme 31. Ring opening reaction of compound **(78)**

3.7 From amino-carboxamide

Tolba *et al*. succeeded in synthesizing some heterocyclic thienopyrimidine compounds **(81-85)** starting from amino-carboxamide **(80)**[38]. Also, the photophysical properties of the selected compounds were investigated at different concentrations of solutions and at high solid-state temperatures and were theoretically confirmed by density functional theory calculations. The studied dyes showed the properties of AIE with spectral shapes related to the overall structure with a quantitative yield of 10.8%. The pigment powder emission efficiency is attributed to the incorporation of the double twisted spindle aryl moieties into the molten heterogeneous cycles. These dyes also showed high thermal stability and strong

antimicrobial activities against many strains of bacteria and fungi. Besides, the cytotoxicity of the novel compounds was estimated against the Caco-2. cell line (**Scheme 32**).[39]



Scheme 32. Reactions of thienopyrimidine derivative (80) with various reagents

4. Pharmacological Activities of pyrimidine and its derivatives

The chemistry of pyrimidine derivatives plays an important role in the field of drugs, agriculture chemicals, and many biological processes. In recent decades, a large number of pharmacological studies have been done on pyrimidines and their derivative. However, still more research is required in order to necessity the biological compounds. Numerous methods for the synthesis of pyrimidine and their diverse reaction generate an enormous scope in the field of medicinal chemistry.[40,41] Pyrimidines have received much attention in medicinal chemistry due to their biological activities and therapeutic applications (**Fig. 3**). One possible reason for their biological activities is the presence of pyrimidine base as nucleobases, which are essential building blocks of nucleic acids, DNA and RNA. Due to the significant biological activity of pyrimidine derivatives, the synthesis of this class of compounds plays an attractive scaffold in the medicinal chemistry and drug discovering.

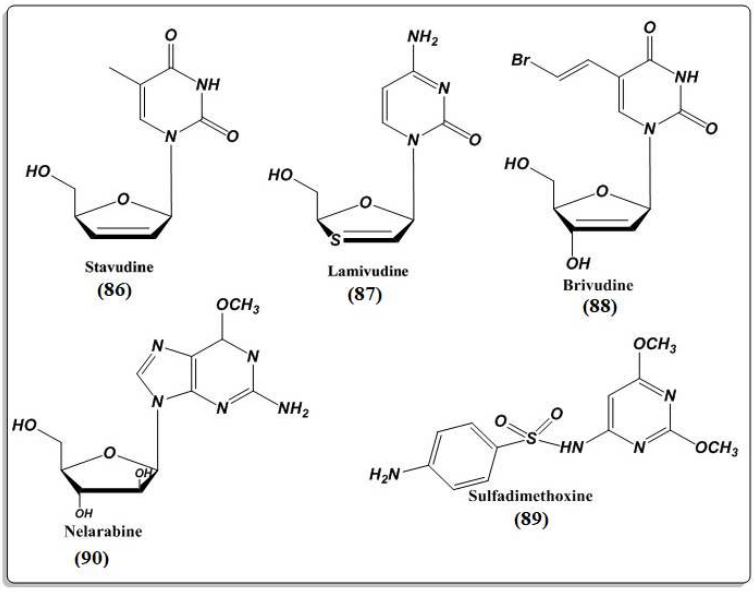


Fig. 3. Some drugs containing pyrimidine nucleus

Sacchi *et al*[42] synthesized a series of imidazo[1,2-*a*]pyrimidine-2-carboxylic acid and acetic acid analogs **(91, 92a,b)** and tested them for anti-inflammatory activity. Almost all the carboxylic acid derivatives showed a remarkable anti-inflammatory activity (**Fig. 4**).

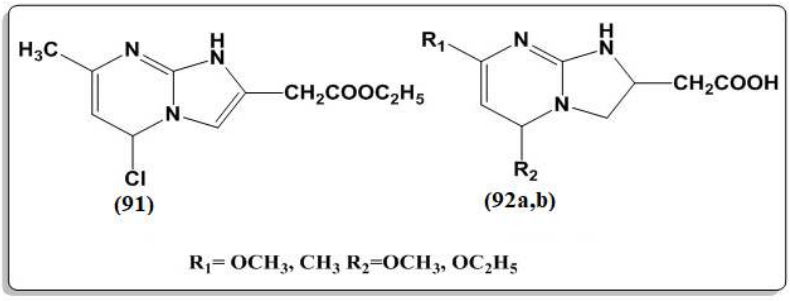


Fig. 4. Pyrimidine derivatives as anti-inflammatory agents

On the other side, 4-(4-aminothieno[2,3-*d*]pyrimidin-5-ylamino)-1,5-dimethyl-2-phenyl-1,2-dihydropyrazol-3-one **(93)** was synthesized by Aly *et al.* and evaluated the antimicrobial activity of the synthesized compound against some strain of bacteria and fungi and exhibited high activity (**Fig. 5**).[43]

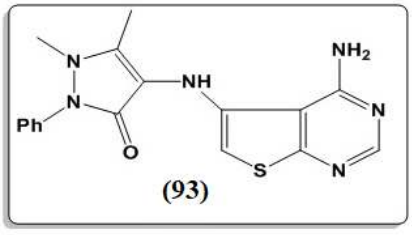


Fig. 5. Compound **(93)** as antimicrobial agents

Several derivatives containing thieno[2,3-*d*]pyrimidine ring systems were prepared from 2-amino-4,5-dihydronaphtho[2,1-*b*]thiophene-1-carbonitrile. The prepared products were tested for antiviral activity against H5N1 virus [A/chicken/Egypt/1/2006 (H5N1)] by determination of both EC50 and LD50 and confirmed by plaque reduction assay on MDCK cells. Compounds (**94** and **95**) showed the highest effect compared with the other reference compounds (**Fig. 6**).[44]

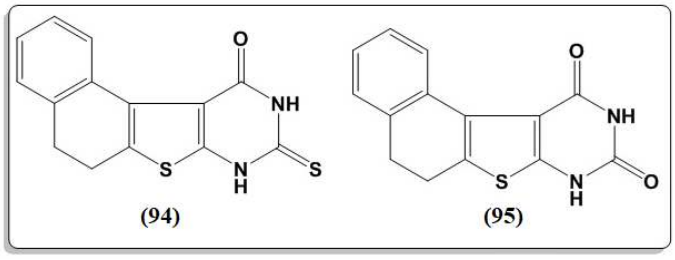


Fig. 6. Compounds **(94,95)** as antiviral agents

Rashmi *et al.* reported on the synthesis of some 4,5-unsubstituted thieno[2,3-*d*] pyrimidine derivatives **(96a,b)** and evaluated their antioxidant activity using DPPH radical scavenging activity, hydrogen peroxide scavenging activity and nitric oxide scavenging activity. The tasted compounds showed moderate free radical scavengering activity (**Fig. 7**).[45]

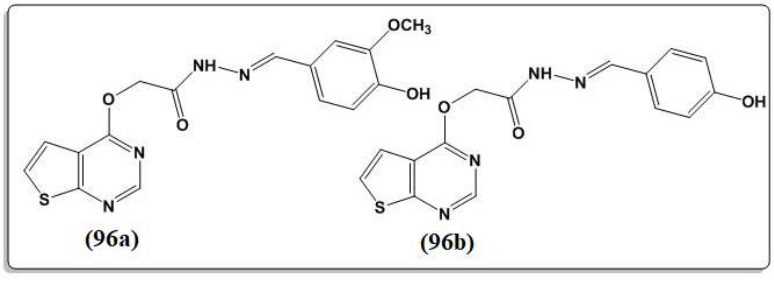


Fig. 7. Some pyrimidine derivatives as antioxidant agents

El-Gazzar *et al.* reported the synthesis of some thieno[3,2-*d*]pyrimidine derivatives and evaluated for their anticancer activity against three human cancer cell lines, including the human breast adenocarcinoma cell line (MCF-7), cervical carcinoma cell line (HeLa) and colonic carcinoma cell line (HCT-116). In addition, the other's reported that compounds **(97-99)** were nearly as active as doxorubicin (reference drug) whereas compounds **(100,101)** exhibited marked growth

inhibition, but still lower than doxorubicin (**Fig. 8**).[46] All these findings confirm the importance of organic compounds in different fields.[47-87]

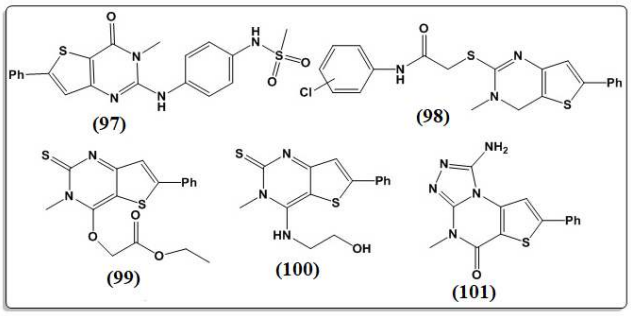


Fig. 8. Compounds **(97-101)** as antitumor agents

5. Conclusions

This review described the several efficient synthetic approaches and reactions of pyrimidine and their related compounds. The synthetic strategies of these pyrimidine derivatives designated in this review comprise the construction of the pyrimidine moiety starting with various organic reagents of them where indicated. The preparatory methods presented in this review are easy to apply, use simple raw materials, and include more environmentally friendly reaction conditions. We hope this review is useful and appealing to researchers in the field of heterocyclic synthesis. Also, it can help them to prepare novel heterocycles containing pyrimidine moiety with promising biological activities.

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