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UTILITY OF 6-AMINOURACILS FOR BUILDING SUBSTITUTED AND HETEROANNULATED PYRIMIDINES: A COMPREHENSIVE REVIEW

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Abstract – 6-Aminouracils are very useful intermediates for building different categories of heterocyclic compounds. 6-Aminouracils are electron rich compounds due to the presence of free amino group which can initiate interactions with electron deficient centres or activate the nearby C-5 position to start the reaction followed by cyclization in most cases. The present review summarizes the different reactions developed for the synthesis of substituted and annulated pyrimidines. A diversity of substituted pyrimidines was prepared directly from reactions of 6-aminouracils with some electrophilic reagents, meanwhile formation of fused pyrimidines were achieved by reaction of 6-aminouracils with a variety of reagents such as aromatic and aliphatic aldehydes, acyclic and cyclic methylene ketones, cyclic enols, alkynes, iminium salts and a diversity of other reagents.

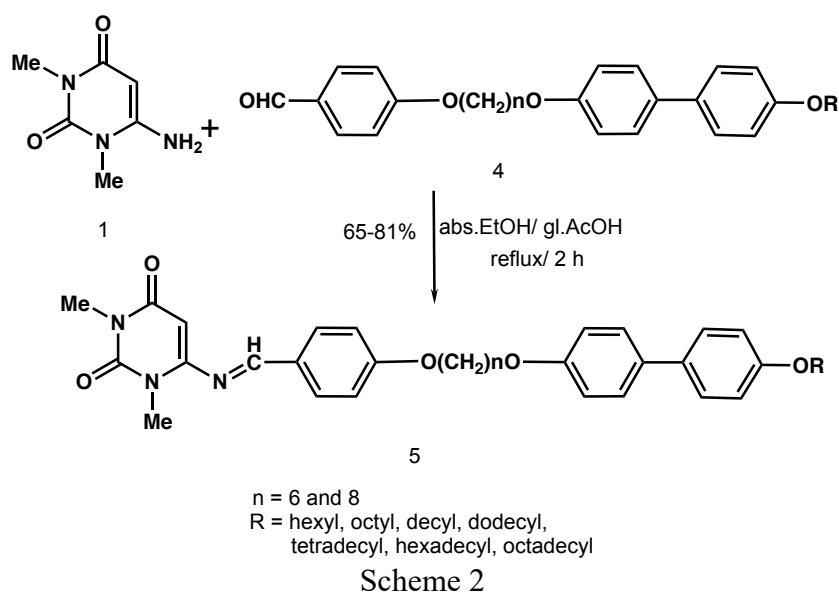
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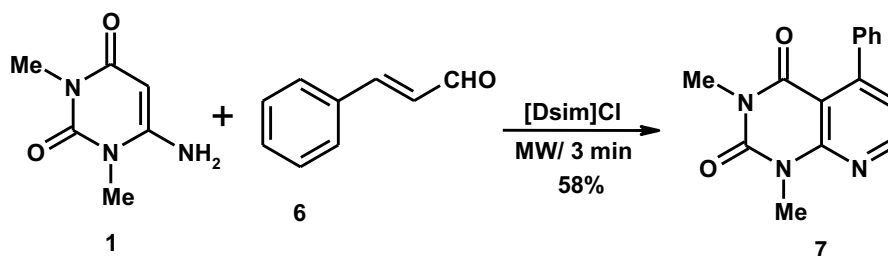
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1. INTRODUCTION

Nitrogen heterocycles in general and pyrimidines in particular have remained promising area in organic synthesis due to their abundance in natural as well as synthetic molecules with diverse applications in pharmaceuticals chemistry.^{1,2} Uracil (pyrimidine-2,4(1*H*,3*H*)-dione) is a common and naturally occurring pyrimidine derivative and represents one of the four nucleobases in the nucleic acid (RNA).³ Numerous derivatives of uracil have incredible utility in biology and in medicinal chemistry⁴ such as anticancer,⁵ antitumor,⁶ antineoplastic,⁷ antiprotozoal,⁸ anti-HIV,⁹ anti-HCMV,¹⁰ antitubercular,¹¹ antiviral,¹² antifungal,¹³ antibacterial,¹⁴ insecticidal,¹⁵ herbicidal,¹⁶ and antimicrobial activities.¹⁷ Azo-uracils have been used as hypotonic drugs.¹⁸ Also, uracil based azo-derivatives and their metal complexes are promising chemosensors.¹⁹ 6-Aminouracils find wide application as starting materials for the synthesis of many isolated and fused uracils of biological significance.²⁰ Herein, the present review covers the chemical reactivity of 6-aminouracils towards electrophilic reagents that led to a diversity of substituted pyrimidines as well as heteroannulataed pyrimidines such as pyranopyrimidine, pyranopyridopyrimidines, pyridopyrimidine, pyrazolopyrimidine, pyrazolopyridopyrimidines, pyrimidopyrimidine, pyrimidoquinolines, chromenopyrimidine, pyridazinopyrimidines, pyrimidotriazines, thiazolopyrimidines, arylazouracil, arylthiouracil, tetrakis-uracil and thiocyanatopyrimidinediones.

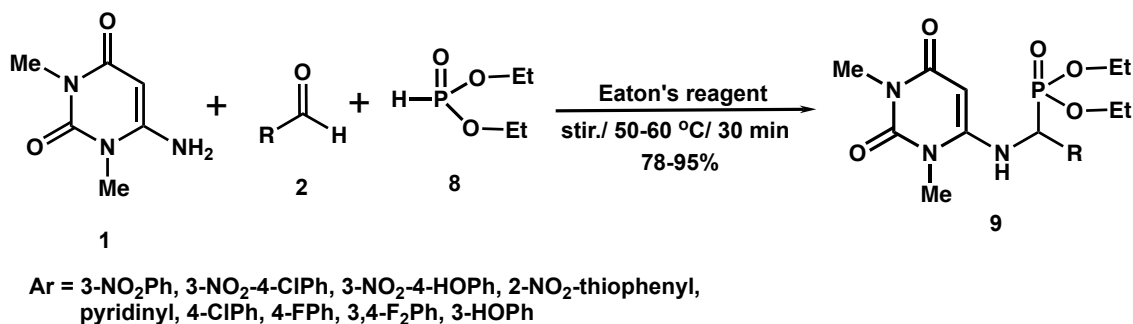


After that, reaction of 6-amino-1,3-dimethyluracil (**1**) with α,β -unsaturated aldehyde such as cinnamaldehyde (**6**) in the presence of 1,3-disulfonic acid imidazolium chloride as catalyst under microwave irradiation afforded pyrido[2,3-*d*]pyrimidine **7** with remarkable activity against *S. aureus* and *K. pneumonia*. This reaction may be occurred *via* formation of Schiff base intermediate followed cyclization (Scheme 3).²³



Scheme 3

Three-component reaction of 6-amino-1,3-dimethyluracil (**1**), aromatic aldehydes **2** and diethylphosphite **8** by using an eco-friendly Eaton's reagent ($\text{P}_2\text{O}_5:\text{MeSO}_2\text{OH}$) as catalyst and solvent produced 6-amino-1,3-dimethyluracil bearing α -aminophosphonates **9** as antioxidant agent (Scheme 4).²⁴



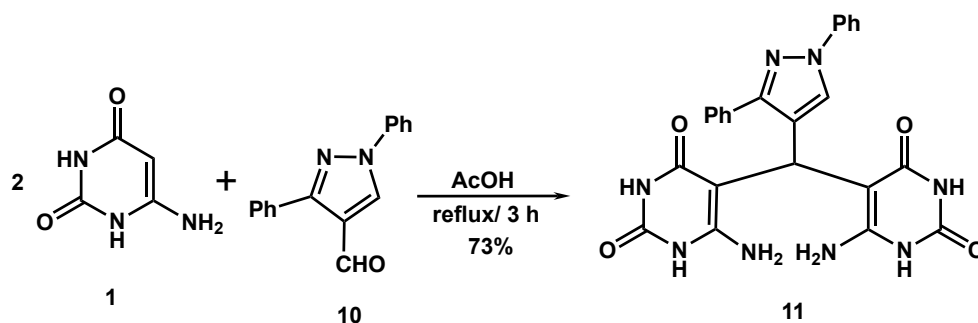
Scheme 4

2.2. Reactions through C-5 position

2.2.1. Reactions with aldehydes

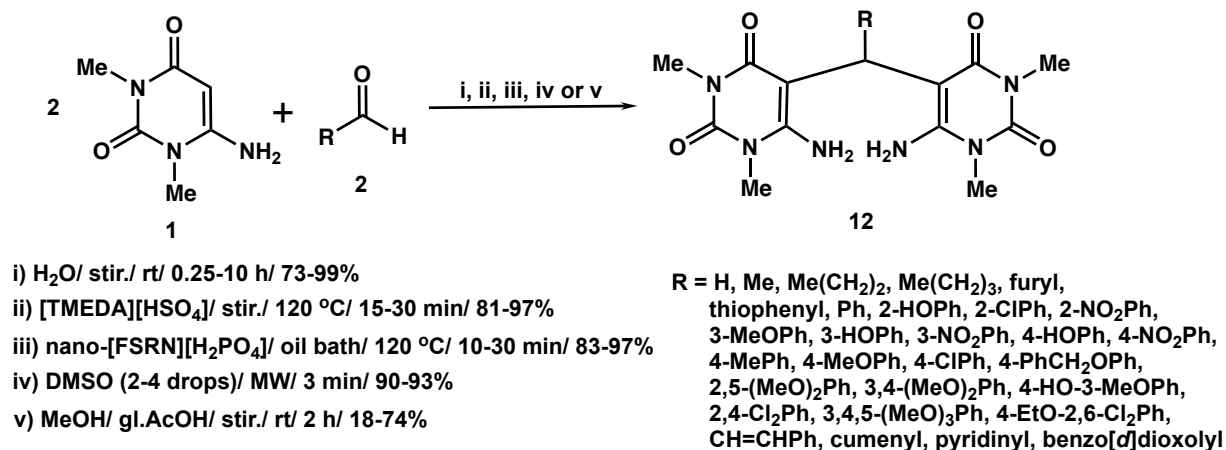
2.2.1.1. Reactions with mono-aldehydes

5,5'-((1,3-Diphenylpyrazol-4-yl)methylene)bis(6-aminopyrimidine-2,4-dione) (**11**) was synthesized, in good yield, *via* treatment of two equivalents of 6-aminouracil (**1**) with one equivalent of 1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde (**10**) in boiling acetic acid (Scheme 5).²⁵



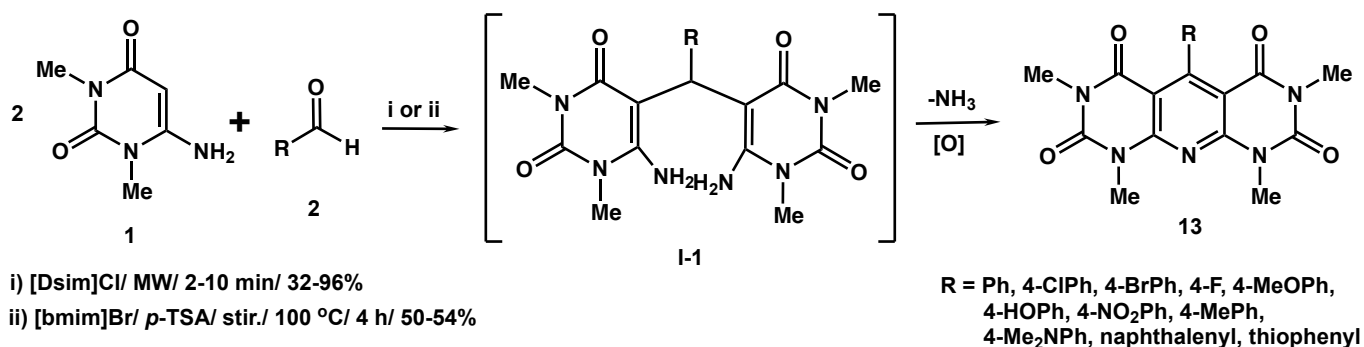
Scheme 5

Similarly, substituted *bis*(6-amino-1,3-dimethyluracil-5-yl)methanes **12** were synthesized by a clean, highly efficient and one-pot green condensation reaction of 6-amino-1,3-dimethyluracil (**1**) with aliphatic or aromatic aldehydes **2** under different reaction conditions (Scheme 6).²⁶⁻³⁰



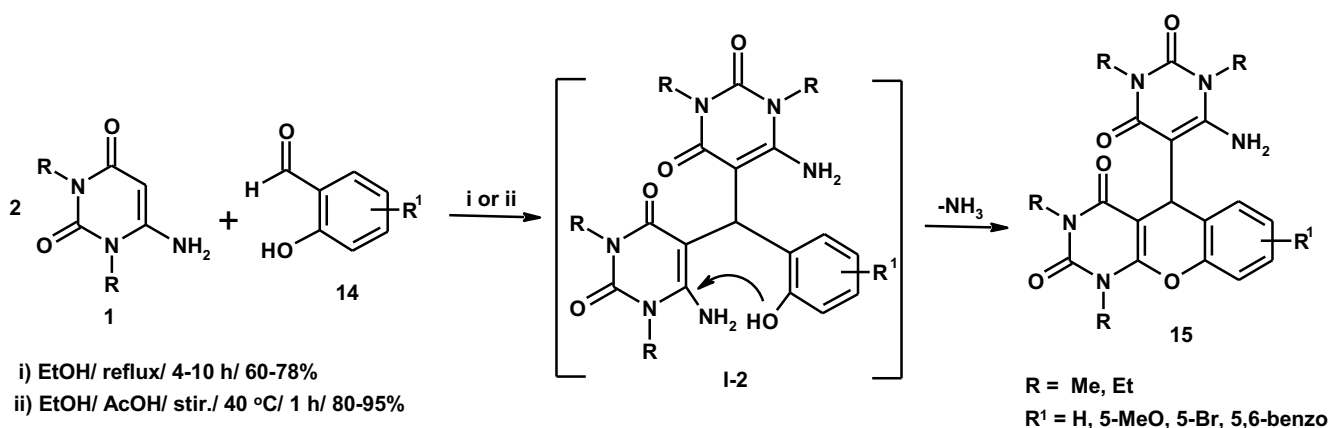
Scheme 6

The condensation reactions of 6-amino-1,3-dimethyluracil (**1**) with aromatic aldehydes **2** yielded pyrido[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8-tetraones **13** via the non-isolable intermediate **I-1** which underwent cyclocondensation with loss of ammonia molecule with subsequent oxidation. These compounds have moderate activity against *S. aureus* and *K. Pneumoniae* (Scheme 7).^{23,31}



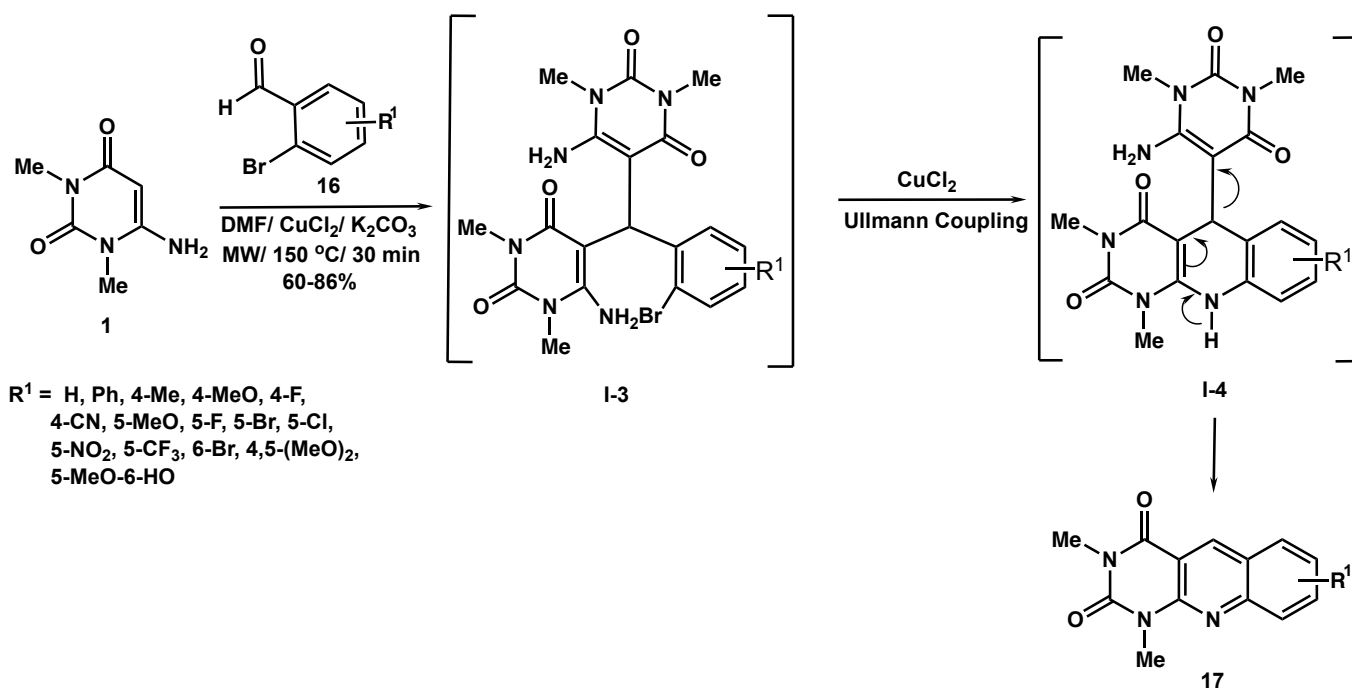
Scheme 7

While, chromeno[2,3-*d*]pyrimidinediones **15**, as antibacterial agents, were synthesized in moderate to good yields by refluxing 6-amino-1,3-disubstituteduracils **1** with 2-hydroxybenzaldehyde (**14**) under variable reaction conditions. The plausible mechanism occurs through reaction of two equivalents of compound **1** with one equivalent of aldehyde derivative (intermediate **I-2**) followed by loss of ammonia molecule as shown in Scheme 8.^{32,33}



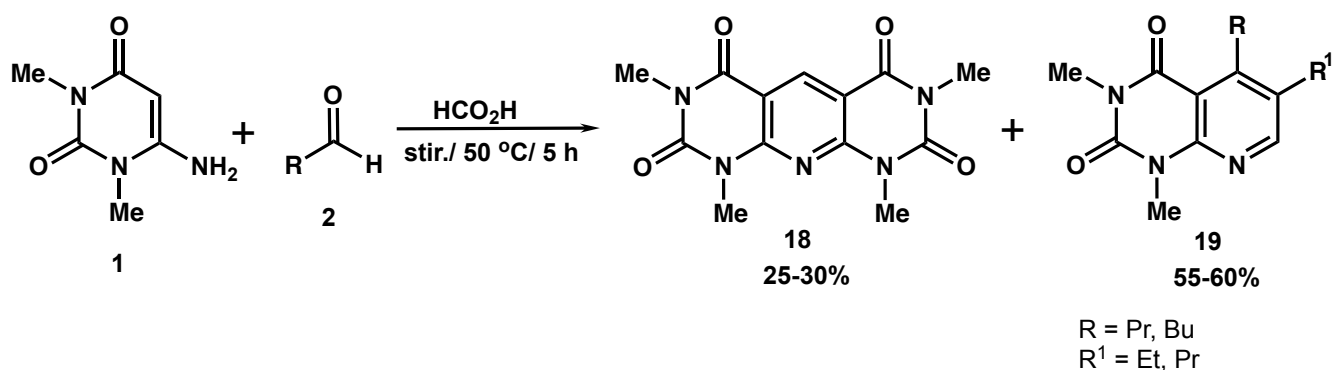
Scheme 8

Moreover, pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-diones **17** were provided, in excellent yields, by reacting 6-amino-1,3-dimethyluracil (**1**) with bromobenzaldehyde **16** in dimethylformamide (DMF) catalyzed by copper chloride (Scheme 9). Formation of compound **17** occurs through intermediate **I-3** followed by Ullman coupling (intermediate **I-4**) with subsequent base catalyzed removal of uracil molecule **1**.³⁴

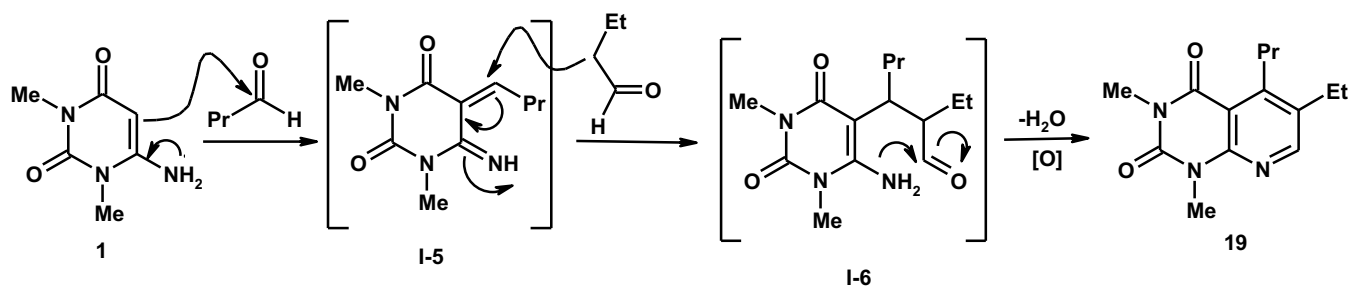


Scheme 9

Heterocyclization reactions of 6-amino-1,3-dimethyluracil (**1**) with two molecules of aliphatic aldehydes **2** in formic acid, yielded a mixture of pyrido[2,3-*d*:6,5-*d'*]dipyrimidine (**18**) and the corresponding 5,6-dialkylpyrido[2,3-*d*]pyrimidines **19** (Scheme 10).³⁵ Compound **18** was obtained as described above *via* reaction of two molecules of compound **1** with one molecule of aldehyde derivative with subsequent cyclization and oxidation. While compound **19** was obtained through condensation of compound **1** with butyraldehyde, as example intermediate **I-5** followed by addition of another molecule of aldehyde onto the exocyclic olefinic bond as shown in intermediate **I-6** associated with cyclodehydration and oxidation as depicted in Scheme 11.³⁵

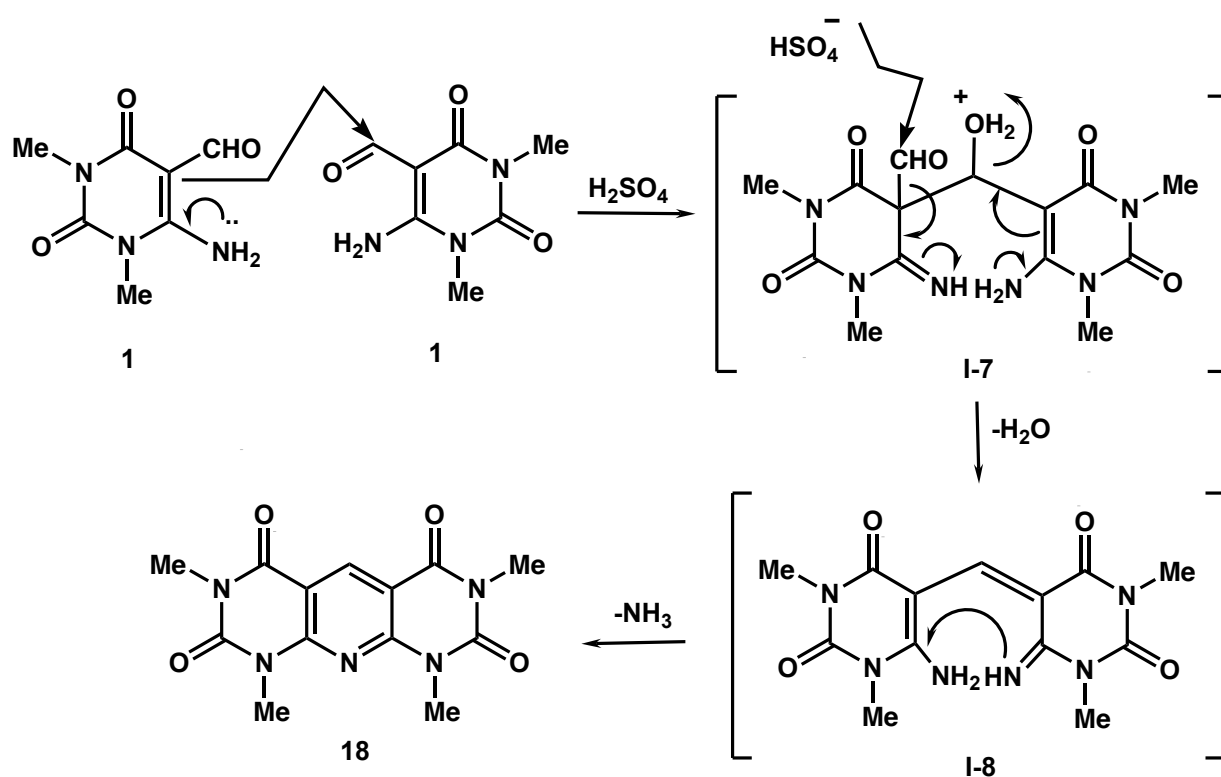


Scheme 10



Scheme 11

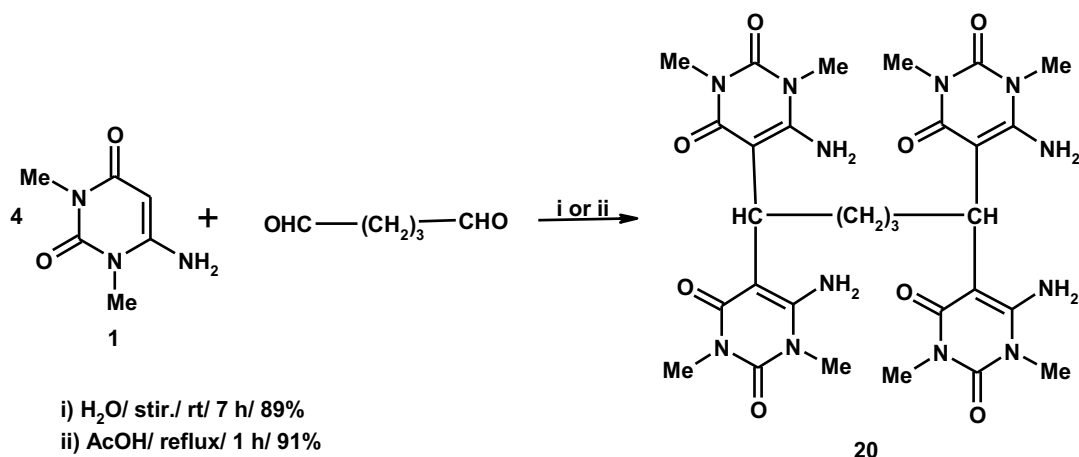
Compound **18** was recently synthesized through the self-condensation of 6-amino-1,3-dimethyl-5-formyluracil in the presence of sulfuric acid and the proposed mechanism is depicted in Scheme 12.³⁶



Scheme 12

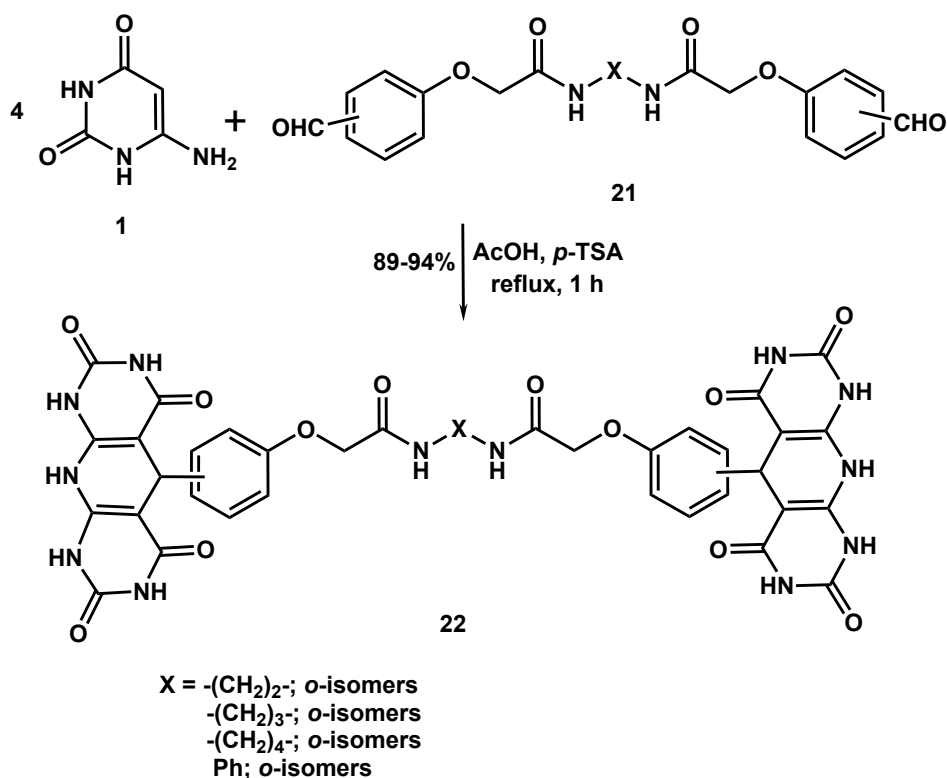
2.2.1.2. Reactions with bis-aldehydes

The reaction of 6-amino-1,3-dimethyluracil (**1**) with glutaraldehyde, as bis-aldehyde, in water at room temperature produced 6,6-diamino-1,1-3,3-tetramethyl-5,5-(glutarylidene)*bis*(pyrimidine-2,4(1*H*,3*H*)-dione) **20** (Scheme 13).²⁶



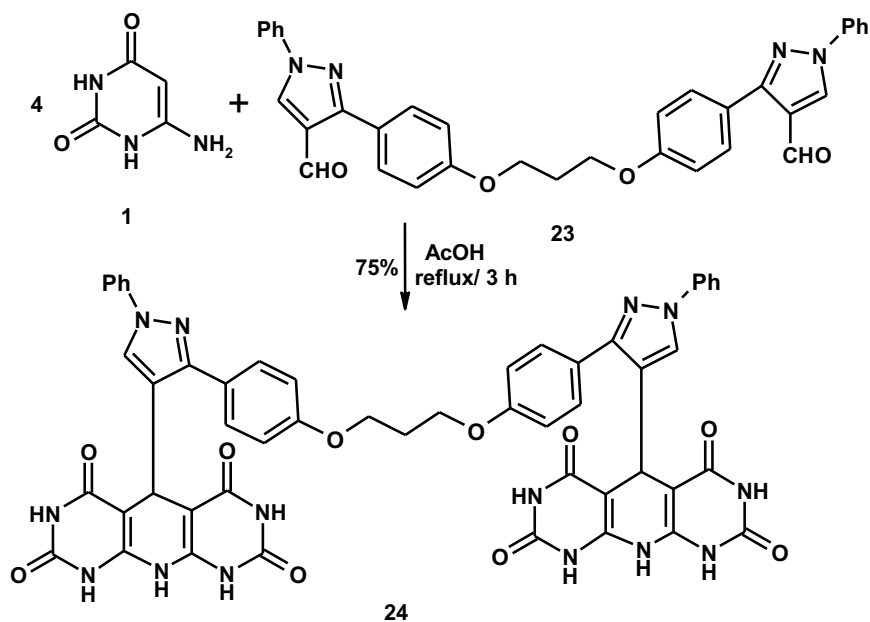
Scheme 13

Moreover, *bis*(decahydropyrido[2,3-*d*:6,5-*d'*]dipyrimidin-5-yl)phenoxyacetamide derivatives **22** were obtained by treating four equivalents of 6-aminouracil (**1**) with one equivalent of bis-aldehydes **21** in acetic acid in the presence of *para* toluene sulphonic acid (*p*-TSA) for 1 hour (Scheme 14).³⁷



Scheme 14

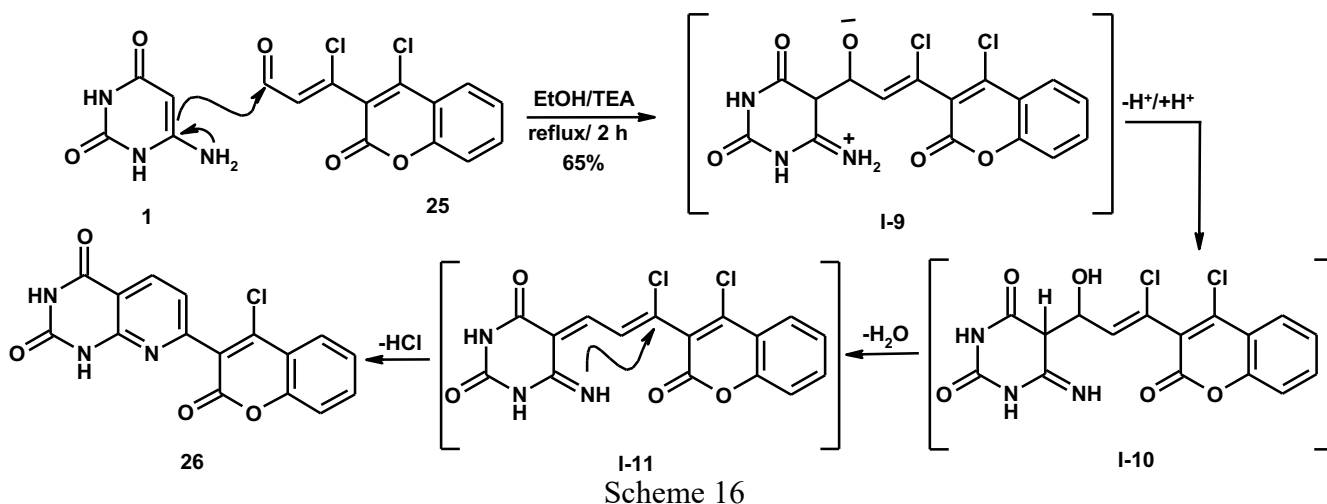
Likewise, *bis*(pyrido[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8-tetraone) **24** was obtained by condensation reaction of four mole equivalents of 6-aminouracil (**1**) with one mole equivalent of *bis*(1-phenylpyrazole-4-carboxaldehydes) **23** in acetic acid for 3 hours (Scheme 15).²⁵



Scheme 15

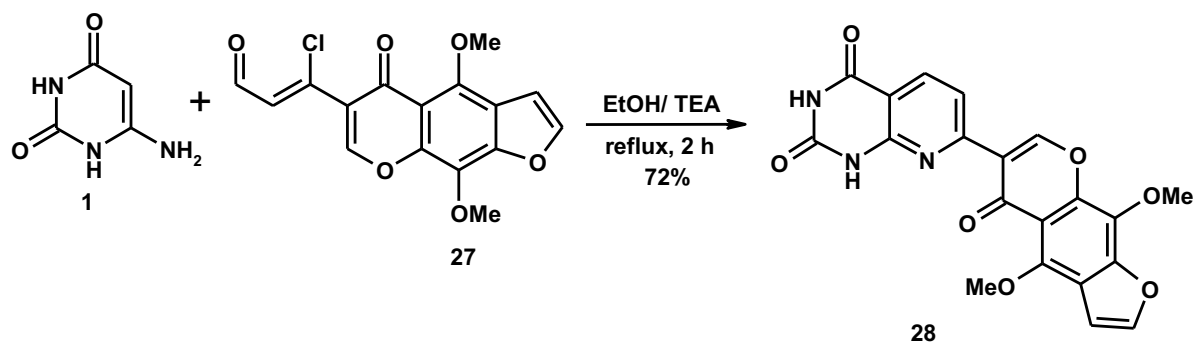
2.2.1.3. Reactions with β -chloroaldehydes

β -Chloroaldehydes are electron deficient substrates and represent an active precursor for building heterocyclic compounds. Thus, 6-aminouracil **1** was allowed to react with a diversity of β -chloroaldehydes. Boiling 6-aminouracil **1** with 3-chloro-3-(4-chlorocoumarin-3-yl)prop-2-enal (**25**) in ethanol containing triethylamine (TEA) gave pyrido[2,3-*d*]pyrimidine incorporating 4-chlorocoumarin **26** in the same molecular frame (Scheme 16). Formation of compound **26** occurred through nucleophilic attack of more nucleophilic center in the 6-aminouracil **1** (C-5) at the aldehydic function in compound **25** producing intermediate **I-9**, followed by proton transfer giving intermediate **I-10**. Dehydration of the latter intermediate afforded intermediate **I-11** which underwent cyclocondensation with loss of HCl molecule yielding the final product **26** as illustrated in Scheme 16.³⁸

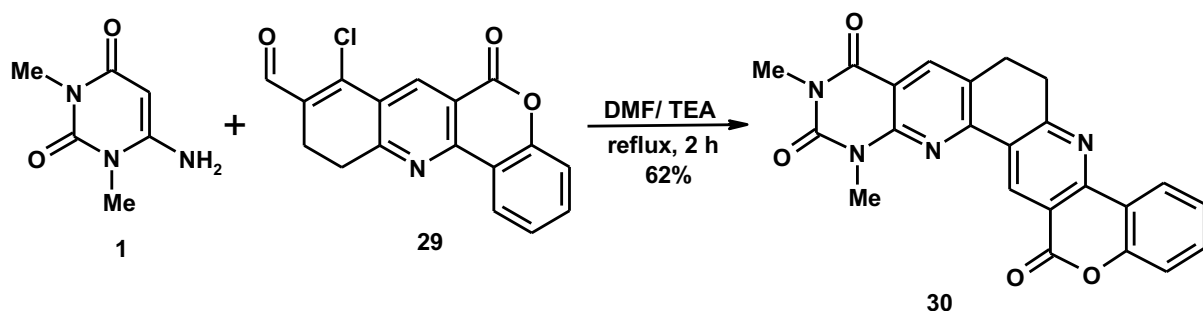


Scheme 16

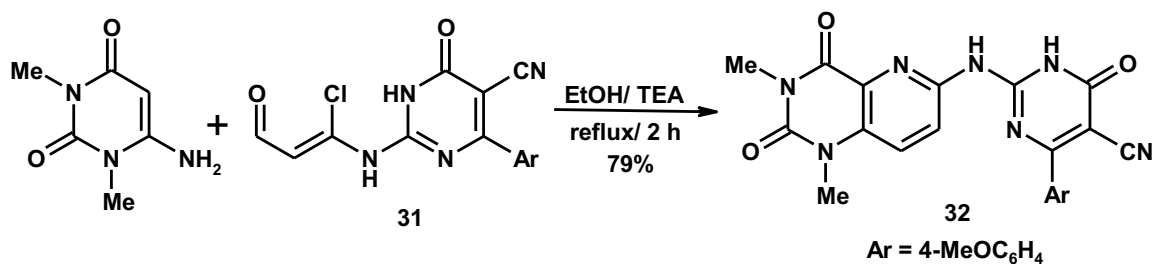
Further, reaction of 6-aminouracil **1** with 3-chloro-3-(4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromen-6-yl)prop-2-enal (**27**) in boiling ethanol containing TEA afforded pyrido[2,3-*d*]pyrimidine directly connected furo[3,2-*g*]chromene **28** with potential anticancer and antimicrobial activity (Scheme 17).³⁹



Recently, 6-amino-1,3-dimethyluracil (**1**) reacted with 1-chloro-11-oxo-3,4-dihydro-11*H*-chromeno[4,3-*b*]quinoline-2-carboxaldehyde (**29**) as cyclic β -chloroaldehyde **1** in boiling DMF containing TEA gave the angular annulated chromeno[4,3-*J*]pyrimido[4,5-*b*] [1,7]phenanthroline **30** (Scheme 18).⁴⁰

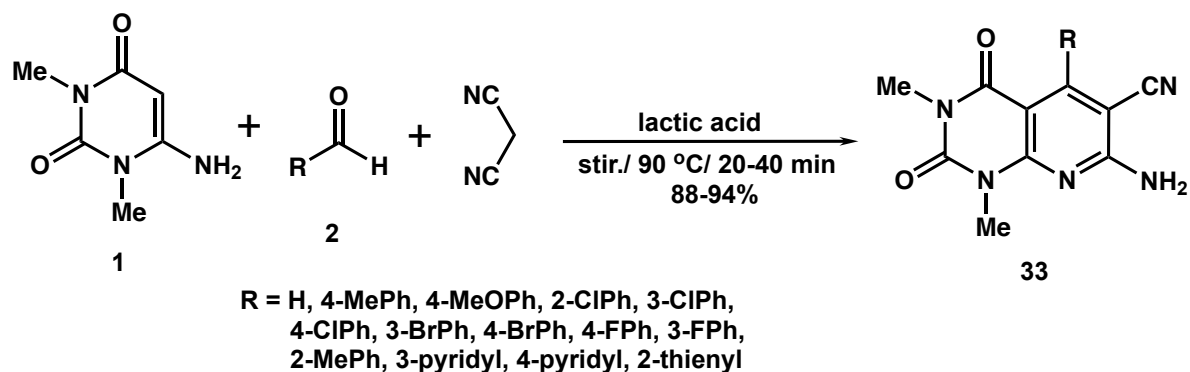


Moreover, reaction of 6-amino-1,3-dimethyluracil (**1**) with electro deficient 2-[(1-chloro-3-oxoprop-1-en-1-yl)amino]-4-(4-methoxyphenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**31**) in boiling ethanol containing TEA afforded pyrido[2,3-*d*]pyrimidine **32** incorporating pyrimidine moiety through NH linkage (Scheme 19).⁴¹



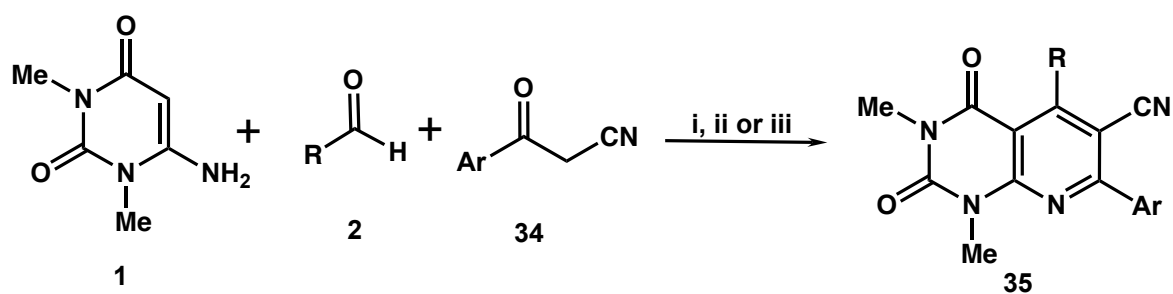
2.2.1.4. Reactions with aldehydes in the presence of active methylene compounds

Condensation reactions of 6-amino-1,3-dimethyluracil (**1**) with aromatic aldehydes **2** and malononitrile, in the presence of lactic acid as green and eco-friendly catalyst, yielded pyrido[2,3-*d*]pyrimidine derivatives **33**, in 88-94% (Scheme 20).⁴²



Scheme 20

A one-pot, three-component condensation reaction of 6-amino-1,3-dimethyluracil (**1**), aromatic aldehydes **2** and acetonitriles **34**, under different reaction conditions, afforded 5,7-disubstituted pyrido[2,3-*d*]pyrimidine-6-carbonitriles **35** with good antibacterial activity (Scheme 21).⁴³⁻⁴⁵



i) H_2O / 90 °C/ 8 h/ 82-97%

ii) EtOH / $\text{Fe}_3\text{O}_4\text{@FAP@Ni}$ / stir./ 60 °C/ 1-4 h/ 75-95%

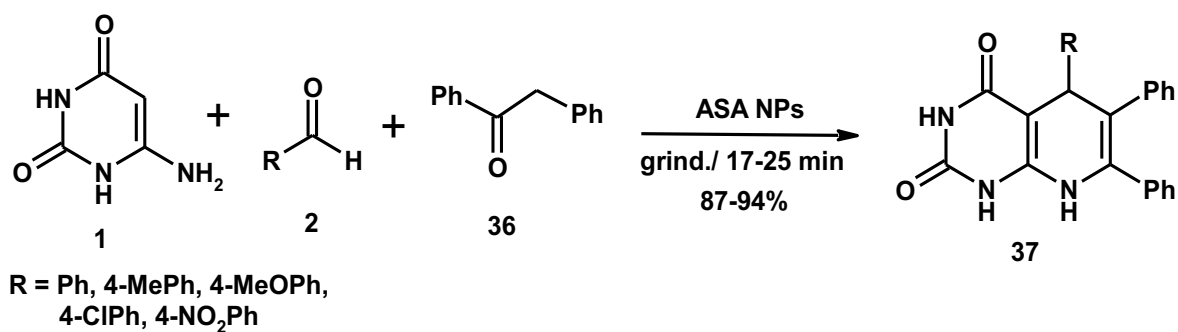
iii) DMF / [cmdmim]/ reflux/ 10-19 min/ 79-88%

Ar = Ph, indol-3-yl, 1-Me-pyrrol-2-yl

R = Ph, 2-ClPh, 2-NO₂Ph, 3-BrPh, 3-NO₂Ph, 3-HOPh, 3-MeOPh, 4-MePh, 4-MeOPh, 4-ClPh, 4-BrPh, 4-FPh, 4-NO₂Ph, 4-CNPh, 4-CF₃Ph, 4-CHOPh, 4-Me₂NPh, 2,4-Cl₂Ph, 3,4-(MeO)₂Ph, naphthalen-2-yl, nicotin-4-yl, 2-thiophenyl, pyridinyl

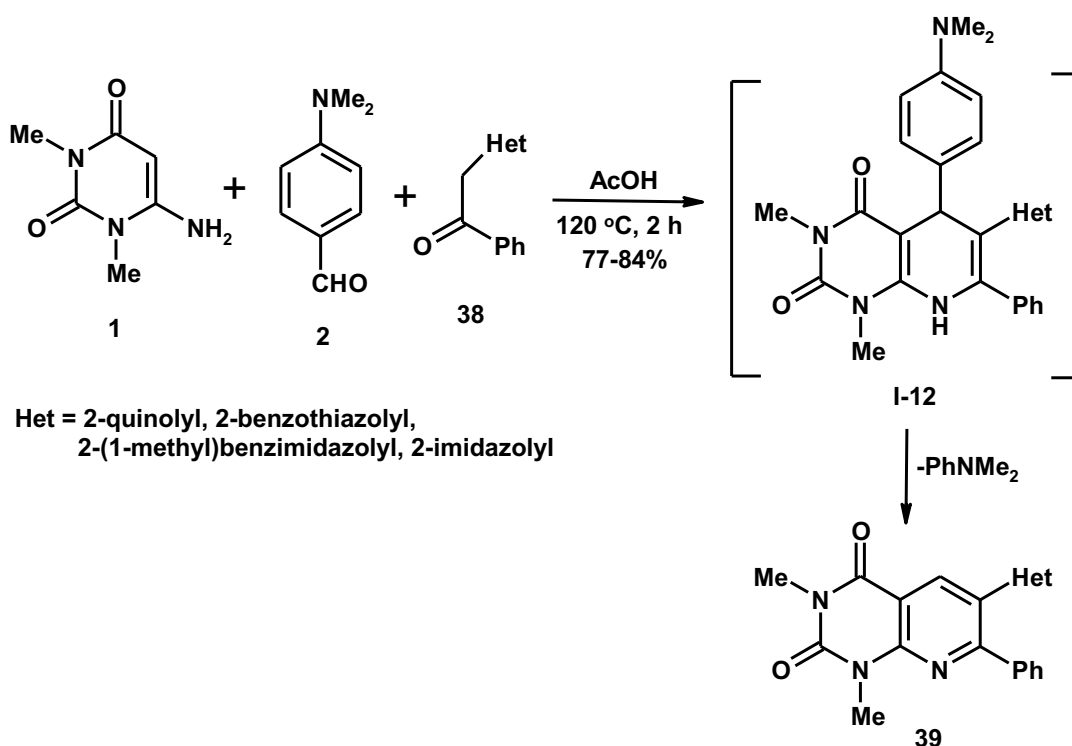
Scheme 21

Grinding a mixture of 6-amino-1,3-dimethyluracil (**1**) with aromatic aldehydes **2** and 1,2-diphenylethanone (**36**), by using aluminate sulfonic acid nanoparticles (ASA NPs) as catalyst, gave pyrido[2,3-*d*]pyrimidinediones **37**, in excellent yields (Scheme 22).⁴⁶



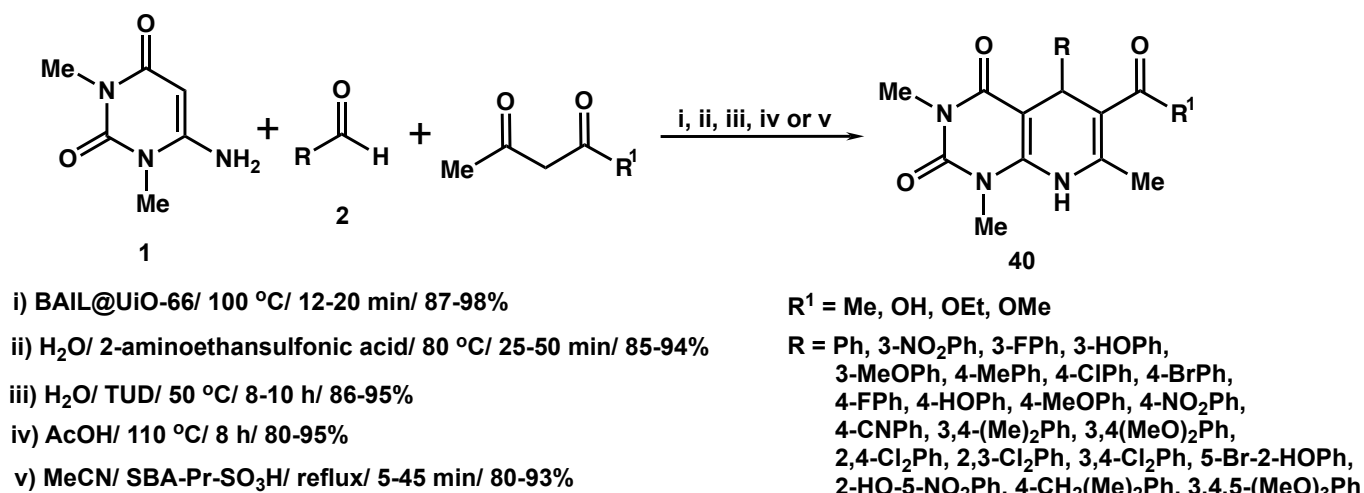
Scheme 22

Meanwhile, pyrido[2,3-*d*]pyrimidines **39** were formed, in good yields, *via* the three-component interaction of 6-amino-1,3-dimethyluracil (**1**), aromatic aldehyde **2** and heterocyclic active methylene ketones **38** in acetic acid. This reaction produced *via* intermediates **I-12** which undergo aromatization, through loss of *N,N*-dimethylaniline to give the desired products **39** (Scheme 23).⁴⁷



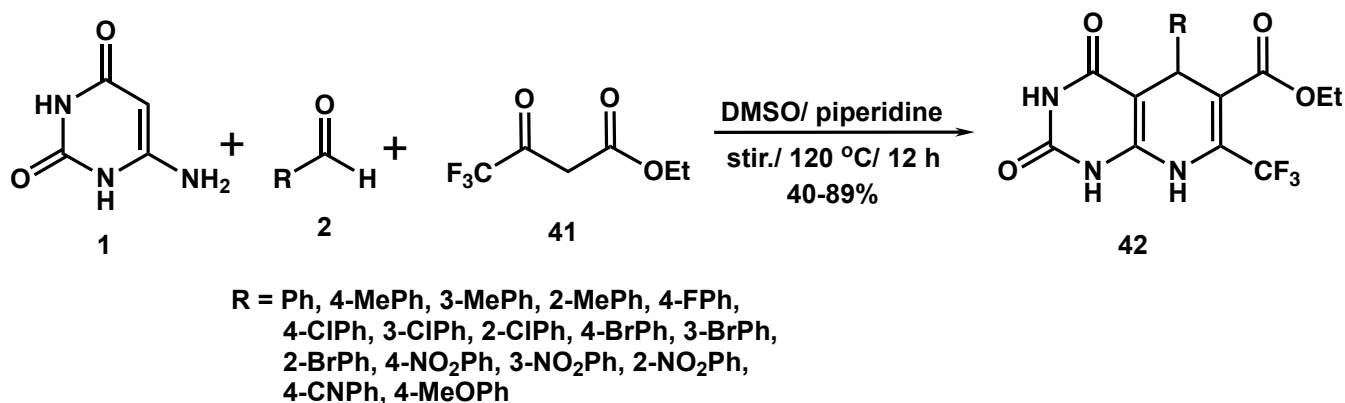
Scheme 23

Multi-component reactions of 6-amino-1,3-dimethyluracil (**1**), various aromatic aldehydes **2** and 1,3-dicarbonyl compounds, under various reaction conditions, provided dihydropyrido[2,3-*d*]pyrimidine derivatives **40** as antimicrobial agents (Scheme 24).⁴⁸⁻⁵²



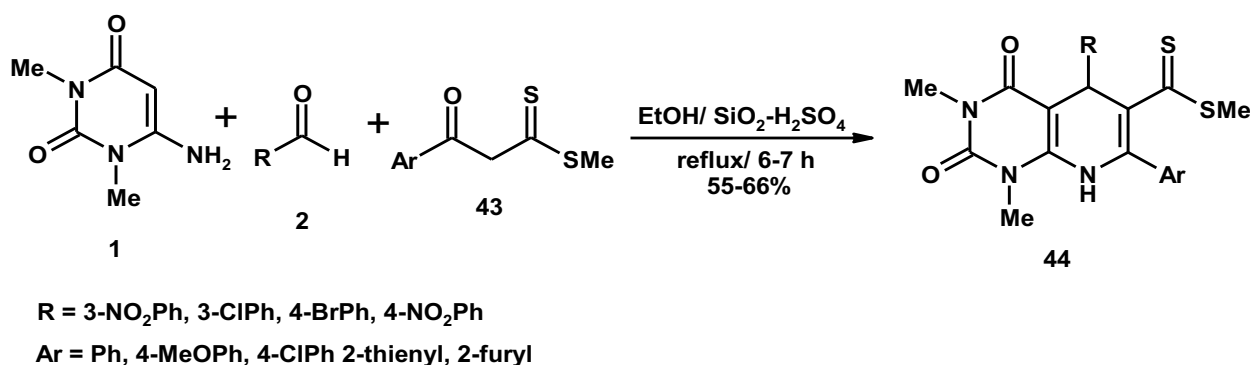
Scheme 24

Ethyl 7-(trifluoromethyl)pyrido[2,3-*d*]pyrimidine-6-carboxylates **42** were synthesized, in moderate yields, *via* three-component reaction of 6-aminouracil (**1**), aromatic aldehydes **2** and ethyl 4,4,4-trifluoro-3-oxobutanoate (**41**) in dimethyl sulfoxide (DMSO) in the presence of piperidine as catalyst (Scheme 25).⁵³



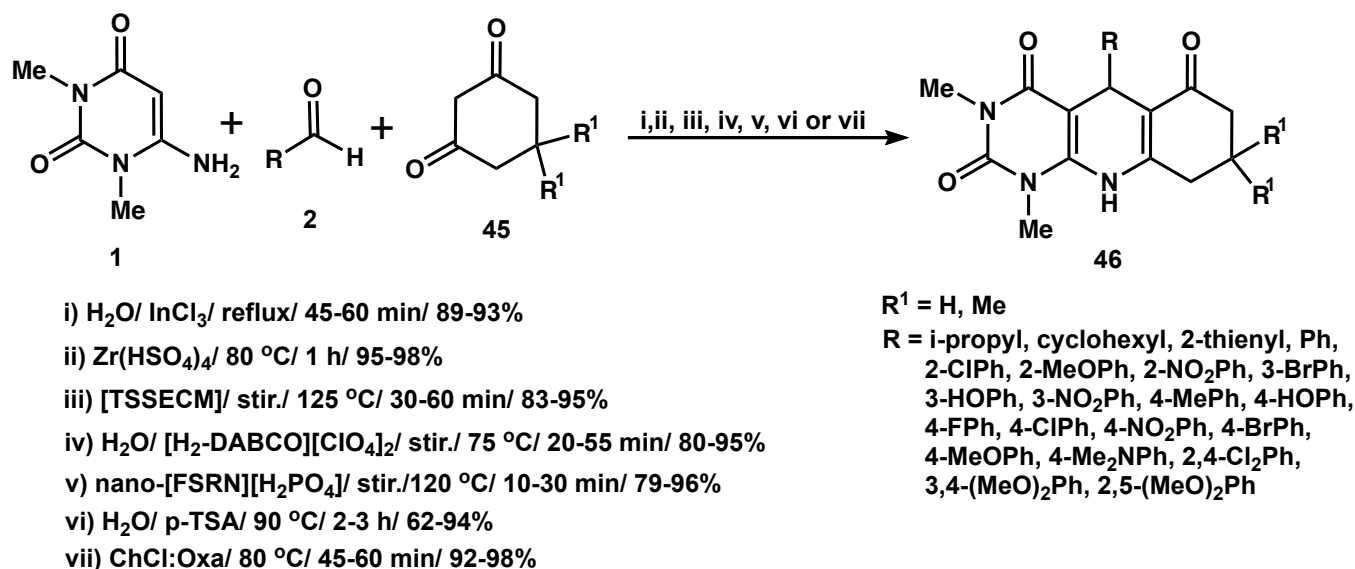
Scheme 25

Highly functionalized pyrido[2,3-*d*]pyrimidines **44** were produced, in a moderate yields, through three-component cyclocondensation reactions of 6-amino-1,3-dimethyluracil (**1**), aromatic aldehydes **2** and β -oxodithioesters **43** in the presence of recyclable SiO₂-H₂SO₄ (Scheme 26).⁵⁴



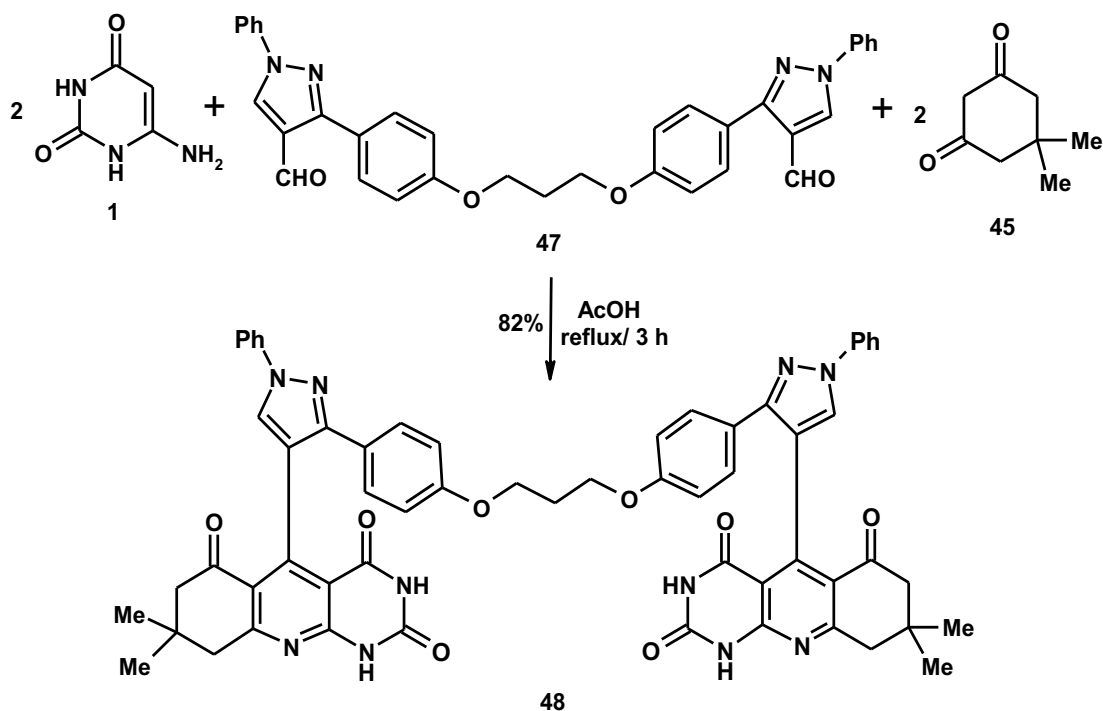
Scheme 26

Tetrahydropyrimido[4,5-*b*]quinoline-2,4,6-triones **46** were synthesized, by three-component reactions of 6-amino-1,3-dimethyluracil (**1**), aromatic aldehydes **2** and various 1,3-dicarbonyl compound **45** such as 1,3-cyclohexanedione and 5,5-dimethyl-1,3-cyclohexanedione (dimedone) under a variety of reaction conditions (Scheme 27).⁵⁵⁻⁶¹



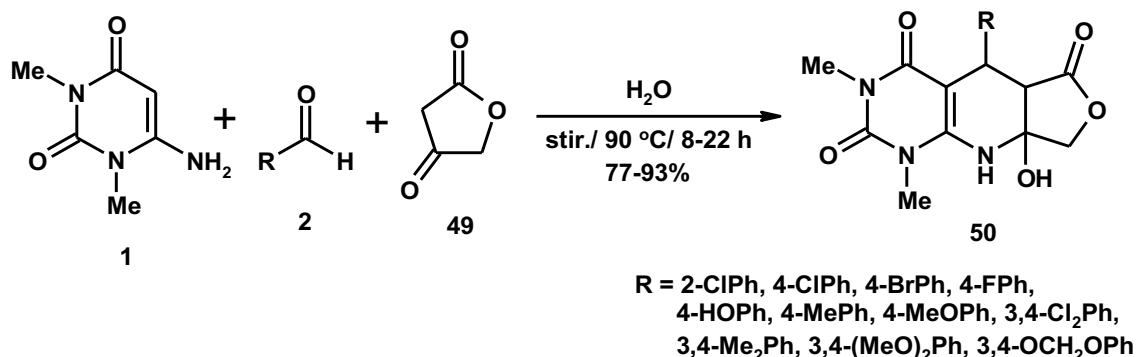
Scheme 27

While, multi-component reactions of two equivalents of both 6-aminouracil (**1**) with *bis*(1-phenylpyrazole-4-carboxaldehyde) **47** and dimedone (**45**) in acetic acid afforded *bis*(8,8-dimethyl-8,9-dihydropyrimido[4,5-*b*]quinolinetrione) **48** in good yield (Scheme 28).²⁵



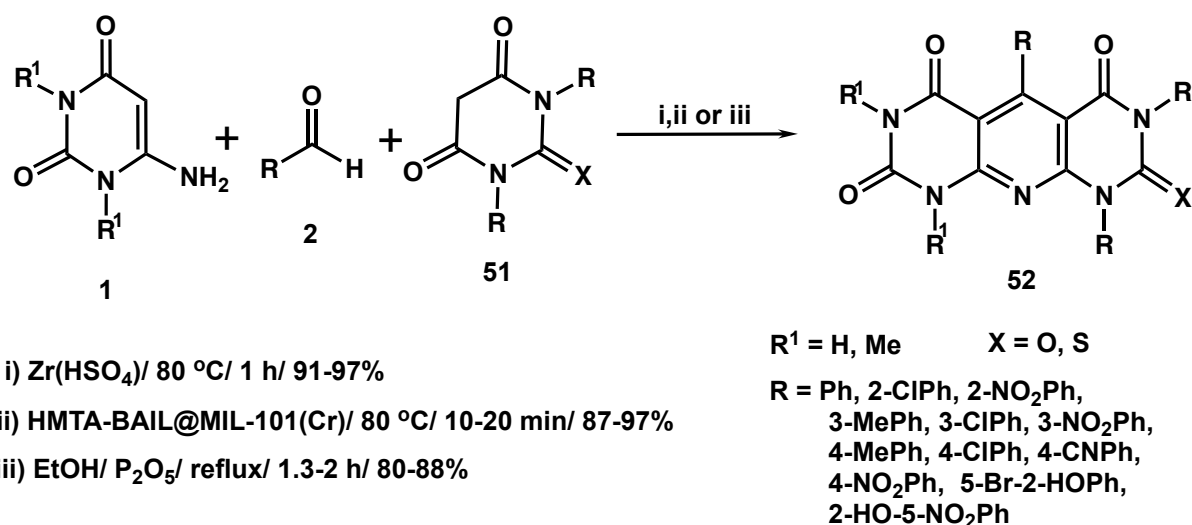
Scheme 28

Furo[2',1':5,6]pyrido[2,3-*d*]pyrimidinetriones **50** were prepared, in 77-93% yields, by treating 6-amino-1,3-dimethyluracil (**1**), aromatic aldehydes **2** and tetrahydrofuran-2,4-dione (tetronic acid) (**49**), in water without catalyst (Scheme 29).⁶²



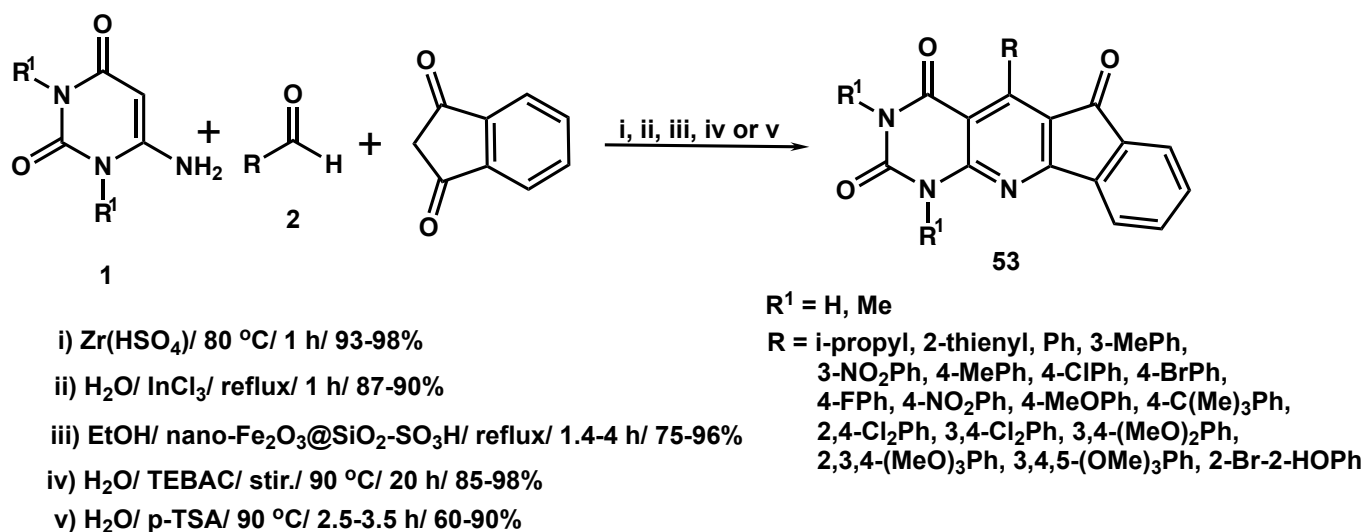
Scheme 29

Also, multi-component reactions of 6-amino-1,3-disubstituted uracils **1**, aromatic aldehydes **2** and barbituric acid derivatives **51**, under different reaction conditions, afforded pyrido[2,3-*d*]dipyrimidine-2,4,6,8-tetraones **52**, in 80-97% yields (Scheme 30).^{56,63,64}



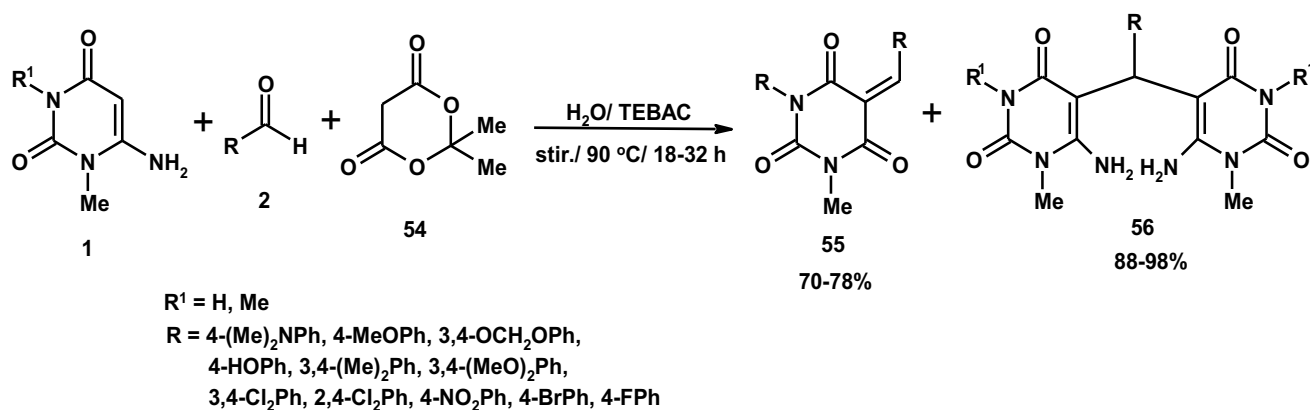
Scheme 30

Similarly, three-component green reaction of 6-amino-1,3-disubstituted uracils **1**, aromatic aldehydes **2**, and 1,3-indanedione, under various reaction conditions, gave 1,3-dimethyl-5-aryl-1*H*-indeno[2',1':5,6]pyrido[2,3-*d*]pyrimidine-2,4,6(3*H*)-triones **53**, in 60-98% yield (Scheme 31).^{56-58,65,66}



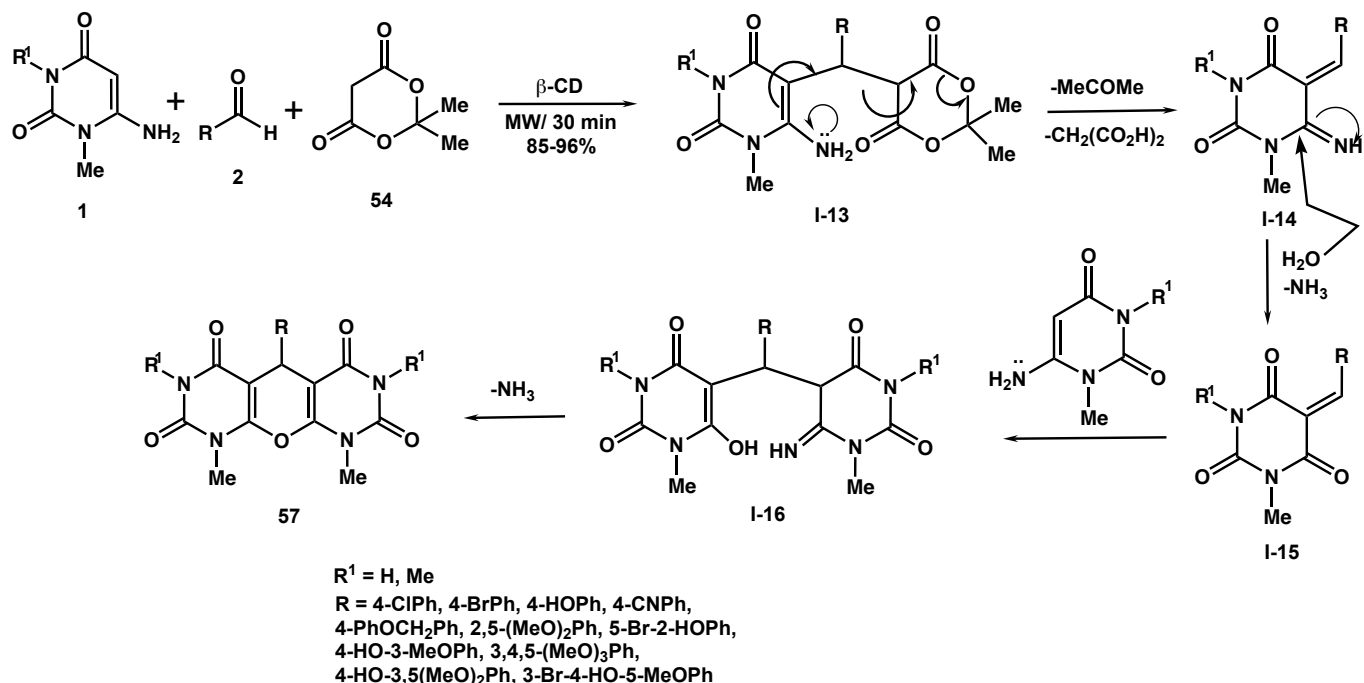
Scheme 31

Two unexpected products which are 5-benzylidenepyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**55**) and 5,5'-(arylmethylene)bis(6-aminopyrimidine-2,4(1*H*,3*H*)-dione) (**56**) were obtained *via* the three-component reactions of 6-amino-1,3-disubstituted uracil **1**, aromatic aldehydes **2** and 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) (**54**) in presence of triethylbenzylammonium chloride (TEBAC) as catalyst (Scheme 32).⁶⁷



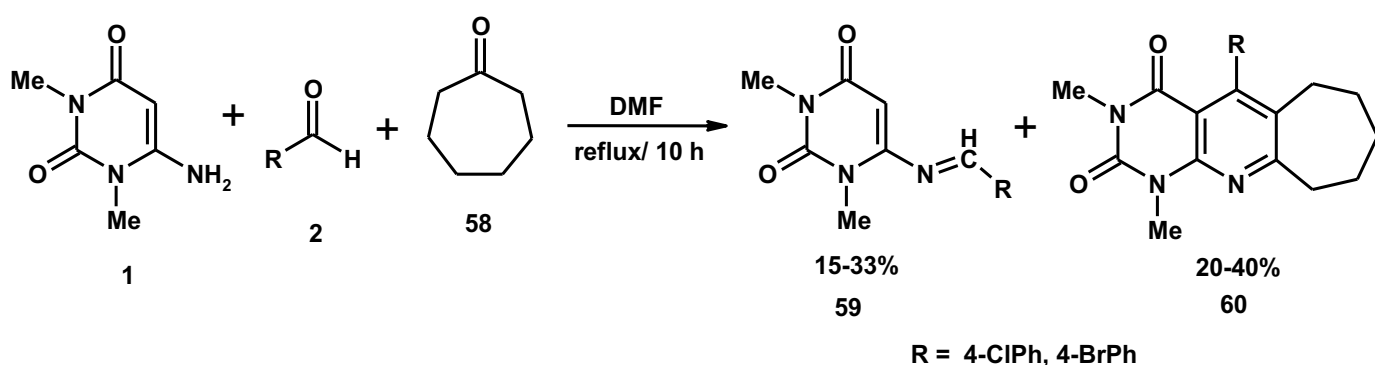
Scheme 32

While grinding 6-amino-1,3-dimethyluracil (**1**) with aromatic aldehydes **2** and Meldrum's acid (**54**) in the presence of β -cyclodextrin (β -CD) under microwave irradiation, afforded pyrano[2,3-*d*:6,5-*d'*]-dipyrimidines **57**. A plausible mechanism for the formation of compound **57** can be explained *via* condensation of aldehyde function with the active hydrogen in both reagents giving intermediate **I-13** followed by rapture of Meldrum's acid through elimination of acetone and malonic acid molecules to give intermediate **I-14**. Hydrolysis of the latter intermediate produced trione (intermediate **I-15**) which added another molecule of compound **1** giving intermediate **I-16** that cyclized with liberation of ammonia molecule (Scheme 33).⁶⁸



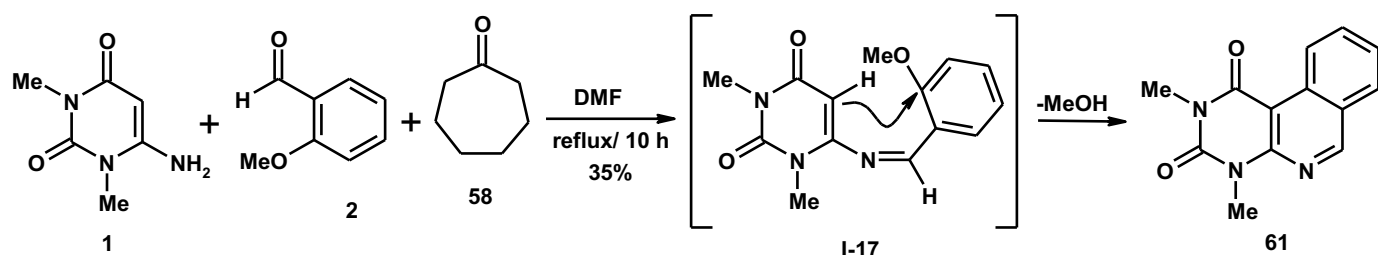
Scheme 33

Hegab *et al.* reported that three-component reaction of 6-amino-1,3-dimethyluracils (**1**) with aromatic aldehydes **2** and cycloheptanone (**58**) in DMF under reflux afforded two products which are Schiff bases **59** and 5-aryl-hexahydrocyclohepta[5,6]pyrido[2,3-*d*]pyrimidine-2,4-diones **60** as anti-inflammatory agents (Scheme 34).⁶⁹ Formation of compound **60** takes place through addition of cycloheptanone to the azomethine function in the Schiff bases **59** (*E*-configuration) followed by cyclo-condensation.



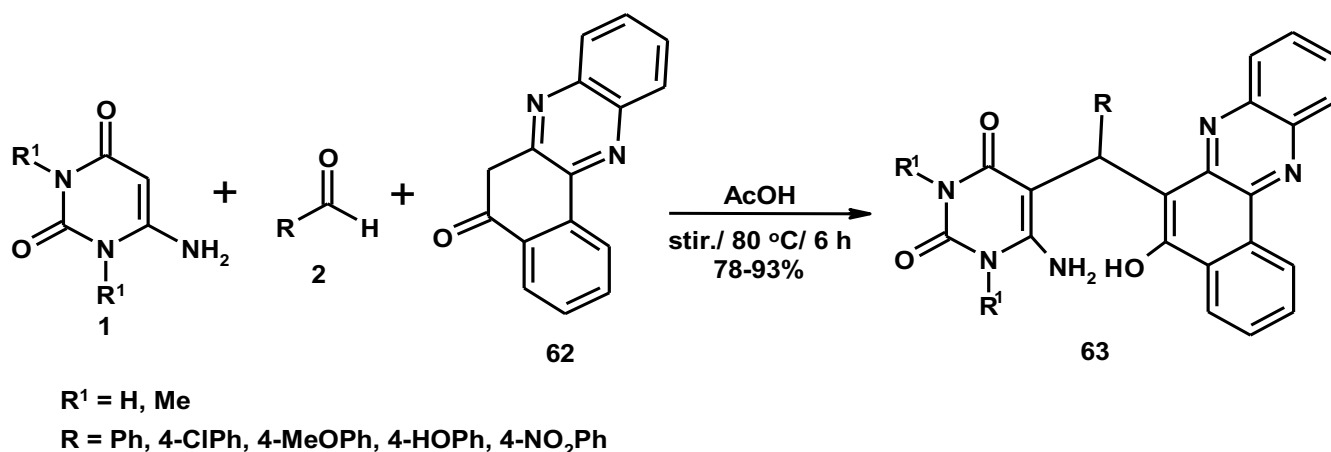
Scheme 34

Meanwhile, the three-component reaction of 6-amino-1,3-dimethyluracil (**1**), 2-methoxybenzaldehyde (**2**) and cycloheptanone (**58**) in DMF afforded only one product; 1,3-dimethylbenzo[4,5]pyrido[3,2-*d*]pyrimidinedione (**61**) which have anti-inflammatory activity. Formation of compound **61** takes place through Schiff base intermediates **I-17** (*Z*-configuration) which facilitates ring closure rather than addition of cycloheptanone to the azomethine group (Scheme 35).⁶⁹



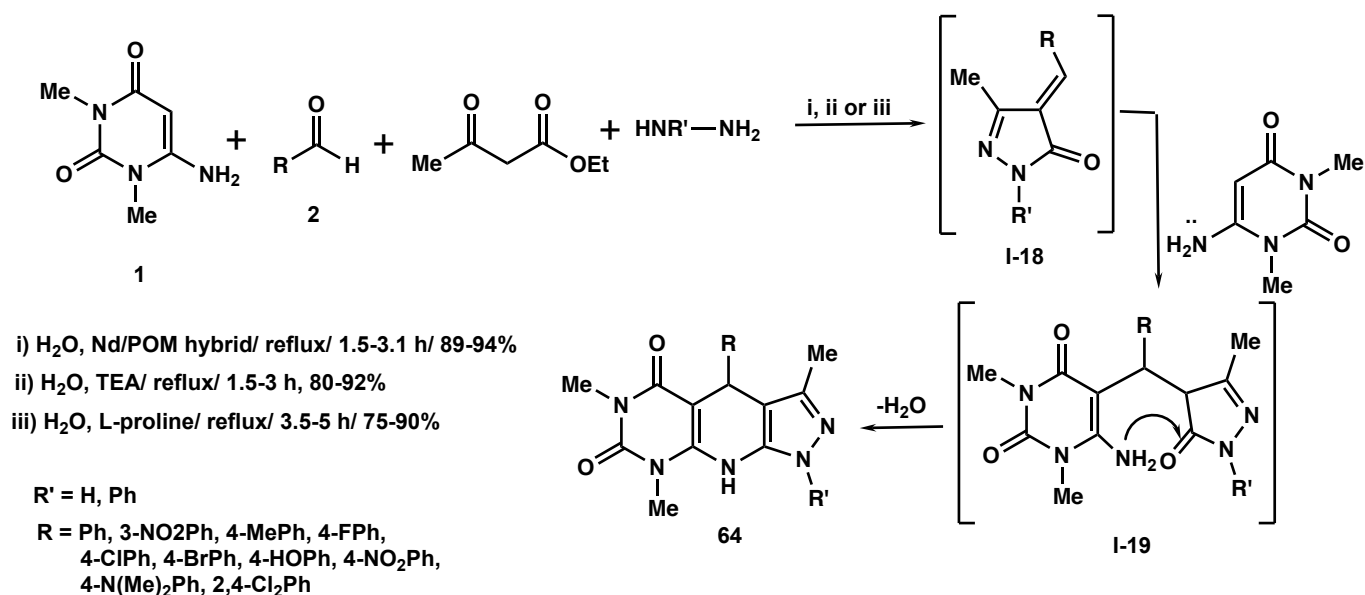
Scheme 35

Similarly, 6-amino-5-(5-hydroxybenzo[*a*]phenazin-6-yl)-1,3-dimethylpyrimidine-2,4-diones **63** were synthesized, *via* condensation of 6-amino-1,3-disubstituted uracils **1** with aldehydes **2** and benzo[*a*]phenazin-5(6*H*)-one (**62**) in acetic acid for 6 hours (Scheme 36).⁷⁰



Scheme 36

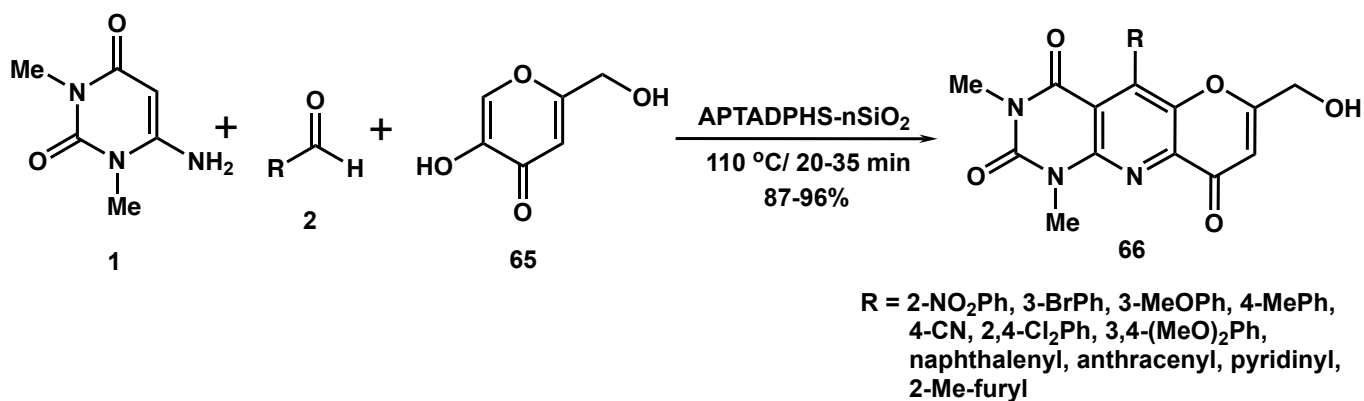
Meanwhile, four-component reaction of 6-amino-1,3-dimethyluracil (**1**), aromatic aldehydes **2**, ethyl acetoacetate and hydrazines, under various reaction conditions, produced a series of pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidinediones **64**, in good to excellent yields. The proposed mechanism occurs through of pyrazole intermediates **I-18** which added compound **1** at the exocyclic olefinic bond giving intermediates **I-19** followed by cyclo-condensation generating the final products **64** (Scheme 37).^{71,72}



Scheme 37

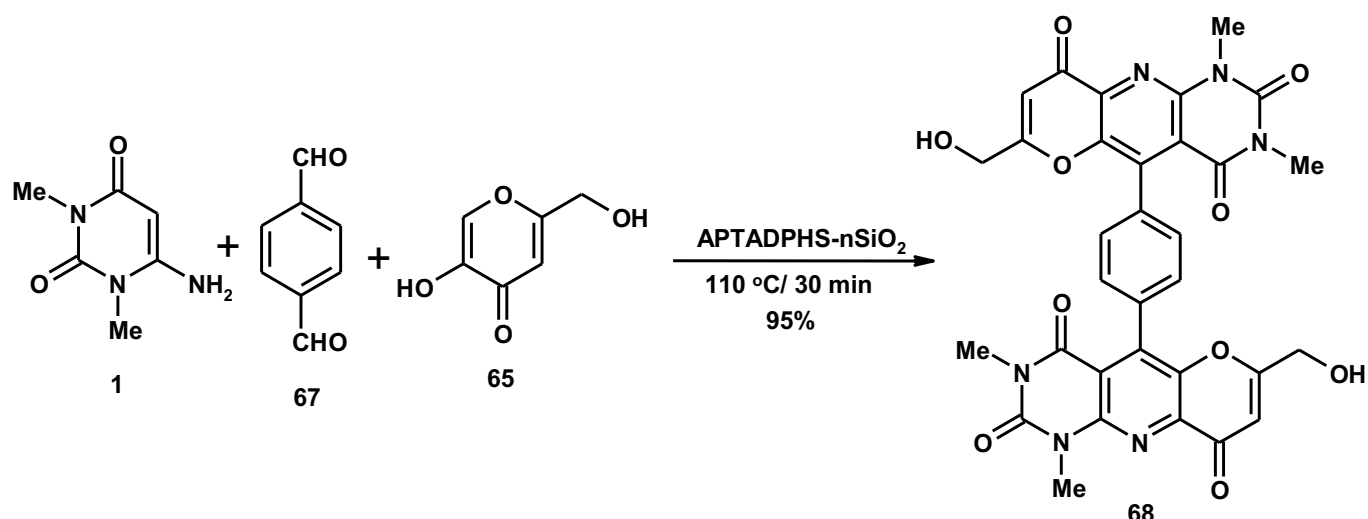
2.2.1.5. Reactions with aldehydes in the presence of cyclic enols

Three-component condensation of 6-amino-1,3-dimethyluracil (**1**), aromatic aldehydes **2** and kojic acid **65**, in the presence of aminopropyl-1,3,5-triazine-2,4-diphosphonium hydrogen sulfate supported on nano-silica (APTADPHS-nSiO₂) as catalyst, gave pyrano[2',3':5,6] pyrido[2,3-*d*]pyrimidines **66** (Scheme 38).⁷³



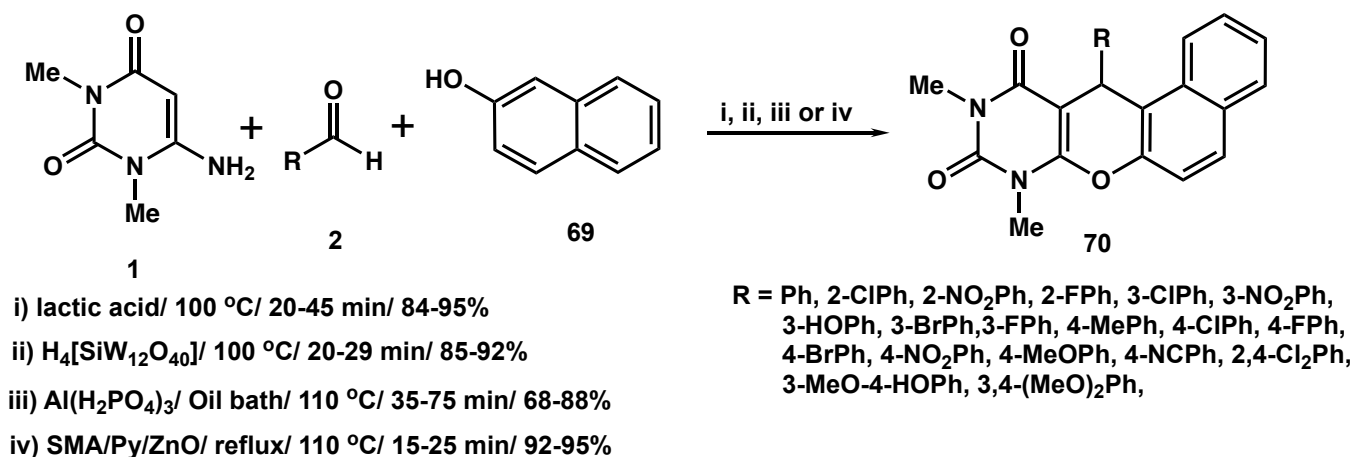
Scheme 38

While *bis*(pyranopyridopyrimidine) **68** was furnished, in excellent yield, *via* multi-component reactions of 6-amino-1,3-dimethyluracil (**1**), terephthalaldehyde (**67**) and kojic acid **65**, in the presence APTADPHS-nSiO₂ as catalyst (Scheme 39).⁷³



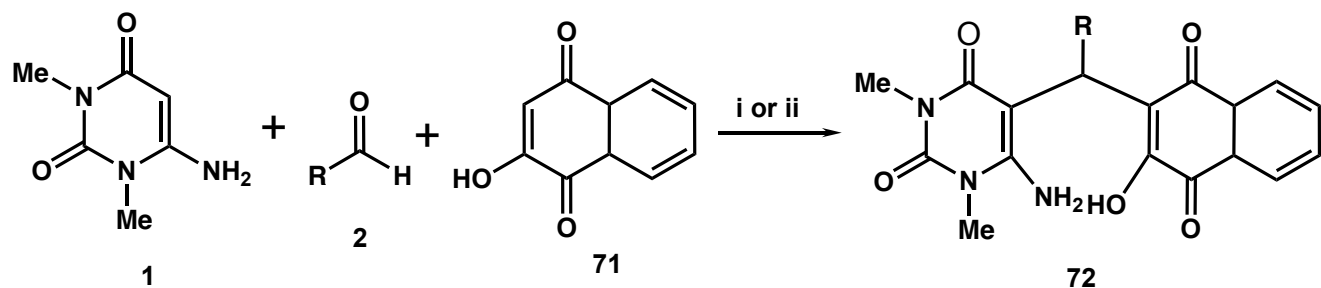
Scheme 39

Also, an efficient one-pot three-component reaction between 6-amino-1,3-dimethyluracil (**1**), aromatic aldehydes **2** and β -naphthol (**69**), under various reaction conditions, yielded chromeno[2,3-*d*]pyrimidine-1,3-diones **70** (Scheme 40).⁷⁴⁻⁷⁷



Scheme 40

Moreover, 6-amino-5-(1,4-dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)methyl)-1,3-dimethylpyrimidine-2,4-diones **72** were prepared through three-component reactions of 6-amino-1,3-dimethyluracil (**1**) with aliphatic or aromatic aldehydes **2** and 2-hydroxynaphthalene-1,4-dione (**71**) (Scheme 41).^{78,79}



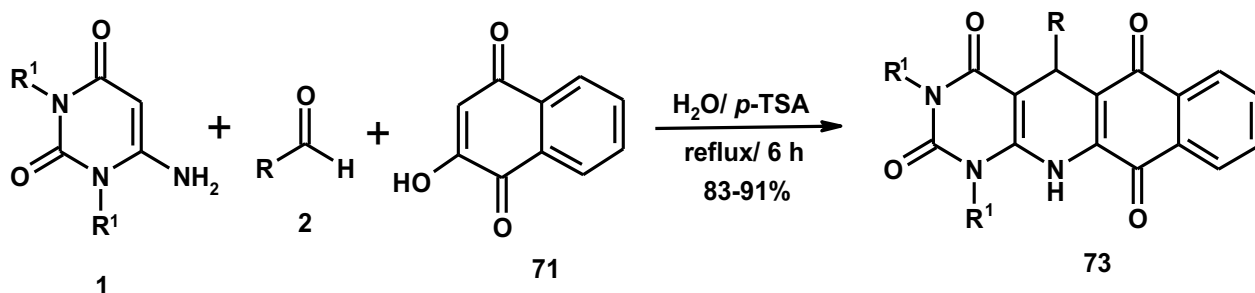
i) H₂O/ I₂ (10 mol%)/ reflux/ 2.5-10 h/ 55-92%

ii) EtOH/ NiCo₂O₄/ CS/ PWA/ reflux/ 60-90 min/ 78-96%

R = *n*-C₄H₉, cyclohexyl, 2-naphthyl, Ph, 2-FPh, 2-MeOPh, 3-CIPh, 3-BrPh, 3-HOPh, 3-NO₂, 4-MePh, 4-MeOPh, 4-CIPh, 4-BrPh, 4-FPh, 4-NO₂Ph, 4-CNPh, 4-*i*-propyl-Ph

Scheme 41

While, three-component reactions of 6-amino-1,3-disubstituted uracils **1**, aromatic aldehydes **2** and 2-hydroxynaphthalene-1,4-dione (**71**), in the presence of *p*-TSA as catalyst, yielded pyrimido[4,5-*b*]quinoline-tetraones **73**, in 83-91% yields (Scheme 42).⁸⁰



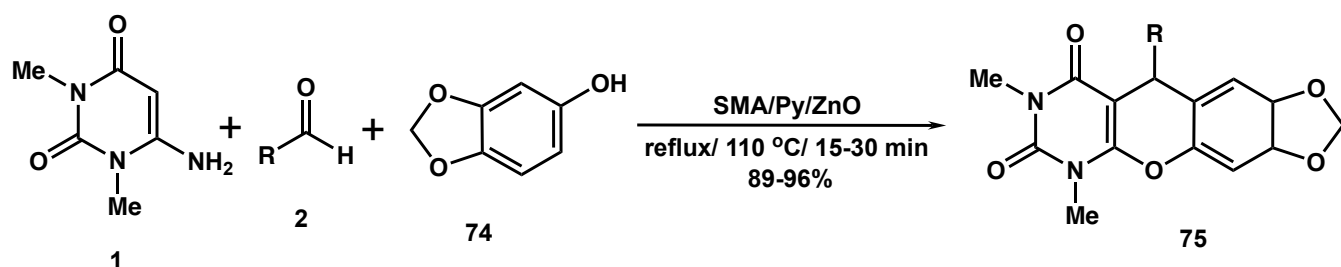
R¹ = H, Me

R = Ph, 4-CIPh, 4-BrPh, 4-NO₂Ph,

2-MePh, 3-MePh, 4-MePh, 4-MeOPh

Scheme 42

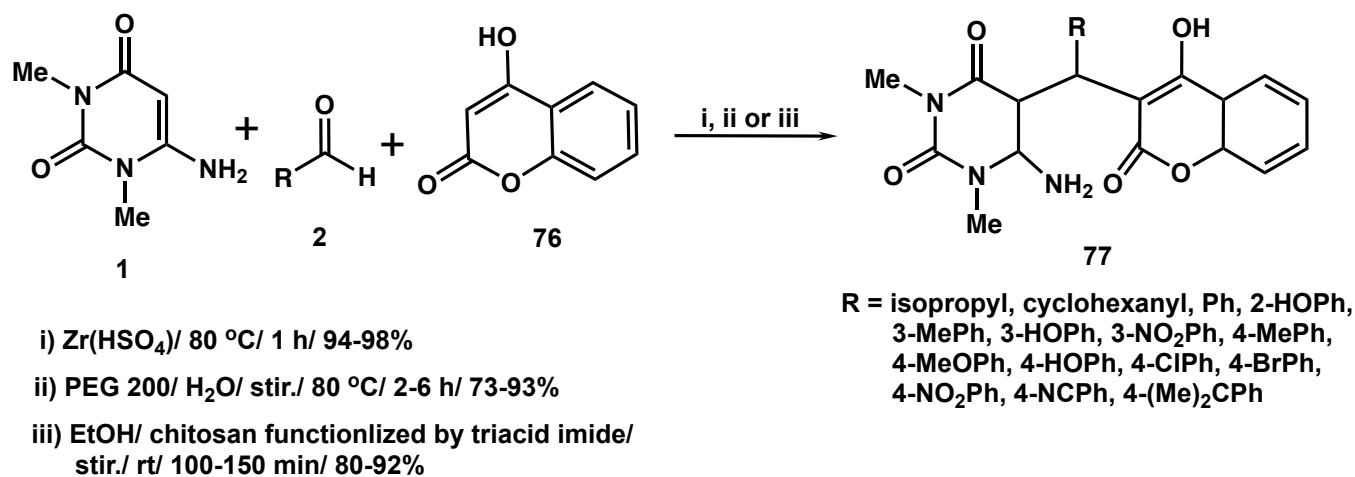
Multi-component reaction of 6-amino-1,3-dimethyluracil (**1**), aromatic aldehydes **2** and benzo[*d*][1,3]dioxol-5-ol (**74**), by using SMA/Py/ZnO as nano catalyst, yielded chromeno[2,3-*d*]pyrimidinediones **75** (scheme 43).⁷⁷



R = Ph, 2-CIPh, 2-BrPh, 3-MeOPh, 3-BrPh, 4-MePh, 4-CIPh, 4-FPh, 4-BrPh, 4-NO₂Ph, 2,4-Cl₂Ph, 2,3-Cl₂Ph, 3,4-Cl₂Ph, 2,4-(MeO)₂Ph

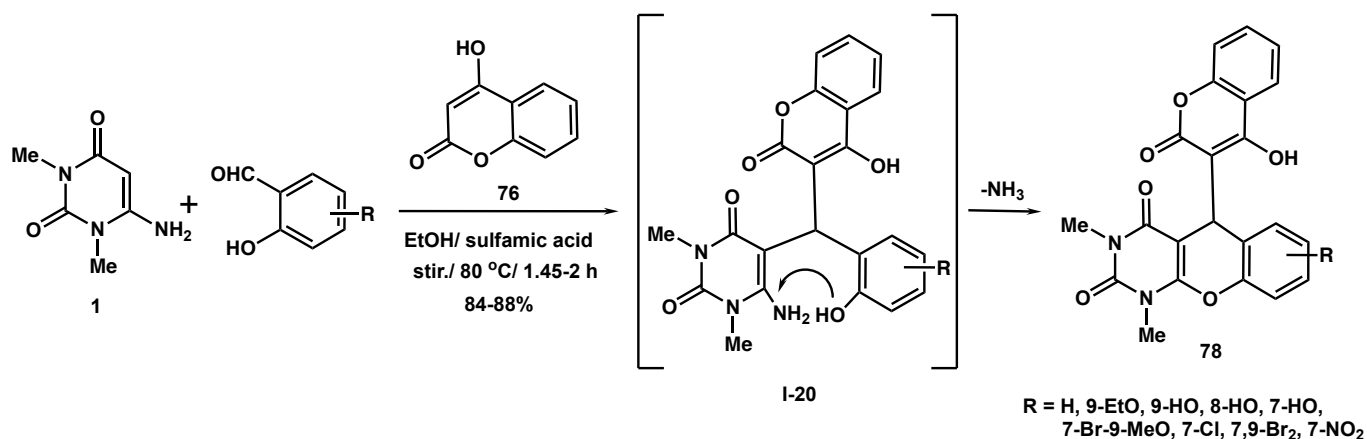
Scheme 43

Meanwhile, treatment of 6-amino-1,3-dimethyluracil (**1**) with aromatic aldehydes **2** and 4-hydroxycoumarin (**76**), under various reaction conditions, provided 6-amino-5-[(4-hydroxy-2-oxo-2*H*-chromen-3-yl)(aryl)methyl]-1,3-dimethyl-2,4,6(1*H*,3*H*)-pyrimidinedione derivatives **77** (Scheme 44).^{56,70,81}



Scheme 44

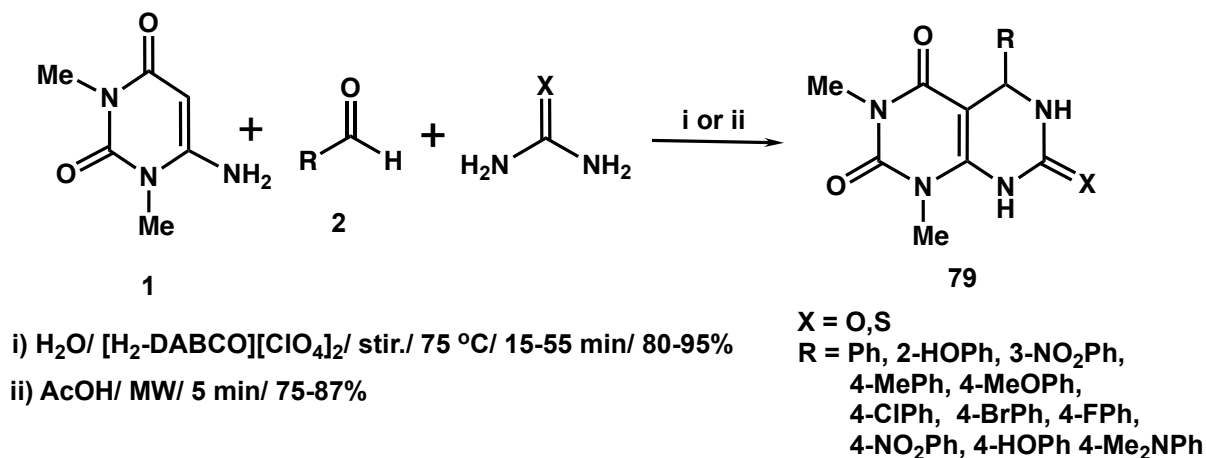
Also, chromeno[2,3-*d*]pyrimidine-2,4(3*H*,5*H*)-diones **78** were synthesized, *via* intermediates **I-20**, through three-component reaction of 6-amino-1,3-dimethyluracil (**1**), substituted salicylaldehydes and 4-hydroxycoumarin (**76**), by using sulfamic acid at 80 °C (Scheme 45).⁸²



Scheme 45

2.2.1.6. Reactions with aldehydes in the presence of nitrogen nucleophiles

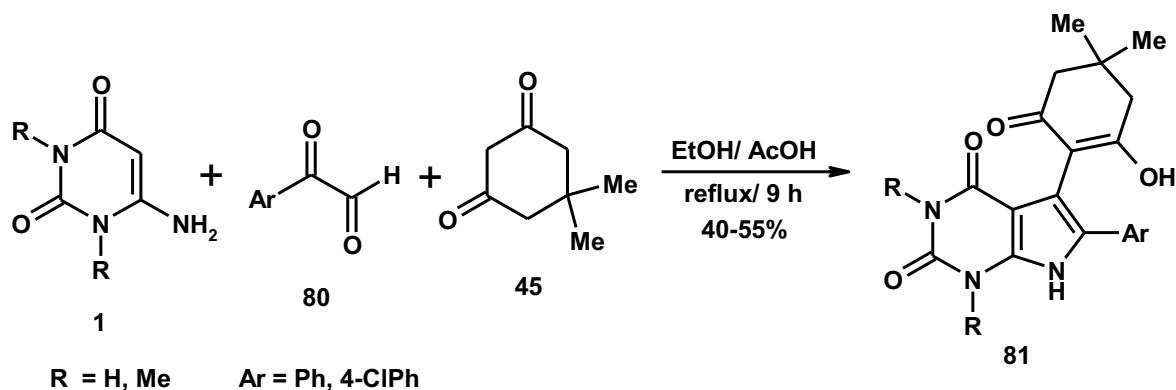
Pyrimido[4,5-*d*]pyrimidines **79** were obtained, in 75-95% yields, *via* multi-component reactions of 6-amino-1,3-dimethyluracil (**1**), aromatic aldehydes **2** and urea or thiourea, under various reaction conditions (Scheme 46).^{31,55}



Scheme 46

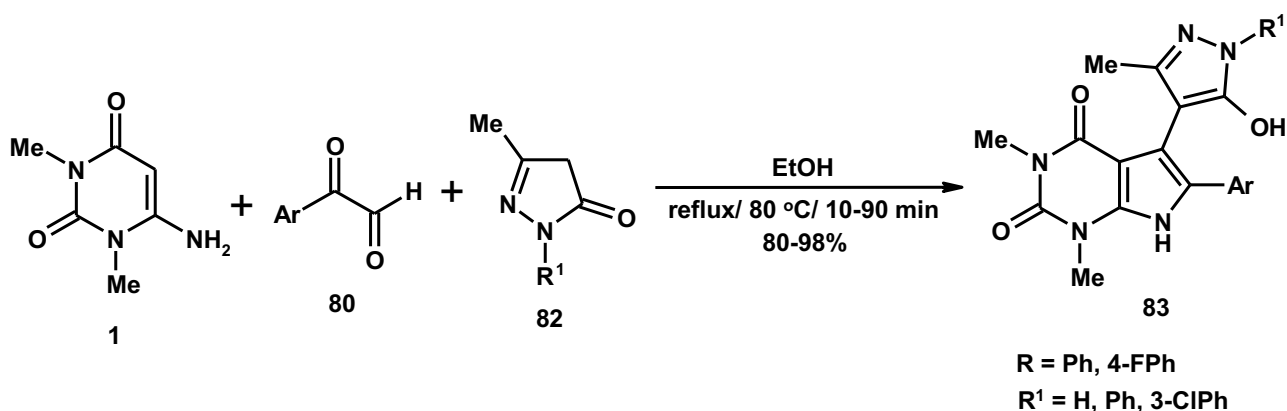
2.2.2. Reactions with arylglyoxals

Pyrrolo[2,3-*d*]pyrimidine derivatives **81** were synthesized *via* a three-component one-step reaction of 6-amino-1,3-disubstituted uracils **1**, arylglyoxales **80** and dimedone (**45**), in ethanol in the presence of catalytic amount of acetic acid (Scheme 47).⁸³



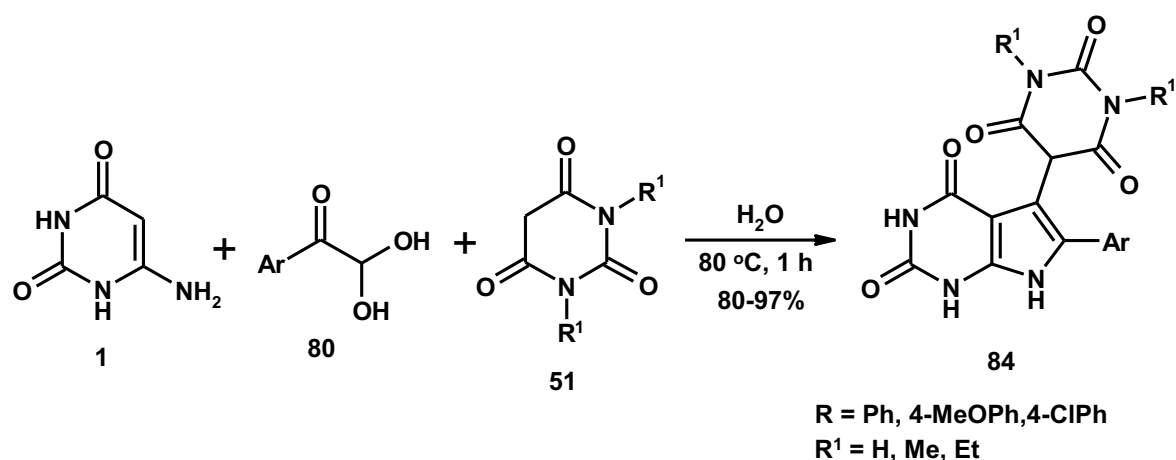
Scheme 47

Further, heterocyclization of 6-amino-1,3-dimethyluracil (**1**) with arylglyoxal hydrate **80** and pyrazolone derivatives **82** in ethanol provided 5-pyrazolyl-6-arylpyrrolo[2,3-*d*]pyrimidines **83**, in 80-98% yields (Scheme 48).⁸⁴



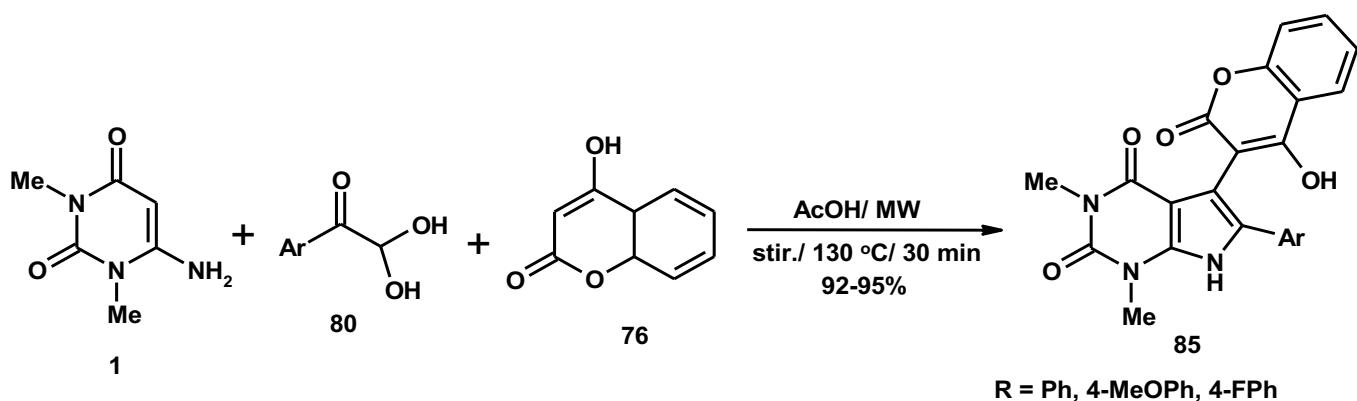
Scheme 48

Similarly, pyrrolo[2,3-*d*]pyrimidines **84** were prepared, through multi-component reaction of 6-aminouracil (**1**), arylglyoxal hydrate **80** and barbituric acids **51** in water for 1 hour (Scheme 49).⁸⁵



Scheme 49

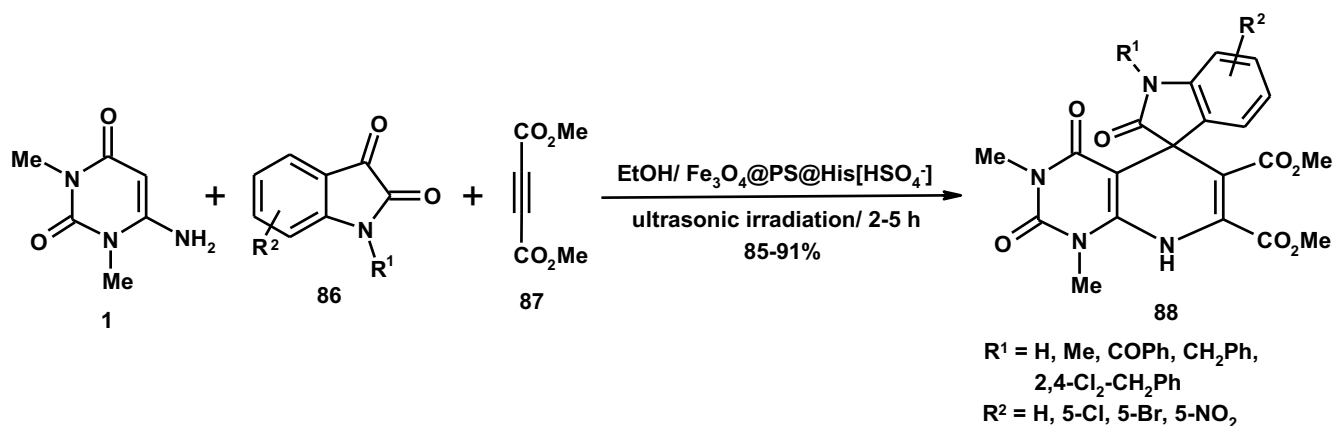
Also, multi-component reactions of 6-amino-1,3-dimethyluracil (**1**), arylglyoxal hydrate **80** and 4-hydroxycoumarin (**76**) in acetic acid under microwave conditions provided pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-diones **85**, in excellent yields (Scheme 50).⁸⁶



Scheme 50

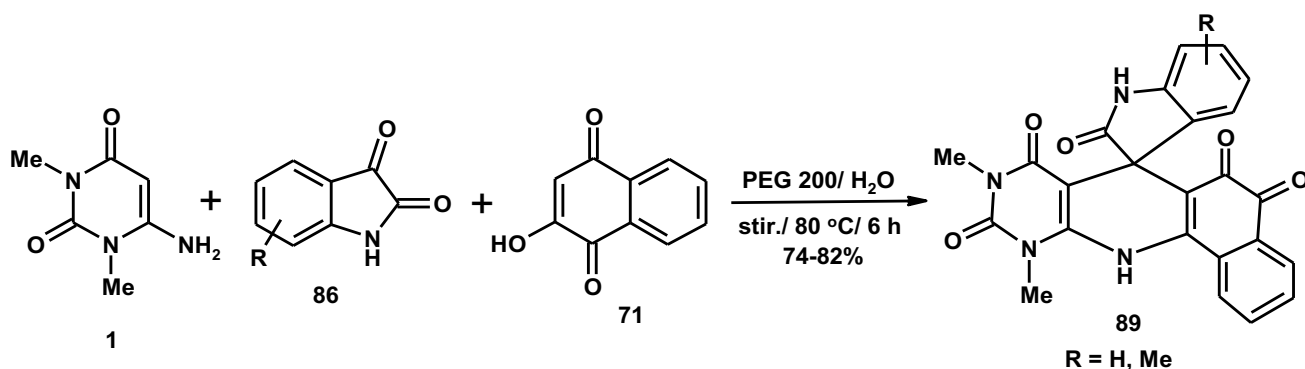
2.2.3. Reactions with isatins

Mousavifar *et al.* reported that an efficient and environment friendly procedure for the synthesis of spiroindoline-3,5'-pyrido[2,3-*d*]pyrimidines **88** via the condensation reaction of 6-amino-1,3-dimethyluracil (**1**) with isatins **86** and dimethyl acetylenedicarboxylate (**87**), in the presence of Fe₃O₄@Propylsilane@Histidine[HSO₄⁻] as a heterogenous catalyst under ultrasound irradiation (Scheme 51).⁸⁷



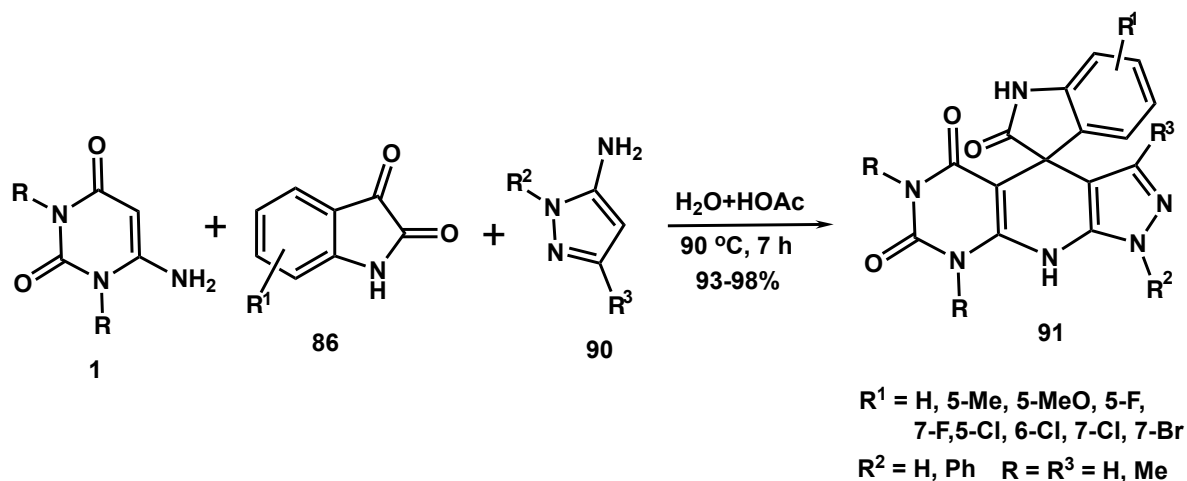
Scheme 51

Spiro-indeno[1,2-*b*]pyrido[2,3-*d*]pyrimidines **89** were obtained, in very good yields, by reacting 6-amino-1,3-dimethyluracil (**1**) with isatins **86** and 2-hydroxynaphthalene-1,4-dione (**71**) in poly(ethylene glycol) 200/H₂O (Scheme 52).⁷⁰



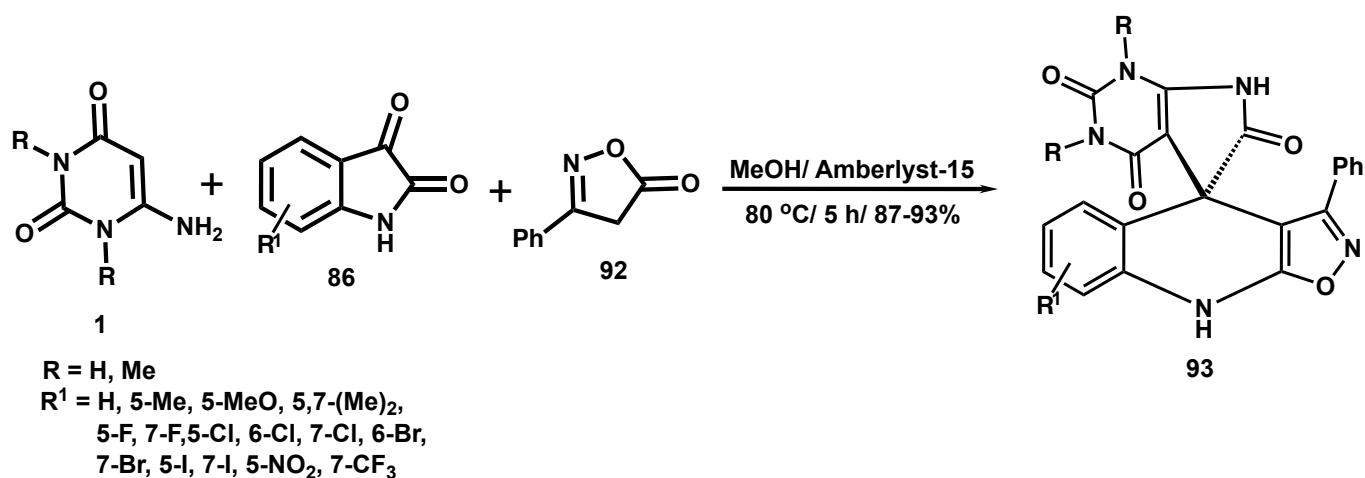
Scheme 52

Spiro-fused 3,4-pyrazolo[4,3:5,6]pyrido[2,3-*d*]pyrimidine derivatives **91** were synthesized, in an excellent yields, by treating 6-amino-1,3-disubstituted uracils **1**, isatins **86** and substituted 5-aminopyrazoles **90** in aqueous acetic acid (Scheme 53).⁸⁸



Scheme 53

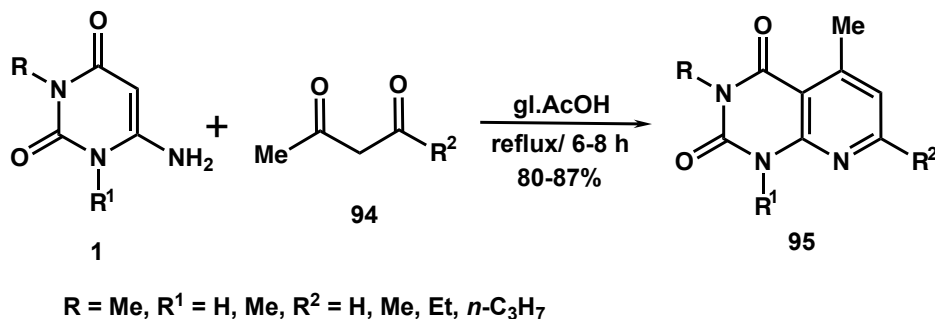
Multi-component reaction of 6-amino-1,3-disubstituted uracil **1**, isatins **86** and 3-phenylisoxazol-5-one (**92**) in methanol afforded spiro compounds **93** by using Amberlyst-15 as catalyst (Scheme 54).⁸⁹



Scheme 54

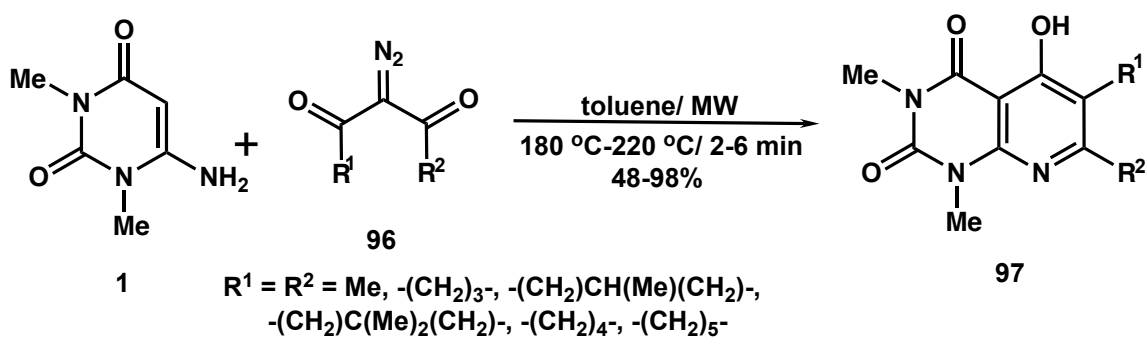
2.2.4. Reactions with carbonyl compounds

5-Methylpyrido[2,3-*d*]pyrimidine-1,4-diones **95** were resulted, as anti-inflammatory agents, by the reaction of 6-amino-1,3-disubstituted uracils **1** with 1,3-dicarbonyl compounds **94** in glacial acetic acid (Scheme 55).⁹⁰



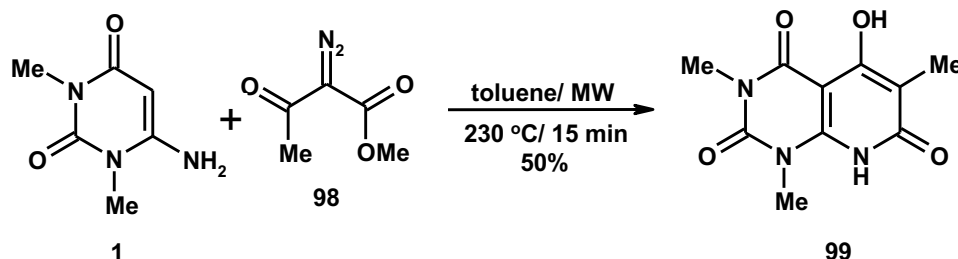
Scheme 55

5-Hydroxypyrido[2,3-*d*]pyrimidinediones **97** were obtained, in a moderate to excellent yields, by using microwave irradiation that assist the Wolff rearrangement of 2-diazo-1,3-dicarbonyl compounds **96** to react with 6-amino-1,3-dimethyluracil (**1**) in toluene (Scheme 56).⁹¹

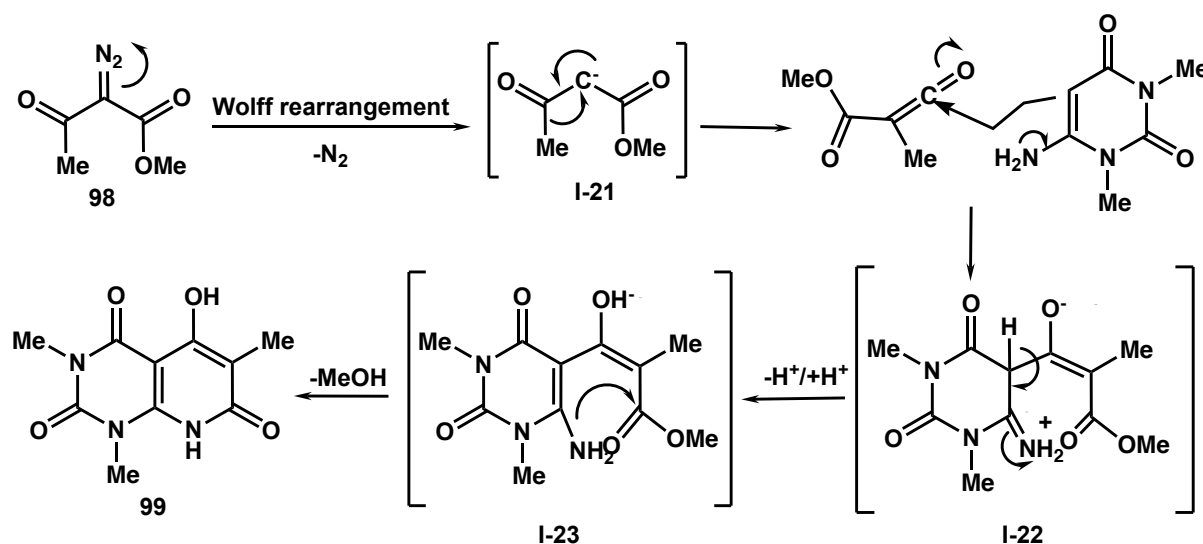


Scheme 56

Similarly, treatment of 6-amino-1,3-dimethyluracil (**1**) with α -diazo- β -ketoester **98** in toluene using microwave irradiation yielded pyrido[2,3-*d*]pyrimidinetriones **99** (Scheme 57).⁹¹ This compound can be explained *via* Wolff rearrangement followed by nucleophilic addition and cyclo-condensation reactions as was shown in Scheme 58.⁹¹

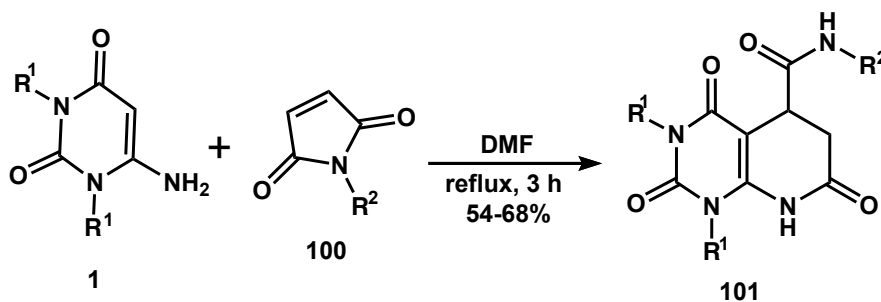


Scheme 57



Scheme 58

2,4,7-Trioxypyrido[2,3-*d*]pyrimidines **101** were synthesized, in 54-68% yields, by heterocyclization of 6-amino-1,3-disubstituted uracils **1** with maleimides **100** in boiling DMF for 3 hours (Scheme 59).⁹²

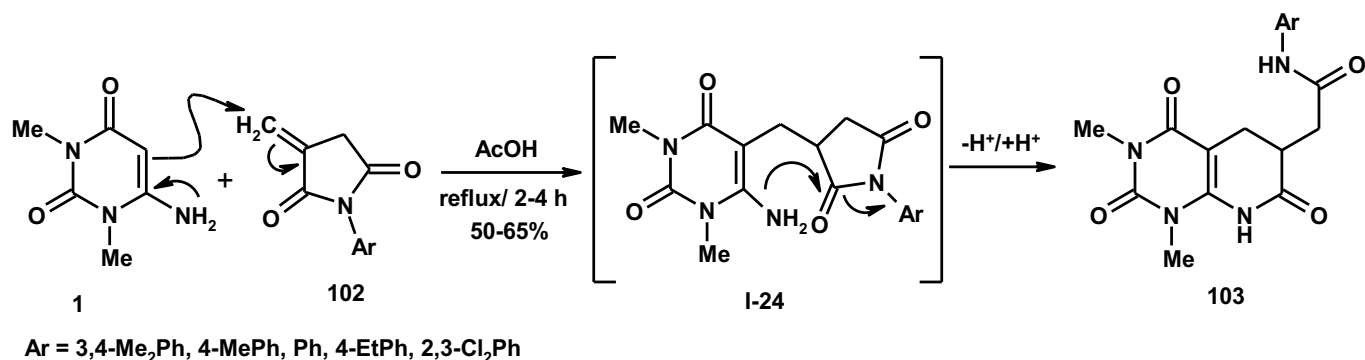


$\text{R}^1 = \text{H, Me}$

$\text{R}^2 = \text{Ph, 4-ClPh, 2,4-Me}_2\text{Ph, 4-MeO-3-ClPh, 4-CF}_3\text{Ph, 2-MeOPh, 4-MeOPh, 3,4-F}_2\text{Ph}$

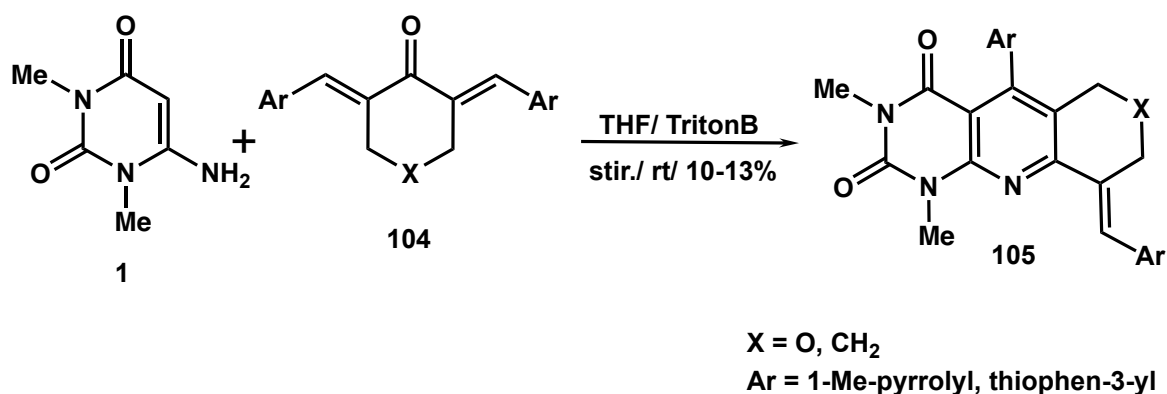
Scheme 59

Aryl-2-(1,3-dimethyl-2,4,7-trioxo-1,2,3,4,5,6,7,8-octahydropyrido[2,3-*d*]pyrimidin-6-yl)acetamides **103** were obtained, in 50-65% yields, *via* the reaction of 6-amino-1,3-dimethyluracil (**1**) with *N*-arylitaconimides **102** in acetic acid. The reaction pathway involves initial attack of the nucleophilic C-5 atom of uracil **1** on the activated exocyclic double bond in compound **102** giving intermediates **I-24** followed by intramolecular recyclization (Scheme 60).⁹³



Scheme 60

After that, treatment of 6-amino-1,3-dimethyluracil (**1**) with α , β -unsaturated ketone such as *bis*-chalcones **104**, in the presence of benzyltrimethylammonium hydroxide (Triton B) yielded tetrahydropyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-diones **105**. These compounds may be useful in the elucidation of the molecular mechanisms of non-apoptotic cell death, for study the vacuoles formation process, and to test autophagy inhibitors (Scheme 61).⁹⁴

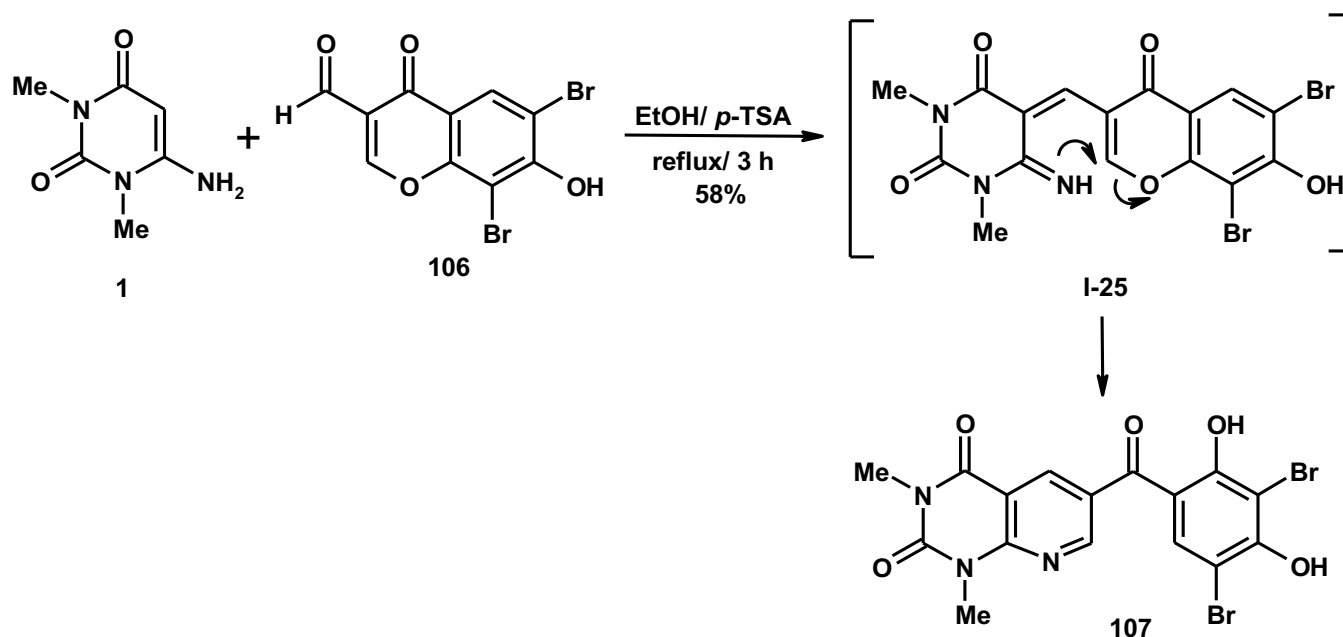


Scheme 61

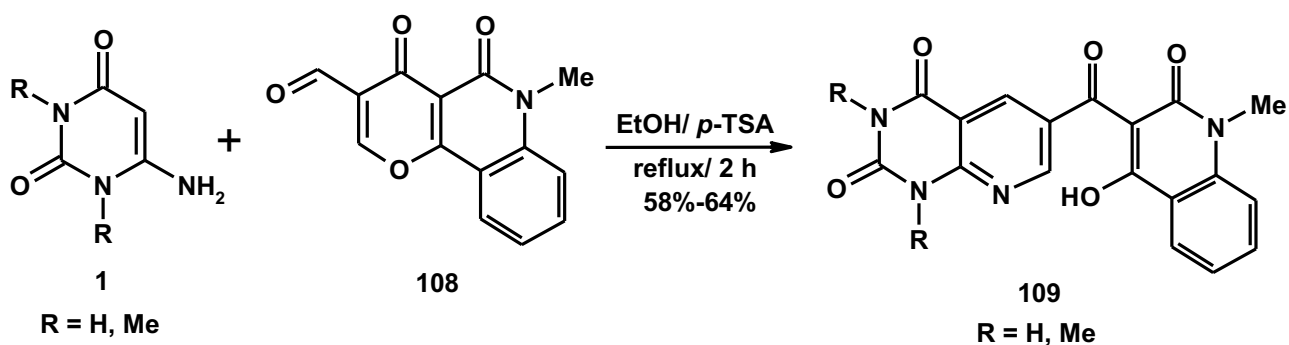
2.2.5. Reactions with substituted chromones

It is known that compounds containing γ -pyrone moiety bearing electron withdrawing functional groups represent good building blocks for a variety of heterocyclic compounds through reaction with electron rich nucleophiles. Ibrahim and his coworkers⁹⁵ studied the chemical behavior of 6-amino-1,3-dimethyluracil (**1**) with 6,8-dibromo-7-hydroxychromone-3-carboxaldehyde (**106**) in absolute ethanol containing one crystal of *p*-toluene sulfonic acid gave pyrido[3,2-*d*]pyrimidine derivative **107** through condensation of the

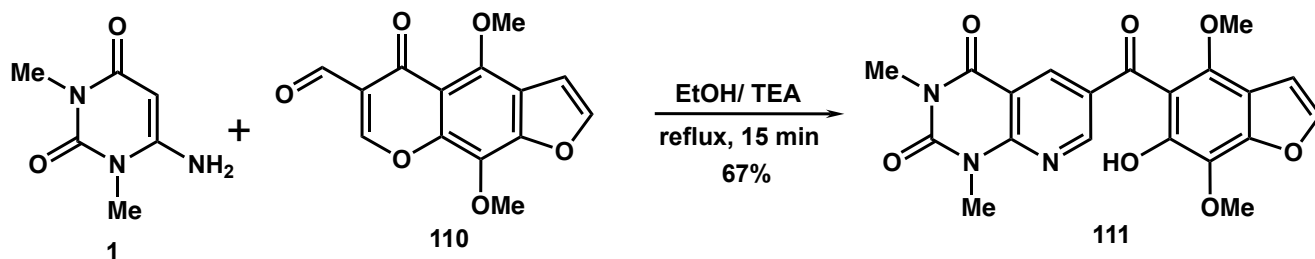
formyl group with the active methylene group gave intermediate **I-25** followed by γ -pyrone ring opening by the imine nitrogen as shown in Scheme 62.⁹⁵



Also, treatment of 6-amino-1,3-disubstituted uracils **1** with carboxaldehyde **108** in absolute ethanol containing *p*-toluenesulfonic acid produced pyrido[2,3-*d*]pyrimidines bearing the quinolinylcarbonyl moieties **109** as antimicrobial agents (Scheme 63).⁹⁶

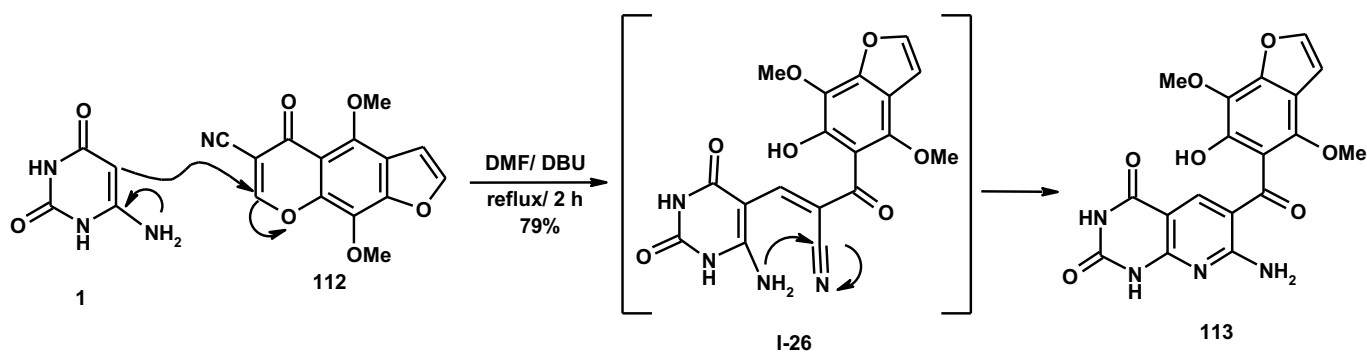


Similarly, reaction of 6-amino-1,3-dimethyluracil (**1**) with 6-formylkhellin (**110**) in boiling ethanol containing few drops of TEA resulted pyrido[2,3-*d*]pyrimidine derivative **111** as antimicrobial agent (Scheme 64).⁹⁷



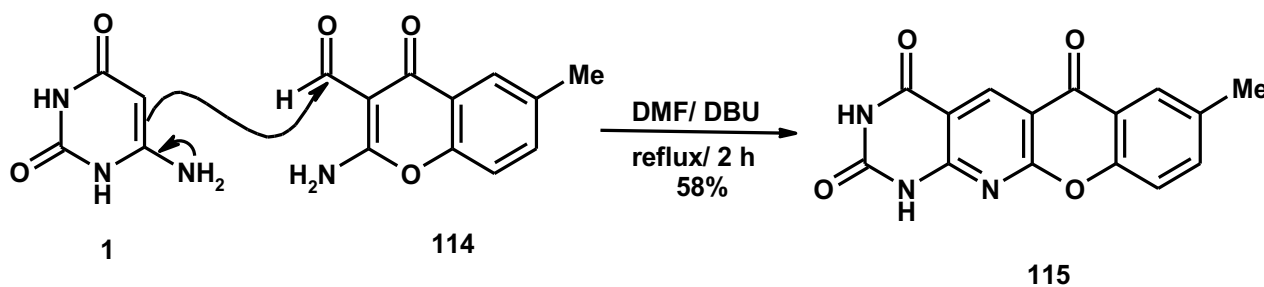
Scheme 64

In a different pathway, reaction of 6-aminouracil (**1**) with khellin-3-carbonitrile **112**, in DMF containing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), proceed through nucleophilic attack at C-7 position with ring opening giving intermediate **I-26** which underwent cycloaddition of the amino group into the nitrile function producing pyrido[2,3-*d*]pyrimidine derivative **113** which has antimicrobial activity (Scheme 65). In this reaction, the cycloaddition into the nitrile group occurs by the nitrogen atom of the amino group not the oxygen atom of the hydroxyl group; due to the higher nucleogilicity of nitrogen as compare with oxygen as reported by Ibrahim *et al.*⁹⁸



Scheme 65

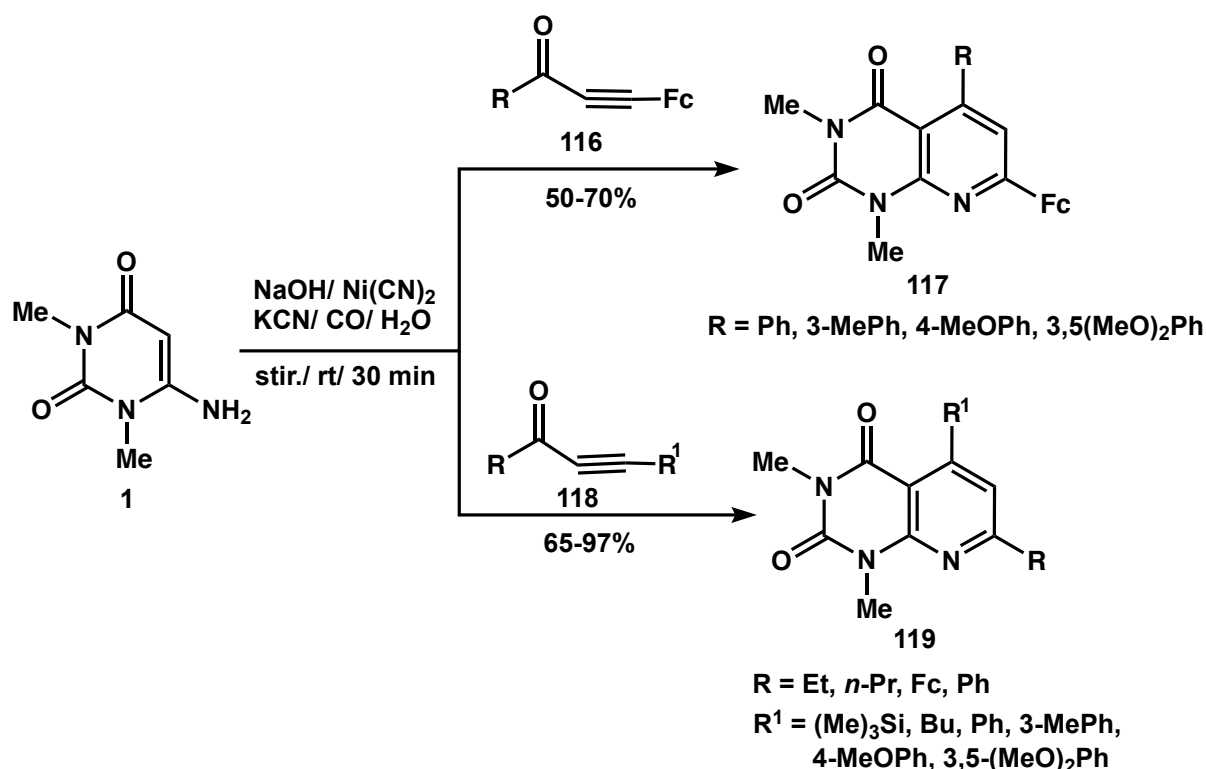
On the other hand, treatment of 6-aminouracil (**1**) with 2-amino-6-methylchromone-3-carboxaldehyde (**114**) in boiling DMF and DBU as catalyst gave 8-methyl-6*H*-chromeno[3',2':5,6]pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*),6-trione (**115**); through condensation of the aldehyde function with active methylene group followed by cyclocondensation with loss of NH₃ molecule (Scheme 66).⁹⁹



Scheme 66

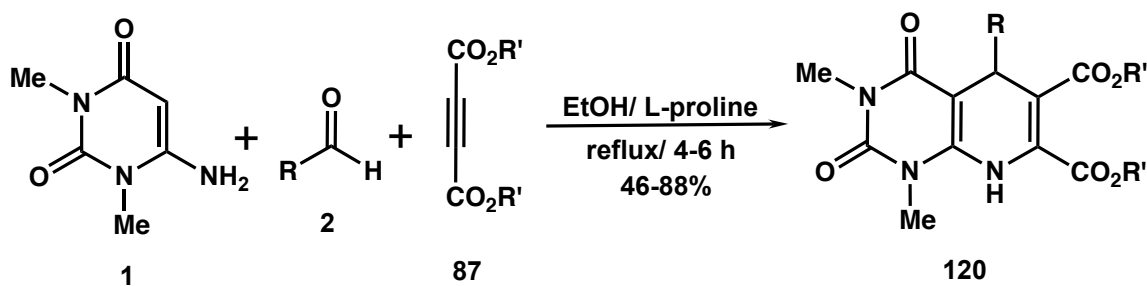
2.2.6. Reactions with alkynes

Arellano *et al.* reported that, 5-substituted-7-ferrocenyl-dioxypyrido[2,3-*d*]pyrimidines derivatives **117** and pyrido[2,3-*d*]pyrimidines **119** were synthesized by the reaction of 6-amino-1,3-dimethyluracil (**1**) with substituted ferrocenyl-ketoalkynes **116** and α -keto-alkynes **118**, in the presence of nickel cyanide as homogeneous catalyst at room temperature (Scheme 67). The synthesized compounds are used as vasorelaxant of smooth muscle *via* cAMP conservation through phosphodiesterase inhibition. It was found that the reaction in the presence of catalytic promoter depends on the nature of the alkynyl substituent. With weak electronic donor groups (as *n*-butyl and Ph), 5-substituted pyrimidines were obtained *via* the 1,4-Michael's type condensation. Whereas, with strong donor groups (as ferrocenyl moiety), the nucleophilic attack (by the $[\text{Ni}(\text{CN})_4]^{-4}$ anion formed *in situ*) seems to be at the carbonyl group of ynone function.^{100,101}



Scheme 67

While, three-component domino coupling of 6-amino-1,3-dimethyluracil (**1**), aliphatic or aromatic aldehydes **2**, and dialkyl acetylenedicarboxylates **87**, which catalysed by L-proline, provided pyrido[2,3-*d*]pyrimidines **120**, in 46-88% yields as shown in Scheme 68.¹⁰²



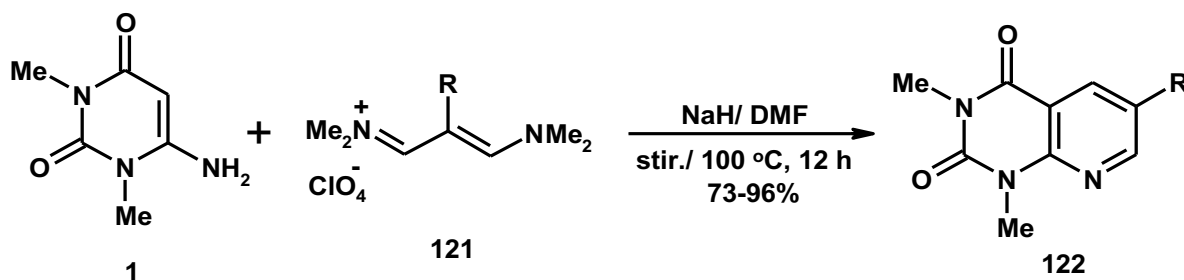
R' = Et, Me

R = Ph, 4-MePh, 4-ClPh, 4-NO₂Ph, 4-MeOPh, 2-Furyl, 2-thienyl, 2,4-Cl₂Ph, 4-BrPh, 4-FPh, 3-ClPh, Me, cyclohexyl, Et, 2-ClPh

Scheme 68

2.2.7. Reactions with iminium salts

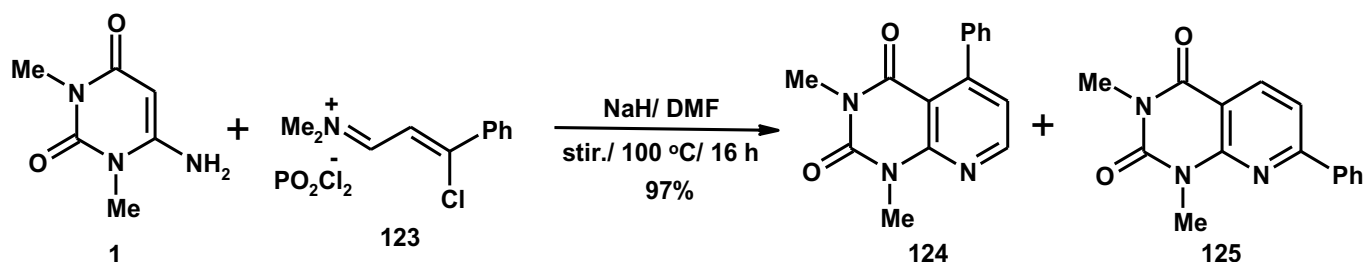
6-Substituted pyrido[2,3-*d*]pyrimidines **122** were prepared by cyclocondensation of 6-amino-1,3-dimethyluracil (**1**) with symmetrical vinamidinium perchlorates **121** under basic reaction conditions (Scheme 69).¹⁰³



R = Ph, 4-MeOPh, 4-MePh, PhSO₂, 4-MePhSO₂

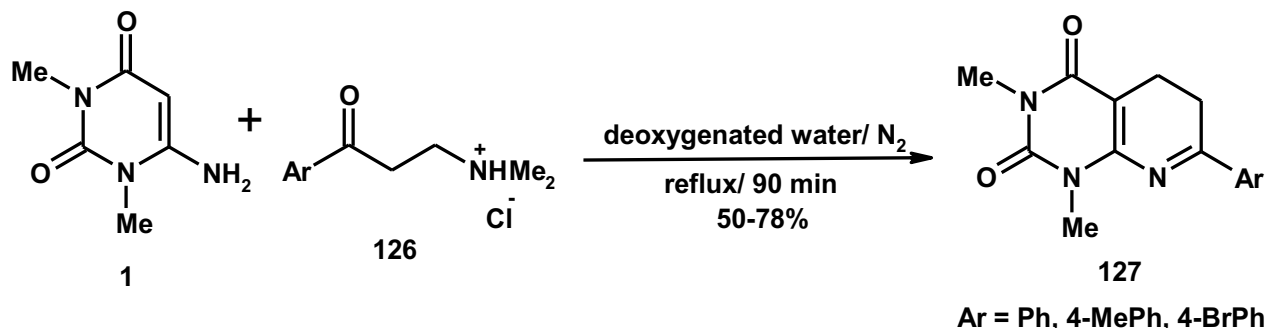
Scheme 69

On the other hand, regioselective condensation of 6-amino-1,3-dimethyluracil (**1**) with chloropropeniminium salt (**123**) in DMF under basic conditions gave two isomers, which are 5-substituted pyrido[2,3-*d*]pyrimidine **124** and 7-substituted isomer **125**, in a ratio of 5:2, respectively (Scheme 70).¹⁰³



Scheme 70

7-Aryl-5,6-dihydropyrido[2,3-*d*]pyrimidine-(1*H*,3*H*)-2,4-diones **127** were produced, in 50-78% yields, by reaction of 6-amino-1,3-dimethyluracil (**1**) with arylalkane Mannich bases **126** under atmosphere of nitrogen (Scheme 71).¹⁰⁴

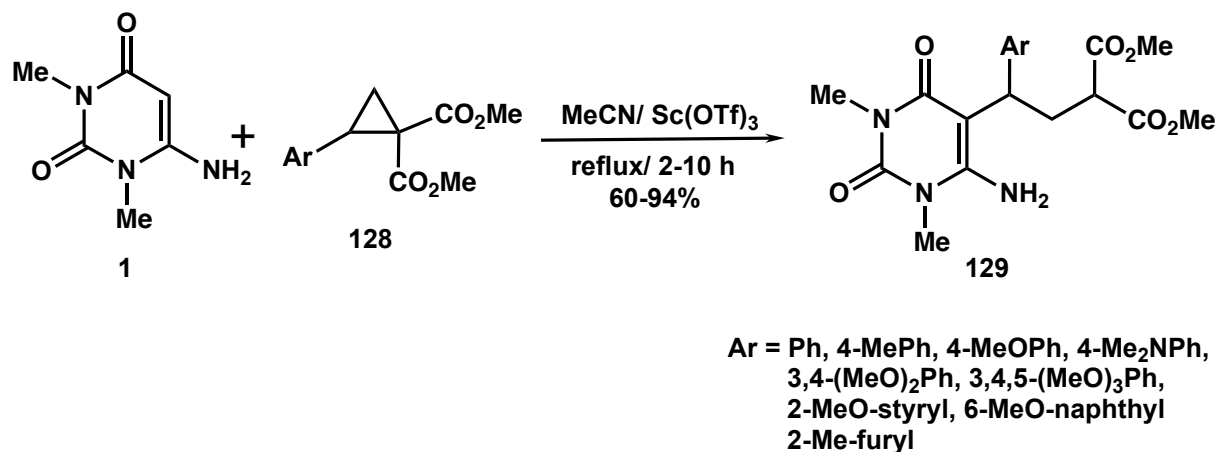


Scheme 71

2.2.8. Electrophilic substitution reactions

2.2.8.1. Alkylation reactions

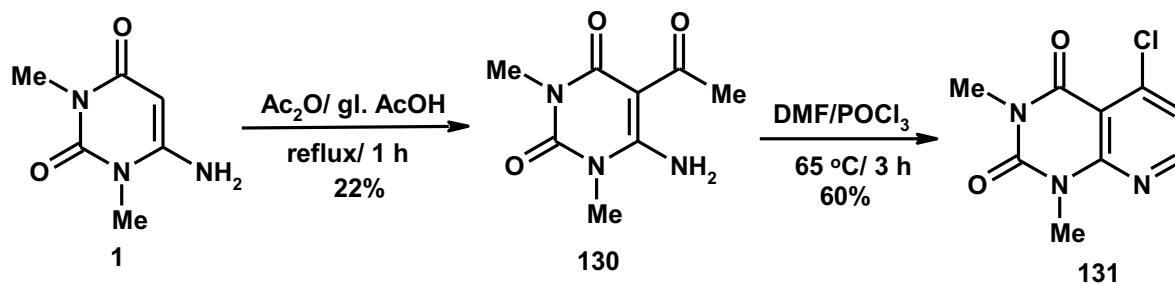
Dimethyl 2-[2-(6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)malonates **129** were obtained by reacting 6-amino-1,3-dimethyluracil (**1**) with substituted cyclopropane-1,1-dicarboxylate **128** which catalyzed by scandium(III) trifluoromethanesulfonate (Scheme 72).¹⁰⁵



Scheme 72

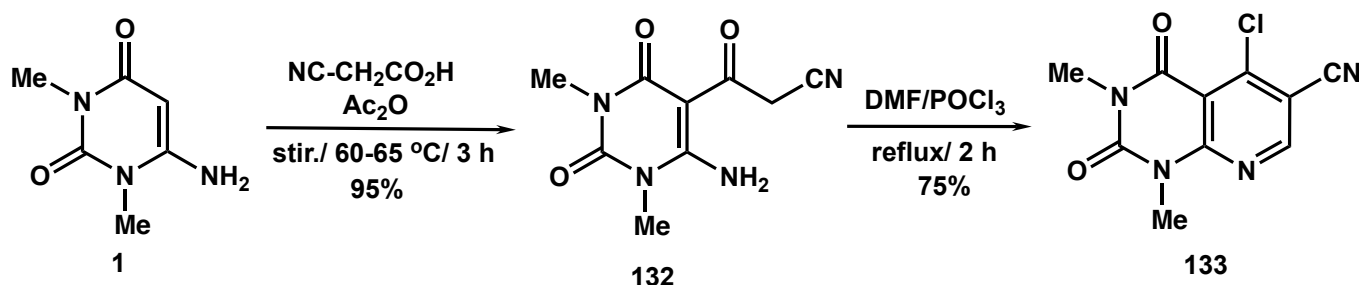
2.2.8.2. Acetylation reactions

Acetylation of 6-amino-1,3-dimethyluracil (**1**) using acetic anhydride in acetic acid furnished the acetylated product **130**, at its C-5 position, which upon Vilsmeier formylation afforded 1,3-dimethyl-5-chloropyrido[2,3-*d*]pyrimidine-2,4-dione (**131**) (Scheme 73).¹⁰⁶⁻¹⁰⁸



Scheme 73

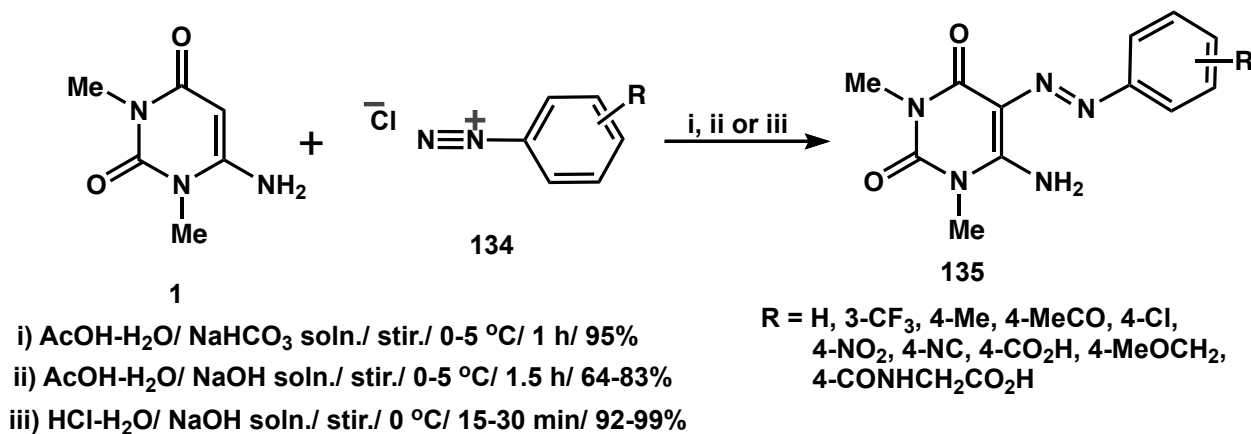
In a similar manner, cyanoacetylation of compound **1** with cyanoacetic acid in acetic anhydride yielded cyanoacetyl derivative **132** which underwent Vilsmeier formylation producing 5-chloropyrido[2,3-d]pyrimidine-6-carbonitrile **133** (Scheme 74).¹⁰⁶⁻¹⁰⁸



Scheme 74

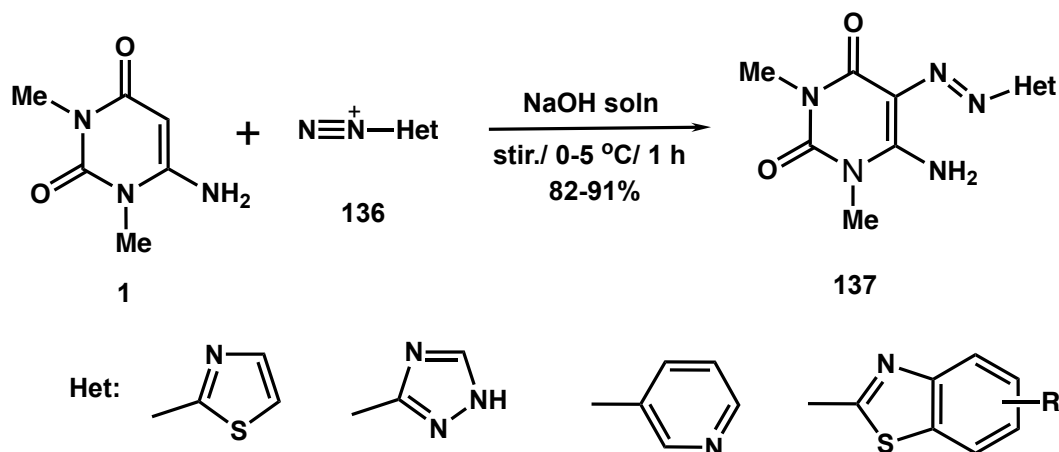
2.2.8.3. Coupling reactions

6-Amino-5-(aryloxy)-1,3-dimethyluracils **135** were synthesized, by coupling 6-amino-1,3-dimethyluracil (**1**) with diazonium salts **134** under different reaction conditions. These compounds show positive solvatochromic property on moving from polar protic to polar aprotic solvents. The dyes exhibit prominent photophysical properties in certain solvents. (Scheme 75).^{109,110}



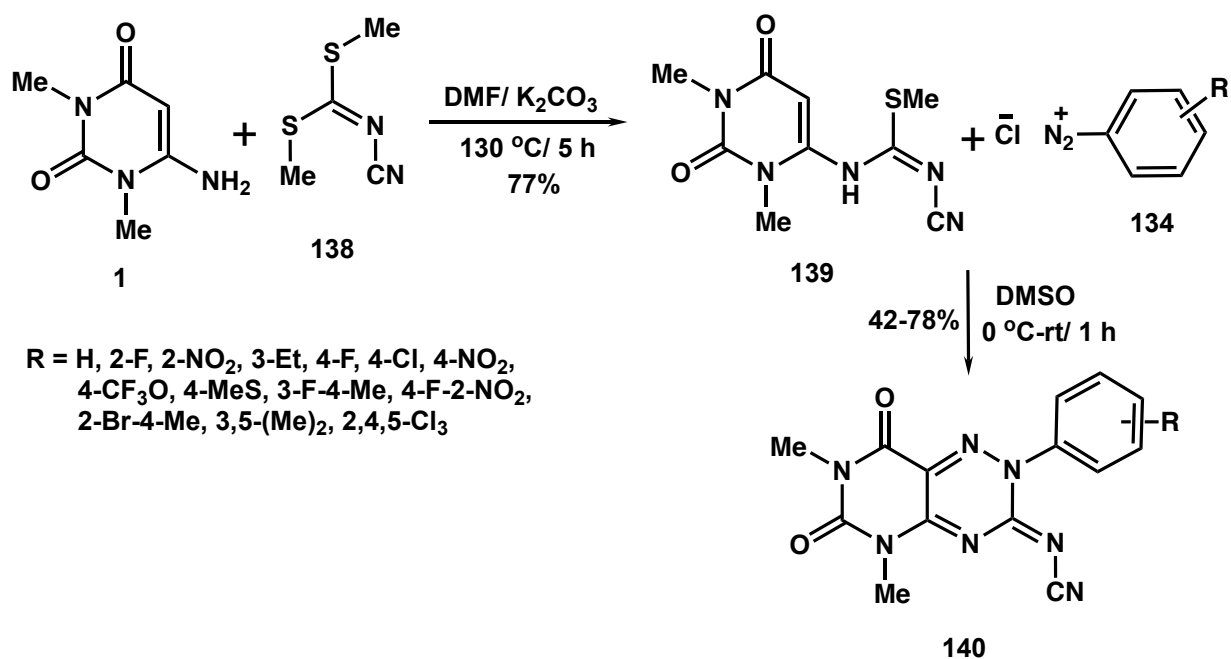
Scheme 75

A series of 6-amino-5-(hetarylazo)-1,3-dimethyluracil **137** were prepared, in excellent yields, by coupling 6-amino-1,3-dimethyluracil (**1**) with diazotized heterocyclic amines **136**, in sodium hydroxide solution. The antimicrobial activity of the synthesized dyes was evaluated on *E. coli*, *B. subtilis*, *M. leuteus* and *P. aeruginosa* (Scheme 76).¹¹¹



Scheme 76

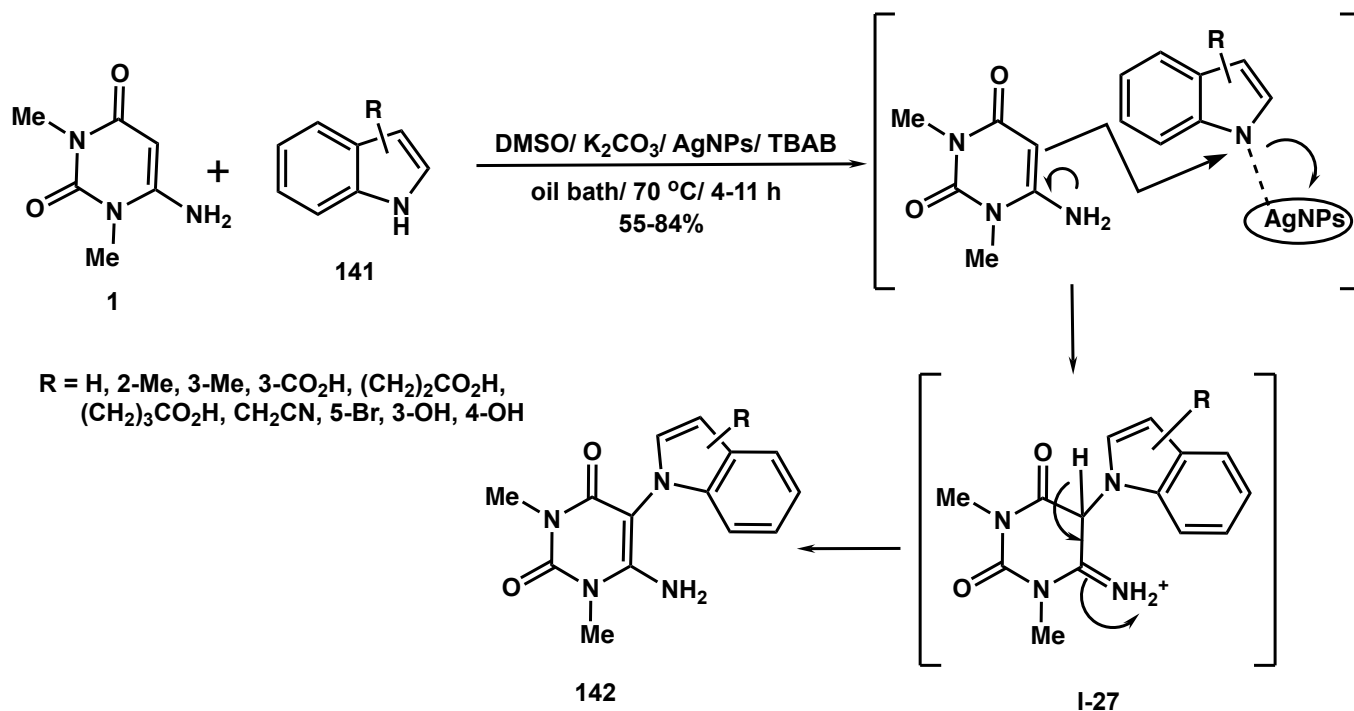
Meanwhile, treatment of 6-amino-1,3-dimethyluracil (**1**) with dimethyl N-cyanodithioimidocarbonate (**138**) in DMF, in the presence of K₂CO₃, afforded 1-cyano-3-(2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-ylamino)-2-methylisothiurea (**139**) which upon coupling with phenyldiazonium salt **134** in DMSO afforded pyrimido[4,5-*e*][1,2,4]triazin-3-ylidenecyanamides **140** (Scheme 77).¹¹²



Scheme 77

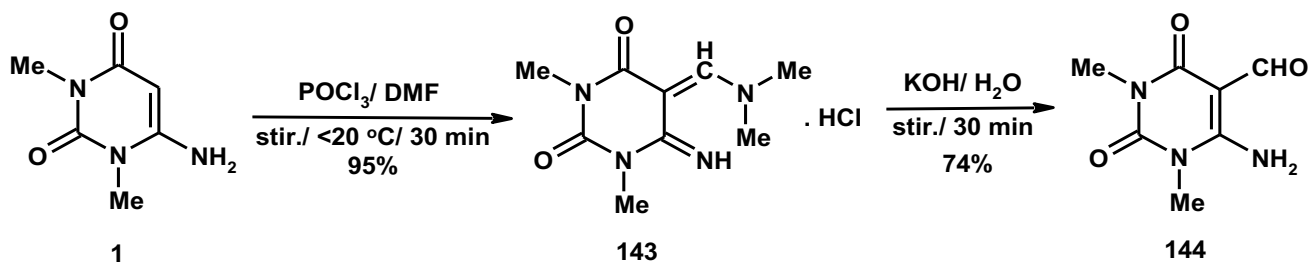
2.2.8.4. Oxidation reactions

Treatment of 6-amino-1,3-dimethyluracil (**1**) with indole derivatives **141** catalyzed by nano-Ag at 70 °C and tetrabutylammonium bromide (TBAB), yielded 6-amino-1,3-dimethyl-5-indolyl-1*H*-pyrimidine-2,4-dione derivatives **142**, in moderate to good yields. A probable mechanism has been proposed through nano-Ag activated indoles **141** for abstraction of a proton followed by nucleophilic attack by uracil **1** to form intermediate **I-27** followed by proton transfer (Scheme 78).¹¹³

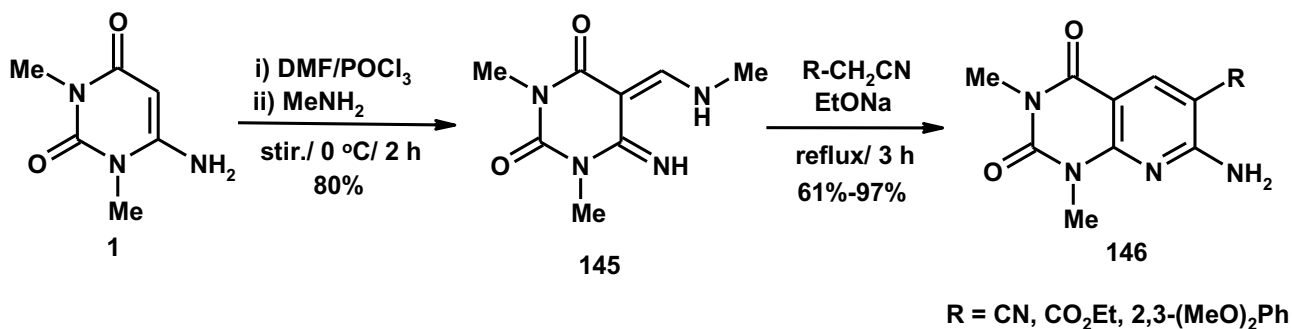


2.2.8.5. Formylation reactions

6-Amino-5-formyl-1,3-dimethyluracil (**144**) was prepared by treatment of 6-amino-1,3-dimethyluracil (**1**) with phosphoryl chloride in DMF giving compound **143** which is easily hydrolyzed to the target product **130** (Scheme 79).¹¹⁴



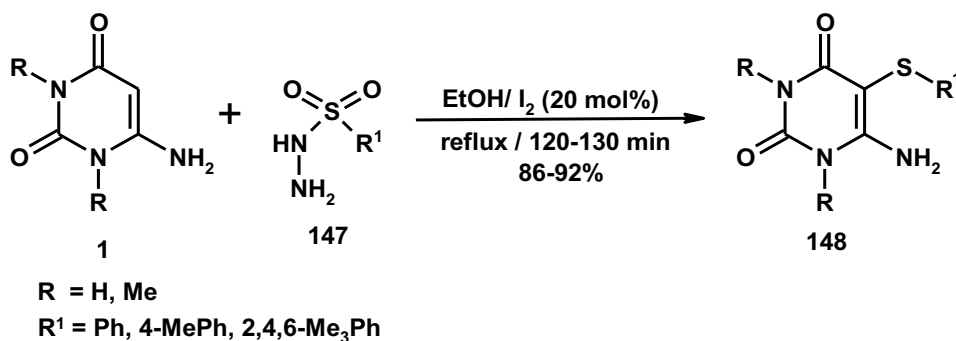
Meanwhile, Vielsmeier formylation of 6-amino-1,3-dimethyluracil (**1**) in the presence of methylamine yielded 6-imino-1,3-dimethyl((methylamino)methylene)pyrimidinedione (**145**) which reacted with acetonitrile derivatives and afforded 7-aminopyrido[2,3-*d*]pyrimidines **146** which act as adenosine receptor antagonists (Scheme 80).^{106,115}



Scheme 80

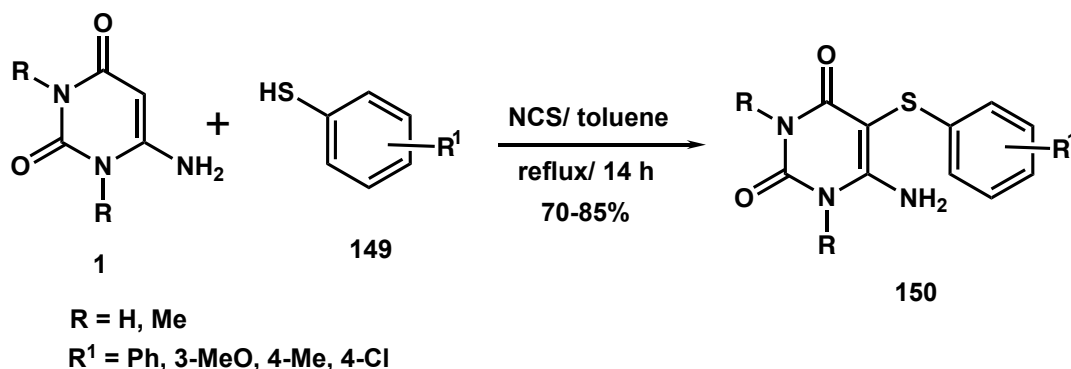
2.2.8.6. Reactions with sulfur compounds

Sulfenylation of 6-amino-1,3-disubstituted uracils **1** with substituted sulfonylhydrazides **147** in ethanol in the presence of iodine afforded 6-amino-1,3-dimethyl-5-arylthiopyrimidine-2,4-diones **148** (Scheme 81).¹¹⁶



Scheme 81

Also, 5-arylthiouracils **150** were prepared, in 70-85% yields, by treating 6-amino-1,3-disubstituted uracils **1** with aryl thiols **149** in the presence of *N*-chlorosuccinimide (NCS) in toluene at room temperature (Scheme 82).¹¹⁷



Scheme 82

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Magdy Ahmed Mohamed Ibrahim was born in Cairo, Egypt, in 1977. He received his B.Sc. degree in physics and chemistry (1999) and his M.Sc. degree in organic chemistry (2004). Also, he received his Ph.D. degree (2007) from the organic division, Department of Chemistry, Faculty of Education, Ain Shams University. He won the award for the best research article in heterocyclic chemistry field at the Egyptian universities and research centers in 2010. In 2012 he was promoted to assistant professor in organic chemistry. In 2017 he was promoted to professor in organic chemistry. His research is focused on the synthesis of new heterocyclic compounds containing chromone, pyridine, quinolin-2(1*H*)-one and 1,2,4-triazine. He published more than hundred scientific papers in the field of organic and theoretical chemistry. In addition, He has published about 90 scientific papers in international scientific journals.



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