CHAPTER 1

Overview of Barbituric Acid Derivatives

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1.1 Brief Introduction

Barbituric acid (pyrimidine 2,4,6(1*H*,3*H*,5*H*)-trione, H_3BA) is an organic compound containing pyrimidine heterocyclic skeleton (**Scheme 1.1**). It is a water soluble, and odorless compound. The chemistry of barbituric acid derivatives, commonly recognized as barbiturates (BAs), has got considerable attention owing to their importance in medicine and biology and they have appeared in a large number of biologically active compounds (**Figure 1.1**) [1-11]. Barbituric acid itself has no bioactivity of its own but its derivatives exhibit good pharmacological activities [12-19]. After invention, barbiturates first came into medical treatment in 1904, modifying access to psychiatric and neurological disorders [20-22]. In 1912, a significant barbituric acid derivative, Phenobarbital (**Figure 1.2**), was discovered and utilized as an antiepileptic drug [23, 24].

Barbituric acids have been generally categorized as compounds that affect the central nervous system and utilized for therapeutic uses such as sedatives [25], anticonvulsants [26, 27] and hypnotics [28, 29]. Current investigations have provided the information that barbituric acids have significant applications in anti-inflammatory [30], antifungal [31], antioxidant [32, 33], antibacterial [34-36], antitumor [11], as well as anti-viral [37] treatments (**Figure 1.3**).

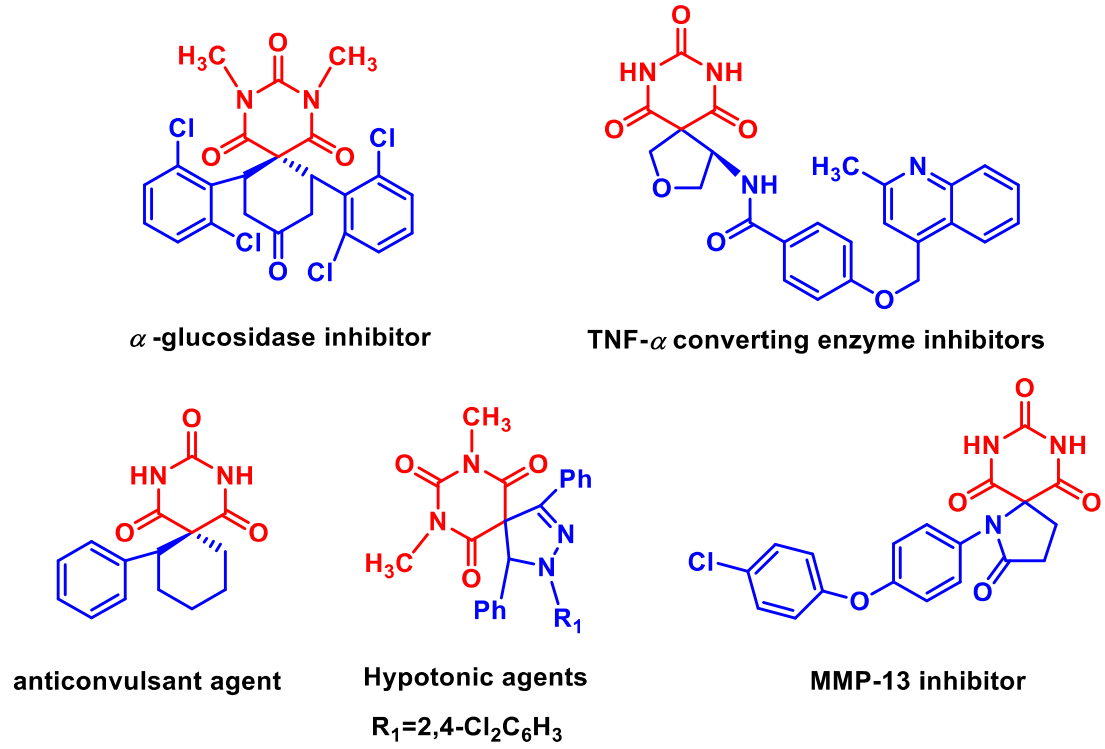


Figure 1.1 Biologically active compounds containing barbituric acid moieties.

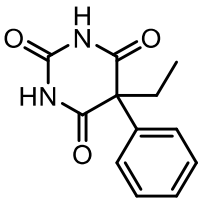


Figure 1.2 Phenobarbital: an antiepileptic drug.

The existence of the pyrimidine-trione ring and the type of the substituent on C-5 position regulate the nature of biological property of the barbiturate derivative [38]. The modifications of barbiturates produce a large number of compounds with varying biological activities enabling the transformation of barbiturates into widely used

pharmaceautical agent [39-43]. 5-Aryl barbituric acid have been used to prevent the tumor necrosis factor alpha (TNF-α) converting enzyme (TACE) [44, 45] and matrix metalloproteinases (MMPs) [46-50], prompting their application *in vivo* imaging [51] and in cancer treatment [52-54].

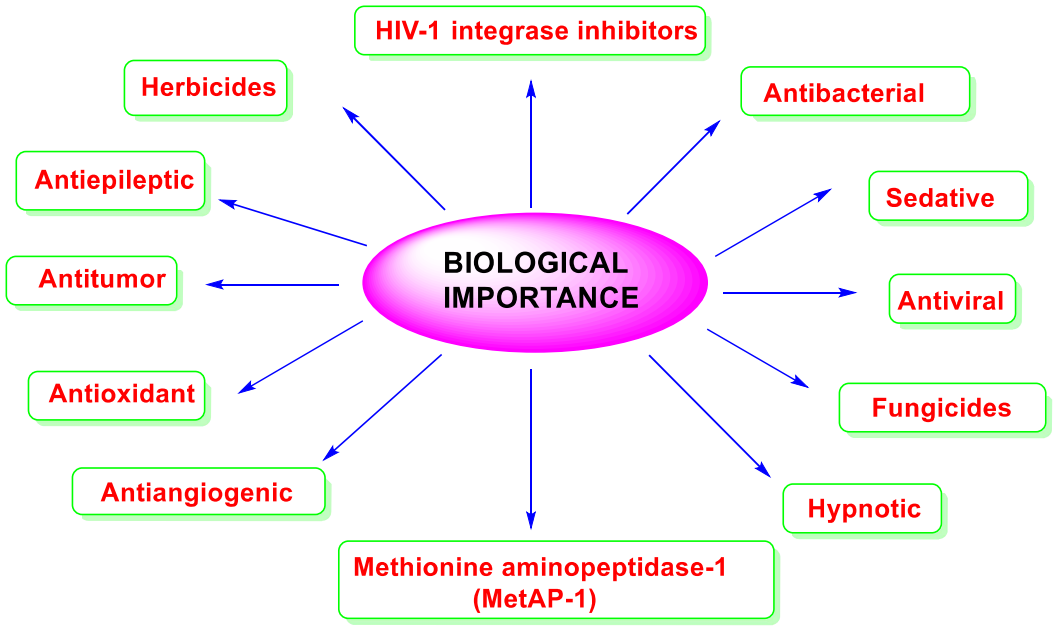
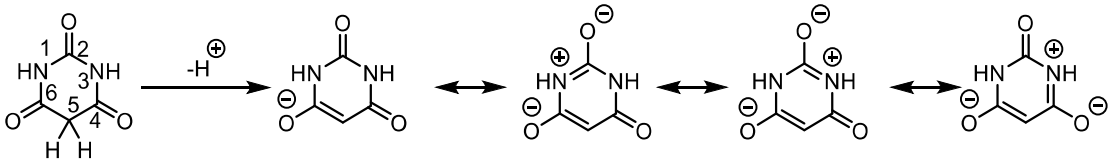


Figure 1.3 Biological importance of barbituric acid derivatives.

Barbituric acid comprises five active metal binding (donor-acceptor) sites (three *O* and two *N*, **Scheme 1.1**), making it a resourceful polyfunctional ligand. The pyrimidine ring is further stabilized by resonance, due to the capacity of the activated CH_2 group to remove one of the protons **(Scheme 1.1)**, however, the donor-acceptor tendency of the heteroatoms fluctuates along the molecule [55]. Consequently, the most acidic proton in barbituric acid is one of the methylenic CH_2 hydrogens with pK_a of 4.03 [56], removal of

proton at this site permits the development of a planar carbanion. Additionally, the pyrimidine ring of barbituric acid can be functionalized very easily at position 5. For example, substitution of a diazo moiety at position 5 leads to formation of arylhydrazones of BAs, which offer fascinating coordination and solvatochromic properties [57, 58].



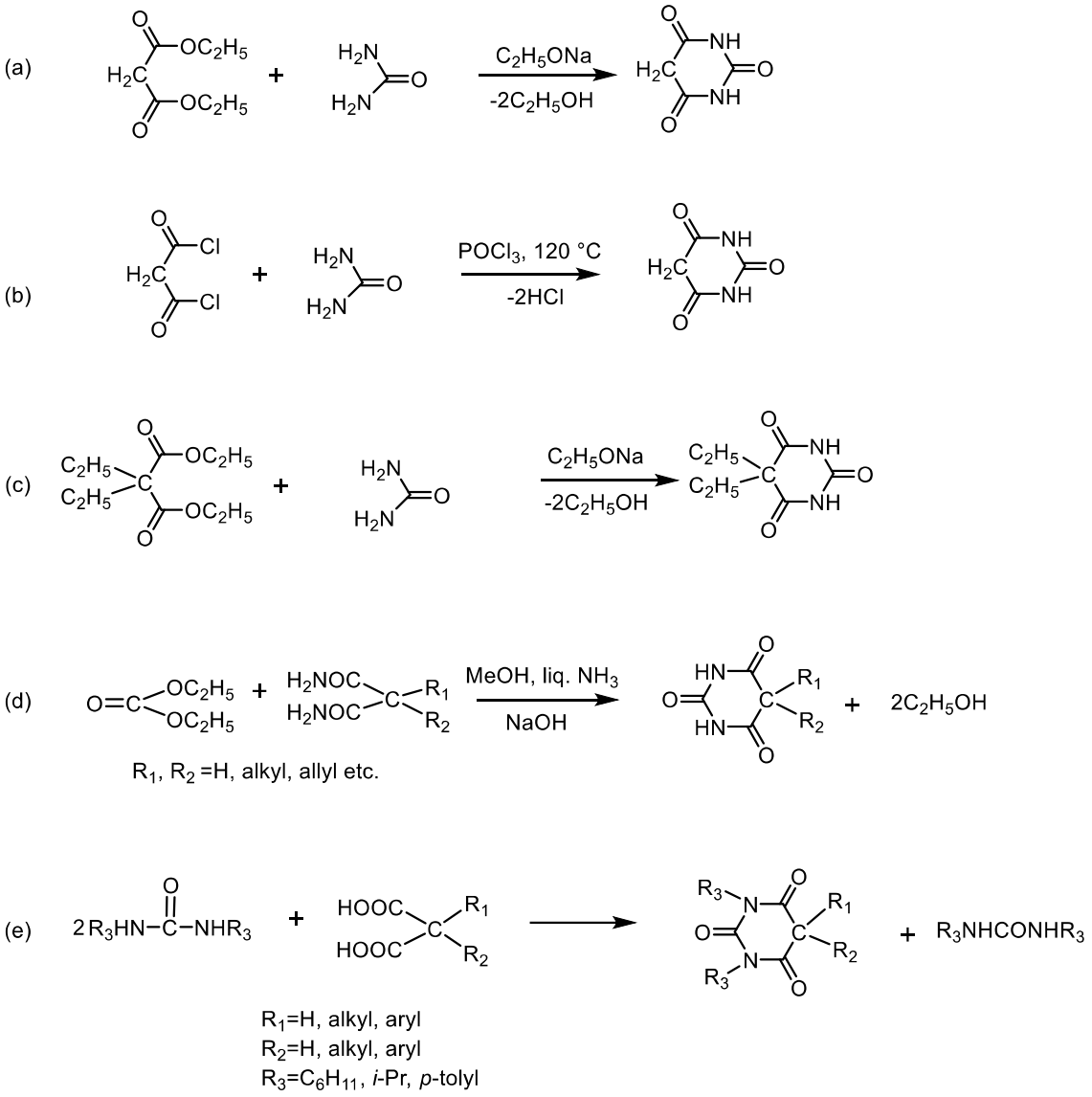
Scheme 1.1 Molecular structure of barbituric acid (H_3BA) and resonance structures of its deprotonated form.

1.2 Synthesis and Physical Properties of Barbituric Acid

1.2.1 Synthesis of Barbituric Acid

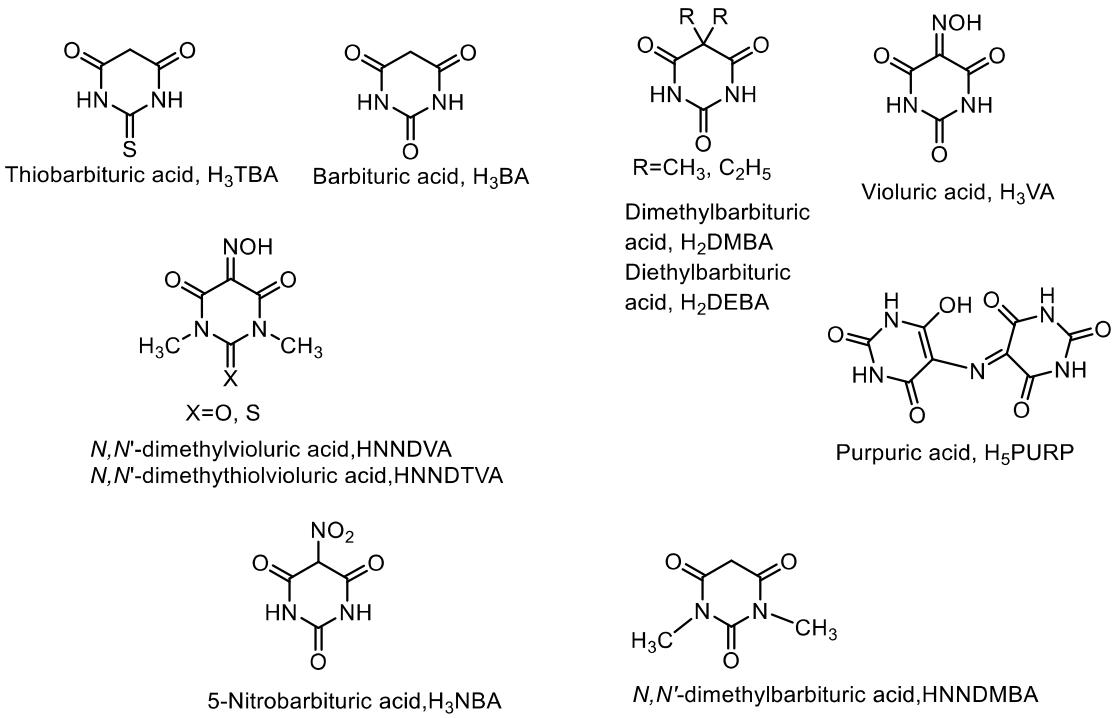
Barbituric acid was first synthesized by Adolf von Baeyer in 1864 by the condensation of diethyl malonate with urea [2, 59, 60]. The barbiturates were incorporated for clinical use in 1900s; further more than 2500 BAs have been prepared, among them 50 were utilized predominantly for pharmacological purposes, showing their wide ubiquity. Various methods have been described in the literature for synthesis of BAs [61-64] and the most significant of them are shown in **Scheme 1.2**. For example, urea condenses with malonic esters or malonic acids, malonyl dichlorides, to give H_3BA (**Scheme 1.2a and b**). The most widely recognized method for barbituric acids synthesis is the Michael method, in which condensation of suitable diethyl malonate with urea takes place in anhydrous alcohol in the presence of sodium ethoxide (**Scheme 1.2a**) [63]. This

procedure has been commonly implemented for the industrial synthesis of barbituric acids and also signifies the most likely used laboratory procedure. In the same way, H_2DEBA [diethylbarbituric acid] can be synthesized by condensation of diethyl-2,2-diethylmalonate with urea in sodium ethoxide followed by the removal of two ethanol molecules (**Scheme 1.2c**) [65]. A modification of synthesis of the BA includes a condensing agent like alkali hydroxide in liquid ammonia resulting to the dialkylbarbituric acids [63]. In this process, a mixture of urea, diethyl dialkylmalonate, and an alkali hydroxide in liquid ammonia produces the desired product. Nevertheless, when monoalkylated diethyl malonates or diethyl malonate were used, none of the corresponding barbituric acids were obtained. Likewise, ethyl carbonate and malonamide or its C-alkyl derivatives in the presence of alkali, in liquid ammonia condense to give the corresponding derivatives of barbituric acid (**Scheme 1.2d**) [63]. This method seems to be very general, resulting to the barbituric acids in good yields from C,C-dialkylmalonamides, C-alkylmalonamides, or malonamide [63]. Various examples are also reported for the synthesis of barbiturates by the reaction of 2,2-disubstituted malonic acids with 1,3-disubstituted urea. Consequently, when reaction of two moles of 1,3-disubstituted urea and 2,2-disubstituted malonic acid was carried out in THF solution, it gave a crystalline 1,3,5,5-tetrasubstitutedpyrimidine-2,4,6(1*H*,3*H*,5*H*)- trione through an exothermic pathway (**Scheme 1.2e**) [62].



Scheme 1.2 Most common synthetic approaches for the preparation of barbituric acids.

There are some most common barbituric acids, viz., thiobarbituric acid (H_3TBA), barbituric acid (H_3BA), dimethylbarbituric acid (H_2DMBA), violuric acid (H_3VA), *N,N′*-dimethylbarbituric acid (HNNDMBA), purpuric acid (H_5PURP), 5-nitrobarbituric acid (H_3NBA), diethylbarbituric acid (H_2DBA), *N,N′*- dimethyltiovioluric acid (HNNDTVA), and *N,N′*-dimethylvioluric acid (HNNDVA) shown in **Scheme 1.3**.

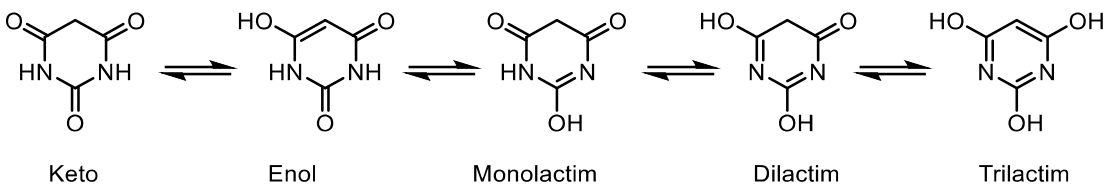


Scheme 1.3 Most common barbituric acids.

1.2.2 Physical Properties of Barbituric Acid

1.2.2.1 Tautomerization

The keto configuration is preferred by most pyrimidine derivatives over the enol configuration [66-79]. However, BAs are pyrimidine-related compounds that show two types of tautomers by transfer of either methylene or imino hydrogen atoms to keto oxygen atoms, through a process known as lactam-lactim tautomerization, NHC=O ⇌ NC− OH. Since BAs have three lactam groups, one, two, or all three groups can theoretically be converted to lactim moieties **(Scheme 1.4)** [67, 80, 81].



Scheme 1.4 Possible tautomeric structures of barbituric acid.

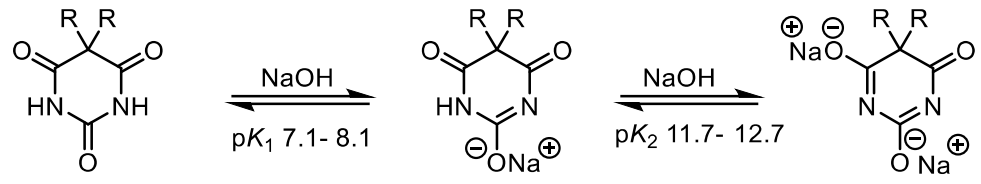
Generally, BA is represented in the keto form because it is definitely the most stable form in solution [67, 76, 77], gas phase and in the solid state [77]. The 2-hydroxy and 4-hydroxy forms are not much common, however, they are also stable and have an impact on the properties of BAs and related moieties [66, 82-90]. The development of additional strong hydrogen bonds explains the stability of the enol form, in the solid state [87, 91]. Evidently, the tautomerization of barbiturates need more investigations to explain the formation of new coordination compounds [92-94] molecular rotors [95], switching systems [96-100], solvatochromic colorants [57, 101, 102], habit modifiers for rock salt crystals [103], the construction of supramolecular architectures [58, 104], and artificial systems mimicking the biological ones [105].

1.2.2.2 Acid-Base Properties

Barbituric acid itself has no anticonvulsant, hypnotic or anesthetic properties. These properties are only observed when H- atoms of C-5 group are substituted by aryl or alkyl groups. The reactive hydrogen containing carbon of barbituric acid is moderately acidic (pK_a = 4.03) than other diketone species (*cf.* acetylacetone with pK_a 8.95 and dimedone with pK_a 5.23) due to extra aromatic stabilisation of the carbanion. It was

proposed that, for a barbituric acid to have good hypnotic activity, it must be a weak acid with a lipid/water partition coefficient within certain limits [106].

The hydrophilicity of the pyrimidinetrione ring of 5,5-disubstituted barbituric acids is associated with the pK_a as well as the nature and number of *N*-substituents. Noticeably, the acidity, in this case results from the tendency of *N*-atoms to lose protons and stability of the resulting conjugate base through resonance delocalization. The acidity of all 5,5-disubstituted barbituric acids is lower than that of the parent H_3BA due to the lack of an active methylene group flanked between two carbonyl groups as well as the inability to produce a symmetrical conjugated ring structure. Alkyl groups further diminishes the acidity of alkyl substituted barbituric acids by donating electrons [107]. Therefore, although unsubstituted barbituric acid has a pK of 4.03 [56] the values of pK_1 of 5,5-disubstituted barbituric acids vary from 7.1 to 8.1 [80]. In aqueous solutions, either the dioxo tautomeric (in alkaline medium) or the trioxo tautomeric (in acidic medium) form predominates [80]. However, the 5,5-disubstituted barbituric acids are mainly found in the trioxo tautomeric form and are weak acids, salts of these barbiturates are readily synthesized by treatment with bases. Subsequently, second ionisation takes place (**Scheme 1.5**), with pK_2 values ranging from 11.7 to 12.7 [108].

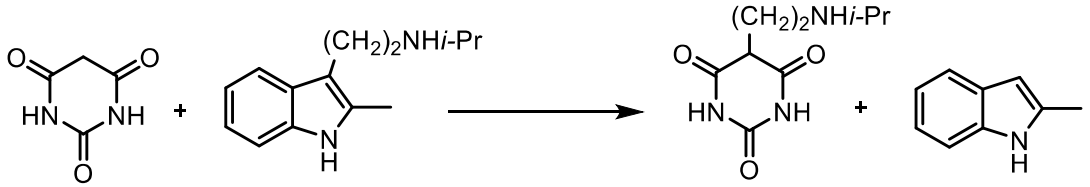


Scheme 1.5 Deprotonation of 5,5 disubstituted barbituric acids.

1.3 Chemical Properties

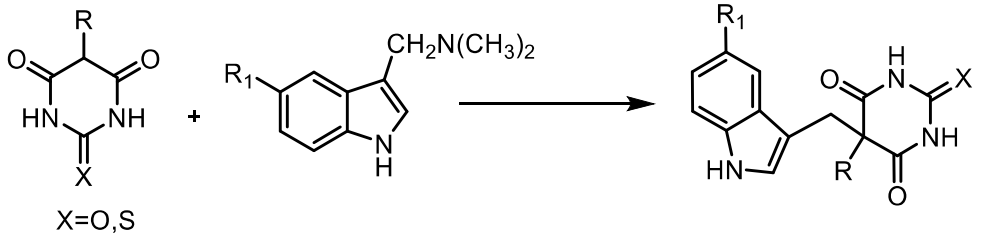
1.3.1 Reactions at the *C-5* Position

Two active hydrogens are present at the 5-position of barbituric acid which can be substituted by different groups to make it biologically active. Simple alkyl substituents can be easily introduced into this position while complex substituents are introduced with the help of indole derivatives. According to Rao and Chalmers, reaction of barbituric acid with 3-isopropylaminoethyl-2-methylindol in the presence of piperidine yields 5-(2'-(isopropylamino)ethyl)barbituric acid (**Scheme 1.6**) [109].



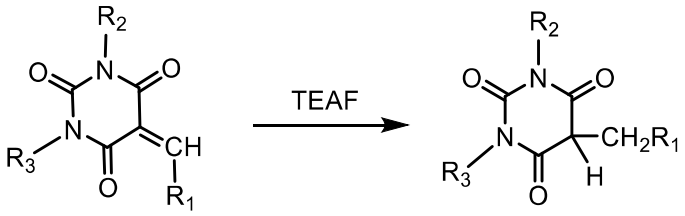
Scheme 1.6 Alkylation of barbituric acid at C-5 position.

The substitution of 2-thiobarbituric/barbituric acids with indole derivatives was also examined **(Scheme 1.7)** [110].



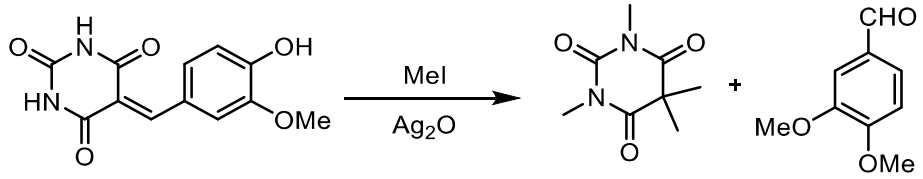
Scheme 1.7 Substitution of thiobarbituric/ barbituric acid.

Sekiya et al. described the synthesis of various 5-aryl or 5-alkylmethylbarbituric acids by the reduction of barbituric acid derivatives containing a methylidene bond at the 5-position **(Scheme 1.8)** [111-113].



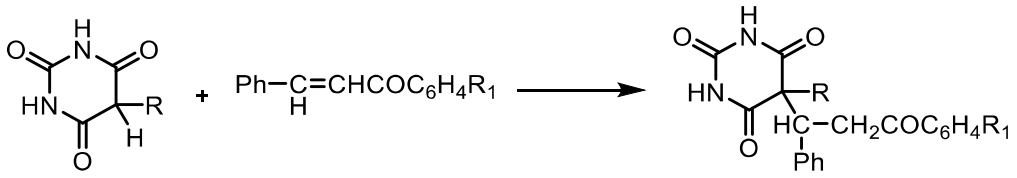
Scheme 1.8 Reduction of barbituric acid derivatives with triethylammonium formate (TEAF).

Ethier and Neville demonstrated the efficient method for oxidative methylation of 5-benzylidene barbituric acid by methyl iodide and Ag_2O in the presence of DMF resulting to the formation of 1,3,5,5-tetramethylbarbituric acid **(Scheme 1.9)** [114].

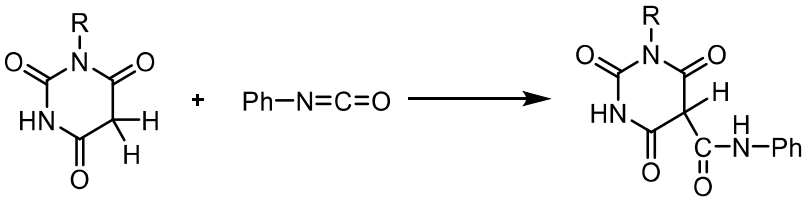


Scheme 1.9 Oxidative methylation of 5-benzylidene barbituric acid.

Barbituric acid gives addition rection with various compounds. 5-alkyl barbituric acids and barbituric or 1-substituted barbituric acids undergo addition reaction with α, β-unsaturated ketones and phenyl isocyanate to yield 5,5-disubstitued derivatives [110] and 5- phenylcarbamoyl barbituric acid respectively (**Scheme 1.10 and 1.11**) [115].

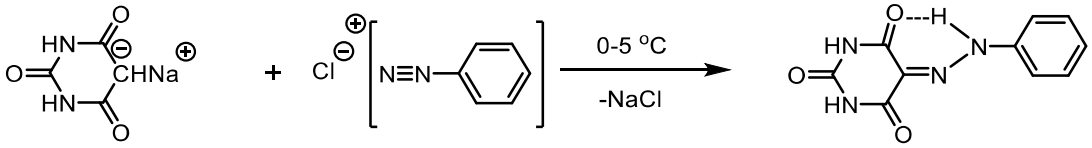


Scheme 1.10 Addition reaction with *α, β*-unsaturated ketones.



Scheme 1.11 Addition reaction with phenyl isocyanate.

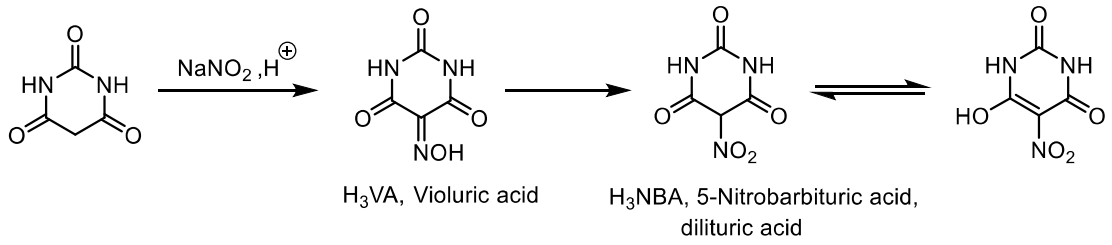
A significant aspect of reactivity includes the capability of BA to be modified further very easily, e.g. at active methylene position 5. Therefore, reaction of barbituric acid with aromatic diazonium salts in presence of base in ethanolic solution (Japp-Klingemann reaction, **Scheme 1.12**) leads to AHBAs (arylhydrazones of barbituric acids) which can be further utilised as ligands in coordination chemistry or as intermediates in organic reactions [58, 116-118].



Scheme 1.12 Japp-Klingemann reaction of barbituric acid.

Likewise, barbituric acid reacts with nitrite in acidic medium to result the nitroso derivative, 5-(hydroxyimino)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (H_3VA, violuric acid, **Scheme 1.13**). Further oxidation of this violuric acid readily gives dilituric acid [119,

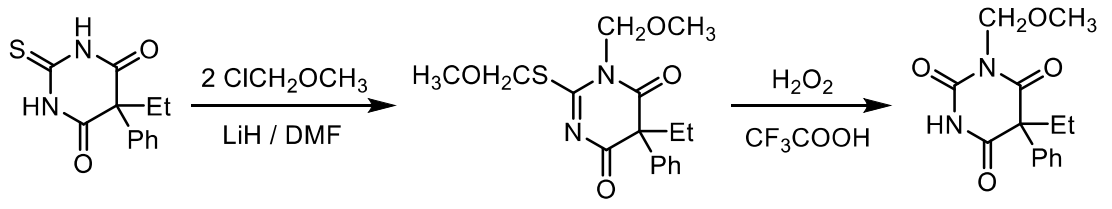
120]. The solvatochromic and other associated properties of these compounds can be of great interest because of the color-dependent tautomerism (pink nitrozoenolic form and colorless oximino-ketonic form) [121].



Scheme 1.13 Reaction of barbituric acid with sodium nitrite.

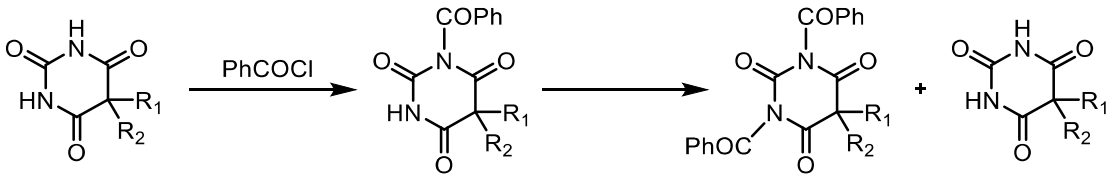
1.3.2 Substitution at Nitrogen

Alkylation of barbituric acids results to the formation of a mixture of *O*- and *N*-alkyl derivatives because these compounds contain imide hydrogen atoms which show tautomerism. *O*- and/or *N*- alkylated products were obtained by the alkylation of 5- or 1-monosubstituted barbiturates. However, alkylation of 1,5,5-trisubstituted and 5,5-disubstituted barbiturates was found to yield *N*-alkylated product predominantly. 5,5-Disubstituted thiobarbituric acid reacts with chloromethyl methyl ether to yield *N, S*-bis(methoxymethyl) derivatives **(Scheme 1.14)** which upon oxidation produces excellent yield of *N*-methoxymethyl barbituric acid derivatives [122].



Scheme 1.14 *N*-alkylation of barbituric acid derivatives.

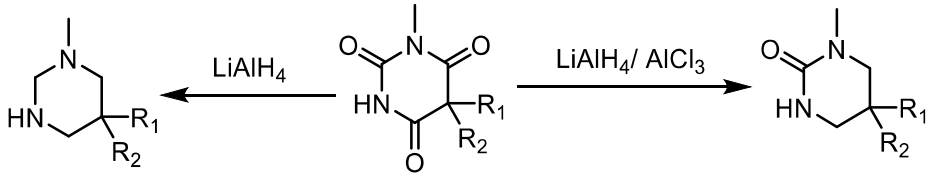
The substitution of hydrogen atom of NH group can also be performed by the acyl residue. 5-Ethyl-5-phenyl- or 5,5-diethylbarbituric acids react with benzoyl chloride in two steps. Reaction of benzoyl chloride with *N*-unsubstituted barbiturates takes place in the first step, resulting to the *N*-monosubstituted derivatives. In the second step, self-acylation reaction takes place between these *N*-monosubstituted derivatives (**Scheme 1.15**) [123, 124].



Scheme 1.15 *N*- acylation of barbituric acid.

1.3.3 Reactions of Carbonyl Groups

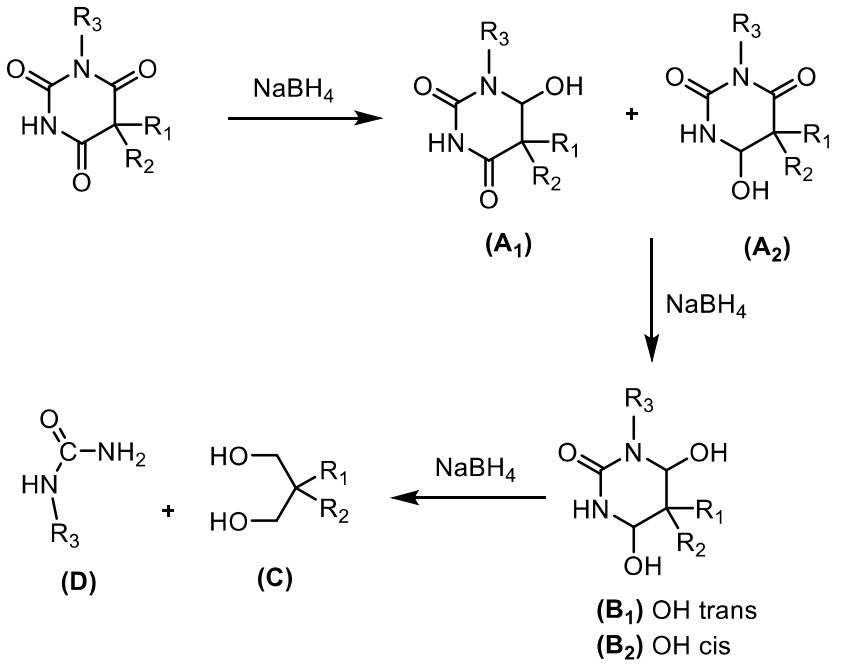
Carbonyl group at 2-position of barbituric acid exhibits a different behaviour from the other two carbonyl groups at 4 and 6-positions in the ring. Reaction of *N*-methylated barbituric acids with $LiAlH_4$, resulted to reduction of all the three carbonyl groups, whereas in the presence of $AlCl_3$ along with $LiAlH_4$, only two carbonyl groups were reduced (**Scheme 1.16)** [125].



Scheme 1.16 Reduction of carbonyl group of barbituric acid.

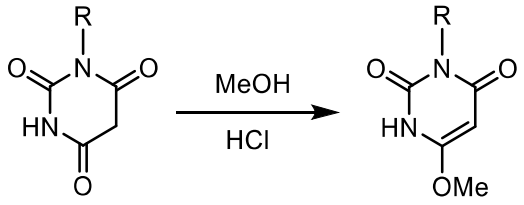
It was proposed that borohydrides would not be able to reduce barbiturates unless they contain a phenyl ring at 5- position. It was considered that $NaBH_4$ to be too

insignificant reducing agent for barbiturates. Despite this, sodium borohydride was observed to react with 5-ethyl-5-phenylbarbituric acid in both organic as well as aqueous media [126, 127]. Furthermore, when the reaction was performed in CH_3OH at r.t. for 1 h, 1,3-dimethyl 5,5-dibenzylbarbituric acid was also reduced [128]. Rautio examined the reduction of barbiturates with $NaBH_4$ in variety of solvents. For each barbiturate**,** four major reduction products were obtained viz., di- and trihydrobarbiturates (A and B respectively) which were formed by reducing one or two carbonyl groups to a secondary hydroxyl group, primary alcohols (C), produced by the reductive cleavage of the ring, and urea derivatives (D), which were generated simultaneously with the primary alcohols from the rest of the barbituric acid ring (**Scheme 1.17**) [129].



Scheme 1.17 Reduction of carbonyl group of barbituric acid with $NaBH_4$.

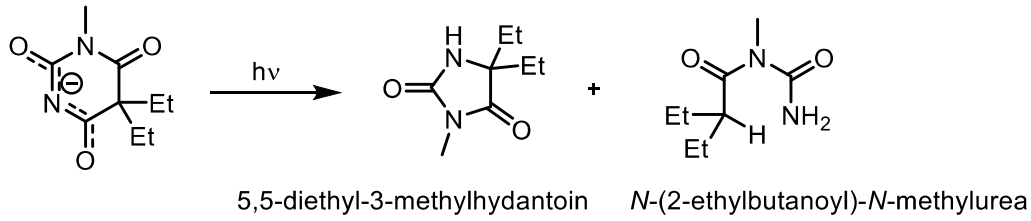
Furthermore, *O*-methylation products have been produced by the action of HCl and methanol on *N*-phenylbarbituric and barbituric acids (**Scheme 1.18**) [130].



Scheme 1.18 *O*-methylation of barbituric acid.

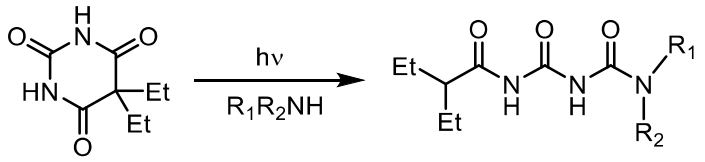
1.3.4 Photochemical Reactions

Otsuji et al. investigated that UV light (254 nm) accelerates the hydrolysis of 5,5-diethylbarbituric acid, under alkaline medium [131]. Bojarski and co-workers, describe the photochemical ring-opening of monoanion of barbituric acid to yield 5,5-diethyl-3-methylhydantoin and *N*-(2-ethylbutanoyl)-*N*-methylurea (**Scheme 1.19**) [132].



Scheme 1.19 Photochemical ring-opening reaction of barbituric acid.

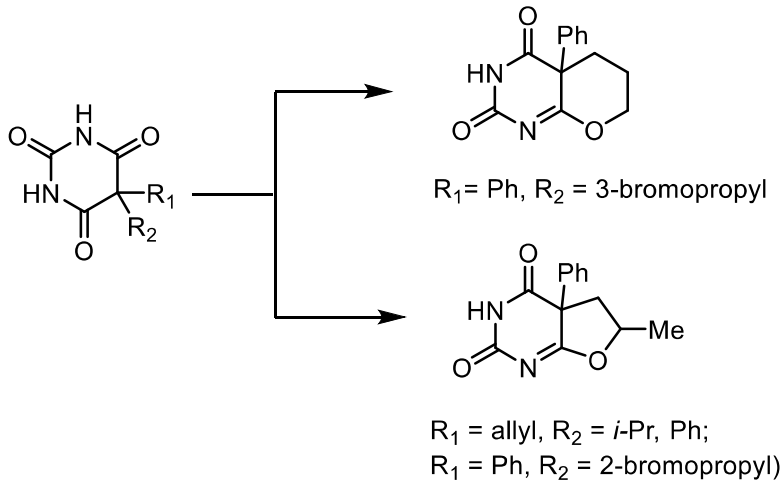
Barton et al. reported the synthesis of *N*-(-2-ethylbutyryl)-*N′*-substituted imidodicarbonic diamides by the photochemical reaction of barbituric acid with amines (**Scheme 1.20**) [133].



Scheme 1.20 Photochemical reaction of barbituric acid with amines.

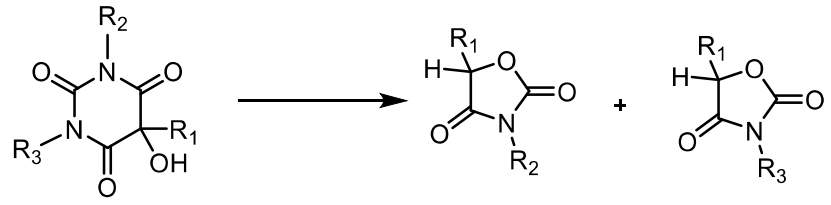
1.3.5 Other Reactions

Bicyclo compounds were formed during the cyclization of 1,5,5-tri- and/or 5,5-disubstituted barbiturates. Therefore, pyranopyrimidine and furanopyrimidine are produced respectively as a result of intramolecular *O*-alkylation of 5,5-disubstituted barbiturates (**Scheme 1.21**) [134, 135].



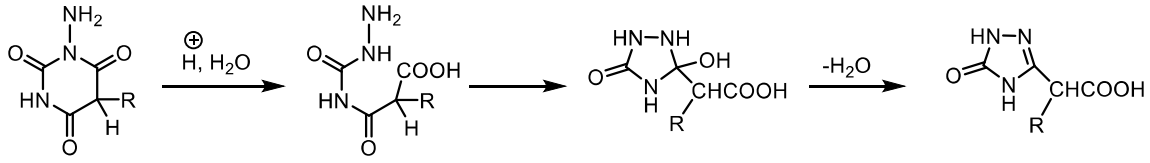
Scheme 1.21 Intramolecular *O*-alkylation of 5,5-disubstituted barbiturates.

Barbiturates undergo ring contraction during hydrolytic degradation. *N,N*-unsymmetrically substituted barbiturates give a mixture of two 5-substituted oxazolidine-2,4-diones (**Scheme 1.22**) [136].



Scheme 1.22 Ring contraction of barbiturates.

In acidic medium, 2-(5-oxo-4,5-dihydro-1*H*-1,2,3-triazol-3-y1) aliphatic acids are produced by the isomerization of 1-aminobarbituric acid. The reaction was observed to be started by hydrolysis of the C-6−N-1 amide bond of 1-aminobarbituric acid under acidic medium, followed by the cyclization of intermediate (I) to the triazole ring system (**Scheme 1.23**) [137].



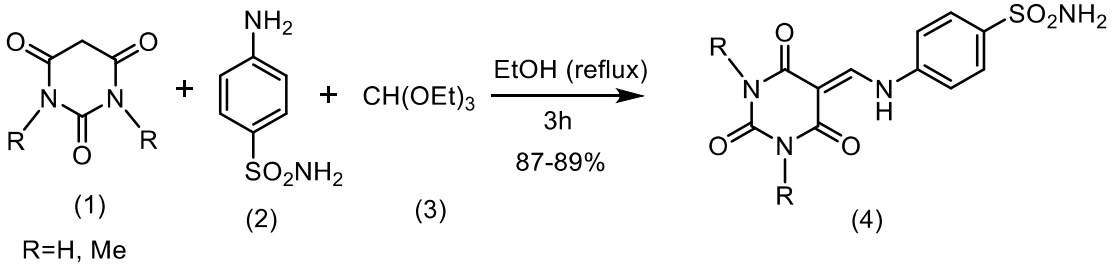
Scheme 1.23 Isomerization of 1-aminobarbituric acid.

1.4 Application of Barbituric Acid in Organic Synthesis

1.4.1 Synthesis of Condensation Product

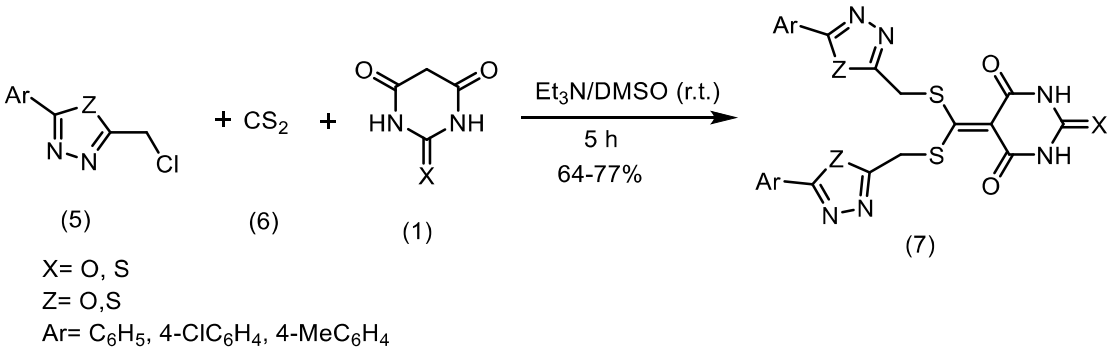
1,3-Dicarbonyl substituted methylaminobenzene-sulfonamide derivative **(4)** is efficiently synthesised by one-pot, three-component reaction of barbituric acid **(1)**, sulfanilamide **(2)** and triethyl[orthoformate] **(3)** in refluxing ethanol (**Scheme 1.24**). The

inhibitory action of the compounds on the properties of purified human carbonic anhydrase (hCA) I and hCA II were estimated [138].



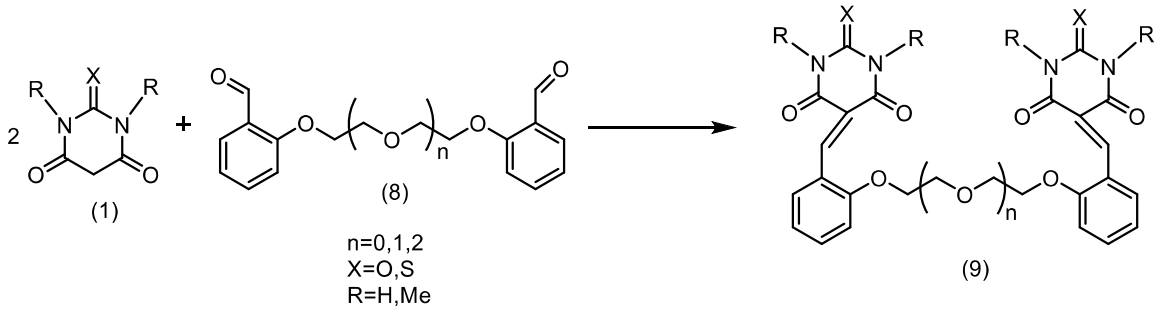
Scheme 1.24 Synthesis of 1,3-dicarbonyl substituted methylaminobenzene-sulfonamide derivative.

A novel class of trisheterocyclic systems, bisthiadiazolyl /bisoxadiazolyl thioxopyrimidinediones /pyrimidinetriones **(7)** was synthesized by the condensation of 1,3,4- thiadiazole /oxadiazole **(5)**, carbon disulfide **(6)** and barbituric acid derivatives **(1)**, under base catalysed medium (**Scheme 1.25**). The antimicrobial property of the produced compounds was studied and it was concluded that compounds having thioxopyrimidinedione along with bisthiadiazole unit displayed high activity [139].



Scheme 1.25 Synthesis of trisheterocyclic systems.

Knoevenagel condensation reaction of barbituric acid derivatives **(1)** with ethylene glycol-based aromatic aldehyde **(8)** resulted to the synthesis of novel benzylidene barbituric acid derivatives **(9)** (**Scheme 1.26**) [140, 141].

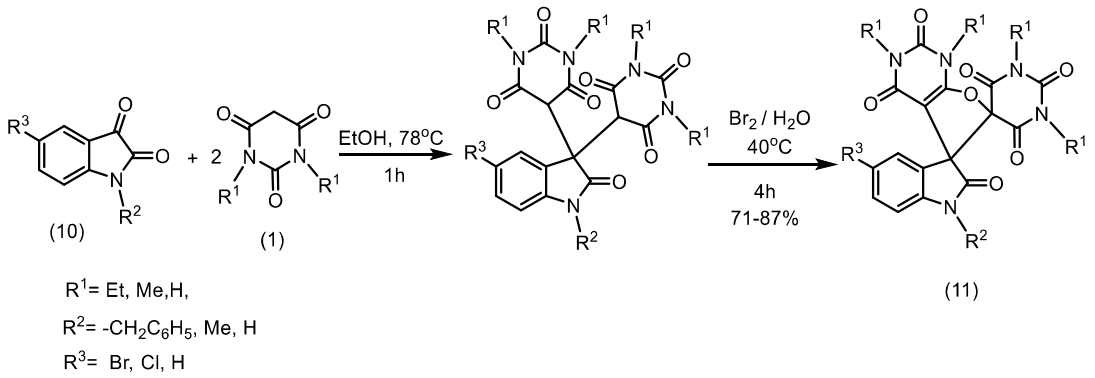


Scheme 1.26 Synthesis of benzylidene barbituric acid derivatives.

1.4.2 Synthesis of Oxygen Containing Heterocyclic Compounds

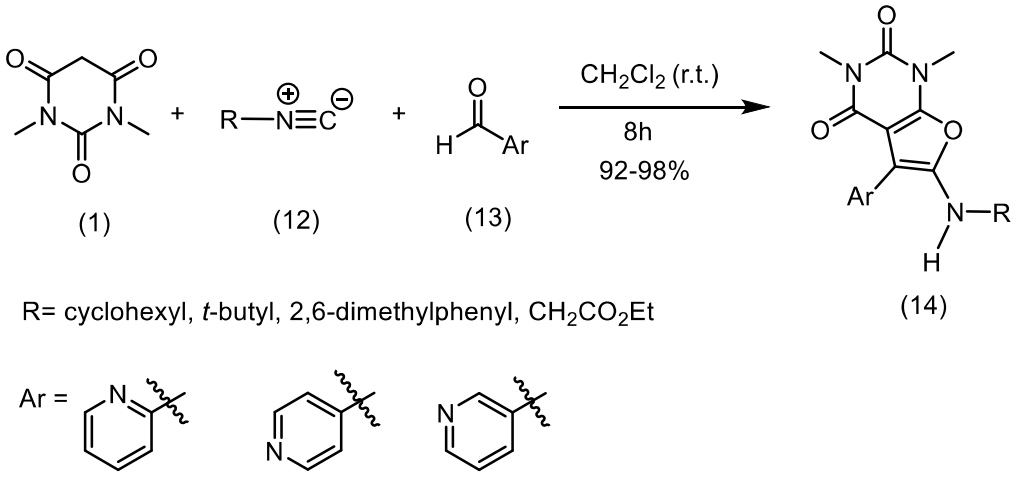
1.4.2.1 5-Membered Heterocyclic Compounds

One-pot reaction of isatins **(10)** and barbituric acids **(1)** by the action of the bromine in ethanolic solution lead to the synthesis of substituted 2″*H*-dispiro[indole-3,5′-furo[2,3-*d*] pyrimidine] system **(11)** in 71–87% yields through cascade process (**Scheme 1.27**) [142].



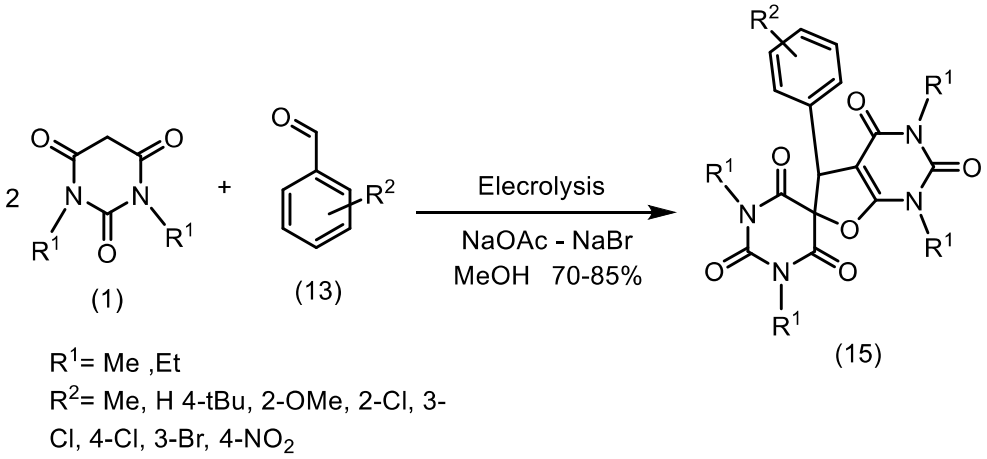
Scheme 1.27 Synthesis of 2″*H*-dispiro[indole-3,5′-furo[2,3-*d*] pyrimidine] system.

A series of novel furo[2,3-*d*]pyrimidine derivatives **(14)** were synthesized via multi-component condensation reaction (**Scheme 1.28**) [143].



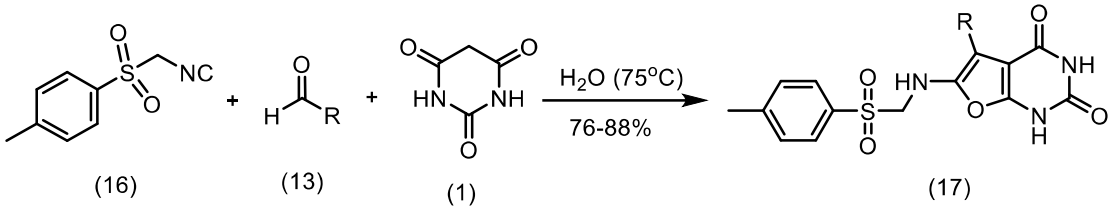
Scheme 1.28 Synthesis of furo[2,3-*d*]pyrimidine derivatives.

Electrocatalytic assembling of *N,N'*-dialkylbarbituric acids **(1)** and aldehydes **(13)** result to the selective synthesis of substituted spirofuropyrimidines **(15)** by complex cascade process (**Scheme 1.29**) [144].



Scheme 1.29 Synthesis of substituted spirofuropyrimidines.

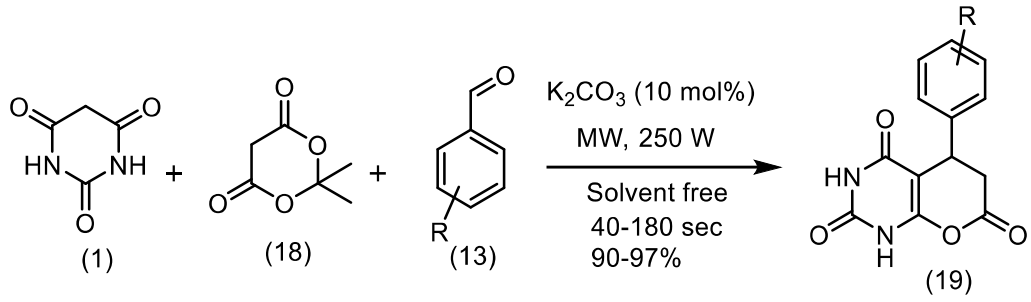
Furo(2,3-*d*)pyrimidine-2,4(1*H*,3*H*)-dione derivatives **(17)** have been prepared by three-component condensation reaction (**Scheme 1.30**). The obtained compounds were tested for their antibacterial and antifungal properties and majority of the compounds displayed good results [145].



Scheme 1.30 Synthesis of furo(2,3-*d*)pyrimidine-2,4(1*H*,3*H*)-dione derivatives.

1.4.2.2 6-Membered Heterocyclic Compounds

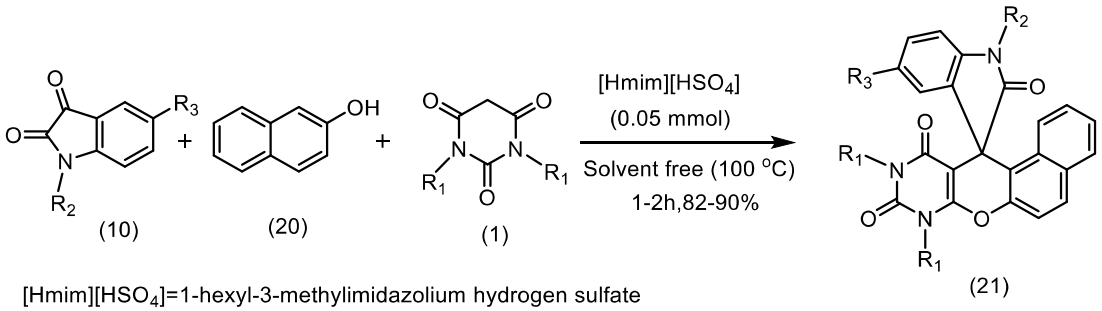
Synthesis of pyrano[2,3-*d*]pyrimidine-2,4,7-triones **(19)** has been done by a three-component reaction (**Scheme 1.31**) [146].



Scheme 1.31 Synthesis of pyrano[2,3-*d*]pyrimidine-2,4,7-triones.

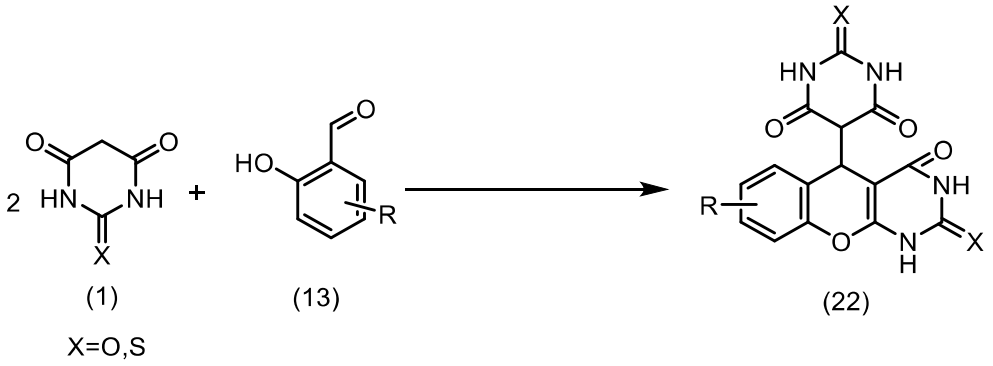
A proficient one-pot three-component procedure has been reported for the preparation of novel spironaphthopyrano[2,3-*d*]pyrimidine-5,3′-indolines **(21)** via condensation reaction of isatins **(10)**, *β*-naphthol **(20)** and barbituric acid derivatives **(1)**,

by exploitation of [Hmim][HSO_4] as a reusable and efficient catalyst (**Scheme 1.32**) [147].



Scheme 1.32 Synthesis of spironaphthopyrano[2,3-*d*]pyrimidine-5,3′-indolines.

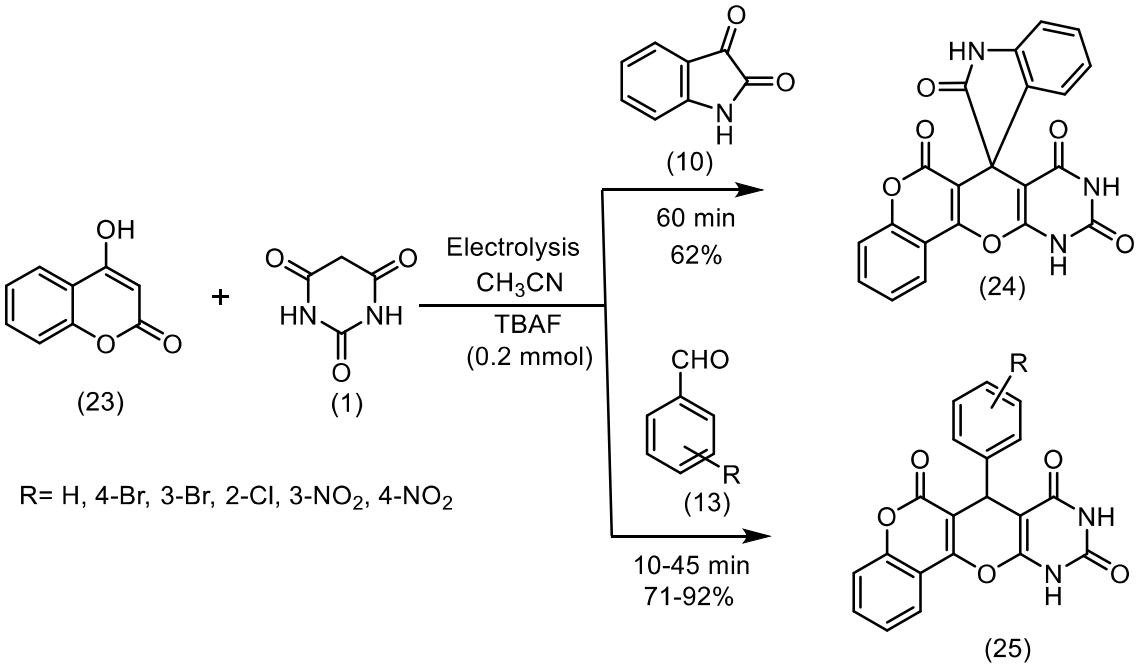
A series of 5-(2,3,4,5-tetrahydro-1*H*-chromeno[2,3-*d*]pyrimidin-5-yl)pyrimidione derivatives **(22)** have been prepared from 2-thiobarbituric acid or barbituric acid **(1)** and substituted salicylaldehydes **(13)** (**Scheme 1.33**). These derivatives displayed significant antioxidant and in vitro antibacterial properties [148-150].



Scheme 1.33 Synthesis of 5-(2,3,4,5-tetrahydro-1*H*-chromeno[2,3-*d*]pyrimidin-5-yl)pyrimidione derivatives.

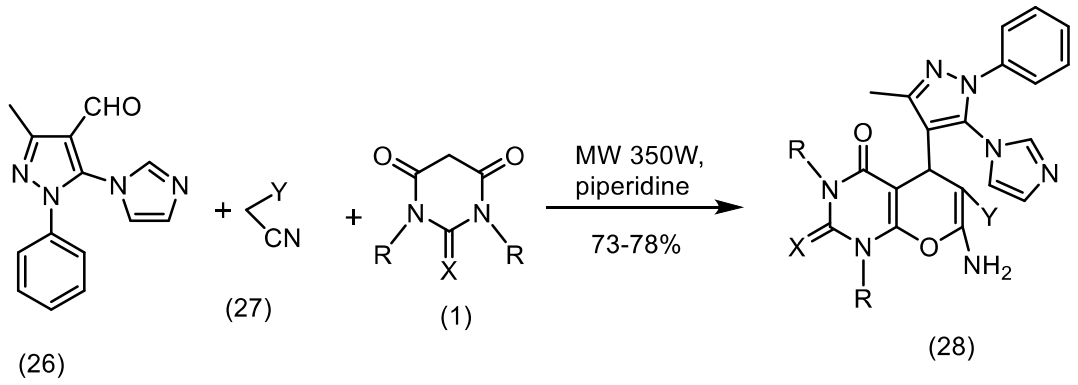
An efficient, one-pot, three-component method for synthesis of novel chromeno[3′,4′:5,6]pyrano[2,3-*d*]pyrimidines **(24-25)** has been reported by utilising

tetrabutylammonium fluoride (TBAF) as a supporting electrolyte and acetonitrile as a base. (**Scheme 1.34**) [151].



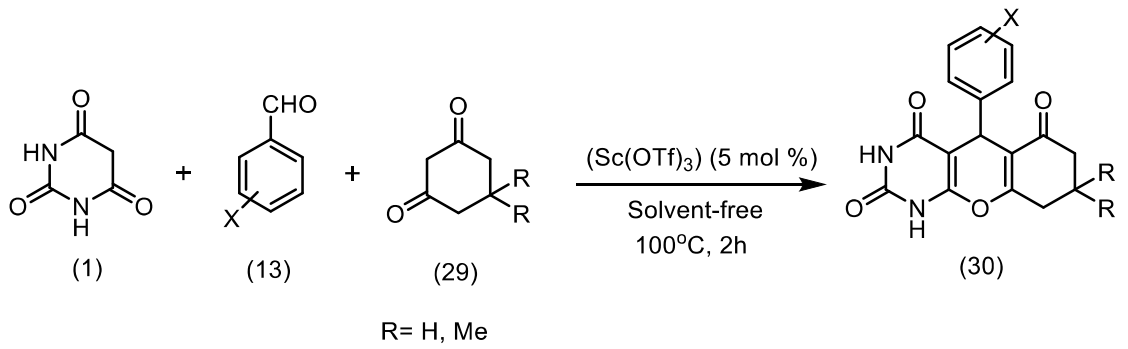
Scheme 1.34 Synthesis of novel chromeno[3′,4′:5,6]pyrano[2,3-*d*]pyrimidines.

One-pot three-component reaction of barbituric acid **(1)**, 5- (1*H*-imidazol-1-yl)-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde **(26)**, and malononitrile/ethylcyanoacetate **(27)** was effectively performed with piperidine as a basic catalyst (**Scheme 1.35**). All the products have been examined for their anti-malarial, anti-tuberculosis, and antibacterial activities [152].



Scheme 1.35 Synthesis of pyranopyrimidines.

A significant, simple, and environmentally benign method for the preparation of chromeno[2,3-*d*]pyrimidine-trione derivatives **(30)** was reported via the one-pot, three-component reaction (**Scheme 1.36**) [153].



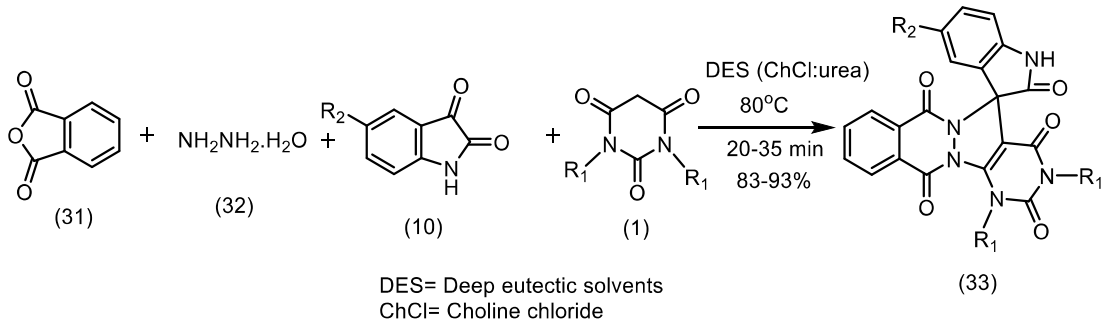
Scheme 1.36 Synthesis of chromeno[2,3-*d*]pyrimidine-trione derivatives.

1.4.3 Synthesis of Nitrogen Containing Heterocyclic Compounds

1.4.3.1 5-Membered Heterocyclic Compounds

The synthesis of spirooxindoles spiroannulated with pyrazolopyrimidophthalazines **(33)** has been done by a one-pot four-component domino

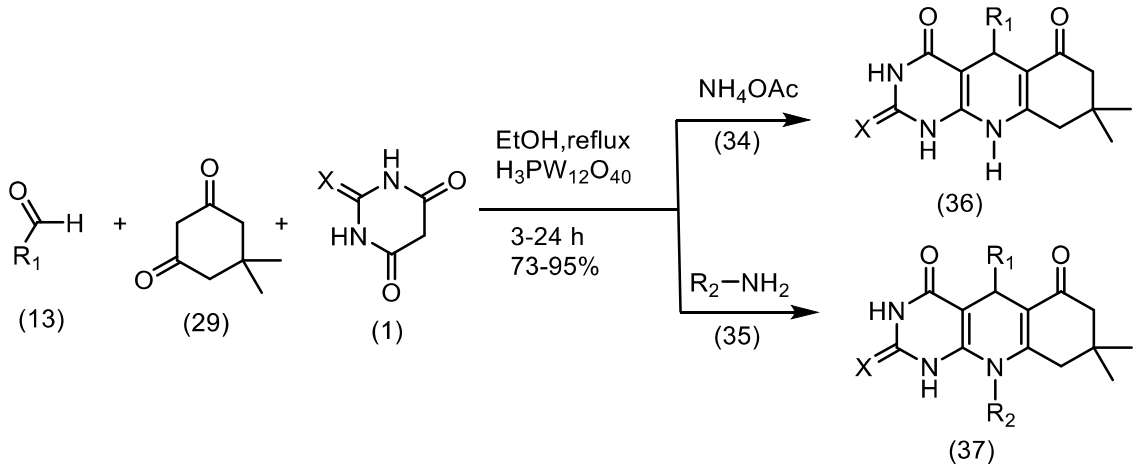
reaction of phthalic anhydride **(31)**, hydrazine hydrate **(32)**, isatins **(10)** and barbituric acid **(1)** in a deep eutectic solvent (choline chloride: urea: 1: 2) (**Scheme 1.37**) [154].



Scheme 1.37 Synthesis of spirooxindoles.

1.4.3.2 6-Membered Heterocyclic Compounds

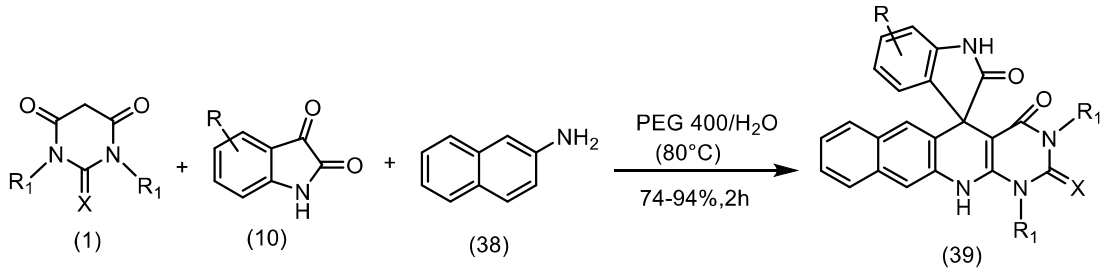
A one- pot four component condensation reaction of aldehydes **(13)**, amines **(34-35)**, dimedone **(29)** and barbituric acid **(1)** has been reported for the preparation of novel



Scheme 1.38 Synthesis of 8,9- dihydro-8,8-dimethyl-5,10-diphenylpyrimido[4,5-*b*]quinoline-2,4,6(1*H*,3*H*,5*H*,7*H*,10*H*)-trione derivatives.

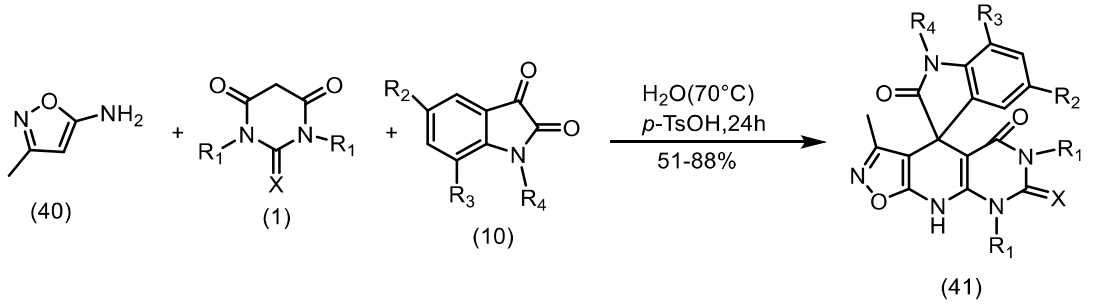
8,9- dihydro-8,8-dimethyl-5,10-diphenylpyrimido[4,5-*b*]quinoline-2,4,6(1*H*,3*H*,5*H*,7*H*,10*H*)-trione derivatives **(36-37)** in the presence of tungstophosphoric acid ($H_3PW_{12}O_{40}$) as a catalyst (**Scheme 1.38**) [155].

An efficient and catalyst-free synthesis of spiro[dihydropyridine-oxindole] moiety **(39)** has been reported by a one-pot three-component reaction of barbituric acids **(1),** 2-naphthylamine **(38)** and isatins **(10)** in poly(ethylene glycol) 400/H_2O (**Scheme 1.39**) [156].



Scheme 1.39 Synthesis of spiro[dihydropyridine-oxindole].

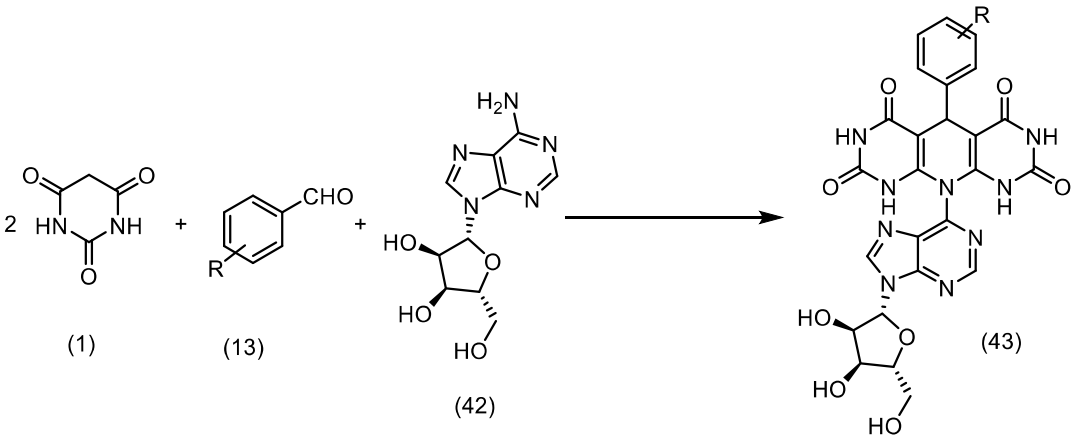
Rahmati and Khalesi reported the *p*-toluenesulfonic acid catalysed synthesis of spiro[indolin-isoxazolo[40,30:5,6]pyrido[2,3-*d*]pyrimidine]triones **(41)** via one-pot,



Scheme 1.40 Synthesis of spiro[indolin-isoxazolo[40,30:5,6]pyrido[2,3-*d*]pyrimidine]triones.

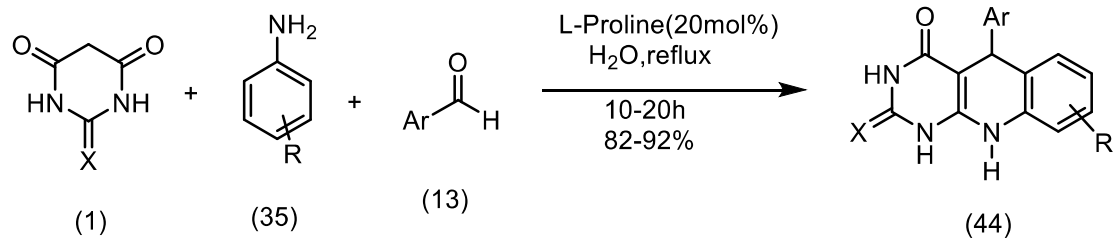
three-component condensation reaction of 5-amino-3-methyl isoxazole **(40)**, isatins **(10)** and barbituric acids **(1)** in water (**Scheme 1.40**) [157].

The synthesis of pyrimidine-fused nucleoside analogues **(43)** has been done by a pseudo four-component coupling reaction of barbituric acid derivatives **(1)**, aldehydes **(13)**, and nucleosides **(42)** (**Scheme 1.41**) [158, 159].



Scheme 1.41 Synthesis of pyrimidine-fused nucleoside analogues.

An efficient and green synthesis of 5-aryl-pyrimido[4,5-*b*]quinoline derivatives **(44)** was carried by a one-pot three-component reaction (**Scheme 1.42**) [160].



Scheme 1.42 Synthesis of 5-aryl-pyrimido[4,5-*b*]quinoline derivatives.

In view of the importance of barbituric acid derivatives, it is our interest to investigate the chemistry of chromenopyrimidines, dibarbiturates of oxindole, arylidene barbituric acid and naphthopyranopyrimidine derivatives. The studies have been described in subsequent **chapters 2-5**.

1.5 References

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