Review

Barbituric Acid Utility in Multi-Component Reactions

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This review describes the multi-component reactions of barbituric acid derivatives as building blocks for the synthesis of heterocyclic compounds with pharmacological interest.

Key words: Barbituric Acid Derivatives, Multi-Component Reactions, Pharmacological Activities

Introduction

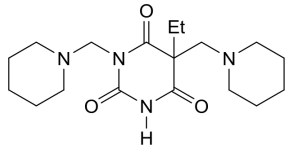
A large number of barbituric acid derivatives have attracted the attention of the pharmaceutical community for more than a century due to their various biological effects [1 – 4]. They are known to possess a wide range of activities, such as inhibiting collagenase-3 (MMP-3) [5], matrix metalloproteinases [6], recombinant cytochrome P450 enzymes [7], methionine aminopeptidase-1 (MetAP-1) [8], hypnotic [9 – 13], sedative [14, 15], antibacterial [8, 16 – 21], anticonvulsant (antiepileptic) [22 – 24], anti-invasive [25], antitumor [25, 26], antiangiogenic [25], anticancer [27 – 30], immuno-modulating [30], herbicides [12], fungicides [31], antiviral [32], antioxidant [33, 34], and HIV-1 integrase inhibitors [35, 36]. Also, barbiturates are a class of drugs that are utilized as anesthetics and sleeping agents and are used for the treatment of anxiety, epilepsy and other psychiatric disorders, and possess effects on the motor and sensory functions [37 – 43]. Structure-activity relationship shows that heterocyclic/substituted aryl moieties at the 5-position of the barbituric [44 – 46] and thiobarbituric [47, 48] nucleus remarkably increase the biological activity. For example, Phenobarbital (5-ethyl-5-phenylbarbituric acid) is the drug used most commonly for convulsive disorders and is the drug of choice for infants and young children [49]. Moreover, spiro barbiturates are a class of compounds with interesting pharmacological and physiological activity [50 – 54].

Multi-component reactions (MCRs) play an increasingly important role in organic and medicinal chemistry because of their convergence, productivity, ease of execution, excellent yields, and broad applications in combinational chemistry [55 – 58].

However, no comprehensive analysis of multi-component reactions with barbituric acids has been made till date, which gave the reason for writing the present review covering the literature from the late 1964 until 2011. Our survey focuses only on MCRs involving at least three different substrates, with no discussion being made of transformations dealing with the two-component reactions of barbituric acids with another substrate. Generally, multi-component treatments of barbituric acids can be divided according to the sections that follow.

MCRs based on the Mannich reaction

The Mannich reaction is a powerful synthetic method for the preparation of β-amino carbonyl compounds, an important class of building blocks of pharmaceutically relevant compounds [59, 60]. In addition it has been reported [61] that insertion of an (arylamino)methyl moiety at position 5 of thiobarbituric acid or barbituric acid enhances the antidepressant activities of the resultant compounds. The aminomethyl group is usually introduced in the 1- and/or 3-position of the barbituric ring, and in some cases at the 5-position. The NH groups of barbituric acids easily take part in Mannich reactions [62, 63]. 5-Ethylbarbituric acid yielded the *N*,*C*-bis(piperidinomethyl) derivative **1** during aminomethylation with formaldehyde and piperidine [64].



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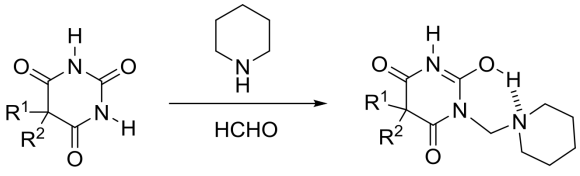
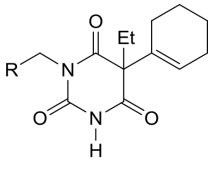
The second NH group in **2** (R^1 = Me, Et; R^2 = Ph, cyclohexenyl) did not undergo further aminomethylation. The reaction led only to the *N*-aminomethyl product **3** (R^1 = Me, Et; R^2 = Ph, cyclohexenyl). This was explained by the formation of the lactim form, which renders the other hydrogen atom inaccessible to a second condensation reaction owing to the stabilization of the lactim moiety by an intermolecular hydrogen bond [65].

On the other hand, Danielsson and Dolby [66] showed that aminomethylation in the 1- and 3-positions was possible in both 5,5-diethyl- and 5-ethyl-5-phenylbarbituric acids when formaldehyde and morpholine were used as the reagents.



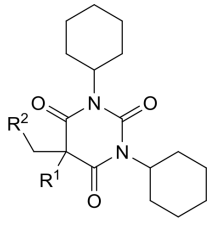
2 **3**

Furthermore, Werner and Fritzsche [67] found that 1-aminomethylated 5,5-disubstituted barbituric acids **4** have nonchelated NH groups, and that a second aminomethylation is possible at the N-3 atom.



4

Also, there are known cases of the Mannich reaction at the 5-position. Thus, Sladowska [68] obtained the series of 5-alkyl-5-aminomethyl-1,3-dicyclohexyl-barbituric acids (**5**, R^1 = Et, allyl; R^2 = 1-piperidinyl, 1-pyrrolidinyl, 1-morpholinyl) from 5-alkyl-1,3-dicyclohexyl-barbituric acids.



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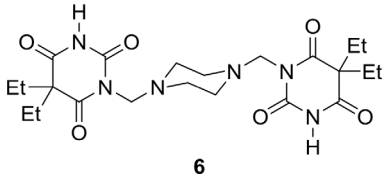
N,*N*′-Bis(5,5-diethyl-1-barbiturylmethyl)piperazine (**6**) has been synthesized by condensation of 5,5-diethylbarbituric acid with formaldehyde and piperazine following a Mannich procedure [69].



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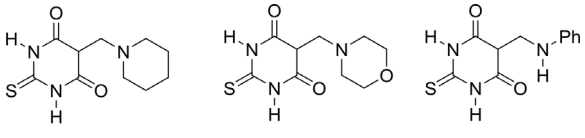
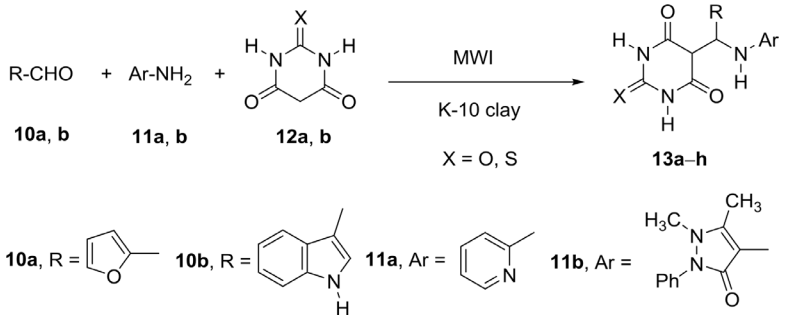
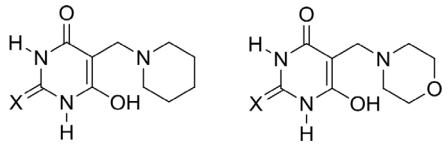
The 2-thiobarbituric acids enter into Mannich reactions with formaldehyde, piperidine [70] or morpholine [70], and with anilines [71, 72] giving rise to the corresponding 5-aminomethyl derivatives **7** – **9**, respectively.



7 **8** **9**

Kidwai *et al.* [73], have described the one-pot synthesis of substituted barbituric and thiobarbituric acids **13a** – **h** using montmorillonite clay in dry media under microwave irradiation (MWI). Reactions between **10a**, **b**, **11a**, **b**, and **12a** (X = O), **b** (X = S) under conven-



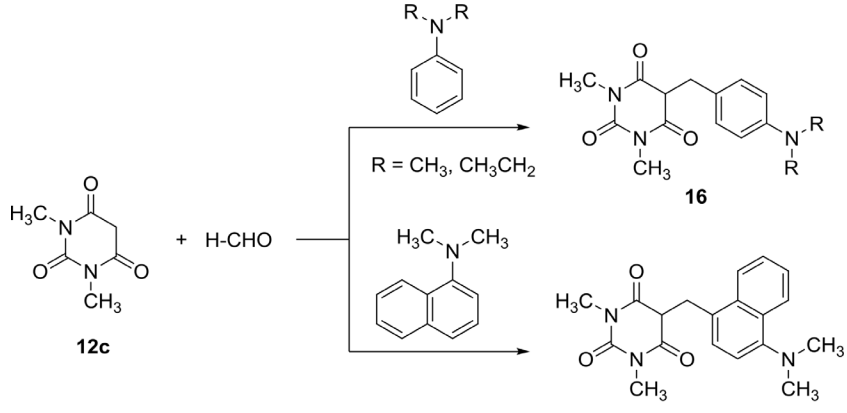


14 **15**

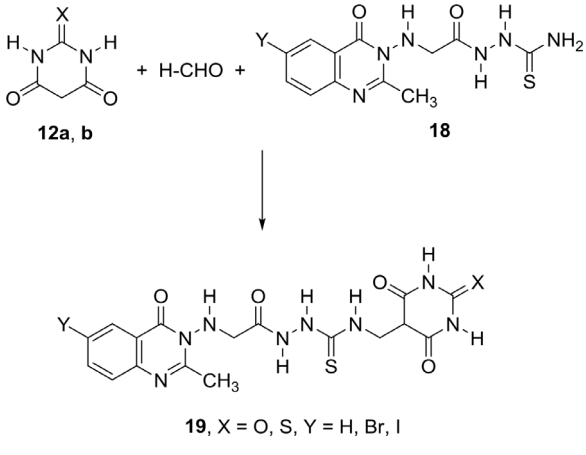
tional heating were completed in 10 – 12 hours with moderate yield, whereas the same reactions under MWI gave excellent yields within few minutes of irradiation. All the compounds synthesized were found to possess good antifungal activity [73].

The reactions of barbituric acids **12a**, **b** with formaldehyde and piperidine or morpholine gave the corresponding Mannich bases **14** and **15** [74].

An efficient, unusual Mannich-type reaction of tertiary aromatic amines, formaldehyde and *N*,*N*′-dimethylbarbituric acid (1,3-dimethylbarbituric acid, **12c**) is described in aqueous micelles catalyzed by boric acid to afford the 5-dialkylaminoaryl-1,3-dimethylpyrimidine-2,4,6-triones **16** and **17** [75]. The reaction is highly regioselective, and exclusively *para*-functionalized products are formed in high yields [75].



12c **16** **17**

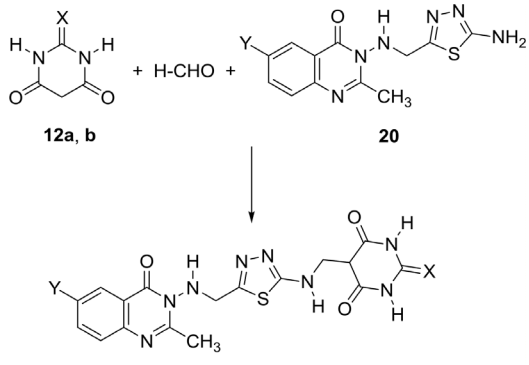


12a, **b** **18**

19, X = O, S, Y = H, Br, I

Anticonvulsant activities of (halosubstituted quinazolinonyl-thiosemicarbazido)-barbituric and -thiobarbituric acids **19**, which were prepared from the reaction of barbituric acids **12a** (X = O), **b** (X = S) with formaldehyde and thiosemicarbazides **18**, have been reported [23]. From the results of studies of the biological activities it was concluded that the presence of the bromo group at the 6-position of the quinazolinone nucleus was found to increase the anticonvulsant activity. Furthermore, incorporation of 2-thiobarbituric acid in **18** was found to increase the potency of these compounds and resulted in the formation of **19** with high anticonvulsant activity [23].

The 1,3,4-thiadiazoles **20** were combined with barbituric and thiobarbituric acid *via* Mannich reaction to yield (1′,3′,4′-thiadiazol-2′-yl)-barbituric and thiobarbituric acids **21** which showed an activity (90 %) more

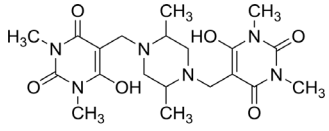


12a, **b** **20**

21, X = O, S, Y = H, Br, I

potent than the standard drug [23]. These compounds showed anticonvulsant activity. Furthermore, incorporation of thiobarbituric acid in **20** was found to increase the potency of these compounds and resulted in the formation of **21** with high anticonvulsant activity [23].

The reaction of 1*N*,*N*′-dimethylbarbituric acid (**12c**) with formaldehyde and 2,5-dimethylpiperazine gave the bis Mannich base **22** [74].



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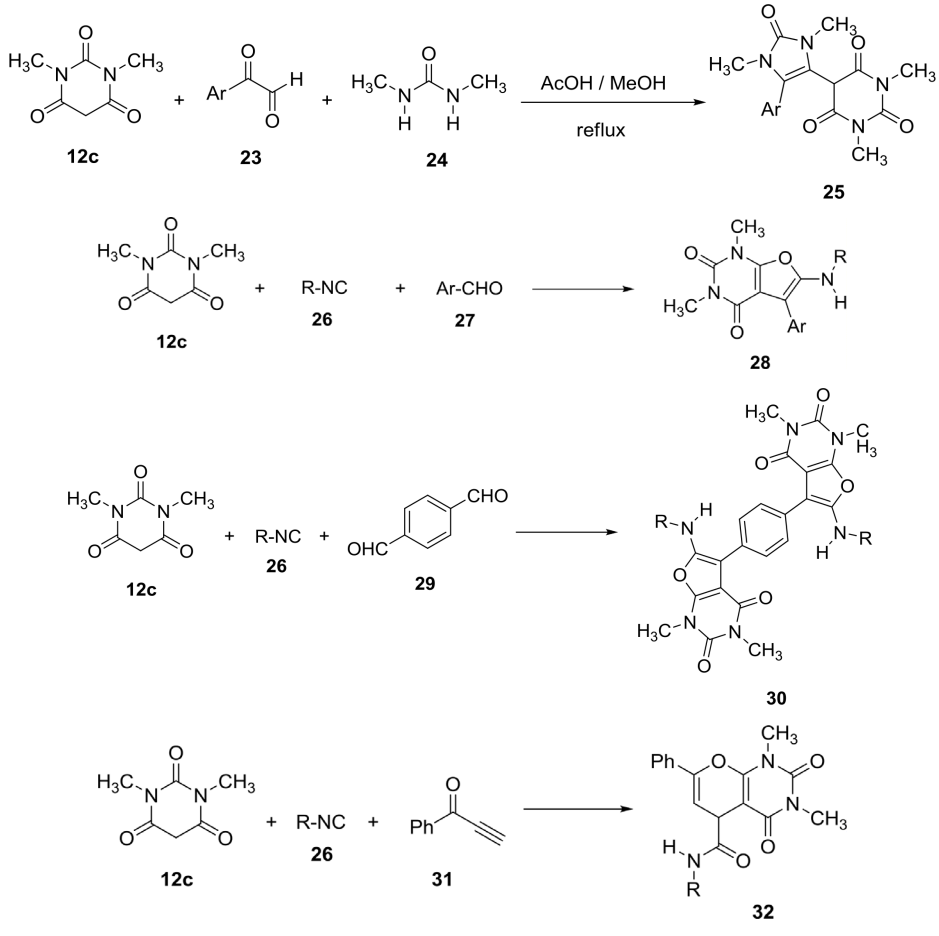
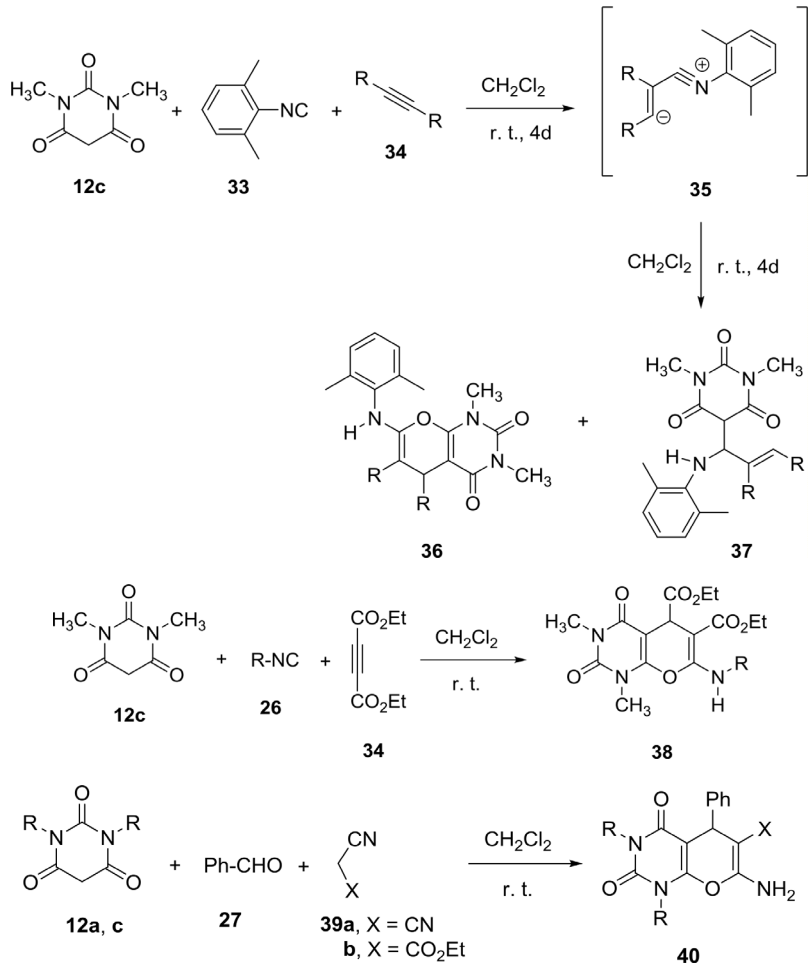
MCRs based on the Knoevenagel Reaction

The Knoevenagel reaction consists of the condensation of aldehydes or ketones with active methylene compounds usually performed in a weakly basic medium [76]. It is well-known that nitrogen-containing compounds such as pyrimidines and imidazole derivatives are of widespread interest in pharmacology. Thus, a catalyst-free three-component transformation combining both heterocycles was developed involving *N*,*N*′-dimethylbarbituric acid (**12c**), arylglyoxals (**23**), and dimethylurea (**24**) in methanol heated at reflux to furnish imidazolylpyrimidinone **25** [77]. Results of mechanistic investigations were in accordance with a Knoevenagel-initiated process followed by an aza-Michael addition of a urea moiety and cyclodehydration.

One-pot three-component condensation reactions of isocyanides **26**, aldehydes **27** and *N*,*N*′-dimethylbarbituric acid (**12c**) afforded furopyrimidinones **28** [78].

The 5,5′-(1,4-phenylene)di(furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione) derivatives **30** were obtained from the reaction of isocyanides **26**, terephthalaldehyde (**29**) and *N*,*N*′-dimethylbarbituric acid (**12c**) *via* efficient one-pot three-component condensation reactions [79].





The reaction of isocyanides **26** and ethynyl phenyl ketone **31** with *N*,*N*′-dimethylbarbituric acid (**12c**) yielded the pyrano[2,3-*d*]pyrimidine-5-carboxamides **32** in good yields after 4 days at r. t. [80].

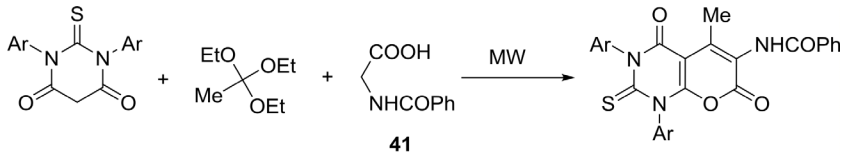
The production of the reactive intermediate **35** in the reaction between 2,6-dimethylphenyl isocyanide (**33**) and acetylenes **34** was described by Yavari *et al.* [81], where the reactive intermediate **35** was trapped by *N*,*N*′-dimethylbarbituric acid (**12c**) to yield the isomeric products **36** and **37** in a nearly 1 : 1 ratio and an overall yield of 85 %.

The isocyanides **26**, dimethyl acetylenedicarboxylate (**34**, R = CO_2Et) and *N*,*N*′-dimethylbarbituric acid (**12c**) undergo smooth 1:1:1 addition reactions in dichloromethane at r. t. to produce the 4*H*-pyrano[3,2-*d*]pyrimidines **38** [82].

Microwave-assisted three-component cyclocondensation of barbituric acids **12a** (R = H) or **12c** (R = Me), benzaldehyde (**27**) and nitriles **39** proceeds in the absence or presence of triethylamine to afford pyrano[2,3-*d*]pyrimidines **40** [83].

Bicyclic compounds of type **40** (R = H, X = CN) have been synthesized by ultrasound (US) promoted three-component reaction between aromatic aldehydes **27**, barbituric acid (**12a**), and malononitrile (**39a**) [84]. The reaction was performed in an aqueous medium without the use of a catalyst, and the products **40** were obtained in good yields.

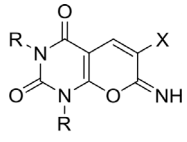
Also, biologically active pyrano[2,3-*d*]pyrimidine derivatives (**40**, R = H, X = CN) were efficiently synthesized in excellent yields by a three-component, one-pot condensation reaction of malononitrile (**39a**), aromatic aldehydes **27** and barbituric acid (**12a**) using Zn[(L)proline] [85, 86] or tetrabutylammonium bromide (TBAB) [87] or in the presence of *N*-methylmorpholine [88] as a catalyst.



41 42

The cyclocondensation of *N*,*N*′-diaryl-2-thiobarbituric acids with hippuric acid (**41**) and triethyl orthoacetate on basic alumina was carried out under MWI to give pyranopyrimidines **42** in 92 – 95 % yields within one minute. More than five hours were required under conventional heating at 110 – 120 °C to afford 60 – 70 % yields [89].

Cycloaddition of barbituric acids **12a** (R = H), **c** (R = Me), triethyl orthoformate, and nitriles **39** in the presence of acetic anhydride under MWI for five minutes afforded pyrano[2,3-*d*]pyrimidines **43** in excellent yields [90].

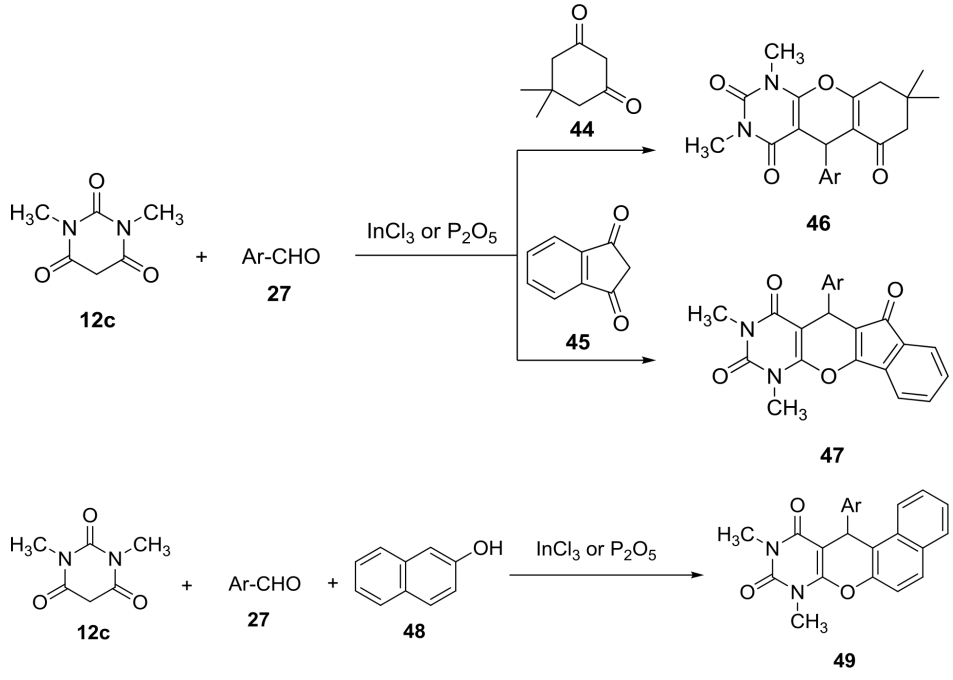


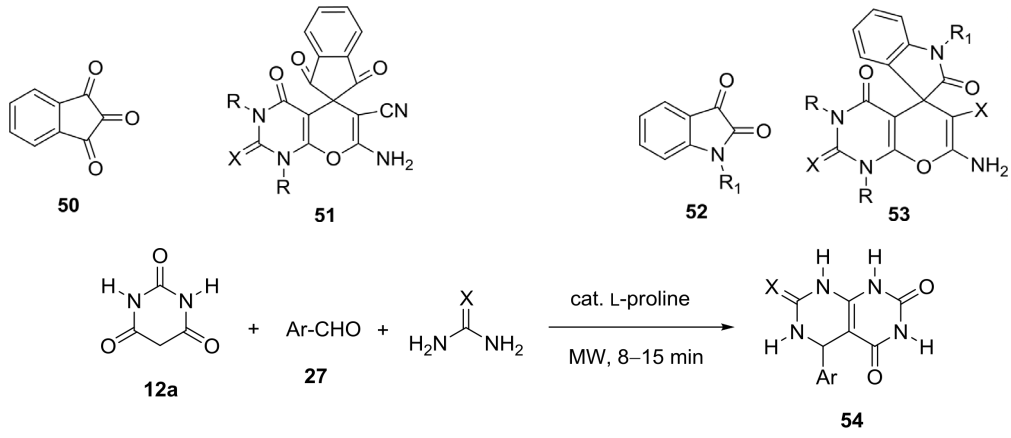
43

The synthesis of chromeno[2,3-*d*]pyrimidinones **46** and diazabenzo[*b*]fluorenones **47** has been developed by one-pot three-component cyclocondensation of *N*,*N*′-dimethylbarbituric acid (**12c**), aldehydes **27**, and dimedone (**44**) or indane-1,3-dione (**45**) in the presence of $InCl_3$ or P_2O_5 under solvent-free conditions [91].

Indium(III) chloride-catalyzed one-pot syntheses of 12-aryl-8,10-dimethyl-8,12-dihydro-7-oxa-8,10-diazabenzo[*a*]anthracene-9,11-dione derivatives **49** have been achieved by three-component cyclocondensation of *N*,*N*′-dimethylbarbituric acid (**12c**), aldehydes **27**, and β-naphthol (**48**) under solvent-free condition in high yields. P_2O_5 too has been found to be an effective catalyst towards this transformation [92].

Shaker *et al*. [93] reported that the three-component condensation of indan-1,2,3-triones (**50**), malononitrile (**39a**) and barbituric acids **12a** (R = H, X = O), **b** (R = H, X = S) as well as *N*,*N*′-diethyl-2-thiobarbituric acid in the presence of piperidine under microwave irradiation without solvent afford the corresponding spiro-fused pyran derivatives **51**.



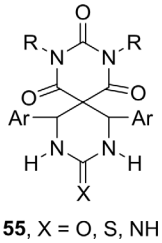


A simple and efficient one-pot three-component synthesis of the biologically important spirooxindoles **53** was carried out by the reaction of isatins **52**, nitriles **39**, and barbituric acids **12** in aqueous medium. A Knoevenagel condensation occurred first between isatin and the malonitrile derivative, followed by Michael addition of barbituric acids and cyclization *via* the cyano moiety [94, 95].

Biginelli heterocyclic synthesis

The Biginelli reaction, discovered by Pietro Biginelli in 1893, is a multicomponent reaction allowing the synthesis of DHPMs by reacting urea, a dicarbonyl derivative, and an aldehydic component. An increased interest in this process has been shown during the past few years; recent investigations aimed at performing the MCR under milder conditions, increasing the yields and opening the scope of the different partners. An abundant literature covers all these aspects including a recent compilation of catalytic systems [96].

4 - Aryl - 3, 4 - dihydropyrimido [4, 5 - *d*] pyrimidine - 2(1*H*)-one **54** has been synthesized under solvent-free microwave conditions using three component condensations of aldehydes **27**, urea or thiourea and barbituric acid (**12a**) [97 – 99].

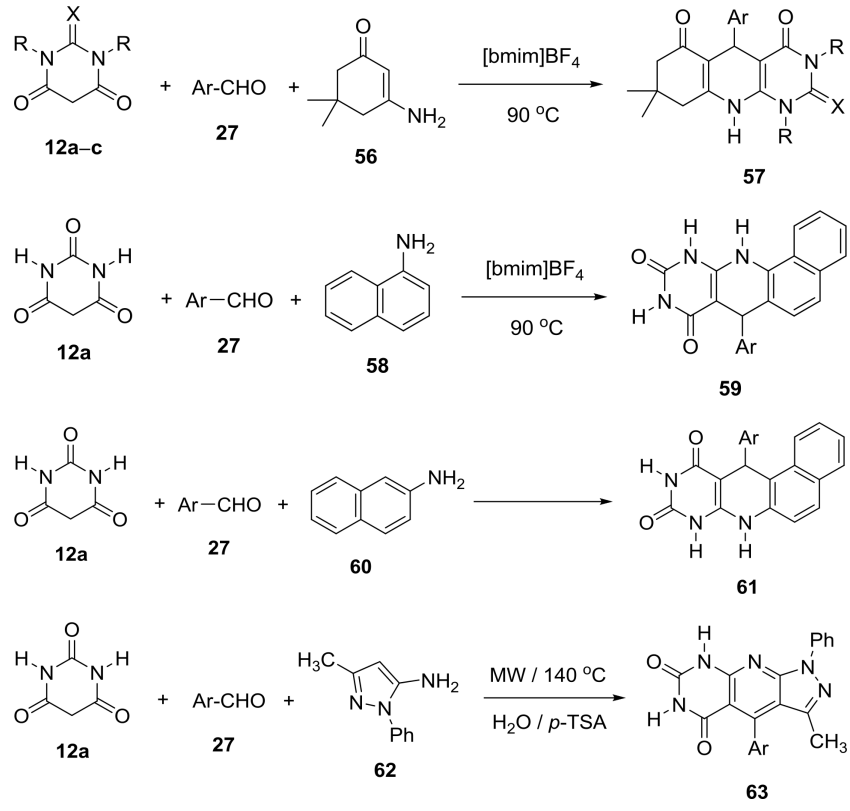


55, X = O, S, NH

The one-pot reaction of a mixture of barbituric acids **12a** (R = H), **c** (R = Me), aldehydes **27** and urea or thiourea gave the 2,4,8,10-tetraazaspiro[5.5]-undecane-1,3,5-trione (**55**). The reaction can be promoted either in acetic acid as solvent or neat under microwave irradiation or in the presence of $H_3PW_{12}O_{40}$ or iodine as catalysts [100 – 104].

Hantzsch heterocyclic synthesis

1,4-Dihydropyridines (1,4-DHPs) and their derivatives are important classes of bioactive molecules in the pharmaceutical field [105] and constitute also interesting biomimetic reducing agents [106, 107]. Over the years, the great biological importance of these various symmetric or unsymmetrical 1,4-DHPs has prompted the development of new improved methodologies for their synthesis. According to the original procedure described by Hantzsch in 1882, the reaction is conducted either in acetic acid or in refluxing alcohols for long reaction times, but these rather harsh conditions typically lead to low yields. Aiming at developing more efficient and environmentally benign Hantzsch reactions, some procedures involving different activating modes such as microwave irradiations [108, 109], ultrasonic irradiations [110, 111], or even use of solar energy as a free energy source [112] have been reported. Conventional organic solvents have also been replaced by water [113] or reusable fluoroalcohols [114]. One example of the synthesis of polyhydroquinolines was also described under solvent-free conditions on grinding [115]. Alternatively, task-specific ionic liquids were used as soluble support on which the β-ketoesters were bound [116].



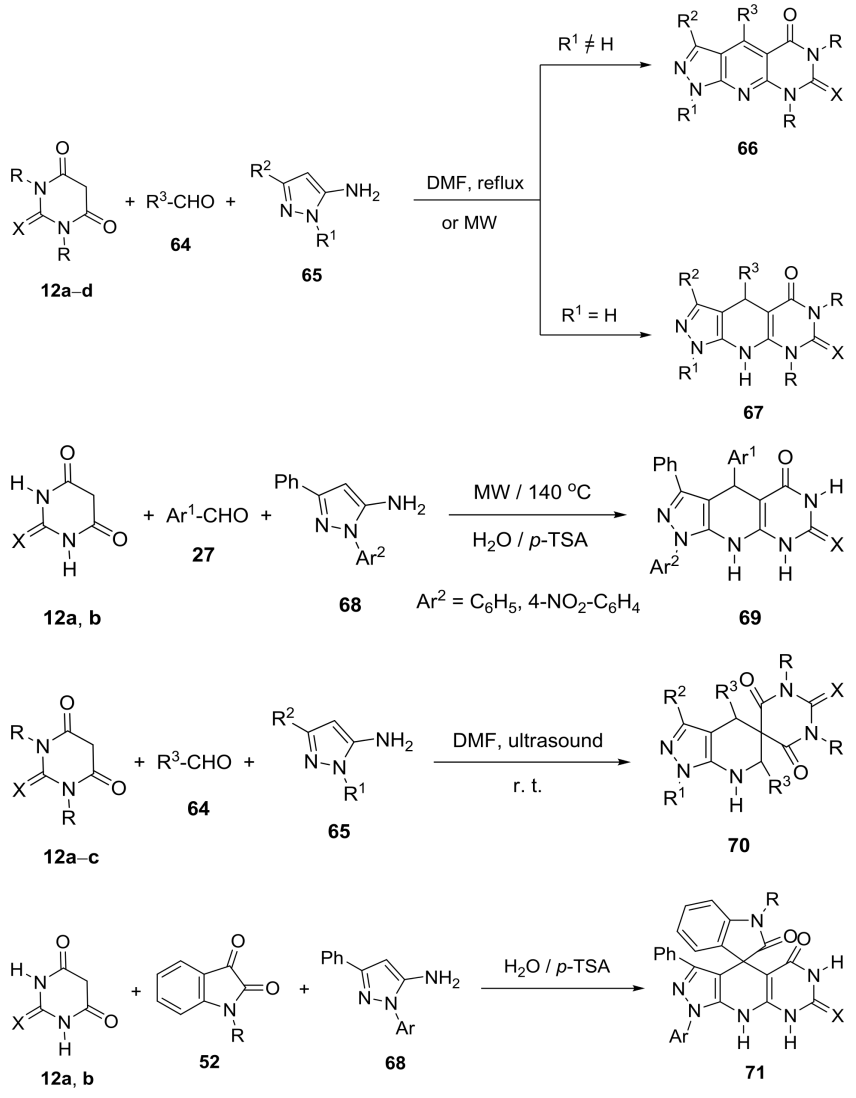
The tetrahydropyrimido[4,5-*b*]quinolines **57** have been synthesized in high yields using ultrasound irradiation in an efficient one-pot, three-component process by a condensation reaction of barbituric and thiobarbituric acids **12a – c**, aldehydes **27** and 3-amino-5,5-dimethylcyclohex-2-enone (**56**) in water [117].

A series of 7-aryl-11,12-dihydrobenzo[*h*]pyrimido-[4,5-*b*]quinoline-8,10(7*H*,9*H*)-diones **59** were synthesized *via* three-component reaction of aldehydes **27**, α-naphthylamine (**58**) and barbituric acid (**12a**) in an ionic liquid [118].

Similarly, the three-component reaction of aldehydes **27**, β-naphthylamine (**60**) and barbituric acid (**12a**) at r. t. yield the benzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione **61** in excellent yields [119 – 121].

The first results in the synthesis of pyrazolopyridopyrimidines by MCR of aminopyrazole **62**, aldehydes **27**, and barbituric acid (**12a**) were published in 2008 by Shi *et al.* [122]. They used "green chemistry" methodology and carried out treatment of the starting materials in water under microwave irradiation. The temperature optimization procedure and the search for the best catalytic system allowed selecting one equivalent of *p*-TSA and 140 °C as optimum conditions for the synthesis. With application of the elaborated procedure, 24 novel pyrazolopyridopyrimidines **63** were generated.

A detailed study of the MCRs involving barbituric acids **12a – d** (R = H, Me; X = O, S) and 5-aminopyrazoles was published by Muravyova *et al.* [123]. The article describes the development of chemoselective cyclocondensations with the help of microwave and ultrasonic irradiation. It was established that the temperature was the main factor in controlling the direction of the MCRs studied. At high temperatures (170 – 190 °C) the starting materials reacted in two different ways. It was found that a substituent in the position 1 of aminopyrazoles strongly influences the nature of the reaction products. In the case of *N*-substituted aminopyrazoles (both with electron-withdrawing and with electron-releasing R^1 groups), the reaction yielded pyrazolopyrido-pyrimidines **66**. When R^1 = H, MCRs at high temperature in DMF always gave dihydro derivatives **67**. Interesting results also concern the microwave-assisted treatment. Application of controlled MW irradiation (temperatures

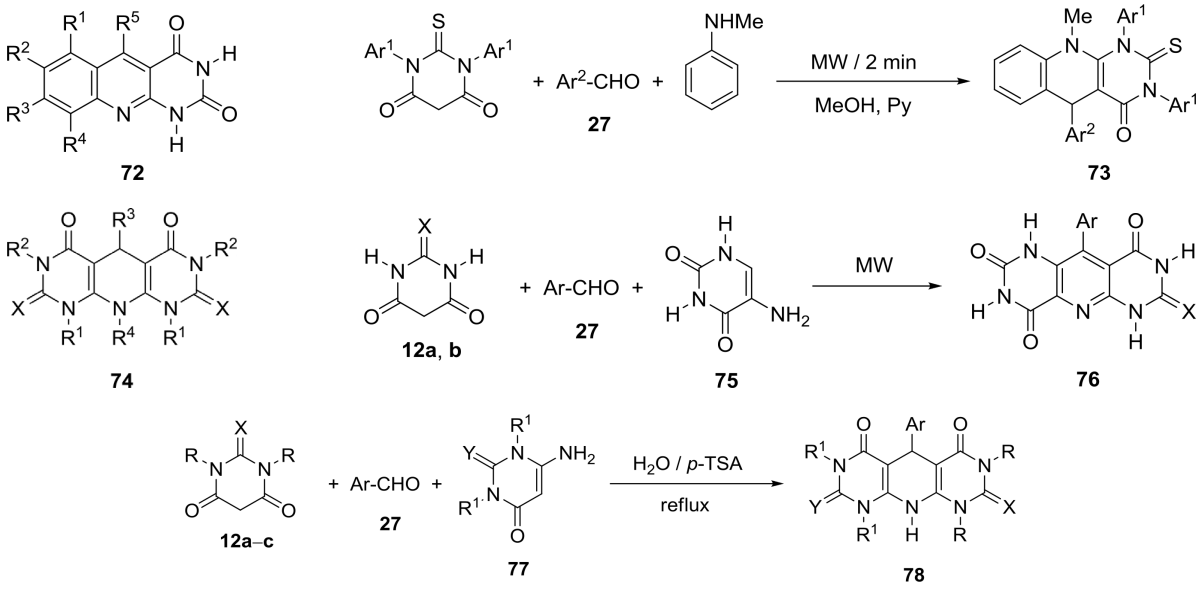


from 150 to 190 °C) when carrying out MCRs involving *N*-unsubstituted pyrazoles did not give any positive result and led to complicated mixtures of several inseparable products. However, using a microwave field to promote the reaction when $R^1 \neq H$ was successful. The most preferable microwave-assisted procedure for the synthesis of compound **67** from the viewpoint of the yields and purity consisted in the treatment of the starting building blocks in DMF under microwave irradiation at 190 °C for 3 min.

It has been found that a mixture of 1*H*-pyrazol-5-amines **68**, aldehydes **27**, and barbituric acids **12a** (X = O), **b** (X = S) in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) at 100 °C under solvent-free condition afforded pyrazolo[4′,3′ : 5,6]pyrido[2,3-*d*]pyrimidinedione derivatives **69** [117, 124]. Most of the compounds exhibited good to excellent antibacterial activity against all the tested strains [124].

On the other hand, unexpectedly it was additionally established that the MCR of barbituric acids **12a**, **b** (R = H; X = O, S), **c** (R = Me; X = O), aldehydes **64** and aminopyrazole **65** at r.t. under ultrasonication or with the help of simple stirring yielded a novel type of spirocompounds **70** [123].

A water-based "green" protocol under conventional heating was used to carry out three-component reactions of 3-substituted 5-aminopyrazoles **68**, bar-



bituric acids **12a** (X = O), **b** (X = S) and isatin **52** derivatives. The reaction produced the required spiroheterocycles **71** in excellent yields and purity [125, 126].

Functionalized pyrimido[4,5-*b*]quinoline-2,4(1*H*, 3*H*)-diones **72** were synthesized by a three-component one-pot reaction involving anilines, barbituric acid (**12a**), and either formaldehyde, an aliphatic, or an aromatic aldehyde [127].

A one-pot synthesis of pyrimido[4,5-*b*]-quinolines **73** under MWI involved the reaction of *N*,*N*′-diaryl-2-thiobarbituric acids, the appropriate aldehydes **27**, and *N*-methylaniline to give 72 – 88 % yield after 2 min, compared to 1.5 – 2 h under conventional thermal conditions [128].

The three-component condensation of barbituric and thiobarbituric acids **12** with aldehydes **27** and ammonia or anilines provides derivatives of pyrido[2,3-*d*:6,5-d′]dipyrimidine **74** [129, 130].

Shaker *et al*. [131] have described the synthesis of pyrido[3,2-*d*:6,5-d′]dipyrimidine derivatives **76** through a one-pot reaction of 5-aminouracil (**75**), aldehydes **27** and barbituric acids **12a**, **b** under microwave irradiation.

The three-component one-pot cyclocondensation reaction of barbituric acids **12a** – **c**, aldehydes **27** and 6-aminouracils **77** for the synthesis of pyrido[2,3-*d*:6,5-*d*′]dipyrimidines **78** in refluxing water has been reported [132]. Most of the compounds have a narrow to good spectrum of antimicrobial activity [132].

Summary

Literature data published in the last 47 years have been summarized to help the reader to find information appropriate for the use of multi-component reactions of barbituric acid derivatives in the synthesis of heterocyclic compounds with pharmacological interest.

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