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ARTICLE

Reaction of 6-aminouracils with aldehydes in water as both solvent and reactant under $FeCl_3.6H_2O$ catalysis: towards 5-alkyl/arylidenebarbituric acids

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5-Alkyl/arylidenebarbituric acids were efficiently synthesized through $FeCl_3.6H_2O$ catalyzed domino reaction of 6-aminouracils, water and aldehydes with water serving a dual role as both solvent and reactant, under benign reaction conditions. A study on comparative substrate scope of 6-aminouracil *versus* barbituric acid showed similar efficacy towards 5-alkyl/arylidenebarbituric acids. The protocol is the first detailed report to prepare regioselectively 5-alkyl/arylidenebarbituric acids starting from 6-aminouracils, which is an alternative and competing strategy to hitherto all known reactions directly employing barbituric acids.

Introduction

The synthesis of alkyl/arylidenebarbituric acids and their thio-analogs has received considerable attention for their potential pharmacological applications such as antioxidant[1] and anticancer[2] agents; inhibitors of methionine aminopeptidase-1 (MetAP-1),[3] urease[4] and mushroom tyrosinase;[5] and against non-alcholic fatty liver disease (NAFLD)[6] (Figure 1). Because of the presence of strongly polarized exocyclic double bond, they are also versatile precursors of wide variety of molecules through reactions with carbanions[7] and typical Lewis bases such as alkoxides,[8] amines,[8a,9] thiols,[10] water[11] and hydrogensulfite ion.[12] Moreover, the easy reducibility of the double bond[13] offers these compounds as suitable candidates in the synthesis of 5-monoalkylbarbiturates such as Uridine Phosphorylase (UrdPase) inhibiting 5-benzylbarbiturates,[14] unsymmetrical disulfides[15] and for the mild oxidation of alcohols.[16] Also, 5-arylidenebarbituric acids and their thio-analogs are important building blocks for biologically active pyrazolo-[3,4-*d*]-pyrimidine derivatives[17] and other fused-pyrimidines.[18] Some 5-arylidenebarbituric acids have also been studied as non-linear optical materials and dyes,[19] and in trapping radicals that they can be used as thermal stabilizers in rigid PVC.[20] They have also found applications in analytical studies.[21]

The classical preparation of 5-arylidenebarbituric acids by Knoevenagel condensation of barbituric acids and aldehydes in either basic or acidic conditions using organic solvents[22] resulted yields that were not quite satisfactory due to the formation of disubstituted products accompanying the desired

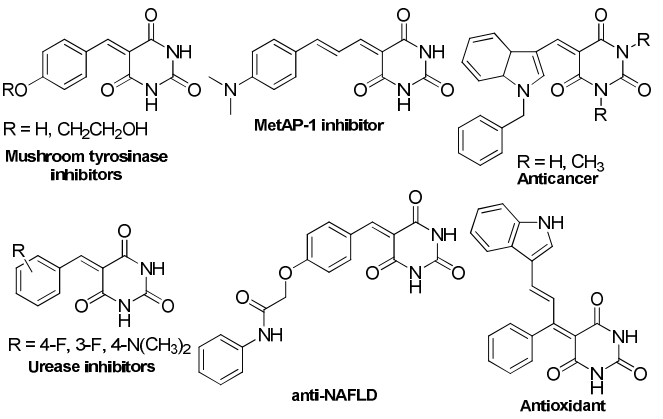

Figure 1. Some biologically active 5-arylidenearbituric acids.

products.[22e,f,23] Consequently, to achieve the mono condensation product, various methods have been put forward by employing different materials like aminosulfonic acid,[24] aluminas,[25] clays,[26] mixed solids,[27] hydrotropes,[28] NaOH/Flyash,[29] ionic liquids,[30] surfactants,[31] TMSCl,[32] Yb(OTf)[33] Nickel nanoparticles,[34] $SiO_2.12WO_3.24H_2O$[35] and gels[36] as catalysts. Efforts for catalyst-free procedures in a suitable solvent[37] and catalyst- and solvent-free[38] approaches have also been made. In a newer method, Lasri *et al.* have also shown that acyclic nitrones on reaction with barbituric acid get

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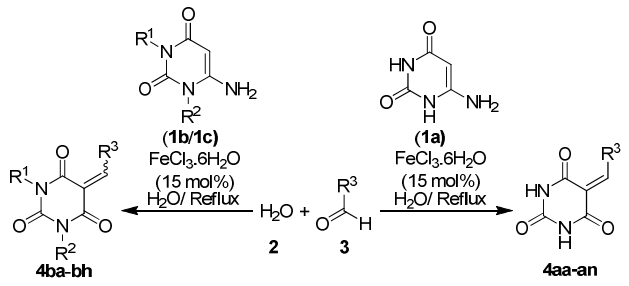
transformed to 5-arylidenebarbituric acids.[39] While these procedures are useful, many of them are also confronted with one or more limitations such as the use of toxic solvents, expensive catalysts, modest product yields, limited substrate scope and long reaction times. Therefore, the development of easy and modular synthetic strategy for this important class of compounds, especially under mild and environmentally benign reaction conditions, still represents a highly rewarding methodological challenge in the rapidly growing field of diversity-oriented synthesis.

Recently, in our $FeCl_3.6H_2O$ catalyzed synthetic program towards 5-monalkylbarbiturates, we have demonstrated that the reaction proceeded through an *in situ* formed barbituric acid.[40] To the best of our knowledge, no detailed investigation has been made on 6-aminouracils as substrates for 5-alkyl/arylidenebarbituric acids. That, barbituric acids have been the only starting materials in all the established protocols except in a report by Daqing and co-workers which however the compounds were obtained as a mixture with bisuracils.[41] This result prompted us to explore for a formal synthetic route towards 5-alky/arylidenebarbituric acids from 6-aminouracils, water and aldehydes. Thus, based on our previous findings, we have now developed a $FeCl_3.6H_2O$ catalyzed pseudo three-component domino reaction of 6-aminouracils, water and aldehydes, where water serves as both solvent and reactant, leading efficiently to 5-alkyl/arylidenebarbituric acids, and the results are presented here in this paper (Scheme 1). This tandem reaction involves an initial $FeCl_3.6H_2O$ and water assisted amine hydrolysis of 6-aminouracil to barbituric acid followed by Knoevenagel condensation with aldehydes.



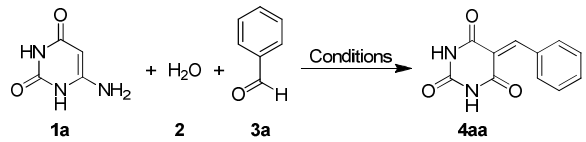
Scheme 1. Domino synthesis of 5-monoalkylbarbiturates.

The reaction has proved to be operationally simple with mild conditions and affords high yields. The use of versatile $FeCl_3.6H_2O$[42] and water provides cost effectiveness and environmental benignity, while the further role of water as both solvent and reactant describes wider scope of the relatively unexplored aqueous media domino-reactions[43] which is a current focal point in promoting greener synthesis. It can also be noted that while the general reactions of 6-aminouracils with aldehydes gave bisuracils,[41,44] this reaction, under the optimized conditions, furnished exclusively 5-alkyl/arylidenebarbituric acids as the end products. Thus, this protocol also shows a new reactivity of 6-aminouracils as valuable substrates for 5-alkyl/arylidenebarbituric acids. In addition, a detailed comparative study of 6-aminouracils versus barbituric acids as substrates for these compounds under the same reaction conditions is also presented.

Results and Discussion

Initially, we found that the reaction of 6-aminouracil (**1a**, 1 mmol), water (**2**, 10 mL) and benzaldehyde (**3a**, 1 mmol) in the presence of $FeCl_3.6H_2O$ (10 mol%) under refluxing condition for 60 minutes gave 5-benzylidenepyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**4aa**) in 70% yield, whose structure was further authenticated through literature data (Table 1, Entry 1).[38d] In subsequent optimization of the reaction under aqueous medium, 15 mol% of $FeCl_3.6H_2O$ was found optimal as the catalyst load which furnished **4aa** with a maximum yield of 85%, since further increase in catalyst load did not raise the product yield (Table 1, Entries 2-4). To acquire the best effect of the reaction, a number of potential Lewis acids as catalysts and various solvents were tried. Interestingly, the reaction was found most effective only in water and $FeCl_3.6H_2O$. Also all the screened catalysts such as $NiCl_2,6H_2O$, $CoCl_2.6H_2O$, $Cu(OAc)_2$ and $CuCl_2.2H_2O$ failed to deliver the desired product, except with *p*-Toluenesulphonic acid monohydrate (*p*TsOH.H_2O) which however, yielded **4aa** only in trace amount (Table 1,

Table 1. Optimization of the reaction under varying conditions.[a]



Entry	Catalyst (mol%)	Solvent[b]	Temp (°C)	Time (min)	Yield (%)[c]
1	$FeCl_3.6H_2O$ (10)	H_2O	Reflux	60	70
2	$FeCl_3.6H_2O$ (15)	H_2O	Reflux	35	85
3	$FeCl_3.6H_2O$ (20)	H_2O	Reflux	35	85
4	$FeCl_3.6H_2O$ (25)	H_2O	Reflux	35	85
5	$NiCl_2.6H_2O$ (15)	H_2O	Reflux	35	0
6	$CoCl_2.6H_2O$ (15)	H_2O	Reflux	35	0
7	$Cu(OAc)_2$ (15)	H_2O	Reflux	35	0
8	$CuCl_2.2H_2O$ (15)	H_2O	Reflux	35	0
9	*p*-TsOH.H_2O (15)	H_2O	Reflux	35	Trace
10	$FeCl_3.6H_2O$ (15)	EtOH	Reflux	35	0
11	$FeCl_3.6H_2O$ (15)	DMSO	Reflux	35	0
12	$FeCl_3.6H_2O$ (15)	CH_3CN	Reflux	35	0
13	$FeCl_3.6H_2O$ (15)	Toluene	Reflux	35	0
14	$FeCl_3.6H_2O$ (15)		Heat	35	0
15	-----	AcOH/H_2O (1:1)	Reflux	35	20%
16	$FeCl_3.6H_2O$ (15)	H_2O	r.t.[d]	600	0

[a] Reaction scale: **1a** (1 mmol), **2** (10 mL) and **3a** (1 mmol). [b] 10 mL. [c] Isolated yield. [d] RT ≈ 24 °C.

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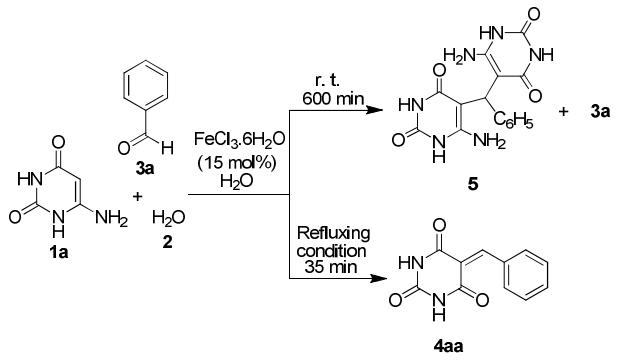
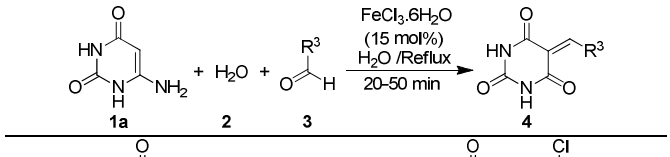
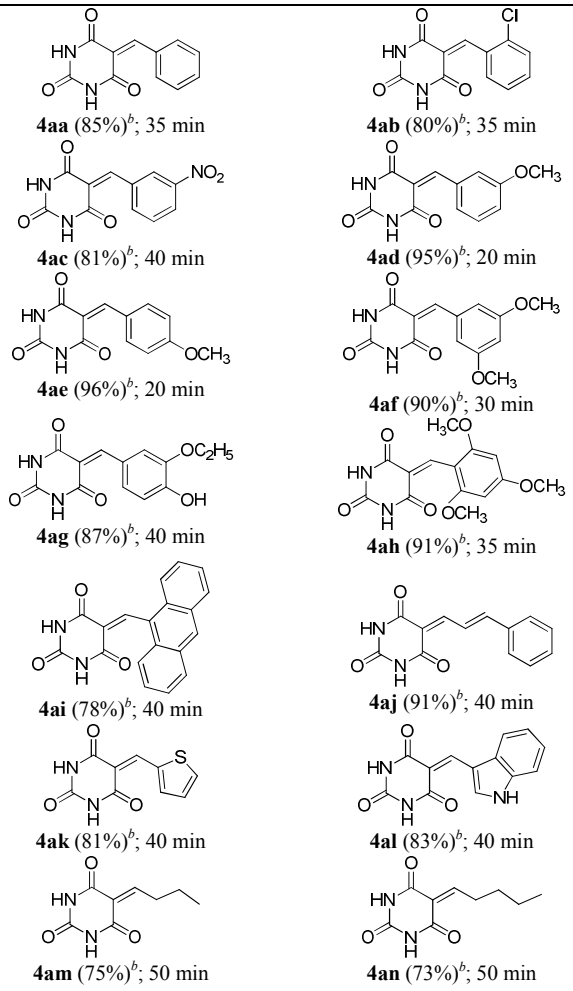


Scheme 2. Reaction study for 5-alkyl/arylidenebarbituric acids.

Table 2. Scope of the domino synthesis of 5-alkyl/arylidenebarbituric acids from 6-aminouracil, water and aldehydes.[a]





4aa (85%)[b]; 35 min
4ab (80%)[b]; 35 min
4ac (81%)[b]; 40 min
4ad (95%)[b]; 20 min
4ae (96%)[b]; 20 min
4af (90%)[b]; 30 min
4ag (87%)[b]; 40 min
4ah (91%)[b]; 35 min
4ai (78%)[b]; 40 min
4aj (91%)[b]; 40 min
4ak (81%)[b]; 40 min
4al (83%)[b]; 40 min
4am (75%)[b]; 50 min
4an (73%)[b]; 50 min

[a] All reactions were carried out using 1 mmol each of **1** and **3**, and 10 mL of **2**. [b] Isolated yield

Entries 5-9). On the other hand, even $FeCl_3.6H_2O$ catalyzed reactions in polar solvents such as EtOH, DMSO, CH_3CN and non-polar solvent like toluene or reactions carried out under solvent-free conditions were also found ineffective (Table 1, Entries 10-14). In one case, the reaction when carried out in CH_3COOH/water (1:1) alone proceeded however it only gave a mixture of **4aa** and **5**, as compared to when $FeCl_3.6H_2O$ was employed (Table 1, Entry 15). Also, in another attempt to succeed the reaction at room temperature by stirring a mixture of **1a**, **2** and **3a** for 10 hours in the presence of $FeCl_3.6H_2O$, bisuracil **5** was isolated along with unreacted **3a** (Table 1, Entry 16). On the contrary, when this same reaction was performed under refluxing conditions, only 5-benzylidenepyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**4aa**) was obtained (Scheme 2). All these observations, therefore, led to an inference that $FeCl_3.6H_2O$ and water were specific and vital for the synthesis of 5-alkyl/arylidenebarbituric acids through this protocol.

Encouraged by the results, the optimized conditions were used for series of reactions of benzaldehydes with 6-aminouracil (**1a**) and the target compounds were obtained in high to excellent yields. The presence of electron releasing or withdrawing groups in the benzene ring of various benzaldehydes did not have significant influence upon the reactions and their corresponding 5-arylidenebarbiturates (**4aa-ah**) were thus conveniently prepared (Table 2). The synthesis was also extended to polyaromatic hydrocarbons and α,β-unsaturated aldehydes such as 9-anthracenaldehyde and cinnamaldehyde where their corresponding products **4ai** and **4aj** respectively were also obtained. Reactions with heterocyclic aldehydes such as thiophene-2-carboxaldehyde and indole-3-carboxaldehye were also found effective and gave their resultant **4ak** and **4al** in 81% and 83% respectively. Aliphatic aldehydes such as butyraldehyde and valeraldehyde also underwent condensation smoothly to give their respective products **4am** and **4an** in good yields (Table 2).

The scope of the synthesis was further expanded towards 1-methyl-6-aminouracil (**1b**) and 1,3-dimethyl-6-aminouracil (**1c**) under the same reaction conditions and the results are shown in Table 3. Both the uracils also underwent reactions well with various aldehydes and their corresponding 5-alkyl/arylidenebarbituric acids were successfully prepared. However, it was observed that reactions involving **1b** and **1c** were found relatively slower and sluggish than when **1a** was

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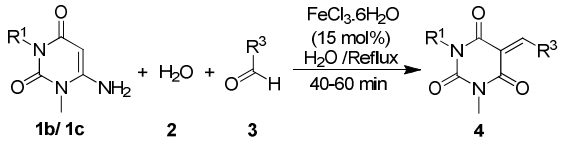
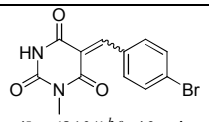
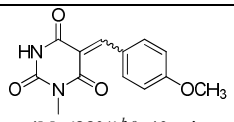
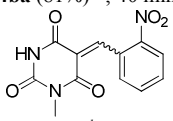
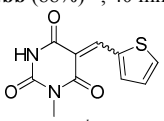
Table 3. Scope of substituted 6-aminouracils towards 5-alkyl/arylidenebarbituric acids.[a]

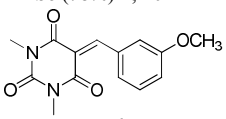


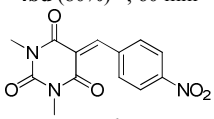

4ba (81%)[b,c]; 40 min

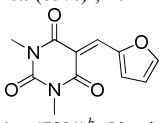

4bb (88%)[b,c]; 40 min

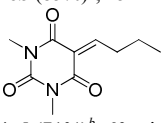

4bc (78%)[b,c]; 40 min


4bd (80%)[b,c]; 60 min


4ca (85%)[b]; 40 min

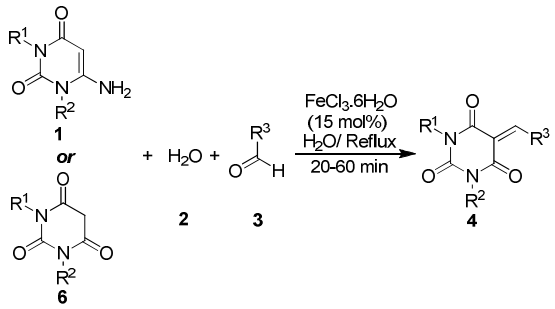

4cb (85%)[b]; 45 min


4cc (78%)[b]; 50 min


4cd (71%)[b]; 60 min

[a] All reactions were carried out with 1 (1 mmol), 2 (10 mL) and 3 (1 mmol). [b] Isolated yield. [c] Combined diastereomeric yield.

Table 4. Comparative substrate scope of 6-aminouracils *versus* barbituric acid towards 5-alkyl/arylidenebarbituric acids.[a]



Entry	Product (4)	Time (min)		Yield (%)[b]	
		1	6	1	6
1	**4aa**	35	30	85	87
2	**4ac**	40	35	81	85
3	**4ad**	20	20	95	95
4	**4ae**	20	20	96	97
5	**4af**	30	25	90	90
6	**4ag**	40	36	87	88
7	**4aj**	40	35	91	91
8	**4al**	40	35	83	85
9	**4an**	50	40	73	75
10	**4bb**	40	35	88[c]	88[c]
11	**4ca**	40	35	85	86
12	**4cb**	45	40	85	86
13	**4cc**	50	45	78	79
14	**4cd**	60	50	71	74

[a] Reactions were carried out using 1 mmol each of **1** and **3**, and 10 mL of **2**. [b] Isolated yield. [c] Combined diastereomeric yield.

used, with **1c** as the slowest. This may be attributed to the effect of the electron releasing methyl group/s present in **1b** and **1c**, which retarded the rate of amine hydrolysis to form barbituric acid. Thus a reactivity aptitude of 6-aminuracil > 1-methyl-6-aminouracil > 1,3-dimethyl-6-aminouracil was observed during the study. Moreover, the products obtained from reactions involving 1-methyl-6-aminouracil were as *E*- and *Z*- isomeric mixture as revealed by their ^{1}H- and ^{13}C NMR spectra.

Next, we turned our attention towards investigating a comparative substrate prospect of 6-aminouracils (**1**) *versus* barbituric acids (**6**) towards 5-alkyl/arylidenebarbituric acids (**4**) under the same reaction conditions. Thus, a series of reactions of barbituric acids and various aldehydes was performed and the comparative results are shown in Table 4. Interestingly, both the reactions showed similar competency for 5-alkyl/arylidenebarbituric acids offering similar yields without significant differences in reaction times. Thus, this observation revealed that 6-aminouracils could be proficient substrates, competent with barbiturates, for the synthesis of 5-alkyl/arylidenebarbituric acids through this method.

All the products were purified by recrystallization and characterized through their ^{1}H-, ^{13}C-NMR, Mass, IR spectral data and elemental analyses. Known compounds were further authenticated with literature reports.

To rationalize the reaction mechanism, 6-aminouracil (**1a**) was refluxed in the presence of $FeCl_3.6H_2O$ and water. The reaction completed swiftly and subsequent isolation yielded barbituric acid (Scheme 3).[45] This result was indicative that the reaction proceeded *via* barbituric acid. Moreover, when uncatalyzed and catalyzed condensation of barbituric acid (**6a**) and benzaldehyde in water was compared, it was found that the latter process in the presence of $FeCl_3.6H_2O$ was more efficient and completed faster. This also suggested for the catalytic role of $FeCl_3.6H_2O$ in the Knoevenagel condensation too. Thus, based upon literature reports[40,41,46] and our results a possible mechanism is outlined in Scheme 4. The coordination of $FeCl_3$ with 6-aminouracil facilitated an amine hydrolysis to form barbituric acid *via* apparent intermediates **7** to **9**. Meanwhile the aldehyde also apparently gets activated by $FeCl_3$ to form **11**, which on subsequent interaction with the $FeCl_3$ activated complex **10** of the then formed barbituric acid (**6a**) prodeeded the Knoevenagel condensation to furnish the final product **4**.

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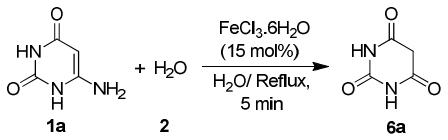
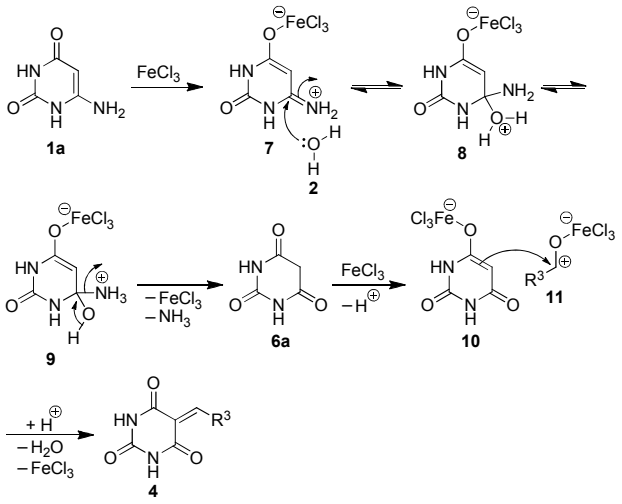


Scheme 3. Barbituric acid from 6-aminouracil.



Scheme 4. Possible reaction mechanism.

Conclusions

In conclusion, we have demonstrated an efficient and operationally simple method for the synthesis of 5-alkyl/arylidenebarbituric acids under environmentally benign conditions, through a $FeCl_3.6H_2O$ catalyzed domino reaction of 6-aminouracils, water and aldehydes, with water as both solvent and reactant. A comparative substrate study of 6-aminouracils *versus* barbituric acids towards 5-alkyl/arylidenebarbituric acids has also been detailed which showed similar efficacy. To the best of our knowledge, while barbituric acid has served as the only starting material for 5-alkyl/arylidenebarbituric acids till date, this work presents as the first detailed report demonstrating that 6-aminouracils can now also be alternative and equally competent substrates for the same compounds. Furthermore, the dual role of water as both solvent and reactant in this method significantly exemplifies for wider scope of aqueous media domino reactions in the light of promoting greener synthesis. Moreover, this report also highlights the hitherto unreported $FeCl_3.6H_2O$ catalyzed aqueous media condensation of barbituric acid and aldehydes. On the whole, this procedure is highly applicable for 5-alkyl/arylidenebarbituric acids as provided by the versatility of the catalyst, operational simplicity, competency of 6-aminouracils and excellent yields of the reaction *vis a vis* to all methods only involving barbituric acids.

Experimental section

All reagents were obtained commercially and were used without further purification. IR spectra were recorded on a SHIMADZU infrared spectrometer as KBr pellets with absorption in cm^{-1}. ^1H- and ^{13}C- NMR data were recorded either on 300 or 600 MHz BRUKER or JEOL 400 MHz NMR spectrometer at ≈ 25 °C using DMSO-d_6 or $CDCl_3$ as the solvent and resonances (δ) are expressed in ppm relative to tetramethylsilane (TMS). Data reported are as follows: Chemical shift (δ), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, ‡ = double signal), coupling constant (Hz) and integration. Mass spectral data were taken on WATERS ZQ 4000 analyzer equipped with ESI source. Melting points were taken through open capillary tube method and were uncorrected. Elemental analysis was done on Perkin Elmer Series II Analyzer 2400. Thin layer chromatography (TLC) was performed using Merck precoated silica gel or silica gel G and the components were visualized under UV or iodine chamber.

General procedure for the synthesis of 5-alkyl/arylidenebarbituric acids from 6-aminouracils, water and aldehydes

6-Aminouracil (1 mmol), aldehyde (1 mmol) and $FeCl_3.6H_2O$ (15 mol%) were added to hot or boiling water (10 mL) and the mixture was refluxed for appropriate time. On completion of the reaction, as indicated by TLC, the mixture was allowed to cool and was extracted with EtOAc (10 mL x 4). Upon drying with anhydrous Na_2SO_4 and subsequent evaporation of the solvent under reduced pressure, the crude product was obtained which was purified further by recrystallization from ethanol.

General procedure for the synthesis of 5-alkyl/arylidenebarbituric acids from barbituric acids and aldehydes:

A mixture of 1 mmol each of barbituric acid and aldehyde was refluxed in water in the presence of $FeCl_3.6H_2O$ (15 mol%) for an appropriate time. On completion of the reaction, as indicated by TLC, the reaction mass was cooled and extracted with EtOAc (10 mL x 4). The organic extract was dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure to afford the product which was purified further by recrystallization from ethanol.

Procedure for the synthesis of barbituric acid from 6-aminouracil

6-Aminouracil (1 mmol) was refluxed in water (10 mL) in the presence of $FeCl_3.6H_2O$ (15 mol%) for 5 minutes. The reaction was cooled and then extracted with EtOAc (10 mL x 4). The organic layer was dried with anhdrous Na_2SO_4 and the solvent removed under reduced pressure to give white solid which was recrystallized from water and ethanol (9:1). The physical and chemical properties were found identical with the literature data.[45]

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Notes and references

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† Electronic Supplementary Information (ESI) available: Compound characterization data, copies of ^{1}H- and ^{13}C-NMR spectra of all compounds see DOI: 10.1039/b000000x/

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