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Ultrasound-assisted rapid synthesis of 2-aminopyrimidine and barbituric acid derivatives

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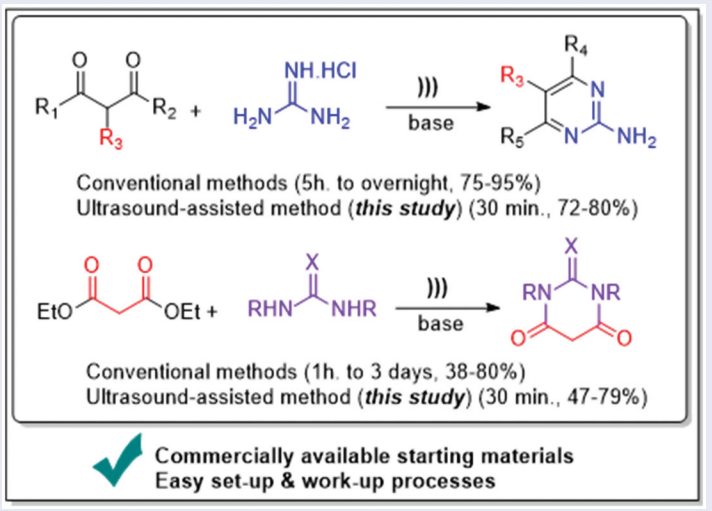
ABSTRACT

Novel, inexpensive, and relatively expeditious procedure to achieve the synthesis of different 2-aminopyrimidine and barbituric acid derivatives is presented here, starting from readily available compounds such as guanidine hydrochloride, urea, 1,3-dialkylurea, or thiourea. Under ultrasonic irradiation, base-driven (Na_2CO_3, NaOH, or $NaOC_2H_5$) heterocyclization reactions of the aforementioned substrates with diethyl malonate, diethyl-2-alkyl malonate, pentane-2,4-dione, or ethyl-3-oxobutanoate yielded corresponding products. Significant advantages of this sonochemical synthetic protocol with regard to the conventional thermal methods include easy reaction setup and work-up steps, reasonably mild conditions, shorter reaction times (~30 min) and comparably high product yields. The characterization of the synthesized compounds was based on melting points, FT-IR, GC-MS, ^{1}H-NMR techniques, and the obtained data were also checked from the previously published studies.

GRAPHICAL ABSTRACT



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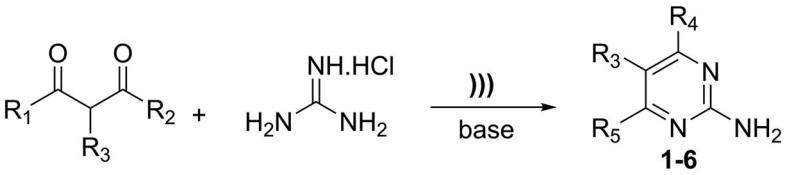
Introduction

The past 30 years have seen increasingly rapid advances to develop environmentally benign, "green" synthetic methods to obtain a myriad of organic compounds by using nontoxic starting materials, catalysts, and/or solvents.[1] Therefore, the use of sonochemical methods in organic synthesis as an alternative energy input to improve and accelerate synthetically valuable reactions has gained considerable importance. Ultrasound-assisted reactions differentiate from the traditional synthetic methods by their potential to be an effective instrument to building-up even the complex molecules with ultimate simplicity and brevity.[2–5] Pyrimidine and barbituric acid derivatives have been extensively studied compounds due to their biocompatibility, and there is extensive literature exploring their structural properties and similarity to the pyrimidine bases of DNA. Therefore, these pharmaceutically active compounds are broadly used in the development of numerous antibacterial, anti-allergic, antimicrobial, anti-HIV, and anti-cancer drug ingredients.[6,7] Several studies have revealed that 2-aminopyrimidine derivatives containing different substituents on their 5-position possess unusual biological activity.[8]

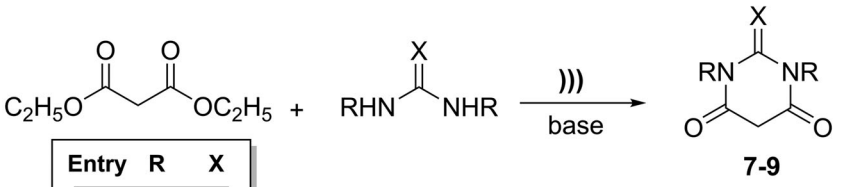
Furthermore, 2-amino-4,6-dihydroxypyrimidine derivatives are also known for their excellent ligand formation capabilities with copper.[9,10] Moreover, barbituric acid derivatives are the most potent central nervous system depressant agents known.[11] Even then, the synthesis of these compounds by known typical cyclization reactions, mostly involving the use of toxic chemicals, high reaction temperatures, and long reaction times restrict the effectiveness and applicability of the methods.[12,13] As an alternative approach, recent developments in ultrasound-assisted heterocyclic chemistry have heightened the need for an appropriate synthesis method to overcome the disadvantages of the conventional cyclization reactions.[14,15] Up to now, the preparation of pyrimidine and barbituric acid derivatives via ultrasound-assisted reactions has received limited attention in the literature. For this purpose, in the presented study, we aimed at examining the emerging role of ultrasound waves in the cyclization reactions and on that account, our primary challenge faced by many experiments is the synthesis of 2-aminopyrimidine and barbituric acid derivatives by following an atom economic reaction procedure preferably ends up with good to excellent yields. In this concept, an extended explanation of the whole procedures is given in the following subtitles. The target 2-aminopyrimidine and barbituric acid derivatives were obtained by following the synthetic pathway illustrated in Figure 1.

Results and discussion

In this study, our primary objective is to ascertain the efficacy of the ultrasonic radiation and the use of different bases on specific heterocyclization reactions and compare the gathered data with the experimental results obtained from the conventional heating processes. Regarding the previous studies, the synthesis of 2-aminopyrimidine and barbituric acid derivatives carried out by the condensation reactions of ß-diketo compounds with nitrogenous compounds such as urea and guanidine in basic medium.[16–23]



Entry	R_1	R_2	R_3	R_4	R_5
1	CH_3	CH_3	H	CH_3	CH_3
2	CH_3	OC_2H_5	H	CH_3	OH
3	OC_2H_5	OC_2H_5	H	OH	OH
4	OC_2H_5	OC_2H_5	C_2H_5	OH	OH
5	OC_2H_5	OC_2H_5	C_4H_9	OH	OH
6	OC_2H_5	OC_2H_5	CH_2	OH	OH



Entry	R	X
7	H	O
8	CH_3	O
9	H	S

Figure 1. Scope of the experimental procedures.

Preparation of 2-aminopyrimidine derivatives

While designing the experimental setup to be carried out, we aimed to obtain alkyl- or hydroxyl- (–OH) substituted 2-aminopyrimidine derivatives following the condensation reactions of guanidine hydrochloride with different β-diketone compounds. The appropriate heterocyclic ring closure reaction mechanism was shown in Figure 2.

Notably, the targeted 2-aminopyrimidine derivatives possessing hydroxyl groups are crucial starting materials because of their susceptibility to derivatization reactions, and thus, their ability to be converted into distinct functional groups. Therefore, primarily, literature data were evaluated and parameters such as reaction temperature, reaction time, and the molar ratio of substrate to reactive were fully optimized (Table 1).

In the following step, the optimized reaction conditions were maintained in order to accomplish the synthesis of the desired 2-aminopyrimidines (**1–6**), and the corresponding reactions were performed under both conventional and ultrasonic irradiation conditions. It is well known from the previous studies that most of the pyrimidine derivatives could be synthesized under reflux by conventional methods, which possess long reaction times (at least 1 h to overnight), and the crude product yields varied between 54% and 78%.[9,16,19,24] In comparison to these synthetic strategies, the ultrasound-assisted

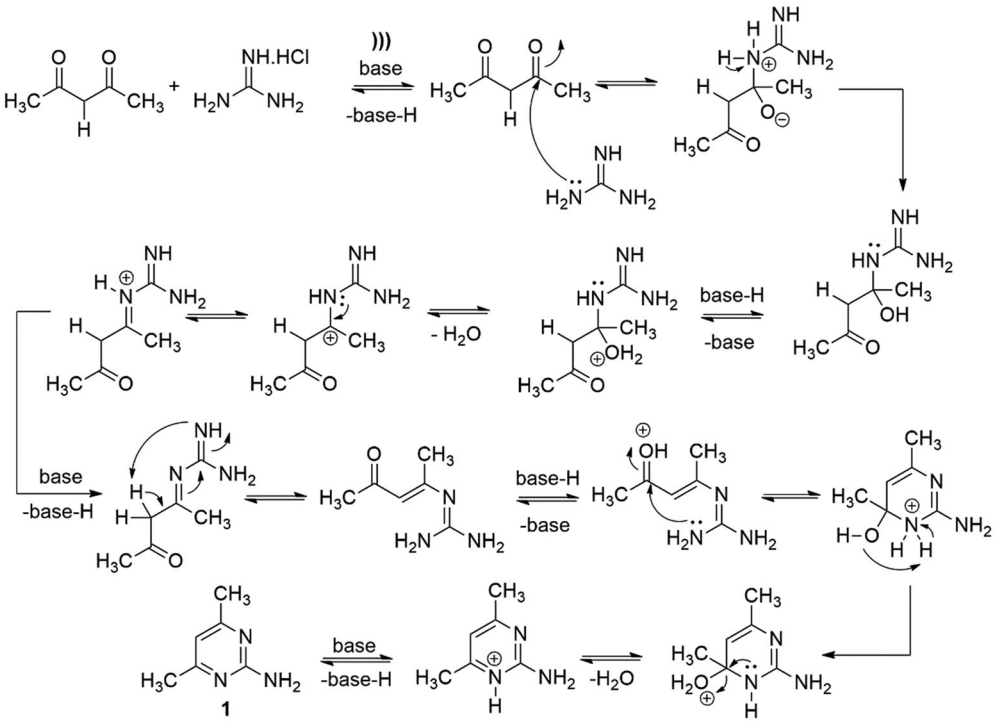
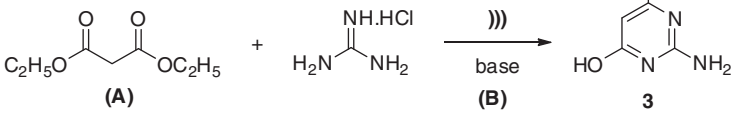


Figure 2. The proposed reaction mechanism for the synthesis of 1.

Table 1. Optimization studies of 2-aminopyrimidine derivatives.

Model reaction[a]

Na_2CO_3	*A:B*[†]	1: 0.5					1: 1					1: 1.5				
	Time (min.)	5	20	30	45	60	5	20	30	45	60	5	20	30	45	60
	Yield (%)	0	10	12	13	12	8	37	55	52	48	9	32	47	43	42
NaOH	*A:B*	1: 0.5					1: 1					1: 1.5				
	Time (min.)	5	20	30	45	60	5	20	30	45	60	5	20	30	45	60
	Yield (%)	0	0	0	0	0	5	11	24	22	20	6	12	16	15	16
$NaOC_2H_5$	*A:B*	1: 0.5					1: 1					1: 1.5				
	Time (min.)	5	20	30	45	60	5	20	30	45	60	5	20	30	45	60
	Yield (%)	10	28	35	36	38	18	45	78	75	76	20	47	74	72	70



poor good

[a]Model reaction was also carried out without base for 60 min of reaction time, and we did not isolate any product.
[b]Molar ratio.
[c]In order to visualize the reaction outputs, we have analyzed the obtained product yields by 3-color conditional formatting (red: poor, yellow to orange: moderate, green: good reaction yields).

Table 2. Comparison between conventional and sonochemical procedures for the synthesis of 2-aminopyrimidine derivatives.

	Conventional procedure			Sonochemical procedure		
Entry	Time	Base	Yield (%)	Time	Base	Yield (%)
1	5 h	Na_2CO_3	75	30 min	Na_2CO_3	66
					NaOH	45
					$NaOC_2H_5$	72
2	5 h	Na_2CO_3	79		Na_2CO_3	76
					NaOH	56
					$NaOC_2H_5$	80
3	Overnight	$NaOC_2H_5$	92		Na_2CO_3	55
					NaOH	24
					$NaOC_2H_5$	78
4	1 h	$NaOC_2H_5$	95		Na_2CO_3	80
					NaOH	54
					$NaOC_2H_5$	79
5	1 h	$NaOC_2H_5$	86		Na_2CO_3	72
					NaOH	57
					$NaOC_2H_5$	75
6	1 h	$NaOC_2H_5$	88		Na_2CO_3	61
					NaOH	26
					$NaOC_2H_5$	73

cyclization reactions facilitated the formation of target molecules in less than 1 h and furthermore, in several experiments with an addition of a strong base, such as $NaOC_2H_5$, final yields were close to those obtained by these antecedent methods. As aforementioned, in this section, numerous experimental parameters have been examined to ensure that synthetic procedures are optimized. To this aim, our first objective is to determine the most suitable base in order to achieve the desired cyclization reactions. Since it is well known from the literature that the most commonly used bases for the synthesis of pyrimidine derivatives are Na_2CO_3, NaOH, and $NaOC_2H_5$, these compounds have also been studied in our sonochemical experiments, and we have found that Na_2CO_3 is sufficiently reactive to act directly for the cyclization reactions of 2-amino-4,6-dimethylpyrimidine and 2-amino-4-hydroxy-6-methylpyrimidine. Whereas, in order to prepare 2-amino-4,6-dihydroxypyrimidine and its derivatives containing different alkyl or alkylidene groups in their 5-position, we have found that it is essential to use a stronger base ($NaOC_2H_5$). The model reaction was also carried out without adding any base for 60 min of reaction time, under ultrasonic conditions, and we could not be able to isolate any product, and this phenomenon clearly demonstrated the necessity of the base catalysis during the targeted syntheses.

Model reactions were also carried out without adding a base for 60 min of reaction time under ultrasonic conditions, and we could not isolate any material, and this phenomenon clearly demonstrated the need for baseline catalysis during the targeted synthesis.

Moreover, we observed that the molar ratio of the starting materials also has a significant influence on our cyclization reactions. Following the determination of the ideal base type, another important aspect is to predict the molar ratio of the respective substrate to base. For this reason, we made several attempts by increasing the base proportion versus 2-aminopyrimidine derivatives albeit we observed that considerably better results were achieved by using 1:1 equivalent quantity. Additionally, in the conventional synthesis of 2-aminopyrimidines, we have found to be essential to keep the temperature

around 100 °C for about 5–8 h, but in the ultrasonic-assisted reactions, we have enlightened that a temperature range of 60–70 °C is sufficient and the reaction time period has drastically decreased to 30 min (Table 2).

Preparation of barbituric acid derivatives

In the scope of the study, similar optimization studies that we conducted for the preparation of 2-aminopyrimidine derivatives were also carried out for the target barbituric acid derivatives. Thus, in the initial stage, we have tried to predict the convenient base to be used for the condensation reactions that occurred between diethyl malonate and (thio)urea. To this aim, a series of experiments have been performed again by using Na_2CO_3, NaOH, and $NaOC_2H_5$. The base strength of Na_2CO_3 and NaOH were found to be inefficient for the condensation reactions, and following the work-up processes, the obtained product yields were found to be insufficient. Therefore, $NaOC_2H_5$ was selected in order to be used for further experiments. Following this step, a number of additional experiments have been conducted to determine the exact molar ratio of the substrate to base. When we tried to use an equal ratio (1:1), it was found that the starting material was not totally consumed in the reaction environment. On the other hand, when the experiments were repeated with higher base proportion (1:1.5), it was found that the excess of the base remained in the medium and resulted in the formation of by-products. On this basis, the equivalent ratio of the base was gradually reduced, and it was observed that the highest yields were obtained when the substrate to base ratio was set to 1:1.2. When the ideal molar ratio was identified, we focused on determining the optimal reaction temperature. In conventional methods, the ring formation of the barbituric acid derivatives occurs approximately at 100 °C. In our case, we first tried to accomplish the reactions aforementioned above at room temperature, but a significant amount of starting materials remained unreacted. Therefore, the reaction temperature was gradually increased, and we determined that the optimum reaction temperature range varies between 60 °C and 70 °C. In the last step, we aimed to optimize the reaction time. Thus, we have first exposed the reaction mixtures to ultrasound irradiation for 10 min but the obtained product yields were not satisfying. Thereby, the reaction durations were prolonged to 30 min whereas no significant increase was detected in the product yields during the experiments exceeding 30 min In this way when compared to conventional thermal methods that needed at least 5 h, we notably shortened the required reaction time. The summary of our optimized reaction conditions is depicted in Table 3.

In the case of compounds **7** and **8**, the obtained yields were found relatively low when compared to corresponding conventional methods (Table 4).[20,25–27]

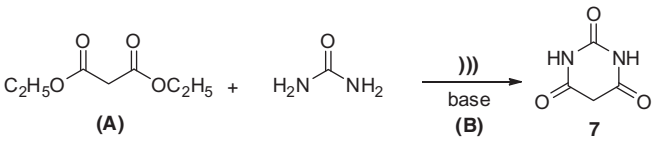
Conclusion

This study set out to evaluate a feasible and inexpensive strategy to enhance the preparation of 2-aminopyrimidine and barbituric acid derivatives. Moreover, in order to predict the optimal conditions for our cyclization reactions, we intended to detect the appropriate base, the molar ratio of substrate to base, reaction time and temperature

Table 3. Optimization studies of barbituric acid derivatives.

Model reaction[a]

Na_2CO_3	*A:B*[†]	1:0.5	1:1					1:1.2					1:1.5				
	Time (min.)	60	5	20	30	45	60	5	20	30	45	60	5	20	30	45	60
	Yield (%)	0	0	< 5				0	< 5				0	<5			
NaOH	*A:B*	1:0.5	1:1					1:1.2					1:1.5				
	Time (min.)	60	5	20	30	45	60	5	20	30	45	60	5	20	30	45	60
	Yield (%)	0	< 5					0	< 5				< 5				
$NaOC_2H_5$	*A:B*	1:0.5	1:1					1:1.2					1:1.5				
	Time (min.)	60	5	20	30	45	60	5	20	30	45	60	5	20	30	45	60
	Yield (%)	0	8	32	46	40	41	12	43	52	50	49	13	35	50	52	51



poor good

[a]Model reaction was also carried out without base for 60 min of reaction time, and we did not isolate any product.
[b]Molar ratio.
[c]In order to visualize the reaction outputs, we have analyzed the obtained product yields by 3-color conditional formatting (red: poor, yellow to orange: moderate, green: good reaction yields).

Table 4. Comparison between conventional and sonochemical procedures for the synthesis of barbituric acid derivatives.

	Conventional procedure			Sonochemical procedure		
Entry	Time	Base	Yield (%)	Time	Base	Yield (%)
7	16 h	$NaOC_2H_5$	64	30 min	Na_2CO_3	<5
					NaOH	<5
					$NaOC_2H_5$	52
8	16 h	$NaOC_2H_5$	78		Na_2CO_3	<5
					NaOH	<5
					$NaOC_2H_5$	47
9	16 h	$NaOC_2H_5$	38		Na_2CO_3	<5
					NaOH	<5
					$NaOC_2H_5$	79

parameters. In this context, synthesis of the target compounds has been completed in low-economic, mild conditions with reaction durations reduced to minute scale. In view of the findings we have obtained, we are persuaded that this new ultrasound-assisted technique will find a broad application for the preparation of larger or condensed rings in further studies.

Experimental section

General procedure for the sonochemical synthesis of 2-aminopyrimidine derivatives

Into the round-bottom reaction vessels having an appropriate thickness for the sonochemical reactions; guanidine hydrochloride (0.052 mol) and corresponding β-diketone

compound (0.052 mol) were placed in water (15 mL) and Na_2CO_3 (0.052 mol). The reaction vessel has been put in a hot water bath at 60 °C, and the flask content was exposed to ultrasonic waves for 30 min. The solid product obtained at the end of the experiment was treated with a small quantity of water and filtered through the Nuche funnel.

2-Amino-4,6-dimethylpyrimidine (1)

White solid, yield: 75%, m.p.: 152–155 °C (Lit. m.p.: 153 °C).[24] FT-IR (KBr), ν_{max}/cm^{-1}: 3395–3310 (s, NH_2 stretching), 3175 (w, aromatic, C–H stretching), 1633 (w, N–H bending), 1575, 1537 (conjugated C = C stretching), 1459, 1381 (aliphatic C–H bending), 1243 (C–NH_2 stretching), 1026, 952, 793. MS (DI) *m/z* (%) calcd for $C_6H_9N_3$: 123.1; found: 123. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.25 (s, 6H, CH_3), 5.36 (bs, 2H, NH_2), 6.33 (s, 1H, Ar–H).

General procedure for the sonochemical synthesis of barbituric acid derivatives

This method consists of two steps. Accordingly, during the first step, $NaOC_2H_5$ was prepared in N_2 atmosphere as described in the previous sections dedicated to conventional methods. In the second step, the prepared base was taken into the reaction vessel for the sonication process, and the base solution interacted with the appropriate reagents. In this concept, first of all, the two-necked flask fitted with a dropping funnel was purified from moisture purging with N_2 for several times and sodium metal slices (0.75 g, 0.016 mol) was added. After then, 20 mL of absolute ethyl alcohol was added dropwise to the reaction mixture at 0 °C. Following the preparation of the $NaOC_2H_5$ solution, a 10 mL of this solution was poured into the reaction vessel in which the sonic probe will be immersed, and guanidine hydrochloride (0.052 mol) -or urea/thiourea- and diethyl malonate derivatives (0.052 mol) were added. The reaction mixture was exposed to ultrasound waves into a water bath at 60 °C and different reaction times. After the completion of the reaction, the crude products were dissolved in a small amount of ice-water, and with the addition of the HCl, the pH of the solution was carefully adjusted to 2. The crude products were filtered off and purified by recrystallization from the appropriate solvent system.

Barbituric acid (7)

White solid, yield: 64%, m.p.: 245–248 °C (Lit. m.p.: 252–253 °C).[25] FT-IR (KBr), ν_{max}/cm^{-1}: 3198, 3086 (s, N–H stretching), 2870 (w, aliphatic C–H stretching), 1673 (s, C = O stretching), 1423, 1344, 1296, 1240, 1030, 903, 775. MS (DI) *m/z* (%) calcd for $C_4H_4N_2O_3$: 128.02; found: 128. ^{1}H-NMR (DMSO-d6, 400 MHz) δ: 3.46 (s, 2H, CH_2), 11.08 (s, 2H, NH).

Supplementary data (Full experimental details and copies of FT-IR, GC-MS, and ^{1}H-NMR spectra of all the synthesized compounds) associated with this article can be found via the "Supplementary Content" section of this article's webpage.

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