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An expedient method for the synthesis of 6-substituted uracils under microwave irradiation in a solvent-free medium

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Abstract—Condensation of malonic acid **1** and ureas **2a**–**f** proceeds smoothly in the presence of acetic anhydride **3** under microwave irradiation in solvent-free conditions to give 6-hydroxy-uracils **4** in excellent yields. Under identical conditions, the condensation of cyanoacetic acid **5** and ureas **2a**,**b**,**g** and **h** in the presence of acetic anhydride **3**, followed by cyclization in the presence of sodium hydroxide affords 6-amino-uracils **6** in high yields. The work-up procedures are simple and products need no purification.

Development of new solid phase (solvent-free) reactions and transferring solution phase reactions to solid phase are subjects of recent interest in the context of generating libraries of molecules for the discovery of biologically active leads and also for the optimization of potent drug candidates.[1] The potential for application of microwave technology in organic synthesis, particularly in solid phase (solvent-free) reactions, is increasing rapidly because of its simplicity, causing less pollution and having minimum reaction times, thus providing rapid access to libraries of diverse small molecules.[2]

6-Hydroxy-uracils (barbituric acids, thiobarbituric acids) and 6-amino-uracils represent two very important classes of functionalized uracils. 6-Hydroxy-uracils[3,4] constitute the basic moiety of a number of clinically used hypnotic drugs of the barbiturate class,[5] for example, veronal, seconal, phenobarbital, sodium pentothal, etc. and are also precursors in the synthesis of drugs, for example, acuracil[6] (antiviral) and the highly selective HIV-1 inhibitor agents HEPT.[7] 6-Amino-uracils are key intermediates in the synthesis of purines[8] which constitute the basic nucleus of a number of drugs, for example, caffeine, penciclovir, theobromine, theophylline, etc. Moreover, 6-hydroxy- and 6-amino-uracils find wide applications as starting materials for the synthesis of a number of fused uracils of biological significance, for example, pyrano-, pyrido-, pyrazolo-, pyrimido-, pyridazino-pyrimidines, etc.[9]

6-Hydroxy-uracil (barbituric acid) was first identified by von Baeyer[10] in 1863 as a breakdown product of uric acid. The first synthesis[11] of this class of compounds was reported in 1879 by condensing urea with malonic acid in the presence of phosphorus oxychloride under harsh conditions. A modified method[12] for the synthesis of barbituric acids and thiobarbituric acids involves condensation of malonic esters with urea or an *N*-alkylurea in the presence of sodium alkoxide as catalyst, but it requires a long reaction time (7 h) and a high temperature (110 °C) to afford 72–78% yields of the products. Presently, the majority of these compounds are synthesized by the method reported by Biltz and Wittek[13] involving condensing malonic acid with urea/*N*-substituted urea in the presence of acetic anhydride using acetic acid as the solvent. However, this process has some drawbacks and limitations, requiring the use of excessive solvent, a high temperature (90 °C) and a long reaction time (7 h). Moreover, in the synthesis of *N*-alkylbarbituric acids, it produces 5-acetyl derivatives along with the desired product. The same condensation reaction performed with controlled heating (4 h, 90 °C), gave exclusively the *N*-alkylbarbituric acid[14a] and *N*,*N*-dimethyl- barbituric acids.[14b]

6-Amino-uracils were first synthesized by Traube[15] via condensation of cyanoacetic acid and *N*,*N*-dialkylurea/*N*-monoalkylurea/urea in the presence of phosphorus

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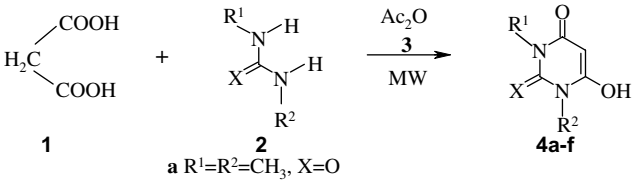
oxychloride, followed by cyclization using sodium hydroxide. These reactions required several hours and refluxing conditions to afford poor yields of the products. In a modification, Speer and Raymond[16] used acetic anhydride instead of phosphorus oxychloride but the use of acetic acid as a solvent meant that the reaction took a long time (3–4 h) and is applicable for the synthesis of only *N*-substituted 6-amino-uracils. Similar reports[17] are available in the literature which lack generality and involve long reaction times, drastic conditions and poor yields of the products.

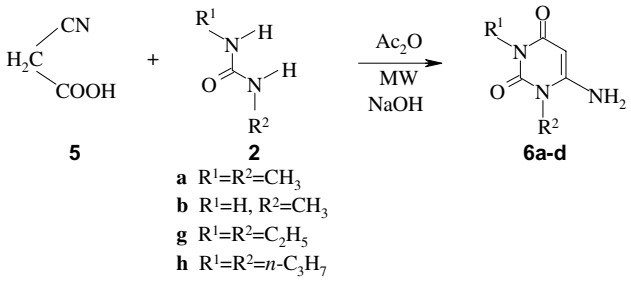
In our continued interest[18] in the development of highly expedient and green methodology for the synthesis of heterocyclic compounds of biological importance, we report here a very simple and highly efficient method for the synthesis of 6-hydroxy-uracils (Scheme 1) and 6-amino-uracils (Scheme 2) under microwave irradiation and solvent-free conditions.

Our synthetic strategy,[19] utilizing equimolar amounts of malonic acid **1**, urea **2a** and 2 equiv of acetic anhydride **3** under microwave irradiation (Synthewave 402 monomode reactor from Prolabo) at 40% power and at 60 °C for 7 min, afforded barbituric acid **4a** in excellent yield. It was very exciting to observe that the reaction occurred very rapidly and the products needed no purification. The yield of the product could be enhanced by distilling out (under reduced pressure) the small amount



a $R^1=R^2=CH_3$, X=O
b $R^1=CH_3$, R^2=H, X=O
c $R^1=R^2$=H, X=O
d $R^1=n$-C_3H_7, R^2=H, X=O
e $R^1=n$-C_4H_9, R^2=H, X=O
f $R^1=R^2$=H, X=S

Scheme 1.



a $R^1=R^2=CH_3$
b R^1=H, $R^2=CH_3$
g $R^1=R^2=C_2H_5$
h $R^1=R^2=n$-C_3H_7

Scheme 2.

of acetic acid that formed during the reaction process. With suitable conditions established for the microwave-assisted reaction, the barbituric acids **4b–e** and thiobarbituric acid **4f** were synthesized by utilizing malonic acid **1** with urea/thioureas **2b–f** in the presence of Ac_2O **3**. The products were characterized from spectral data and by comparison with authentic samples (Table 1).

Under identical conditions,[20] the reaction of equimolar amounts of cyanoacetic acid **5**, urea **2a** and 2 equiv of freshly distilled acetic anhydride **3** under microwave irradiation at 40% power and at 60 °C for 10 min followed by treatment with aqueous sodium hydroxide afforded *N*,*N*-dimethyl-6-amino-uracil **6a** in excellent yield. Similarly, 6-amino-uracils **6b–d** were synthesized by utilizing cyanoacetic acid **5** with ureas **2b** and **2g–h** in the presence of Ac_2O **3**. Products were characterized from spectral data and by comparison with authentic samples (Table 2).

In conclusion, we have demonstrated a simple, highly expedient and green method for the synthesis of various 6-hydroxy- and 6-amino-uracils under microwave irradiation and solvent-free conditions. Furthermore, the results delineated above demonstrate that microwave-assisted reactions in the solid state allow easy and rapid access to heterocycles of biological significance and can reduce the reaction times from many hours to a few minutes with improved yields.

Table 1. Synthesis of barbituric and thiobarbituric acids under microwave-assisted conditions

Product	R^1	R^2	X	Time (min)	Yield (%)	Mp (°C)
4a	CH_3	CH_3	O	7	78	121–122[14b]
4b	CH_3	H	O	10	75	129–131[14a]
4c	H	H	O	5	95	253–254[12d]
4d	n-C_3H_7	H	O	10	70	105–106[14a]
4e	n-C_4H_9	H	O	10	68	109–110[14a]
4f	H	H	S	8	60	232–234[12a]

Table 2. Synthesis of 6-amino-uracils under microwave-assisted conditions

Product	R^1	R^2	MW (%)	Time (min)	Yield (%)	Mp (°C)
6a	CH_3	CH_3	40	10	80	290–292[17b]
6b	H	CH_3	50	10	70	305–306[17a]
6c	C_2H_5	C_2H_5	70	10	70	197–198[17a]
6d	n-C_3H_7	n-C_3H_7	70	10	63	135–137[17a]

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19. Malonic acid **1** (1.24 g, 0.012 mol), *N*,*N*-dimethylurea **2a** (1.06 g, 0.012 mol) and acetic anhydride **3** (2.448 g, 0.024 mol) were added to the reaction vessel of the microwave reactor (Synthewave 402 monomode reactor from Prolabo) and were allowed to react under microwave irradiation, 40% power at 60 °C, for 7 min. The automatic mode stirrer assisted in mixing and uniform heating of the reactants. The reaction vessel was cooled to room temperature. The small amount of acetic acid produced was removed under reduced pressure and to the residue was added ethanol (10 ml). The resulting light yellow solid was filtered off and recrystallized from ethanol as a white crystalline solid (1.45 g, 78%), mp (121–122 °C).
20. Equimolar amounts of *N*,*N*-dimethylurea **2a** (1.10 g, 0.0125 mol) and cyanoacetic acid **5** (1.06 g, 0.0125 mol) were thoroughly mixed and then acetic anhydride **3** (1.275 g, 0.025 mol) was added to the reaction vessel of the microwave reactor. The reaction mixture was exposed to microwave irradiation at 40% power for 10 min keeping the temperature below 60 °C. The reaction vessel was cooled to room temperature and ethanol (5 ml) added. A 5% NaOH solution (6 ml) was added with stirring whereby *N*,*N*-dimethyl-6-aminouracil **6a** precipitated. The white solid compound was collected by filtration and recrystallized from water as a white crystalline solid (1.54 g, 80%), mp (291–293 °C).