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Studies on uracils: a facile one-pot synthesis of oxazino[4,5-*d*]-, pyrano[2,3-*d*]-, pyrido[2,3-*d*]- and pyrimido[4,5-*d*]pyrimidines using microwave irradiation in the solid state

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Abstract—*N*,*N*-Dimethyl-5-formylbarbituric acid **1** reacts with maleimide **2** and phenyl isocyanate/phenyl isothiocyanate **4** under microwave-assisted conditions in the solid phase to afford pyrano[2,3-*d*]pyrimidines **3** and oxazino[4,5-*d*]pyrimidines **5** in excellent yields. Under identical conditions, *N*,*N*-dimethyl-6-amino-5-formyluracil **6** reacts with **2** and **4** to give pyrido[2,3-*d*]pyrimidine derivative **7** and pyrimido[4,5-*d*]pyrimidines **8** in high yields.

Development of new solid phase reactions[1] and transferring solution phase to solid phase reaction 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 drug candidates. The potential application of microwave technology in organic synthesis,[2] particularly in solid phase organic reactions is increasing rapidly because of reaction simplicity, less pollution and minimum reaction times providing rapid access to large libraries of diverse small molecules.

The importance of oxazines and their annelated substrates[3] is well recognized by synthetic as well as biological chemists. One of the most important examples is the 3,1-benzoxazine derivative *Efavirenz*,[4] which has recently been approved as an anti-HIV drug. Analogues of this ring system such as quinazoline derivative DPC 961 have also been reported as anti-HIV agents.[5] Thieno[2,3-*d*]oxazinones are potent antiviral agents and Herpes-protease inhibitors.[6] Although a number of compounds with this ring system have been synthesized with diverse biological activities,[7] to our knowledge there is no report of oxazine derivatives fused to uracil. Pyrano[2,3-*d*]pyrimidines, pyrido[2,3-*d*]pyrimidines and pyrimido[4,5-*d*]pyrimidines represent broad classes of annelated uracils, which have received considerable attention over the past years due to their wide range of biological activities. Compounds with these ring systems have bronchiodilator,[8] vasodilator,[8] antiallergic,[9] cardiotonic,[10] antihypertensive[10a] and hepatoprotective[10a] activity. Some of them exhibit antimalarial,[11] analgesic[12] and antifungal[13] properties. As such, the synthesis of these ring systems is well documented[14] but the synthetic methods rely mostly on cyclocondensation and usually require drastic conditions, long reaction times and complex synthetic pathways. Wamhoff reported a new route for the synthesis of some annelated uracils based on [4+2] cycloaddition,[15] but these reactions have some limitations and are confined to the preparation of pyrido[2,3-*d*]pyrimidines and quinazolines only. In continuation of our studies and the development of highly expedient methods for the synthesis of annulated uracils[16] of biological importance, we report in this communication a novel microwave-assisted one-pot synthesis of oxazino[4,5-*d*]-, pyrano-[2,3-*d*]-, pyrido[2,3-*d*]- and pyrimido[4,5-*d*]pyrimidines, based on [4+2] cycloaddition reactions in the solid state, which allows access to a range of structural variations by modification of the reacting components.

Our synthetic strategy, reacting *N*,*N*-dimethyl-5-formylbarbituric acid **1** with maleimide **2** under microwave

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Table 1. Microwave-assisted solid state/thermal reactions

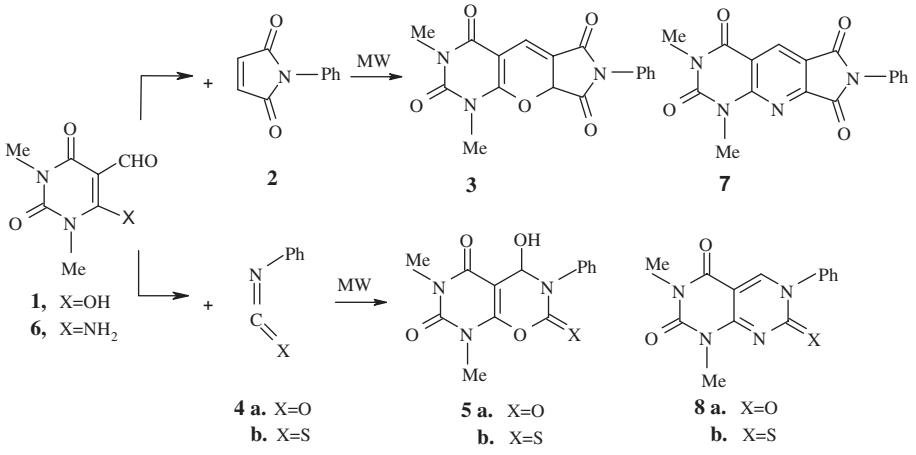
Entry	Product	MW		Reaction time		Yield (%)		Mp (°C)
		Power (%)	Temperature (°C)	MW (min)	Thermal (h)	MW	Thermal	
1	**3**	80	120	5	5	90	70	229
2	**5a**	60	60–65	5	5	87	65	181–182
3	**5b**	60	80–90	7	6	85	60	228–230
4	**7**	80	120–125	6	5	85	65	266
5	**8a**	60	100	6	6	84	57	215–217
6	**8b**	60	100–110	7	6	80	54	241–242

irradiation (Synthwave 402 Monomode Reactor From Prolabo) in the solid state, afforded the pyrano[2,3-*d*]pyrimidine derivative **3** in excellent yields. Compound **1**, which was synthesized by treating *N*,*N*-dimethylbarbituric acid with the Vilsmeier reagent in refluxing benzene[17] gave, on treatment with an equimolar amount of maleimide **2** under microwave irradiation at 120 °C for 5 min followed by work-up, compound **3**[19] in 90% yield. The structure of this compound was confirmed on the basis of spectroscopic data and elemental analysis. The ^{1}H NMR spectrum showed the absence of the aldehyde proton and the presence of one proton at δ 8.30 and another at δ 3.60. The mass spectrum revealed a strong molecular ion peak at 339 M^+. With suitable conditions established, the microwave-assisted reaction was extended by utilizing some other active dienophiles like isocyanates and isothiocyanates with the compound **1**. Thus the reaction of *N*,*N*-dimethyl-5-formylbarbituric acid **1** with phenyl isocyanate **4a** under microwave-assisted conditions in the absence of solvent gave the corresponding oxazino[4,5-*d*]pyrimidine **5a** in very high yield (Table 1). The structure of the compound was ascertained from spectroscopic data and elemental analysis. Under identical conditions, compound **1** reacted with phenyl isothiocyanate **4b** to afford the corresponding thiooxazino[4,5-*d*]pyrimidine analogue **5b**. The reactions were then performed thermally using a number of solvents, and chloroform was found to be the most suitable solvent in terms of solubility of the reactants, time required and overall yield of the products. Our observations with the thermal reactions, using chloroform as solvent are recorded in Table 1. It is very interesting to note that elimination of the solvent and shifting from conventional thermal to microwave heating reduced the reaction times from hours to minutes with improved yields besides simplifying the work-up procedure (Scheme 1).

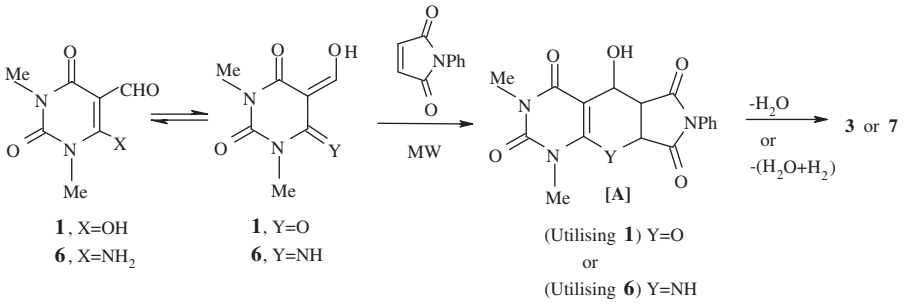
In order to explore the synthetic utility of the process, we have investigated the reactivity pattern of 6-amino-1,3-dimethyl-5-formyluracil **6**[18] with maleimide **2** under microwave-assisted conditions in the solid state. This reaction was found to proceed in a smooth manner providing pyrido[2,3-*d*]pyrimidine **7** in excellent yield. The structure of the compound was confirmed from spectroscopic data and elemental analysis. The ^{1}H NMR spectrum showed the characteristic signal at δ 8.25 for one proton and absence of an aldehydic proton. The mass spectrum revealed a molecular ion peak at 336 M^+. In a similar way, treatment of *N*,*N*-dimethyl-6-amino-5-formyluracil **6** with phenyl isocyanate **4a** and phenyl isothiocyanate **4b** under microwave-assisted conditions afforded pyrimido[4,5-*d*]pyrimidines **8a** and **8b** in very good yields (Table 1).

The formation of the products can be explained by the mechanism outlined in Scheme 2. Potentially, the *N*,*N*-dimethyl-5-formylbarbituric acid **1** and *N*,*N*-dimethyl-6-amino-5-formyluracil **6**, which can also exist as 1,4-diene following tautomeric shifts, first react with the dienophile maleimide **2** to give the intermediates [**A**]. The intermediates [**A**] then lose water or water followed by oxidation to afford the products **3** and **7**.

Further studies of the reaction are in progress. In conclusion, we have demonstrated a novel microwave-



Scheme 1.



Scheme 2.

assisted solid state synthesis of a number of annelated uracils of biological significance in excellent yields. Furthermore, the results delineated above have demonstrated that microwave-assisted reactions in the solid state can replace classical methods, allowing easy and rapid access to novel heterocycles of biological significance and reducing the reaction times from hours to minutes with improved yields.

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19. In a typical experimental procedure, equimolar amounts of *N*,*N*-dimethyl-5-formylbarbituric acid **1** (0.184 g, 1 mmol), and *N*-phenylmaleimide **2** (0.173 g, 1 mmol), were added to the reaction vessel of the microwave reactor (Synthewave 402 Monomode Reactor from Prolabo) and allowed to react under microwave irradiation at 80% (480 W) power and 120 °C for 5 min. The automatic mode stirrer helps in mixing and the uniform heating of the reactants. The reaction vessel was cooled to room temperature and the solid compound obtained was crystallized from ethanol to give a product **3** (0.306 g, 90%). The structure was confirmed from spectroscopic data and elemental analysis. Mp 229 °C ^{1}H NMR (300 MHz $CDCl_3$) δ 3.05 (s, 3H), 3.15 (s, 3H), 3.60 (s, 1H), 7.00–7.15 (m, 5H), 8.30 (s, 1H). IR 1720, 1710, 1695, 1610 cm^{-1}. MS 339 M$^+$. CHN analysis (calcd %) C, 60.17; H, 3.83; N, 12.39; $C_{17}H_{13}N_3O_5$ (found %) C, 60.10; H, 3.90; N, 12.35. Similarly, the other reactions have been carried out and the products have been characterized (Table 1).
5a. Mp 181–82 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.00 (s, 3H), 3.10 (s, 3H), 6.65 (s, 1H), 7.00–7.20 (m, 5H). IR 3400, 1710, 1695 cm^{-1}. MS 303 M$^+$. CHN analysis (calcd %) C, 55.44; H, 4.29; N, 13.86; $C_{14}H_{13}N_3O_5$ (found %) C, 55.40; H, 4.25; N, 13.80. **5b**. Mp 228–230 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.00 (s, 3H), 3.10 (s, 3H), 6.50 (s, 1H), 6.95–7.15 (m, 5H). IR 3435, 1710, 1695 cm^{-1}. MS 319 M$^+$. CHN analysis (calcd %) C, 52.66; H, 4.07; N, 13.16; $C_{14}H_{13}N_3O_4S$ (found %) C, 52.60; H, 4.00; N, 13.10.
7. Mp 266 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.00 (s, 3H), 3.15 (s, 3H), 6.95–7.15 (m, 5H), 8.25 (s, 1H). IR 1715, 1700, 1695, 1610 cm^{-1}. MS 336 M$^+$. CHN analysis (calcd %) C, 60.71; H, 3.57; N, 16.66; $C_{17}H_{12}N_4O_4$ (found %) C, 60.65; H, 3.50; N, 16.65.

8a. Mp 215–217 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.05 (s, 3H), 3.15 (s, 3H), 6.90–7.15 (m, 5H), 8.20 (s, 1H). IR 1710, 1695 cm^{-1}. MS 284 M^+. CHN analysis (calcd %) C, 59.15; H, 4.22; N, 19.71; $C_{14}H_{12}N_4O_3$ (found %) C, 59.10; H, 4.15; N, 19.66.

8b. Mp 241–242 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.05 (s, 3H), 3.15 (s, 3H), 6.90–7.15 (m, 5H), 8.15 (s, 1H). IR 1710, 1695 cm^{-1}. MS 300 M^+. CHN analysis (calcd %) C, 56.00; H, 4.00; N, 18.66; $C_{14}H_{12}N_4O_2S$ (found %) C, 55.95; H, 3.95; N, 18.61.