Pergamon

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Tetrahedron Letters 44 (2003) 8307–8310

TETRAHEDRON LETTERS

A novel three-component one-pot synthesis of pyrano[2,3-*d*]pyrimidines and pyrido[2,3-*d*]pyrimidines using microwave heating in the solid state

Ipsita Devi,[a] B. S. D. Kumar[b] and Pulak J. Bhuyan[a,*]

[a]*Medicinal Chemistry Division, Regional Research Laboratory, Jorhat 785 006, Assam, India*
[b]*Soil Microbiology Division, Regional Research Laboratory, Jorhat 785 006, Assam, India*

Received 17 June 2003; revised 27 August 2003; accepted 5 September 2003

Abstract—Microwave-assisted three-component cyclocondensation of barbituric acids **1**, benzaldehyde **2** and alkyl nitriles **3** proceeds in the absence or presence of triethylamine to afford pyrano[2,3-*d*]pyrimidines **4** and 6-aminouracils **5** or 6-hydroxyaminouracils **6** react with **2** and **3** under identical conditions to yield pyrido[2,3-*d*]pyrimidines **7**, all in high yields.

Multicomponent reactions (MCRs) by virtue of their convergence, productivity, ease of execution and generally high yields of products have attracted considerable attention from the point of view of combinatorial chemistry.[1] The first MCR was described by Strecker in 1850 for the synthesis[2] of amino acids. However, in the past decade there have been tremendous development in three- and four-component reactions and great efforts continue to be made to develop new MCRs.[3] Solid-phase organic synthesis is a subject of recent interest[4] in the context of generating libraries of molecules for the discovery of biologically active leads and also for the optimisation of potent drug candidates. The potential application of microwave technology in organic synthesis,[5] particularly in the solid state, is increasing rapidly because of its reaction simplicity, less pollution, and minimum reaction time providing rapid access to large libraries of diverse molecules.

Pyrano[2,3-*d*]- and pyrido[2,3-*d*]pyrimidines are annelated uracils which have received considerable attention over the past years due to their wide range of biological activity. Compounds with these ring systems have diverse pharmacological activity such as antitumour,[6] cardiotonic,[7] hepatoprotactive,[7a] antihypertensive,[7a] antibronchitic[8] and antifungal activity.[9] Therefore, for the preparation of these complex molecules large efforts have been directed towards the synthetic manipulation of uracils. As a result, a number of reports have appeared in literature[10] which usually require forcing conditions, long reaction times and complex synthetic pathways. Thus new routes for the synthesis of these molecules have attracted considerable attention in search for a rapid entry to these heterocycles.

In our continued interest[11] in the development of highly expedient methods for the synthesis of annelated uracil libraries, we report in this paper a novel three-component one-pot synthesis of well functionalised pyrano[2,3-*d*]- and pyrido[2,3-*d*]pyrimidines under microwave irradiation in the solid state (Scheme 1).

The experimental procedure is simple: equimolar amounts of *N*,*N*-dimethylbarbituric acid **1a** (0.156 g, 1 mmol), benzaldehyde **2** (0.106 g, 1 mmol) and malononitrile **3a** (0.066 g, 1 mmol) were added in the reaction vessel of the microwave reactor (Synthewave 402 Monomode Reactor from Prolabo) and allowed to react under microwave irradiation at 60% power and 80°C for 4 min. The automatic mode stirrer helps in mixing and uniform heating of the reactants. The reaction vessel was cooled to room temperature and the solid compound obtained was recrystallised from acetonitrile to give **4a** (0.248 g 80%) mp 210°C. The structure was confirmed as **4a** from the spectroscopic data and elemental analysis. The IR spectra exhibited sharp bands at 3250 cm^{-1} (NH_2) and 2218 cm^{-1} (CN). The NMR spectra showed the absence of the methylene proton of the barbituric acid and the presence of a proton at 5.10 (s, 1H). The other signals appeared at δ

* Corresponding author. E-mail: pulak_jyoti@yahoo.com

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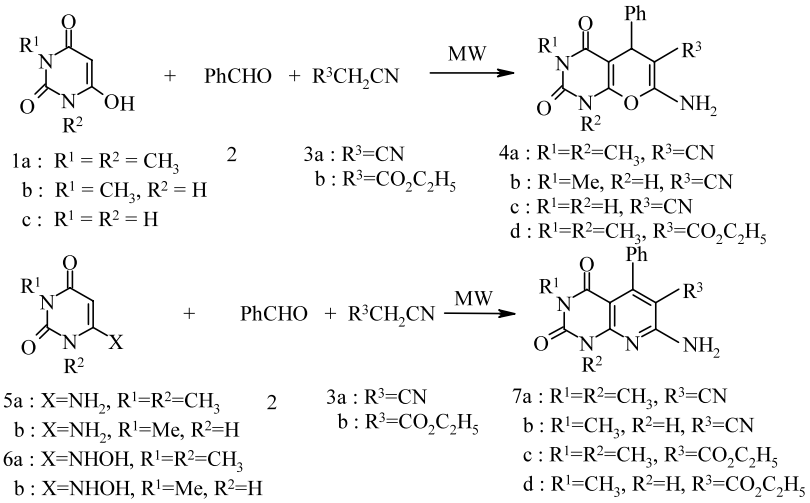
doi:10.1016/j.tetlet.2003.09.063



Scheme 1.

3.00 (s, 3H, NCH_3), 3.15 (s, 3H, NCH_3). The mass spectrum revealed a strong molecular ion peak at m/z 310. Similarly compound **4b–d** were synthesized by utilizing **1a–c**, **2** and **3a–b** and the structures were confirmed from the spectroscopic data and elemental analysis.[12] The study of the three-component reaction was then extended by performing the reactions seperately in presence of triethylamine as catalyst and by using dimethylformamide as solvent. In the presence of catalyst the reactions occurred at a comparatively lower power (40%). However the use of solvent afforded a poor yield of the products and took more time (Table 1).

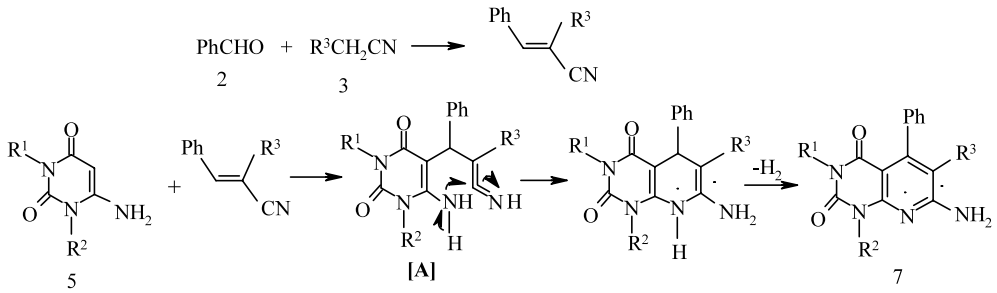
Under identical conditions, when *N*,*N*-dimethyl-6-aminouracil **5a** (0.155 g, 1 mmol) was treated with **2** (0.106 g, 1 mmol) and **3a** (0.066 g, 1 mmol) under microwave irradiation at 60% power and 80°C in a reactor for 5 min, it gave pyrido[2,3-*d*]pyrimidine **7a** (0.276 g, 90%). The structure of the compound was ascertained by spectroscopic data and elemental analysis.[13] Similarly other pyrido[2,3-*d*]pyrimidines **7b–d** were synthesised from the reactions of **5a–b**, **2** and **3a–b** and the structures were confirmed from their spectroscopic data and elemental analysis.[13] The reactions were then performed in the presence of the catalyst as well as by using DMF as solvent and our observations are recorded in Table 1.

In order to explore the synthetic utility of the reaction *N*,*N*-dimethyl-6-hydroxyamino uracils **6a** was reacted with **2** and **3a** in a similar way under microwave-assisted conditions. The reaction was found to proceed smoothly providing the same product **7a** obtained from the reaction of 6-amino uracils. This can be explained by the mechanism given in Scheme 2.

A reasonable mechanism for the formation of the product **7** is outlined in Scheme 2. The reaction occurs via an initial formation of the cyano-olefin, from the condensation of benzaldehyde and alkyl nitriles as shown in Scheme 2, which suffers nucleophilic attack to give the Michael adduct [A]. The intermediate [A] then cyclizes and subsequently loses a hydrogen molecule to afford the fully aromatized compound. This type of hydrogen loss is well precedented.[14] In the case of the 6-hydroxyaminouracils **6** the cyclic intermediate aromatizes by eliminating water. The initial formation of the cyano-olefins was confirmed by synthesizing the compounds from the reaction of benzaldehyde **2** and alkyl nitriles **3** under identical conditions in the microwave reactor, which on direct irradiation with **5** afforded the same compounds **7**. Although we could not isolate any intermediate, it is well established fact that the electrophiles like cyano-olefins attack at the C-5 position of the compounds **1**, **5** or **6** to give the

Table 1. Microwave-assisted three-component reactions (in the absence or presence of catalyst/in solvent and solvent free)

Entry	Product	Time/power			Yield (%)		
		Without Et_3N	With Et_3N	In solvent (DMF)	Without Et_3N	With Et_3N	In solvent (DMF)+Et_3N
1	**4a**	4 min	4 min	10 min	80	80	65
2	**4b**	4 min	4 min	10 min	80	76	60
3	**4c**	4 min	4 min	10 min	75	78	60
4	**4d**	4 min	4 min	10 min	95	90	70
5	**7a**	5 min	5 min	12 min	90	90	70
6	**7b**	5 min	5 min	12 min	85	85	65
7	**7c**	8 min	8 min	10 min	85	80	65
8	**7d**	8 min	8 min	10 min	70	70	65



Scheme 2.

Michael adducts (*C*-alkylation) instead of *O*-alkylated or *N*-alkylated compounds.[15] The formation of the Michael adduct is the key to explain the right orientation of the reaction.

In conclusion, we have demonstrated a novel multicomponent reaction in the solid state that offers a simple and efficient route for the synthesis of highly functionalized pyrano[2,3-*d*]pyrimidines and pyrido[2,3-*d*]-pyrimidines of potential biological importance in excellent yields. Furthermore, the results delinated above have demonstrated that microwave assisted multicomponent reactions in the solid state can replace classical methods allowing easy and rapid access to novel heterocycles of biological significance with improved yields.

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12. Compound **4a**: mp 210°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.00 (s, 3H), 3.15 (s, 3H), 5.10 (s, 1H), 6.85–7.10 (m, 5H); IR: 3300, 2195, 1710 cm^{-1}; MS: 310 M$^+$. CHN analyses (calcd %): C, 61.93; H, 4.51; N, 18.06 ($C_{16}H_{14}N_4O_3$) (found %): C, 61.90; H, 4.45; N, 18.00. Compound **4b**: mp 217°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.05 (s, 3H), 4.95 (s, 1H), 6.90–7.10 (m, 5H); IR: 3310, 2205, 1715 cm^{-1}; MS: 296 M$^+$. CHN analyses (calcd %): C, 60.81, H, 4.05; N, 18.91 ($C_{15}H_{12}N_4O_3$) (found %): C, 60.75; H, 4.10; N, 18.95. Compound **4c**: mp 225°C; ^{1}H NMR (300 MHz, $CDCl_3$+TFA): δ 4.95 (s, 1H), 6.90–7.15 (m, 5H); IR: 3325, 2200, 1705 cm^{-1}; MS: 282 M$^+$. CHN analyses (calcd %): C, 59.57, H, 3.54; N, 19.85 ($C_{14}H_{10}N_4O_3$) (found %): C, 59.50; H, 3.55; N, 19.90. Compound **4d**: mp 231°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, 3H, J=7.3 Hz), 3.05 (s, 3H), 3.10 (s, 3H), 4.20 (q, 2H, J=7.3 Hz), 4.95 (s, 1H), 6.90–7.20 (m, 5H); IR: 3345, 1730, 1695 cm^{-1}; MS: 357 M$^+$. CHN analyses (calcd %): C, 60.50, H, 5.32; N, 11.76 ($C_{18}H_{19}N_3O_5$) (found %): C, 60.50; H, 5.25; N, 11.80.

13. Compound **7a**: mp 308°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.00 (s, 3H), 3.15 (s, 3H), 6.78–7.25 (m, 5H); IR: 3350, 2195, 1710 cm^{-1}; MS: 307 M$^+$. CHN analyses (calcd %): C, 62.53; H, 4.26; N, 22.79 ($C_{16}H_{13}N_5O_2$) (found %): C, 62.45; H, 4.20; N, 22.70. Compound **7b**: mp 320°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.20 (s, 3H), 7.10–7.30 (m, 5H); MS: 293 M$^+$; IR: 3345, 2210, 1710 cm^{-1}. CHN analyses (calcd %): C, 61.43, H, 3.78; N, 23.88 ($C_{15}H_{11}N_5O_2$) (found %): C, 61.55; H, 3.70; N, 23.63. Compound **7c**: mp 151°C; ^{1}H NMR (300 MHz, $CDCl_3$+ TFA): δ 1.25 (t, 3H, J=7.2 Hz), 3.25 (s, 3H), 3.30 (s, 3H), 4.25 (q, 2H, J=7.2 Hz), 6.90–7.95 (m, 5H); MS: 354 M$^+$; IR: 3340, 1730, 1705 cm^{-1}. CHN analyses (calcd %): C, 61.00, H, 5.12; N, 15.81 ($C_{18}H_{18}N_4O_4$) (found %): C, 60.95; H, 5.20; N, 15.70. Compound **7d**: mp 215°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (t, 3H, J=7.3 Hz), 3.10 (s, 3H), 4.30 (q, 2H, J=7.3 Hz), 6.90–7.20 (m, 5H); IR: 3350, 1730, 1700 cm^{-1}; MS: 340 M$^+$. CHN analyses (calcd %): C, 60.00; H, 4.74; N, 16.46 ($C_{17}H_{16}N_4O_4$) (found %): C, 60.12; H, 4.65; N, 16.41.
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