Green synthesis of 5-aryl-(1*H*,3*H*,5*H*,10*H*)-pyrimido[4,5-b]quinoline-2,4-diones catalysed by 1,4-diazabicyclo[2.2.2]octane in water

Mohammad Hossein Mosslemin[a]*, Elham Zarenezhad[a], Nasim Shams[a], Mohammad Navid Soltani Rad[b], Hossein Anaraki-Ardakani[c] and Rassol Fayazipoor[a]

[a]*Department of Chemistry, Yazd Branch, Islamic Azad University, PO Box 89195-155, Yazd, Iran*

[b]*Department of Chemistry, Shiraz University of Technology, Shiraz 71555-313, Iran*

[c]*Department of Chemistry, College of Chemistry, Mahshahr Branch, Islamic Azad University, Mahshahr, Iran*

A green and efficient synthesis of 13 of the title compounds, three of which are novel, has been achieved via a one-pot, three-component reaction of anilines, aldehydes and barbituric acids, catalysed by 1,4-diaza-bicyclo[2.2.2]octane (DABCO) in water at reflux. Using microwave heating, reaction times were shortened from 12 h to under a minute and yields were generally higher.

Keywords: green synthesis, 1,4-diaza-bicyclo[2.2.2]octane, microwave irradiation, multi-component reactions

Recently, considerable attention has been paid to multi-component reactions (MCRs) for the synthesis of heterocycles.[1] Many such procedures, for example, have been developed for the quinoline compounds,[2] which show a wide range of biological activities including antimalarial, antitumor, anthelmintic, antibacterial, antiasthmatic, and antiplatelet properties.[3–5]

It has very recently been reported that a one-pot three-component reaction between aldehydes, anilines and barbituric acids in water at reflux using proline as a catalyst produces 5-aryl-(1*H*,3*H*,5*H*,10*H*)-pyrimido[4,5-b]quinoline-2,4-diones in moderate to good yields.[6] We have now found that the reaction can be carried out much more rapidly and in good to excellent yields using 1,4-diazabicyclo[2.2.2]octane (DABCO) as a catalyst.

DABCO has been used in many organic preparations as a good solid catalyst,[7] and has received considerable attention as an inexpensive, eco-friendly, highly reactive, easy to handle and nontoxic basic catalyst for various organic transformations, affording the corresponding products in excellent yields with high selectivity. The reactions are environmentally friendly and the catalyst can be recycled in some cases.[8]

Microwave assisted organic synthesis has become an increasingly popular technique in academic and industrial research laboratories due to certain advantages, particularly shorter reaction times and rapid optimisation of chemical reactions.[9,10]

We here describe our results in which we have synthesised all of the 5-aryl-(1*H*,3*H*,5*H*,10*H*)-pyrimido[4,5-b]quinoline-2,4-diones reported previously[6] and three new ones, and we have compared yields by both conventional and microwave heating in water (Scheme 1).

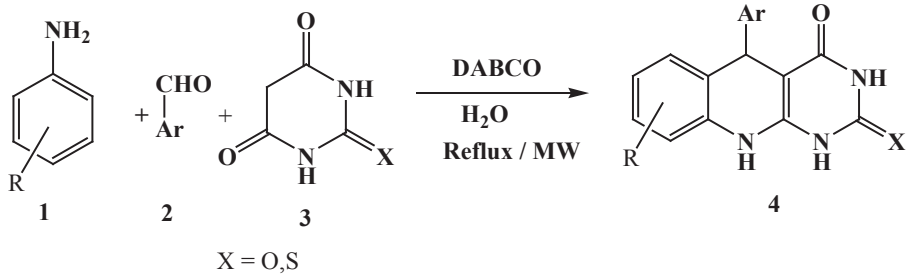
Results and discussion

A mixture of an aniline **1**, an aromatic or heterocyclic aldehyde **2** and (thio)barbituric acid **3** in water (10 mL) in the presence of a catalytic amount of DABCO at 100 °C for 12 h (Scheme 1), afforded 5-aryl-pyrimido[4,5b]quinoline-2,4-diones **4a**–**m** in good yields (Table 1). Then the reaction was repeated with less water (2 mL), using microwave irradiation in order to decrease the reaction time and to improve the yield of 5-aryl-pyrimido[4,5-b]quinoline-2,4-diones. The results are compared with conventional heating in Table 1. As can be seen, yields using microwave heating are generally higher than conventional heating and, importantly, reaction times are reduced from 12 h to 30s.

Ten of the synthesised products **4d**–**m** were known compounds and their identity was confirmed by a comparison of their melting point (Table 1) and their spectral properties with literature data.[1]

Three products **4a**–**c** were new, and they were characterised by their IR, ^{1}H NMR and ^{13}C NMR spectral data and their elemental analyses.

We propose the following mechanism for the reaction (Scheme 2). Activation of the aldehyde is achieved by DABCO. Simultaneously, DABCO as Brønsted acid/base assists the enolisation of the barbituric acid where barbituric acid in the enol form is then reacted with adduct **I** to form intermediate **II**. Intermediate **II** can lose a water molecule and so barbiturate **III** as an unsaturated carbonyl compound is generated. On the other hand, DABCO can activate the adduct **III** to form intermediate **IV**, to undergo reaction with aniline, resulting in the production of the adduct **V**. DABCO could function



Scheme 1

* Correspondent. E-mail: mhmosslemin@gmail.com

Table 1 Comparison between classical and microwave heating for synthesis of 5-aryl-pyrimido[4,5-b]quinoline-diones

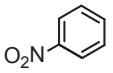
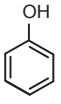
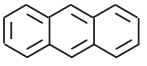
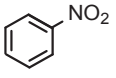
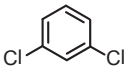
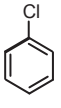
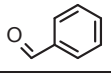
Entry	R	Ar	X	Product	M.p./°C Found Reported[21]	Classical heating		Microwave irradiation	
						Time/h	Yield/%	Time/s	Yield/%
1	H		O	**4a**	196–198	12	95	30	97
2	H		O	**4b**	268–270	12	96	30	98
3	4-CH_3		O	**4c**	249–252	12	96	30	97
4	4-OMe		O	**4d**	185–191 183–190	12	85	30	94
5	4-Br		S	**4e**	336–340 335–339	12	86	30	93
6	4-OMe		S	**4f**	Decompose > 370	12	90	30	92
7	H		O	**4g**	225–230 225–230	12	90	30	95
8	2,5-Di-OMe		O	**4h**	185–190 185–190	12	86	30	92
9	2-OMe		S	**4i**	310–312 310–312	12	85	30	92
10	4-OMe		O	**4j**	187–194 188–195	12	86	30	90
11	3-NO_2		O	**4k**	298–304 300–305	12	83	30	91
12	3-OH		O	**4l**	285–290 285–289	12	83	30	92
13	4-OMe		O	**4m**	260–265 260–265	12	78	30	89

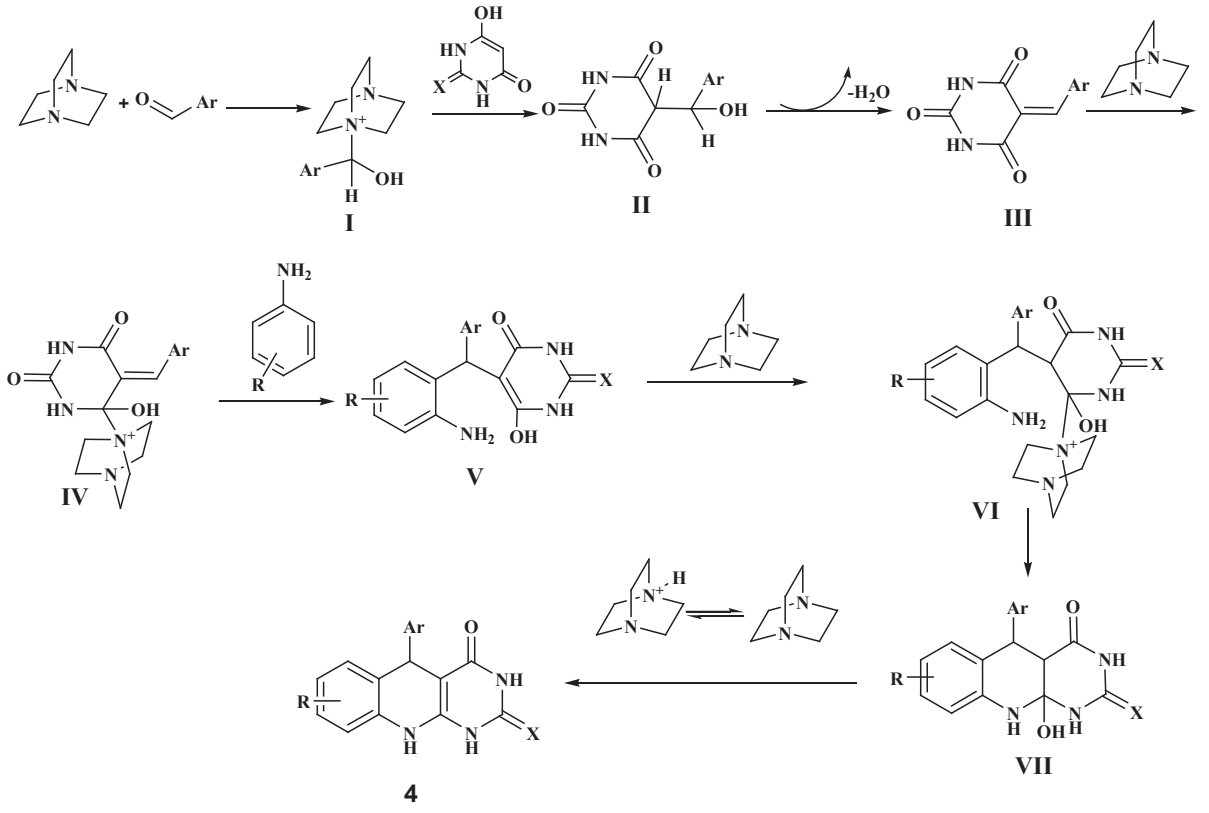
Table 2 Optimisation of the one-pot synthesis of **4c** via reaction between 4-methylaniline, 4-bromobenzaldehyde, and barbituric acid (Scheme 1; R = 4-Me, Ar = 4-Br-C_6H_4, X = O)

Entry	Catalyst/mol%	Solvent temperature	Time/h	Yield/%[b]
1	DABCO (15)	EtOH R.t	12	50
2	DABCO (15)	MeOH Reflux	12	60
3	DABCO (15)	CH_2Cl_2 Reflux	12	52
4	DABCO (15)	MeCN Reflux	12	59
5	DABCO (15)	H_2O Reflux	12	90
6	DABCO(15)	H_2O r.t	12	40
7	Hexamine (15)[c]	H_2O r.t	24	0
8	Hexamine (15)[c]	H_2O Reflux	24	0

[a]Reaction conditions: 4-Me-aniline (1 mmol), 4-Br-benzaldehyde (1 mmol), barbituric acid (1 mmol) and solvent (10 mL).
[b]Yield of isolated products.
[c]Hexamine = 1,3,5,7-tetraazaadamantane.

as nucleophilic catalyst and react with adduct **V** to generate intermediate **VI**. Intermediate **VI** subsequently undergoes an intramolecular reaction to give compound **VII**, DABCO can assist compound **VII** to lose a water molecule and afford the corresponding products **4a**–**m.**

In order to establish optimised reaction conditions, the effect of varying the solvent and temperatures of reaction and using different catalysts, on the model reaction of 4-methylaniline, 4-bromobenzaldehyde and barbituric acid in the presence of DABCO were evaluated. The results are depicted in Table 2 and as the data indicate, the use of EtOH, MeOH, CH_2Cl_2 and MeCN as solvents at reflux, (entries 1–4**)** gave only moderate yields of product. Among the examined solvents H_2O at reflux **(**entry 5**)** afforded the best result. The use of 1,3,5,7-tetraazaadamantane as catalyst gave no product, even after 24 h **(**entries 7 and 8**)** Thus 15 mol% DABCO was the preferred catalyst for this reaction.



Scheme 2 Suggested mechanism for the synthesis of 5-aryl-pyrimido[4,5-b] quinoline-diones using DABCO as catalyst.

Experimental

Melting points were measured on the Electrothermal 9100 apparatus and are uncorrected. Elemental analyses were performed using a Heracus CHN-O-Rapid analyser. IR spectra were determined as KBr discs on a Shimadzu IR-460 spectrophotometer. NMR spectra were obtained on a Bruker Avance DRX-300 MHz spectrometer (^{1}H NMR at 400 Hz, ^{13}C NMR at 100 Hz) in DMSO-d_6 using TMS as internal standard. Mass spectra were recorded on a Hewlett-Packard 5973 mass spectrometer operating at an ionisation potential of 70 eV. Microwave reactions were carried out in a microwave oven (2500 W power; Micro-Synth, Milestone). The chemicals used in this work purchased from Fluka (Buchs, Switzerland) and were used without further purification.

Synthesis of 5-aryl-pyrimido[4,5-b]-quinoline-diones; general procedure

(i) Thermal method: In a round-bottomed flask (10 mL), a mixture of an aromatic amine (1 mmol), barbituric acid (0.13 g, 1 mmol), an aldehyde (1 mmol) and DABCO (15 mol%) in H_2O (10 mL) was heated to reflux for the time indicated in (Table 2). The progress of the reaction was monitored by TLC. After cooling to room temperature, the reaction mixture was poured into cold water, and washed with H_2O (10 mL) and EtOH (5 mL) to afford the pure product (Table 1).

(ii) Microwave irradiation method: A mixture of an aromatic amine (1 mmol), barbituric acid (0.13 g, 1 mmol), an aldehyde (1 mmol) and DABCO (15 mol%) in H_2O (2 mL) was placed in a screw capped Teflon vessel. Microwave irradiation was applied for 30 s at 90 °C (400 W). After the completion of reaction (TLC analysis), the residue was washed with water H_2O (10 mL) and EtOH (5 mL) to give pure product in high yield.

4-Bromophenyl-(1H,3H,5H,10H)-pyrimido[4,5-b]quinoline-2,4-dione (**4a**): Yield 96%; pink powder, m.p. 196–198 °C; IR (ν_{max}) 3200, 3470, 3615, 3095, 1698, 1614, 632 cm^{-1}. ^{1}H NMR: 6.49 (1H, s, CH–Ph), 6.51–7.62 (8H, m, aromatic), 11.16 (2H, s, NH), 11.32 (1H, s, NH); ^{13}C NMR: 49.7, 79.1, 120.8, 121.1, 127.4, 129.4, 129.7, 130.7, 130.7, 131.4, 141.2, 144.4, 150.4, 166.2, 169.3. Anal. calcd for $C_{17}H_{12}$ Br N_3O_2: C, 55.15; H, 3.27; N, 11.35; found: C, 55.37; H, 3.03; N, 11.61%.

p-Tolyl-(1H,3H,5H,10H)-pyrimido [4,5-b] quinoline-2,4-dione (**4b**): Yield 95%; white powder, m.p. 268–270 °C; IR (ν_{max}): 3210, 3410, 3560, 3095, 1701, 1656 cm^{-1}; ^{1}H NMR 3.65 (3H, s, CH_3), 5.91 (1H, s, CH), 6.60–7.14 (8H, m, Aromatic), 9.96 (1H, s, NH), 11.13 (2H, s, NH); ^{13}C NMR: 20.9, 42.9, 79.2, 108.7, 119.5, 126.7, 127.5, 127.8, 129.2, 130.3, 137.0, 142.5, 144.4, 152.8, 164.5, 165.6. Anal. calcd for $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.95; N, 13.76; found: C, 70.72; H, 5.07; N, 13.57%.

4-Bromophenyl-7-methyl-(1H,3H,5H,10H)-pyrimido[4,5-b] quinoline-2,4-dione **(4c):** Yield 96%; white powder, m.p. 249–252 °C; IR (ν_{max}): 3195, 3425, 3620, 2990, 1694, 658 cm^{-1}; ^{1}H NMR: 3.47 (3H, s, CH_3), 5.91 (1H, s, CH), 6.69–7.34 (7H, m, Aromatic), 10.17 (2H, s, NH), 11.14 (1H, s, NH); ^{13}C NMR: 21.2, 42.6, 80.1, 109.7, 121.2, 127.5, 128.6, 129.7, 130.3, 131.4, 133.4, 139.7, 147.5, 152.5, 162.2, 163.9. Anal. calcd for $C_{18}H_{14}$ Br N_3O_2: C, 56.27; H, 3.67; N, 10.94; found: C, 56.43; H, 3.48; N, 11.05%.

Received 11 December 2013; accepted 18 January 2014
Paper 1302331 doi: 10.3184/174751914X13917105358323
Published online: 7 March 2014

References

1 J. Hzhu and H. Bienayme, eds, *Multicomponent reactions.* Wiley-VCH, Weinheim, 2005.
2 J.J. Li and E.J. Corey, eds, *Name reactions in heterocyclic chemistry.* Wiley Interscience, 2005**.**
3 A.P. Kozikowski, *J. Med. Chem*., 2009, **52**, 2109.
4 V.K. Hzishiri, M.C. Joshi, R. Hunter, K. Chibale, P.J. Smith, R.L. Summers, R.E. Martin and T.J. Egan, *J. Med. Chem.,* 2011, **54**, 6956.
5 R. Daoud, J. Desneves, L.W. Deady, L. Tilley, R.J. Scheper, P. Gros and E. Georges, *Biochemistry*, 2000, **39**, 6094.
6 A. Khalafi-Nezhad, S. Sarikhani, E.S. Shahidzadeh and F. Panahi, *Green Chem.,* 2012, **14**, 2876.
7 H. Yang, R. Tian and Y. Li, *Front. Chem. China*, 2008, **3**, 279.
8 B. Baghernejad, *Eur. J. Chem*., 2010, **1**, 54.
9 C.O. Kappe, *Angew. Chem. Int. Ed*., 2004, **43**, 6250.
10 A. Loupy, ed. *Microwaves in organic synthesis.* Wiley-VCH, Weinheim, 2002.