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Environmentally Benign Synthesis of Benzopyranopyrimidines*

M. Kidwai, S. Saxena, and R. Mohan

Department of Chemistry, University of Delhi, Delhi, 110007, India
e-mail: kidwai_chemistry@yahoo.co.uk

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Abstract—An ecologically benign method has been proposed for the synthesis of benzopyranopyrimidines by reaction of 4-hydroxycoumarins with aldehydes and urea or thiourea in the absence of a solvent under microwave irradiation. The proposed procedure improves the product yield and shortens the reaction time.

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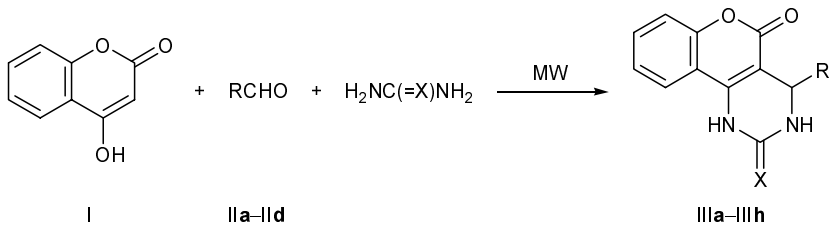
Environmental protection is a pressing need which requires chemical processes to be performed with higher yields, minimal expenses, and the use of nontoxic solvents, reagents, and catalysts. Development of microwave-assisted solid-phase syntheses [1, 2] is a step forward in this direction. The use of mineral solid supports such as alumina, silica, and clays [3] has contributed to the synthesis of a variety of organic compounds with higher selectivity and yield in shorter time. However, these techniques do not exactly meet the ecologically friendly goals of clean synthesis since appreciable amounts of solvents are used for adsorption of reagents and later for extraction of products. In order to circumvent these problems there is a need for development of newer methods which utilize solvent-free conditions [4, 5]. An advance in this area, where substantial progress is to be made, is development of microwave-assisted neat syntheses [6] which eliminate the use of solvent and solid support and offer potential advantages of higher yields, shorter reaction time, enhanced selectivity, and associated ease of manipulations.

Fused pyrimidine derivatives attract interest due to their diverse biological activity. For example, some pyridopyrimidines are known as analgetics [7] and CNS depressants [8], while pyranopyrimidines exhibit antifungal and antibacterial activity [9]. Taking into account that coumarin derivatives themselves possess a variety of pharmacological properties [10], their fusion with a pyrimidine fragment could give rise to compounds with enhanced biological activity. Although many synthetic strategies [11] have been applied for the preparation of fused pyrimidine derivatives, most of these methods suffer from some drawbacks including the use of expensive reagents, drastic reaction conditions, long reaction time, and laborious isolation procedure.

In continuation of our attempts [12, 13] aimed at developing new selective and environmentally safe methodologies for the synthesis of bioactive compounds [14], we have synthesized benzopyranopyrimidines via a three-component Biginelli reaction [15, 16] under solvent-free conditions. 4-Substituted benzopyrano[4,3-*d*]pyrimidines **IIIa**–**IIIh** are usually obtained by heating a mixture of 4-hydroxycoumarin, aldehyde **IIa**–**IId**, and urea or thiourea in ethanol in the presence of concentrated hydrochloric acid [11]. This procedure requires prolonged heating of the reaction

Scheme 1.



I IIa–IId IIIa–IIIh

II, R = Ph (**a**), 1,3-2*H*-benzodioxol-5-yl (**b**), 3-indolyl (**c**), 2-chloroquinolin-3-yl (**d**); **III**, R = Ph (**a**, **b**), 1,3-2*H*-benzodioxol-5-yl (**c**, **d**), 3-indolyl (**e**, **f**), 2-chloroquinolin-3-yl (**g**, **h**); X = O (**a**, **c**, **e**, **g**), S (**b**, **d**, **f**, **h**).

* The text was submitted by the authors in English.

Synthesis of benzopyranopyrimidines **IIIa**–**IIIh** by different methods

Compound no.	Method *a*		Method *b*		Method *c*	
	time, h	yield, %	time, min	yield, %	time, min	yield, %
IIIa	12	59	4.5	70	2.6	94
IIIb	13	54	4.9	68	2.2	92
IIIc	15	56	5.1	65	2.9	93
IIId	14	58	5.4	67	3.1	95
IIIe	16	52	6.2	63	3.3	90
IIIf	18	50	6.0	61	3.4	88
IIIg	19	48	7.4	60	4.1	86
IIIh	17	50	7.1	62	4.3	87

mixture and tedious workup and gives low yields of the products.

We previously [17] examined the effect of different acidic inorganic solid supports on this reaction under microwave activation conditions. Apart from acidic solid supports, we also tried to carry out the process over neutral alumina. Surprisingly, the corresponding products were isolated in good yield without much loss in reaction time. This inspired us to modify the solid-supported synthesis to an environmentally benign neat synthesis in the absence of solvent, solid support, and acid. The reaction of equimolar amounts of neat reactants under microwave irradiation in a few minutes gave the desired products **IIIa**–**IIIh** in 90–95% yields (Scheme 1), which were isolated by treatment of the mixture with several drops of methanol. The structure of compounds **IIIa**–**IIIh** was determined on the basis of their analytical and spectral data. The IR spectra of **IIIa**–**IIIh** contained absorption bands at 3425–3450 (NH), 1725–1745 (C=O, lactone), and 1615–1665 cm^{-1} (C=C). In the ^1H NMR spectra, a singlet at δ 6.1 ppm due to 4-H was present.

Thus we have developed a highly efficient environmentally benign method of synthesis of benzopyranopyrimidines under microwave activation, which utilizes neither solvent nor solid support nor acid catalyst. The proposed procedure requires no special equipment, ensures high yields of the target products in a short reaction time, and minimizes hazardous pollution.

EXPERIMENTAL

The melting points were determined on a Thomas Hoover melting point apparatus; uncorrected values are given. The IR spectra were recorded in KBr on a Perkin–Elmer FTIR-1710 spectrometer. The ^1H NMR spectra were measured on a Hitachi R-600 Fourier spectrometer (60 MHz) using TMS as internal reference. The elemental compositions were determined using a Heraeus CHN Rapid Analyzer instrument. The reactions were carried out in a Kenstar Model OM-9925E microwave oven (2450 MHz, 800 W). The purity of the products was checked by TLC on silica gel plates (Merck). Approximate temperatures of the reaction mixtures were measured with an AZ mini Non-contact Infrared Thermometer Model 8868 (90–110°C at 800 W).

4-Aryl-1,2,3,4-tetrahydro[4,3-*d*]pyrimidine-2,5-diones and 4-aryl-2-thioxo-1,2,3,4-tetrahydro-[4,3-*d*]pyrimidin-5-ones IIIa–IIIh (*general procedure***).** *a.* A mixture of 0.037 mol of 4-hydroxycoumarin (**I**), 0.024 mol of aldehyde **IIa**–**IId**, and 0.024 mol of urea or thiourea in 20 ml of ethanol containing 4 drops of concentrated hydrochloric acid was heated under reflux for a time indicated in table. The progress of reaction was monitored by TLC. When the reaction was complete, the mixture was kept for several hours at room temperature. The precipitate was filtered off, washed with cold methanol, dried, and recrystallized from methanol.

b. Neutral aluminum oxide, (Aldrich, Brockman activity grade I, 150 mesh, 58 Å, 155 m^2/g), 20 g, was added to a solution of 0.037 mol of 4-hydroxycoumarin (**I**), 0.024 mol of aldehyde **IIa**–**IId**, and 0.024 mol of urea or thiourea in 15 ml of ethanol. The mixture was thoroughly stirred, dried in air, placed into an aluminum bath, and subjected to microwave irradiation. When the reaction was complete (according to the TLC data; samples were withdrawn every 30 s), the

product was extracted into ethanol (3×15 ml). The solvent was removed, and the residue was recrystallized from methanol.

c. A mixture of 0.024 mol of 4-hydroxycoumarin (**I**), 0.024 mol of aldehyde **IIa**–**IId**, and 0.024 mol of urea or thiourea was placed in an Erlenmeyer flask and was subjected to microwave irradiation. When the reaction was complete (according to the TLC data; samples were withdrawn every 30 s), the resulting sticky material was treated with a few drops of methanol and recrystallized from aqueous methanol.

4-Phenyl-1,2,3,4-tetrahydro[4,3-*d*]pyrimidine-2,5-dione (IIIa). mp 162°C [11]. IR spectrum, ν, cm^{-1}: 3450 (NH), 1730 (C=O, lactone), 1615 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 6.1 s (1H, 4-H), 7.2–8.1 m (9H, H_{arom}), 11.5 br.s (2H, NH, exchanges with D_2O). Found, %: C 69.80; H 4.01; N 9.49. $C_{17}H_{12}N_2O_3$. Calculated, %: C 69.88; H 4.10; N 9.58.

4-Phenyl-2-thioxo-1,2,3,4-tetrahydro[4,3-*d*]pyrimidin-5-one (IIIb). mp 188°C [11]. IR spectrum, ν, cm^{-1}: 3440 (NH), 1745 (C=O, lactone), 1625 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 6.0 s (1H, 4-H), 7.2–8.0 m (9H, H_{arom}), 11.4 br.s (2H, NH, exchanges with D_2O). Found, %: C 66.31; H 3.80; N 9.01. $C_{17}H_{12}N_2O_2S$. Calculated, %: C 66.23; H 3.89; N 9.09.

4-(1,3-2*H*-Benzodioxol-5-yl)-1,2,3,4-tetrahydro-[4,3-*d*]pyrimidine-2,5-dione (IIIc). mp 243–244°C. IR spectrum, ν, cm^{-1}: 3428 (NH), 1738 (C=O, lactone), 1655 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 5.9 s (2H, OCH_2), 6.2 s (1H, 4-H), 6.7–7.2 m (3H, H_{arom}), 11.2 br.s (2H. NH, exchanges with D_2O). Found, %: C 64.15; H 3.48; N 8.25. $C_{18}H_{12}N_2O_5$. Calculated, %: C 64.28; H 3.57; N 8.34.

4-(1,3-2*H*-Benzodioxol-5-yl)-2-thioxo-1,2,3,4-tetrahydro[4,3-*d*]pyrimidin-5-one (IIId). mp 250–252°C. IR spectrum, ν, cm^{-1}: 3435 (NH), 1725 (C=O, lactone), 1664 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 5.8 s (2H, OCH_2), 6.1 s (1H, 4-H), 6.8–7.1 m (3H, H_{arom}), 11.3 br.s (2H, NH, exchanges with D_2O). Found, %: C 61.26; H 3.48; N 7.88. $C_{18}H_{12}N_2O_4S$. Calculated, %: C 61.36; H 3.40; N 7.95.

4-(3-Indolyl)-1,2,3,4-tetrahydro[4,3-*d*]pyrimidine-2,5-dione (IIIe). mp 210–212°C [17]. IR spectrum, ν, cm^{-1}: 3445 (NH), 1748 (C=O, lactone), 1612 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 6.1 s (1H, 4-H), 7.2–8.0 m (9H, H_{arom}), 8.8 br.s (1H, NH, indole), 11.5 br.s (2H, NH, exchanges with D_2O). Found, %: C 68.76; H 3.81; N 12.56. $C_{19}H_{13}N_3O_3$. Calculated, %: C 68.88; H 3.92; N 12.68.

4-(3-Indolyl)-2-thioxo-1,2,3,4-tetrahydro[4,3-*d*]-pyrimidin-5-one (IIIf). mp 192–194°C [17]. IR spectrum, ν, cm^{-1}: 3435 (NH), 1735 (C=O, lactone), 1620 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 6.2 s (1H, 4-H), 7.3–8.1 m (9H, H_{arom}), 8.9 br.s (1H, NH, indole), 11.5 br.s (2H, NH, exchanges with D_2O). Found, %: C 65.76; H 3.79; N 12.02. $C_{19}H_{13}N_3O_2S$. Calculated, %: C 65.70; H 3.74; N 12.10.

4-(2-Chloroquinolin-3-yl)-1,2,3,4-tetrahydro-[4,3-*d*]pyrimidin-2,5-dione (IIIg). mp 256–257°C. IR spectrum, ν, cm^{-1}: 3425 (NH), 1728 (C=O, lactone), 1635 (C=C). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 6.0 s (1H, 4-H), 7.6–8.6 m (5H, quinoline), 11.8 br.s (2H, NH, exchanges with D_2O). Found, %: C 63.40; H 3.36; N 11.22. $C_{20}H_{13}ClN_3O_3$. Calculated, %: C 63.49; H 3.43; N 11.11.

4-(2-Chloroquinolin-3-yl)-2-thioxo-1,2,3,4-tetrahydro[4,3-*d*]pyrimidin-5-one (IIIh). mp >300°C. IR spectrum, ν, cm^{-1}: 3430 (NH), 1740 (C=O, lactone), 1640 (C=C). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 5.9 s (1H, 4-H), 7.5–8.7 m (5H, quinoline), 11.7 br.s (2H, NH, exchanges with D_2O). Found, %: C 60.82; H 3.21; N 10.54. $C_{20}H_{13}ClN_3O_2S$. Calculated, %: C 60.91; H 3.29; N 10.66.

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