Solid-supported Hantzsch—Biginelli reaction for syntheses of pyrimidine derivatives

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The microwave-assisted dry media technology was utilized for the synthesis of some novel derivatives in the Hantzsch—Biginelli reaction. In this eco-friendly approach, the usage of organic solvents and hazardous reagents resulting in corrossion of materials was minimized, giving high yields of products within a short reaction time.

Key words: 1,4-dihydropyridine, 3,4-dihydropyrimidine, thiobarbituric acid, microwave irradiation, supported catalyst.

The drive towards clean technology has enforced the application of solvent-free conditions[1] into practice. A paradigm shift away from using solvents into organic synthesis has lead to improved results and more benign synthetic procedures.[2] The development of microwave-assisted solid-phase synthesis[3] has added a new dimension to organic synthesis, because these high-yield protocols offer benefits of enhanced reaction rates, greater selectivity, and experimental ease of manipulation.[4] The absence of solvent coupled with microwave irradiation[5] makes this approach an attractive synthetic methodology.

A continuous interest in synthesis of new 4-aryl-1,4-dihydropyridine derivatives is evoked by their pharmacological application as vasodilators[6] and antihypertensive agents.[7]

The synthesis of 1,4-dihydropyridine (1,4-DHP) by the Hantzsch[8] method generally involves the reaction of one mole of aldehyde, two moles of β-ketoester, and one mole of concentrated ammonia. Various modified methods have been reported that involve variation in β-ketoester, aldehyde, or the amine component.[9] The condensation of cyclic 1,3-diketone with aromatic aldehyde and β-aminocrotonate resulting in bicyclic 1,4-DHP has been reported.[10] However, this methodology suffers from setbacks of a longer reaction time, poor yield, and excess use of solvents.

In view of the biological importance of 1,4-DHP and in continuation to our endeavor towards "green" synthesis,[11] it was thought worthwhile to synthesize 4-aryl-1,4-dihydropyridines using a supported catalyst under microwave irradiation.

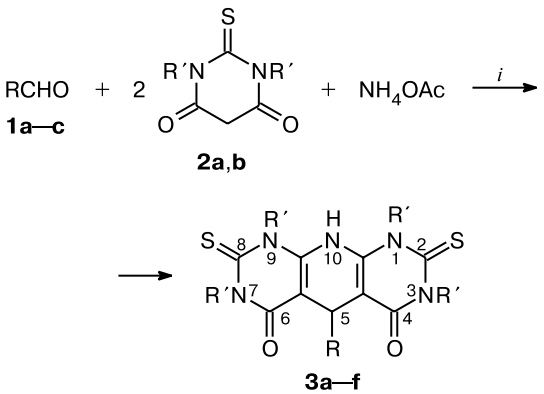
Another well-known reaction that continues to attract attention of the researchers is the Biginelli reaction[12] that involves the cyclocondensation of ethyl acetoacetate, aromatic aldehyde, and urea (thiourea) to yield 3,4-dihydropyrimidinones, which are pharmacologically important as calcium channel blockers, antihypertensive agents, anti-inflammatory agents, and α-1a-antagonists.[13,14]

In addition to its simplicity, the Biginelli reaction has one salient feature in its ability to tolerate a variety of substituted β-ketoesters.[15] Inspired by the positive results obtained in the Hantzsch reaction, ethyl acetoacetate was replaced by cyclic-1,3-diketone in the Biginelli reaction also.

Results and Discussion

One mole each of aromatic aldehyde **1a—c** and ammonium acetate were condensed with two moles of 2-thiobarbituric acid **2a,b** using Al_2O_3 (acid.) as a solid support under microwave irradiation (MWI). Products **3a—f** were obtained (Scheme 1) in a good yield within

Scheme 1



3a—f

R = Ph (**a**), 2-furyl (**b**), benzo[1,3]dioxol-5-yl (**c**)
R′ = H (**a**), Ph (**b**)

i. μν, Al_2O_3 (acid.)

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Table 1. Comparison of the reaction times and yields of the Hantzsch and Biginelli reactions

Compound	R	R′	M.p. (°C)	Standard heating in liquid phase		Microwave heating* in solid phase	
				t/h	yield (%)	*t*/h	yield (%)
3a	Ph	H	211	48	68	6.0	86
3b	Ph	Ph	251	50	67	6.5	85
3c	2-Furyl	H	222	42	65	7.5	82
3d	2-Furyl	Ph	>300	40	66	8.5	83
3e	Benzo[1,3]dioxol-5-yl	H	299	72	67	9.0	81
3f	Benzo[1,3]dioxol-5-yl	Ph	>300	72	64	9.5	80
4a	Ph	H	289	48	65	7.5	82
4b	Ph	Ph	291	48	64	8.0	80
4c	2-Furyl	H	>300	24	63	6.0	84
4d	2-Furyl	Ph	276	24	62	6.5	83
4e	Benzo[1,3]dioxol-5-yl	H	>300	25	68	3.5	86
4f	Benzo[1,3]dioxol-5-yl	Ph	291	26	67	3.5	87

* Microwave heating (800 W, 2450 MHz).

few minutes of irradiation (Table 1), while the same reaction under conventional heating (in a solution) gave the required product within several hours in a moderate yield. The structures of the products were established on the basis of their spectroscopic data. Bands at 1610 cm^{-1} corresponding to the C=C bonds appear in the IR spectra. In the ^1H NMR spectra, signals at δ 3.2 (CH_2) disappear and singlets at δ 5.8 (H(5)) appear.

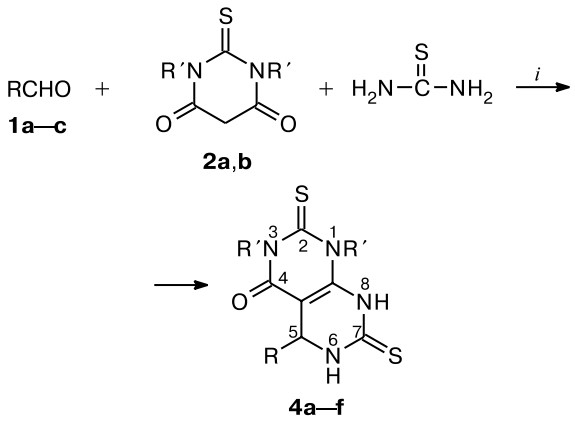
The condensation of 2-thiobarbituric acid **2a,b** (0.037 mol) with aromatic aldehyde **1a—c** (0.024 mol) and thiourea (0.024 mol) using Al_2O_3 (acid.) as the solid support under MWI (Scheme 2) gave products **4a—f** in good yield within few minutes of irradiation. Conventionally, the same reaction took approximately 48 h to complete giving the product in moderate yields (Table 1). The structures of the products were established on the basis of their analytical and spectroscopic data (Table 2): doublets at δ ~5.8 (H(5)) appear in the ^1H NMR spectra.

In continuation to our earlier work,[16] an attempted neat reaction of 2-thiobarbituric acid, aldehyde, and thiourea or ammonium acetate in the absence of a solid support, solvent, and acid proved to be unsuccessful, because direct irradiation of neat reactants leads to the decomposition of 2-thiobarbituric acid.

Comparison with the conventional procedure shows that acidic alumina coupled with microwave heating is the best condensing method for the preparation of polycyclic 1,4-dihydropyridines and 3,4-dihydropyrimidines.

Using reagents supported on inorganic solid materials in the absence of solvents is not only advantageous from the environmental point of view but also offers rate enhancement and improved yields. This makes this technology economical and environmentally benign for organic synthesis.

Scheme 2



i. μv, Al_2O_3 (acid.)

Experimental

Microwave irradiation was carried out in a Kenstar OM9925E microwave oven (2450 MHz, 800 W). IR spectra were recorded on a Perkin Elmer FTIR-1710 spectrophotometer using KBr pellets. ^1H NMR spectra were recorded on a FT NMR Hitachi R-600 (60 MHz) instrument using $SiMe_4$ as internal standard. Elemental analyses were performed using a Heraeus CHN-Rapid analyzer. The temperature of the reaction mixture was measured through a non-contact thermometer (AZ, Mini Gun Type, model 8868). Melting points were determined on a Thomas Hoover Melting Point Apparatus instrument. The purity of compounds was checked by TLC on plates coated with silica gel (Merck).

Synthesis of 5-aryl-2,8-dithioxo-2,3,5,8,9-10-hexahydropyrimido[5′,4′:5,6]pyrido[2,3-*d*]pyrimidine-4,6-diones 3a—f (general procedure). A solution of aldehyde **1a—c** (0.01 mol),

Table 2. Spectroscopic and analytical characteristics of compounds **3a—f** and **4a—f**

Compound	Molecular formular	Found / Calculated (%)			IR spectrum, ν/cm^{-1}	^1H NMR, δ (DMSO-d_6, $CDCl_3$)
		C	H	N		
3a	$C_{15}H_{11}N_5O_2S_2$	50.40 50.42	3.10 3.08	19.62 19.60	3280 (NH), 3130 (NH), 1670 (C=O), 1612 (C=C)	5.8 (s, 1 H, H(5)); 6.4—6.6 (br.s, 2 H, NH(1), NH(3), NH(7), NH(9)); 7.2—7.4 (m, 5 H, H aryl); 9.6 (s, 1 H, NH)
3b	$C_{39}H_{27}N_5O_2S_2$	70.78 70.80	4.05 4.08	10.60 10.59	3251 (NH), 1690 (C=O), 1610 (C=C)	5.8 (s, 1 H, H(5)); 7.2—7.6 (m, 25 H, H aryl); 9.9 (s, 1 H, NH)
3c	$C_{13}H_9N_5O_3S_2$	44.98 44.95	2.60 2.59	20.19 20.17	3230 (NH), 3135 (NH), 1690 (C=O), 1615 (C=C)	5.9 (s, 1 H, H(5)); 6.4—6.6 (br.s, 2 H, NH(1), NH(3), NH(7), NH(9)); 6.8—7.0 (m, 3 H, furan); 9.8 (s, 1 H, NH)
3d	$C_{37}H_{25}N_5O_3S_2$	68.22 68.20	3.87 3.84	10.76 10.75	3287 (NH), 1671 (C=O) 1620 (C=C)	5.9 (s, 1 H, H(5)), 6.8—7.0 (m, 3 H, furan); 7.2—7.4 (m, 20 H, H aryl); 9.8 (s, 1 H, NH)
3e	$C_{16}H_{11}N_5O_4S_2$	47.79 47.80	2.77 2.74	17.49 17.45	3293 (NH), 3155 (NH), 1668 (C=O), 1596 (C=C)	5.8 (s, 1 H, H(5)); 5.9 (s, 2 H, CH_2); 6.6—7.0 (m, 7 H, H aryl, NH(1), NH(3), NH(7), NH(9)); 10.1 (s, 1 H, NH)
3f	$C_{40}H_{27}N_5O_4S_2$	68.10 68.08	3.85 3.82	9.91 9.92	3158 (NH), 1668 (C=O), 1595 (C=C)	5.8 (s, 2 H, CH_2); 5.9 (s, 1 H, H(5)); 6.6—7.0 (m, 3 H, H aryl); 7.2—7.4 (m, 20 H, H aryl); 10.2 (s, 1 H, NH)
4a	$C_{12}H_{10}N_4OS_2$	49.62 49.65	3.42 3.44	19.30 19.31	3416 (NH), 3195 (NH), 1680 (C=C)	5.8 (d, 1 H, H(5)); 6.5—6.8 (br.s, 2 H, NH(1), NH(3)); 7.2—7.4 (m, 5 H, H aryl); 8.5, 10.2 (both s, 1 H each, NH)
4b	$C_{24}H_{18}N_4OS_2$	65.18 65.15	4.08 4.07	12.62 12.66	3428 (NH), 1678 (C=C)	5.8 (d, 1 H, H(5)); 7.2—7.4 (m, 15 H, H aryl); 8.4, 10.1 (both s, 1 H each, NH)
4c	$C_{10}H_8N_4O_2S_2$	42.82 42.85	2.86 2.85	20.02 20.00	3425 (NH), 3133 (NH), 1676 (C=C)	5.9 (d, 1 H, H(5)); 6.3—6.7 (br.s, 2 H, NH(1), NH(3)); 6.8—7.0 (m, 3 H, furan); 8.6, 10.4 (both s, 1 H each, NH)
4d	$C_{22}H_{16}N_4O_2S_2$	61.13 61.11	3.72 3.70	12.94 12.96	3420 (NH), 1675 (C=C)	5.9 (d, 1 H, H(5)); 6.8—7.0 (m, 3 H, furan); 7.2—7.4 (m, 10 H, H aryl); 8.5, 10.5 (both s, 1 H each, NH)
4e	$C_{13}H_{10}N_4O_3S_2$	46.71 46.70	2.94 2.99	16.74 16.76	3425 (NH), 3165 (NH), 1669 (C=C)	5.7 (d, 1 H, H(5)); 5.9 (s, 2 H, CH_2); 6.6—6.9 (m, 5 H, H aryl, NH(1), NH(3)); 8.3, 10.8 (both s, 1 H each, NH)
4f	$C_{25}H_{18}N_4O_3S_2$	61.70 61.72	3.72 3.70	11.50 11.52	3420 (NH), 1664 (C=C)	5.8 (d, 1 H, H(5)); 5.9 (s, 2 H, CH_2), 6.6—7.0 (m, 3 H, H aryl); 7.2—7.4 (m, 10 H, H aryl); 8.3, 10.7 (both s, 1 H each, NH)

ammonium acetate (0.01 mol), and 2-thiobarbituric acid **2a,b** (0.02 mol) in methanol (30 mL) with few drops of acetic acid was refluxed for the time indicated in Table 1. On completion of the reaction (TLC monitoring), the reaction mixture was kept in a refrigerator for 24 h. The solid precipitate was filtered off, dried, and recrystallized from methanol.

Irradiation on solid support (general procedure). A mixture of 2-thiobarbituric acid **2a,b** (0.02 mol), aldehyde **1a—c** (0.01 mol), and ammonium acetate (0.01 mol) in methanol (15 mL) was taken in a beaker and adsorbed on Al_2O_3 (acid.)* (20 g).[17] The mixture was stirred well, dried in air, and subjected to MWI for the time indicated in Table 1. On completion of the reaction (TLC, sampling at an interval of 30 s), the product was extracted with ethanol (3×10 mL). Recovery of the solvent under a reduced pressure gave the required product, which was recrystallized from methanol.

Synthesis of **5-aryl-2,7-dithioxo-2,3,5,6,7,8-hexahydropyrimido[4,5-*d*]pyrimidin-4-ones (4a—f)** was similar to that of compounds **3a—f** from 2-thiobarbituric acid **2a,b** (0.037 mol), aldehyde **1a—c** (0.024 mol), and thiourea (0.024 mol) with the only distinction that experiments without microwave irradiation were carried out in EtOH (20 mL) in the presence of concentrated HCl (4 drops).

* Aluminum oxides, acidic, Brockmann I, ~150 mesh, 58 Å CAMAG 506-C-1, surface area 155 $m^2\,g^{-1}$ (Aldrich).

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