Ecofriendly synthesis of substituted pyridine and pyrido[2,3-*d*]pyrimidine derivatives

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An environmentally benign novel one-pot synthesis of pyridines and pyrido[2,3-*d*]pyrimidines from chalcones and malononitrile was described. In the reaction under neat conditions using microwave irradiation, enhancement in the reaction rate and high yields were observed.

Key words: pyridines, pyrido[2,3-*d*]pyrimidine derivatives, microwave irradiation, supported catalysts, neat reaction conditions.

The increasing environmental consciousness throughout the world has trigged the search for new products and processes that are compatible with the ecofriendly environment. The strict legislative restrictions on pollution exposure has enforced the application of solvent-free conditions in practice.[1] In this endeavor, inorganic solid supports such as zeolites, alumina, bentonite, montmorillonite K-10 clay, *etc*. are strikingly appealing, because the reaction can be performed in "dry media."[2—4] Furthemore, the usage of solid supports in conjunction with microwaves[5,6] leads to higher yield and reaction rate enhancement.[7] The minute observation of the usage of solid supports reveals that an appreciable amount of solvent is required for the adsorption of the reactants and desorption of products. An alternative solvent-free approach is the "neat reaction" technique. This has made a landmark as it aims at the complete elimination of solvent from the reaction. These solventless reactions proved to be advantageous for environmental reasons especially when coupled with microwaves, since they provide an opportunity to conduct various transformations more efficiently and expeditiously.

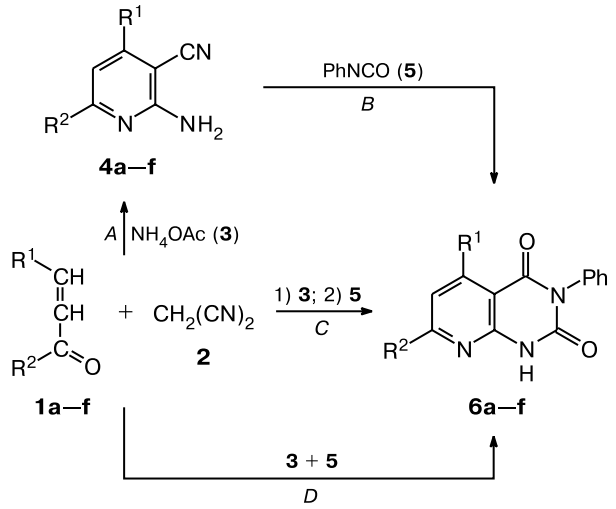
Pyridines generate a widespread interest due to diverse pharmacological activities.[8,9] Pyrimidines owing to their natural occurrence in human genetic material are especially important as antiinfective agents.[10—12] Thus fused pyrido[2,3-*d*]pyrimidine derivatives are associated with numerous biological activities,[13—16] *viz*., antitumor[17] and anticonvulsant.[18] This is responsible for the abiding interest in this class of compounds.

Various conventional methods are known for the synthesis of pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones starting from 6-aminouracil,[19] 6-imino-1,3-dialkyluracil,[20,21] and arylidene derivatives of barbituric acids.[22] All these procedures are not readily accessible, since they demand synthesis even at the precursor stage and require long reaction time and appreciable amount of solvent.

Results and Discussion

In the present paper we are reporting a facile and rapid synthesis (Scheme 1) of 4,6-disubstituted 2-amino-3-cyanopyridines **4a—f** and 5,7-disubstituted 3-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **6a—f** with-

Scheme 1



Reagents and conditions: *A*. μν, 3.1—5.1 min, clay K-10 (*A*-1) or neutral Al_2O_3 (*A*-2); *B*. μν, 4.2—5.9 min, clay K-10 (*B*-1) or basic Al_2O_3 (*B*-2); *C*. μν, 1.5—2.3 min (after addition of NH_4OAc), clay K-10; *D*. μν, 2.8—4.3 min.

1, **4**, **6**	R^1	R^2
a	4-$MeOC_6H_4$	Ph
b	2-Furyl	Me
c	3-Indolyl	4-BrC_6H_4
d	Benzo[1,3]dioxol-5-yl	4-BrC_6H_4
e	3,4-$(MeO)_2C_6H_3$	Ph
f	3,4-$(MeO)_2C_6H_3$	4-$MeOC_6H_4$

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out solvent or on a solid support under microwave irradiation from α,β-unsaturated carbonyl compounds of the chalcone type. Moreover, we have studied the influence of different solid supports under microwave irradiation for the synthesis of the above pyridine and pyrido[2,3-*d*]pyrimidine derivatives and developed the one-pot synthesis of **6a—f**.

The reported synthesis of 5,7-disubstituted 3-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **6** starting from chalcone and malononitrile[23] is a two-step reaction performed in ethanol or dioxane during 22—24 h. Thereby 4,6-disubstituted 2-amino-3-cyanopyridines **4** were formed as intermediates, and the final products **6** were obtained in a very low yield. In an attempt to "greenify" the synthetic procedure and increase its rate and yield, experiments were done under microwave irradiation. The above-mentioned conventional procedure is modified by using chalcones and their heterocyclic analogs on solid supports (montmorillonite clay K-10 or alumina); after microwave irradiation for several minutes, 4,6-disubstituted 2-amino-3-cyanopyridines **4a—f** were obtained in 79—82% yields (see Scheme 1, method *A*; Table 1).

In the second step, compounds **4a—f** were condensed with phenyl isocyanate (**5**), adsorbed over K-10 montmorillonite clay or alumina (see Scheme 1, method *B*), and irradiated under microwaves to afford the final 5,7-disubstituted 3-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **6a—f** in 82—89% yields (see Table 1). Further, the formation of both intermediates **4a—f** and the final cyclized products **6a—f** prompted us to carry out the one-pot synthesis of pyrido[2,3-*d*]pyrimidines **6a—f** on a solid support using chalcones **1**, malononitrile (**2**), NH_4OAc (**3**), and PhNCO (**5**) (see Scheme 1, method *C*). In an improved method, compounds **1**, **2**, and **3** were adsorbed on clay K-10 and irradiated. Upon intermediates **4** formation (TLC examination), a solution of PhNCO (**5**) was added and further irradiated under microwaves. Thus, products **6a—f** were obtained directly without eluting in the middle of the process. This is attributed to the dual nature[24] of K-10 montmorillonite clay, which can act as both cyclizing and condensing agent.[25] In continuation to our interest in the development of environmentally benign protocol,[26—28] we carried out the neat synthesis of 5,7-disubstituted 3-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **6a—f** without solvent (see Scheme 1, method *D*). In this method, neat reactants **1**, **2**, **3**, and **5** were mixed without using any solid support or solvent and irradiated. To our surprise, products **6** were obtained in excellent yields (see Table 1) with not much change in the reaction time, when compared with the one-pot solid-supported synthesis.

The structures of compounds **4a—f** and **6a—f** were proved from IR and ^{1}H NMR spectra (Table 2). The IR spectra of pyridines **4** contain vibrations of the conjugated nitrile group (2180—2230 cm^{-1}) and amino group of the enaminonitrile fragment (three bands at 3100—3440 cm^{-1}). Their ^{1}H NMR spectra exhibit a broadened singlet at δ 7.25—7.55 belonging to the NH_2 group. The IR spectra of pyridopyrimidines **6** contain a band at 1600—1630 cm^{-1} corresponding to the carbonyl group of amides. Their ^{1}H NMR spectra have one signal

Table 1. Reaction time (*t*) and yields of pyridine derivatives **4a—f** and pyrido[2,3-*d*]pyrimidine derivatives **6a—f**

Compound	R^1	R^2	Method *A*		Method *B*		Method *C* [a]	Method *D*
			A-1[a]	*A*-2[b]	*B*-1[a]	*B*-2[c]		
			t/min (yield (%))					
4a	4-$MeOC_6H_4$	Ph	4.2 (79)	4.8 (78)	—	—	—	—
4b	2-Furyl	Me	4.1 (80)	4.5 (82)	—	—	—	—
4c	3-Indolyl	4-BrC_6H_4	3.7 (76)	4.2 (74)	—	—	—	—
4d	Benzo[1,3]dioxol-5-yl	4-BrC_6H_4	3.1 (78)	4.6 (75)	—	—	—	—
4e	3,4-$(MeO)_2C_6H_3$	Ph	3.9 (81)	4.8 (82)	—	—	—	—
4f	3,4-$(MeO)_2C_6H_3$	4-$MeOC_6H_4$	4.1 (84)	5.1 (83)	—	—	—	—
6a	4-$MeOC_6H_4$	Ph	—	—	5.6 (79)	5.9 (73)	8.6 (84)	4.1 (97)
6b	2-Furyl	Me	—	—	5.1 (82)	5.6 (79)	6.4 (88)	3.4 (96)
6c	3-Indolyl	4-BrC_6H_4	—	—	4.7 (77)	4.9 (75)	7.1 (85)	4.2 (94)
6d	Benzo[1,3]dioxol-5-yl	4-BrC_6H_4	—	—	4.2 (79)	4.8 (72)	6.8 (82)	2.8 (95)
6e	3,4-$(MeO)_2C_6H_3$	Ph	—	—	4.6 (83)	5.1 (76)	7.4 (85)	4.3 (96)
6f	3,4-$(MeO)_2C_6H_3$	4-$MeOC_6H_4$	—	—	5.8 (87)	6.0 (82)	8.2 (89)	3.5 (93)

[a] Montmorillonite clay K-10.
[b] Neutral Al_2O_3.
[c] Basic Al_2O_3.

Table 2. Physicochemical, spectral, and analytical data for compounds **4a—f** and **6a—f**

Compound	M.p. /°C	Found / Calculated (%)			Molecular formula	IR, ν/cm^{-1}	^{1}H NMR ($CDCl_3$ + DMSO-d_6), δ
		C	H	N			
4a	176—177[23b]	—	—	—	—	2182 (C≡N), 3110 (NH)	3.73 (s, 3 H, OMe); 6.83—7.01 (m, 10 H, H arom.); 7.25 (br.s, 2 H, NH)
4b	169—171	66.14 / 66.33	4.38 / 4.52	21.24 / 21.10	$C_{11}H_9N_3O$	2198 (C≡N), 3120 (NH)	2.55 (s, 3 H, Me); 6.31 (dd, 2 H, furyl); 6.90—7.00 (m, 2 H, H arom.); 7.32 (br.s, 2 H, NH)
4c	246—248	61.59 / 61.71	3.32 / 3.34	14.21 / 14.39	$C_{20}H_{13}BrN_4$	2230 (C≡N), 3312 (NH)	6.81 (d, 1 H, H(2) of indole); 7.28 (br.s, 2 H, NH); 7.01—7.88 (m, 9 H, H arom.); 10.10 (s, 1 H, NH of indole)
4d	215—217	51.52 / 55.88	3.15 / 3.04	10.48 / 10.66	$C_{19}H_{12}BrN_3O_2$	2210 (C≡N), 3400 (NH)	5.86 (s, 2 H, OCH_2O); 6.79—7.88 (m, 8 H, H arom.); 7.35 (br.s, 2 H, NH)
4e	159—160	72.48 / 72.50	5.20 / 5.13	12.59 / 12.68	$C_{20}H_{17}N_3O_2$	2280 (C≡N), 3300 (NH)	3.71 (s, 6 H, OMe); 6.71—7.31 (m, 9 H, H arom.); 7.46 (br.s, 2 H, NH)
4f	126—129	69.58 / 69.80	5.42 / 5.26	11.48 / 11.63	$C_{21}H_{19}N_3O_3$	2220 (C≡N), 3210 (NH)	3.60 (s, 9 H, OMe); 7.11—7.40 (m, 8 H, H arom.); 7.55 (br.s, 2 H, NH)
6a	224—226	74.12 / 74.10	4.48 / 4.51	9.82 / 9.97	$C_{26}H_{19}N_3O_3$	1610 (C=O), 3100 (NH)	3.73 (s, 3 H, OMe); 6.13 (s, 1 H, NH of pyrimidine); 6.83—7.99 (m, 15 H, H arom.)
6b	228—229	67.63 / 67.71	4.18 / 4.07	13.25 / 13.16	$C_{18}H_{13}N_3O_3$	1625 (C=O), 3120 (NH)	2.55 (s, 3 H, Me); 6.11 (s, 1 H, NH of pyrimidine); 6.31 (dd, 2 H, furyl); 7.01—7.62 (m, 7 H, H arom.)
6c	239—240	60.62 / 60.71	3.36 / 3.15	11.25 / 11.04	$C_{27}H_{16}BrN_4O_2$	1620 (C=O), 3110 (NH)	6.40 (s, 1 H, NH of pyrimidine); 6.81 (d, 1 H, H(2) of indole); 7.02—7.83 (m, 13 H, H arom.); 10.10 (s, 1 H, NH of indole)
6d	252—254	60.63 / 60.71	3.23 / 3.11	8.38 / 8.17	$C_{26}H_{16}BrN_3O_4$	1614 (C=O), 3130 (NH)	5.90 (s, 2 H, OCH_2O); 6.60 (s, 1 H, NH of pyrimidine); 6.72—7.88 (m, 13 H, H arom.)
6e	150—151[23a]	—	—	—	—	1630 (C=O), 3140 (NH)	3.71 (s, 6 H, OMe); 6.21 (s, 1 H, NH of pyrimidine); 6.71—7.92 (m, 14 H, H arom.)
6f	120—122[23a]	—	—	—	—	1624 (C=O), 3148 (NH)	3.62 (s, 9 H, OMe); 6.66 (s, 1 H, NH of pyrimidine); 7.11—7.63 (m, 13 H, H arom.)

at δ 6.11—6.66 characteristic of the NH fragment of the pyrimidinedione ring.

Thus, we have developed facile, economical, and ecofriendly synthetic procedures for the synthesis of 4,6-disubstituted 2-amino-3-cyanopyridines **4** and 5,7-disubstituted 3-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **6** under microwave irradiation using solvent-free techniques. All the reactions under neat conditions gave excellent yields with reduced reaction time when compared with solid-support synthesis. This keeps modernization and simplification of classical procedures toward green synthesis.

Experimental

Microwave irradiation was carried out on a Kenstar-OM9925E microwave oven (2450 MHz, 800 W). The temperature of the reaction mixture was measured with a non-contact mini-gun-type IR thermometer (model 8868). IR spectra were recorded on a Perkin—Elmer FTIR-1710 spectrophotometer using KBr pellets. ^{1}H NMR spectra were obtained on a Hitachi R-600 spectrometer (300 MHz); chemical shifts are given in the δ scale relative to Me_4Si as internal reference. Elemental analyses were performed using a Heraeus CHN-Rapid analyzer. The melting points (uncorrected) were determined on a Thomas Hoover Melting Point apparatus. The purity of compounds and the reaction course were monitored by TLC on aluminum plates coated with silica gel (Merck) using ethanol as eluent.

The following solid supports were used: montmorillonite clay K-10 (Fluka, 200±20 m^2 g^{-1}), neutral and basic aluminas, (Brockmann activity grade I (Aldrich), ~150 mesh, 58 Å, 155 m^2 g^{-1}).

4,6-Disubstituted 2-amino-3-cyanopyridines 4a—f

Solid-supported synthesis (general procedure *A*). Montmorillonite clay K-10 (15 g) (method *A*-1) or neutral Al_2O_3 (20 g) (method *A*-2) was added to a solution of chalcone **1** (0.05 mol), malononitrile (**2**) (0.05 mol) and ammonium acetate (**3**) (0.4 mol) in ethanol (10 mL) with constant stirring (see Table 1). The reaction mixture was air-dried at room temperature, placed in an alumina bath,[29] and subjected to microwave irradiation for 4.2—5.1 min (method *A*-1) or 3.1—4.2 min (method *A*-2). Upon completion of the reaction as followed by TLC at an interval of

30 s, the mixture was cooled to room temperature, and products **4a—f** were extracted with ethanol (3×15 mL). Removal of the solvent *in vacuo* yielded products **4a—f**, which were recrystallized from petroleum ether.

5,7-Disubstituted 3-phenylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-diones 6a—f

Solid-supported synthesis from intermediates 4 (general procedure *B*). Clay K-10 (10 g) (method *B*-1) or basic Al_2O_3 (15 g) (method *B*-2) was added to an equimolar mixture of compounds **4a—f** (prepared by method *A*) and phenyl isocyanate (**5**) with constant stirring (see Table 1). The reaction mixture was air-dried, placed in an alumina bath,[29] and irradiated for 4.2—5.8 min (method *B*-1) or 4.8—6.0 min (method *B*-2). Upon completion of the reaction (TLC monitoring), the mixture was cooled to room temperature, and reaction products **6** were extracted with ethanol (3×10 mL). Removal of the solvent *in vacuo* afforded products **6a—f**, which were recrystallized from ethanol.

Solid-supported synthesis from reactants 1—3, and 5 (general procedure *C*). Montmorillonite clay K-10 (10 g) was added to a mixture of compounds **1** and **2** (0.05 mol each), ammonium acetate (**3**) (0.4 mol), and ethanol (10 mL) at room temperature. The reaction mixture was thoroughly mixed and dried in air. Then it was placed in an alumina bath[29] and subjected to microwave irradiation. Upon intermediates **4** formation (1.5—2.3 min, TLC monitoring), a solution of phenyl isocyanate (**5**) (0.05 mol) was adsorbed over the solid support, and the mixture was further irradiated. Upon completion of the reaction, the mixture was cooled, the product was extracted with ethanol (3×10 mL), and the solvent was removed *in vacuo*. Products **6a—f** were recrystallized from ethanol.

One-pot neat (solvent-free) synthesis of compounds 6a—f (general procedure *D*). Equimolar amounts of compounds **1**, **2**, and **5** (0.05 mol each) and ammonium acetate (**3**) (0.4 mol) were mixed in a 250-mL Erlenmeyer flask. The reaction mixture was irradiated for 2.8—4.3 min. Progress of the reaction was monitored by TLC examination at an interval of 30 s. Upon reaction completion, the resulting sticky mass was triturated with cold methanol. Solid products **6a—f** formed were filtered off, washed with cold ethanol, and recrystallized from ethanol.

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