Base Catalysed Pyrimidine Synthesis Using Microwave

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An environmentally benign approach for the synthesis of 2-substituted-4,6-diaryl pyrimidines using inorganic solid supports for its catalytic role as well as an energy transfer medium is described. The methodology eliminates the usage of solvent during the reaction. The reaction time is brought down from hours to minutes along with yield enhancement. The rate enhancement and high yield is attributed to the coupling of solvent free conditions with microwaves. Further, the role of base is studied in the reaction and it is concluded that microwave assisted basic alumina catalysed reaction is the best in terms of catalysis as well as reaction time and yield.

Key Words : Pyrimidine, SBT, Microwave irradiation, Alumina, Environmentally benign

Introduction

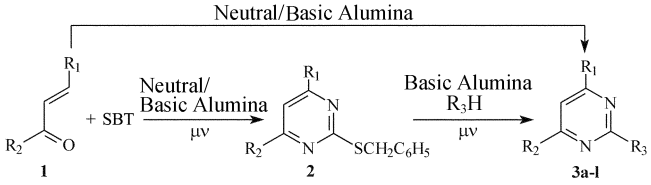
The environmental protection has become a global concern and the chemical industry is increasingly searching the ways of developing and applying more efficiently and environmentally benign strategies for future sustainable growth.[1] An important part of our effort towards ecofriendly synthesis is aimed at reduction of use of solvents. Usually organic solvents in classical procedures are used in much larger quantities than the solutes they carry. In this endeavour, inorganic solid supports have made a landmark as the reactions can be performed in dry media or solvent free conditions.[2] Further the usage of solid support in conjunction with microwaves[3] leads to high yield, remarkable reaction rate enhancement, high catalytic activity with the optimum utilisation of energy. This solventless approach provides an opportunity to conduct selective organic functional group transformations more efficiently and also allows the work to be conducted in open vessels, thus avoiding the risk of high pressure development.[4]

The basic skeleton of chalcones which possess α,β-unsaturated carbonyl group is useful as the starting material for the synthesis of various heterocyclic compounds of physiological importance viz. pyrazoline,[5] thiophenes,[6] etc. The presence of enone functionality in chalcone moiety is the key factor for its biological activity as agrochemical,[7] antimalarial,[8] antiviral,[9] UV absorbers,[10] etc. Further, the importance of pyrimidines and analogous compounds in pharmaceutical and biological fields[11] is well known. With the development of clinically useful pyrimidine based antitumor[12] and antiviral[13] drugs there has been noticeable interest in synthetic manipulations of pyrimidines and thus developing dry media techniques for their ecofriendly synthesis.

In view of the environmentally benign role of solventless approach under microwaves (MW), the biopotential of pyrimidines and our ongoing program towards green synthesis, we herein report a facile, rapid one pot condensation of chalcone with *S*-benzylthiuronium chloride (SBT) to afford 2-substituted-4,6-diaryl pyrimidines. Further, we studied the role of different solid supports under microwaves for the pyrimidines synthesis.

Results and Discussion

Numerous synthetic modes of pyrimidines have been reported starting from thiobarbituric acid[14] (TBA), chalcones[15] and thioureas.[16] But these generally afford pyrimidinone derivatives. In the present communication, we describe the MW accelerated solid supported synthesis of 4,6-diaryl-2-(4-morpholinyl/1-piperidinyl/1-pyrrolidinyl)-pyrimidines (**3a-l**). Classically,[17] 2,4,6-trisubstituted pyrimidines are obtained by refluxing α,β-unsaturated ketones (**1**) with SBT and heterocyclic secondary amines in ethanol (20 mL) for 10-18 hrs. Oily liquid obtained afforded the product upon tritur-



3a $R_1 = R_2$ = Phenyl, R_3 = Morpholinyl
3b R_1 = Piperonyl, R_2 = 4-Br-C_6H_4, R_3 = Morpholinyl
3c R_1 = 2-Furyl, $R_2 = CH_3$, R_3 = Morpholinyl
3d R_1 = 3-Indolyl, R_2 = 4-Br-C_6H_4, R_3 = Morpholinyl
3e $R_1 = R_2$ = Phenyl, R_3 = Pyrrolidinyl
3f R_1 = Piperonyl, R_2 = 4-BrC_6H_4, R_3 = Pyrrolidinyl
3g R_1 = 2-Furyl, $R_2 = CH_3$, R_3 = Pyrrolidinyl
3h R_1 = 3-Indolyl, R_2 = 4-Br-C_6H_4, R_3 = Pyrrolidinyl
3i $R_1 = R_2$ = Phenyl, R_3 = Piperidinyl
3j R_1 = Piperonyl, R_2 = 4-BrC_6H_4, R_3 = Piperidinyl
3k R_1 = 2-Furyl, $R_2 = CH_3$, R_3 = Piperidinyl
3l R_1 = 3-Indolyl, R_2 = 4BrC_6H_4, R_3 = Piperidinyl

Scheme 1

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ation with methanol. Solid was separated out in 40-50% yield (Method A) (Scheme 1). This classical procedure is tedious, time consuming, gives low yield and requires an appreciable amount of solvent as well as secondary amines which is used as base. In order to study the role of base used in excess and to develop an environmentally benign synthetic procedure utilising microwave irradiation (MWI) under solventfree conditions, the reactions are attempted over different solid supports, basic alumina and neutral alumina.

Different experimental trials were carried out to standardise the reaction under MW. To the *S*-benzyl pyrimidine derivative (**2**), added heterocyclic secondary amine (morpholine/ piperidine/pyrrolidine), adsorbed over basic alumina and irradiated under MW. The product was obtained in 85% yield within 3 minutes. *S*-benzyl derivative (**2**) was obtained by irradiating the adsorbed reaction mixture of chalcone (**1**) and SBT over neutral[18]/basic[19] alumina. Further the formation of the precursor (**2**) as well as the final cyclised product (**3a-l**) over neutral/basic alumina prompted us to attempt one pot synthesis of the required pyrimidine derivative starting from the reactants, chalcone (**1**), SBT and heterocyclic secondary amines. This one pot synthesis minimised the yield loss, energy loss and limited the necessity of solvent. Best result in terms of yield and reaction time was obtained with basic alumina under MW (Table 1). Furthermore, it is observed that amount of base required in the case of basic alumina is just ~1 mL instead of 6-7 mL as required in neutral alumina or the conventional method. This is attributed to the requirement of basic conditions for the nucleophilic displacement of *S*-benzyl group by heterocyclic secondary amine. These solid supports act as both catalysts as well as energy transfer media. The structure of the compounds were established on the basis of spectroscopic data and elemental analysis (Table 2). In IR, the disappearance of band at 1685-1710 cm^{-1} due to carbonyl of chalcone and the appearance of band at 1590-1620 cm^{-1} confirmed the formation of product (Table 2).

That the effect is not purely thermal[20] is obvious from the fact that for similar product yield longer time periods are needed using oil bath at the same temperature of 110-120 °C.[21]

Experimental Section

Melting points were taken in Thomas Hoover melting point apparatus and were uncorrected. IR (KBr) spectra (ν in cm^{-1}) were obtained on Perkin-Elmer FTIR 1710 spectrophotometer. ^1H NMR spectra were recorded in $CDCl_3$ on FT NMR Hitachi R-600 spectrometer operating at 60 MHz using TMS as internal standard (chemical shifts in δ ppm). Elemental analyses were performed on Haraeus CHN Rapid Analyser. A Kenstar (Model No. OM9925E) household microwave oven (2450 MHz, 800 W) was used for all experiments. The purity of compounds was checked on silica gel coated aluminium plates (Merck).

General Procedure for the Synthesis of 4,6-Diaryl-2-(4-morpholinyl/1-piperidinyl/1-pyrrolidinyl) pyrimidines (3a-l).

Method A: Conventional Solution Phase. A mixture of chalcone **1** (0.01 mol), SBT (0.25 mol), morpholine/piperidine/pyrrolidine (0.76 mol, 7-8 mL) in ethanol (20 mL) was refluxed for 10-18 hrs. The progress of reaction was monitored through TLC examination. Upon completion of reaction the reaction mixture was cooled and concentrated. The oily liquid obtained upon cooling was triturated with methanol and recrystallised from ethanol and benzene mixture.

Method B: One Pot Solid Support Microwave (Neutral Alumina). To the solution of chalcone **1** (0.02 mol), SBT (0.25 mol) and morpholine/piperidine/pyrrolidine (0.76 mol, 7-8 mL) in ethanol, neutral alumina (15 g) was added with stirring and air dried. It was then placed in an alumina bath used as heat sink and subjected to MWI intermittently (approx. bulk temp. reached[21] ~100-120 °C). The progress of the reaction was monitored by TLC examination. Upon completion of reaction, the product was eluted from ethanol. Recovering the solvent under reduced pressure gave the required product (**3a-l**) which was then recrystallised from ethanol and benzene mixture.

Table 1. Comparison of reaction time and yield of compounds **3a-l**

Compd. No.	R^1	R^2	R^3	M.Pt. (°C)	Method A a (h)/b	Method B a (min)/b	Method C a (min)/b
3a	Phenyl	Phenyl	Morpholinyl	188-190[17]	12/40	1.4/90	2.5/85
3b	Piperonyl	4-Br-C_6H_4	Morpholinyl	145-147	11/44	1.2/85	3.0/78
3c	Furyl	CH_3	Morpholinyl	164-166	10/44	2.0/84	3.5/75
3d	Indolyl	4-Br-C_6H_4	Morpholinyl	160-162	15/49	1.9/80	3.5/74
3e	Phenyl	Phenyl	Pyrrolidinyl	176-178[17]	14/40	1.5/92	2.5/82
3f	Piperonyl	4-BrC_6H_4	Pyrrolidinyl	198-200	10/50	1.6/90	2.6/80
3g	Furyl	CH_3	Pyrrolidinyl	170-172	13/42	2.0/88	3.2/75
3h	Indolyl	4-BrC_6H_4	Pyrrolidinyl	100-102	16/47	2.0/85	3.5/75
3i	Phenyl	Phenyl	Piperidinyl	163-165[17]	12/40	1.5/94	2.5/82
3j	Piperonyl	4-BrC_6H_4	Piperidinyl	126-128	13/52	1.6/93	2.6/85
3k	Furyl	CH_3	Piperidinyl	187-189	18/42	2.0/84	3.5/77
3l	Indolyl	4-BrC_6H_4	Piperidinyl	108-110	17/45	2.0/87	3.4/80

a = Time. b = Yield

Table 2. Spectroscopic data and elemental analysis of compounds **3a-l**

Compd. No.	IR (KBr) (ν/cm^{-1}) C=N	^{1}H NMR ($CDCl_3$, 60 MHz, δ ppm)	Elemental analysis (Calcd./%)		
			C	H	N
3a	1598	2.8 (t, 4H, CH_2OCH_2), 3.6 (t, 4H, CH_2NCH_2), 6.5-8.0 (m, 11H, Ar-H)	75.70 (75.69)	5.97 (5.99)	13.25 (13.24)
3b	1600	2.9 (t, 4H, CH_2OCH_2), 3.6 (t, 4H, CH_2NCH_2), 5.9 (s, 2H, CH_2), 6.9-8.1 (m, 8H, Ar-H)	57.27 (57.29)	4.09 (4.12)	9.55 (9.54)
3c	1595	2.3 (s, 3H, CH_3), 2.9 (t, 4H, CH_2OCH_2), 3.7 (t, 4H, CH_2NCH_2), 6.7-7.4 (m, 4H, furan and Ar-H)	63.67 (63.66)	6.18 (6.16)	17.12 (17.13)
3d	1595	3.0 (t, 4H, CH_2OCH_2), 3.8 (t, 4H, CH_2NCH_2), 6.6-7.5 (m, 11H, indole and Ar-H)	60.69 (60.70)	4.43 (4.40)	12.86 (12.87)
3e	1600	2.0 (t, 4H, 3',4'-CH_2), 3.7 (t, 4H, CH_2NCH_2), 6.9-8.2 (m, 11H, Ar-H)	79.71 (79.70)	6.38 (6.35)	13.92 (13.94)
3f	1610	2.0 (t, 4H, 3',4'-CH_2), 3.8 (t, 4H, CH_2NCH_2), 6.0 (s, 2H, CH_2), 7.0-8.2 (m, 8H, Ar-H)	59.43 (59.45)	4.29 (4.27)	9.91 (9.90)
3g	1599	1.8 (t, 4H, 3',4'-CH_2), 2.3 (s, 3H, CH_3), 3.7 (t, 4H, CH_2NCH_2), 6.5-7.3 (m, 11H, furan and Ar-H)	68.12 (68.10)	6.57 (6.59)	18.31 (18.32)
3h	1594	1.8 (t, 4H, 3',4'-CH_2), 3.8 (t, 4H, CH_2NCH_2), 6.5-8.0 (m, 11H, indole and Ar-H)	62.99 (63.01)	4.58 (4.57)	13.35 (13.36)
3i	1599	1.6 (m, 6H, 3',4',5'-CH_2), 2.9 (t, 4H, CH_2NCH_2), 7.3-8.2 (m, 8H, Ar-H)	80.00 (79.96)	6.70 (6.71)	13.33 (13.32)
3j	1595	1.6 (m, 6H, 3',4',5'-CH_2), 3.0 (t, 4H, CH_2NCH_2), 6.0 (s, 2H, CH_2), 7.3-8.3 (m, 8H, Ar-H)	60.27 (60.28)	4.62 (4.60)	9.59 (9.58)
3k	1598	1.7 (m, 6H, 3',4',5'-CH_2), 2.2 (s, 3H, CH_3), 3.2 (t, 4H, CH_2NCH_2), 6.6-7.3 (m, 4H, furan and Ar-H)	67.52 (67.51)	7.41 (7.40)	18.16 (18.17)
3l	1595	1.6 (m, 6H, 3',4',5'-CH_2), 3.2 (t, 4H, CH_2NCH_2), 6.6-7.9 (m, 11H, indole and Ar-H)	63.74 (63.75)	4.83 (4.80)	12.95 (12.93)

Method C: One Pot Solid Support Microwave (Basic Alumina). To the solution of chalcone **1** (0.02 mol), SBT (0.25 mol) and morpholine/piperidine/pyrollidine (0.04 mol) was added basic alumina (15 g) with stirring and air dried. Rest experimental procedure is same as described above in method B.

Conclusion

The proposed methodology provides an easier, facile, practically convenient and environmentally benign one pot synthesis of bioactive pyrimidines. The microwave assisted procedure is modified in such a way that one pot condensation is the best in view of the fact that the excess of base used in conventional/neutral alumina procedure is eliminated by using basic alumina. However, basic alumina further catalysed the reaction in comparison to neutral alumina in which the reaction time is further reduced with comparable yields and is the best solid support.

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