A FACILE ONE POT MICROWAVE- ASSISTED SOLID PHASE SYNTHESIS OF 2-AMINO-4, 6-DIARYL PYRIMIDINES AND THEIR ANTIBACTERIAL ACTIVITY

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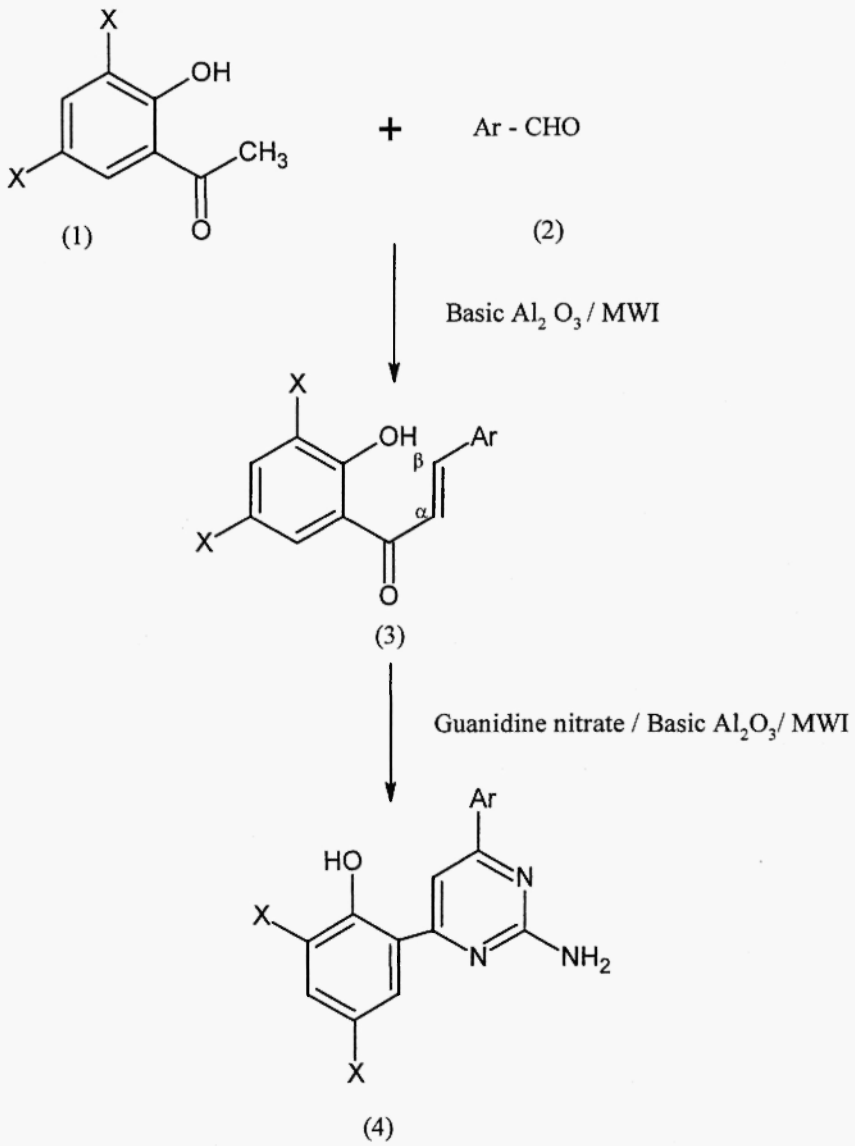
Abstract: An environmentally benign, manipulatively simple & rapid method for the synthesis of 2-amino-4, 6-diaryl pyrimidines (4a-f) from corresponding chalcones (3a-f) & guanidine nitrate using basic alumina under solvent free dry condition and microwave irradiation is described. Antibacterial activity of the synthesized compounds has also been described.

Introduction

Cleaner technology which combines the technological progress with environmental safety, is one of the key challenges of the millennium. Sustainability, eco-efficiency & green chemistry are new principles that is guiding the development of next generation of products and processes[1]. One of the thrust areas for achieving this target is to explore alternative reaction conditions and reaction media to accomplish the desired chemical transformation with minimized by-products or waste as well as eliminating the use of conventional organic solvents if possible. Among the important tools the use of microwave (MW) is very attractive alternative for chemical applications[2-5] and has become a widely accepted non-conventional energy source for performing organic synthesis[6-8]. Spectacular accelerations, higher yield under milder condition and higher product purities have all been reported. The effect of microwave [9] irradiation on a chemical reaction is very complex in nature & involves thermal (e.g. hot spots, super heating) and non-thermal (e.g. molecular mobility, field stabilization) effects. More experimentation, computational calculations & the development theories are still required. An important part of our effort towards ecofriendly synthesis is aimed at reduction of solvents. In this context, inorganic solid support have made a land mark as the reaction can be performed in dry media or solvent free conditions[10, 11]. Further the usage of solid support in conjunction with microwaves[12] leads to enhanced reaction rates, higher yields, high catalytic activity with the optimum utilization of energy and associated ease of manipulation.

Chalcones having a α,β–unsaturated carbonyl compound have been popular substrates for the generation of various heterocyclic compounds of therapeutic importance. The presence of enone functionality in chalcone moiety is the key factor for its biological activity as antimalarial[13], antileishmanial[14], anticancer[15, 16], anti-inflamatory[15, 16], antibacterial[16], antineoplastic[17] and diuretic[17] activities. Further the importance of pyrimidines & analogous compounds in pharmaceutical & biological field is well known[18].

In view of the biopotential of pyrimidines and the environmentally benign role of solvent less approach under microwaves (MW) and our ongoing programme towards green synthesis[19-23], we herein report a facile rapid one pot condensation of chalcones with guanidine nitrate in presence of basic alumina as solid support under microwave for the synthesis of 2-amino-4, 6-diaryl pyrimidines (4a-f) (Scheme-1)



3, 4a X = H, Ar = 4 - $Cl.C_6H_4$-

3, 4b X = H, Ar =3, 4, 5 -$OCH_3.C_6H_2$-

3, 4c X = H, Ar = 4 -$N(CH_3)_2.C_6H_4$ -

3, 4d X = H, Ar = 2 -Furyl

3, 4e X = I, Ar = 4 - $Cl.C_6H_4$-

3, 4f X = I, Ar = 2 -Furyl

Scheme -1

Experimental

Material and Methods

All melting points were determined in open capillaries on electrically heated metal blocks and are uncorrected. IR spectra (ν_{max} in cm^{-1}, KBr) were recorded on a Perkin Elmer 16pc (FTIR) spectrophotometer. Mass spectra were taken on a Jeol D-300 (EI) & VG-70S mass spectrometer and ^{1}H-NMR spectra in $CDCl_3$ and acetone d_6 on a BrukerDRX-300 (300MHz, FTNMR) spectrometer (δ, ppm downfield from TMS). The reactions were carried out in unmodified microwave oven (Kenstar, Output energy 1200 W, frequency 2450MHz model no. M69706). Microwave assisted synthesis of chalcones have been carried out by reported procedure [22]

General Procedure for the Synthesis of 2-amino-4, 6-diaryl pyrimidines (4a-f):

(A) Conventional Method:

A mixture of chalcone (0.01 mole) and guanidine nitrate (0.01 mole) was dissolved in ethanol (50 ml). Aqueous sodium hydroxide solution (40%, 2 ml) was added and the reaction mixture was refluxed. Further installments of sodium hydroxide (3 x 2 ml) were added during 3 hours, to the refluxing solution. The progress of reaction was monitored by TLC, using benzene: ethylacetate (9: 1 v/v) as eluent. The resultant mixture was cooled at room temperature and diluted with water. The separated product was recrystallised from appropriate solvent to afforded analytical samples of compound (4 a-f).

(B) Solvent Free Microwave Assisted Method:

To a mixture of chalcone (0.01 mole) and guanidine nitrate (0.01 mole) in ethanol (5 ml), basic alumina (4 gm) was added. This was grinded in a pestle and mortar till homogeneous powder was obtained. It was transferred in to 100 ml borosil beaker and adsorbed material was air dried. The solid matrix so obtained was irradiated for 4-8 min. in a microwave oven at 50% microwave power (600 W). On completion of the reaction (TLC examination), the mixture was cooled at room temperature and then product was extracted with ethanol (2 X 20 m L). Recovering the solvent under reduced pressure gave product which on recrystallisation from ethanol afforded analytical samples of (4 a-f). The support was reused after simple washing with ether.

4a. IR: 3451, 3215 (NH_2), 3030 (Ar-H), 1657(C=N) 1545 (C=C), 800, 710 (substituted phenyl).
^{1}H NMR: 5.2 (s, 2H, NH_2), 7.2 (s, H, OH), 7.32 (s, 1H, H_5 of pyrimidine ring), 7.4-8.0 (m, 12H, Ar- H)
MS: m/z (%) 297(10) (M^+), 261 (35), 258 (100), 241 (18), 230 (4), 212 (4), 205 (5), 195 (5), 186 (2), 176 (5), 165 (27), 147 (98), 138 (30), 128 (83), 111 (13), 101 (38), 197 (14), 93 (24), 82 (8), 75 (22).

4b. IR: 3410, 3204 (NH_2), 3062 (Ar-H), 1668 (C=N), 1503 (C=C), 823, 758 (substituted phenyl).
^{1}H NMR: 3.7-3.8 (m, 9H, 3 X OCH_3), 3.9 (s, 2H, NH_2), 7.2 (s, 1H, OH), 7.41 (s, 1H, H_5 of pyrimidine ring), 7.5-7.9 (Complex, 12H, Ar- H)
MS: m/z (%) 353 (2) (M^+), 314 (100), 299 (14), 283 (20), 271 (8), 256 (2), 239 (3), 221 (3), 211 (4), 194 (42), 101 (58), 168 (10), 147 (15), 133 (6), 121 (24), 105 (6), 93 (8), 77 (7).

4c. IR: 3434, 3350 (NH_2), 3045 (Ar-H), 1615 (C=N), 1521 (C=C), 812, 764 (substituted phenyl).
^{1}H NMR: 3.1 (s, 2H, NH_2), 7.2 (s, 1H, OH), 7.3 (s, 1H, H_5 of pyrimidine ring), 7.4 -7.8 (m, 12H, Ar- H)
MS: m/z (%) 305 (5) (M^+), 285 (1), 267 (76), 250 (10), 238 (1), 223 (3), 213 (1), 205 (1), 194 (1), 174 (12), 147 (100), 134 (49), 121 (15), 102 (7), 93 (7), 77 (8).

4d. IR: 3426, 3280 (NH_2), 3027 (Ar-H), 1639 (C=N), 1543 (C=C), 720, 671 (substituted phenyl).

4e. IR: 3408, 3275 (NH_2), 3055 (Ar-H), 1657 (C=N), 1525 (C=C), 870, 620 (substituted phenyl).
MS: m/z (%) 549 (11) (M^+), 510 (70), 493 (1), 475 (1), 459 (1), 446 (2), 399 (5), 384 (3), 372 (100), 344 (6), 316 (3), 284 (1), 245 (21), 217 (6), 189 (16), 165 (8), 138 (15), 125 (5), 103 (11), 83 (7).

4f. IR: 3451, 3350 (NH_2), 3030 (Ar-H), 1639 (C=N), 1545 (C=C), 740, 672 (substituted phenyl).
MS: m/z (%) 479 (21) (M^+), 466 (100), 446 (3), 423 (1), 409 (4), 398 (1), 372 (48), 344 (4), 317 (1), 299 (1), 282 (1), 256 (4), 245 (6), 233 (4), 218 (8), 189 (4), 169 (1), 155 (6), 121 (24), 94 (56), 81 (12).
Table-1: Characterization data of 2-amino-4, 6-diaryl pyrimidines (4a-f).

Table 1

Compd†	m.p. (°C)	Colour	Reaction time		Yield (%)	
			Microwave (min.)	Classical (hrs.)	*Microwave*	Classical
4a	204	Pale yellow	4	9	91	50
4b	200	Yellow	5	10	82	57
4c	164	Light brown	4	9	75	51
4d	208	Brown	4	8	84	52
4e	189	Pale yellow	6	11	77	53
4f	205	Brown	5	9	80	51

† All the compounds gave satisfactory elemental analyses

Results and Discussions

The synthesis of pyrimidines has been carried out in our laboratories classically [24,25] or through microwave assisted reactions[26, 27] in presence of solvent. However, there has been noticeable interest in synthetic manipulation of pyrimidines and thus developing dry media technique for their ecofriendly synthesis.

The synthesis of chalcone has been carried out using acetophenones and aromatic aldehyde in presence of basic alumina under solvent free conditions[22]. In order to develop an environmentally benign synthetic procedure utilizing microwave irradiation under solvent free conditions, chalcones on treatment with guanidine nitrate in presence of basic alumina under microwave irradiation resulted 2-amino-4, 6-diaryl pyrimidines (4 a-f). The structure of compounds was confirmed on the basis of spectroscopic data & elemental analysis. The classical procedure is tedious, time consuming, gives low yield and requires an appreciable amount of solvent as well as base. The present solvent free dry media microwave irradiation one pot synthesis minimized the yield loss, energy loss and time loss. Basic alumina in the form of solid support as both catalyst as well as energy transfer media. A comparative study in terms of yield and reaction time is summarized in table 1.

Antibacterial Activity

The title compound were screened for their antibacterial activity using paper disc method and tested against gram+ve organisms: *Staphylococcus aureus*, *Streptococcus fecalis* and gram–ve organisms: *Escherichia coli*, *Proteus mirabilis*, using DMF as solvent at 200 µg/ml. concentration. The zone of inhibition was recorded after 18 hrs. of incubation at 37°C and the results were compared with that of standard drugs Amicacin and Tobramycin.

Amongst the 2- amino-4, 6-diaryl pyrimidines 4 e showed excellent activity against *S. fecalis*. 4c, d & f showed moderate activity against *S. aureus, E. coli & P. mirabilis,* whereas other compounds showed low to moderate activity.

Conclusion

The present methodology provides a convenient, facile, easy, economic and environmentally benign one-pot synthesis of bioactive pyrimidines. Use of basic alumina as solid support eliminated the use of toxic solvents & bases used in classical & microwave irradiation reaction in presence of solvent, it catalyzed the reaction reducing the reaction time and improving the yields.

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