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Microwave assisted synthesis of N-substituted Pyrimidines Using $AlCl_3$ as catalyst and their antimicrobial Activities

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ABSTRACT

*The three component condensation of an aldehyde, Substituted urea and 3-oxobutanamide in presence of catalytic amount of $AlCl_3$ is disclosed for the synthesis of pyrimidine under solvent free microwave irradiation conditions. High yields are achieved even 1 g scale, while reaction times are considerably shortened compare to conventional method The antimicrobial activities of the pyrimidines (**1**$_{a-t}$) are compared with those of known chosen standard drugs, viz. ampicillin, chloramphenicol, ciprofloxacin, norfloxacin and griseofulvin.*

Keywords: N-substituted, pyrimidines, $AlCl_3$ catalyst, microwave irradiation, antimicrobial activity.

INTRODUCTION

Development of simple, safe, ecofriendly and economic synthetic routs for widely used organic compounds from the readily available reagents are one of the major challenges in organic synthesis pyrimidines derivatives are such type of organic compounds which belong to an important class with significant therapeutic and medicinal properties[1], some of which have antiviral, antitumor, antibacterial and anti-inflammatory activity[2-6]. Servel marine alkaloids having the pyrimidine core unit are showing interesting biological activities[7]such as calcium channel blockers[8], antihypertensive agents[9] and adrenoreceptor antagonist[10]. The structurally rather simple pyrimidine monastrol specifically inhibits the mitotic kinesin Eg-5 motor protein and can be considered as a new lead for the development of anticancer drugs[11]. The batzelladine alkaloids containing the pyrimidine core unit inhibit the binding of HIV envelopprotein gp-120 to human CD_4 cells and therefore, are potential new lead for AIDS therapy[12]. Therefore, the synthesis of compound with pyrimidines core unit has gained much importance. Although many synthetic methods have been developed[13-16], most of these methods suffer from one or the other disadvantages such as long reaction time, harsh reaction

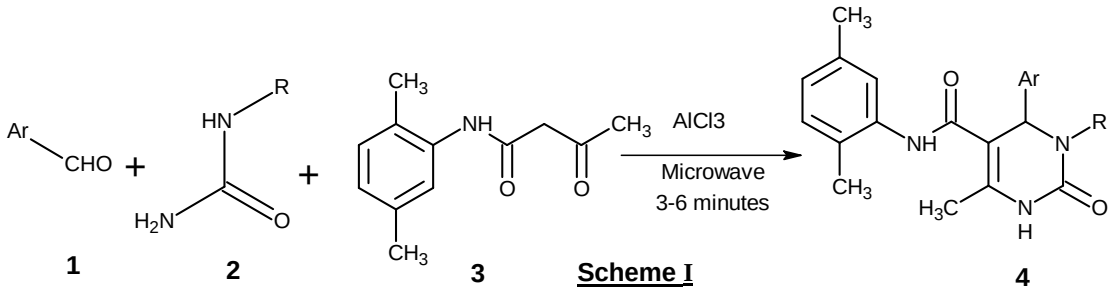
conditions, and the use of stoichiometric reagents or of toxic and inflammable solvents, difficult work-ups or low yields of product. Hence it is desirable to develop an easy, safe and economical procedure, avoiding strong acids, hazardous or expensive reagents and other corrosive media. In this regard $AlCl_3$ is use as a catalyst [17] for the synthesis of pyrimidines as it participates as a catalyst in important biological processes.

In continuation of our interest to develop new methodologies in organic reaction , in this communication, a simple and effective Biginelli reaction that produce high yields of said pyrimidines in short reaction time is disclosed under microwave irradiation using a catalytic amount of $AlCl_3$

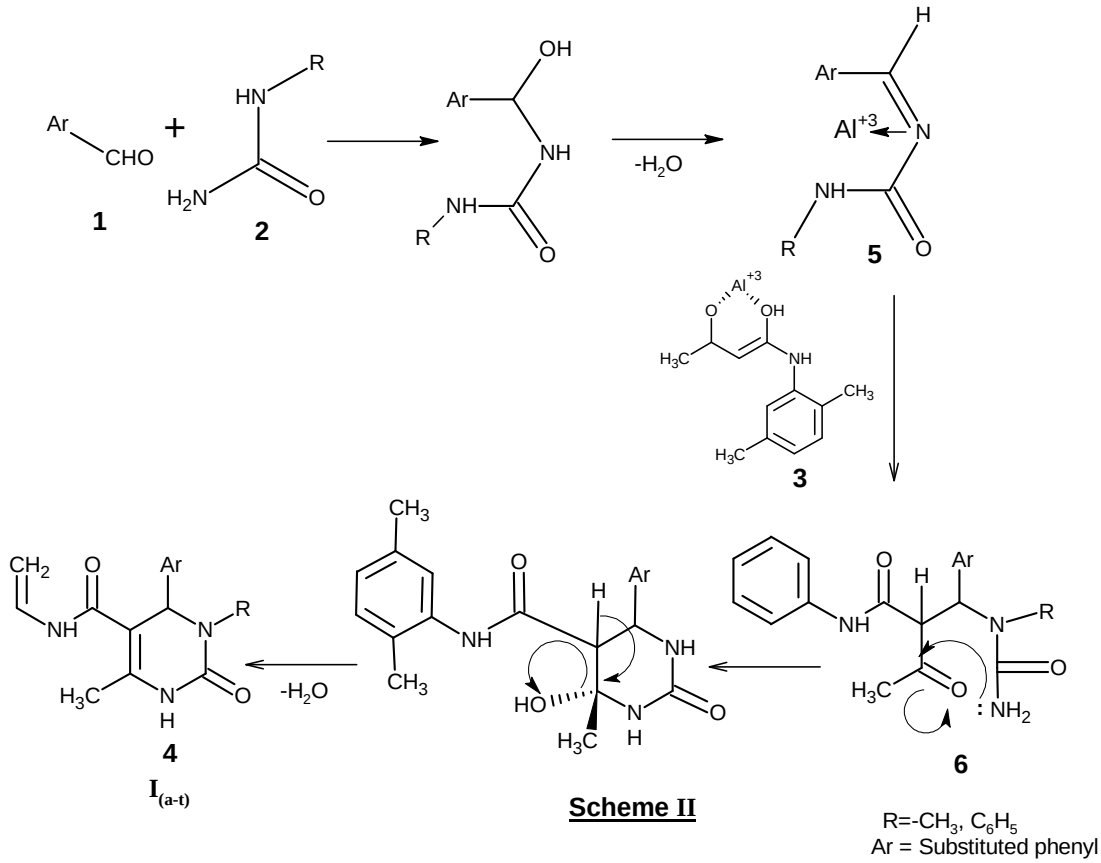
In order to explore the catalytic activity of $AlCl_3$ and also the effect of microwave irradiation of the Biginelli reaction, a mixture of *N*-(2,5-dimethylphenyl)-3-oxo- butanamide, 4-chloro benzaldehyde, N-methylurea (1:1:2 molar ratio) and a catalytic amount of $AlCl_3$ in DMF as solvent was irradiated microwave irradiation at 360 W for 3.5 minutes, which gave **(I_e)** in an excellent yield. Under similar conditions different substituted aldehyde were converted to their corresponding pyrimidines (Scheme I) in good yields and the result are summarized in Table I and TableII.

The important feature of microwave/ $AlCl_3$ mediated Biginelli protocol are In many cases the product obtained is at least 95% purity, high yields, survival of variety of functional groups such as mehoxy, halide and nitro. It presumed that the reaction may proceed through imine intermediate formed from the aldehyde and substituted urea and stabilized by the aluminium ion, followed by the addition of enolate of the di-keto and cyclodehydration of 6 to afford the pyrimidines (Scheme II) and then all the components were screened for their *in vitro* biological activity, such as antimicrobial activity towards gram positive and gram negative bacterial strains and antifungal activity at different concentrations. The biological activities of the synthesized components are compared with standard drugs, such as ampicillin, chloramphenicol , ciprofloxacin, norfloxacin and griseofulvin. The structures of the synthesized compounds are supported by elemental analysis, as well as FTIR, PMR and mass spectral data.

REACTION SCHEME



Scheme I



MATERIALS AND METHODS

Melting points were determined routinely in an open capillary tube and are uncorrected. Formation of compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and the spots were located by iodine. Ascientific Qpro-M microwave oven was used and the irradiation time varied by 3-5 mins. The PMR spectra were recorded in CDCl3 on a Brucker DRX-300 at 300 MHz. The IR spectra were recorded on a Shimadzu-8400 FT-IR spectrometer in KBr (λ in cm-1).Elemental analyses of the newly synthesized compounds were carried out on a Carlo Erba 1108 analyzer and results within the range of the theoretical value were found. Mass spectra were scanned on a GCMS-QP200 instrument. A scientific Qpro-M microwave oven was used for the rapid and eco-friendly synthesis.

Preparation of N-(2,5-dimethylphenyl)-3,6-dimethyl/3-phenyl-6-methyl-2-oxo-4-(Substituted phenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide ($1_{a\text{-}t}$):

A mixture of *N*-(2,5-dimethylphenyl)-3-oxobutanamide (0.01 M), Aldehyde (0.01 M) and N-methyl urea / N-phenyl urea (0.02 M) in DMF (10.0 ml) and catalytic amount of $AlCl_3$ were exposed to microwave irradiation for the indicated time(See Table I). On completion of reaction, indicated by TLC, The mixture was cooled and quenched with water. The solid separated was filtered and recrystallized from DMF to afford pure product in good yields. The other compounds($I_{a\text{-}t}$) were prepared by similar procedure and physical data are recorded in Table II.

Antimicrobial activity

Antimicrobial activity testing was carried out using the cup-plate method,7 which is described below.

Antibacterial activity:

Streptococcus pyogenes MTCC-442, *Streptococcus aureus* MTCC-96 and *Bacillus subtilis* MTCC-441 (Gram positive bacteria) were grown in nutrient broth and *E. coli* MTCC-443 (Gram negative bacterium) in Peptone water (PW, 1%bacteriological peptone and 0.5%NaCl) for 24 h; this gave the optimum growth of the test bacteria. Each purified compound was dissolved in dimethylformamide (DMF), which had been sterilized by filtration through a sintered glass filter, and stored at 4 °C. Each agent was then added tomolten nutrient agar in the following concentrations (λg/ml): 0 (control), 5, 10, 25, 50, 100, 200,500 and poured into a sterile petri dish. The pH of the media was maintained at 7.2 to 7.4. The inoculum consisted of an overnight growth broth culture of a bacterium diluted in such a manner that a 2 mm (internal diameter) loopful of the culture contained 105 colony- forming units (CFU). These were then spot inoculated onto nutrient agar plates containing increasing amounts of a compound, incubated at 37 °C for up to 24 h to determine the minimum inhibitory concentration (MIC), [18,19] which were recorded as zones of inhibition in mm for the bacteria.

Antifungal activity:

Candida albicans MTCC-227 and *Aspergillus niger* MTCC-282 were employed for the testing of the antifungal activity using the cup-plate method. The culture was maintained on Sabouraud's agar for 72 h; this gave the optimum growth of the test fungal spores. Each purified compound was dissolved in dimethylformamide, sterilized by filtration using a sintered glass filter and stored. Each agent was then added to Sabouraud's agar in the following concentrations (λg/ml): 0 (control), 5, 10, 25, 50, 100, 200, 500 and poured into a sterile petri dish. The inoculum consisted of an overnight-grown broth culture of a fungus diluted in such a manner that a 2 mm (internal diameter) loopful of the culture contain 105 colony-forming units (CFU).These were then spot inoculated onto Sabouraud's agar plates containing increasing amounts of the compound and then incubated at 37 °C for up to 48 h to determine the minimum inhibitory concentration (MIC)[18,19].

RESULTS AND DISCUSSION

The physical data for compound **Ie** are as follows: Yield 95 %, m.p. 221 °C. Anal. Calcd. for $C_{21}H_{22}ClN_3O_2$; Required: C, 65.79; H, 5.74; N, 10.96 % Found: C, 65.83; H, 5.80; N, 11.00 %. IR (KBr) λ max cm–1: 3396 (N–H str.), 3036 (C–H str.), 2924 (C–H str., asym.), 2860 (C–H str., sym.), 1617 (N–N def.), 1590 (N–H def.), 1545 (C=N), 1465 (C–H def., asym.), 1432 (–CH_2 bending), 1378 (–CH_3 bending), 1367 (C–H def., sym.), 1327 (C–N str.), 1175 (C–H i.p. def.), 1125 (C–N str.), 688 (C–H o.o.p.def.). PMR _ /ppm (TFA): 1.80 (*s*, 3H, – CH_3), 2.364 (*s* 3H, –$2CH_3$), 1.673 (*m*, 2H, –CH_2), 6.526–7.356 (*m*, 7H, Ar-H), 9.526(s,1H, NH). Mass spectrum of the compound exhibited a molecular ion peak at *m/z* 382 (M+). The physical data of the other prepared compounds (I_{a-t}) are given in Table II.

Antimicrobial activity

The MIC values of the test solutions are recorded in Tables III which is given in zones of inhibition in mm for the bacteria and fungi.

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Table I: $AlCl_3$ catalyzed synthesis of N-Substituted pyrimidines (I_{a-t})

mp. No	Ar	R	Reaction Time (min)	Yield (%)
I_a	4-NO_2-C_6H_4	-CH_3	3.5	93
I_b	4-OCH_3-C_6H_4	-CH_3	3.0	94
I_c	4-OH-C_6H_4	-CH_3	3.5	92
I_d	4-F-C_6H_4	-CH_3	3.0	93
I_e	4-Cl-C_6H_4	-CH_3	3.5	95
I_f	3-NO_2-C_6H_4	-CH_3	3.5	87
I_g	3-Cl-C_6H_4	-CH_3	4.0	86
I_h	2-NO_2-C_6H_4	-CH_3	4.5	79
I_i	2-Cl-C_6H_4	-CH_3	4.5	78
I_j	2-OH-C_6H_4	-CH_3	4.5	76
I_k	4-NO_2-C_6H_4	-C_6H_5	3.0	92
I_l	4-OCH_3-C_6H_4	-C_6H_5	3.5	93
I_m	4-OH-C_6H_4	-C_6H_5	3.5	90
I_n	4-F-C_6H_4	-C_6H_5	3.5	91
I_o	4-Cl-C_6H_4	-C_6H_5	3.0	92
I_p	3-NO_2-C_6H_4	-C_6H_5	4.5	88
I_q	3-Cl-C_6H_4	-C_6H_5	5.0	85
I_r	2-NO_2-C_6H_4	-C_6H_5	5.0	77
I_s	2-Cl-C_6H_4	-C_6H_5	5.0	76
I_t	2-OH-C_6H_4	-C_6H_5	5.5	73

Table II: Physical constant of N-Substituted pyrimidines (I_{a-t})

Comp. No	Ar	R	Molecular Formula	M.W.	Yield %	M.P. ^{0}C	R_f Value	% of Nitrogen Calcd.	% of Nitrogen Found
I_a	4-NO_2-C_6H_4	-CH_3	$C_{21}H_{22}N_4O_4$	394	93	206	0.52	14.21	14.25
I_b	4-OCH_3-C_6H_4	-CH_3	$C_{22}H_{25}N_3O_3$	379	94	209	0.53	11.08	11.12
I_c	4-OH-C_6H_4	-CH_3	$C_{21}H_{23}N_3O_3$	365	92	211	0.50	11.50	11.54
I_d	4-F-C_6H_4	-CH_3	$C_{21}H_{22}FN_3O_2$	367	93	199	0.51	11.44	11.49
I_e	4-Cl-C_6H_4	-CH_3	$C_{21}H_{22}ClN_3O_2$	383	95	221	0.49	10.96	11.00
I_f	3-NO_2-C_6H_4	-CH_3	$C_{21}H_{22}N_4O_4$	394	87	219	0.54	14.21	14.25
I_g	3-Cl-C_6H_4	-CH_3	$C_{21}H_{22}ClN_3O_2$	383	86	215	0.60	10.96	11.00
I_h	2-NO_2-C_6H_4	-CH_3	$C_{21}H_{22}N_4O_4$	394	79	210	0.62	14.21	14.25
I_i	2-Cl-C_6H_4	-CH_3	$C_{21}H_{22}ClN_3O_2$	383	78	213	0.58	10.96	11.00
I_j	2-OH-C_6H_4	-CH_3	$C_{21}H_{23}N_3O_3$	365	76	218	0.46	11.50	11.54
I_k	4-NO_2-C_6H_4	-C_6H_5	$C_{26}H_{24}N_4O_4$	456	92	231	0.56	12.28	12.35
I_l	4-OCH_3-C_6H_4	-C_6H_5	$C_{27}H_{27}N_3O_3$	441	93	225	0.51	09.52	09.57
I_m	4-OH-C_6H_4	-C_6H_5	$C_{26}H_{25}N_3O_3$	427	90	228	0.54	09.83	09.88
I_n	4-F-C_6H_4	-C_6H_5	$C_{26}H_{24}FN_3O_2$	429	91	235	0.62	09.79	09.84
I_o	4-Cl-C_6H_4	-C_6H_5	$C_{26}H_{24}ClN_3O_2$	445	92	268	0.52	09.43	09.48
I_p	3-NO_2-C_6H_4	-C_6H_5	$C_{26}H_{24}N_4O_4$	456	88	258	0.63	12.28	12.35
I_q	3-Cl-C_6H_4	-C_6H_5	$C_{26}H_{24}ClN_3O_2$	456	85	241	0.68	09.43	09.48
I_r	2-NO_2-C_6H_4	-C_6H_5	$C_{26}H_{24}N_4O_4$	456	77	269	0.60	12.28	12.35
I_s	2-Cl-C_6H_4	-C_6H_5	$C_{26}H_{24}ClN_3O_2$	456	76	200	0.64	09.43	09.48
I_t	2-OH-C_6H_4	-C_6H_5	$C_{26}H_{25}N_3O_3$	427	73	271	0.49	09.43	09.48

Table II: Physical constant of N-Substituted pyrimidines (I_{a-t}):

Comp. No.	Ar	R	Antibactrial activity (Zones of inhibition in m.m.)									
			S.pyogens MTCC-442					S.aureus MTCC-96				
			5	25	50	100	250	5	25	50	100	250
I_a	4-NO_2-C_6H_4	-CH_3	-	13	15	19	21	-	13	15	18	20
I_b	4-OCH_3-C_6H_4	-CH_3	-	13	16	17	19	-	13	16	19	20
I_c	4-OH-C_6H_4	-CH_3	-	12	13	14	18	-	13	14	18	19
I_d	4-F-C_6H_4	-CH_3	-	14	16	19	21	-	15	17	20	22
I_e	4-Cl-C_6H_4	-CH_3	-	11	15	17	18	-	11	14	17	19
I_f	3-NO_2-C_6H_4	-CH_3	-	12	16	17	19	-	14	15	18	19
I_g	3-Cl-C_6H_4	-CH_3	-	13	12	15	16	-	13	14	16	18
I_h	2-NO_2-C_6H_4	-CH_3	-	14	13	16	21	-	13	14	19	21
I_i	2-Cl-C_6H_4	-CH_3	-	12	15	18	19	-	11	14	16	20
I_j	2-OH-C_6H_4	-CH_3	-	11	14	15	17	-	11	12	16	19
I_k	4-NO_2-C_6H_4	-C_6H_5	-	13	16	17	20					
I_l	4-OCH_3-C_6H_4	-C_6H_5	-	13	14	15	17	-	13	15	17	19
I_m	4-OH-C_6H_4	-C_6H_5	-	12	12	16	18	-	12	16	17	18
I_n	4-F-C_6H_4	-C_6H_5	-	15	16	19	22	-	15	15	20	22
I_o	4-Cl-C_6H_4	-C_6H_5	-	12	12	16	17	-	11	14	18	19
I_p	3-NO_2-C_6H_4	-C_6H_5	-	14	16	17	20	-	11	14	19	20
I_q	3-Cl-C_6H_4	-C_6H_5	-	12	12	15	17	-	13	16	18	20
I_r	2-NO_2-C_6H_4	-C_6H_5	-	15	15	18	22	-	13	14	18	21
I_s	2-Cl-C_6H_4	-C_6H_5	-	12	12	16	18	-	13	14	19	20
I_t	2-OH-C_6H_4	-C_6H_5	-	11	11	14	17	-	11	13	16	18

Comparative activity of (I_{a-t}) with known chosen standard drugs Standard drug	Antibacterial activity									
Amplicilline	11	14	16	18	19	10	13	14	16	18
Chloramphenicol	10	13	19	20	20	12	14	19	20	21
Ciprofloxacin	16	19	21	21	22	17	19	21	22	21
Norfloxacin	18	19	20	21	21	19	22	25	26	28

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