December 2007 Volume 3 Issue 4

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 3(4), 2007 [237-241]

Facile synthesis of chloro substituted chalcones using claisen-schimdt condensation and its aminopyrimidine and acetylpyrazoline derivatives

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Received: 8th December, 2007 ; Accepted: 13th December, 2007

ABSTRACT

Some *s*-triazine based chalcones **(6a-e)** have been prepared starting from ketone **(5)** and different aromatic aldehydes. These chalcones further on cyclocondensation with guanidine nitrate and hydrazine hydrate in presence of glacial acetic acid give aminopyrimidines **(7a-e)** and pyrazolines **(8a-e)** respectively. The structure of newly synthesized compounds have been characterized on the basis of elemental analysis, IR and ^{1}H NMR spectra. All the synthesized compounds have been screened for their antibacterial activity.

KEYWORDS

Chalcones;
Aminopyrimidines;
Acetylpyrazolines;
Antibacterial activity.

INTRODUCTION

Biological activities of several heterocyclic analogues of chalcones have reported in the literature[1]. Presence of enone function in the chalcone molecule confers antibiotic activity[2-4]. Some substituted chalcones and their derivatives including some of their heterocyclic analogues have been reported to possess some interesting biological properties[5]. They are also reported to exhibit inhibitory action on several enzymes[6] and fungi[7]. It also exhibits antitubercular[8], antimicrobial[9] and anticancer[10] activities.

Nitrogen containing heterocyclic compounds like pyrazolines have been received considerable attention in recent years due to their biological and physiological activities. Among several pyrazoline derivatives, acetyl pyrazoline exhibit anticancer[11], anti-inflammatory[12], antitubercular[13] and antibacterial[14] activities. Aminopy rimidines exhibit antibacterial[15], anticancer[16] and antitubercular[17] activities.

In continuation of our work on chalcones and their derivatives[18-19], we have undertaken the systhesis of chalcones **(6a-e)** by the cyclocondensation of 2,4-bis-(4'-chlorophenyl amino)-6-(4'-acetylphenylamino)-*s*-triazine **(5)** with different aromatic aldehydes. Compound **(5)** is prepared by the condensation of cyanuric chloride **(1)** and 4-chloroaniline **(2)** at 0-5°C to form **(3)**, which reacts with 4-chloroaniline at room temperature to form **(4)** which is further treated with 4-aminoaceto phenone to form compound **(5)**. Chalcones **(6a-e)** are cyclised with guanidine nitrate and hydrazine hydrate in presence of glacial aceticacid to form 2,4-bis-(4'-chlorophenylamino)-6-[4'-{2''-amino-6''-(phenyl/ substitutedphenyl)-pyrimidine-4''-yl}phenylamino]-*s*-triazine**(7a-e)** and 2,4-bis-(4'-chlorophenylamino)-6-[4'-{1''-acetyl-5''-(phenyl/ substitutdphenyl)-2''-pyrazoline-3''-yl}phenylamino]-*s*-triazine **8(a-e)** respectively. The structures of newly synthesized com-

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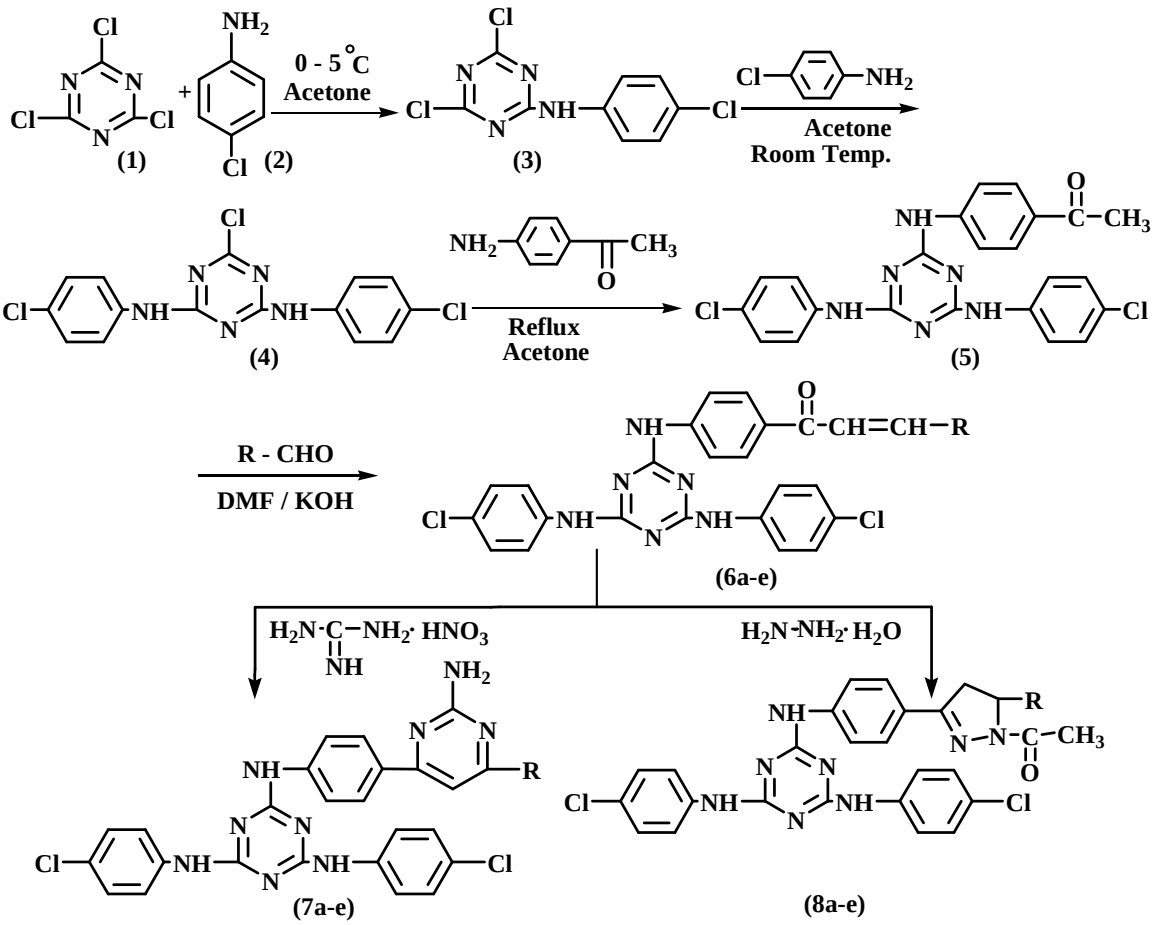

SCHEME 1

pounds have been characterized on the basis of elemental analysis, IR and ^{1}H NMR spectra.

Antibacterial activity

All the synthesized compounds were screened for their antibacterial activity by using agar diffusion method [20] against *S.aureus* (MTCC 96), *B.subtilis* (MTCC 441) Gram positive and *E.coli*(MTCC 443), *S.paratyphi-B*(MTCC 733) Gram negative bacteria in nutrient agar medium. The sterilized agar media [2.4 % (w/v) agar-agar, 5%(w/v) NaCl, 3%(w/v) peptone, pH(6.8 to 7.0)] was poured into petridishes and allowed to solidify. On the surface of the media microbial suspension was spread over the agar plates to solidify. A stainless steel cylinder(pre-sterilized) was used to bore the cavities. All the synthesized compounds (100µg/ml) in DMF were placed serially in the cavities, with the help of micropipette. It is then allowed to diffuse for 10 minutes in a refrigerator. The plates were incubated at 37°C for 24 hours. After incubation the diameter of zone of inhibition was measured in mm. Under similar conditions controlled experiment was carried out by using Ciprofloxacin as standard drugs for comparison.

EXPERIMENTAL

All the melting points were determined in an open capillary and are uncorrected. The IR spectra were recorded on Perkin-Elmer 237 spectrophotometer.^{1}H NMR spectra on a Brucer Avance DPX 300MHz spectrometer with $CDCl_3$ as a solvent, using TMS as internal reference. Purity of the compounds were checked on TLC using silica gel-G.

Preparation of 2-(4'-chlorophenylamino)-4,6-dichloro-*s*-triazine (3)

4-Chloroaniline **(2)** (0.01 mole) was added slowly to cyanuric chloride **(1)** (0.01mole) in acetone (30ml) with constant stirring for 4 hours at 0-5ºC. Sodium carbonate solution was added to neutralize HCl evolved

during the reaction. Finally the content was poured into crushed ice. The solid separated out was filtered, washed with water and recrystallised from alcohol to give **(3)**.
Yeild 94%; m.p. 238°C.

Preparation of 2,4-bis-(4'-chlorophenylamino)-6-chloro-*s*-triazine (4)

4-Chloroaniline (0.01mole) was added slowly to 2-(4'-chlorophenylamino)-4,6-dichloro-*s*-triazine **(3)** (0.01mole) in acetone (35ml) with constant stirring for 6-hours at room temperature. Sodium carbonate solution was added to neutralize HCl evolved during the reaction. Finally the content was poured into crushed ice. The solid separated out was filtered, washed with water and recrystallised from alcohol to give **(4)**.
Yield 87%; m.p. 212°C; IR(KBr, cm^{-1}): 813(C-N, *s*-triazine), 770(C-Cl); ^1H NMR($CDCl_3$): δ 7.00 to 7.75 (m, 8 Ar-H and 2NH). Anal.Calcd. for $C_{15}H_{10}N_5Cl_3$: C,49.11; H,2.73; N,19.10. Found: C,49.13; H,2.70; N,19.12.

Preparation of 2,4-bis-(4'-chlorophenylamino)-6-(4'-acetylphenylamino)-s-triazine (5)

4-Aminoacetophenone(0.01mole) and 2,4-bis-(4'-chlorophenylamino)-6-chloro-*s*-triazine **(4)** (0.01mole) were dissolved in acetone(40ml). The reaction mixture was refluxed for 6 hours. Periodically sodium carbonate solution was added to neutralize HCl evolved during the reaction. Finally the reaction mixture was cooled and the content was poured into crushed ice. The solid separated out was filtered, washed with water and recrystallised from alcohol to give **(5)**.
Yield 82%; m.p. 195°C; IR(KBr, cm^{-1}): 1662(C=O), 818(C-N, *s*-triazine), 773(C-Cl); ^1H NMR($CDCl_3$): δ 2.54(s, 3H, $-COCH_3$), δ 7.26 to 8.41(m, 12 Ar-H and 3NH). Anal.Calcd. for $C_{23}H_{18}N_6OCl_2$: C,59.35; H,3.87; N,18.06. Found: C,59.36; H,3.85; N,18.09.

Preparation of 2,4-bis-(4'-chlorophenylamino)-6-[4'-{3''-(2'''-methoxyphenyl)-2''-propenon-1''-yl}phenylamino]-*s*-triazine (6e)

2,4-Bis-(4'-chlorophenylamino)-6-(4'-acetyl phenylamino)-*s*-triazine **(5)** (0.01mole) was dissolved in DMF(30ml) and 40% KOH (3-4 drops) in distilled water was added to it. Then 2-methoxy benzaldehyde (0.01mole) was added with constant stirring at room temperature. After 24 hours the reaction mixture was poured into crushed ice and neutralize with HCl. The product separated out was filtered, washed with water and recrystllised from alcohol to give **(6e)**.
Yield 69%; m.p. 148°C; IR(KBr, cm^{-1}):1658(C=O), 1022 (C-O-C), 815(C-N, s-triazine), 726(C-Cl); ^1H NMR($CDCl_3$): δ3.70(s, 3H, o-OCH_3), δ7.33(d, 1H, -CO-CH=), δ7.10 to 7.81(m, 16 Ar-H and 3 NH), δ8.05(d, 1H, Ar-CH=). Anal. Calcd. for $C_{31}H_{24}N_6O_2Cl_2$: C, 63.81; H,4.12; N, 14.41. Found: C, 63.82; H,4.15; N, 14.39.

Preparation of 2,4-bis-(4'-chlorophenylamino)-6-[4'-{2''-amino-6''-(2'''-methoxyphenyl)-pyrimidine-4''-yl}phenylamino]-*s*-triazine (7e)

A mixture of 2,4-bis-(4'-chlorophenylamino)-6-[4'-{3''-(2'''-methoxyphenyl)-2''-propenon-1''-yl}-phenylamino]-*s*-triazine **(6e)** (0.01mole) in 25ml dioxane, guanidine nitrate (0.01mole) and 40% KOH in distilled water (2ml) was refluxed for 10 hours. Then the reaction mixture was cooled and poured into crushed ice. The product separated out was filtered, washed with water and recrystallised from alcohol to give **(7e)**.
Yield 65%; m.p. 138°C; IR(KBr, cm^{-1}): 3378($-NH_2$), 1619 (C=N, pyrimidine moiety), 1018(C-O-C), 813 (C-N, *s*-triazine), 767(C-Cl); ^1H NMR($CDCl_3$): δ 3.74 (s, 3H, o-OCH_3), δ5.18 (s, 2H, $-NH_2$), 7.0 to 8.12(m, 17 Ar-H and 3NH). Anal. Calcd. for $C_{32}H_{25}N_9OCl_2$: C,61.74; H,4.02; N,20.26. Found: C,61.76; H,4.05; N,20.24.

Preparation of 2,4-bis-(4'-chlorophenylamino)-6-[4'-{1''-acetyl-5''-(2'''-methoxyphenyl)-2''-pyrazoline-3''-yl}-phenylamino]-*s*-triazine (8e)

A mixture of 2,4-bis-(4'-chlorophenylamino)-6-[4'-{3''-(2'''-methoxyphenyl)-2''-propenon-1''-yl}-phenyl amino]-*s*-triazine **(6e)** (0.01mole) in 20ml glacial aceticacid, hydrazine hydrate (0.01mole) was refluxed for 8 hours. Then the reaction mixture was cooled and poured into crushed ice. The product separated out was filtered, washed with water and recrystallised from alcohol to give **(8e)**.
Yield 64%; m.p. 186°C; IR(KBr, cm^{-1}): 1560(C=N, pyrazoline moiety), 1041 (C-O-C), 819 (C-N, *s*-triazine), 760(C-Cl); ^1H NMR ($CDCl_3$): δ2.45 (s, 3H, -

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TABLE 1 : Physical and analytical data of compounds (6a-e), (7a-e) and (8a-e)

No.	R	M.P. °C	Yield (%)	M.F.	Found (calcd)%		
					C	H	N
6a	Phenyl	147	76	$C_{30}H_{22}N_6OCl_2$	65.13(65.10)	3.96(3.98)	15.21(15.19)
6b	2-Chlorophenyl	171	75	$C_{30}H_{21}N_6OCl_3$	61.30(61.28)	3.58(3.57)	14.33(14.30)
6c	3-Chlorophenyl	141	73	$C_{30}H_{21}N_6OCl_3$	61.27(61.28)	3.59(3.57)	14.27(14.30)
6d	4-Chlorophenyl	168	76	$C_{30}H_{21}N_6OCl_3$	61.32(61.28)	3.60(3.57)	14.32(14.30)
6e	2-Methoxyphenyl	148	69	$C_{31}H_{24}N_6O_2Cl_2$	63.82(63.81)	4.15(4.12)	14.39(14.41)
7a	Phenyl	92	72	$C_{31}H_{23}N_9Cl_2$	62.83(62.84)	3.88(3.89)	21.30(21.28)
7b	2-Chlorophenyl	161	70	$C_{31}H_{22}N_9Cl_3$	59.36(59.38)	3.54(3.51)	20.13(20.11)
7c	3-Chlorophenyl	156	68	$C_{31}H_{22}N_9Cl_3$	59.39(59.38)	3.53(3.51)	20.14(20.11)
7d	4-Chlorophenyl	169	73	$C_{31}H_{22}N_9Cl_3$	59.34(59.38)	3.55(3.51)	20.09(20.11)
7e	2-Methoxyphenyl	138	65	$C_{32}H_{25}N_9OCl_2$	61.76(61.74)	4.05(4.02)	20.24(20.26)
8a	Phenyl	260	71	$C_{32}H_{26}N_8OCl_2$	63.08(63.05)	4.24(4.27)	18.36(18.39)
8b	2-Chlorophenyl	168	68	$C_{32}H_{25}N_8OCl_3$	59.70(59.67)	3.90(3.89)	17.37(17.40)
8c	3-Chlorophenyl	148	69	$C_{32}H_{25}N_8OCl_3$	59.68(59.67)	3.92(3.89)	17.36(17.40)
8d	4-Chlorophenyl	175	70	$C_{32}H_{25}N_8OCl_3$	59.66(59.67)	3.86(3.89)	17.39(17.40)
8e	2-Methoxyphenyl	186	64	$C_{33}H_{28}N_8O_2Cl_2$	61.95(61.97)	4.36(4.38)	17.53(17.52)

TABLE 2 : Antimicrobial activity of compounds (6a-d), (7a-d), (8a-d) and (9a-d)

No.	R	Zone of inhibition (mm)			
		S.aureus	*B.subtilis*	*E.coli*	*S.paratyphi-B*
6a	Phenyl	11	10	-	-
6b	2-chlorophenyl	12	10	-	-
6c	3-chlorophenyl	10	12	-	-
6d	4-chlorophenyl	10	10	-	-
6e	2-Methoxyphenyl	10	11	11	-
7a	Phenyl	12	10	-	-
7b	2-chlorophenyl	10	11	-	-
7c	3-chlorophenyl	-	-	-	-
7d	4-chlorophenyl	10	-	11	-
7e	2-Methoxyphenyl	-	11	-	-
8a	Phenyl	10	10	-	-
8b	2-chlorophenyl	10	-	-	-
8c	3-chlorophenyl	-	-	-	12
8d	4-chlorophenyl	10	-	-	12
8e	2-Methoxyphenyl	10	-	-	-
Standard Drug	Ciprofloxacin	22	20	20	18

$COCH_3$), δ3.05 (dd, 1H, -CH_A), δ3.48 (dd, 1H, -CH_B), δ3.72(s, 3H, o-OCH_3), 5.62 (dd, 1H, -CH), 6.90 to 7.70 (m, 16 Ar-H and 3 NH). Anal. Calcd. for $C_{33}H_{28}N_8O_2Cl_2$: C,61.97; H,4.38; N,17.52. Found: C,61.95; H,4.36; N,17.53.

CONCLUSION

By visualizing activity data, it is observed that compounds **(6b)** and **(7a)** showed moderately active against *S.aureus*. Compound **(6c)** exhibited moderate active against *B.subtilis*. Compounds **(8c)** and **(8d)** showed moderately active against *E.coli*. While, the remaining compounds are less or inactive against all the bacteria.

ACKNOWLEDGMENT

We are grateful to B.K.M. Science College, Valsad for providing research facilities and to microbiology department for carrying out antimicrobial activity.

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