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An efficient and facile synthesis of chloro, fluoro susbstituted chalcones, acetylpyrazolines and aminopyrimidines

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ABSTRACT

2-(4'-Chlorophenylamino)-4-(4'-fluorophenylamino)-6-(4'-acetyl phenylamino)-*s*-triazine **(5)** on treatment with different aromatic aldehydes yields chalcones **(6a-e)**, which on cyclisation with hydrazine hydrate in presence of glacial acetic acid give acetyl pyrazolines **(7a-e)** and also on cyclisation with guanidine nitrate in presence of alkali give aminopyrimidines **(8a-e)**. The constitutions of newly synthesized compounds have been established on the basis of their elemental analysis, IR and ^{1}H NMR spectral data.

KEYWORDS

Chalcones;
Acetylpyrazolines;
Aminopyrimidines.

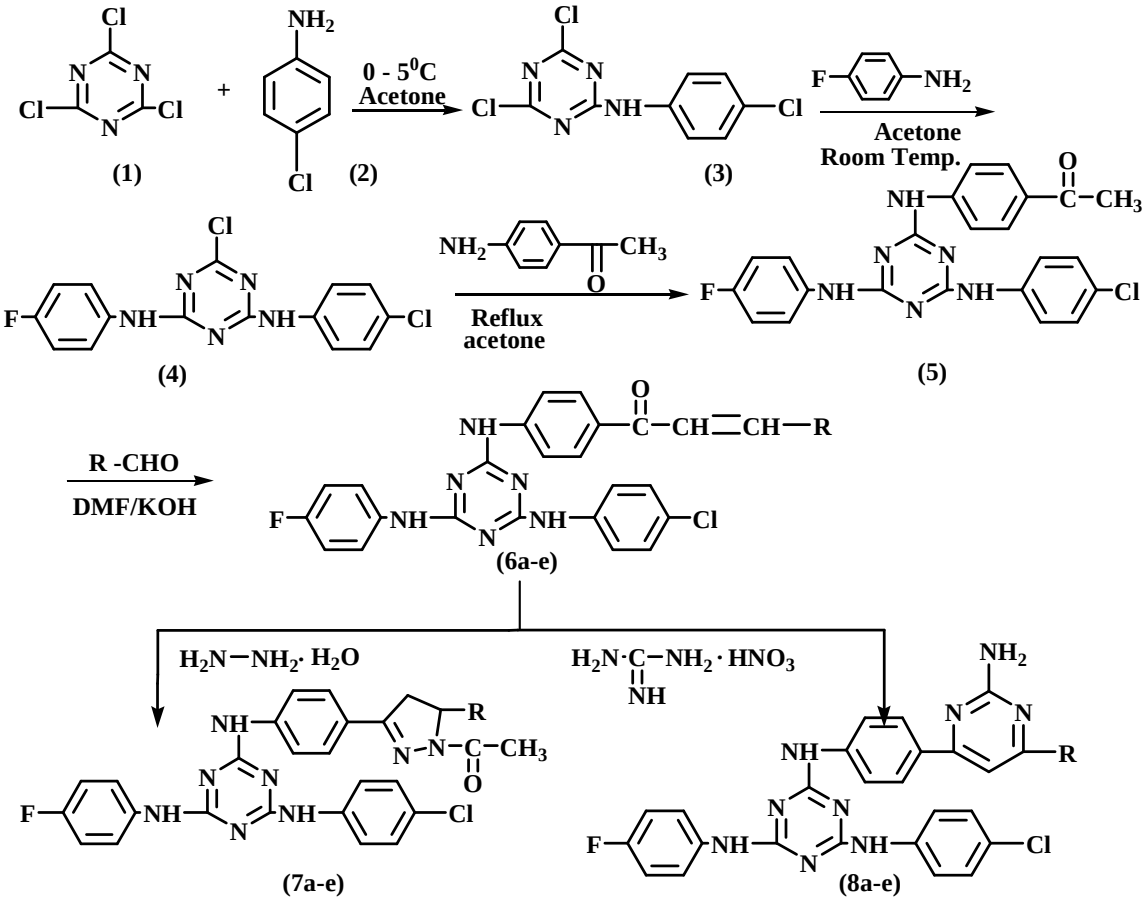
INTRODUCTION

The synthesis of α,β-unsaturated carbonyl compounds is one of the main structural component in various naturally occurring and biologically essential substance[1]. Several strategies for the synthesis of these systems based on formation of carbon-carbon bond have been reported and among them the direct Aldol condensation and Claisen-Schimdt condensation still occupy prominent position[2]. Moreover, α,-unsaturated ketones are important intermediates in many addition reaction due to carbonyl group at β-position[3]. It is well know that most natural or synthetic chalcones are highly active with extensive pharmaceutical and medicinal application[4]. Recently, chalcones have been used as anti-AIDS[5], antimalarial[6], antitumor[7], anti-inflammatory[8] and antibacterial[9] agents.

The literature survey reveals that pyrazolines have been found to possess many biological activities and have variety of industrial applications[10]. It has been reported that introduction of acetyl group at 1st-position enhances the mollucicidal[11] activity as well as increases the stability of pyrazolines. Pyrazoline derivatives have been found to possess insecticidal[12], antiinflammatory[13] and anticancer[14] properties.

Pyrimidine derivatives play a vital role in many biological processes and in synthesis of drugs. Pyrimidine derivatives which occur in natural products[15] like nucleic acid and vitamine-B_1 have remarkable pharmaceutical importance because of their biological activities[16-17]. Amino pyrimidine derivatives have been possess antiulcer[18] and anti-AIDS[19] properties.

In continuation of our work on chalcones and their derivatives[20], we have synthesized 2-(4'-chlorophenyl amino)-4-(4'-fluorophenylamino)-6-[4'-{3''-(substituted phenyl)-2''-propenon -1''-yl} phenyl amino]-*s*-tiazine**(6a-e)** according to Claisen-Schmidt condensation by using ketone **(5)** with different aromatic aldehydes. Further these chalcones **(6a-e)** on cyclisation with hydrazine hydrate in presence of glacial acetic acid



SCHEME 1

give acetylpyrazolines**(7a-e)** and also on cyclisation with guanidine in presence of alkali it give aminopyrimidines **(8a-e)**. (SCHEME 1)

The IR spectrum of **(6a)** shows the characteristic band at 1650cm^{-1} due to –C=O group. The IR spectrum of **(7a)** shows characteristic band at 1573cm^{-1} due to –C=N group. The IR spectrum of **(8a)** shows the characteristic band at 3405cm^{-1}, which indicate the presence of primary amine. The IR spectrum of **(8a)** do not show any absorption bands in the region of 1700-1600cm^{-1} which indicate the absence of –C=O group. The NMR spectrum of **(6a)** shows a doublet at δ 6.9 due to(-CO-CH=). The NMR spectrum of **(7a)** shows a sharp singlet at δ 2.53 due to(-$COCH_3$). The NMR spectrum of **(8a)** shows a singlet at δ 5.72 due to -NH_2 protons.

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 Bruker Avance DPX 300MHz spectrometer with $CDCl_3$ as a solvent and 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 (0.01 mole,1.275g in 10ml acetone) was added slowly to cyanuric chloride (0.01 mole,1.845g in acetone 30ml) with constant stirring for 4 hours at 0 to 5°C. Periodically sodium carbonate solution (0.005 mole, 0.53g in 10ml water) was added dropwise to neutralize HCl evolved during the reaction. Finally the content was poured into crushed ice. The solid separated out was filtered, washed with water, dried and recrystallised from alcohol to give **(3)**. Yield 90% ; mp. 220 °C.

Preparation of 2-(4'-chlorophenylamino)-4-(4'-

Full Paper

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

Sr. no	R	M.P^{0}C	Yield %	Molecular formula	Elemental analysis found/(calcd.)%		
					C	H	N
6a	3-Methoxyphenyl	172	71	$C_{31}H_{24}N_6O_2ClF$	65.64(65.66)	4.20(4.23)	14.80(14.82)
6b	4-Chlorophenyl	135	69	$C_{30}H_{21}N_6OCl_2F$	63.06(63.04)	3.66(3.67)	14.69(14.71)
6c	3-Phenoxy phenyl	100	70	$C_{36}H_{26}N_6O_2ClF$	68.70(68.73)	4.12(4.13)	13.34(13.36)
6d	2-Nitrophenyl	210	71	$C_{30}H_{21}N_7O_3ClF$	61.88(61.90)	3.60(3.61)	16.83(16.85)
6e	3-Nitrophenyl	185	70	$C_{30}H_{21}N_7O_3ClF$	61.88(61.90)	3.62(3.61)	16.83(16.85)
7a	3-Methoxyphenyl	139	66	$C_{33}H_{28}N_8O_2ClF$	63.59(63.61)	4.47(4.49)	17.97(17.99)
7b	4-Chlorophenyl	130	63	$C_{32}H_{25}N_8O_2Cl_2F$	61.23(61.24)	3.96(3.98)	17.85(17.86)
7c	3-Phenoxy phenyl	109	64	$C_{38}H_{30}N_8O_2ClF$	66.59(66.61)	4.36(4.38)	16.34(16.36)
7d	2-Nitrophenyl	170	60	$C_{32}H_{25}N_9O_3ClF$	60.20(60.23)	3.90(3.92)	19.74(19.76)
7e	3-Nitrophenyl	168	58	$C_{32}H_{25}N_9O_3ClF$	60.21(60.23)	3.90(3.92)	19.74(19.76)
8a	3-Methoxyphenyl	182	65	$C_{32}H_{25}N_9OClF$	63.39(63.41)	4.10(4.12)	20.78(20.80)
8b	4-Chlorophenyl	158	60	$C_{31}H_{22}N_9Cl_2F$	60.96(60.98)	3.59(3.60)	20.63(20.65)
8c	3-Phenoxy phenyl	192	63	$C_{37}H_{27}ON_9ClF$	66.49(66.51)	4.02(4.04)	18.85(18.87)
8d	2-Nitrophenyl	167	63	$C_{31}H_{22}N_{10}O_2ClF$	59.93(59.95)	3.52(3.54)	22.54(22.56)
8e	3-Nitrophenyl	163	62	$C_{31}H_{22}N_{10}O_2ClF$	59.93(59.95)	3.52(3.54)	22.54(22.56)

fluorophenylamino)-6-chloro-s-triazine (4)

4-Fluoroaniline(0.01mole,1.11g in 10ml acetone) was added slowly to compound **(3)** (0.01 mole,2.75g in 35 ml acetone) with constant stirring for 6 hours at room temperature. Periodically sodium carbonate solution (0.005mole,0.53g in10ml water) was added dropwise to neutralize HCl evolved during the reaction. Finally the contents was poured into crushed ice. The solid separated out was filtered, washed with water, dried and recrystallised from alcohol to give (4). Yield 85%; m.p. 193^{o}C; IR (KBr, cm^{-1}) 1035 (C-F); 805 (C-N, *s*-triazine);770 (C-Cl); ^{1}H NMR ($CDCl_3$): δ 7.20 -7.80 (m,10H, 8 Ar-H and 2 NH).

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

4-Aminoacetophenone(0.01mole,1.35g) and compound**(4)**(0.01mole,3.50g) were dissolved in acetone(40ml). The reaction mixture was refluxed for 6 hours, cooled and poured into crushed ice. Periodically sodium carbonate solution (0.005,0.53g in 10ml water) was added to neutralize HCl evolved during the reaction. The solid separated out was filtered, washed with water, dried and recrystallised from alcohol to give (5). Yield 79%; m.p. 208 ^{o}C; IR(KBr, cm^{-1}) 1658(-C=O), 1020(C-F), 800(C-N, *s*-triazine), 786 (C-Cl); ^{1}H NMR ($CDCl_3$): δ2.6(s, 3H, -$COCH_3$), δ6.9 - 8.9(m,15H, 12 Ar-H and 3 NH).

Preparation of 2-(4'-chlorophenylamino)-4-(4'-fluorophenylamino)- 6-[4'-{3''-(3'''-methoxy phenyl)-2''-propenon-1''-yl}-phenylamino]-*s*-triazine(6a)

Compound **(5)** (0.01mole,4.48g) was dissolved in DMF (30ml) and 40% KOH in distilled water was added to it. Then benzaldehyde/substituted benzaldehyde (0.01 mole) 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 **(6a)**. Yield 71%; m.p.122^{o}C; IR (KBr, cm^{-1}) 1650 (-C=O), 1012(C-F), 806(C-N, *s*-triazine),788 (C-Cl); ^{1}H NMR ($CDCl_3$): δ3.84 (s, 3H, -OCH_3), δ6.9(d, lH, -CO-CH=), δ 7.1 - 7.8 (m,19H, 16 Ar-H and 3 NH), δ 8.10 (d, 1H, Ar-CH=) .Anal. Calcd for $C_{31}H_{24}N_6O_2ClF$: C,65.66; H;4.23; N,14.82. Found: C,65.64; H;4.20; N,14.80.

Similarly the remaining compounds**(6b-e)** were prepared by this method. Their physical and analytical data are given in TABLE.

Preparation of 2-(4'-chlorophenylamino)-4-(4'-fluorophenylamino)- 6-[4'-{1''-acetyl-5''-(3'''-methoxyphenyl)-2''-pyrazoline-3''-yl}-phenyl amino]-s-triazine (7a)

Compound **(6a)** (0.01mole,5.66g) was dissolved in glacial acetic acid(25ml) and hydrazine hydrate (0.01mole,0.5g) was added to it. Then the reaction mixture was refluxed for 6 hours. The reaction mixture was then cooled , poured into crushed ice and product separated out was filtered, washed with water, dried

and recrystallized from alcohol to give **(7a)**.
Yield 66%; m.p. 139°C; IR (KBr,cm^{-1}) 1573 (-C=N), 1225(C-O-C), 1015 (C-F), 810 (C-N, *s*-triazine), 785 (C-Cl); ^{1}H NMR($CDCl_3$): δ 2.53 (s,3H,-$COCH_3$), δ 3.1(dd, 1H, -CH_A), δ 3.3(dd, 1H, -CH_B), δ 3.85 (s, 3H, -OCH_3), δ 5.71(dd, 1H, -CH), δ 6.8 - 7.8 (m,19H, 16 Ar-H and 3 NH). Anal. Calcd for $C_{33}H_{28}N_8O_2ClF$: C,63.61; H;4.49; N,17.99. Found: C,63.59; H;4.47; N,17.97.

Similarly the remaining compounds **(7b-e)** were prepared by this method. Their physical and analytical data are given in TABLE.

Preparation of 2-(4'-chlorophenylamino)-4-(4'-fluorophenylamino)- 6-[4'-{2''-amino-6''-(3'''-methoxyphenyl)-pyrimidine-4''-yl}-phenylamino]-s-triazine (8a)

Compound **(6a)** (0.01mole,5.66g) was dissolved in alcohol (25ml) and guanidine nitrate (0.01mole,1.22g) was added to it. Then solution of KOH(5ml of 40%) was added to the reaction mixture and refluxed for 10 hours. The reaction mixture was then cooled , poured into crushed ice and product separated out was filtered, washed with water, dried and recrystallized from alcohol to give **(8a)**.
Yield 65%; m.p. 182 °C; IR (KBr, cm^{-1}) 3405 (-NH_2), 1580 (C=N), 1227(C-O-C), 1013(C-F), 806 (C-N, *s*-triazine), 783(C-Cl); ^{1}H NMR ($CDCl_3$): δ3.81(s, 3H, -OCH_3), δ 5.72(s, 2H, -NH_2), δ7.0 - 8.4 (m, 20H,17 Ar-H and 3 NH). Anal. Calcd for $C_{32}H_{25}N_9OClF$: C,63.41; H;4.12; N,20.80. Found: C,63.39; H;4.10; N,20.78.

Similarly the remaining compounds**(8b-e)** were prepared by this method. Their physical and analytical data are given in TABLE.

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