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AN EFFICIENT SYNTHESIS OF SOME NEW FLUORINE CONTAINING ACETYL PYRAZOLINE AND ISOXAZOLE DERIVATIVES AND THEIR ANTIBACTERIAL ACTIVITY

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ABSTRACT

Acetyl pyrazolines (7a-f) and isoxazole (8a-f) have been prepared from chalcones (6a-f) on reaction with hydrazine hydrate and hydroxylamine hydrochloride respectively. All the synthesized compounds have been screened for their antibacterial activity against S. aureus (MTCC 96), B. subtilis (MTCC 441) (Gram-positive) and E. coli. (MTCC 443) and S. paratyphi-B (MTCC 733) (Gram-negative) bacteria by using agar diffusion method. The structures of the compounds have been established on the basis of their IR and ^{1}H NMR spectral data.

Keywords: Pyrazolines, isoxazoles, antibacterial activity

INTRODUCTION

Synthesis and characterization of pyrazoline[1,2] and isoxazole[3,4] derivatives has been a developing field within the realm of heterocyclic chemistry. Because of their diverse properties, fairly assessable path of synthesis, wide range of therapeutic activities and variety of industrial application, the pyrazoline and isoxazole ring became a center of attraction for organic chemists. Pyrazoline derivatives are well known for their versatile pharmacological activities such as antimicrobial[5], anticonvulsant[6], antiinflammatory[7], analgesic[8], anticancer[9], antitubercular[10] and herbicidal[11]. The synthesis of isoxazole derivatives attracted considerable attention of the medicinal chemists due to their significant biological activities such as antibacterial[12], antifungal[13], neuroleptic[14], antitumor[15], antileukemia[16], antipyretic[17] and anthelmintic[18].

In view of this and in continuation of our work[19-21] on potential synthetic heterocycles, herein we report the reaction of cyanuric chloride **(1)** with 4-fluoroaniline **(2)** at 0-5 ºC to give compound **(3)**, which further reacts with 4-fluoroaniline at room temperature to give compound **(4).** Compound **(4)** is further treated with 4-aminoacetophenone to give 2,4-bis-(4'-fluorophenylamino)-6-(4'-acetylphenylamino)-*s*-triazine **(5).** Compound **(5)** on reaction with different aldehydes to give chalcones **(6a-f)**. Further these chalcones on reaction with hydrazine hydrate in glacial acetic acid and with hydroxylamine hydrochloride in presence of 40% KOH to give acetyl pyrzolines **(7a-f)** and isoxazoles **(8a-f)** respectively **(Scheme-I, Table-I)**. The structures of the newly synthesized compounds have been identified on the basis of their elemental analysis, IR and ^{1}H NMR spectra.

EXPERIMENTAL

Melting points were taken in an open capillary and are uncorrected. The IR spectra were recorded on Perkin Almer 237 spectrometer. ^{1}H NMR spectra were recorded on the Bruker Avance 400 MHz spectrometer, using TMS as internal reference and $CDCl_3$ as a solvent. Purity of the compounds was checked on TLC using precoated Merck Silica Gel 60 F_{254} aluminium foil.

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

4-Fluoroaniline (0.01 mol, 1.11g) was added slowly to cyanuric chloride (0.01 mol, 1.845g) in acetone (30 mL) with constant stirring for 4 h at 0-5ºC. Periodically, sodium carbonate solution (0.005 mole, 0.53g in 20 mL water) was added drop wise to neutralized 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)**.

IR (KBr) cm^{-1}: C-F (1067), C-N, s-triazine (807), C-Cl (769).

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

4-Fluoroaniline (0.01mol, 1.11g) was added slowly to 2-(4'-fluorophenylamino)-4,6-dichloro-s-triazine (0.01 mole, 2.59g) in acetone (35 mL) with constant stirring for 6 h at room temperature. Periodically, sodium carbonate solution (0.005 mole, 0.53g in 20 mL water) was added drop wise to neutralized 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)**.

IR (KBr) cm^{-1}: C-F (1060), C-N, s-triazine (808), C-Cl (770).

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

4-Aminoacetophenone (0.01 mol, 1.35g) and 2,4-bis-(4'-fluorophenylamino)-6-chloro-s-triazine (0.01 mol, 3.335g) were dissolved in 40 mL acetone. The reaction mixture was refluxed for 6 h. Periodically, sodium carbonate solution (0.005 mol, 0.53g in 20 mL water) was added drop wise to neutralized HCl evolved during the reaction. Finally, the reaction mixture was cooled and poured into crushed ice. The solid separated out was filtered, washed with water and recrystallised from alcohol to give **(5)**.

IR (KBr) cm^{-1}: C=O (1665), C-F (1057), C-N, s-triazine (804); ^{1}H NMR ($CDCl_3$) δ ppm : 2.6 (s, 3H, -$COCH_3$), 7.20 to 7.90 (m, 13 Ar-H and 3-NH).

General procedure for the preparation of 2,4-bis-(4'-fluorophenylamino)-6-[4'-{3''-(substituted phenyl)-2''-propenon-1''-yl} phenylamino]-*s*-triazine (6a-f)

Compound **(5)** (0.01 mol, 4.32 g) was dissolved in DMF (30mL) and 40 % KOH (4mL) was added to it. Then different aromatic aldehydes (0.01 mol) were added with constant stirring at room temperature. After 24 h reaction mixture was poured into crushed ice and neutralize with HCl. The product separated out was filtered, washed with water and recrystallised from alcohol to give **(6a-f).**

Preparation of 2,4-bis-(4'-fluorophenylamino)-6-[4''-{1''-acetyl-5''-(4'''-methoxyphenyl)-2''-pyrazoline-3''-yl} phenylamino]-*s*-triazine (7a)

Chalcone, 2,4-bis-(4'-fluorophenylamino)-6-[4'-{3"-(4'"-methoxyphenyl)-2"-propenon-1"-yl}phenylamino]-*s*-triazine **(6a)** (0.01 mol) in minimum amount of glacial acetic acid and hydrazine hydrate (0.015 mol, 0.75g) was refluxed for 4 h. Then the reaction mixture was cooled and poured into crushed ice and the product separated out was filtered, washed with water and recrystallised from alcohol to give **(7a)**.

IR (KBr) cm^{-1}: -NH (3272), C=O (1650), C=N, pyrazoline moiety (1613), C-F (1075), C-O-C (1039). ^{1}H NMR ($CDCl_3$) δ ppm: δ 2.5 (s, 3H, -COC$\underline{H}_3$), 3.0 (d, 1H, -C$\underline{H}$a-CH-), 3.4 (d, 1H, -C$\underline{H}$b-CH-), 3.7 (s, 3H, p-OC$\underline{H}_3$), 5.7 (dd, 1H, -C$\underline{H}$-CH_2), 6.8 to 7.8 (m, 19H, 16Ar-$\underline{H}$ and 3-N$\underline{H}$).

Similarly the remaining compounds **(7b-f)** were prepared by this method. Their physical data are given in Table-1.

Preparation of 2,4-bis-(4'-fluorophenylamino)-6-[4'-{5''-(4'''-methoxyphenyl)-2''-isoxazole-3''-yl} phenylamino]-*s*-triazine (8a)

Chalcone, 2,4-bis-(4'-fluorophenylamino)-6-[4'-{3"-(4'"-methoxyphenyl)-2"-propenon-1"-yl} phenylamino]-*s*-triazine **(6a)** (0.01 mol), hydroxylamine hydrochloride (0.01mol, 0.695g) in ethanol and 40% KOH solution were refluxed for 10 h. Then the reaction mixture was cooled and poured into crushed ice and the product separated out was filtered, washed with water, dried and recrystallised from alcohol to give **(8a).**

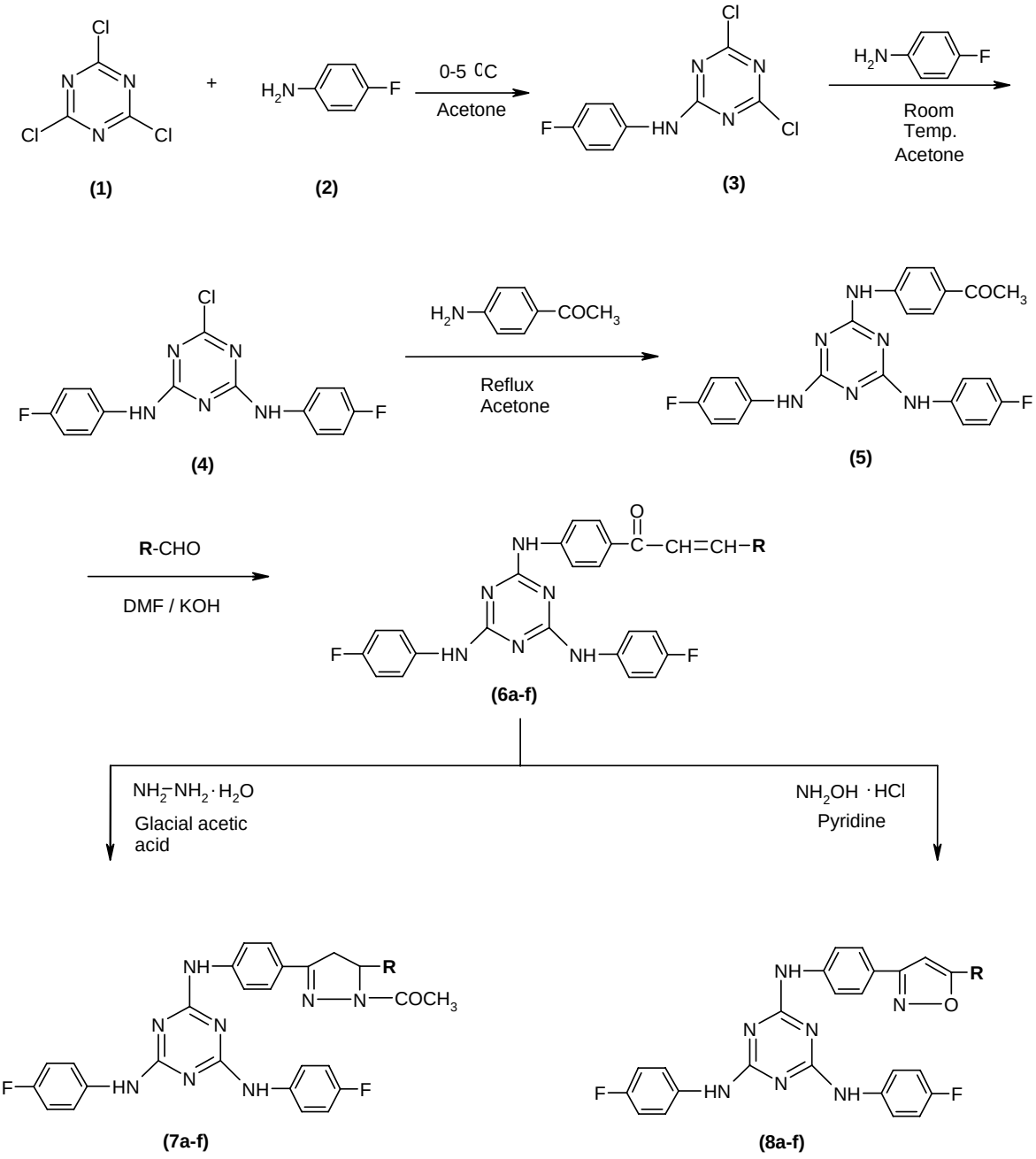
IR (KBr) cm^{-1}: C=N, isoxazole moiety (1585), C-F (1096), C-O-C (1031); ^1H NMR ($CDCl_3$) δ ppm : 3.88 (s, 3H, p-OC<u>H</u>$_3$), 6.7 (s, lH, -C<u>H</u>- of isoxazole moiety), 6.92-7.88 (m, 19H, 16Ar-<u>H</u> and 3-N<u>H</u>).
Similarly the remaining compounds **(8b-f)** were prepared by this method. Their physical data are given in Table-1.

Table-1: Physical data of compounds (7a-f) and (8a-f)

Comp.	R	MP (˚C)	Yield (%)
7a	4-Methoxyphenyl	214	78
7b	3,4-Dimethoxyphenyl	168	76
7c	3,4,5-Trimethoxyphenyl	164	72
7d	2,3-Dichlorophenyl	144	75
7e	4-N,N-dimethylaminophenyl	150	69
7f	4-N,N-diethylaminophenyl	212	71
8a	4-Methoxyphenyl	226	74
8b	3,4-Dimethoxyphenyl	191	76
8c	3,4,5-Trimethoxyphenyl	156	72
8d	2,3-Dichlorophenyl	203	70
8e	4-N,N-dimethylaminophenyl	214	68
8f	4-N,N-diethylaminophenyl	225	67

Table-2: Antibacterial activity data of compounds (7a-f) and (8a-f)

Comp.	R	Antibacterial Activity			
		Diameter of zone of inhibition (in mm)			
		S. aureus MTCC-96	**B. subtilis MTCC-441**	**E. coli MTCC-443**	**S. paratyphi-B MTCC-733**
7a	4-Methoxyphenyl	-	11	13	-
7b	3,4-Dimethoxyphenyl	-	10	16	-
7c	3,4,5-Trimethoxyphenyl	14	12	11	-
7d	2,3-Dichlorophenyl	-	13	17	-
7e	4-N,Ndimethylaminophenyl	-	13	17	-
7f	4-N,Ndiethylaminophenyl	-	14	15	-
8a	4-Methoxyphenyl	11	11	-	18
8b	3,4-Dimethoxyphenyl	-	11	16	13
8c	3,4,5-Trimethoxyphenyl	12	12	14	13
8d	2,3-Dichlorophenyl	-	-	-	-
8e	4-N,Ndimethylaminophenyl	11	12	15	14
8f	4-N,Ndiethylaminophenyl	11	11	15	14
Ciprofloxacin (Standard Drug)		20	22	24	25



SCHEME-I

RESULTS AND DISCUSSION

Antibacterial activity

All the synthesized compounds have been screened for their antibacterial activity against *S. aureus* (MTCC 96), *B. subtilis* (MTCC 441) (Gram-positive bacteria) and *E. coli* (MTCC 443), *S. paratyphi-B* (MTCC 733) (Gram-negative bacteria) by using agar diffusion method[7]. The zone of inhibition was

measured in mm. Under similar conditions controlled experiment was carried out using Ciprofloxacin as a standard drug for comparison **(Table-No. 2)**.

By the visualizing the antibacterial activity data, it has been observed that the compound **(7d)** containing R = 2,3-dichlorophenyl and **(7e)** containing R = 4-N,N-dimethylaminophenyl were found to be moderately active against *E. coli* (MTCC 443). Compound **(8a)** containing R = 4-methoxyphenyl was found to be moderately active against *S. paratyphi-B* (MTCC 733); where as remaining compounds were found less active or inactive against all the bacterial strain.

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