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NOTE

Synthesis and Biological Screening of Substituted 2-Aminocyano Pyridines

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A variety of novel 2-aminocyano pyridines were prepared by reacting different chalcones with malonitrile. All the newly synthesized compounds were characterized by spectral analysis (^{1}H NMR and IR spectra). Newly synthesized compounds were screened for their antiinflammatory and antibacterial activity.

Key Words: Chalcones, Malonitrile, Cyanopyridines, Antiinflammatory activity, Antibacterial activity.

Pyridine containing heterocyclic compounds have shown a variety of useful pharmacological activities[1-3] and many of these have gained wide acceptance in clinical practice. Amino cyanopyridines were prepared by refluxing chalcones with malonitrile in ethanol. The starting material, chalcones were prepared by condensing appropriate acetophenone with different aldehydes in alkaline medium.

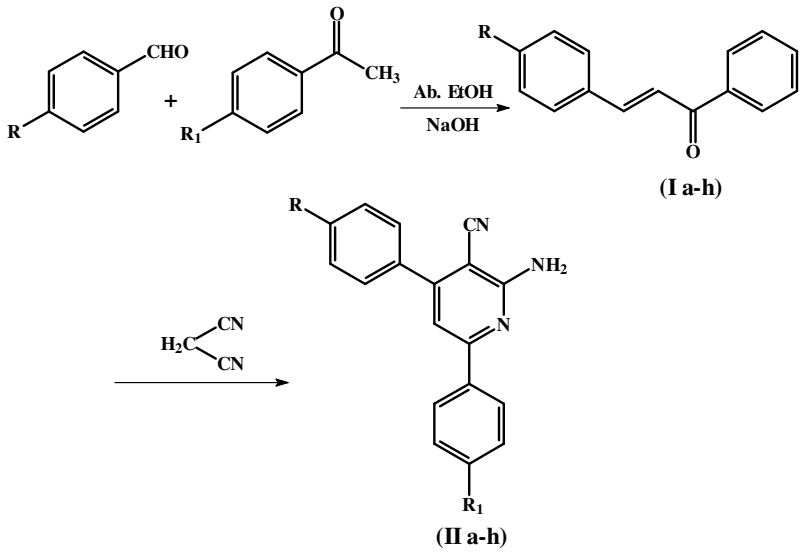
Melting points were determined in capillaries in liquid paraffin and are uncorrected. Purity of the compounds was checked with TLC. IR spectra were recorded using KBr pellets on Hitachi spectrometer 270-30 (cm^{-1}). ^{1}H NMR spectra were recorded on Bruker DRX-300 (300 MHz FT NMR) spectrometer using TMS as an internal standard (chemical shift value are expressed in ppm).

Step-I: General synthesis of substituted chalcones (Ia-h): To an aqueous solution of potassium hydroxide and ethanol, acetophenone (0.03 mol) and aromatic aldehyde (0.01 mol) were added. The reaction mixture was stirred vigorously for 3 h and poured into crushed ice, a solid mass was separates out. It was filtered washed with cold water (50 mL) and then recrystallized from methanol.

Chalcone (1a): Yield: 69.44 %; m.p. 80°C; IR (KBr, cm^{-1}): 1660 ν(C=O), 1580 ν(C=C), 680; ^{1}H NMR ($CDCl_3$): δ 8.16 (d, 2H, H-2 & H-6), 7.98 (s, 1H, β-alkenyl proton), 7.92-7.90 (m, 3H, H-3, H-4 & H-5), 7.78 (s, 1H, α-alkenyl proton), 7.67 (d, 2H, H-2' & H-6'), 7.47 (m, H-3', H-4' & H-5').

Step-II: General synthesis of 2-aminocyanopyridines (IIa-h): The equimolar amount of compound **Ia-h**, malonitrile and ammonium acetate (0.08 mol, 6.16 g) dissolved in ethanol and were refluxed for 8 h. The completion of the reaction was checked by TLC with benzene:acetone (9:1) as the mobile phase. After the completion of the reaction, the reaction mixture was concentrated, cooled and poured into crushed ice. The product separated was filtered, dried and recrystallized from ethanol.

2-Amino, 3-cyano, 4-phenyl, 6-(4'-nitrophenyl) pyridine (**2d**): IR (KBr, cm^{-1}): 3353 ν(N-H), 2204 ν(C=N), 1515 ν(C=C), 1491 ν(C=N), 829; ^1H NMR ($CDCl_3$): δ 8.36 (d, 2H, H-3' & H-5'), 7.94 (d, 2H, H-2' & H-6'), 7.8 (m, 1H, H-5), 7.6-7.4 (m, 3H, H-3", H-4" & H-5"), 6.9 (m, 2H, H-2" & H-6"), 6.07(m, 2H, NH_2).



Scheme

The physical characteristics of the synthesized compounds are given in Table-1.

Antiinflammatory activity: All the derivatives of 2-amino cyanopyridines were screened for antiinflammatory activity by carrageenan induced rat paw edema method[4] in Albino rats at a dose of 20 mg/kg. The test compounds were made into homogeneous suspension with distilled water, 1 % CMC and were administered orally. The percentage inhibition was noted at the end of first and third hour of administration of carrageenan. Carrageenan induced paw edema method of the test compounds was compared with known standard compound (Indomethacin). Among the synthesized compounds, **IId** and **IIh** showed significant antiinflammatory activity.

TABLE-1
PHYSICAL CHARACTERISTICS OF SYNTHESIZED COMPOUNDS

Compound	R	R_1	m.p. (ºC)	Yield (%)
IIa	H	H	225	58.0
IIb	H	Cl	290	49.0
IIc	H	NO_2	195	51.0
IId	H	CH_3	210	54.0
IIe	OCH_3	H	205	67.0
IIf	OCH_3	Cl	170	54.5
IIg	OCH_3	NO_2	185	56.6
IIh	OCH_3	CH_3	219	61.0

Antibacterial activity: All the synthesized compounds were screened *in vitro* for their antibacterial activity at the concentration of 50 µg/mL against gram +ve (*S. aureus*, NCTC 10418) and gram -ve (*E. coli*, NCTC 6571) organism by cup plate method using DMF as solvent. After 24 h of incubation at 37ºC, the zone of inhibition was measured in mm. Compound **IIh** showed significant activity against gram -ve bacteria while compounds **IId** and **IIf** have good antimicrobial activity against gram +ve bacteria.

All the synthesized compounds were characterized by spectral techniques. Among the synthesized compounds, **IId** and **IIh** were found to be potent than the other compounds. Compound **IId** and **IIh** show 50 % and 64 % inhibition respectively after 3 h. Compound **IIh** (zone of inhibition 26 mm) showed significant activity against gram -ve bacteria while compounds **IId** (zone of inhibition 20 mm) and **IIf** (zone of inhibition 22 mm) have good anti microbial activity against gram +ve bacteria.

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