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Synthesis of some new 2-amino-3-cyano-4-aryl-6-(1-napthyl amino)-pyridines as antibacterial agents

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Abstract

Variety of 2-amino-3-cyano-4-aryl-6-(1-napthyl amino)-pyridines **3(a-h)** have been synthesized by reacting 1-(1-napthyl amino)-3-aryl-2-propen-1-ones **2(a-h)** with malononitrile and ammonium acetate in methanol under reflux condition. Structures of the synthesized compounds were confirmed by the spectral analysis. Furthermore, all the synthesized products were screened for their antibacterial activity.

Keywords: 1, 3-diaryl-2-propen-1-ones, malononitrile, ammonium acetate, 2-amino-3-cyano-pyridines, antibacterial activity

Introduction

Among the wide variety of heterocycles that have been explored developing pharmaceutically important molecules like pyridines, cyano-pyridines have played an important role in the heterocyclic chemistry. Pyridine derivatives have occupied a unique position in medicinal chemistry. The naturally occurring B_6-vitamins pyridoxine, pyrodoxal, pyridoxamine, and codecarbaxylase contain a pyridine nucleus. In addition to this, many naturallly occurring and synthetic compounds containing the pyridine scaffold possess interesting pharmacological properties [1]. Among them, 2-amino-3-cyanopyridines have been identified as IKK-β inhibitors [2]. Besides, they are important and useful intermediates in preparing variety of heterocyclic compounds [3-5]. Therefore, the synthesis of 2-amino-3-cyanopyridine derivatives continues to

attract much interest in organic chemistry. In this respect, and also in continuation of our earlier work [6-9] on synthesis of different heterocyclic system that containing highly biological activity, these assets prompted us to prepare some new cyano-pyridines with potential biological activity.

Materials and Methods

General procedure for the synthesis of 1-(1-napthyl amino)-3-aryl-2-propen-1-ones 2(a-h)

A mixture of N-(1-napthyl)-acetamide (1 Mmol), aromatic aldehyde (1 Mmol) and KOH (2 Mmol) were dissolved in ethanol solution. The reaction mixture was heated for 2-3 hr. The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, the contents were poured in ice-cold water and then acidified by dil. HCl. The solid obtained was filtered, washed with cold water. Then crude product was crystallized from ethanol to give the corresponding product.

Spectroscopic data of selected compounds

(**2b**)**:** IR (KBr): 3218 (-NH), 3042 (-OH), 1638 (>C=O),cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.15-8.21 (m, 12H, -CH=CH + Ar-H), δ 8.68 (s, 1H, -NH) δ 10.51 (s, 1H, -OH) ppm; EIMS (*m/z*): 323 (M^+), 325 (M+2); Anal. Calcd. For $C_{19}H_{14}O_2NCl$: C, 70.48; H, 4.36; N, 4.33%. Found: C, 70.56; H, 4.41; N, 4.21%

(**2f**)**:** IR (KBr): 3198 (-NH), 3056 (-OH), 1640 (>C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.06-8.28 (m, 13H, -CH=CH + Ar-H), δ 8.56 (s, 1H, -NH) ppm; EIMS (*m/z*): 307 (M^+), 309 (M+2); Anal. Calcd. For $C_{19}H_{14}ONCl$: C, 74.15; H, 4.58; N, 4.55%. Found: C, 74.23; H, 4.69; N, 4.46%

General procedure for the synthesis of 2-amino-3-cyano-4-aryl-6-(1-napthyl amino)-pyridines 3(a-h)

An equimolar mixture of 1-(1-napthyl amino)-3-aryl-2-propen-1-one (1 Mmol), malononitrile (1 Mmol) and ammonium acetate (1.5 Mmol) taken in methanol was heated under reflux for 5 hr. The progress of the reaction was monitored by thin layer chromatography (TLC) by time to time. After completion of the reaction, the contents were kept at room temperature and poured into cold water. The solid obtained was filtered, washed with cold water. Then crude product was crystallized from aqueous acetic acid to give the corresponding product.

Spectroscopic data of selected compounds

(**3a**)**:** IR (KBr): 3363 (-NH_2), 3096 (-OH), 2218 (-C≡N), 1615 (-C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.42 (s, 2H, -NH_2), δ 7.16-8.28 (m, 12H, Ar-H), δ 8.46 (s, 1H, -NH) δ 11.42 (s, 1H, -OH) ppm; EIMS (*m/z*): 352 (M^+); Anal. Calcd. For $C_{22}H_{16}ON_4$: C, 74.98, H, 4.58; N, 15.91%. Found: C, 74.86; H, 4.63; N, 15.98%

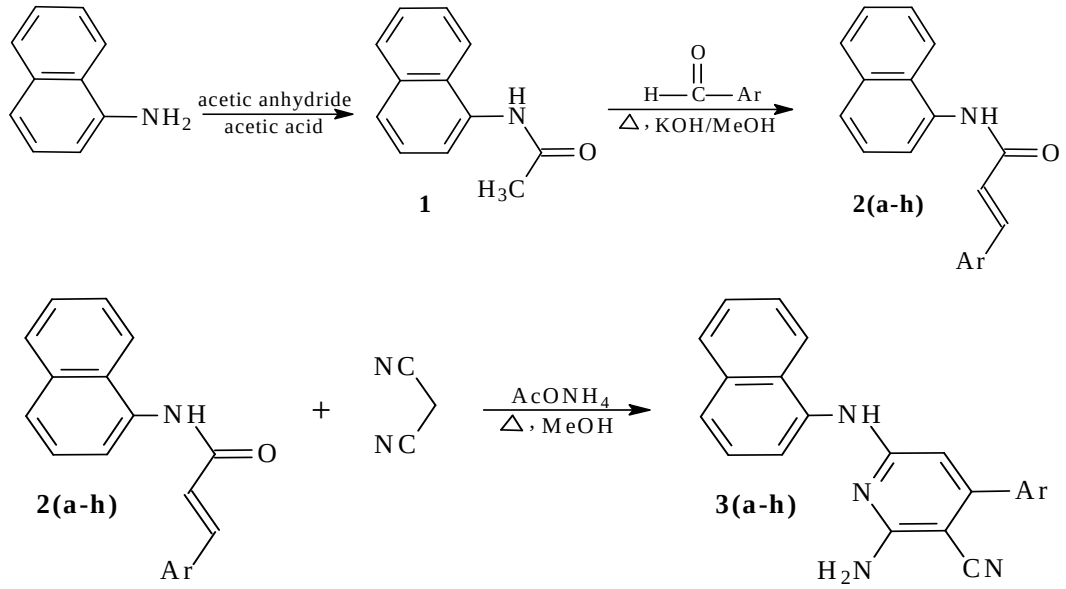
(**3b**)**:** IR (KBr): 3355 (-NH_2), 3088 (-OH), 2215 (-C≡N), 1618 (-C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.48 (s, 2H, -NH_2), δ 7.11-8.22 (m, 11H, Ar-H), δ 8.51 (s, 1H, -NH) δ 11.62 (s, 1H, -OH) ppm; EIMS (*m/z*): 386 (M^+), 384 (M+2); Anal. Calcd. For $C_{22}H_{15}ON_4Cl$: C, 68.31; H, 3.91; N, 14.48%. Found: C, 68.38; H, 3.98; N, 14.41%

(**3f):** IR (KBr): 3323 (-NH_2), 2220 (-C≡N), 1614 (-C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 3.36 (s, 2H, -NH_2), δ 7.18-8.31 (m, 12H, Ar-H), δ 8.62 (s, 1H, -NH) ppm; EIMS (*m/z*): 370 (M^+), 372 (M+2); Anal. Calcd. For $C_{22}H_{15}N_4Cl$: C, 71.25; H, 4.08; N, 15.11%. Found: C, 71.31; H, 4.15; N, 15.18%

(**3g):** IR (KBr): 3334 (-NH_2), 2218 (-C≡N), 1618 (-C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 3.28 (s, 2H, -NH_2), δ 3.65 (s, 3H, -OCH_3), δ 7.11-8.25 (m, 12H, Ar-H), δ 8.56 (s, 1H, -NH) ppm; EIMS (*m/z*): 366 (M^+); Anal. Calcd. For $C_{23}H_{18O}N_4$: C, 75.39; H, 4.95; N, 15.29%. Found: C, 75.44; H, 4.88; N, 15.35%

Results and Discussion

Our approach to the synthesis of target molecules started from the reaction of acetylation of 1-napthylamine with acetic anhydride in acetic acid, which gave the pale white crystalline N-(1-napthyl)-acetamido product **1**. The key intermediate 1-(1-napthyl amino)-3-aryl-2-propen-1-ones (chalcones) **2(a-h)** required for the synthesis of pyridine derivatives were obtained by the Claisen-Schmidt condensation of N-(1-napthyl)-acetamide with various aromatic aldehydes in alkaline ethanolic solution. Finally, the ring closure reaction of 1-(1-napthyl amino)-3-aryl-2-propen-1-ones with malononitrile and ammonium acetate in presence of methanol under reflux condition for 5 hr gave the corresponding pyridine derivatives (scheme-1). Structures of the synthesized compounds were established on the basis of spectral analysis (IR, ^1H NMR and Mass).



Scheme-1

Table-1: Physico-chemical data of 2-amino-3-cyano-pyridine derivatives

Entry	Product	Ar	Yield (%)	M. P. (°C)
1	3a	2-OH-C_6H_4	68	184
2	3b	2-OH-5-Cl-C_6H_3	65	170
3	3c	2-OH-3-Br-5-Cl-C_6H_2	65	191
4	3d	2-OH-3,5-dibromo-C_6H_2	66	228
5	3e	4-OH-C_6H_4	72	205
6	3f	4-Cl-C_6H_4	69	161
7	3g	4-OCH_3-C_6H_4	68	152
8	3h	3-OCH_3-4-OH-C_6H_3	64	179

The IR spectra of the products **3(a-h)** showed a characteristic bands at 2210-2225 and 1610-1620 cm^{-1} due to the -C≡N and –C=N stretching respectively. ^1H NMR data showed a characteristic singlet at δ 2.5-2.8 ppm revealed the presence of $–NH_2$ protons in the product. The aromatic and aliphatic protons are appeared at expected region. The mass spectra of the compounds are also in agreement with their molecular formula weight.

Antibacterial activity

All the synthesized products **3(a-h)** were evaluated for their antibacterial activity by agar well diffusion method [10] against gram-positive *Bacillus subtilis, Staphylococcus aureus* and gram-negative *Escherichia coli* and *Proteus vulgaris* bacteria species. The antibiotic tetracycline (25 µg/mL) was used as reference antibacterial substance for comparison. Dimethyl sulphoxide (1%, DMSO) was used a control. The culture strains of bacteria were maintained on nutrient agar slant at 37±0.5 °C for 24 h. The antibacterial activity was evaluated using nutrient agar plate seeded with 0.1 mL of respective bacterial culture strain suspension prepared in sterile saline (0.85%) of 10^5 CFU/mL dilutions. The wells of 6 mm diameter were filled with 0.1 mL of compound solution at fixed concentration 25 µg/mL separately for each bacterial strain. All the plates were incubated at 37±0.5 °C for 24 h. Zone of inhibition of compounds in mm were noted. The results of antimicrobial studies are given in Table-2.

Table-2: Antibacterial activity of 2-amino-3-cyano-pyridines

Entry	Product	Bs	Sa	Ec	Pv
1	**3a**	11	15	10	12
2	**3b**	10	14	12	10
3	**3c**	15	18	14	12
4	**3d**	12	16	12	11
5	**3e**	14	15	16	14
6	**3f**	15	16	14	13
7	**3g**	14	18	12	10
8	**3h**	10	11	09	11
9	**Reference**	18	20	18	16

Bs- *Bacillus subtilis,* Sa- *Staphylococcus aureus* Ec- *Escherichia coli,* Pv- *Proteus vulgaris,* Reference- *Tetracycline, Zone of inhibitions are given in mm*

The investigation of antimicrobial screening data revealed that all the tested compounds showed moderate to good bacterial zone of inhibition. Compounds **3c** and **3f** were showed comparable activity against *Bacillus subtilis*. In comparison with standard tetracycline, compounds **3c**, **3d**, **3f** and **3g** showed very good activity against *Staphylococcus aureus*. Compounds **3c**, **3e** and **3f** were also showed good zone of inhibition against showed *Escherichia coli*.

Conclusion

In summary, we have synthesized a series of 2-amino-3-cyano-4-aryl-6-(1-napthyl amino)-pyridines derivatives by the condensation of 1-(1-napthyl amino)-3-aryl-2-propen-1-ones with malononitrile and ammonium acetate in presence of methanol. The investigation of antibacterial screening data reveled that most of the compounds showed good zone of inhibition. Only the compounds **3e** and **3f** showed promising activity against all tested bacterial strains.

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