**Cu(OAc)$_2$ AS A GREEN PROMOTER FOR ONE-POT SYNTHESIS OF 2-AMINO-4,6-DIARYLPYRIDINE-3-CARBONITRILE AS ANTIBACTERIAL AGENTS**

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**ABSTRACT.** The extensive use of antimicrobial drugs and their resistance against bacterial infections have led to discover new antimicrobial compounds. In this study, we wish to report, one-pot synthesis of 2-amino-3-cyanopyridine derivatives (1a-14a). These compounds were synthesized in the presence of Cu(OAc)$_2$ as a highly effective heterogeneous acid catalyst. Here we evaluated the antimicrobial activities of these compounds against different species of microorganisms including gram positive and gram negative bacteria as well as fungi. Standard antimicrobial methods include disc diffusion and Broth microdilution method according to the protocol of the Clinical and Laboratory Standards Institute (CLSI). Synthesis of 2-amino-3-cyanopyridine derivatives were done via reaction of aromatic aldehydes, acetoephone derivatives, malononitrile and ammonium acetate in the presence of Cu(OAc)$_2$ under reflux condition. The results show compound 2-amino-6-(4-chlorophenyl)-4-phenylicarbonitrile (10a) had the best antimicrobial efficacy toward C. albicans, E. faecalis, P. aeruginosa and E. coli. In conclusion, comparing the structure and activity of the compounds (10a), this compound with the presence of Cl residue at para-position of phenyl ring improves the antibacterial and antifungal activity.

**KEY WORDS:** Multicomponent reaction, 2-Amino-4,6-diarylpypidine-3-carbonitrile, One-pot reaction, Cu(OAc)$_2$, Antimicrobial

**INTRODUCTION**

The pyridine ring is one of the most important heterocyclic structural moieties which are found in pharmaceuticals and natural products [1, 2]. Among pyridine derivatives, 2-amino-3-cyanopyridines have been found to be an important materials which exhibit optical [3], and biological activities such as anti-fungal [4], antimicrobial [5], antitumor [6], anti-inflammatory activities [7, 8], cannabindin receptor agonists [9], and kinase inhibitors [10]. 2-Amino-3-cyanopyridines are important and also very versatile intermediates in preparing variety of heterocyclic compounds [11, 12]. Numerous methods have been reported for the synthesis of 2-amino-3-cyanopyridines. This method involves the condensation of a chalcone or carbonyl compound with malononitrile and ammonium acetate. However, some of the commonly used methods are plagued by certain drawbacks such as long reaction time, use of volatile solvents, low yields, harsh reaction conditions, critical isolation procedures, and expensive catalysts. Therefore, it is necessary to develop an improved route for the synthesis of 2-amino-3-cyanopyridines under mild reaction conditions. Recently, ytterbium perfluorooctanoate in ethanol [13], 2,2,2-trifluoroethanol [14], N,N,N',N'-tetra- bromobenzene-1,3-disulfonamide [TBDDA] and poly(n-bromo-n-ethylbenzene-1,3-disulfonamide) [PBBSS] [15], [Bmim][BF$_4$] [16], MgO [17], bismuth nitrate pentahydrate [18], cellulose sulfuric acid [19], SnO$_2$/SiO$_2$ nanocomposite [20], ethylammonium nitrate [21], were used for the synthesis of 2-amino-3-cyanopyridines. In this regard, a part of our research program aimed at developing of organic synthesis via solid acid catalyst. We reported Cu(OAc)$_2$ as an new catalyst for the synthesis of 2-amino-4,6-diarylpypidine-3-carbonitrile and also we have intended to evaluate the antimicrobial potencies of the synthesized compounds.

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EXPERIMENTAL

Chemistry

All compounds were purchased from Merck and Fluka chemical company and used without any additional purification. FT-IR spectra were run on a Bruker, Equinox 55 spectrometer. A Bruker (DRX-400 Avanes) NMR was used to record the $^1$H-NMR spectra. Melting points were determined by a Buchi melting point B-540 B.V.CHI apparatus and were uncorrected. The products were characterized by FT-IR, $^1$H-NMR, and their physical properties were compared with those reported in the literature.

Typical procedure for preparation of 2-amino-4,6-diarylpuridine-3-carbonitrile in the presence of Cu(OAc)$_2$

In a 25 mL round bottom flask, aldehyde (1 mmol), acetophenone derivative (1 mmol), malononitrile (1 mmol), ammonium acetate (1.5 mmol), Cu(OAc)$_2$ (0.1 g) and ethanol (3 mL) were charged and mixed under reflux condition. The progress of reaction was monitored by TLC. After completion of the reaction, the mixture was cooled and filtered to isolation of solid product. To obtain pure product, it was washed with ethanol.

Antimicrobial assays

Antimicrobial effect of all agents against two Gram-positive and two Gram-negative bacteria including Staphylococcus aureus (ATCC29737), Escherichia coli (ATCC15224), Pseudomonas aeruginosa (ATCC9027), Enterococcus faecalis and Candida albicans as fungus strain was carried out by two standard antimicrobial method include disc diffusion and Broth microdilution method according to the protocol of the Clinical and Laboratory Standards Institute (CLSI). A stock suspension of each synthesized agent was made in suitable solvent and final suspension was prepared in Mueller-Hinton Broth (MHB) media at 4500 to 1 µg/mL concentrations.

Primary disc diffusion method

Disc diffusion method was used for the primary evaluation of antimicrobial susceptibility of the tested agents. A total of 100 µL of each bacterial suspension (with turbidity of $1.5 \times 10^8$ CFU/mL) were streaked on brain heart infusion (BHI) agar plates separately. Then, sterile blank 6-mm filter paper discs contain 50 µL of each agent was placed on the plates. The plates were left under laminar air flow for 15 min and incubated for 24 h. After incubation, the zone of inhibition around each disc was measured. Paper disc containing solvent and sterile water were used as control group and negative control, respectively. Also, antibiotic standards for each microorganism according to performance standards for antimicrobial susceptibility testing were applied for standard control. These procedures were repeated for 6 times.

Determination of minimum inhibitory (MIC) and bactericidal (MBC) concentrations

To prepare bacterial suspensions for inoculation, microorganisms were cultured in MHB up to reach turbidity of the 0.5 McFarland standards (equivalent to OD600 = 0.12) using a biophotometer, then were diluted 1:20 to yield $5 \times 10^6$ CFU/mL. Using a 96-well micro plate containing 90 µL MHB medium with the desired concentration of each compound, 10 µL of prepared inoculums suspension was inoculated to obtain final microbial concentration at approximately $5 \times 10^5$ CFU/mL or $5 \times 10^4$ CFU/well.
Cu(OAc)$_2$ as a promoter for one-pot synthesis of 2-amino-4,6-diarylpyridine-3-carbonitrile

MHB without any agent and microbe was used as negative control, MHB cultured microorganisms were used as positive controls, ampicillin and gentamycin were applied as standard controls and blank wells contain MHB media with the desired concentration of agent with no bacteria inoculation. Optical density of each well was measured at OD600 by microplate reader (BioTek, Power Wave XS2) after 24 h incubation at 37 °C. In the case of fungi *candida albicans*, all microdilution tests were done in RPMI 1640 media.

MIC value was defined as the lowest concentration of antimicrobial agent in which 90% of the growth of microorganism is inhibited.

To determine MBC, three concentrations of each agent that was equal and higher than MIC, were spread on BHI agar plates and incubated for 24 h in 37 °C incubator and then, the colonies were counted. The MBC was defined as the lowest concentration in which the number of colonies was less than 3 on each plate. These procedures were repeated for 3 times.

Statistical analysis

The results obtained from each antimicrobial test were analyzed using one-way analysis of variance (one-way ANOVA). Due to the presence of interaction effect, multiple comparisons were performed using One-way ANOVA/Tamhane post hoc tests to determine the differences between means. A P value of ≤0.01 was considered to be statistically significant. Values are expressed as means ± SD.

RESULTS AND DISCUSSION

Initially, we have carried out the four-component reaction of benzaldehyde (1 mmol), acetophenone (1 mmol), malononitrile (1 mmol) and ammonium acetate (1.5 mmol) in the presence of Cu(OAc)$_2$ under various conditions (Table 1). Ethanol was found to be the preferred solvent for this one-pot transformation under reflux condition in the presence of Cu(OAc)$_2$ (0.1 g) after 2 hours (Table 1, entry 7). At the beginning of the reaction, the substrates were dissolved completely in the medium to form a homogeneous mixture, but near the completion of the reaction, the system became a suspension, and the product precipitated at the end of the reaction. To our delight, almost full conversion of substrates into a product was found according to TLC. The mixture was allowed to cool at room temperature and then, the resultant precipitate was isolated by filtration, washed with cold ethanol carefully and recrystallized from ethanol. Scope of the synthesis of 2-amino-3-cyanopyridines was investigated in Table 2.

Various aromatic ketones are suitable substrates for the reaction. Electron-deficient aromatic aldehydes could react very readily at shorter time with higher yields. Aliphatic aldehydes gave just moderate yields. Surprisingly, while para-substituted and meta-substituted aromatic aldehydes tolerated very well for the transformation, ortho-substituted aromatic aldehydes gave trace products. There was also no report for the product coming from ortho-substituted aromatic aldehydes. Obviously, the reactivity of aldehyde is the key factor for this one-pot transformation. According to the above results, our proposed mechanism is depicted in Scheme 1.

Antimicrobial assessment

Among tested agents, compound (10a) presented the greatest inhibition zones against all organisms tested, except *S. aureus*. Although 2-amino-6-(4-methylphenyl)-4-(4-chlorophenyl)pyridine-3-carbonitrile (3a) showed sufficient antibacterial activity in concentration tested against *C. albicans* only. According to the results of microdilution susceptibility test, sterile water and DMSO did not induce antimicrobial effect against all tested microorganisms. The one way ANOVA and Tukey tests revealed that there was a significant difference amongst the groups. Compound (10a) showed the lowest MIC and therefore greatest inhibitory effect among the medicaments tested followed by the (3a). The results of MICs and MBCs are summarized in Table 3.
Table 1. Synthesis of 4,6-diphenyl-2-amino-3-cyanopyridine under various conditions.

| Entry | Catalyst (g) [mol %] | Condition | Time (h) | Yield\(^{\circ}\) (%) |
|-------|----------------------|-----------|----------|----------------------|
| 1     | Cu(OAc)\(_2\) (0.05) | 70-80 °C  | 48       | 73                   |
| 2     | Cu(OAc)\(_2\) (0.1)  | 70-80 °C  | 48       | 92                   |
| 3     | Cu(OAc)\(_2\) (0.15) | 70-80 °C  | 48       | 92                   |
| 4     | Cu(OAc)\(_2\) (0.2)  | 70-80 °C  | 48       | 80                   |
| 5     | Cu(OAc)\(_2\) (0.05) | EtOH/reflux\(^{a}\) | 2 | 85                   |
| 6     | Cu(OAc)\(_2\) (0.05) | EtOH/reflux | 4 | 85                   |
| 7     | Cu(OAc)\(_2\) (0.1)  | EtOH/reflux | 2 | 95                   |
| 8     | Cu(OAc)\(_2\) (0.15) | EtOH/reflux | 2 | 95                   |
| 9     | Cu(OAc)\(_2\) (0.2)  | EtOH/reflux | 2 | 95                   |
| 10    | Yb(PFO)\(_3\) [2.5] | EthOH/reflux\(^{b}\) | 4 | 90 [22] |
| 11    | TBBDA [4,53]         | EthOH/reflux\(^{c}\) | 1.5 | 90 [24] |
| 12    | TFE                  | EthOH/reflux\(^{c}\) | 6 | 90 [23] |
| 13    | [Bmin][BF\(_4\)]    | Stirred at 60 °C\(^{e}\) | 4 | 92 [25] |
| 14    | Cellulose-\(\text{SO}_3\)\(_2\H [0.05] | H\(_2\)O/60 °C\(^{f}\) | 2.5 | 95 [28] |
| 15    | SnO\(_2\)/SiO\(_2\) (0.1) | EthOH/reflux\(^{d}\) | 4 | 91 [29] |

*Reaction condition: a mixture of benzaldehyde (1 mmol), acetophenone (1 mmol), malononitrile (1 mmol) and ammonium acetate (1.5 mmol) was used. \(^{\circ}\)Isolated yields. \(^{a}\)A mixture of benzaldehyde (1 mmol), acetophenone (1 mmol), malononitrile (1 mmol) and ammonium acetate (1.5 mmol) and catalyst were stirred in one-pot in ethanol (2 mL) at refluxing temperature. \(^{b}\)A mixture of benzaldehyde (2 mmol), acetophenone (2 mmol), malononitrile (2 mmol) and ammonium acetate (2.5 mmol) was used. \(^{c}\)A mixture of benzaldehyde (1 mmol), acetophenone (1 mmol), malononitrile (1 mmol) and ammonium acetate (8 mmol) was used. \(^{d}\)A mixture of benzaldehyde (1 mmol), acetophenone (1 mmol), malononitrile (1 mmol), ammonium acetate (1 mmol) and water (5 ml) was used. \(^{e}\)A mixture of benzaldehyde (2 mmol), acetophenone (2 mmol), malononitrile (2 mmol) and ammonium acetate (3 mmol) was used.

In comparison to the compounds (10a) and (3a), based on variation of substitutions on the phenyl rings, we found that, the both compounds (10a) and (3a) have an Cl residue in the para-position on the one of phenyl rings, but compound (10a) did not have any residue on the other phenyl ring, in the event that, compound (3a) have an methyl residue in para-position of the phenyl ring. Although compounds (10a) and (3a) showed the same antibacterial activities against C. albicans.

As can be seen in Table 2, all compounds with nitro group in their structures did not show any antibacterial effect. Also compound (6a) with chlorine atom at meta-position of phenyl ring is not able to inhibit the antimicrobial strain. We can predict that for 2-amino-4,6-diarylpyridine-3-carbonitrile compounds only chlorine atom at one para-position of the phenyl rings can be more effective than methyl or nitro groups at this position.
Scheme 1. Suggested mechanism for the synthesis of 2-amino-4,6-diarylpyridine-3-carbonitrile derivatives.

Table 2. Scope of one-pot synthesis of 2-amino-4,6-diarylpyridine-3-carbonitrile catalyzed by Cu(OAc)$_2$.

| Entry | $R^1$ | $R^2$ | Time (h) | Yield$^b$ (%) |
|-------|-------|-------|----------|---------------|
| 1a    | H     | 4-CH$_3$ | 2       | 95            |
| 2a    | 4-iso-propyl | 4-NO$_2$ | 3       | 92            |
| 3a    | 4-Cl  | 4-CH$_3$ | 3.5     | 89            |
| 4a    | H     | 4-NO$_2$ | 3       | 93            |
| 5a    | 4-Cl  | 4-NO$_2$ | 3.5     | 90            |
| 6a    | 3-Cl  | H      | 2       | 97            |
| 7a    | 3-NO$_2$ | 4-CH$_3$ | 2.5     | 88            |
| 8a    | 3-NO$_2$ | 4-Cl    | 3       | 85            |
| 9a    | 4-NO$_2$ | 4-Cl    | 4       | 94            |

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Table 3. The size of the zones of inhibition in mm against target organisms when treated with tested agents and standard antibiotics.

| Compounds | E. coli (HD*) | P. aeruginosa (HD) | S. aureus (HD) | E. faecalis (HD) | C. albicans (HD) |
|-----------|---------------|--------------------|----------------|-----------------|-----------------|
| 1a        | ND*           | ND                 | ND             | ND              | ND              |
| 2a        | ND            | ND                 | ND             | ND              | ND              |
| 3a        | ND            | ND                 | ND             | ND              | 12              |
| 4a        | ND            | ND                 | ND             | ND              | ND              |
| 5a        | ND            | ND                 | ND             | ND              | ND              |
| 6a        | ND            | ND                 | ND             | ND              | ND              |
| 7a        | ND            | ND                 | ND             | ND              | ND              |
| 8a        | ND            | ND                 | ND             | ND              | ND              |
| 9a        | ND            | ND                 | ND             | ND              | ND              |
| 10a       | 20            | 17                 | ND             | 13              | 11              |
| 11a       | ND            | ND                 | ND             | ND              | ND              |
| 12a       | ND            | ND                 | ND             | ND              | ND              |
| 13a       | ND            | ND                 | ND             | ND              | ND              |
| 14a       | ND            | ND                 | ND             | ND              | ND              |
| Cefazoline| 12            | -                  | -              | -               | -               |
| Ceftriaxone| -             | 26                 | -              | -               | -               |
| Azithromycin| -            | -                  | 20             | -               | -               |
| Vancomycin | -             | -                  | -              | 7               | -               |
| Amphotericin B | -   | -                  | -              | -               | 12              |

*HD: Hallow Diameter. *ND: Not Detected.

CONCLUSIONS

In conclusion, an extremely efficient and green protocol has been developed for the synthesis of 2-amino-3-cyanopyridine derivatives via one-pot condensation of aldehydes, ketones, malononitrile, and ammonium acetate in ethanol in the presence of Cu(OAc)$_2$ as catalyst. This method tolerates most of the substrates with merits like ease of work-up, no side reaction, low costs and simplicity in process, and handling and environmentally benign catalyst. Biological studies showed that compound (10a) had good antibacterial effect on E. coli, P. aeruginosa, E. faecalis and C. albicans strain. This compound with the presence of Cl residue in para-position of phenyl ring improves the antibacterial and antifungal activity.

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