A simple and ecofriendly synthesis in water of fully functionalized pyridines via an efficient one-pot three-component reaction

A. S. Shehata¹, Faida H. Ali Bamanie², M. A. Moustafa²,³, M. M. Mashaly⁴

¹Chemistry Department, Faculty of Science, (New) Damietta, Mansoura University, Egypt.
²Pharmaceutical Chemistry Department, Faculty of Pharmacy, King Abdulaziz University, KSA
³Medicinal Chemistry Department, Faculty of Pharmacy, Mansoura University, Mansoura, Egypt.


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1. Introduction

The chemistry and applications of pyridine have recently received much attention due to their usefulness as synthetic intermediates and their biological importance as agrochemicals[1-3], pharmaceuticals[4-8], dye intermediates[9-10], insecticides, adhesives[11], antifungal, antibacterial [12-14], antidepressant agents [15, 16], and antitumor activities[17]. In the light of the above findings and in continuation of our work on developing synthetic routes to heterocyclic derivatives of potential biological activity[18-20], e.g., pyridines[20], we, herein, report on safe, facile, fast and high yielding, ecofriendly synthesis of fully functionalized pyridines via an efficient one-pot three-component reaction in water.

2. Results and Discussion

It has been reported that the reaction of cyanoacetamide 1a [21] or cyanoacetic acid hydrazide 1b [22] with ylidenenitriles 2a-f had afforded 6-amino-1,6-diamino) -3-cyano-2-pyridone derivatives 5a,b[21] or 5c-h[22], respectively, (A, Scheme 1). These reactions were carried out in refluxing ethanol for 180 minutes, using piperidine or triethylamine as catalyst, and the 2-pyridones 5a-h were obtained in 66-85% yields[21,22]. These conventional methods for the synthesis of pyridines suffer at least one drawback of using hazardous solvents, long reaction time, tedious work up procedure and moderate yield of products. In addition to repeating the reported procedure A, Scheme 1 to obtain 5[21,22], we, herein, report on reobtaining the 2-pyridones 5 through modified facile, fast, higher yielding and ecofriendly procedures (B&C, Scheme 1). We have replaced ethanol by water, the most clean, safe, healthy, simple, available and economic solvent (B&C, Scheme 1). Stirring 1a,b and the ylidenemalononitrile 2a,c,e,f in water contain catalytic amount of either piperidine (Pip.) or ethanolamine (EA), at room temperature (r.t.), 25-35 °C, for as short as just 15-30 minutes reaction time, afforded the expected solid products 5a,c,e,g,h in 90-95 % yields based on the isolated products, which were in considerable degrees of purity. The unambiguous synthesis of the 2-pyridone 5a,c,e,g,h, by the recent facile, fast and efficient technique of one-pot three-component reaction, confirmed its structure (C&D, Scheme 1). Thus, 1a,b, the appropriate aldehyde 6a-d and malononitrile 7a were allowed to react together, under the suitable reaction conditions, to afford the same respective 2-pyridone 5. This confirmation reaction was carried out twice, once in water (C, Scheme 1) and once, else, in ethanol (D, Scheme 1) as the reaction solvent and, always, the planned 2-pyridone 5 were obtained. On replacing the ylidenemalononitrile 2a,c,e,f by the, relatively, lesser reactive ethyl ylideneacetoacetate 7b,d in the above mentioned reactions A&B, Scheme 1, the corresponding 2-pyridone derivative 5b,d,f was obtained, but after a much larger reaction time of 120-180 minutes and in a lesser yield of products of 77-83%. The same trend of results was, generally, obtained on carrying out the one-pot three-component reactions of 1a,b, the appropriate aldehyde 6a,d and ethyl cyanoacetate 7b (C&D, Scheme 1) as an unambiguous synthesis, confirming the formation of the respective 2-pyridone 5b,d,f.

Melting points (m.p.), mixture melting points (mix.m.p.), (of 2-pyridone mixtures prepared by mixing of equal amounts of 5 obtained out of procedures A-D, Scheme 1), thin layer chromatography (TLC) and infrared (IR) spectroscopy have been used to confirm obtaining the same respective derivative 5 through the different procedures A-D, Scheme 1.
Formation of 5 (Scheme 1) could be explained via initial Michael addition of the active methylene group of 1 to the β-carbon of 2 to form the acyclic intermediate 3a-h. The amic nitrogen of 3 attacks a cyano carbon to form the six membered ring intermediate 4a-h, which tautomerises and undergoes dehydrogenation to achieve the conjugated and more stable polysubstituted 2-pyridone system of 5 as the final reaction product[21,22].

General procedure C:

The suitable aliphatic or aromatic aldehyde 6a-d (0.01 mol) and the appropriate active methylene compound 7a,b (0.01 mol), was added to a solution of cyanoacetamide 1a or cyanoacetic acid hydrazide 1b (0.01 mol) in 30 ml of distilled water, which was containing 2 drops of ethanolamine or piperidine as a catalyst. The reaction mixture was stirred at room temperature for 15–180 minutes. The solid product that was formed was collected by filtration, washed by cold 1:1 ethanol: water solution and crystallized from 1:1 ethanol: N,N-Dimethylformamide (DMF).

6-Amino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (5a).

Orange crystals: yield: 88 %; m.p: 300 °C; mix. m.p: 300 °C [21]; IR (KBr, cm⁻¹): γ = 3396, 3190 (NH, NH₂), 2216 (2CN), 1682 (CO).

Ethyl 6-Amino-3-cyano-2-oxo-1,2-dihydropyridine-5-carboxylate (5b).

Orange crystals: yield: 77 %; m.p: 299-300 °C; mix. m.p: 299-300 °C [21]; IR (KBr, cm⁻¹): γ = 3387, 3192 (NH, NH₂), 2210 (CN), 1701 (CO ester), 1630 (CO amide); ¹H-NMR (600MHz, DMSO), δ ppm = 7.9 (1H, s, ring CH), 6.7 (2H, q, OCH₂), 4.27 (2H, q, OCH₂), 1.23 (3H, t, CH₃).

Anal. for C₇H₁₀N₂O₃ (207.2): Caled.: C, 52.17; H, 4.38; N, 20.28%; Found: C, 52.08; H, 4.22; N, 20.17%.

1.6-Diamino-2-oxo-1H-pyridine-3,5-dicarbonitrile (5c).

Orange crystals: yield: 89 %; m.p: 272-4 °C; mix. m.p: 270-2 °C [21]; IR (KBr, cm⁻¹): γ = 3351, 3204 (2NH, 2NH₂), 2200-2100 (CN), 1729 (CO ester), 1650 (CO). ²H-NMR (600MHz, DMSO), δ ppm = 7.9 (1H, s, ring CH), 6.7 (2H, q, OCH₂), 4.27 (2H, q, OCH₂), 1.23 (3H, t, CH₃).

Anal. for C₇H₁₀N₂O₃ (207.2): Caled.: C, 52.17; H, 4.38; N, 20.28%; Found: C, 52.08; H, 4.22; N, 20.17%.

1.6-Diamino-2-oxo-1H-pyridine-3,5-dicarbonitrile (5d).

Orange crystals: yield: 80 %; m.p: 289-290 °C; mix. m.p: 289-290 °C [21]; IR (KBr, cm⁻¹): γ = 3434 (2NH₂), 2246 (2CN), 1652 (CO).

Ethyl 1,6-diamino-3-cyano-2-oxo-1H-pyridine-5-carboxylate (5f).

Colorless crystals: yield: 90 %; m.p: 286-7 °C; mix. m.p: 285-7 °C [21]; IR (KBr, cm⁻¹): γ = 3361, 3166 (2NH₂), 2222 (2CN), 1682 (CO).

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Colorless crystals: yield: 83.5 %; m.p: 143-4 °C ; mix. m.p: 140-2 °C [21]; IR (KBr, cm⁻¹): γ = 3447, 3308 (2NH₂ ), 2943 (CH aliphatic ), 2218 (CN), 1697 (CO ester), 1651 (CO).

1,6-Diamino-3,5-dicyano-4-(4-chlorophenyl)-2-pyridone (5g).
Colorless crystals: yield: 95 %; m.p: >320 °C; mix. m.p: >320 °C [22]; IR (KBr, cm⁻¹): γ = 3455, 3397, 3307, 3262, 3206 (2NH₂), 2219 (CN), 1650(CO).

1,6-Diamino-3,5-dicyano-4-(4-methoxyphenyl)-2-pyridone (5h).
Colorless crystals: yield: 93%; m.p: >320 °C; mix. m.p: >320 °C [22]; IR (KBr, cm⁻¹): γ = 3457, 3392, 3307, 3323, 3215 (2NH₂), 2220 (CN), 1690(CO).

Corresponding Author:
Prof Dr M. M. Mashaly
Chemistry department
Faculty of Science (Damietta)
Mansoura University, Egypt

4. References

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