

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

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Abstract: Fully functionalized pyridines **5a-h** are synthesized in 90-95 % yields, in water, *via* one-pot three-component reaction of cyanoacetamide **1a**, cyanoacetic acid hydrazide **1b**, aldehydes **6a-d** and active methylene nitriles **7a,b** [A. S. Shehata, Faida H. Ali Bamanie, M. A. Moustafa, M. M. Mashaly: **A simple and ecofriendly synthesis in water of fully functionalized pyridines *via* an efficient one-pot three-component reaction.** Journal of American Science 2011;7(11):240-242]. (ISSN: 1545-1003). <http://www.americanscience.org>.

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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.

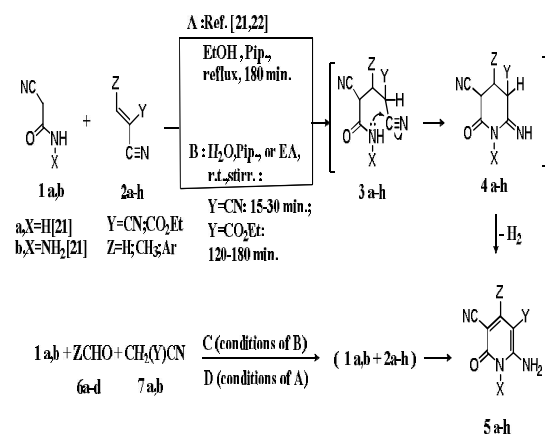
2. Results and Discussion

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 -(or 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 draw back 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 ylidenecyanoacetate **2b,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 amidic 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].



Scheme 1

3. Experimental

All melting points were obtained on a Gallenkamp melting point apparatus (open capillary tubes) and were uncorrected; IR spectra were performed on a Jasco 4100 FTIR spectrophotometer (KBr pellet) at the Department of Chemistry, Faculty of Science at (New) Damietta, Mansoura University, Damietta branch, Egypt. $^1\text{H-NMR}$ spectra were performed on a BRUKER (600 MHz) ultra shield Avance III Spectrometer at the Faculty of Science, King Abd-Elaziz University, Jeddah, K.S.A, using (TMS) as an internal stander and DMSO as a solvent. Chemical shifts were expressed as δ ppm. Microanalytical data were performed on a PERKIN-ELMER 2400 C, H, N Elemental Analyzer at the Microanalytical Unit, Cairo University, Egypt.

Preparation of 2-pyridone derivatives: for procedures A&D, see Scheme 1.

General procedure B:

A solution the suitable cinnamionitrile **2a-e** (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).

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 and was treated as in procedure B.

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}): $\gamma = 3396, 3190$ (NH, NH_2), 2216 (CN), 1640 (CO amide).

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}): $\gamma = 3387, 3192$ (NH, NH_2), 2210 (CN), 1701 (CO ester), 1630 (CO amide); $^1\text{H-NMR}$ (600MHz, DMSO), δ , ppm = 7.9 (1H, s, ring CH), 6.7 (2H, s, NH_2), 4.27 (2H, q, OCH_2), 1.23 (3H, t, CH_3).

Anal. for $\text{C}_9\text{H}_9\text{N}_3\text{O}_3$ (207.2): Calcd.: 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}): $\gamma = 3351, 3204$ (2NH_2), 2246 (2CN), 1652 (CO).

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

Orange crystals: yield: 80 %; m.p: 289-290 °C; mix. m.p: 289-290 °C [21]; IR (KBr, cm^{-1}): $\gamma = 3434$ (2NH_2), 2210 (CN), 1729 (CO ester), 1650 (CO).

1,6-diamino-4-methyl-2-oxo-1H-pyridine-3,5-dicarbonitrile (**5e**).

Colorless crystals: yield: 90 %; m.p: 286-7 °C; mix. m.p: 285-7 °C [21]; IR (KBr, cm^{-1}): $\gamma = 3361, 3166$ (2NH_2), 2222 (2CN), 1682 (CO).

Ethyl 1,6-diamino-3-cyano-4-methyl-2-oxo-1H-pyridine-5-carboxylate (**5f**).

Colorless crystals: yield: 83.5 %; m.p: 143-4 °C ; mix. m.p: 140-2 °C [21]; IR (KBr, cm^{-1}): γ = 3447, 3308 (2NH_2), 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 (2NH_2), 2219 (CN), 1650(CO).
Anal. Calcd for $\text{C}_{13}\text{H}_8\text{ClN}_5\text{O}$ (Cl=35.45, Mol.Wt: 285.7): C, 54.65; H, 2.82; N, 24.51%; Found: C, 54.45; H, 2.78; N, 24.13%.

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 (2NH_2), 2220 (CN), 1690(CO).
Anal. Calcd for $\text{C}_{14}\text{H}_{11}\text{N}_5\text{O}_2$ (Mol.Wt: 281.3): C, 59.78; H, 3.94; N, 24.9%; Found: C, 59.34; H, 3.96; N, 24.82%.

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