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# Green and eco-friendly multicomponent synthesis of 2-Hydroxypyridines under free solvent †

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**Abstract:** 2-Hydroxypyridines (or commonly named 2-pyridones) are widespread nitrogen heterocycles in natural and synthetic products and their applications in biological,

pharmaceutical and agrochemical compounds are becoming increasingly important. Therefore, several procedures have been described in the literature for the preparation of this heterocyclic framework. Among them, multicomponent reactions are current in synthetic organic chemistry where reducing reaction times, high yields and ease of product isolation are the main benefits of this method.

In order to study the effect of the aforementioned method under greener medium, we herein describe a novel one-pot route for the design of 4,6-diaryl-3-cyano-2-pyridone derivatives under free solvent conditions. The three-component condensation of alkenes, ketones and ammonium acetate afforded efficiently the target heterocycles with higher yields in short time reaction comparing to a classical method.

**Keywords:** green chemistry; multicomponent; nitrogen-heterocycles; 2-Hydroxypyridines; solventless conditions.

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## 1. Introduction

2-Pyridones and their derivatives are widely found in bioactive natural products and therapeutical molecules. Their broad ranging biological activities comprise antibacterial [1], antiviral [2], anti-asthmatic agents [3], antifungal [4], anticancer [5], anti-inflammatory [6] and antidiabetic [7]. They have been useful scaffolds for synthesizing pharmacological compounds due to their attractive structural and biological features. Examples for substantial active pyridone containing drugs are shown in figure 1 [8].

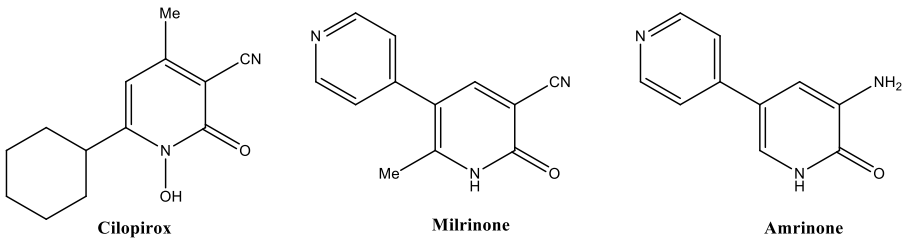



**Figure 1.** Examples of drugs with 2-pyridone moiety

Multicomponent reactions (MCRs) are considered as a powerful method in developing green synthetic strategy. They are known to make a unique product selectively via three or more components in only one step [9]. Moreover, MCRs form one of the most efficient tools in new chemical synthesis, with high atom economy, rapid and easy implementation, environmentally friendly and a various target-oriented synthesis [10]. In addition, the use of organic synthesis under free solvent conditions is one of the fundamental objectives of green chemistry. These reactions are much facile for the work up and proceed effectively and cleanly. Therefore, these reactions acquired high celebrity and worth rapidly. [11]

The development of an easy and effective procedure for the synthesis of 2-Hydroxpyridines is an active field of study, and there is still room for improvement implying milder reaction conditions and better product yields [12]. Encouraging by these facts and in continuous of our efforts to apply green synthesis and especially solventless conditions to the preparation of heterocycles [13-19] we herein report a simple and convenient three-component reaction for the preparation of 4,6-diaryl-3-cyano-2-pyridone derivatives (figure 2).

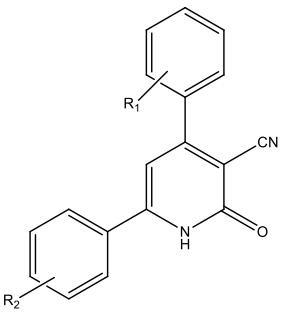


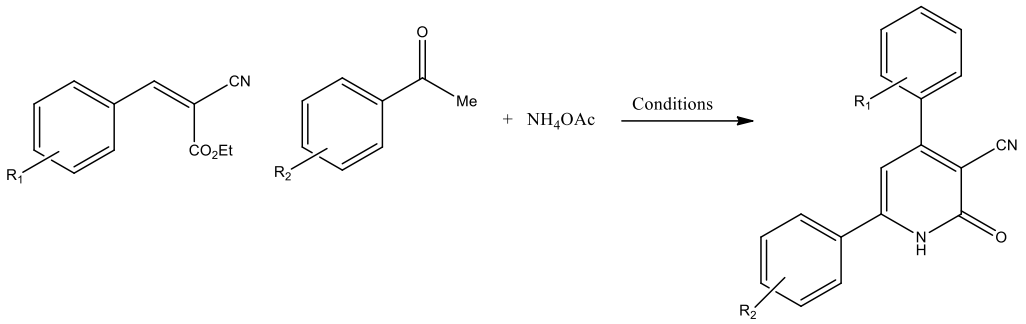

**Figure 2.** Structure of 4,6-diaryl-3-cyano-2-pyridones.

## 2. Results and Discussion

The present study was carried out to evaluate the effect of solvent on the multi-component condensation of alkenes (**1**) with ketones (**2**) and ammonium acetate (**3**) in the aim to synthetizes 4,6-substituted aryl-3-cyano-2-pyridones (**4**)**.**

The reagents were mixed and heated according to two methods, the first by using ethanol as solvent and the second under dry conditions. The progress of reaction was monitored by TLC and after completion, the crude was washed by ethanol and diethyl ether to afford the corresponding products. The results of reaction are listed in Table 1.

**Table 1.** Synthesis of 2-pyridone derivatives.




| Product | 1 | 2 | 3 |
|---|---|---|---|
| $R_1$ | 4-F | 2-Cl | 4-F |
| $R_2$ | 3,4-diMe | 4-OMe | 4-Me |
| Yield (%) | 60 | 46 | 62 |

Reaction conditions: Alkenes (0.01 mol), ketones (0.01 mol) and ammonium acetate (0.01 mol) under free solvent conditions.

## 3. Experimental Procedure

A mixture of aromatic alkenes (0.01 mol), aromatic ketones (0.01 mol) and ammonium acetate (0.01 mol) was heated up to 80°C without any solvent. Once the reaction is completed as indicated by TLC (3-6 h), the crude product was cooled to room temperature and washed few times with diethyl ether and ethanol. The product was filtered to afford the corresponding heterocycle.

Product **3:** Yield: 62%; white solid; m.p. > 266 °C; IR (KBr): 3845(N-H); 3393(C-$H_{arom}$); 2212 (CN); 1643 (C=O) and 1513(C=C).

## 4. Conclusion

In this paper, we have reported a novel, simple and easy synthesis of 2-pyridones based on condensation of three components in a single reaction under solvent-free and green chemistry conditions. This procedure includes some advantages like short time reaction, higher yields, benign reaction conditions and ecofriendly method.

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