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Efficient Multicomponent Catalyst-Free Synthesis of Substituted 2-aminopyridines †

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† Presented at the 24th International Electronic Conference on Synthetic Organic Chemistry, 15 November–15 December 2020; Available online: https://ecsoc-24.sciforum.net/.

Published: date

Abstract: 2-aminopyridines scaffolds are an important class of nitrogen heterocyclic compounds with a wide range of biological activities [1,2] (Figure 1). Multicomponent reactions (MCRs) are useful method for the construction of nitrogen heterocyclic compounds. In this context, syntheses of 2-aminopyridines derivatives via MCRs have attracted considerable attentions in recent years [3,4]. We present, in this work, a rapid and efficient synthesis of 2-aminopyridine derivatives, via catalyst-free four-component method. This protocol provides a simple and practical approach to functionalized 2-aminopyridnes from readily available substrates under solvent free conditions.

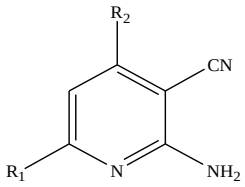

Figure 1: Structure of 2-aminopyridines

Keywords: 2-aminopyridine; catalyst-free; solvent-free; green conditions; MCRs

1. Introduction

The development of new methods for the synthesis of nitrogenous heterocyclic compounds represents a great challenge in organic synthesis and in medicinal chemistry [5]. 2-Aminopyridines are promising substituted pyridines which have been shown to be biologically active molecules. Additionally 2-aminopyridines are often used as ligands in inorganic and organometallic chemistry because of their chelating abilities. They could potentially serve, if substituted with optically active groups, as chiral auxiliaries or chiral ligands in asymmetric reactions [6,7]. For these reasons, 2-aminopyridines are valuable synthetic targets. Due to their high pharmacological interests, there are a considerable number of synthetic methods which have been described in the literature for a long time [5,7–9].

Recently, the use of solvent-free methods represents a very powerful green chemical technology procedure from both the economical and synthetic point of view. There is also another route to combine economic aspects with the environmental, that is, the multicomponent reaction [10].

In this context, we present here an efficient multicomponents catalyst-free synthesis of substituted 2-aminopyridines. This green approach was developed using readily available compounds, inexpensive and free solvent conditions.

2. Results and Discussion

In the present study, a novel and efficient procedure for the synthesis of 2-aminopyridines has been presented. In connection with our recent investigation on the synthesis of nitrogen heterocycles under solvent-free conditions, we describe here multicomponent method to the synthesis of 2-aminopyridines efficiently without catalyst. This approach is a process in which four easily accessible components are combined in a single reaction to produce a final product. Initially, a model reaction was conducted using acetophenone (0.1 mol), malononitrile (0.1 mol), benzaldehyde (0.1 mol) and (0.1 mol) of ammonium carbonate at room temperature in the under solvent-free conditions (Table 1); the product is confirmed by their NMR, IR and MS analysis.

Table 1. optimization of conditions**.**

R_1	R_2	Yield (%)
C_6H_5-	4-Cl-C_6H_4-	65 [a]; 80 [b]

[a]: room temperature**;** [b]: 80°C.

In order to evaluate the generality of this model reaction, we encouraged to extend this reaction to a variety of acetophenone, so we have examined this reaction employing the optimized conditions. As results we have found that using heating method gives good yields (Table 2).

Table 2. Synthesis of 2-aminopyridines**.**

R_1	R_2	Yield (%)
C_6H_5-	4-Cl-C_6H_4	65 [a]; 80 [b]
p-Cl-C_6H_4-		50 [a]; 90 [b]
p-$CH_3C_6H_4$-		45 [a]; 88 [b]
m-$CH_3OC_6H_4$-		58 [a]; 95 [b]
2,4-Cl-C_6H_3-		

3. Experimental Procedure

Herein, we describe a simple and efficient synthesis of 2-aminopyridines derivatives udderssolvent free conditions.

General procedure: A mixture of acetophenone derivatives (0.1 mol), malononitrile (0.1 mol), 4-Cl-benzaldehyde (0.1 mol) and (0.1 mol) of ammonium carbonate was stired at room temperature under solvent-free. After cooling, the solid obtained was washed several times with diethyl ether to give 2- aminopyridines derivatives.

4. Conclusions

We have developed an efficient synthesis of 2-aminopyridines via a reaction between acetophenone derivatives, malononitrile, aldehyde derivatives and ammonium carbonate. The compounds structure is confirmed by spectral analysis. This approach includes some advantages such as mild reaction conditions, high yields and environmentally friendly process. The simplicity of this synthetic route will offer an attractive alternative to the conventional methods.

Acknowledgments: The authors wish to thank Directorate General for Scientific Research and Technological Development (DGRSDT), the University of Tlemcen and the University Center of Ain Témouchent for the

financial support. We also thank the Ministerio de Economía, Industria y Competitividad (Spain) (Project MAT2017- 86109-P) for financial support.

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