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# Multicomponent, Solvent-Free Synthesis of 4-Substituted Aminopyrido[2,3-*d*]pyrimidines Derivatives †

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† Presented at the 27th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-27), 15–30 November 2023; Available online: https://ecsoc-27.sciforum.net/.

**Abstract:** 4-substituted aminopyrido [2,3-*d*]pyrimidines derivatives **1a–f** were synthesized via the multicomponent reaction of 2-aminopyridines, triethyl orthoformate, and diverse primary amines under solvent-free conditions. The present work creates a variety of fluorescent heterocyclic compounds in a short time and with good yields. The structures of all synthesized compounds were established by IR, $^{1}$H, and $^{13}$C NMR analysis.

**Keywords:** pyrido[2,3-*d*]pyrimidine; 2-aminopyridine; solvent-free conditions; multi-component reaction



**Citation:** Belhadj, F.; Kibou, Z.; Seijas, J.A.; Vázquez-Tato, M.P.; Choukchou-Braham, N. Multicomponent, Solvent-Free Synthesis of 4-Substituted Aminopyrido[2,3-*d*]pyrimidines Derivatives. *Chem. Proc.* **2023**, *14*, 113. https://doi.org/10.3390/ecsoc-27-16080

Academic Editor: Enrique Cabaleiro Lago

Published: 15 November 2023



## 1. Introduction

Pyrido[2,3-*d*]pyrimidines are one of the most interesting nitrogen heterocycles and play a vital role in progressive drug design and discovery [1]. They also have various biological activities such as antitumor [2], antipyretic [3], antihypertensive [4], antifungal [5], antibacterial [6], and anti-inflammatory activities [7]. More specifically, pyrido[2,3-*d*] pyrimidines have been shown to be effective against dihydrofolate reductases (DHFR) [8], tyrosine kinases, and adenosine kinase [9]. Moreover, the synthesis of these fused heterocyclic compounds provides an interesting challenge in medicinal chemistry [10–12].

Continuing our research in the field of new heterocyclic compounds of biological interest [13–15], we previously reported the synthesis of functionalized pyrido[2,3-*d*]pyrimidines [16] (Figure 1). Encouraged by these results, we decided to extend this methodology to the synthesis of new pyrido [2,3-*d*] pyrimidines via a multi-component reaction under solvent-free conditions.

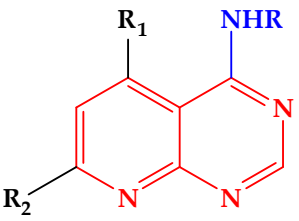



**Figure 1.** General structure of 4-substituted aminopyrido[2,3-*d*]pyrimidines.

## 2. Results and Discussion

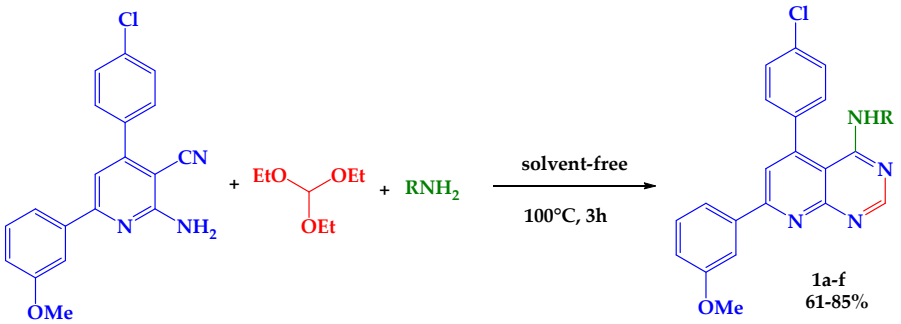
In our current studies on the synthesis of 4-substituted aminopyrido [2,3-*d*] pyrimidines, we reported a simple and new multicomponent reaction in eco-friendly economical and environmental conditions.

Recently, multi-component reactions (MCRs) have become a promising approach to achieve such molecular diversity and complexity [17]. In this work, we present a new efficient method for the synthesis of aminopyrido [2,3-*d*] pyrimidines derivatives from 3-cyano-2-aminopyridine under solvent-free conditions.

*Synthesis of 4-Aminopyrido[2,3-d]pyrimidines Derivatives*

The 4-aminopyrido [2,3-*d*] pyrimidines **1a–f** were easily obtained via a one-pot reaction of 3-cyano-2-aminopyridines, triethyl orthoformate, and diverse primary amines. The mixture was heated for 3h without a solvent to obtain compounds **1a–f** in good yields (61–85%). The primary amines used were benzylamine, butylamine, propylamine, hexylamine, phenylethylamine, and tryptamine (Table 1).

**Table 1.** Synthesis of 4-aminopyrido[2,3-*d*]pyrimidines derivatives.




| Product | Primary Amine | Yield (%) |
|---|---|---|
| 1a | Benzylamine | 85 |
| 1b | Butylamine | 79 |
| 1c | Butylamine | 71 |
| 1d | Cyclohexylamine | 69 |
| 1e | Phenylethylamine | 65 |
| 1f | Tryptamine | 61 |

The structures of the compounds **1a–f** were confirmed by spectral analysis. The IR spectra (KBr, $\nu_{max}$, $cm^{-1}$) showed the absence of $NH_2$ and CN as well as the appearance of (C=C) at 1542–1559 $cm^{-1}$, (C=N) at 1669–1690 $cm^{-1}$, and NH at 3462–3540 $cm^{-1}$.

$^1$H NMR ($CDCl_3$, δ, ppm) showed the appearance of $OCH_3$ stretch at $\delta_H$ 3.86–3.88 ppm and NH stretch at $\delta_H$ 5.17–5.79 ppm, as well as $H_{pyrid}$ stretch at $\delta_H$ 7.09–7.36 ppm and $H_{pyrimid}$ stretch at $\delta_H$ 7.76–8.65 ppm.

## 3. The Proposed Mechanism for the Formation of 4-Aminopyrido[2,3-*d*]pyrimidines 1a–f

The proposed mechanism for the formation of 4-aminopyrido[2,3-*d*] pyrimidines **1a–f** is described in Figure 2.

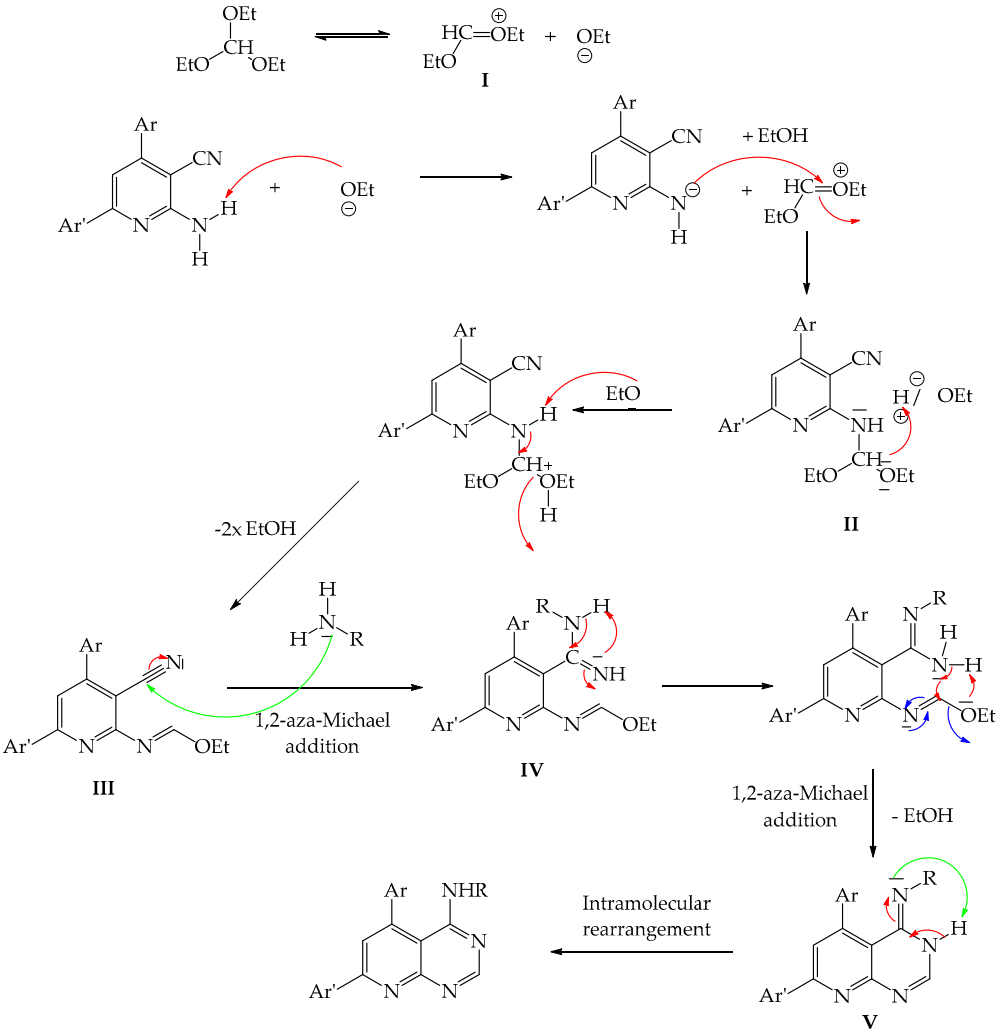



**Figure 2.** The proposed mechanism for the formation of 4-aminopyrido[2,3-*d*]pyrimidines **1a–f**.

The reaction begins with the formation of intermediate **I** followed by nucleophilic addition of the "$NH_2$" group of 2-aminopyridines on the double bond to form intermediate **II**. After rearrangement and 1,2-aza-Michael addition between the primary amine and the "CN" group of product **III**, intermediate **IV** is obtained. The latter undergoes a rearrangement and a 1,2-aza-Michael addition intramolecularly to form product **V.** Finally, an aromatization step to obtain the desired 4-aminopyrido[2,3-*d*]pyrimidines.

## 4. Experimental Procedure

General procedure for the synthesis of 4-aminopyrido[2,3-*d*]pyrimidines **1a–f:**

The products **1a–f** were obtained by the reaction between 10 mmol of 3-cyano-2-aminopyridine, 10 mmol of primary amine, and 10 mmol of triethyl orthoformate. The mixture was heated for 3h at 100 °C. After the completion of the reaction (TLC), the residue was purified by column chromatography over silica gel using a mixture of nhexane–EtOAc (5:5) as the eluent. All the desired compounds were obtained as a white solid [16].

## 5. Conclusions

In conclusion, we have successfully developed a new route for the synthesis of 4-substituted aminopyrido[2,3-*d*]pyrimidines derivatives via a multi-component reaction under solvent-free conditions with good yields. This new MCR provides a general and efficient strategy for the construction of structurally diverse fused pyridopyrimidines skeleton.

**Author Contributions:** Conceptualization, N.C.-B. and Z.K.; validation, Z.K., J.A.S., and M.P.V.-T.; formal analysis, F.B.; investigation, F.B.; writing—original draft preparation, F.B.; writing—review and editing, N.C.-B.; supervision, N.C.-B. All authors have read and agreed to the published version of the manuscript.

**Funding:** The study is supported by the General Directorate for the Scientific Research and Technological Development (DGRSDT) and the Universities of Tlemcen, Algeria.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** The original contributions presented in the study are included in the article, and further inquiries can be directed to the corresponding author.

**Acknowledgments:** The authors wish to thank Directorate General for Scientific Research and Technological Development (DGRSDT) and the University of Tlemcen, Algeria, for the financial support. We also thank the Ministerio de Economía, Industria y Competitividad (Spain) for financial support.

**Conflicts of Interest:** The authors declare no conflicts of interest, financial or otherwise.

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