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Proceeding Paper

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

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Abstract: 4-substituded aminopyrido [2,3-*d*] pyrimidine derivatives **1a-f** were synthesized via multicomponent reaction of 2-aminopyridines, triethyl orthoformate and various primary amines under solvent-free conditions. The present work creates a variety of fluorescent heterocyclic compounds in short time and 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

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1. Introduction

Pyrido [2,3-*d*] pyrimidine ring structure is one of the most interesting heterocycles in drug design [1], these later witches containing this moiety have various pharmacological 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 were considered as inhibitors of 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 have previously reported on 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 mulicomponent reaction under solvent-free conditions.

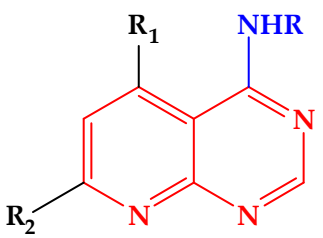


Figure 1. General structures of 4-substituted aminopyrido [2,3-*d*] pyrimidines.

2. Results and Discussion

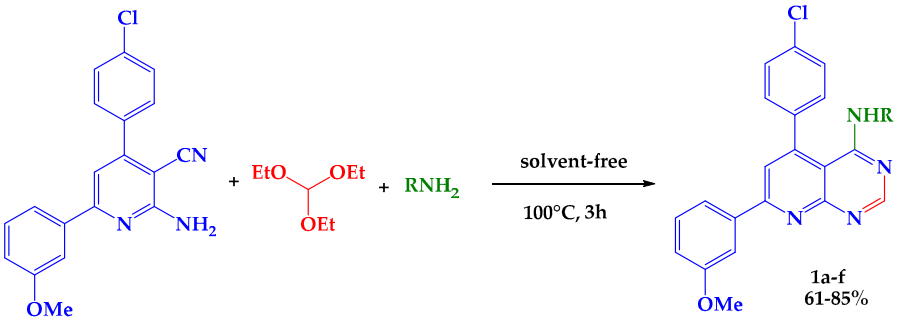
In our current studies on the synthesis of 4-substitute aminopyrido [2,3-*d*] pyrimidines, we have reported a simple and new multicomponent reaction in the eco-friendly economical and environmental conditions.

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

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

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

Table 1. Synthesis of 4-aminopyrido [2,3-*d*] pyrimidines derivatives. The primary amines used are: benzylamine, butylamine, propylamine, hexylamine, phenylethylamine and tryptamine.



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

The Structure of the synthesized compounds **1a-f** were confirmed by spectral analysis. The IR spectra (KBr, ν_{max}, cm^{-1}) showed the absence of NH_2, CN and the appearance of (C=C) at 1542–1559 cm^{-1}, (C=N) at 1669–1690 cm^{-1} and NH at 3462–3540 cm^{-1}.
the ^1H NMR ($CDCl_3$, δ, ppm) showed the appearance of OCH_3 stretch at δ_H 3.86–3.88 ppm and NH stretch at δ_H 5.17–5.79 ppm, H_{pyrid} stretch at δ_H 7.09–7.36 ppm and $H_{pyrimid}$ stretch at δ_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.

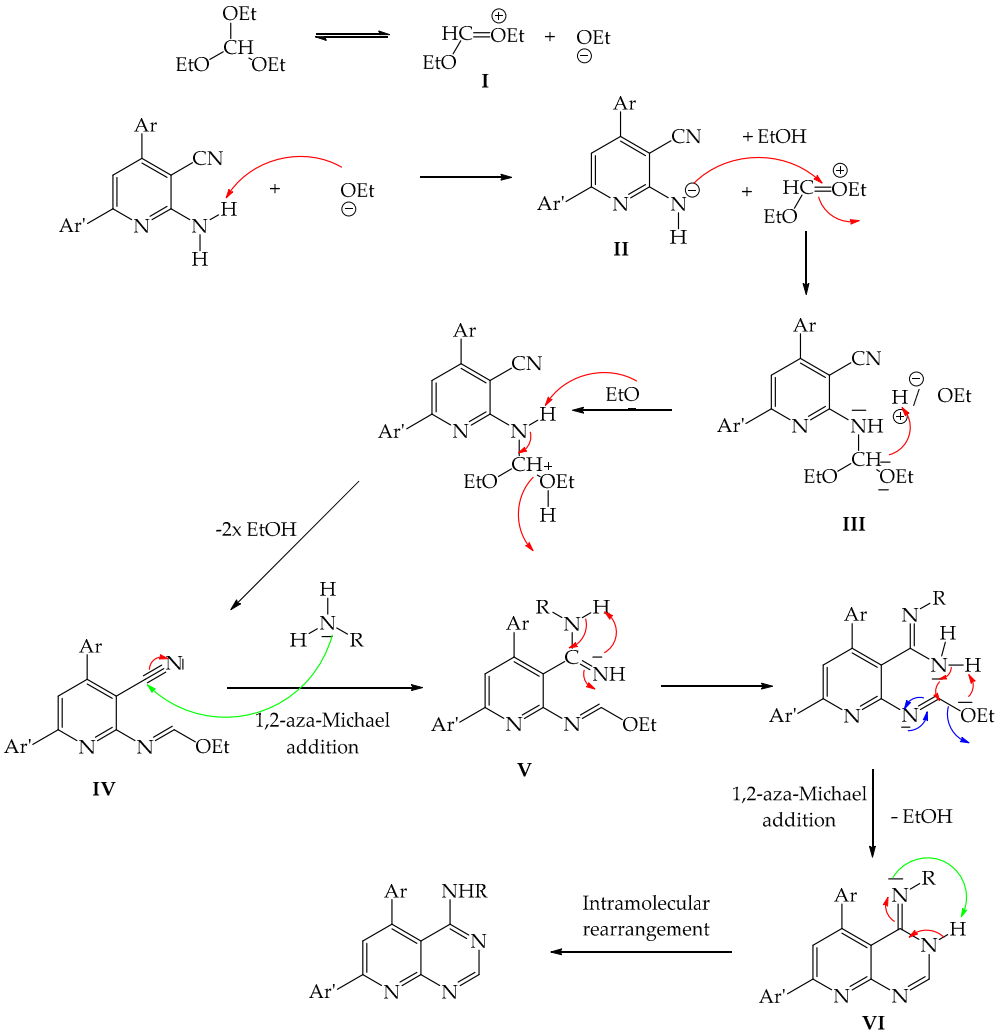


Figure 2. The proposed mechanism for the formation of 4-aminopyrido [2,3-*d*]pyrimidines **1a-f**. The reaction begins with the formation of the intermediate **I** followed by nucleophilic addition of the "NH_2" group of 2-aminopyridines on the double bond to form intermediate **III**. After rearrangement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

4. Experimental Procedure

General procedure for the synthesis of pyrido [2,3-*d*] pyrimidines **1a-f:** A mixture of 3-cyano-2-aminopyridine (10 mmol), primary amine (10 mmol) and triethyl orthoformate (10 mmol) was heated for 3 h. 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 white solid [16].

5. Conclusions

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

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

References

1. Buron, F.; Mérour, J.Y.; Akssira, M.; Guillaumet, G.; Routier. S. Recent advances in the chemistry and biology of pyridopyrimidines. *Eur. J. Med. Chem.* **2015**, *95*, 76–95. https://doi.org/10.1016/j.ejmech.2015.03.029.
2. Grivsky, E.M.; Lee, S.; Sigel, C.W.; Duch, D.S.; Nichol, C.A., Synthesis and antitumor activity of 2, 4-diamino-6-(2,5-dimethoxybenzyl)-5-methylpyrido [2,3-d] pyrimidine. *J. Med. Chem.* **1980**, *23*, 327–329. https://doi.org/10.1021/jm00177a025.
3. Piper, J.; McCaleb, G.; Montgomery, J.; Kisliuk, R.; Gaumont, Y.; Sirotnak, F., Syntheses and antifolate activity of 5-methyl-5-deaza analogs of aminopterin, methotrexate, folic acid, and N10-methylfolic acid. *J. Med. Chem.* **1986**, *29*, 1080–1087. https://doi.org/10.1021/jm00156a029.
4. Broom, A.D.; Shim, J.L.; Anderson, G.L., Pyrido [2, 3-d] pyrimidines. IV. Synthetic studies leading to various oxopyrido [2, 3-d] pyrimidines. *J. Org. Chem.* **1976**, *41*, 1095–1099. https://doi.org/10.1021/jo00869a003.
5. Hanafy, F.I., Synthesis and antifungal activity of some new pyrido [2, 3-*d*] pyrimidines. *Eur. J. Chem.* **2011**, *2*, 65–69. https://doi.org/10.5155/eurjchem.2.1.65-69.303.
6. Panneerselvam, P.; Rather, B.A.; Reddy, D.R.S.; Kumar, N.R., Synthesis and anti-microbial screening of some Schiff bases of 3-amino-6, 8-dibromo-2-phenylquinazolin-4(3H)-ones. *Eur. J. Med. Chem.* **2009**, *44*, 2328–2333. https://doi.org/10.1016/j.ejmech.2008.04.010.
7. Alagarsamy, V.; Raja Solomon, V.; Sheorey, R.; Jayakumar, R., 3-(3-Ethylphenyl)-2-substituted hydrazino-3H-quinazolin-4-one Derivatives: New Class of Analgesic and Anti-Inflammatory Agents. *Chem. Biol. Drug Des.* **2009**, *73*, 471–479.
8. https://doi.org/10.1111/j.1747-0285.2009.00794.x.
9. Le Corre, L.; Girard, A.-L.; Aubertin, J.; Radvanyi, F.; Benoist-Lasselin, C.; Jonquoy, A.; Mugniery, E.; Legeai-Mallet, L.; Le Merrer, Y., Synthesis and biological evaluation of a triazole-based library of pyrido [2, 3-d] pyrimidines as FGFR3 tyrosine kinase inhibitors. *Org. Biomol. Chem.* **2010**, *8*, 2164–2173. https://doi.org/10.1039/B923882D.
10. Gangjee, A.; Adair, O.; Queener, S.F., Synthesis of 2, 4-diamino-6-(thioarylmethyl) pyrido [2, 3-d] pyrimidines as dihydrofolate reductase inhibitors. *Bioorg. Med. Chem.* **2001**, *9*, 2929–2935. https://doi.org/10.1016/s0968-0896(01)00223-1.
11. Shakir, M.A.; Jaafar, A.A. and Rafid, M.M.H., Synthesis and Preliminary Antimicrobial Activity of New Schiff Bases of Pyrido [1,2-A] Pyrimidine Derivatives with Certain Amino Acids. *Med. Chem.* **2014**, *22*, 2161–0444. https://doi.org/10.4172/2161-0444.1000206.
12. Tare. M.; Mandeep.K. M. and Praveen. P. N. R., Application of quinazoline and pyrido [3,2-d] pyrimidine templates to design multi-targeting agents in Alzheimer's disease. *RCS Adv.* **2017**, *7*, 22360–22368. https://doi.org/10.1039/C7RA02889J.
13. Wang. D.W.; Li.Q.; Wen.K.; Ismail.I.; Liu.D.D.; Niu.C.W.; Wen. X.; Yang.G.F.; Xi.Z. Synthesis and Herbicidal Activity of Pyrido [2,3-d] pyrimidine-2,4-dione-Benzoxazinone Hybrids as Protoporphyrinogen Oxidase Inhibitors. *J. Agric. Food Chem.* **2017**, *65*, 5278–5286. https://doi.org/10.1021/acs.jafc.7b01990.
14. Baba-Ahmed, I.; Kibou, Z.; Daoud, I.; Belhadj, F.; Belarbi, L.; Daich, A.; Choukchou-Braham, N. Synthesis, Molecular Docking and ADME-TOX Studies of New Tacrine Analogs as Promising for Alzheimer's Disease Therapy. *Curr. Org. Chem.* **2022**, *26*, 1218-1233. https://doi.org/10.2174/1385272826666220914114544.
15. Belhadj, F.; Kibou, Z.; Vázquez-Tato, M.P.; Seijas, J.A.; Choukchou-Braham. N. Highly Efficient Approach o the Synthesis of New Cromeno [2,3-d] pyrimidine Derivatives. *Chem Proc* **2022**, *4*.
16. Belhadj, F.; Kibou, Z.; Benabdallah, M.; Aissaoui, M.; Rahmoun, M.N.; Villemin, D.; Choukchou-Braham, N. Synthesis and Biological Evaluation of New Chromenes and Chromeno [2,3-d] pyrimidines. *S. Afr. J. Chem.* **2021**, *75*, 150–155. https://doi.org/10.17159/0379-4350/2021/v75a18.
17. Belhadj, F.; Kibou, Z.; Cheikh, N.; Choukchou-Braham, N.; Villemin, D. Convenient access to new 4-substituted aminopyrido [2, 3-d] pyrimidine derivatives. *Tetrahedron Lett.* **2015**, *56*, 5999–6002. https://doi.org/10.1016/j.tetlet.2015.09.042.
18. Graebin, C.S.; Ribeiro, F.V.; Rogério, K.R.; Kümmerle, A.E. Multicomponent Reactions for the Synthesis of Bioactive Compounds: A Review. *Curr. Org. Synth* **2019**, *16*, 855–899. https://doi.org/10.2174/1570179416666190718153703.