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Convenient Access to New 4-Substituted Aminopyrido [2,3-*d*]pyrimidine derivatives

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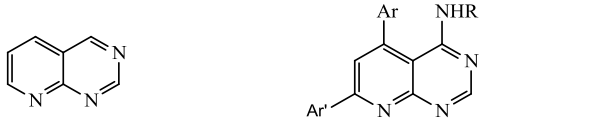
ABSTRACT

We describe in this paper, a novel series of pyrido[2,3-*d*]pyrimidines **6-11** derived from 3-cyano-2-aminopyridines **4a-f** via formamidine formation **5a-f** followed by selective nucleophilic addition, with different primary amines, under solvent-free conditions. The structures of the newly synthesized compounds are confirmed by spectral analysis. This new approach includes some important aspects such as mild reaction conditions, high yields, and environmental friendly process. The operational simplicity of this synthetic route will offer an attractive alternative to the conventional methods.

1. Introduction

The pyrimidine structures are an important class of nitrogen heterocyclic compounds with a wide range of biological activities such as antitumor [1], antipyretic [2], antihypertensive [3], antifungal [4], antibacterial [5], and anti-inflammatory activity [6]. Some pyrido[2,3-*d*]pyrimidines (Fig 1) were considered as inhibitors of dihydrofolate reductases (DHFR) [7] or tyrosine kinases [8]. Moreover, these fused pyrimidine systems are present in purine bases of DNA and RNA [9].



Pyrido[2,3-*d*]pyrimidines 4-substituted amino pyrido[2,3-*d*]pyrimidines

Figure1. Structures of pyrimidines

Therefore, these fused heterocyclic compounds have been extensively investigated and their synthetic preparations are well-documented [10-14]. However, the synthesis of pyrimidine ring required strict reaction conditions, long reaction time and low yields [15-17].

As part of our ongoing development of efficient protocols for the preparation of biologically active heterocyclic derivatives with versatility of organic synthon [18-20], we present, in this work, a new synthesis of 4-substituded amino pyrido[2,3-*d*]pyrimidine derivatives starting from 2-aminopyridines via formamidines formation, followed by a selective nucleophilic addition, with different primary amines, under solvent-free conditions. Structures of these compounds were confirmed by spectroscopy analysis.

2. Results and discussion

The retro-synthetic analysis prompted us to investigate the applicability of 3-cyano-2-aminopyridines **4a-f** as starting materials, so our new approach for the synthesis of this pyrido[2,3-d]pyrimidine derivatives **6-11** is a multistep one (Scheme 1). The first step based on the formation of 3-cyano-2-aminopyridine **4a-f,** then, the second step involved the use of formamidines **5a-f** as key intermediates. Finally, pyrido[2,3-d]pyrimidine derivatives **6-11** are easily prepared by a cyclisation reaction between compounds **5a-f** and various primary amines as nucleophilic agents.

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