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Synthesis of novel tetrahydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridine derivatives

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A series of new tetrahydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridine derivatives were synthesized in refluxing acetic acid *via* one-pot, three-component condensation of 4-hydroxy coumarine, aldehydes and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine.

Introduction

Pyrazoles and fused pyrazoles are well-recognized as a central unit in medicine and therapeutics.[1] Among differently connected heterocyclic cores to pyrazoles, pyrazolo pyridines are subjected to intense research due to their promising biological activities such as anti-bacterial,[2] antitumor,[3] antiviral,[4] corticotropin-releasing factor 1 (CRF_1) antagonist,[5] psychotropic,[6] antichagasic,[7] anti-inflammatory.[8] They are also known to be cholesterol formation,[9] Acetyl-CoA carboxylase (ACC),[10] HIV reverse transcriptase,[11] phosphodiesterase 3/4 (PDE3/4) cyclin dependent kinase 1 (CDK1),[12] and B-Raf kinase inhibitors.[13] Several methods have been devised for the synthesis of substituted pyrazolopyrimidines,[14] among them multi-component reactions[15] are of increasing importance because of their convergent, atom economical and productive nature.

Multi-component reactions (MCRs)[16] constitute an important pathway for one-pot construction of polycyclic compounds. This valuable feature have made the MCR chemistry a powerful procedure, underwent various modifications to increase the synthetic efficiency of this reaction. The changes should be shifted toward using reduced amounts of toxic reagents and solvents which aiming to resolve growing concerns about environmental issues. This is an important point in the production of new drug molecules considering economic and industrial aspects.[17]

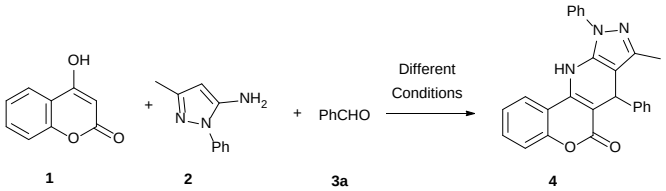
Considering our interests toward developing new and environmentally benign pathways for the synthesis of novel heterocycles,[18-22] herein we report the synthesis of dihydrochromeno[4,3-*b*]pyrazolo incorporated coumarine and pyrazolopyridine moieties.

Results and discussion

Chemistry

At first, the reaction of 4-hydroxy coumarine (**1**), 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**2**) and benzaldehyde (**3a**) was selected as a model reaction to establish the appropriate condition (Table 1). Literature surveys investigated that the presence of acidic catalyst is necessary for this reaction. So, we chosen sulfamic acid as a cheap and powerful catalyst. The reaction was investigated in different solvents at reflux temperature (including ethanol, methanol, water, dimethyl formamide and acetonitrile). These solvents needed longer times (24-36 h) for completion, affording the desired product in moderate yields. Due to the obtained results, we decided to try the reaction in acetic acid acting as solvent and catalyst (entry 8). Performing the reaction in acetic acid revealed as the most suitable solvent system. The product was obtained in comparable yield in 18 h.

Table 1 Optimization of model reaction.



1 2 3a 4

Entry	Solvent	Catalyst	Yield (%)[a]
1	EtOH[b]	Sulfamic acid	31
2	H_2O[b]	Sulfamic acid	43

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