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Highly Efficient Approach to the Synthesis of New Chromeno[2,3-*d*] Pyrimidines Derivatives †

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Abstract: A simple, easy and efficient approach has been developed for the synthesis of new and functionalized chromeno [2,3-*d*] pyrimidines derivatives by treatment of 2-amino-3-cyano-4*H*-chromenes with acetic anhydride under solvent-free conditions., this new protocol presents several advantages such as mild conditions, higher yields and greener work-up.

Keywords: 5*H*-chromeno [2,3-*d*] pyrimidines; 2-amino-3-cyano-4*H*-chromene; solvent-free conditions

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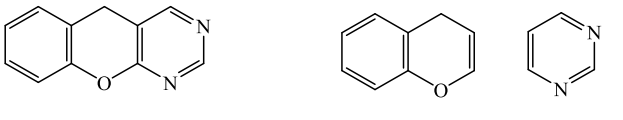
1. Introduction

Chromeno[2,3-*d*] pyrimidines constitute an important class of heterocyclic compounds having diverse biological activities such as antifungal [1], anti-tumor [2], antibacterial [3], antihypertensive [4]. Chromeno [2,3-d] pyrimidine structure is constituted from two rings: 4*H*-Chromene and Pyrimidine (Figure 1).



Chromeno[2,3-*d*]pyrimidine 4*H*-Chromene pyrimidine

Figure 1. General structure of chromeno [2,3-*d*] pyrimidines.

Chromenes scaffolds represent a privileged structural motif well-distributed in biologically active natural products and also in cosmetics and pigment industries [5]. The pyrimidine structure is a basic nucleus present in DNA and RNA [6] with a wide range of biological activities ranging from antitumor [7] to antipyretic [8], antihypertensive [9], anti-fungal [10], antibacterial [11], and anti-inflammatory activities [12].

As part of our continuous effort towards the development of useful synthetic methodologies toward heterocyclic compounds [13–17], the present work reports an efficient process for the synthesis of chromeno[2,3-d] pyrimidines derivatives while trying to respect the criteria of the green chemistry in which we employed, as a key step the condensation of 2-amino-3-cyano-4*H*-chromenes with acetic anhydride, this latter is an excellent

intermediate in the synthesis of various nitrogenous heterocycles, more particularly the synthesis of pyrimidines by their reaction with unsaturated 2-aminonitriles [18–20].

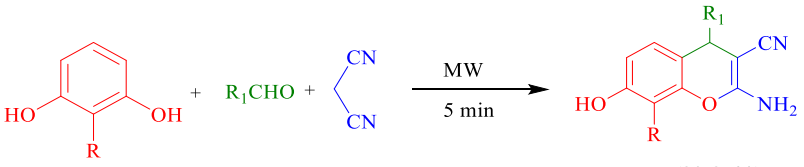
2. Results and Discussion

The synthesis of the new chromeno [2,3-*d*] pyrimidines derivatives were obtained through a two following steps: the first step was based on the synthesis of 2-amino-3-cyano-4*H*-chromenes followed by cyclization and condensation to the chromeno[2,3-*d*] pyrimidines in the second and last step.

2.1. Synthesis of 2-Amino-3-cyano-4H-chromenes

2-amino-3-cyano-4*H*-chromenes were obtained by condensation of substituted resorcinol, malononitrile and aromatic aldehydes in stoichiometric amounts under microwave irradiations for 5 min [21] (Table 1).

Table 1. Synthesis of 2-amino-3-cyano-4*H*-chromenes.



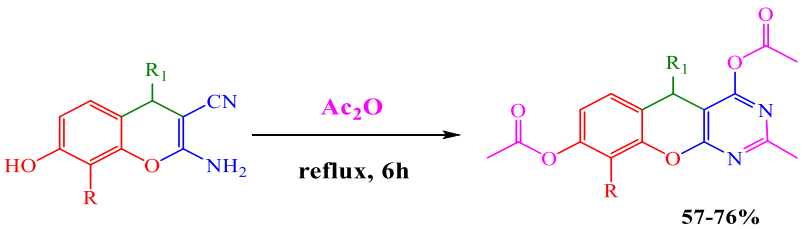
R = H, Me
R_1 = C_6H_5, 4-ClC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4, 2,4-diClC_6H_3

R	R_1	Yield (%)
H	C6H5	90
H	4-ClC6H4	93
H	4-BrC6H4	91
H	4-MeC6H4	90
H	2,4-diClC6H3	95
Me	C6H5	85
Me	4-ClC6H4	89

2.2. Synthesis of Chromeno[2,3-d] Pyrimidins Derivatives

In the aim of obtaining new derivatives of chromeno[2,3-*d*] pyrimidines, we have decided to perform the reaction of 2-amino-3-cyano-4*H*-chromenes with acetic anhydride. The mixture was heated for 6 hours under solvent-free conditions (Table 2).

Table 2. Synthesis of chromeno[2,3-d] pyrimidines.



R = H, Me
R_1 = C_6H_5, 4-ClC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4, 2,4-diClC_6H_3

R	R_1	Yield (%)
H	C6H5	65
H	4-ClC6H4	76
H	4-BrC6H4	72

H	4-MeC6H4	67
H	2,4-diClC6H3	70
Me	C6H5	57
Me	4-ClC6H4	65

The synthesized compounds were obtained with good yields and were confirmed by spectral analysis. The IR spectra showed the absence of NH_2, CN and OH, the ^1H NMR showed the appearance of CH_3 stretch at δ_H 2.26 ppm and OCH_3 stretch at 2.24–2.48 ppm. The ^{13}C NMR showed δ_C at 21.28–26.08 ppm.

3. Experimental Procedure

General procedure for the synthesis of 2-amino-3-cyano-4*H*-chromenes:

A mixture of aromatic aldehyde (10 mmol), substituted resorcinol (10 mmol), malononitrile (10 mmol) was irradiated in microwave single mode to 300 W during 5 min and under pressure of 12 bar. After the completion of the reaction (TLC). the residue was diluted with 30 mL of CH_2Cl_2. The organic layer obtained was washed with water (3 × 20 mL), then with solution of saturated NaCl (10 mL), dried on $MgSO_4$, filtered and evaporated under vacuum. The desired compounds were obtained as white solids.

General procedure for the synthesis of chromeno[2,3-*d*] pyrimidines:

A mixture of 2-amino-3-cyano-4*H*-chromenes (5 mmol) and anhydride acetic 20 mL was heated for 6 h. The reaction mixture was cooled down to room temperature, diluted with 30 mL of CH_2Cl_2. The organic layer obtained was washed with water (3 × 20 mL), then with solution of saturated NaCl (10 mL), dried on $MgSO_4$, filtered and evaporated under vacuum. The desired compounds were obtained as white solids.

4. Conclusions

In conclusion, we have successfully developed a novel and efficient approach for the synthesis of new chromeno[2,3-*d*] pyrimidines derivatives under solvent free conditions with good yields. The originality of our synthetic strategy is based on the use of acetic anhydride as cyclization agents. This methodology, easy to execute, with rapid access and giving good yields, opens a new route for the synthesis of various substituted nitrogen heterocycles of biological and pharmaceutical importance.

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

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