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Synthesis of Heterocycle via Vilsmeier-Haack Reaction †

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Abstract: Since its discovery, the Vilsmeier-Haack reaction has always been a subject of great interest to organic chemists and continues to attract considerable attention. It is a powerful tool for synthesis in organic chemistry. For years of research our laboratory interested in the development and functionalization of heterocyclic compounds; as a part of our research, new heterocyclic systems were achieved in good yields via the Vilsmeier-Haack reaction starting from derivatives of 2-aminothiophene. All newly synthesized compounds were confirmed by ^{1}H NMR, ^{13}C NMR analysis and some showed a positive biological activity.

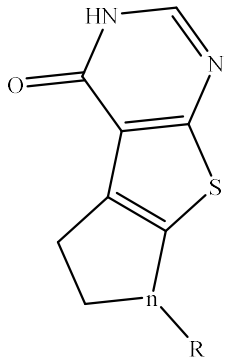
Keywords: heterocycle; thiophene; aminothiophene; vilsmeier-haack reaction; gewald reaction; biogical activities

1. Introduction

Inorganic acid halides react with disubstituted amides to form active complexes, halomethyl-eniminium salts, called Vilsmeier-Haack reagents [1] initially used to introduce formyl groups into activated aromatic and heteroatom compounds [2], and then it knows several uses in chlorination [3], chloroformylation [4], aromatization [5], cyclization [6,7], ... etc.

In recent years, Thiophene and its derivatives have known an increasing importance as intermediates to biologically active compounds [8] and in organic synthesis [9]. 2-Amino-3-functionally substituted thiophene derivatives are useful precursors in the azo dye and pharmaceutic industries [10]. Thieno[2,3-*d*]pyrimidin-4(3*H*)-one is a common building block for drugs with diverse pharmaceutical activities [11]. It has been widely used for the preparation of new antibacterial [8], antitumor agents [12], and as central nervous system agents [13].

Our laboratory since its opening interested in the development and functionalization of heterocyclic compounds [13–17] as a part of our research, we try to introduce Vilmeier-Haack reaction in the synthesis of new Thieno[2,3-*d*]pyrimidin-4(3*H*)-one derivatives (Figure 1) combining the easiness and efficiency.

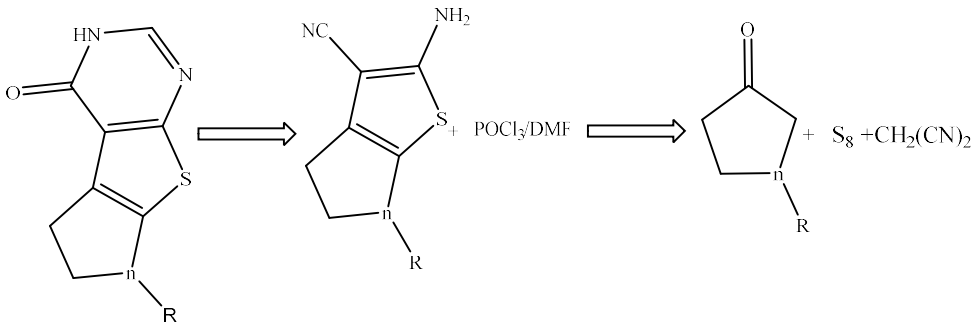


n:CH_2,C_2H_4,C_4H_8,..
R:H,CH_3

Figure 1. Thieno[2,3-*d*]pyrimidin-4(3*H*)-one derivatives.

2. Results and Discussion

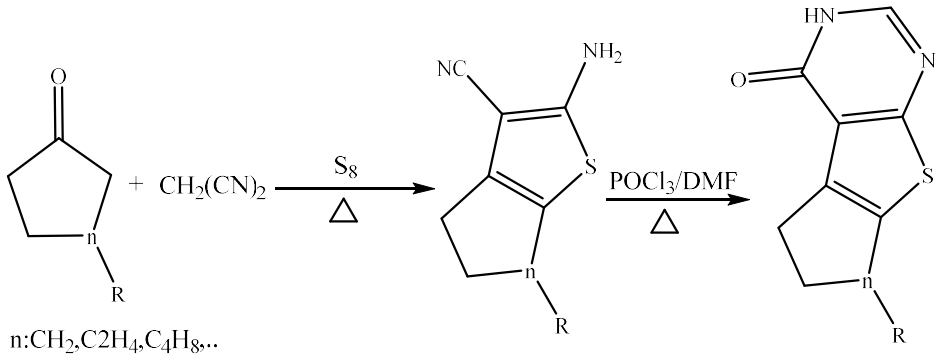
We propose the retrosynthesis showed below (Scheme1).



n:CH_2,C_2H_4,C_4H_8,..
R:H,CH_3

Scheme 1. retrosynthetic scheme of the synthesis of Thieno[2,3-*d*]pyrimidin-4(3*H*)-one derivatives.

By a modification of the Gewald reaction [18], we obtained derivatives of 2-amino-3-cyanothiophene, which contain 2 reactive sites to aim the cyclisation and then prepare derivatives of Thieno[2,3-*d*]pyrimidin-4(3*H*)-one (Scheme 2).



n:CH_2,C2H_4,C_4H_8,..
R:H,CH_3

Scheme 2. synthesis of Thieno[2,3-*d*]pyrimidin-4(3*H*)-one derivatives.

Then we tried to extend our study on acetophenone derivatives since thiophenes prepared from cyclones give a positive biological activity. However, in this communication we report that the conditions described above led to the formylation of thiophene instead of cyclisation confirmed by the NMR spectrum (1H δ = 9.55 ppm) and the presence of $2CH_3$ δ = 3.22 ppm shown in (Figure 2).

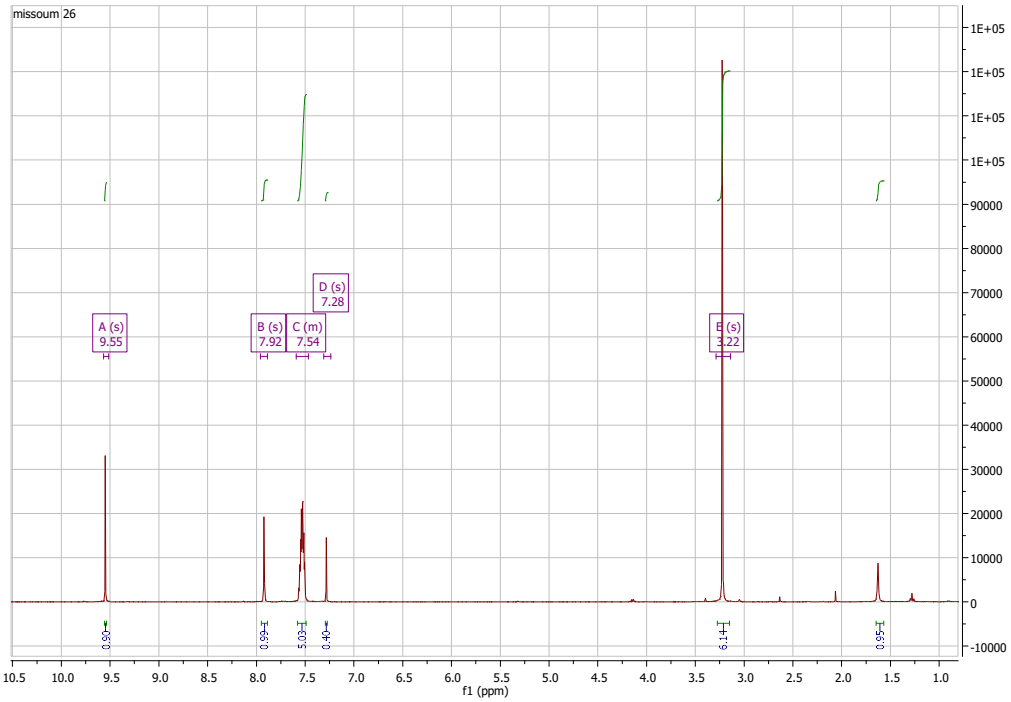


Figure 2. NMR spectrum of (Z)-N′-(3-cyano-5-formyl-4-phenylthiophen-2-yl)-N,N-dimethylformimidamide.

Recently we are working on an alternative route to prepare the corresponding 5-phenyl-thieno[2,3-d]pyrimidin-4(3*H*)-one derivatives.

3. Conclusions

In the present study, we have developed a simple, rapid and effective way to synthesis different derivatives of thieno[2,3-d]pyrimidin-4(3*H*)-one. Coming studies will give more results about of 2-amino-4-phenylthiophene-3-carbonitrile.

4. Experimental Porcedure

4.1. Synthesis of 2-Aminothiophene-3-crabonitrile

0.01 mol (1 eq.) cyclohexanone, 0.01 mol (1 eq.), malononitrile and 0.011 mol (1.1 eq.) of sulfur was stirred, then morpholine (10 mL, 1.1 eq.) is added under agitation. The mixture is then heated to 50–60 °C after the completion of the reaction (verified by TLC analysis) The solution is then decomposed on a mixture of water and ice. The solid obtained was recrystallized from methanol to give aminothiophene as a brown solid.

4.2. Synthesis of Thieno[2,3-d]pyrimidin-4(3H)-one

The Vilsmeier-Haack reagent is first prepared then 2-amino-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carbonitrile dissolved in a minimum of DMF is added drop by drop, once the addition is completed, the mixture is stirred for 3 h, and then carried to reflux. The evolution of the

reaction was followed by TLC. The solution is then decomposed on a mixture of water and ice. The solid obtained was recrystallized from ethanol.

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