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Development of Bioactive Poly-Heterocycles via the Synthesis of Substituted 2-Acetylthiophenes †

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Abstract: Thiophenes are versatile compounds with diverse applications in chemistry, pharmacy, and advanced materials due to their stable structure and unique properties. 2-Acetylthiophene and thiophene-2-carbaldehyde analogues of 2-substituted thiophenes are highly interesting chemical compounds in scientific research due to their use as scaffolds in the synthesis of novel bioactive polyheterocycles. In our research, we established a rapid and efficient two-step procedure to synthesize a novel series of sulfur and nitrogen heterocycles from the chloroformylation of β-chloroacroleins by the Vilsmeier-Haack reaction followed by a two-step cyclization process to obtain 2-acetylthiophene in moderate yields, which is then used to prepare novel polyheterocyclic compounds, including bis-thiophenes and thieno-pyrroles. This innovative approach opens up new possibilities for the development of bioactive compounds with potential applications in various fields.

Keywords: 2-acetylthiophenes; bis-thiophenes; Vilsmeier-Haack reagent; β-chloroacroleins; chloroformylation; bioactive poly-heterocycles.

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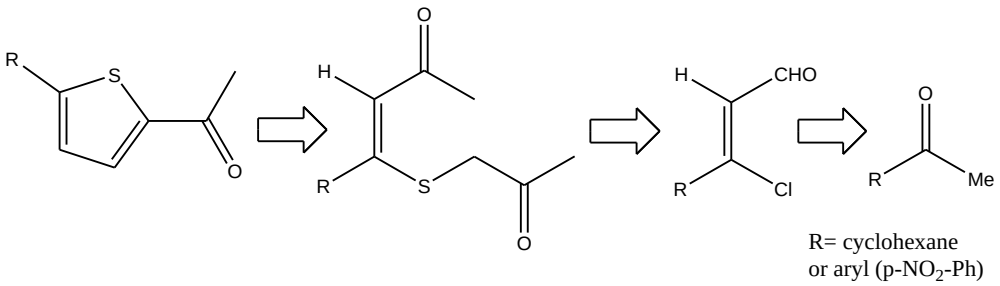
1. Introduction

Sulfur heterocycles, valued for their bioactive properties [1,2], are essential in the treatment of cardiovascular diseases, cancer [3,4], and Alzheimer's disease [5]. 2-Acetylthiophene is an organic compound characterized by an aromatic thiophene ring with an acetyl group at the 2-position. It is often used as an intermediate in the synthesis of various chemicals, including fragrances, drugs [6], and functional materials. In our work, we start with the preparation of β-chloroacroleins via the Vilsmeier-Haack [7,8] reaction, which has a co-determinable value in heterocycle chemistry, followed by cyclization to obtain our target molecule. Our laboratory has extensive experience in the synthesis of variously substituted thiophenes [9]. We have established a rapid, efficient, and environmentally friendly method to synthesize 2-acetylthiophene derivatives. These derivatives are obtained in good yields and serve as valuable intermediates for new medicinal compounds.

2. Results and Discussion

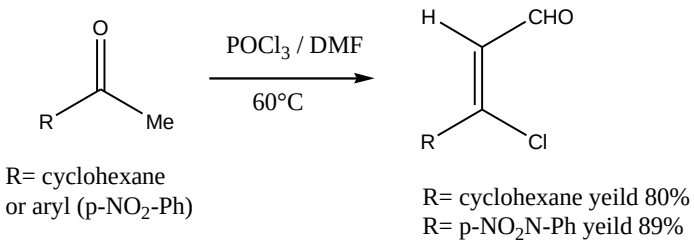
In our research, we have established a rapid and efficient two-step procedure to synthesize a novel series of sulfur and nitrogen heterocycles from the chloroformylation [7,8] of ketone derivatives to prepare β-chloroacroleins by the Vilsmeier-Haack reaction [10]

followed by a two-step cyclization process to obtain the corresponding 2-acetylthiophene in moderate yields [11].



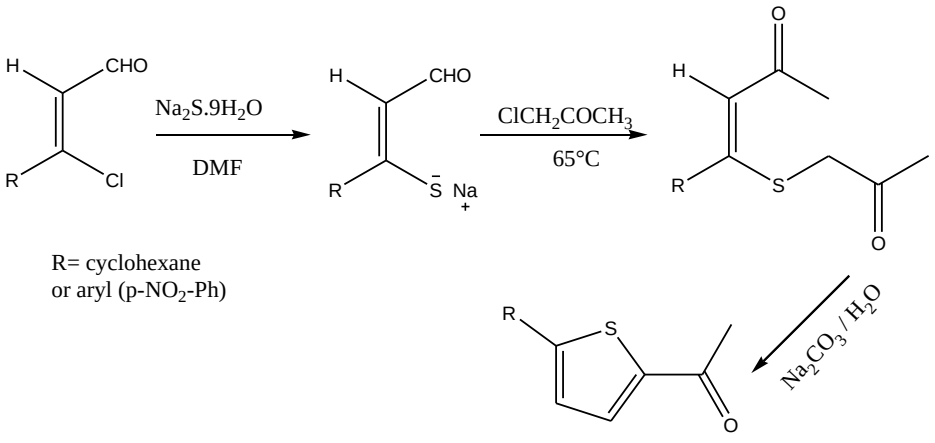
Scheme 1. Retrosynthetic scheme of the synthesis of 5-aryl-2-acetylthiophenes derivatives.

First, the Vilsmeier-Haack reagent prepared by reacting phosphorus oxychloride POCl3 and DMF at 0 °C. The chloromethyleneiminium salt interacts with the enol of acetophenone to form an iminium salt which is rapidly hydrolyzed to isolate the corresponding β-chloroacroleins in good yields.



Scheme 2. Syhthesis of β-chloroacroleïne derivatives.

The intermediates obtained were reacted with sodium sulfide nonahydrate ($Na_2S.9H_2O$) which formed thiolate as an intermediate, chloroketone was added followed by sodium carbonate to give 2-acetylthiophene derivatives in moderate yields.



Scheme 3. Synthesis of 2-acetylthiophene derivatives.

3. Experimental

3.1. Synthesis of β-Chloroacroleïne Derivatives

1.5 eq of DMF were added dropwise to 1.5 eq of phosphoryl chloride $POCl_3$ at 0 °C. The mixture was stirred until salt was formed. 1 eq of ketone dissolved in DMF was added

slowly with stirring. The reaction medium was maintained at 60 °C. The progress of the reaction was monitored by TLC until the end of the reaction, the solution was brought back to room temperature and then poured onto a sodium acetate solution (10%). The pH was then adjusted to 4. The precipitated β-chloroacrolein was filtered and washed with water. Yields (80–89%).

The structures of all products were confirmed by FT-IR spectrum. The spectrum of 3-chloro-3-(4-nitrophenyl)prop-2-enal (R=p-NO2-Ph): υmax cm-1: 1683 (C=O aldehyde), 3113(C-H sp2), 1516 (C=C aromatic). Mp (76 °C).

3.2. Synthesis of 2-Acetylthiophene Derivatives

1 eq of a recently prepared β-chloroacrolein was slowly added to a solution of 1 eq of $Na_2S.9H_2O$ in DMF. The reaction mixture was stirred at 65 °C for 3 h. 1 eq of chloroacetone was added at one time. The progress of the reaction was monitored by TLC. 1 eq of Na_2CO_3 dissolved in 1 mL of water was then added to the reaction under stirring for 30 min. After cooling; the mixture was poured into an ice-water mixture. The solid obtained was isolated by filtration and washed with water then recrystallized from ethanol.yeilds (57–75%).

The structures of all products were confirmed by FT-IR spectrum. The spectrum of 1-(5-(4-nitrophenyl)thiophen-2-yl)ethanone(R=p-NO2-Ph): υmax cm-1: 1663 (C=O cétone),3113 (C-H sp2), 1558 (C=C aromatique). Mp (172 °C).

4. Conclusions

In the current communication, we discussed the synthesis of 2-acetylthiophene derivatives. In perspective, we will be interested in synthesizing a new sulfur and nitrogen poly-heterocycle from the same 2-acetylthiophene molecule following a rapid and easy synthetic approach under very mild operating conditions.

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Conflicts of Interest:

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