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Synthesis of New Thiophenic Derivatives †

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Abstract: In recent years, Thiophene and its derivatives have known an increasing importance as intermediates to biologically active compounds and in organic synthesis. 2-Amino-3-functionally substituted thiophene derivatives have been studied as probe molecules in chemical biology and drugs or hits in medicinal chemistry. The presence of the two active sites CN and NH2 in 2-Amino-3-cyano substituted thiophene derivatives offers a large number of interesting reactions such as the preparation of tetrazole derivatives very well-known by their exceptional properties. Our laboratory interested in the development and functionalization of heterocyclic compounds with promising biological and pharmacological activities including some new concept of green chemistry; as a part of our research, different types of 2-aminothiophenes were achieved in good yields that are then used to prepare tetrazole derivatives.

Keywords: thiophene; 2-aminothiophene; Gewald reaction; tetrazole; biologically active compounds

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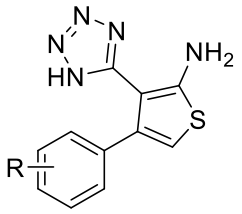
1. Introduction

2-Aminothiophene is a five-membered heterocyclic core used as precursors in the azo dye, pharmaceutic industries, and medicinal chemistry [1–3]. The most widely used technique for the preparation of this class of compounds is the condensation of a carbonyl with an active methylene and sulfur, this reaction was first described in the 1960s by Gewald [4], which has known several modifications to target a wide range of substrates, such as the use of inorganic bases such as sodium bicarbonate, sodium hydroxide, sodium carbonate instead of morpholine, pyridine, triethylamine [5], and heterogeneous phase organic reactions [6]. Although the one-pot procedure is well established, the two-step procedure in which the α,β-unsaturated alkene is first prepared by the Knoevenagel condensation of a ketone or aldehyde with an activated nitrile, followed by reaction with sulfur , gives good yields [5].

The research teams of our laboratory focus their efforts on the synthesis of new heterocyclic compounds with promising biological and pharmacological activities via modern and ecofriendly strategies [7–11]. As a part of our research, we prepared 2-aminothiophenes derivatives **2** (Scheme 1) which will be used to prepare tetrazole derivatives **1** (Figure 1).

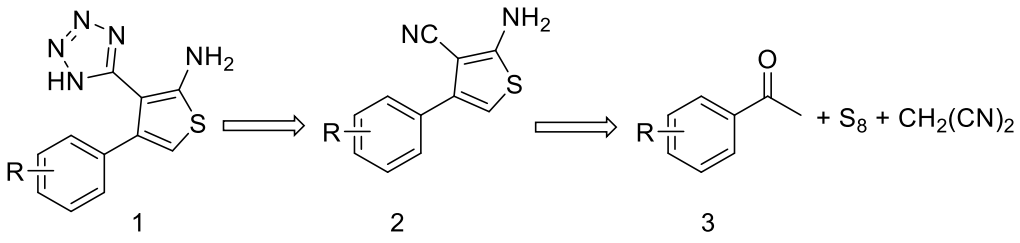


1

Figure 1. 4-Phenyl-3-(1H-tetrazol-5-yl)thiophen-2-amine derivatives.

2. Results and Discussion

In this communication, the retrosynthetic scheme that has been propounded is the following (Scheme 1).

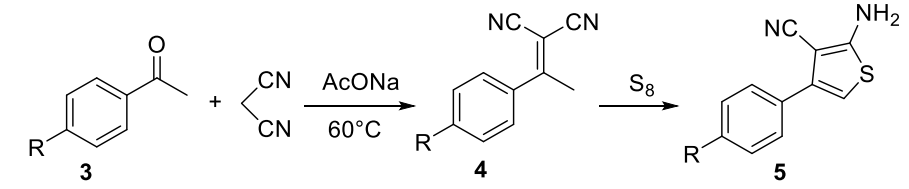


1 2 3

R:H,4-OMe,4-Me, 4-Br

Scheme 1. Retrosynthetic scheme of the synthesis of 4-phenyl-3-(1H-tetrazol-5-yl)thiophen-2-amine derivatives.

The classical Gewald reaction conditions have been modified to prepare 2-substituted aminothiophenes **2**, employing the Knoevenagel condensation between acetophenone derivatives **3**, malononitrile and sulfur giving the corresponding 2-(1-phenylethylidene)malononitrile derivatives **4** followed by Gewald's condensation (Scheme 2).



3 **4** **5**

R= H,4-OMe,4-Me, 4-Br

R= H Yield: 59%
R= 4-OMe Yield: 64%
R= 4-Me: Yield: 69%
R= 4-Br Yield 44%

R= H Yield: 91.05%
R= 4-OMe Yield: 93%
R= 4-Me: Yield: 87%
R= 4-Br Yield75%

Scheme 2. Synthesis of 2-amino-4-phenylthiophene-3-carbonitrile derivatives.

The structures of all products were confirmed by 1H NMR spectrum. The spectrum (Figure 2) of 2-amino-4-(4-methoxyphenyl)thiophene-3-carbonitrile (5, R = OMe) shows the presence of a signal at δ = 4.85 ppm corresponding to the two hydrogens of the amino group, another characteristic signal is the one that appears at δ = 6.27 ppm that integrates for a hydrogen and corresponds to the atom in position 5 of the thiophene ring.

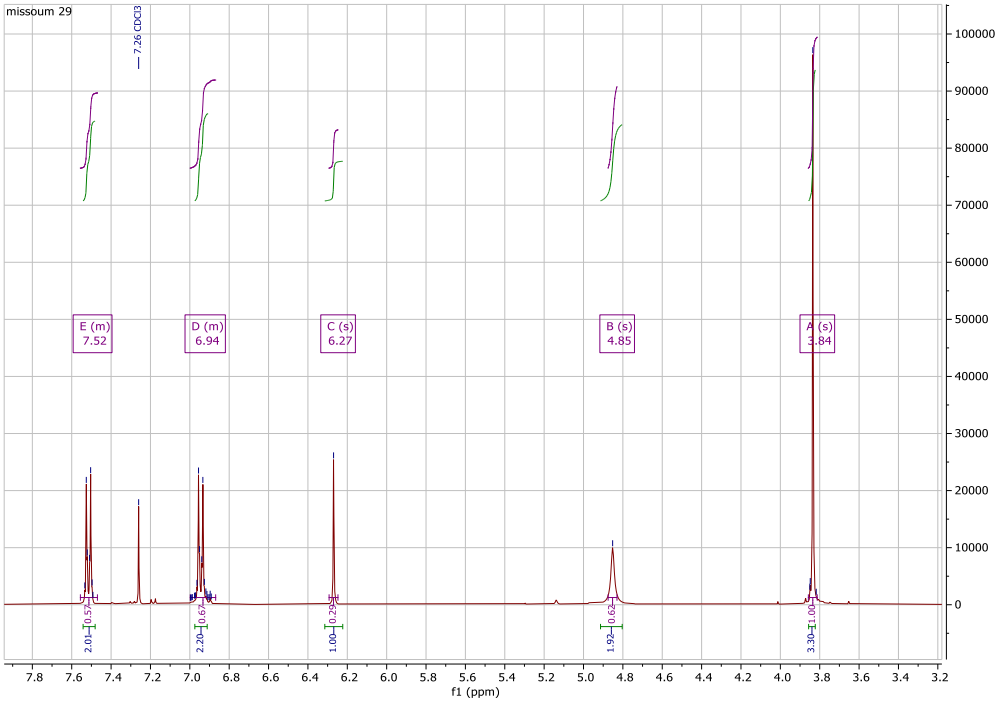


Figure 2. ^{1}H-NMR spectrum of 2-amino-4-(4-methoxyphenyl)thiophene-3-carbonitrile.

The presence of the two active sites CN and NH_2 in 2-Amino-3-cyano substituted thiophene derivatives **2** offers a multitude of interesting reactions such as the preparation of tetrazole derivatives **1** very well-known by their exceptional properties; a large number of nitrogen atoms, good stability, acidity and basicity in addition to several properties in medicinal, biological and material sciences [12–14].

The reaction between one of the aminothiophene 2 already synthesized and sodium azide in the presence of zinc chloride was carried out. However, in this communication we report that the conditions described don't lead to any new product; we replaced the $ZnCl_2$ by ZnI_2 we didn't notice any new product in the TLC. We are working on an alternative route to prepare the corresponding 4-phenyl-3-(1H-tetrazol-5-yl)thiophen-2-amine derivatives 1.

General experimental procedure:

(1) Synthesis of 2-(1-phenylethylidene)malononitrile (4):

In a 50 mL flask equipped with a condenser and a magnetic stirring bar, 0.016 mol of acetophenone, 0.019 mol of malononitrile and 0.019 mol of ammonium acetate were introduced. The mixture is heated at 60 °C for 7 h. After cooling, dichloromethane (30 mL) is added. The organic phase is washed with water (2 × 20 mL), dried over magnesium sulfate, filtered, and evaporated under reduced pressure. After recrystallization from methanol, 2-(1-phenyltylidene)malononitrile is obtained.

(2) Synthesis of 2-aminothiophene-3-carbonitrile (2):

The ylidene prepared above and elemental sulfur (1.2 eq.) were suspended in tetrahydrofuran. The mixture was heated to 35 °C and sodium bicarbonate solution, 1.0 equivalent, was added. The mixture was stirred for 1 h, transferred to a separatory funnel and washed with 12.5% aqueous NaCl. The products were isolated by crystallization.

3. Conclusions

In the present study, we have synthesized 2-Amino-3-cyano substituted thiophene derivatives (2) through simple, rapid and effective way. Coming works will give solutions to prepare 4-phenyl-3-(1H-tetrazol-5-yl)thiophen-2-amine derivatives **1**.

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