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Mechanistic study on a novel pseudo-five-component synthesis of 4*H*-thiopyrans

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Abstract

The use of carbon disulfide provides a novel and efficient route for the synthesis of thiopyrans. Herein we describe a study on the pseudo-five-component preparation of 4*H*-thiopyran derivatives by condensation of aldehydes, malononitrile, carbon disulfide, and primary amines in the presence of trimethylamine. Separation and identification of the reaction intermediates and products, additional starting materials designing, repeating of the reaction, and determining of the products, NMR and GC-mass analysis of the reaction mixtures, were used to evaluate and confirm the reaction pathway.

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Keywords

Mechanistic study, Multicomponent reaction, Thiopyrans, Carbon disulfide, Isothiocyanate

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Introduction

A reaction mechanism consists in the series of actual events that occur as reactant molecules are stepwise transformed into products. All facts available must fit into a suggested mechanism. The usual approach is, at first, the recognition of outstanding features of the mechanism and then, secondly, paying attention to finer details.[1-3] Albeit with a good degree of confidence, mechanisms can be written for most chemical reactions nowadays. However, mechanism frequently were not definitely and thoroughly identified. For the reason that there are numerous variables, the problems involved are laborious. For several reactions, there are various suggested mechanism that will fit the data equally well. On the other hand, certain reactions are recognized where diverse mechanisms are observed under different conditions.[4-6] There are a number of commonly used methods for determining mechanisms: Separation and identification of the reaction products, additional starting materials designing, various aspects of the mechanism testing, the reaction repeating and the determining of products are the preliminary methods for mechanism determination. Study of the kinetic evidence, catalysis, stereochemical evidence, solvents and isotopic effects are other methods for validating of mechanisms. In most reactions, one method is not sufficient, and the problem is usually approached from numerous directions.[4,7]

Sulfur-containing heterocyclic compounds have gained pointedly increased attention, since a broad range of biological activities related with the scaffold have been recognized.[8] Thiopyrans are attractive heterocyclic compounds that are interesting for their pharmacological activities, which include anti-hyperplasia,[9] anti-bacterial,[10] anti-psychotic,[11] analgesic, anti-inflammatory,[12] and anticancer activity.[13,14] Over the past few years, several methods with use of 2-cyanothioacetamide as the sulfur source for the synthesis of thiopyran derivatives have been

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developed.[15-22] There are several drawbacks of these synthetic methods such as the cost of reagents, need of multiple reaction steps, long reaction times and low yields. Therefore, the improvement of methods for the synthesis of thiopyrans continues to be an exciting goal in both medicinal and synthetic chemistry.

Recently, we reported results on the reaction of aldehydes (**1**) with malononitrile (**2**), carbon disulfide (**3**), and primary amines (**4**) the in presence of triethylamine as a catalyst at room temperature that produced 4*H*-thiopyrans (Scheme 1).[23,24] Since the use of carbon disulfide is a novel and efficient route in this area, a detailed mechanistic study is described here.

Results and discussion

Mechanistic investigation

A probable mechanism for the formation of 2,6-diamino-4-phenyl-4*H*-thiopyran-3,5-dicarbonitrile is proposed in Scheme 2. Initially, a standard Knoevenagel condensation of benzaldehyde **1** with malononitrile **2** in the presence of triethylamine takes place to form 2-benzylidenemalononitrile **A** as an intermediate. Then adduct **B** furnished *via* a Michael addition of **2** to intermediate **A**. Then intermediate **C** (benzylcarbamodithioic acid) is formed *via* the reaction of benzylamine **4** with carbon disulfide **3**. Subsequently a nucleophilic attack of **C** on a **B** cyanide group affords the adduct **D**. A hydrogen transfer and carbon-sulfur bond disconnection leads to formation of benzyl isothiocyanate **5** and intermediate **E**. Another H-shift, followed by attack on C≡N of **E** and cyclization leads to **F**. Finally the H-shift (tautomerization) in **F** gives product **6**.

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We found that the primary amine is essential for enabling the reaction. If it is left out, no formation of the desired product occurs. It is notable that no product was formed when secondary or tertiary amines instead of primary amines were used in this reaction.

NMR and GC-mass study of the reaction mixture

The GC-mass spectrum of the reaction mixture proved the releasing of benzyl isothiocyanate as a byproduct in the reaction. This can be taken as evidence for the proposed mechanism. A concise literature survey indicates four distinct references that 2-cyanothioacetamide is produced only *via* the reaction of hydrogen sulfide with malononitrile.[25-28] The *in-situ* formation of 2-cyanothioacetamide in our reaction is only possible *via* the interaction of benzylamine, carbon disulfide and malononitrile. For the examination and consolidation of the proposed mechanism, a control test on the probability of the production of 2-cyanothioacetamide was carried out. The reaction of benzylamine, carbon disulfide and 1 equivalent of malononitrile under similar conditions did not lead to 2-cyanothioacetamide (Scheme 3).

NMR analysis of the reaction mixture and comparison with authentic samples were performed. The result is shown in Fig. S1 and S2 (Supplemental materials). A CH_2 singlet peak due to malononitrile appears at 3.60 ppm in the ^{1}H NMR spectrum. Two further peaks appear at 8.7 and 109.2 ppm for malononitrile carbons while the CH_2 singlet of the 2-cyanothioacetamide appears at 3.98 ppm. Three peaks at 33.9, 116.5 and 194.5 ppm are due to its carbons.[29] ^{1}H NMR and ^{13}C NMR analysis of the reaction mixture after 5 and 20 minutes shows distinguished peaks of malononitrile and implicate that 2-cyanothiacetamide under this condition cannot be formed.

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The GC-mass spectrum of the reaction mixture after 2 minutes demonstrated the presence of malononitrile, benzylamine, triethylamine and benzyl isothiocyanate (maybe formed in the mass spectrometer from benzylcarbamodithioic acid). It is obvious that no peak appeared for 2-cyanothioacetamide (*m/z* = 100.0). GC-mass spectra of the reaction mixture after 15 minutes indicate no remarkable changes in the products distribution (see Fig. S3, Supplemental materials).

There are many references related to the reaction of malononitrile and the isothiocyanate group in organic syntheses.[30-32] If the production of benzyl isothiocyanate takes place in the reaction mixture, it can be reacted with malononitrile as well as the released H_2S can convert the malononitrile to 2-cyanothioacetamide. As mentioned above, the NMR analysis shows that the malononitrile maintenance in the reaction mixture after 20 minutes and 2-cyanothioacetamide was not made. Thus, benzyl isothiocyanate appeared in the mass spectrum which can be attributed to the elimination of hydrogen sulfide (H_2S) from benzylcarbamodithioic acid under mass spectroscopy conditions.

For further corroboration of the mechanism, we performed the reaction of benzylamine with carbon disulfide under similar conditions. The GC-MS of the reaction mixture after 5 hours shows the same product formation (Scheme 3 products) in the absence of malononitrile (Figure S4).

Formation of the intermediate **B** and its kinetic study was reported in the literature.[33] Moreover, we synthesized the benzylidenemalononitrile (intermediate **A**) and benzylcarbamodithioic acid (intermediate **C**) and performed the reaction shown in Scheme 4.

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This reaction resulted in the formation of 2,6-diamino-4-phenyl-4*H*-thiopyran-3,5-dicarbonitrile **6** and confirmed the presence of the proposed intermediates during the reaction process.

Experimental

General Information

Synthesis grade reagents were commercially available and were used without further purification. All solvents were dried by standard procedures before use. Melting points were measured on an Electrothermal 9100 apparatus in open capillaries without correction. IR spectra were recorded on a Unicom Galaxy Series FT-IR 5000 spectrophotometer using KBr pellets and are expressed in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded in the indicated deuterated solvents with a Bruker Avance 400 MHz spectrometer at 400 MHz (^{1}H) and 100 MHz (^{13}C), respectively. Mass spectra were recorded with an Agilent-5975 C inert XL MSD mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed by Vario EL equipment at Arak University. The progress of the reaction was monitored by TLC (EtOAc-hexane). The Supplemental Materials contains sample NMR and GC-MS spectra of the products and characterization data (Figures S 1 – S 4).

General procedure

To a magnetically stirred mixture of aldehyde (1 mmol), malononitrile (2 mmol) and a catalytic amount of triethylamine in 5 mL dichloromethane, primary amines (1 mmol) and carbon disulfide (1.2 mmol) were added. The reaction mixture was stirred at room temperature and the progress of the reaction was monitored by TLC. After the reaction was complete, solid products were filtered off, washed with EtOH, and dried. The reaction of benzaldehyde, malononitrile, benzylamine and carbon disulfide was selected for the mechanism determination.

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Benzyl isothiocyanate (5)

IR: 3065, 3030, 2174, 2091, 1465, 1436, 1344, 1332, 1026, 734, 697, 677. EI-MS *(m/z)*: 149 (M^+, 23), 91 (100), 65 (18).

2,6-Diamino-4-phenyl-4H-thiopyran-3,5-dicarbonitrile (6)

Orange powder; m.p. 186-188 °C; ^{1}H NMR (DMSO-d_6): δ 4.26 (s, 1H, CH), 6.95 (br s, 4H, 2 NH_2), 7.28-7.23 (m, 3H, Ar-H), 7.38-7.34 (m, 2H, Ar-H); ^{13}C NMR (DMSO-d_6): δ 43.3, 71.9, 118.8, 128.7, 127.1, 126.6, 143.5, 151.2; Anal. Calcd. for $C_{13}H_{10}N_4S$ (254.31): C, 61.40; H, 3.96; N, 22.03; S, 12.61%, found: C, 61.38; H, 3.99; N, 21.97; S, 12.70 %. IR: 3433, 3396, 3317, 3198, 3024, 2183, 1633, 1599, 1448, 1367, 1263, 1151, 887, 713, 599.

Conclusions

We describe a successful strategy for the synthesis of 4*H*-thiopyran using aldehydes, malononitrile, carbon disulfide and primary amine in the presence of triethylamine as a catalyst at ambient temperature. Use of carbon disulfide is a novel and efficient method in this area. Furthermore, a method for the consolidation of the proposed reaction mechanism is described. Separation and identification of the reaction products and intermediates, designing of the starting materials, various aspects of the mechanism testing, the reaction repeating and the determining of products or intermediates, NMR and GC-mass analysis of reaction mixtures were used to evaluate and confirm the reaction pathway.

Acknowledgments

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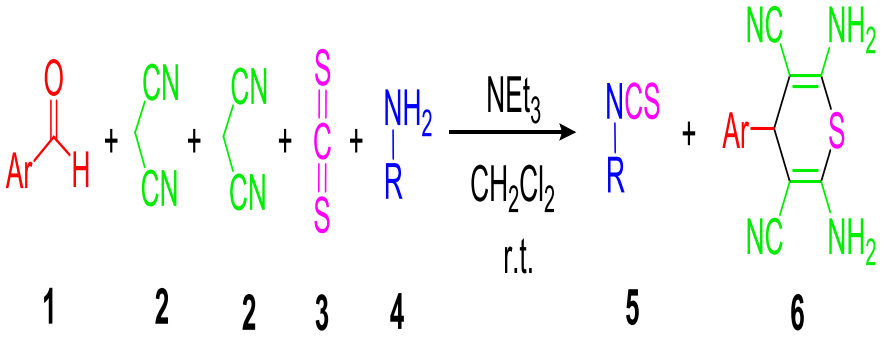

Scheme 1. Pseudo-five-component synthesis of 4*H*-thiopyran derivatives

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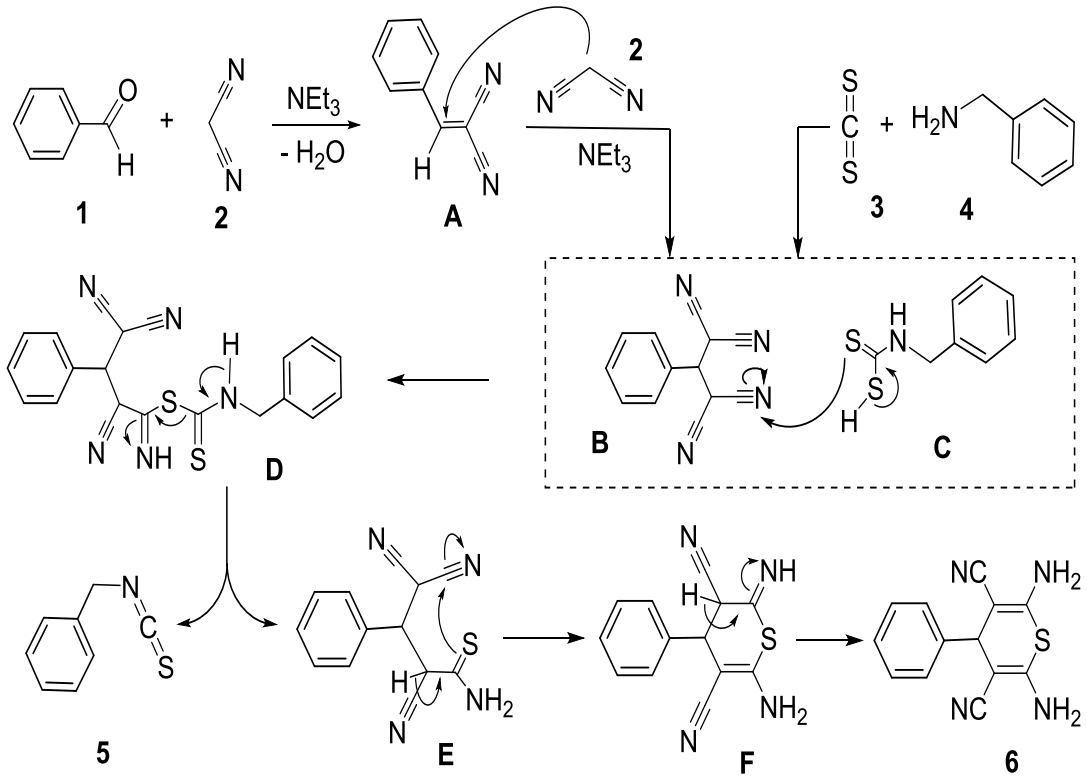

Scheme 2. Proposed reaction mechanism for the thiopyran ring formation.

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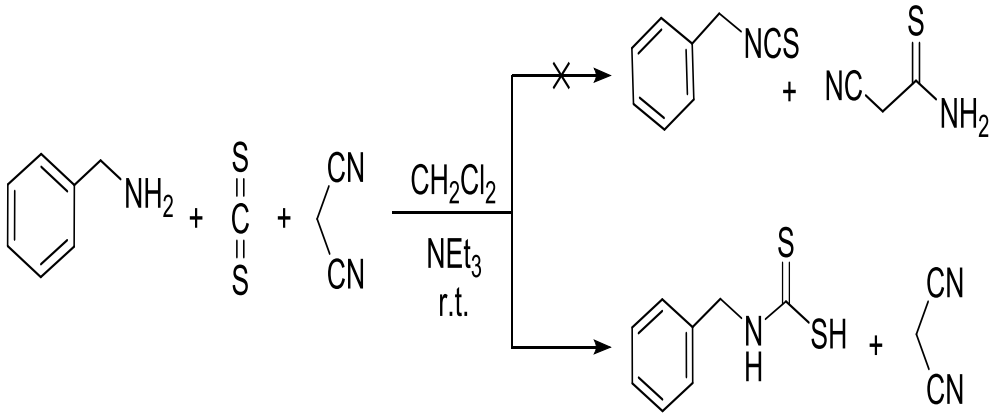

Scheme 3. Control test for probability of 2-cyanothioacetamide production.

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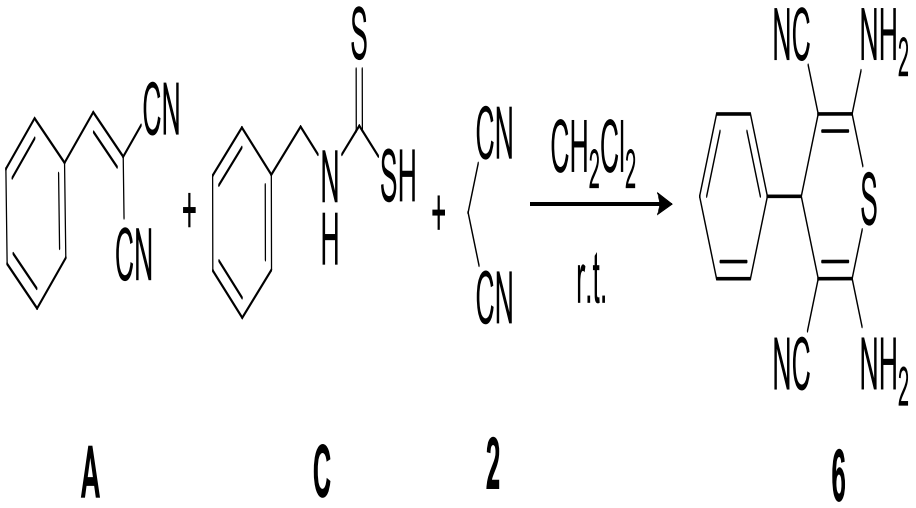

Scheme 4. 2,6-diamino-4-phenyl-4*H*-thiopyran-3,5-dicarbonitrile synthesis *via* prepared intermediates.

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