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RESEARCH ARTICLE

# Studies on Aminobenzothiazole and Derivatives: Part-2. Synthesis of Intermediates -Substituted Phenylthiourea using Ammonium Thiocyanate

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## ABSTRACT

The substituted phenylthiourea is used as intermediate in different reactions because they play an important role in synthesizing the heterocyclic compounds. These reactions involve the synthesis of an intermediate phenylammonium chloride which is converted to substituted thiourea using ammonium thiocyanate. The final product formed, substituted phenylthiourea has potential to use as an intermediate in the synthesis of a building block for the heterocyclic compound, 2-aminobenzothiazole.

**Keywords:** Aminobenzothiazole and heterocyclic compound, building block, phenylammonium chloride, phenylthiourea

## INTRODUCTION

Urea is the first organic compound which was synthesized in laboratory in 1928, and it became the important synthesis step in the history of synthetic organic chemistry and played important physiological and biological roles in animal kingdom.[1,2]

Thiourea is the analog compound to urea with replacement of oxygen atom by sulfur atom. Thiourea is known for its wide range of applications. The properties of urea and thiourea differ significantly due to the difference in electronegativity between sulfur and oxygen. Thiourea compounds work as building blocks in the synthesis of heterocyclic compounds[3] of therapeutic and pharmacological properties. Substituted thiourea has recently gained much interest in the preparation of wide variety of pharmaceutical and biological compound of prime importance.[4]

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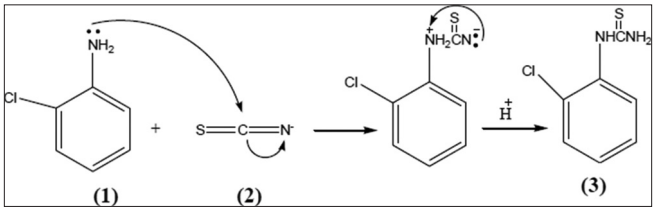
Thiourea is important organic compounds, also known as thiocarbamide. It is a white crystalline solid compound with a chemical formula of $CSN_2H_4$ and molecular weight of 76.12 g/mol. Thiourea is soluble in water but insoluble in non-polar solvents. It is also soluble in polar protic and aprotic organic solvents such as acetone and dimethyl sulfoxide[5] possess high biological activity, act as corrosion inhibitors and antioxidant, and are polymer components.[6] Thiourea and urea derivatives show a broad spectrum of biological activities as anti-HIV and antibacterial activities;[7] acylthiourea derivatives are well known for wide range of biological activities such as bactericidal, fungicidal, herbicidal, insecticidal action, and regulating activity for plant growth.[8] The synthesis of the thiourea derivatives can be easily done with good yield.[9] Thiourea and its derivatives represent well-known important group of organic compounds due to the diverse application in fields such as medicine, agriculture, coordination, and analytical chemistry.[5] On the other hand, some thiourea derivatives have been used in commercial fungicides.[10] They are also can be used as

selective analytical reagents, especially for the determination of metals in complex interfering materials.[11,12] As one of important thiourea derivatives is benzoyl thiourea compound which have a wide range of biological activities including antiviral,[13] antibacterial,[14] antifungal,[15] antitubercular,[16] herbicidal,[17] insecticidal,[18] and pharmacological properties[19] and acting as chelating agents.[20] Thiourea derivatives and their transition metal complexes have been known since the beginning of the 20th century.[21] Furthermore, these complexes display a wide range of biological activity including antibacterial and antifungal properties.[22] The complexes of ligands containing sulfur as donor atoms are known to possess antifungal and antibacterial activities.[12] Thiourea and its derivatives coordinate to several transition metal ions to form stable complexes. Thiourea is versatile ligands, able to coordinate to metal centers either as neutral ligands, monoanions, or dianions.[22] In addition, benzoyl thiourea derivatives were often used in analytical and biological applications.[23] These molecules serve as an intermediate for the synthesis of 2-aminobenzothiazoles.[24] 2-Aminobenzothiazole is a vital intermediate to form many Schiff bases,[25] thiazolidinones,[26] and azetidinones.[26]




**Scheme 1:** General mechanism to synthesis thiourea

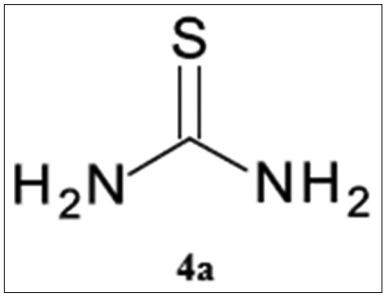



**Figure 1:** Thiourea

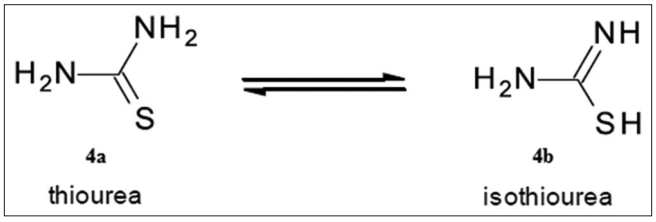



**Figure 2:** Tautomeric forms of thiourea

## Chemistry of the synthesis of thiourea derivatives

Thiourea derivatives, **3** can be synthesized by direct reaction of isocyanate, **2** with amine, **1**. The reaction mechanism involved nucleophilic attack at the electrophilic carbon of thiocyanate ion by amine.[27-29] The general mechanism is shown in Scheme 1. Thiourea, **(4a)** (and isothiourea, **[4b]**) is a compound which consists of sulfur and nitrogen and a chemical formula of $CSN_2H_4$. The basic structure of thiourea is shown in Figure 1. Thiourea has become intensely synthesized due to its ability to undergo structural modifications. It is a unique compound having three different functional groups which are amino, imino, and thiol and it can occur in tautomeric forms as shown in Figure 2. There is a lot of possible reactions that can lead to the synthesis of new derivatives that may be applicable.[5]

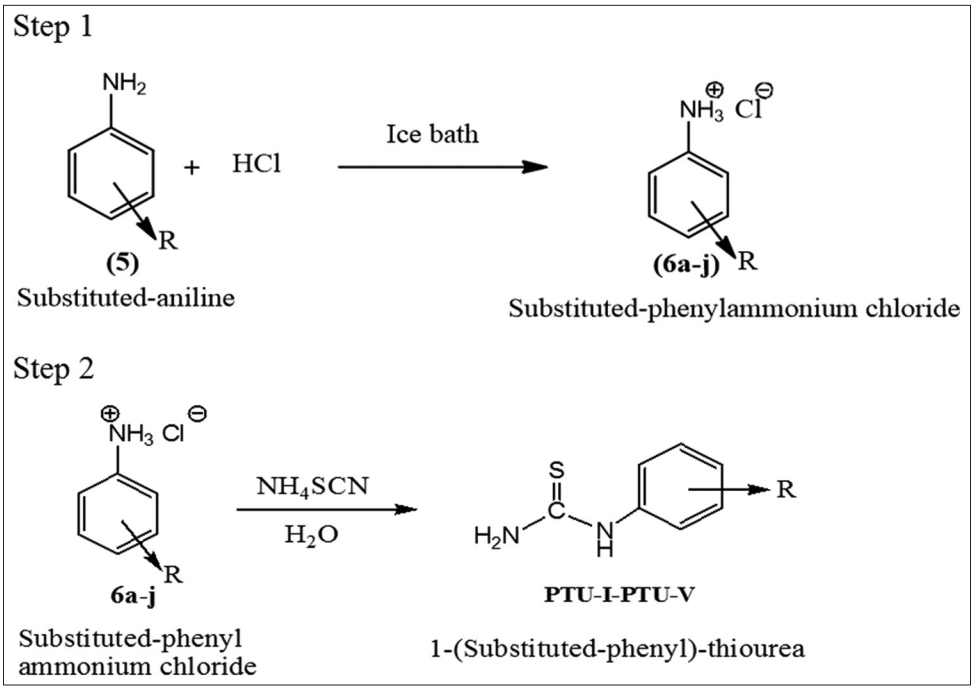
## Solvent in synthesis of thiourea derivatives

Solvent plays a crucial role in the synthesis of thiourea. Several types of solvent have been

**Table 1:** Physical and analytical data for the compound synthesized **PTU-I** to **PTU-V**

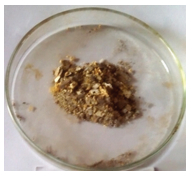
| S. No. | Compound ID | Aniline used | M. wt. of product | Color of product | M.P. (°C) | Wt. in gram (ml) | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | **PTU-I** | 3-Methoxyaniline | 182 | Light gray | 136–138 | 1.30 | 10.32 |
| 2 | **PTU-II** | 4-Ethylaniline | 180 | Regatta | 129–131 | 4.17 | 38.00 |
| 3 | **PTU-III** | 2-Chloroaniline | 185 | White | 146–148 | 6.85 | 42 |
| 4 | **PTU-IV** | 2-Fluoroaniline | 170 | Pale pink | 137–139 | 3.69 | 22.82 |
| 5 | **PTU-V** | 2,6-Dimethylaniline | 180 | Regatta | 196–198 | 1.43 | 9.94 |

PTU: Phenylthiourea




**Scheme 2:** Step 1 - Preparation phenylammonium chloride, Step 2 - preparation of phenylthiourea

**Table 2:** Recrystallized photographic representation of **PTU-I** to **PTU-V**

| S. No. | Compound ID | Aniline used | Purified product |
|---|---|---|---|
| 1 | **PTU-I** | 3-Methoxyaniline |  |
| 2 | **PTU-II** | 4-Ethylaniline |  |
| 3 | **PTU-III** | 2-Chloroaniline |  |
| 4 | **PTU-IV** | 2-Fluoroaniline |  |
| 5 | **PTU-V** | 2,6-Dimethylaniline |  |

reported to be used in the synthesis of thiourea derivatives [Scheme 2]. Acetone is commonly used as a solvent to synthesize thiourea and their derivatives and produces higher yield compared to other solvents such as THF and benzene.

Recently, we have communicated[30] the studies on synthesis of intermediates 1,3-di(substituted-phenyl)-thiourea using ammonium thiocyanate. Looking to all literature survey, we have undertaken the synthesis of an intermediate phenyl ammonium chloride and further to substituted phenylthiourea (PTU) derivatives using ammonium thiocyanate.

## EXPERIMENTAL DETAIL

### Materials and methods

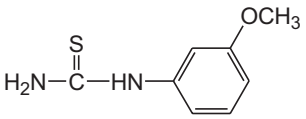
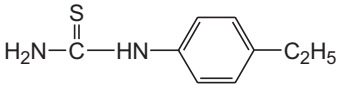
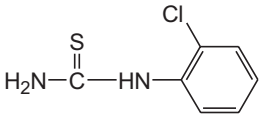
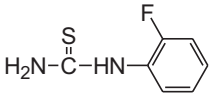
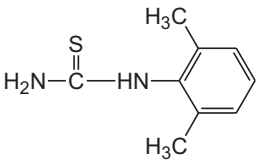
All the melting points were determined in open capillaries. Infrared (IR) spectra (KBr) were recorded on Fourier-transform IR (FTIR) spectrophotometer (Shimadzu PC, 4000–400 $cm^{-1}$). The nuclear magnetic resonance spectra were recorded on dpx-300 spectrophotometer in dimethyl sulfoxide; tetramethylsilane was the internal reference, chemical shift is express in δ ppm.

**Table 3:** The UV-Vis data for the phenylthiourea compounds, **PTU-I-PTU-V**

| S. No. | Compound ID | UV max | Conc. | Absorbance | ε |
|---|---|---|---|---|---|
| 1 | **PTU-I** | 265.00 | | 3.514 | 21,962 |
| | | 258.60 | $1.6 \times 10^{-6}$ | 3.465 | 21,656 |
| | | 214.00 | | 3.469 | 21,681 |
| 2 | **PTU-II** | 339.80 | | 0.008 | 484.84 |
| | | 248.20 | $1.6 \times 10^{-5}$ | 1.819 | 110,242.42 |
| | | 211.20 | | 3.418 | 207,151 |
| 3 | **PTU-III** | 374.00 | | 0.012 | 7058.82 |
| | | 341.00 | $1.7 \times 10^{-6}$ | 0.029 | 17,058.82 |
| | | 255.40 | | 1.139 | 670,000 |
| 4 | **PTU-IV** | 377.20 | | 0.014 | 848.48 |
| | | 341.20 | $1.6 \times 10^{-5}$ | 0.014 | 848.48 |
| | | 249.60 | | 3.729 | 2260.00 |
| 5 | **PTU-V** | 344.40 | | 0.005 | 303.030 |
| | | 340.00 | $1.6 \times 10^{-5}$ | 0.006 | 363.630 |
| | | 248.60 | | 3.366 | 204,000 |

UV: Ultraviolet, PTU: Phenylthiourea

**Table 4:** FTIR spectral frequencies of the synthesized, substituted phenylthiourea compounds, **PTU-I-PTU-V**

| S. No. | FTIR frequencies in ($cm^{-1}$) | Structure of substituted phenylthiourea name with ID |
|---|---|---|
| 1 | $\nu_{C=C}$ = 1592.58<br>$\nu_{N-H}$ = 3370.51<br>$\nu_{C=S}$ = 1113.47<br>$\nu_{C-NH2}$ = 1611.38<br>$\nu_{\mathbf{C-O-C}}$ = 1235.61 |  <br>*m*-Tolyl-thiourea<br>**PTU-I** |
| 2 | $\nu_{C=S}$ = 1113.47<br>$\nu_{NH2}$ = 1611.38<br>$\nu_{C=C}$ = 1513.11<br>$\nu_{N-H}$ = 3429.43<br>$\nu_{C-CH3}$ = 2960.78<br>$\nu_{C-N}$ = 1235.61 |  <br>(4-Ethyl-phenyl)-thiourea<br>**PTU-II** |
| 3 | $\nu_{C=S}$ = 1129.10<br>$\nu_{C-NH2}$ = 1603.22<br>$\nu_{C=C}$ = 1540.51<br>$\nu_{N-H}$ = 3340.91<br>$\nu_{C-Cl}$ = 757<br>$\nu_{C-N}$ = 1320.74 |  <br>(2-Chloro-phenyl)-thiourea<br>**PTU-III** |
| 4 | $\nu_{C=S}$ = 1099.17<br>$\nu_{N-H}$ = 3412.60<br>$\nu_{C-N}$ = 1305.45<br>$\nu_{C-F}$ = 1362.41<br>$\nu_{NH2}$ = 1617.41<br>$\nu_{C=C}$ = 1523.50 |  <br>(2-Fluoro-phenyl)-thiourea<br>**PTU-IV** |
| 5 | $\nu_{C=S}$ = 1065.33<br>$\nu_{C=C}$ = 1494.93<br>$\nu_{N-H}$ = 3408.02<br>$\nu_{C-CH3}$ = 2922.51<br>$\nu_{C-NH2}$ = 1607.92<br>$\nu_{C-N}$ = 1281.68 |  <br>(2,6-Dimethyl-phenyl)-thiourea<br>**PTU-V** |

FTIR: Fourier transform infrared, PTU: Phenylthiourea

**General method for the synthesis of substituted phenylammonium chloride (6a-j)**

In a 250 ml beaker No. (a) take (0.1 M) 3-methoxyaniline and in another 250 ml beaker No. (b) take 10 ml conc. HCl. When beaker No. (a) put in ice bath an add conc. HCl slowly drop by drop to obtain solid mass in beaker and filtered in suction pump, **6a** ("y" g, % yield). Similarly, other compounds (**6b-j**) were synthesized.

**General method for the synthesis of phenylthiourea**

The ammonium thiocyanate (0.1 M) was dissolved in 15 ml of water, added to 0.1 mol of the 1st stage compound, in R.B. flask. The content was refluxed on rotamantle for 1.30 h (clear thin-layer chromatography [TLC]), then poured down into the 150 g ice water under vigorous stirring. The product which separated out was collected by filtration, washed with water, and dried. Further, it is recrystallized from ethanol so as to obtain pure substituted PTU compound, **PTU-I**. Similarly, other compounds, **PTU-II** to **PTU-V,** were synthesized.

## RESULTS AND DISCUSSION

In the synthesis or substituted aniline is reacted with ammonium thiocyanate to give thio compound. These are colored product and gave experimental yields in the range of 42–4%, their physical constants are determined and given in Table 1.

The photographs of the products as they are observed after purification by different method are as given in Table 2.

The TLC of reactant aniline and the final purified product id monitored, indicated the single spots. The ultraviolet-Vis data of the phenylthiourea compound are shown in Table 3.

In general the compounds exhibits the expected features of the standard FTIR spectra for this type. The spectra of **PTU-I** and the other compounds, **PTU-II** to **PTU-V,** show that absorption at about 3475–3340 $cm^{-1}$ indicates the presence of N-H stretching frequency. The absorption at about 2960–2920 $cm^{-1}$ indicated the presence of C-$CH_3$ stretching frequency. The absorption at 1617–1595 $cm^{-1}$ indicated the presence of C-$NH_2$ stretching frequency. The band at 1592–1446 $cm^{-1}$ indicated the presence of > C = C< aromatic ring. The absorption at about 1320–1230 $cm^{-1}$ indicated the presence of C-N stretching frequency. The band at 1402–1248 $cm^{-1}$ indicated the presence of C-F stretching frequency. Band at 1175–1065 $cm^{-1}$ indicated the presence of C = S stretching frequency. The absorption at 770–715 $cm^{-1}$, ~ 685, and ~ 650 $cm^{-1}$ indicated the presence of C-Cl, C-$CH_3$, and C-S stret. frequency, respectively.

The FTIR spectra of the studied compounds were recorded and their assigned frequencies are depicted in Table 4.

## CONCLUSION

The substituted phenylthiourea is used as intermediate in different reactions because they play an important role in synthesizing the heterocyclic compounds. These reactions involve the synthesis of an intermediate phenylammonium chloride which is converted to substituted thiourea using ammonium thiocyanate. In the present piece of work, we have reached an intermediate phenylammonium chloride which is converted to substituted thiourea using ammonium thiocyanate. TLC method developed in this reaction, for more research to be done in this field.

**Scope**

The final product formed has potential to use as an intermediate in the synthesis of a building block for the heterocyclic compound, 2-aminobenzothiazole. There is a future scope for using these compounds for the organic transformations and screening of these compounds against different microorganism and the data obtained will be useful for the society to study their further studies for budding organic and the other researchers.

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