

RESEARCH ARTICLE

Studies on Aminobenzothiazole and Derivatives: Part-1. Synthesis of Intermediates –1,3-Di(substituted-phenyl)-thiourea using Ammonium Thiocyanate

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ABSTRACT

1,3-Di(substituted-phenyl)-thiourea is used as intermediate in different reactions because they play an important role in synthesizing the different heterocyclic compounds. These reactions involve the synthesis of an intermediate, substituted-phenylammonium chloride which is converted to 1,3-Di(substituted-phenyl)-thiourea using ammonium thiocyanate. The final product formed, 1,3-Di(substituted-phenyl)-thiourea has potential to use as an intermediate in the synthesis of a building block for the heterocyclic compound, 2-aminobenzothiazole.

Keywords: 1,3-Di(substituted-phenyl)-thiourea, 2-Aminobenzothiazole, building block, diphenyl-thiourea, phenylammonium chloride

INTRODUCTION

Similar to urea, thiourea is the analog compound to urea with the 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^[1] of therapeutic and pharmacological properties. Substituted thiourea have recently gained much interest in the preparation of a wide variety of pharmaceutical and a biological compound of prime importance.^[2]

Thiourea 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^[3] possess high biological activity, act as corrosion inhibitors and antioxidant, and are polymer components.^[4] Thiourea and urea derivatives show a broad spectrum of biological

activities as anti-HIV and antibacterial activities^[5] Acylthiourea derivatives are well known for wide range of biological activities such as bactericidal, fungicidal, herbicidal, insecticidal action, and regulating activity for plant growth.^[6] The synthesis of the thiourea derivatives can be easily done with good yield.^[7] Thiourea and its derivatives represent a well-known important group of organic compounds due to the diverse application in fields such as medicine, agriculture, coordination, and analytical chemistry.^[3] On the other hand, some thiourea derivatives have been used in commercial fungicides.^[8] They are also can be used as selective analytical reagents, especially for the determination of metals in complex interfering materials.^[9,10] As one of important thiourea derivatives is benzoyl thiourea, which have a wide range of biological activities including antiviral,^[11] antitubercular,^[12] insecticidal,^[13] herbicidal^[14] and pharmacological properties^[15] and acting as chelating agents further, few similar compounds were synthesized.^[16] Thiourea derivatives and their transition metal complexes have been known since the beginning of the 20th century.^[17] Furthermore, these complexes display a wide range of biological activity including antibacterial and antifungal properties.^[18] Thiourea and its derivatives coordinate to several transition metal ions to form

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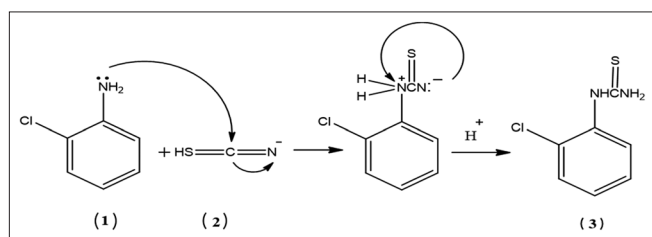
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stable complexes. Thiourea is versatile ligands, able to coordinate to metal centers either as monoanions, dianions, or neutral ligands.^[19] The compounds of N-benzoyl-N/-alkylthiourea and N-benzoyl-N, N-dialkylthiourea have recently attracted interest in view of the potential use of these compounds as highly selective reagents for the concentration and separation of metal cations.^[20] In addition, benzoyl thiourea derivatives were often used in analytical and biological applications.^[21] These molecules serve as an intermediate for the synthesis of 2-aminobenzothiazoles.^[22] Recently, we have reported the synthesis of Schiff bases,^[23] thiazolidinones,^[24] and azetidinones^[24] from 2-Aminobenzothiazole, which is a vital intermediate. In continuation of these studies herein, we report the trials of synthesis of substituted diphenyl thiourea derivatives using ammonium thiocyanate.

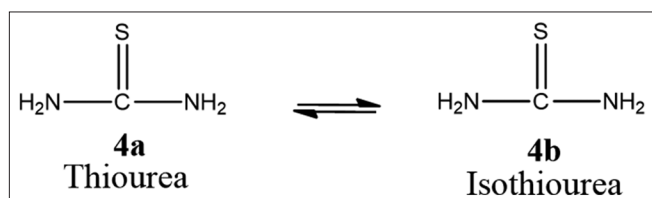
Chemistry of synthesis of thiourea derivatives

Thiourea derivatives, **3** can be synthesized by direct reaction of an isocyanate, **2** with an amine, **1**. The reaction mechanism involved a nucleophilic attack at the electrophilic carbon of thiocyanate ion by an amine.^[25-27] The general mechanism is shown in **Scheme 2**.

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 and isothiourea is depicted in **Scheme 2**. Thiourea has become intensely synthesized due to its ability to undergo structural modifications. Thiourea and its derivatives display a broad spectrum of applications in industries, chemistry, medicine, and others.



Scheme 1: General mechanism to synthesis thiourea



Scheme 2: Structures of thiourea and isothiourea

Solvent in the synthesis of thiourea derivatives

Solvent plays a crucial role in the synthesis of thiourea. Several types of solvent have been reported to be used in the synthesis of thiourea derivatives. Acetone is commonly used as a solvent to synthesize thiourea and their derivatives and produce higher yield compared to other solvent such as THF and benzene.

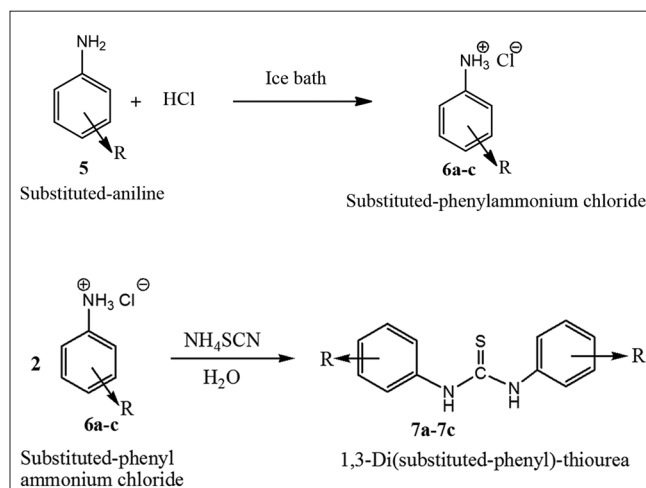
Recently, we have communicated^[28] the studies on synthesis of intermediates substituted-phenylthiourea using ammonium thiocyanate. Looking to all above literature survey, we have undertaken the synthesis of Di(substituted-phenyl)thiourea derivatives using ammonium thiocyanate [**Scheme 3**].

MATERIALS AND METHODS

All the melting points were determined in open capillaries. The ultraviolet-visible (UV-Vis) spectra were recorded (absolute alcohol) on Shimadzu (UV-1800) spectrophotometer. Fourier-transform infrared (FTIR) spectra were recorded on FTIR spectrophotometer (Shimadzu PC, 4000–400 cm^{-1}).

Synthesis of substituted-phenyl-ammonium chloride, **6a**

In a 250 ml beaker No.-(a) take (0.1 M) 3-Bromo-aniline, and in another 250 ml beaker No.-(b) take 10 ml concentration HCl, when beaker No.(a)



Scheme 3: Experimental detail: Step 1: Preparation phenyl-ammonium; chloride, Step 2: Preparation of Di(substituted-phenyl)-thiourea

Table 1: Physical and analytical data for the compound synthesized, 7a–7c

ID	Aniline used	M. Wt. of product	Color of product	M.P. (°C)	Wt. in gram	Yield (%)
7a	3-Bromo Aniline	366	Light Gray	151–152	x=12.75	37.34
7b	2-Fluoro Aniline	246	Brown	145–146	y=5.62	28.43
7c	2-Chloro Aniline	280	Regatta	147–149	y = 3.60	30.64

put in ice bath and add concentrated HCl slowly drop by drop to obtain solid mass in a beaker and filtered on a suction pump, (“x” g, % yield), 6a. Similarly, other intermediate compounds, 6b–c were synthesized.

Synthesis of 1,3-di(substituted-phenyl)-thiourea, 7a

The ammonium thiocyanate (0.1 M) was dissolved in 15 ml of water, added to 0.2 mol of 1st stage compound in R. B. Flask. The content was refluxed on rota-mantle for 1.30–2.0 h, then poured down into the 150 g ice water under vigorous stirring. The product which separated out was collected by filtration, washed with cold water and dried. Further, it is recrystallized from ethanol, so as to obtain pure substituted diphenyl thiourea compound, (“y” g, % yield), 7a. Similarly, other compounds, 7b–7c were synthesized.

RESULTS AND DISCUSSIONS



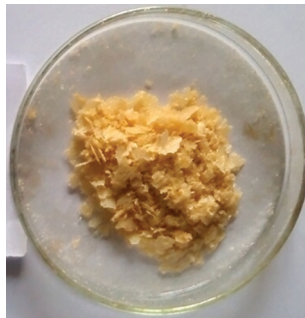
In the synthesis of substituted aniline is reacted with ammonium thiocyanate to give thio compound. These are colored products and gave experimental yields in the range of 37.34%–30.64% their physical constants are determined and given in Table 1.

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

The thin-layer chromatography (TLC) of reactant 3-Bromo-aniline and the final purified product ID monitored indicated the single spots. The TLC of the completed reaction is as depicted in Figure 1.

The UV-Vis spectra for the representative 1,3-Bis-(3-bromophenyl)-thiourea, 7a, are depicted in Figure 2. The UV-Vis data of the 1,3-Di(substituted-phenyl)-thiourea compound are shown in Table 3.

Table 2: Photographic representation of recrystallized compounds, 7a–7c

ID	Aniline used	Recrystallized product
7a	3-Bromoaniline	
7b	2-Fluoroaniline	
7c	2-Chloroaniline	

In general, the exhibits the expected features of the standard FTIR spectra for this type of compound. The FTIR spectra of 7a are depicted in Figure 3. The spectra of 7a and the other compounds show absorption at about 3434–3342 cm^{-1} indicate the presence of N-H stretching frequency. The absence of absorption around 1617–1595 cm^{-1} indicated the absence of C-NH₂ stretching frequency, which, in turn, provides proof for the formation of the substituted-diphenyl derivative of thiourea. The band at 685, 1248, and 715 cm^{-1} indicated the presence of >C=C< aromatic ring. The absorption at about 1318–1301 cm^{-1} indicated the presence

of C-N stretching frequency. The band at 1402–1248 cm^{-1} indicated the presence of C-Br, C-F, and C-Cl stretching frequency. The band at 1175–1098 cm^{-1} indicated the presence of $>\text{C}=\text{S}$ stretching frequency.

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

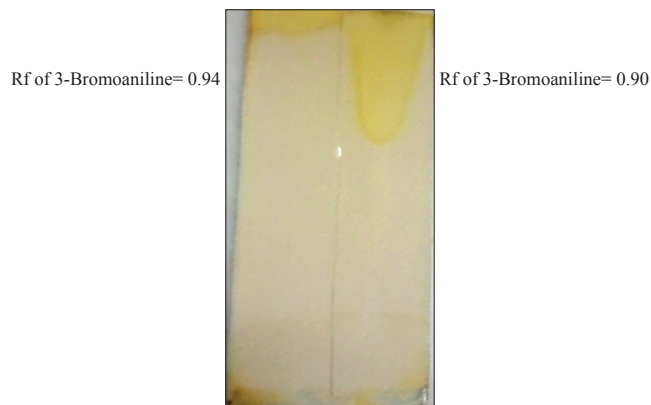


Figure 1: The thin-layer chromatography for the representative 1,3-Bis-(3-bromophenyl)-thiourea, 7a

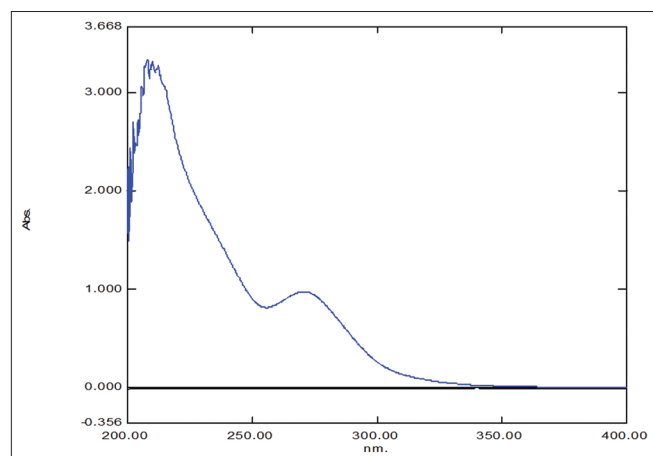


Figure 2: Ultraviolet-visible spectra for 1,3-Bis-(3-bromophenyl)-thiourea, 7a

CONCLUSION

The substituted diphenyl-thiourea 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 1,3-Di(substituted-phenyl)-thiourea using ammonium thiocyanate. In the present piece of work, we have reacted an intermediate phenylammonium chloride which is converted to 1,3-Di(substituted-phenyl)-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 the potential to use as an intermediate in the synthesis of a building block for the heterocyclic compound, 2-aminobenzothiazole. There is future scope for using these compounds for the organic transformations and screening of these compounds against different microorganism

Table 3: The UV-Vis data for the 1,3-Di (substituted-phenyl)-thiourea, 7a–7c

ID	UV max	Concentration	Absorbance	ϵ
7a	341.20	1.2×10^{-6}	0.048	40
	255.00		2.159	1799167
	210.80		3.609	7174167
7b	341.60	1.0×10^{-5}	0.036	36000
	249.40		1.687	16870
	212.20		3.575	35750
7c	269.80	1.6×10^{-6}	2.754	17212
	222.40		3.604	22525
	218.20		3.665	22906

UV-Vis: Ultraviolet-visible

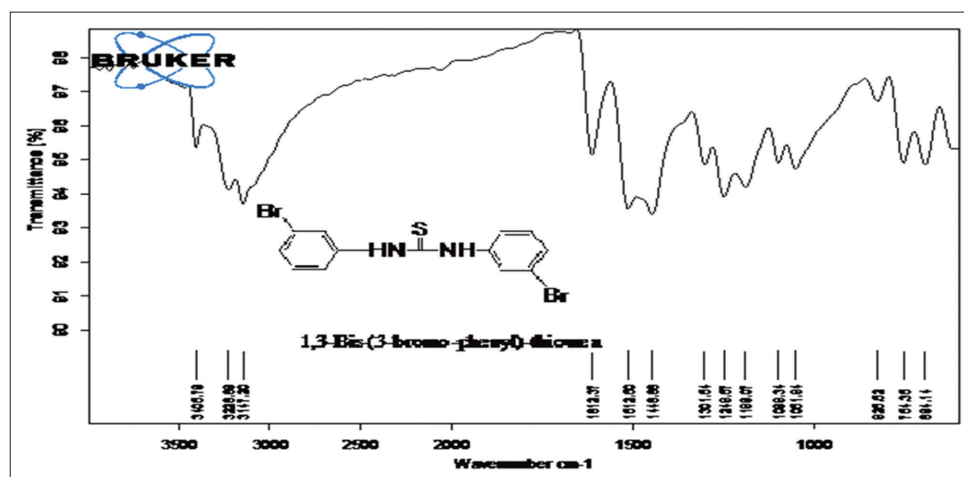
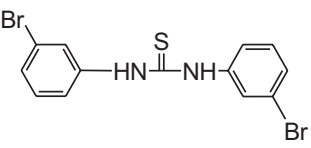
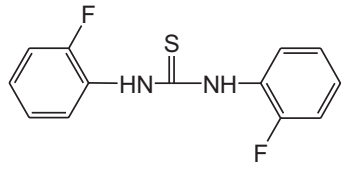
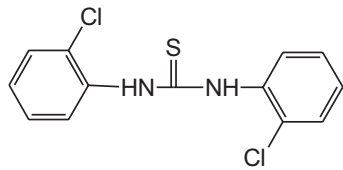


Figure 3: Fourier-transform infrared spectra for 1,3-Bis-(3-bromophenyl)-thiourea, 7a.

Table 4: FTIR spectral frequencies for synthesized, 1,3-Di (substituted-phenyl)-thiourea, 7a–7c

Sr. No.	FTIR frequencies in (cm ⁻¹)	Structure of Di (substituted-phenyl)- and phenyl thiourea Name with ID
1	$\nu_{\text{C=S}}=1175.42$ $\nu_{\text{N-H}}=3434.49$ $\nu_{\text{C-Br}}=685.95$ $\nu_{\text{C=C}}=1571.00$ $\nu_{\text{C-N}}=1301.48$	 1,3-Bis-(3-bromo-phenyl)-thiourea 7a
2	$\nu_{\text{C=S}}=1098.34$ $\nu_{\text{N-H}}=3405.79$ $\nu_{\text{C=C}}=1512.50$ $\nu_{\text{C-N}}=1301.54$ $\nu_{\text{C-F}}=1248.57$	 1,3-Bis-(2-fluoro-phenyl)-thiourea 7b
3	$\nu_{\text{C=S}}=1126.14$ $\nu_{\text{C-N}}=1318.45$ $\nu_{\text{C=C}}=1537.98$ $\nu_{\text{N-H}}=3342.14$ $\nu_{\text{C-Cl}}=715.55$	 1,3-Bis-(2-chloro-phenyl)-thiourea 7c

FTIR: Fourier-transform infrared

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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