Research Article

Studies on Aminobenzothiazole and Derivatives: Part -3. Synthesis of Intermediates - Substituted monophenylthiourea using Ammonium Thiocyanate

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ABSTRACT

The substituted-phenyl-thiourea are used as intermediate in different reactions because they play an important role in synthesizing the heterocyclic compounds. These reactions involve 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: Phenylammonium chloride, mono-phenyl-thiourea, Building block, Aminobenzothiazole and heterocyclic compound.

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INTRODUCTION

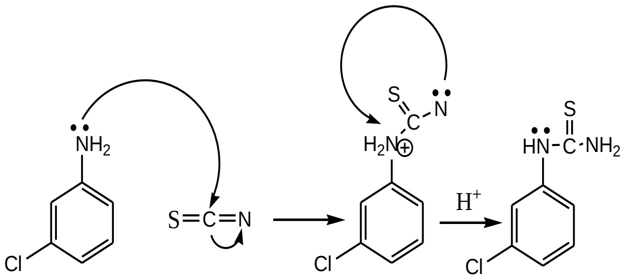
Urea is the first organic compound which was synthesized in the lab in 1928, and it became the important synthesis step in the history of synthetic organic chemistry and played important physiological and biological roles in the animal kingdom[1-2].

Thiourea is the analogue 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 because of the difference in electronegativity between sulfur and oxygen. Thiourea compounds work as building blocks in the synthesis of heterocyclic compounds[3] of theraupetic and pharmacological properties. Substituted thiourea have recently gained much interest in the preparation of a wide variety of pharmaceutical and biological compounds of prime importance[4].

Thiourea are 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 dimethylsulfoxide[5] possess high biological activity, act as corrosion inhibitors and antioxidants, 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 like 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 a well-known important group of organic compounds due to their diverse application in fields such as medicine, agriculture, coordination, and analytical chemistry[5]. They can also be used as selective analytical reagents, especially for the determination of metals in complex interfering materials[10-11]. As one of important thiourea derivatives is benzoyl thiourea compounds which have a wide range of biological activities including antibacterial[12], antitubercular[13], herbicidal[14], insecticidal[15], and pharmacological properties[16]. Thiourea derivatives and their transition metal complexes have been known since the beginning of the 20th century[17]. Also, these complexes display a wide range of biological activity including antibacterial, antifungal properties[18]. The complexes of ligands containing sulfur as donor atoms are known to possess antifungal and antibacterial activities[11]. 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[18]. In addition, benzoyl thiourea derivatives were often used in analytical and biological applications[19]. These molecules serve as an intermediate for the synthesis of 2-Aminobenzothiazoles[20]. Further, 2-Aminobenzothiazole is a very useful intermediate to form many schiff bases[21], thiazolidinones[22] and azetidinones[22].

Chemistry of Synthesis of Thiourea Derivatives

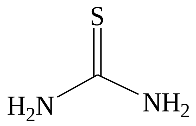
Thiourea derivatives, (**3**) can be synthesized by direct reaction of isocyanate, (**2**) with amine, (**1**). Reaction mechanism involved nucleophilic attack at the electrophilic carbon of thiocyanate ion by amine[23-25]. The general mechanism is shown in **Scheme-I**.



(1) (2) (3)

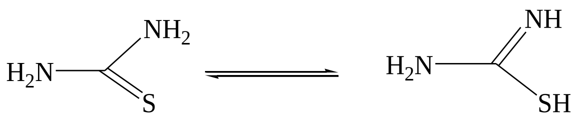
Scheme-I: General mechanism for synthesis of thiourea

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 **Fig. 1** below. 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 **Fig. 2**. There are a lot of possible reactions that can lead to synthesis of new derivatives that may be applicable[5].



(4a)

Fig. 1: Thiourea



(4a) Thiourea **(4b)** Isothiourea

Fig. 2: Tautomeric forms of thiourea

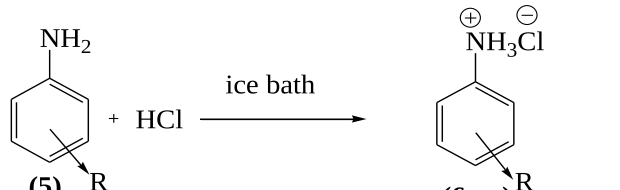
Solvent in Synthesis of Thiourea Derivatives

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 benzene and THF. Recently, we have reported the synthesis of intermediates Substituted diphenylthiourea[26] the studies on synthesis of intermediates 1,3-Di(substituted-phenyl)thiourea[27] using ammonium thiocyanate.

Looking, at all the literature reports and importance as to increase the ring size and in order of increasing numbers of heteroatoms in heterocyclic chemistry. Thioureas are useful in the preparation of two four-membered ring systems: Thietanes and 1,3-thiazetidin-4-ones. Also, the oxidation of heterocyclic thioureas to form benzothiazoles. Hence, we have undertaken the synthesis of an intermediate phenyl ammonium chloride and further to substituted-phenyl thiourea derivatives using ammonium thiocyanate as shown in **Scheme-II**.

Scheme-II:

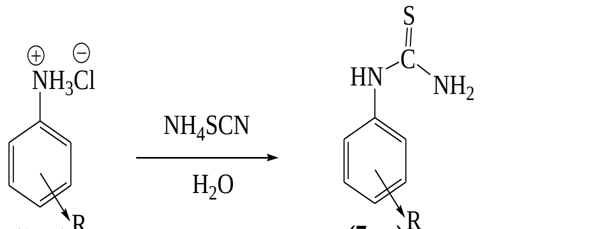
Step: 1st Preparation Phenyl-ammonium chloride



(5) Substituted aniline

(6a-e) Substituted-phenyl-ammonium chloride

Step: 2nd Preparation of mono-phenyl thiourea



(6a-e) Substituted-phenyl-ammonium chloride

(7a-e) 1-(Substituted-phenyl)thiourea

EXPERIMENTAL DETAILS

Material and Method: All the melting points were determined in open capillaries. IR Spectra (KBr) were recorded on the FTIR Spectrophotometer (Shimadzu PC, 4000-400 cm^{-1}).

General Method for the Synthesis of Substituted-phenyl-ammonium chloride(6a-j): In a 250 ml beaker No.-(a) take (0.05 M) 3-Methoxyaniline, and in another 250 ml beaker No.-(b) take 10 ml conc. HCl. When beaker No.(a) put in an ice bath and add conc. HCl slowly drops by drop to obtain solid mass in the beaker and filtered in the suction pump. Similarly, the other compounds(**6b-e**) were synthesized.

General method for the synthesis of mono-phenyl thiourea(7a-j): The ammonium thiocyanate (0.05 M) was dissolved in 15 ml of water, added to 0.05 mol of 1st stage compound, in R.B. Flask. The contents were refluxed on the rotamantle for 1.30 hour(clear TLC), then poured down into the 150 gm 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 phenylthiourea compound, **7a**. Similarly, other compounds, (**7b-e**) were synthesized.

RESULTS AND DISCUSSION

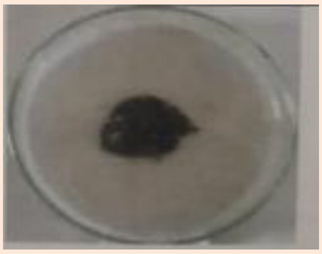
In the synthesis substituted anilines were reacted with ammonium thiocyanate to give thio compound. These are colored products and give experimental yields in the low range of 36.75 % to 4.35 % their physical constants are determined and given in **Table 1**.

Table 1: Physical and Analytical Data for the compound synthesized **7a** to **7e.**

Sr. No.	ID	Aniline Used	M. Wt. of Product	Color of Product	m.p. (°C)	Wt. in gram	Yield (%)
1	7a	2-Methoxy-aniline	182	Regatta	154-156	1.62	17.0
2	7b	2-Amino-thiophenol	184	Pale yellow	107-108	0.96	11.25
3	7c	4-Fluoro-aniline	170	Brown	166-167	0.37	4.35
4	7d	2,4-Dimethyl-aniline	180	Copper	170-171	1.26	16.77
5	7e	3-Chloro-aniline	185	Gold	129-131	3.36	36.75

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

Table 2. Recrystallized Photographic Representation of **7a** to **7e.**

ID	Aniline used	Purified Product
7a	2-Methoxy-aniline	
7b	2-Amino-thiophenol	
7c	4-Fluoro-aniline	
7d	2,4-Dimethyl-aniline	
7e	3-Chloro-aniline	

The TLC of reactant aniline and the final purified product id monitored, indicated the single spots. The UV-Vis data of mono-phenyl thiourea compound is shown in **Table 3**. The typical UV-Vis spectra of 1(2-Methoxyphenyl)thiourea is depicted in **Fig. 3**.

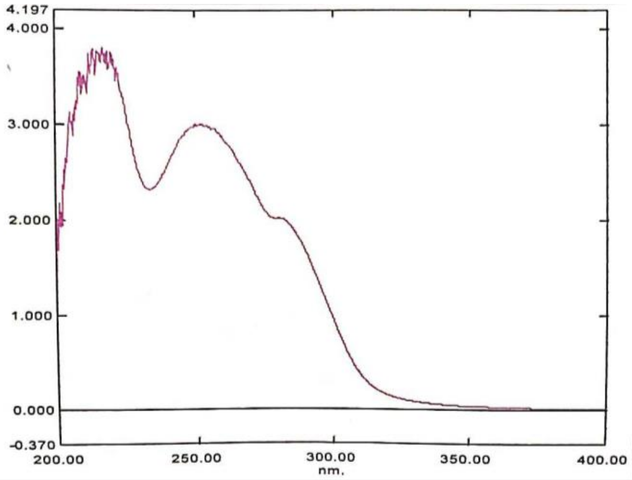


Figure 3: The typical UV-Vis spectra of 1-(2-Methoxyphenyl) thiourea, **7a**.

In general the exhibits the expected features of the standard FTIR spectra for this type of compound. The spectra of **7a** and the other compounds, **7b** to **7e** show absorption at about 3475-3372 cm^{-1} indicate the presence of N-H stretching frequency. The absorption at about 2966 cm^{-1} indicated the presence of $C\text{-}CH_3$ stretching frequency. The absorption at 1630-1596 cm^{-1} indicated the presence of $C\text{-}NH_2$ stretching frequency. The band at 1579-1447 cm^{-1} indicated the presence of >C=C< aromatic ring. The absorption at about 1302-1257 cm^{-1} indicated the presence of C-N stretching frequency. The band at 1402 cm^{-1} indicated the presence of C-F stretching frequency. Band at 1287-1110 cm^{-1} indicated the presence of C=S stretching frequency. The absorption at 771 cm^{-1} and frequencies 649 cm^{-1} indicated the presence of C-Cl and C-S stret. frequency. The typical FTIR of 1-(2-Methoxyphenyl)thiourea is depicted in **Fig. 4**.

Table 3: The UV-Vis data for the Phenyl thiourea compounds**, 7a** to **7e.**

Sr. No.	ID	UV max	Conc.	Absorbance	ε
1	**7a**	252.60 216.80 208.40	1.62×10^{-7}	3.024 3.816 3.559	1.86×10^{-7} 2.35×10^{-7} 2.20×10^{-7}
2	**7b**	325.00 207.40 287.40	0.0000016	0.726 2.519 0.212	448148 155493 103791
3	**7c**	357.00 339.80 261.00	0.0000017	0.027 0.032 1.774	155117.2 18390.8 101954
4	**7d**	344.40 340.00 248.60	0.000016	0.005 0.006 3.366	303.030 363.630 204000
5	**7e**	341.20 270.00 238.00	0.0000016	0.041 1.224 0.954	2530864 755555 588888

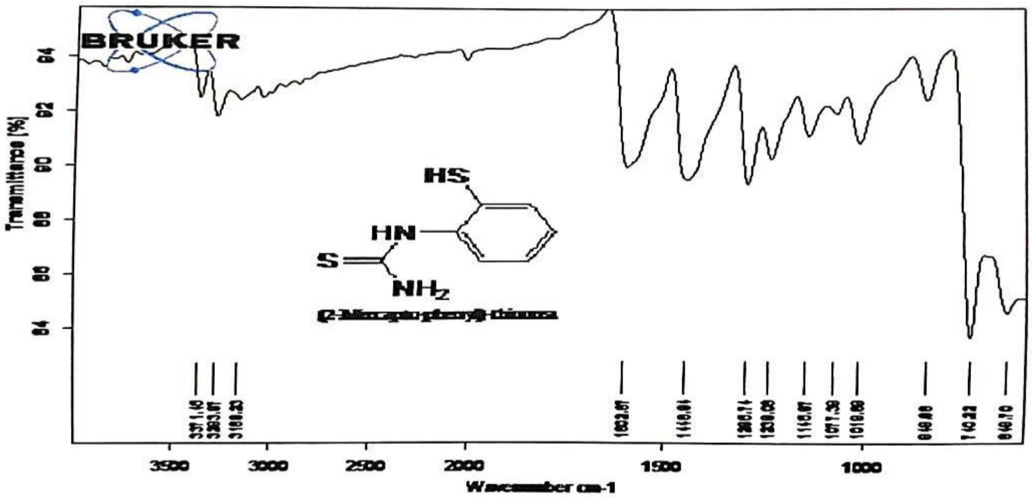
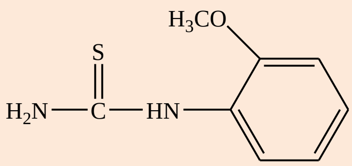
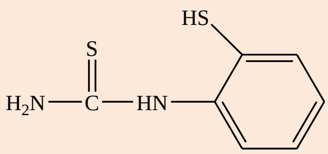
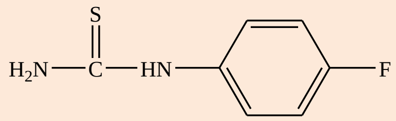
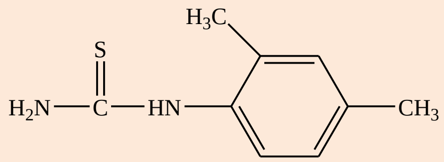
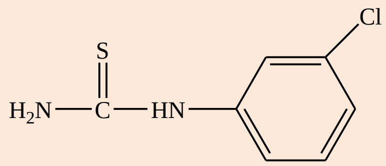


Figure 4: The typical FTIR of 1-(2-Methoxyphenyl)thiourea, **7a**

Table 4 FTIR Spectral Frequencies of the synthesized, Substituted-phenyl thiourea compounds, **7a-e.**

Sr. No.	FTIR Frequencies in (cm^{-1})	Structure of Substituted-phenyl thiourea Name with ID
1	V_{N-H} = 3428.1 V_{C-NH2} = 1595.8 $V_{C=C}$ = 1527.6 V_{C-N} = 1257.0 $V_{C-O-CH3}$ = 1168.4 $V_{C=S}$ = 1110.0	 1-(2-Methoxyphenyl)thiourea **7a**
2	V_{N-H} = 3371.5 V_{NH2} = 1602.7 $V_{C=C}$ = 1446.9 V_{C-N} = 1295.7 $V_{C=S}$ = 1146.0 V_{C-S} = 648.7	 1-(2-Mercaptophenyl)thiourea **7b**

3	ν_{N-H} = 3437.3 ν_{C-NH2} = 1619.4 $\nu_{C=C}$ = 1529.1 ν_{C-F} = 1402.3 ν_{C-N} = 1302.7 $\nu_{C=S}$ = 1137.9	 1-(4-Fluorophenyl)thiourea **7c**
4	ν_{N-H} = 3416.3 ν_{C-CH3} = 2967.9 ν_{NH2} = 1608.9 $\nu_{C=C}$ = 1515.7 ν_{C-N} = 1286.6 $\nu_{C=S}$ = 1114.1	 1-(2,4-Dimethylphenyl)thiourea **7d**
5	$\nu_{C=C}$ = 1579.3 ν_{N-H} = 3475.4 ν_{C-NH2} = 1630.0 ν_{C-N} = 1277.7 $\nu_{C=S}$ = 1150.0 ν_{C-Cl} = 770.7	 1-(3-Chlorophenyl)thiourea **7e**

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

CONCLUSION

In the present piece of work Substituted-phenyl-thiourea were synthesized which are used as an intermediate in different reactions (viz. synthesis of 2-Aminobenzothiazoles) because further these play an important role in synthesizing the heterocyclic compounds. These reactions involve synthesis of an intermediate phenylammonium chloride which is converted to substituted thiourea using ammonium thiocyanate as reagent. 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. importance as to increase the ring size and in order of increasing numbers of heteroatoms in heterocyclic chemistry. Thioureas are useful in the preparation of two four-membered ring systems: Thietanes and 1,3-thiazetidin-4-ones. They are also involved in the oxidation of heterocyclic thioureas to form benzothiazoles. There is a future scope for using these compounds for the organic transformations and screening of these compounds against different microorganisms 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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