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IODINE PROMOTED SYNTHESIS AND CONSTRUCTION OF AROMATIC THIOUREAS FROM AMINES

Yazala Jyothsna Pragathi[1], Pinapati Srinivasa Rao[1], Deekala Veronica[1] and Rudraraju Ramesh Raju*[1]

Department of Chemistry, Acharya Nagarjuna University, Nagarjuna-Nagar 522510, Andhra Pradesh, India.

***Corresponding Author: Rudraraju Ramesh Raju**
Department of Chemistry, Acharya Nagarjuna University, Nagarjuna-Nagar 522510, Andhra Pradesh, India.

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ABSTRACT
A new facile methodology for the synthesis of aromatic thioureas by desulphurization and addition reaction of the required amine, carbon disulfide and ammonia solution in the presence of DMSO solvent using iron at room temperature. The structures of the synthesized compounds were confirmed by IR, and, 1H-NMR methods The synthetic benefits of the presented methods are reflected in the operational simplicity, mild reaction conditions, short reaction times, high purity and yield of the products. Considering the commercial importance of thioureas, it should be emphasized that implementation of the optimal synthesis of thiourea determined good intermediate for the synthesis heterocyclic compounds having good biological activity from amines using iodine as a reagent.

KEYWORDS: Amine, carbon disulfide and ammonia.

INTRODUCTION

Thiourea is a very important functional group and good intermediate for the synthesis heterocyclic compounds such as benzothiozole,1 iminothiazolines, 2 thiohydantoins, 3 1, 3, 5-triazines, 4 2-amino-oxazolidines 5 and other compounds such as minoxidil6 and herbicides, 7 which have biological activity. In addition, thioureas are useful precursors in the synthesis of pharmaceutically important heterocycles8 and N-alkyl or N-aryl imides. 9 Many methods for the synthesis of thioureas have been reported, for example, N-substituted thioureas are commonly prepared from the reaction of amines with alkali metal thiocyanates in the presence of a strong acid,10 aroyl isothiocyanates with amines followed by basic hydrolysis, 11 isothiocyanates with ammonia or amines in two step reactions, 12 unsubstituted thioureas with primary amines with carbon disulfide in the presence of mercury acetate aqueous ammonia, primary alkyl amines at high temperature, 13 and disubstituted cyanamides with hydrogen chloride and LiAlHSH or hydrogen sulfide in the presence of ammonia.

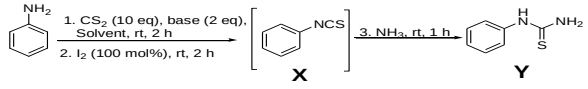
Several new methods for the preparation of substituted thioureas have been recently reported.

14 Apart from previous reports still mild, efficient and environment friendly method is desired. Therefore, we wish to demonstrate the construction of thioureas from amines using cheap and readily available Iodine as reagent.

Experimental Section

Herein, we report a three-component reaction between amine, CS2 and ammonia solution in the the presence of DMSO solvent using iron at room temperature. The optimization of the reaction conditions was carried out with aniline as model substrate using different bases, solvents and Iodine at varied temperatures (Table 1). The best result was obtained when the reaction was pursued at room temperature using 1 eq of the Iodine with bases like Et3N, NaOAc and NaHCO3 in the presence of DMF affording the phenylthiourea (Scheme 1) in 95% conversion (Table 1, entries 5 & 101-11).

Table 1: Optimization reaction conditions for the synthesis thiourea.



Entry	Solvent	Base	Yield (%)
1	Ethanol	Et_3N	45
2	Ethyl acetate	Et_3N	80
3	DCM	Et_3N	75
4	DMSO	Et_3N	75
5	**DMF**	**Et_3N**	**95**
6	H_2O	Et_3N	ND
7	n-Hexane	Et_3N	ND
8	n-Heptane	Et_3N	ND
9	DMF	Pyridine	55
10	DMF	$NaHCO_3$	95
11	DMF	NaOAc	95
12	DMF	Na_2HPO_4	95
13	DMF	NaOAc	67
14	-	-	ND

[a]Reaction conditions: Aniline (2 mmol), CS2 (10 eq), Et3N (2 eq), I2 (100 mol%), Ammonia solution (2 ml) were stirred at room temperature in the presence of respective solvent for 5 h.

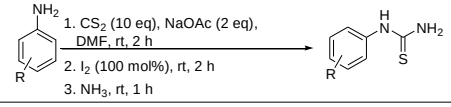
Firstly, the reaction was checked in the presence of different solvents. Among the solvents DMF gave target product in excellent yield. Other solvents like ethyl acetate, ethanol, DCM and DMSO could give target product in good yield. We have also examined with polar grenary solvent H_2O and no product was observed. Later we have checked with the non-polar solvents like n-Hexane and n-Heptane. Unfortunately no non-polar solvent could give target product. The reaction with other organic base pyridine couldn't give expected product. However, the inorganic bases sodium bicarbonate, sodium acetate and disodium phosphate could give target products in good yield. Finally the less amount of reagent like 50 mol % was examined, however the reaction to provide target product in moderate yield. The control experiment is confirmed that the reaction don't provide final product in the absence of solvent and base, and the strating material is recovered intact.

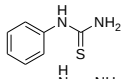
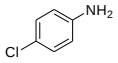
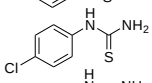
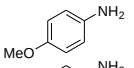
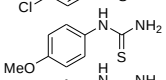
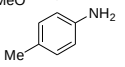
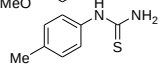
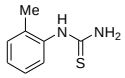
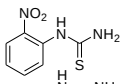
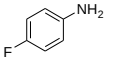
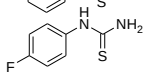
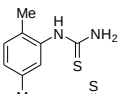
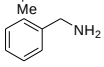
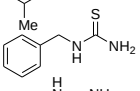
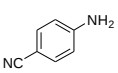
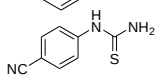
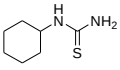
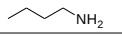
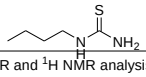
Having the optimal conditions in hand, we explored the scope of this procedure for the substrates having electron donating and electron withdrawing substituent's on the aryl rings. In this connection the various substrates bearing electron donating and electron withdrawing groups were examined under the standard reaction conditions (Table 2). The phenyl ring having electron donating groups such as 4-methyl, 4-methoxy could give their respective aromatic thioureas (Table 2, entries 3-4) in high yield. The unsubstituted phenyl ring also gave target product in quantitative yield (table 2, entry 1). Electron withdrawing groups such as 4-fluoro and 4-chloro substituents gave their final products in 75-84% yield (Table 2, entries 2 and 7). The aryl ring having strong electron withdrawing group $–NO_2$ on second position gave no product (table 2, entry 6). 4-Cyano aniline activity was also examined under optimized reaction conditions, but unfortunately no reaction was observed. Later, the same reaction was tested using strong base, anhydrous potassium hydroxide (KOH) and no target product could observe. Subsequent optimization for the reaction led to increase in yield; we did the reaction with anhydrous potassium hydroxide (KOH) at 80°C. Very interestingly the reaction could produce target product in moderate yield (Table 2, entry 10). Di-substituted and ortho-substituted aryl rings could obtain their respective thioureas in good yield (Table 2, entries 5 and 8).

Mechanism of the Reaction

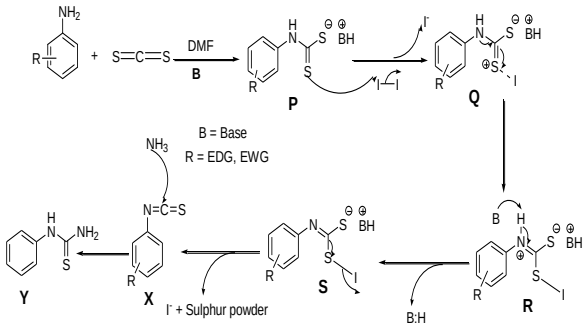
The mechanism of formation for phenyl thiourea from aniline is shown in below Scheme 1. The experimental evidence and from the literature reports the mechanism is proposed. As we shown in scheme 1, aniline (**1**) reacts with carbondisulphide in the presence of base (Et_3N) and respective solvent to give thiocarbomate salt **P**. It may co-ordinate with iodonium and followed by remove the proton to afford the intermediate **S** *via* intermediate complexes **Q** and **R**. Desulfurization of **S** afforded thioisocynate X that reacts with ammonium to give target thiourea **Y**.

Table 2: Substrate scope for the synthesis thiourea.



entry	Substrate	Product	Isolated yield (%)[a]
1			95
2			84
3			95
4			92
5			62
6			ND[b]
7			75
8			87
9			88
10			65[b]
11			88
12			82

[a]Compounds were confirmed by both IR and ^{1}H NMR analysis. [b] Base (KOH (1 eq)) and temp 85 °C were used.



RESULT AND CONCLUSION

In conclusion, we have developed neat, clean and efficient methodology for the synthesis of aromatic thioureas. This reaction involved consecutive desulphurization and addition. The reactions are rapid and facile and accomplished under mild reaction conditions. All the reactions readily underwent optimized

conditions to provide target products in moderate to excellent yield.

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