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An efficient methodology for the synthesis of thioureas from amine mediated by a cobalt source

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ABSTRACT

The cheap, readily available and air stable cobalt catalyst was used as the desulfurization agent for the conversion of aniline to thioureas in one pot three step reaction under mild reaction conditions. The reactions are rapid and facile and accomplished at room temperature 2009 Elsevier Ltd. All rights reserved.

1. Introduction

Due to its unique reactivity, thiourea is an important functional group in synthetic organic chemistry. Thioureas are useful precursors in the synthesis of pharmaceutically important heterocycles¹ and *N*-alkyl or *N*-aryl imides.² Thioureas are also important intermediates for the synthesis of many biologically active compounds such as minoxidil³ and herbicides.⁴ Apart from that, thioureas are important compounds as building blocks in the synthesis of heterocycles. For example, thioureas condense with α -halocarbonyl compounds to afford 2-amino-1,3-thiazoles.⁵ Benzothiazoles can be prepared from arylthioureas in the presence of bromine. The use of thioureas to make iminothiazolines,⁶ thiohydantoins,⁷ 1,3,5-triazines,⁸ and 2-amino-oxazolidines⁹ was also described recently. 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 α -aryl 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 and aqueous ammonia, primary alkyl amines at high temperature,¹³ and disubstituted cyanamides with hydrogen chloride and LiAlH₄ or hydrogen sulfide in the presence of ammonia. Several new methods for the preparation of substituted thioureas have been recently reported.¹⁴ However, these methods have several drawbacks, namely, the need for high reaction temperature, long reaction time, the use of noxious reagents such as hydrogen

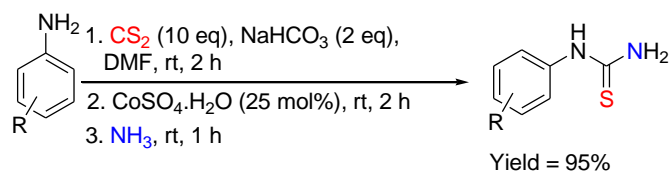
sulfide, and special starting materials. The development of mild, efficient and environmentally friendly method is still desired.

Herein we report a three-component reaction between amine, CS₂ and ammonia solution in the presence of DMF solvent using cobalt sources at room temperature. The optimization of the reaction conditions was carried out with aniline as model substrate using different bases, solvents and cobalt sources at varied temperatures (Table 1). The best result was obtained when the reaction was pursued at room temperature using 25 mol % of the cobalt salts such as CoCl₂·6H₂O, CoSO₄·H₂O and Co(NO₃)₂·6H₂O with bases like Et₃N, NaOAc and NaHCO₃ in the presence of DMF affording the phenylthiourea (Scheme 1) in 95% conversion (Conversion was confirmed by both TLC and GC).

Firstly, the reaction was checked in the presence of different solvents. In case of polar solvent ethyl acetate could give target product in good yield (Table 1, entry 2). Other polar solvents like ethanol gave final product in moderate yield. The reaction could give expected product in fewer yields in the presence of DMSO. The polar solvent DMF could get target product in excellent yield. We have also examined with polar greenery solvent H₂O and no product was observed (Table 1, entry 5). Later we have checked with the non-polar solvents like *n*-hexane and *n*-heptane. Unfortunately no non-polar solvent could give target product (Table 1, entries 6 and 7). Very interestingly, no reaction was occurred in the absence of solvent and the starting material was recovered intact. We have also checked the reaction in the

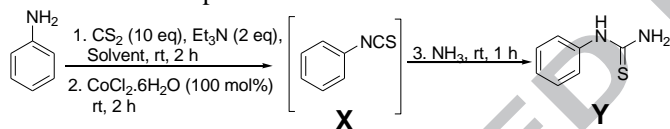
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presence of Toluene and THF solvents. THF could give target product in fewer yield (Table 1, entry 14), whereas the non polar solvent toluene couldn't give target product (Table 1, entry 15). Finally the reaction was checked in the presence of homogeneous (DMF and water) and heterogeneous (ethyl acetate and water) solvents. The homogeneous solvent mixtures (DMF: H₂O (1:1 and 1:2)) could give target product in moderate to good yield (Table 1, entries 9-10). The heterogeneous solvent mixture (Ethyl acetate: H₂O (1:1)) gave target product in 70% yield (Table 1, entry 11). We have also checked another heterogeneous reaction mixture ratio (Ethyl acetate: Water (1:2)) and we could obtain target product in 50% yield (Table 1, entry 12). The reaction with other organic base pyridine couldn't give expected product. Later, the inorganic bases sodium bicarbonate, sodium acetate could give target products in good yield. Later, we have also checked disodium phosphate activity and it showed less effect. Finally, the effect of different cobalt sources was also examined and we could find all the cobalt sources showed similar activity. Finally the less amount of catalyst like 50 mol %, 25 mol % and 10 mol % were examined. In among them 50 mol %



Scheme 1

Table 1: Solvent optimization



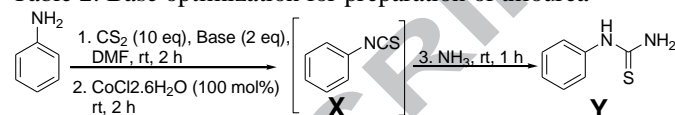
Entry	Solvent	Yield (%)
1	Ethanol	60
2	Ethyl acetate	80
3	DCM	75
4	DMSO	75
5	DMF	95
6	H ₂ O	ND
7	n-Hexane	ND
8	n-Heptane	ND
9	-	ND
10	DMF/H ₂ O (1:1)	85
11	DMF/H ₂ O (1:2)	70
12	EtOAc/H ₂ O (1:1)	70
13	EtOAc/H ₂ O (1:2)	50
14	THF	20
15	Toluene	ND

^aReaction conditions: Aniline (2 mmol), CS₂ (10 eq), Et₃N (2 eq), CoCl₂.6H₂O (100 mol%), Ammonia solution (2 ml) were stirred at room temperature in the presence of respective solvent for 5 h.

and 25 mol % catalyst could give target product in excellent yield. But unfortunately 10 mol % catalyst gave target product in less yield. The reaction was also examined with 5 mol % catalyst

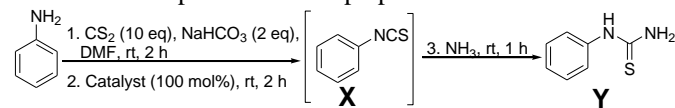
(CoSO₄.H₂O) and we could obtain target product in 10% yield only. The remaining starting material was recovered, which was observed by both TLC and GC. Similarly, we have also examined lowering of the reaction temperature (10 °C) or base (1 equiv). Unfortunately it gave lower yields. The control experiment confirmed that in the absence of the cobalt salts no reaction was occurred and starting material was 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

Table 2: Base optimization for preparation of thiourea^a

entry	Base	conversion (%) ^a (C)
1	Et ₃ N	95
2	Pyridine	ND
3	NaHCO ₃	>95
4	NaOAc	>95
5	Na ₂ HPO ₄	50

^a Reaction conditions: Aniline (2 mmol), CS₂ (10 eq), Base (2 eq), CoCl₂.6H₂O (100 mol%), Ammonia solution (2 ml) were stirred at room temperature in the presence of DMF for 5 h.

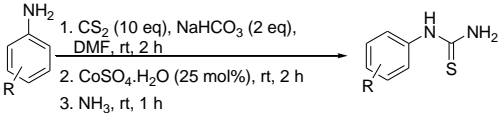
Table 3: Base optimization for preparation of thioureas^a

entry	Catalyst	conversion (%) ^a
1	CoCl ₂ .6H ₂ O	95
2	CoSO ₄ .H ₂ O	95
3	Co(NO ₃) ₂ .6H ₂ O	95
4 ^b	CoSO ₄ .H ₂ O	95
5 ^c	CoSO ₄ .H ₂ O	95
6 ^d	CoSO ₄ .H ₂ O	60
7	-	ND
8 ^e	CoSO ₄ .H ₂ O	10

^a Reaction conditions: Aniline (2 mmol), CS₂ (10 eq), NaHCO₃ (2 eq), Cobalt catalyst (100 mol%), Ammonia solution (2 ml) were stirred at room temperature in the presence of DMF for 5 h. The reaction conversion was determined by TLC. ^b Catalyst (CoSO₄.H₂O (50 mol %)) was used. ^c Catalyst (CoSO₄.H₂O (25 mol %)) was used. ^d Catalyst (CoSO₄.H₂O (10 mol %)) was used. ^e Catalyst (CoSO₄.H₂O (10 mol %)) was used.

electron withdrawing groups were examined under the standard reaction conditions (Table 4). The phenyl ring having electron donating groups such as 4-methyl, 4-methoxy could give their respective aromatic thioureas (Table 4, entries 3-4) in high yield. The unsubstituted phenyl ring also gave target product in quantitative yield (table 4, entry 1). Electron withdrawing groups such as 4-fluoro and 4-chloro substituents gave their final products in 75-90% yield (Table 4, entries 2 and 7). The aryl ring having strong electron withdrawing group -NO₂ on second position gave no product (table 4, entry 6). 4-Cyano aniline

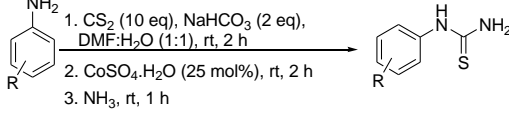
Table 4: Substrate scope



entry	Substrate	Product	Isolated yield (%) ^a
1			95
2			90
3			98
4			94
5			65
6			ND ^b
7			75
8			85
9			88
10			72 ^b
11			88
12			82

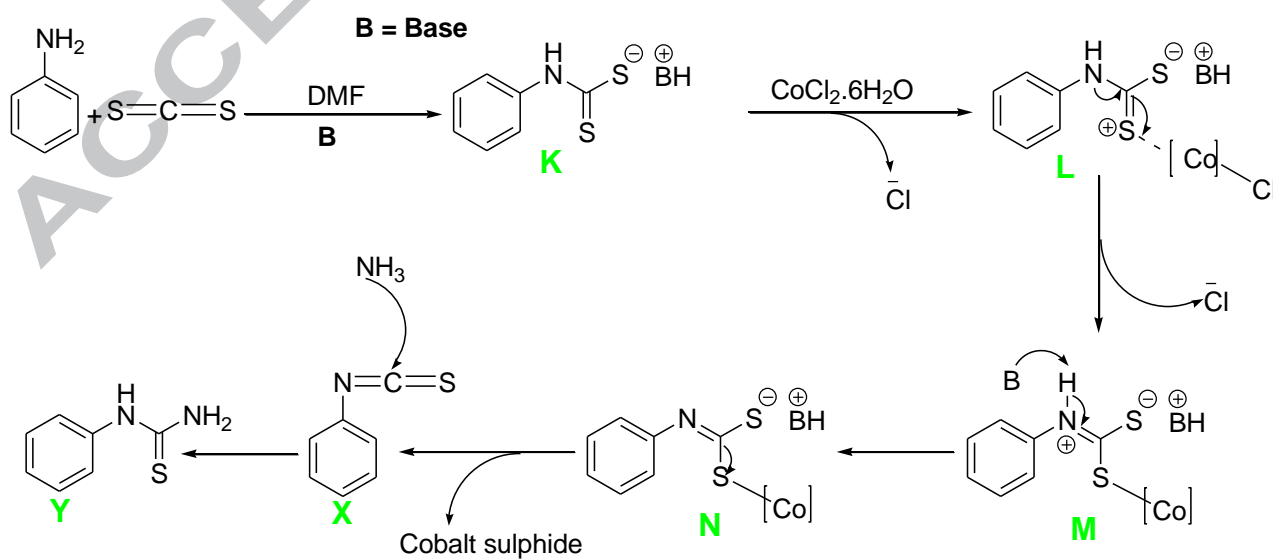
^aCompounds were confirmed by both IR and ¹H NMR analysis. ^b Base (K₂CO₃ (1 eq)) and temp 80 °C were used.

Table 5: substrate scope for the synthesis of thioureas



entry	Substrate	Product	Isolated yield (%) ^a
1			85
2			79
3			87
4			81
5			56
6			ND ^b
7			59
8			79
9			83
10			63 ^b
11			82
12			78

^aCompounds were confirmed by both IR and ¹H NMR analysis. ^b Base (K₂CO₃ (1 eq)) and temp 80 °C were used.



Scheme 2: Plausible mechanism

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 carbonate (K_2CO_3) and no target product could observe. Subsequent optimization for the reaction led to increase in yield; we did the reaction with anhydrous potassium carbonate (K_2CO_3) at 80 °C. Very interestingly the reaction could produce target product in moderate yield (Table 4, entry 10). Disubstituted and ortho-substituted aryl rings could obtain their respective thioureas in good yield (Table 4, entries 5 and 8). Finally we have also studied about aliphatic anilines. The aliphatic substrates readily underwent the reaction to produce the target products in high yields (Table 4, entries 9 and 10-11).

The substrate scope was also developed using another optimal reaction DMF/ H_2O (2:1) (Table 5). As we shown in Table 5, both electron donating and electron withdrawing substituents on aryl ring could give their respective target products in 56-87% yields. Following similar methodology, aliphatic amines such as n-butyl, cyclohexyl and benzyl amines could give their respective target products in 78%, 82% and 83% yield.

We proposed the mechanism of formation of phenyl thiourea from aniline (Scheme 2). The reaction of aniline with carbon disulfide catalyzed by base (**B**) gave thiocarbamate salt (**K**). Then, cobalt co-ordinates to sulfur in thiocarbamate and another chloride anion is abstracted to give thiocarbamate **N**. Desulfurization of **N** afforded thioisocyanate **X** that reacts with ammonium to give target thiourea **Y**.

Conclusion

We have developed methodology for the synthesis of both aromatic and aliphatic thioureas in one pot three step reaction using cheap, readily available and air stable cobalt catalyst under mild reaction conditions. All reactions could give their target products in good to excellent yield. The reactions are rapid and facile and accomplished at room temperature.

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Graphical Abstract

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We have developed methodology for the synthesis of both aromatic and aliphatic thioureas in one pot three steps reaction using cheap and readily available Cobalt catalyst under mild reaction conditions.

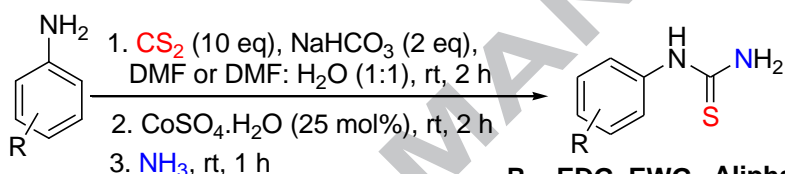
An efficient methodology for the synthesis of thioureas from amine mediated by a cobalt source

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R = EDG, EWG, Aliphatic aniline

22 examples

Yield 65-98%

EDG = Electron donating groups

EWG = Electron withdrawing groups

Highlights

- We have developed methodology for the synthesis of thioureas in one pot three step reactions.
- The cheap, readily available and air stable Cobalt catalyst is used as the desulfurization agent.
- The reactions are neat, clean and efficient.
- The reactions are rapid, facile and accomplished at room temperature.
- All the substrates could obtain their target products in good to excellent yields.

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