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Synthesis of Thiourea from Dithiocarbamate and Aromatic alkyl azide

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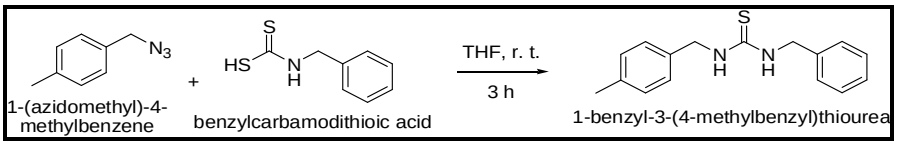
ABSTRACT

Thiourea and its derivatives show broad spectrum of biological activities. Hence, herein a series of thioureas have been synthesized. The process is simple and mild, employing dithiocarbamates and alkyl azides.

Graphical Abstract



Synthesis of thiourea derived from aromatic alkyl azide and dithiocarbamates

Keywords: Thiourea, Carbon di sulfide, aromatic alkyl azide, dithiocarbamates.

INTRODUCTION

Thioureas have a special importance due to their bioactivity in the field of pharmacy and agriculture [**1-3**]. For example a variety of thioureas and its derivatives serves as anticancer [**4, 5**], antimicrobial [**6, 7**] analgesic [**8**], anti-inflammatory [**9**], anti-fungal [**10**], as well as pesticides [**11**], fungicides, rodenticides and herbicides agents [**12, 13**]. Thioureas are also valuable building blocks for the synthesis of heterocyclic compounds [**14**]. In recent years thiourea derivatives have been employed as organocatalysts [**15-17**] and ligands in organic synthesis (Figure 1) [**18**].

Many methods are available for the synthesis of thioureas, such as direct reaction of isothiocyanates with anilines [**19, 20**], condensation of primary and secondary amine with thiophosgene and its derivatives [**21, 22**], reaction of 2-chloro-pyridinium salts with sodium trithiocarbonates and amines [**23**], reaction of disubstituted cyanamides with LiAlHSH and hydrogen chloride [**24**] and synthesis of 1,3-bis(2-substituted aryl)-4,5-di phenyl oxazol-3(2H-yl) thioureas from dihydrazinium thiocarbazinate [**25**] (figure 2). However, these methods have some limitations, such as harsh reaction conditions, long reaction duration, multistep protocol, need for high temperature, poor yields due to side products formation, etc.

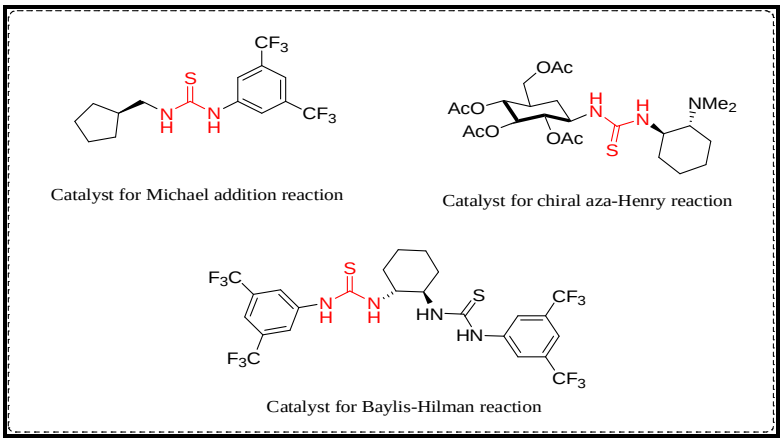


Figure 1. Thiourea based organocatalysts.

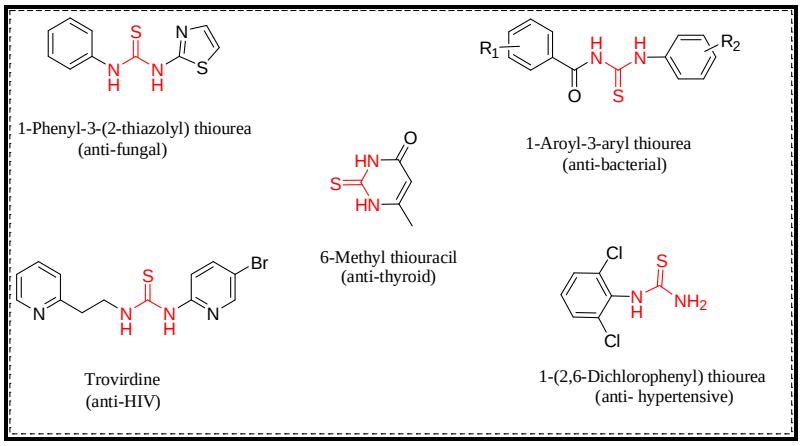


Figure 2. Thiourea containing medicinally useful compounds.

MATERIALS AND METHODS

Instrumentation: All the chemicals used were purchased from Sigma Aldrich, USA. The solvents were freshly distilled and dried. TLC analysis was done using Merck aluminium TLC sheets (silica gel 60 F_{254}), the chromatograms were observed by UV light and also by iodine chamber whenever it was necessary. HRMS spectra were recorded in Micromass Q-TOF mass spectrometer. 1H and 13C NMR were determined in Brucker AV NMR (400 MHz, 100 MHz) spectrometer.

General procedure

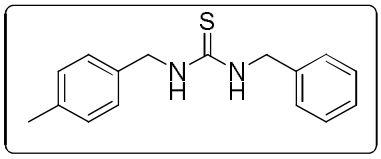
General method for the preparation of azides starting from iodides: 4-Methyl benzyl alcohol (1.0 equiv.) in dry DCM (5 mL) was added to the mixture of PPh_3 (3.0 equiv.), imidazole (5.0 equiv.) and iodine (3.0 equiv.) in DCM (5 mL) for 6 h and monitored by TLC. The solvent was evaporated under reduced pressure and crude compound was purified by column chromatography. The pure product iodide was dissolved in (2.0 mL) DMF, mixed with NaN_3 (1.5 equiv.) and stirred at room temperature for 5 h. The solvent was evaporated under vacuum followed by simple work up. The solvent was concentrated to dryness. The crude product was purified by column chromatography.

General experimental condition for the preparation of thiourea: To the solution of aromatic amine (1.0 equiv.), TEA (1.2 equiv.) and CS_2 (1.2 equiv.) in THF (5 mL) was added at 0°C. After 15 min, to the above solution aromatic alkyl azide (1.5 equiv.) in THF was added. The stirring was continued at 0°C to room temperature under nitrogen atmosphere for about 3 h and monitored by

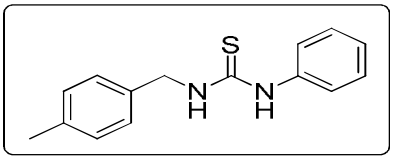
TLC. The reaction mixture was concentrated to dryness under reduced pressure. The residue was extracted into ethyl acetate. The organic layer was washed with 10% citric acid solution, brine and dried over anhydrous sodium sulfate. The solvent was removed in vacuo and crude product was purified over column chromatography using hexane-ethyl acetate to get pure product.

Spectral Data

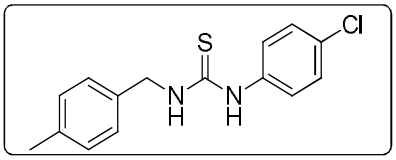
3a] 1-benzyl-3-(4-methylbenzyl)thiourea: ^{1}H NMR (400MHz, $CDCl_3$): δ 8.40 (br s, 1H), 8.15 (br s, 1H), 7.58-7.09 (m, 8H), 4.74 (d, 2H), 4.63 (d, 2H), 2.30 (s, 3H). ^{13}C NMR (100MHz, $CDCl_3$): δ 180.7, 136.8, 134.9, 131.0, 129.3, 128.9, 128.6, 127.3, 122.0, 53.0, 52.8, 21.3.HRMS: m/z cal for $C_{16}H_{18}N_2NaS$ $(M+Na)^+$293.1088; found: 293.1087.



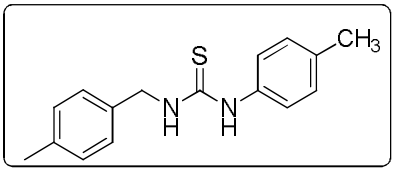
[3b] 1-(4-methylbenzyl)-3-phenylthiourea: ^{1}H NMR (400MHz, $CDCl_3$): δ 8.29 (s, 1H), 7.69 (s, 1H), 7.42-7.20 (m, 9H), 4.87(d, J= 5,2 Hz, 2H), 2.38 (s, 3H).^{13}C NMR (100MHz, $CDCl_3$): δ 181.0, 137.2, 135.9, 130.2, 129.2, 128.8, 127.7, 127.6, 127.4, 49.2, 21.4. HRMS: m/z cal for $C_{15}H_{16}N_2NaS$ $(M+Na)^+$279.0932; found: 279.0931.



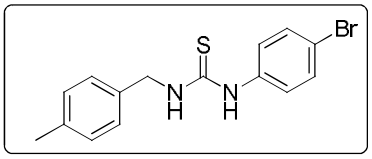
[3c]1-(4-chlorophenyl)-3-(4-methylbenzyl)thiourea: ^{1}H NMR (400MHz, $CDCl_3$): δ 8.42 (br s, 1H), 8.15 (br s, 1H), 7.49-7.10 (m, 8H), 4.85 (s, 2H), 2.40 (s, 3H), ^{13}C NMR (100MHz, $CDCl_3$): δ 179.5, 136.6, 136.4, 134.9, 133.7, 131.1, 129.1, 128.8, 128.1, 50.8, 21.3. HRMS: m/z cal for $C_{15}H_{15}ClN_2NaS$ $(M+Na)^+$313.0542; found: 313.0541.



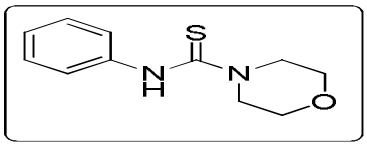
[3d] 1-(4-methylbenzyl)-3-(p-tolyl)thiourea: ^{1}H NMR (400MHz, $CDCl_3$): δ 8.38 (br s, 1H), 8.19 (br s, 1H), 7.48-7.07 (m, 8H), 4.71 (s, 2H), 2.32 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (100MHz, $CDCl_3$): δ 180.9, 137.0, 134.8, 131.2, 129.4, 128.9, 128.7, 127.4, 122.3, 53.4, 21.9, 21.3. HRMS: m/z cal for $C_{16}H_{18}N_2NaS$ $(M+Na)^+$293.1088; found: 293.1087.



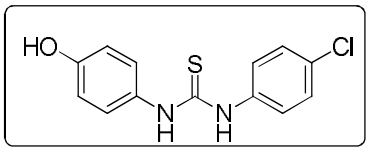
[3e] N-(4-bromophenyl)-N-(4-methylbenzyl)ethene-1,1-diamine: ^{1}H NMR (400MHz, $CDCl_3$): δ 8.38 (br s, 1H), 8.13 (br s, 1H), 7.48-7.00 (m, 8H),4.63 (s, 2H), 2.29 (s, 3H). ^{13}C NMR (100MHz, $CDCl_3$): δ 180.6, 136.6, 135.1, 130.7, 129.2, 129.0, 128.3, 127.1, 121.8, 52.9, 21.5. HRMS: m/z cal for $C_{15}H_{15}BrN_2NaS$ $(M+Na)^+$357.0037; found: 357.0036.



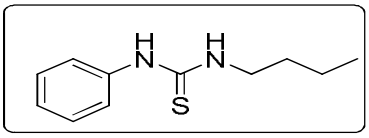
[3f] N-phenylmorpholine-4-carbothioamide: ^{1}H NMR(400MHz, $CDCl_3$):δ 8.07(br s, 1H), 7.71-7.83 (m, 5H), 3.82 (t, *J*= 5.2Hz, 4H), 3.73 (t, *J*= 6.0 Hz, 4H). ^{13}C NMR (100MHz, $CDCl_3$):δ 183.9, 139.8, 129.2, 125.4, 123.0, 66.1, 49.7. HRMS: m/z cal for $C_{11}H_{14}N_2NaOS$ $(M+Na)^+$245.0725; found: 245.0724.



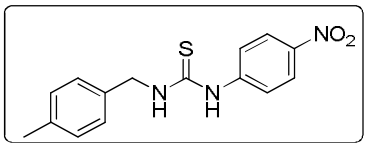
[3g] 1-(4-chlorophenyl)-3-(4-hydroxyphenyl)thiourea: ^{1}H NMR (400MHz, $CDCl_3$): δ 8.37(br s,1H), 8.12 (br s, 1H), 7.19-7.13 (m, 8H), 6.54 (s, 1H).^{13}C NMR (100MHz, $CDCl_3$):δ 180.4, 153.9, 136.0, 134.7, 134.2, 133.9, 127.2, 125.6, 118.7. HRMS: m/z cal for $C_{13}H_{11}ClN_2NaOS$ $(M+Na)^+$301.0178; found: 301.0179.



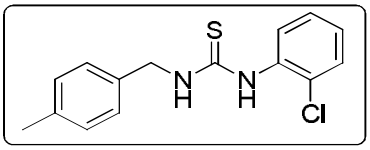
[3h] 1-butyl-3-phenylthiourea: ^{1}H NMR (400MHz, $CDCl_3$): δ 8.18 (br s, 1H), 7.96 (br s, 1H), 7.47-7.20 (m, 5H), 3.62 (q, J= 5.6Hz, 2H), 1.61-1.50 (m, 2H), 1.38-1.28 (m, 2H), 0.91 (t, J= 5.2 Hz, 3H). ^{13}C NMR (100MHz, $CDCl_3$):δ 180.5, 136.3, 130.1, 127.1, 125.2, 45.3, 31.9, 20.0, 13.7. HRMS: m/z cal for $C_{11}H_{16}N_2NaS$ $(M+Na)^+$231.0932; found: 231.0931.



[3i] 1-(4-methylbenzyl)-3-(4-nitrophenyl)thiourea: ^{1}H NMR (400MHz, $CDCl_3$): δ 8.25 (br s, 1H), 8.20 (br s, 1H), 7.53-7.12 (m, 8H), 4.70 (s, 2H), 2.33 (s, 3H). ^{13}C NMR (100MHz, $CDCl_3$):δ 180.9, 140.9, 138.0, 135.1, 134.7, 128.9, 128.5, 122.5, 122.1, 53.3, 21.3. HRMS: m/z cal for $C_{15}H_{15}N_3NaO_2S$ $(M+Na)^+$324.0783; found: 324.0781.

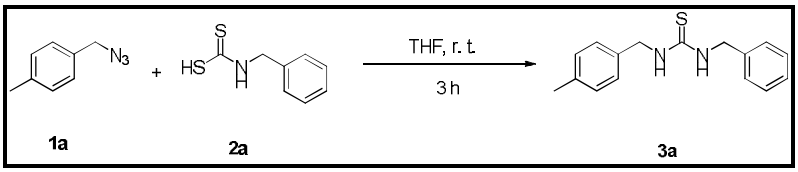


[3j] 1-(2-chlorophenyl)-3-(4-methylbenzyl)thiourea: ^{1}H NMR (400MHz, $CDCl_3$): δ 8.30 (br s, 1H), 8.17 (br s, 1H), 7.45-7.09 (m, 8H), 4.73 (s, 2H), 2.34 (s, 3H). ^{13}C NMR (100MHz, $CDCl_3$): 180.3, 137.5, 135.9, 134.9, 131.5, 130.4, 130.1. 128.9, 128.0, 127.5, 122.6, 53.5, 21.4. HRMS: m/z cal for $C_{15}H_{15}ClN_2NaO_2S$ $(M+Na)^+$313.0542; found: 313.0540.



RESULTS AND DISCUSSION

In organic synthesis, efforts have been done to develop new strategies for the synthesis of thioureas. Among the numerous methods, condensation of primary and secondary amine with isothiocyanate [**26, 27**], thiophosgene [**28, 29**] and its derivatives [**30, 31**]are the most commonly employed routes for the synthesis of thioureas. However, these protocols suffer from few drawbacks such as harsh reaction conditions, use of toxic reagents and low chemo selectivity. Therefore, we initiated our studies on the synthesis of thiourea, using 4-methyl benzyl azide and benzyl dithiocarbamate as model substrates for the optimization of reaction conditions (Scheme 1). Initially, we screened various bases



Scheme 1. Synthesis of thiourea derived from aromatic alkyl azide and dithiocarbamates

and solvents such as N-methylmorpholine, pyridine, trimethylamine and diisopropylamine and solvents like toluene, acetone, THF and DMF (Table 1, entries 1-7) at room temperature for 3-14 h. After screening with various base and solvent a significant increase in the amount of benzyl dithiocarbamate (2a) was detected in presence of N-methylmorpholine and THF as base and solvent at room temperature. Therefore, thiourea (3a) was obtained in 90% yield.

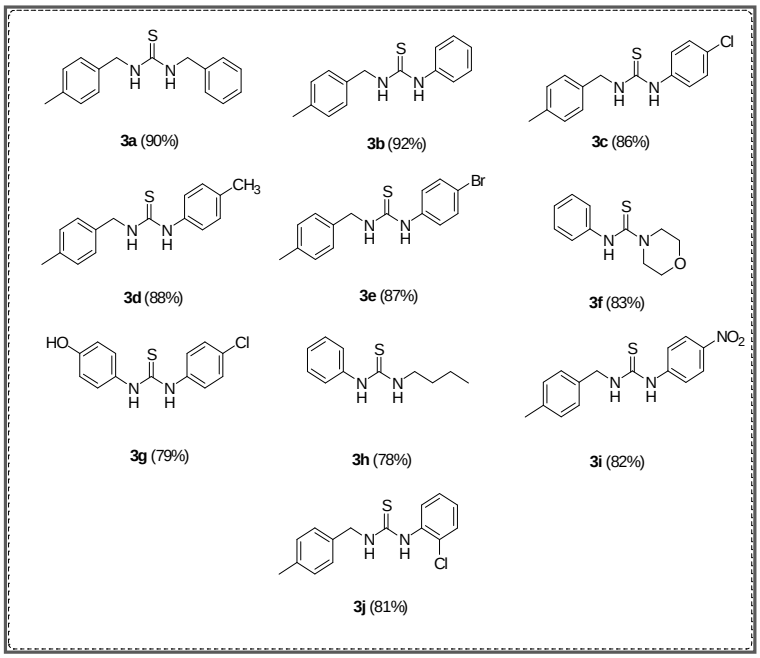


Figure 3. List of thioureas

In a typical experiment, a solution of benzyl amine in THF was treated with CS_2 in presence of NMM at 0^oC for 15 min, and the in situ generated benzyl dithiocarbamate (2a) was treated with 4-methyl benzyl azide (1a) at 0^oC to room temperature. Upon completion of the reaction (from TLC analysis) thiourea (3a) was isolated by a simple work up and then purified by column chromatography. The generality of this protocol is demonstrated by the synthesis of ten thioureas

(Figure 3). All the products were isolated as solids and fully characterized through NMR and mass spectrometry.

Table 1. Comparative studies of base and solvent for the synthesis of **3a**

Entry	Base	Solvent	Temperature (0 °c)	Time (h)	Yield (%)[a]
1	TEA	THF	R.T	14	20
2	DIPEA	THF	R.T	10	35
3	Pyridine	THF	Reflux	12	50
4	NMM	THF	R.T	3	90
5	NMM	Toluene	Reflux	1	40
6	NMM	Acetone	Reflux	4	45
7	NMM	DMF	R.T	5	32

APPLICATION

Thiourea on desulfurization lead to the formation of cyanamides and carbodiimides. Thiourea acts as an precursor for guanidines formation and it is also applicable for the formation of complex heterocyclic molecules.

CONCLUSION

In conclusion, thioureas are prepared by the reaction of benzyl amines with CS_2 in presence of NMM to form dithiocarbamates and then by coupling with aromatic alkyl azide. This reaction works well for electron donating azides also.

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