SYNTHESIS OF UNSYMMETRICAL THIOUREA DERIVATIVES

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A series of thiourea derivatives have been synthesized. Thiourea derivatives show a broad spectrum of biological activities such as antibacterial, antiviral, anticancer, anticonvulsion, analgesic an HDL-elevating. Ethyl isothiocyanate and aromatic amines were mixed and stirred at room temperature in acetone for 15 h to give the corresponding thioureas in high yields. Their structures were confirmed by IR and ^{1}H-NMR. By addition e-donor groups to aromatic amines, thioureas were synthesized in high yields.

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INTRODUCTION

Thiourea is an important industrial chemical product. Animal studies on the chronic toxicity of thiourea have shown that the compounds, when administered in drinking water, induces thyroid adenomas and carcinomas in rats.[1]

Thiourea and uera derivatives show a broad spectrum of biological activities such as antibacterial, antiviral, anticancer, anticonvulsion, analgesic and HDL-elevating properties. Furthermore, structural studies of active thiourea derivatives have shown that these compounds contain a central hydrophilic part and two hydrophobic moieties forming a butterfly-like conformation. This conformation is a part of structure of anti-HIV agent.[2] A variety of thiouera derivatives and their metal complex exhibit analgesic, anti-inflammatory, anticancer and antifungal activities. Moreover, thiourea is important building block in the synthesis of heterocycle.[3]

For the past few decades, thiourea derivatives have attracted great attention as versatile ligands in numerous applications. This is due to its unique properties which enable to coordinate with various transition metal ions as monodenate or bidentate ligands. Thiourea derivatives for instance derived as substituted benzoylthiourea or phenylthiourea derivatives are attractive model compounds for the formation of nitra-and intermolecular hydrogen bonds of the N-H proton–donor groups to sulfur and carbonyl oxygen atoms.[4-5]

Thioureas have also found use in organocatalysis. There are several reports on the synthesis of thioureas, which include many hazardous and toxic procedures. For example, thioureas have been synthesized by the reaction of primary and secondary amines with phosgene and thiocyanates, which are hazardous protocols. There are safer, non-toxic and user-friendly procedures to synthesize thioureas.[6-11]

In the present study, we focus on the synthesis and characterization of 10 new synthetic derivatives which their structures were confirmed by spectroscopic methods namely IR, ^{1}H-NMR spectroscopy.

EXPERIMENTS

General Remarks

High-resolution 1H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectrawere obtained with a Bruker 500 DRX-Avance NMR spectrometer. Compounds were dissolved in deuterated DMSO as NMR solvent. IR data were obtained with a Shimadzu 470 spectrometer. Melting points of crystalline compounds were measured with an Electrothermal melting point apparatus and have not been corrected. Mass spectra were obtained using a GCMS

Agilent Technologies QP-5973N MSD instrument. Purification of crystalline compounds was performed by recrystallization and in some cases by preparative thin-layer chromatography with silica gel 60 GF254. All chemicals were purchased from Aldrich Chemical Company, Merck or Fluka.

General method for the synthesis of thiourea derivatives 2a-i

To a solution of aromatic amines **1a-i** (3 mmol), and ethylisothiocyanate (3 mmol) in acetone (6 mL) was added with stirring at room temperature. The mixture stirring for 15h until the completion of the reaction and resultant precipitate was filtered, washed with petroleum ether, dried and recrystallized from 95% ethanol. The physical data of the compounds are presented in Table 1. The spectral data of the compounds are as follows.

1-Ethyl-3-(3-hydroxyphenyl)thiourea 2a: IR (KBr) 3300, 3200, 3150, 1240, 1500, 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.59 (br. s, 1H, OH), 7.32 (t, J 8.2 Hz, 1H, H_{Ar}), 6.75-6.81 (br. m, 2H, H_{Ar}), 6.71 (br. s, 1H, H_{Ar}), 6.12 (br. s, 1H, NH), 3.73 (d, J 7.2 Hz, 2H, CH_2), 1.27 (br. s, 1H, NH), 1.23 (t, J 7.4 Hz, 3H, CH_3) ppm.

Table 1. Physical characterization data of the compounds **2a-i**

Entry	Substrate	Product 2a-i	M.P., °C	Yeld, %
a	3-$HOC_6H_4NH_2$	3-$HOC_6H_4NHCSNHCH_2CH_3$	138-140	67
b	4-$CH_3CH_2C_6H_4NH_2$	4-$CH_3CH_2C_6H_4NHCSNHCH_2CH_3$	85-90	80
c	2-$_2HNC_6H_4NH_2$	2-$H_2NC_6H_4NHCSNHCH_2CH_3$	102-110	82
d	4-$CH_3CH_2OC_6H_4NH_2$	4-$CH_3CH_2OC_6H_4NHCSNHCH_2CH_3$	105-109	85
e	3-$H_2NC_6H_4NH_2$	3-$H_2NC_6H_4NHCSNHCH_2CH_3$	105-112	75
f	4-$HOC_6H_4NH_2$	4-$HOC_6H_4NHCSNHCH_2CH_3$	150-154	78
j	3,4,5-$CH_3OC_6H_4NH_2$	3,4,5-$(CH_3O)_3C_6H_2NHCSNHCH_2CH_3$	168-170	85
h	4-$CH_3OC_6H_4NH_2$	4-$CH_3OC_6H_4NHCSNHCH_2CH_3$	125-130	85
i	2$CH_3OC_6H_4NH_2$	2$CH_3OC_6H_4NHCSNHCH_2CH_3$	99-101	80

1-Ethyl-3-(4-ethylphenyl)thiourea 2b: IR (KBr) 3200, 3000, 1560, 1500, 1465, 1450, 1375, 1260, 1200 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 7.87 (br. s, 1H, NH), 7.27 (d. J 2.0 Hz, 2H, H_{Ar}), 7.13 (d, J 4.8 Hz, 2H, CH_{Ar}), 5.96 (br. s, 1H, NH), 3.70 (q. J 7.2 Hz, 2H, CH_2), 2.70 (q, J 7.6 Hz, 2H, CH_2), 1.27 (t, J 7.6 Hz, 3H, CH_3), 1.207 (t, J 7.2 Hz, 3H, CH_3) ppm.

1-(2-Aminophenyl)-3-ethylthiourea 2c: IR (KBr) 3400, 3200, 3000, 1500, 1220, 1150 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 7.61 (br. s, 1H, NH), 7.28 (s, 1H, H_{Ar}), 7.19 (t, J 6.0 Hz, 1H, H_{Ar}), 7.07 (d. J 6.4 Hz, 1H, H_{Ar}), 6.80 (t, J 1.2 Hz, 1H, H_{Ar}), 5.82 (s, 1H, NH), 3.99 (br. s, 2H, NH_2), 3.67 (q, J 7.2 Hz, 2H, CH_2), 1.17 (t, J 7.2 Hz, 3H, CH_3) ppm.

1-(4-Ethoxyphenyl)-3-ethylthiourea 2d: IR (KBr) 3220, 3000, 1500, 1450, 1375, 1290, 1250, 1150 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 7.28 (s, 1H, NH), 7.16 (d, J 8.8 Hz, 2H, CH_{Ar}), 6.95 (d, J 8.8 Hz, 2H, CH_{Ar}), 5.78 (br. s, 1H, NH), 4.07 (q, J 6.9 Hz, 2H, CH_2), 3.68 (q, J 7.3 Hz, 2H, CH_2), 1.45 (t, J 7.0 Hz, 3H, CH_3), 1.18 (t, J 7.2 Hz, 3H, CH_3) ppm.

1-(3-Aminophenyl)-3-ethylthiourea 2e: IR (KBr) 3200, 3000, 1500, 1300, 1200 cm^{-1} ; ^{1}H-NMR ($CDCl_3$): 7.76 (br. s, 1H, NH), 7.28 (s, 1H, CH_{Ar}), 7.20 (t, J 8.0 Hz, 1H, CH_{Ar}), 6.61 (d, J 2.0 Hz,1H, H_{Ar}), 6.59 (d, J 1.6 Hz, 1H, H_{Ar}), 6.47 (s, 1H, NH), 6.14 (br. s, 1H, NH_2), 3.71 (q, J 7.2 Hz, 2H, CH_2), 1.21 (t, J 7.2 Hz, 3H, CH_3) ppm.

1-Ethyl-3-(4-hydroxyphenyl)thiourea 2f: IR (KBr) 3300, 3200, 3100, 1550, 1250, 1220 cm^{-1} ; ^{1}H-NMR ($CDCl_3$): 9.38 (s, 1H, OH), 9.12 (s, 1H, NH), 7.35 (br. s, 1H, NH), 7.05 (d, J 4.0 Hz, 2H, H_{Ar}), 6.73 (d, J 3.4 Hz, 2H, H_{Ar}), 3.45 (q, J 6.8 Hz, 2H, CH_2), 1.08 (t, J 7.0 Hz, 3H, CH_3) ppm.

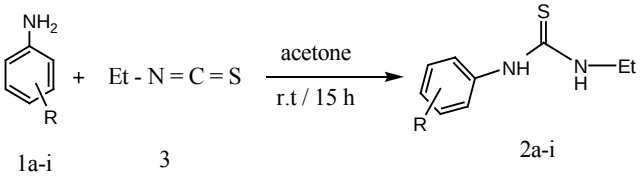
1-Ethyl-3(3,4,5-trimethoxyphenyl)thiourea 2g: IR (KBr) 3200, 3000, 1500, 1290, 1250, 1120 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 7.93 (s, 1H, NH), 6.46 (s, 2H, H_{Ar}), 6.04 (br.s, 1H, NH), 3.85 (s, 3H, CH_3), 3.84 (s, 6H, CH_3), 3.70 (q, J 7.2 Hz, 2H, CH_2), 1.22 (t, J 7.2 Hz, 3H, CH_3) ppm.

1-Ethyl-3-(4-methoxyphenyl)thiourea 2h: IR (KBr) 3200, 3000, 1500, 1290, 1250, 1150 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 7.79 (s, 1H, NH), 7.17 (d, J 3.12 Hz, 2H, H_{Ar}), 6.96 (d, J 3.12 Hz, 2H, H_{Ar}), 5.79 (br. s, 1H, NH), 3.82 (s, 3H, CH_3), 3.67 (q, J 7.2 Hz, 2H, CH_2), 1.18 (t. J 7.4 Hz, 3H, CH_3) ppm.

1-Ethyl-3-(2-methoxyphenyl)thiourea 2i: IR (KBr) 3100, 3090, 1500, 1200, 1050 cm^{-1} ; ^{1}H-NMR ($CDCl_3$): 8.03 (s, 1H, NH), 7.94 (t, J 9.6 Hz, 2H, H_{Ar}), 7.62–7.57 (q, J 5.6 Hz, 2H, H_{Ar}), 7.55 (t, J 7.6 Hz, 1H, NH), 3.82 (s, 3H, CH_3), 3.66–3.61 (q, J 7.2 Hz, 2H, CH_2), 1.10 (t, J 7.2 Hz, 3H, CH_3) ppm.

RESULTS AND DISCUSSION

Thioureas **2a-i** were prepared in acetone with constant stirring at room temperature with 1.0 equiv of aromatic amines **1a-i** and 1.0 equiv of ethylisothiocyanate (Scheme 1). Aromatic amines **1a-i** afforded thioureas **2a-i** in high yield after purification by pethrolium ether.[7] All compounds had IR, ^{1}H-NMR spectra in accord with their anticipated structure. The physical characterization data of the compounds are given in Table 1. Using the method, by addition e-donor groups to aromatic amines, thiourea **2a-i** were synthesized in high yields.



Scheme 1. Synthesis of thioureas **2a-i** from aromatic amines **1a-i**

Spectroscopic studies

Infrared spectra of these title compounds reveal all the expected frequency region of the υ (N-H), (C-N) and (C=S). The bands at 3100-3200 cm^{-1} represent stretching vibration of the (N-H) in the derivatives thiourea. The (C-N) stretching frequencies have been found at around 1050-1250 cm^{-1}. These vibrational frequencies occur at variation intensities in IR spectra because of the polarity of the double bond and electron donating groups at ortho, meta or para position of the substituent on the aromatic. The characteristic region of the high frequency (C=S) in the aromatics thioureas are described as large double bond character and the lower nucleophilic character of the sulphur atom in comparison with alkylthioureas. The bands at 1190-1250 cm^{-1} represent vibration of the υ (C=S) in the derivatives thiourea. In ^{1}H-NMR spectra, the unresolved resonance of aromatic protons can be clearly observed as distinctive multiplet resonances between δ_H 7.15-8.80 ppm. These characteristics are strongly influenced by the ortho, meta and para-substituent methyl groups at the phenyl ring

and due to the overlapping proton signals in the aromatic rings. Two signals noted as singlet, corresponds to one proton at δ_H 6.12 and 1.27 ppm is assigned to the N(1)H proton which is substituted to the thiocarbonyl and N(2)H proton.

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