

SYNTHESIS CHARACTERIZATION AND ANTIBACTERIAL ACTIVITY OF SOME 1-AROYL-3-ARYL THIOUREAS

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Abstract. An efficient, synthesis of some 1-aryl-3-aryl thioureas (**1a-j**) is reported. Substituted aroyl chlorides were treated with an equimolar quantity of potassium thiocyanate in acetone to afford the corresponding isothiocyanates which were not separated followed by reaction with an equimolar amount of substituted anilines to furnish the 1-aryl-3-arylthiourea derivatives (**1a-j**). The structures were confirmed by spectroscopic data and elemental analyses. All of the synthesized compounds (**1a-j**) were assayed *in vitro* for their antimicrobial activity against Gram positive and Gram negative bacteria and were found to exhibit moderate to potent activity towards the tested microorganisms, compared to the standard drugs.

Keywords: 1-aryl-3-aryl thioureas, antibacterial, synthesis

Introduction

Various 1,3-disubstituted thiourea derivatives are extremely versatile building blocks for the synthesis of a variety of heterocyclic compounds and exhibit a wide spectrum of bioactivities. N, N-Dialkyl-N-aryl thioureas are efficient ligands for the separation of platinum group metals [1]. 1,3-Dialkyl or diaryl thioureas exhibit significant antifungal activity against plant pathogens *Pyricularia oryzae* and *Drechslera oryzae* [2. N-(substituted phenyl)-N-phenylthioureas have been developed as anion-binding site in a hydrogen-bonding receptor [3], calix[4]arenes containing thioureas as neutral receptors towards α , α -dicarboxylate anions [4], and N-4-substitued-benzyl-N-ter-

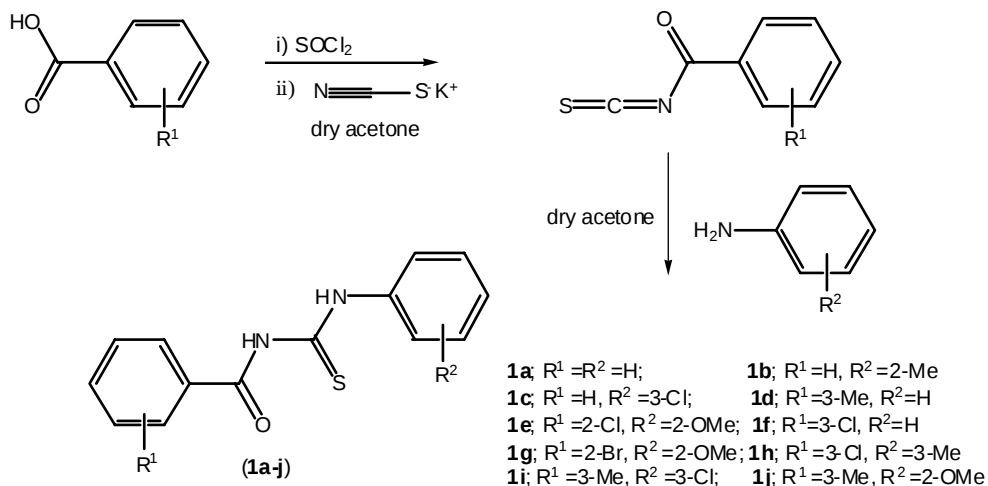
butylbenzyl thioureas as vanilloid receptors ligands and antagonists in rat DRG neurons [5]. 1-Benzoyl-3-(4,6-disubstituted-pyrimidin-2-yl)thioureas have displayed excellent herbicidal activity [6]. Solid-phase Biginelli pyrimidine synthesis and synthesis of imidazoline derivatives [7] have been carried out using resin bound thioureas [8]. 2-Methylamino-thiazolines were synthesized by cyclization of N-(2-hydroxyethyl)-N'-methylthioureas [9] and N-Alkyl thioureas have been used in the synthesis of thienopyrimidines [10]. A series of N-(*o*-fluorophenoxy- acetyl)thioureas derivatives were converted into fluorophenoxy- acetylimino-2*H*-1, 2, 4-thiadiazolo [2,3-*a*] pyrimidines possessing herbicidal activity by oxidative cyclization [11]. In addition, the thioureas have been used in the synthesis of 1,3-thiazines [12], 1,3-diazine [13], 1,3-quinazolines [14] and 1,2,4-triazines [15]. Thioureas are efficient guanylate agents [16]. Acyl thioureas are well known for their superior pesticidal, fungicidal, antiviral and regulating activity for plant growth [17]. Furthermore, thioureas have widely been used in enantioselective synthesis, such as in nitro-Mannich reactions, aza-Henry reaction, and the Michael Addition [18,19]. Symmetrical and asymmetrical phenethyl thioureas, 5-halo-substituted thiophene pyridyl thioureas and heterocyclic thiourea compounds are non-nucleoside inhibitors of HIV-1 reverse transcriptase [20-22]. Synthesis and anion recognition of molecular tweezers receptors based on acyl thioureas [23] and efficient colorimetric anion sensors based on a thiourea group has recently been reported [24]. Moreover, thiourea analogues are potent influenza virus neuraminidase inhibitors [25].

Condensation of thiourea derivatives with carbonyl compounds have been used in the synthesis of N-alkyl-1,3-thiazol-2-amines, 3-alkyl-1,3-thiazolines [26], 1-aryl-3-aryl-4-substituted imidazole-2-thiones [27,28], 2-(aroylimino)-3-aryl-4-methyl/phenyl-1,3-thiazolines [29]. Cyclocondensation of unsymmetrical perfluoroalkyl-substituted β -diketones with urea, thiourea, and guanidine leads to various heterocycles [30], regioselective synthesis of 2*H*-[1,2,4]thiadiazolo[2,3-*a*]pyrimidine derivatives [31] and synthesis of 2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-thiazole-4-carboxylic acid via N-Fmoc thioureas [32] have recently been described.

Synthesis of title thiourea was carried out in continuation of our interest in the synthesis of thioureas as precursors towards synthesis of novel heterocycles and for the systematic study of their bioactivity and complexation behavior.

Results and Discussion

Substituted benzoic acids were converted into corresponding aroyl chlorides by treatment with thionyl chloride according to standard procedure. The aroyl chlorides were treated with an equimolar quantity of potassium thiocyanate in acetone to afford the corresponding isothiocyanates intermediates which were not separated. Addition of an equimolar quantity of substituted anilines in acetone to isothiocyanates furnished the 1-aryl-3-arylthiourea derivatives (**1a-j**) [33] (Scheme 1).



Scheme 1. Synthesis of 1-aryl-3-aryl thioureas

Typically, thioureas are characterized by IR absorptions at 3350, 3200 for free and associated NH, at 1660-1670 for carbonyl and at 1230-1250 cm^{-1} for thiocarbonyl groups respectively. The characteristic broad singlets at $ca \delta$ 9.0 and 12 ppm for HN(1) and HN(3) and peaks at ca 170, 179 for carbonyl and thiocarbonyl were also observed in the ^1H and ^{13}C NMR spectra respectively. The physicochemical properties and the spectroscopic data of thioureas **1a-j** are given in Tables 1 and 2, respectively. Mass spectra of all of the compounds showed the molecular ion peaks. The major fragments correspond to the N-McLafferty rearrangement and the base peaks derived from the aroyl cation.

Table 1. Physicochemical data of thioureas (**1a-j**)

Compd	Yield (%)	R_f^a	Mp ($^{\circ}\text{C}$)	Molecular formula (MW)	MS
1a	70	0.48	114-115	$\text{C}_{14}\text{H}_{12}\text{N}_2\text{OS}$ (256.32)	256.0
1b	65	0.45	121-122	$\text{C}_{15}\text{H}_{14}\text{N}_2\text{OS}$ (270.34)	270.0
1c	68	0.49	119-120	$\text{C}_{14}\text{H}_{11}\text{ClN}_2\text{OS}$ (290.76)	290.0
1d	72	0.53	113-114	$\text{C}_{15}\text{H}_{14}\text{N}_2\text{OS}$ (270.37)	270.0
1e	69	0.35	113-114	$\text{C}_{14}\text{H}_{11}\text{ClN}_2\text{OS}$ (290.76)	290.5
1f	72	0.50	136-137	$\text{C}_{15}\text{H}_{14}\text{N}_2\text{OS}$ (270.37)	270.0
1g	63	0.33	102-103	$\text{C}_{15}\text{H}_{13}\text{BrN}_2\text{O}_2\text{S}$ (365.24)	365.9
1h	71	0.50	120-121	$\text{C}_{15}\text{H}_{13}\text{ClN}_2\text{OS}$ (304.79)	304.1
1i	69	0.55	122-123	$\text{C}_{15}\text{H}_{13}\text{ClN}_2\text{OS}$ (304.79)	304.1
1j	68	0.43	104-105	$\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2\text{S}$ (300.37)	300.0

a Solvent system: Pet. ether: Ethyl acetate (1: 0.25);

Recrystallization solvent: aqueous ethanol

In vitro evaluation of antibacterial activity was carried out by disk diffusion method (Kirby-Bauer method) against different bacterial strains. The tests were repeated thrice and the results are reported as means of at least three determinations. Table 3 gives the antibacterial activity of the compounds, the figures represent the zone of inhibition in millimeters. All of the compounds **1a-j** exhibited potent inhibitory activity against the four strains compared to standard drugs at the tested concentrations. The presence of halo groups results in enhancement of inhibitory activity. It is quite interesting to compare the activity of isomeric compounds **2h** and **2i** having 3-chloro and 3-methyl substituents interchanged on the aroyl and aryl rings. Compounds **2c** and **2j** show overall best activity against all of the tested bacterial strains, especially, against the *E. coli* resistant to standard drug.

Table 2. Spectral data (IR, ^1H , ^{13}C NMR) of thioureas (**1a-j**)

Compd	IR (ν , cm^{-1})	^1H NMR (δ , ppm, J (Hz))	^{13}C NMR (δ , ppm)
1a	3280 (NH), 1673 (C=O), 1605 (C=C), 1258 (C=S), 1146 (C-N)	12.6 (NH), 9.18 (NH), 7.25-7.57 (m, 5H, Ar'), 7.61-7.95 (m, 5H, Ar)	120.25, 124.15, 124.46, 126.91, 127.13, 127.56, 128.7, 128.9, 129.0, 129.2, 131.62, 131.77, 133.75, 137.62, 167.73 (C=S), 179.0 (C=O)
1b	3269 (NH), 1669 (C=O), 1586 (C=C), 1258 (C=S), 1154 (C-N)	12.76 (NH), 9.21 (NH), 7.23-7.60 (m, 5H, Ar'), 7.64-7.96 (m, 5H, Ar), 2.42 (s, 3H, CH_3).	21.27 (CH_3), 120.20, 124.19, 124.46, 126.91, 127.13, 127.56, 128.7, 129.0, 131.62, 133.75, 137.62, 167.73 (C=S), 179.0 (C=O)
1c	3298 (N-H), 1671 (C=O), 1591 (C=C), 1257 (C=S), 1142 (C-N)	12.76 (NH), 9.18 (NH), 7.23-7.60 (m, 5H, Ar'), 7.64-7.96 (m, 4H, Ar)	126.77, 127.21, 128.59, 129.30, 131.2, 132.40, 133.75, 133.97, 166.7 (C=S), 178.69 (C=O)
1d	3200 (N-H), 1667 (C=O), 1590 (C=C), 1261 (C=S), 1151 (C-N)	12.72 (NH), 9.19 (NH), 7.23-7.60 (m, 5H, Ar'), 7.64-7.96 (m, 5H, Ar), 2.43 (s, 3H, CH_3).	21.27 (CH_3), 120.25, 124.15, 126.91, 127.13, 127.56, 128.9, 129.2, 131.62, 131.77, 133.75, 137.62, 167.4 (C=S), 179.4 (C=O)
1e	3261 (N-H), 1690 (C=O), 1605 (C=C), 1247 (C=S), 1153 (C-N)	12.81 (NH), 9.24 (NH), 7.23-7.60 (m, 5H, Ar'), 7.64-7.96 (m, 5H, Ar), 3.15 (s, 3H, OCH_3).	55.93 (OCH_3), 126.77, 127.21, 128.59, 129.30, 131.2, 132.40, 133.75, 133.97, 166.7 (C=S), 178.69 (C=O)
1f	3216 (N-H), 1673 (C=O), 1590 (C=C), 1232 (C=S), 1150 (C-N)	12.5 (br s, 1H, NH), 10.75 (br s, 1H, NH), 7.58-7.84 (Ar-Hx9).	126.70, 126.11, 128.59, 129.31, 131.8, 132.41, 133.75, 133.97, 166.7 (C=S), 178.69 (C=O)
1g	3260 (N-H), 1688 (C=O), 1604 (C=C), 1246 (C=S), 1151 (C-N)	12.5 (br s, 1H, NH), 10.75 (br s, 1H, NH), 7.58-7.84 (Ar-Hx9), 3.81 (s, 3H, OCH_3).	56.10 (OCH_3), 126.77, 127.21, 128.59, 129.30, 131.2, 132.40, 133.75, 133.97, 168.7 (C=S), 179.21 (C=O)
1h	3326 (N-H), 1662 (C=O), 1595 (C=C), 1254 (C=S), 1144 (C-N)	12.5 (br s, 1H, NH), 10.7 (br s, 1H, NH), 7.58-7.84 (Ar-Hx9), 3.81 (s, 3H, OCH_3), 2.42 (s, 3H, CH_3).	21.6, 126.77, 127.21, 128.59, 129.30, 131.2, 132.40, 133.75, 133.97, 166.7 (C=S), 178.69 (C=O)
1i	3233 (N-H), 1665 (C=O), 1591 (C=C), 1242 (C=S), 1158 (C-N)	12.42 (br s, 1H, NH), 10.7 (br s, 1H, NH), 7.58-7.84 (Ar-Hx9), 2.42 (s, 3H, CH_3).	21.01, 126.77, 127.21, 128.59, 129.30, 131.2, 132.40, 133.75, 133.97, 166.8 (C=S), 177.9 (C=O)
1j	3233 (N-H), 1665 (C=O), 1591 (C=C), 1242 (C=S), 1158 (C-N)	12.64 (br s, 1H, NH), 10.7 (br s, 1H, NH), 7.58-7.84 (Ar-Hx9), 3.81 (s, 3H, OCH_3), 2.42 (s, 3H, CH_3).	255.7, 21.01, 126.77, 127.21, 128.59, 129.30, 131.2, 132.40, 133.75, 133.97, 167.4 (C=S), 179.0 (C=O)

Experimental

Melting points were recorded using a digital Gallenkamp (SANYO) model MPD.BM 3.5 apparatus and are uncorrected. ^1H NMR spectra were determined in CDCl_3 at 300 MHz using a Bruker machine. FTIR spectra were recorded on an FTS

3000 MX spectrophotometer. Mass Spectra (EI, 70eV) on a MAT 312 instrument, and elemental analyses were conducted using a LECO-183 CHNS analyzer. Bioactivities were carried out at the Department of Microbiology, Quaid-I-Azam University Islamabad. Thin layer chromatography (TLC) was conducted on 0.25 mm silica gel plates (60 F254, Merck). Visualization was made with ultraviolet light. Reagents were obtained commercially and used as received.

Table 3. Antibacterial bioassay screening of thioureas (**2a-j**)

Compound	<i>Staphylococcus aureus</i>	<i>Bacillus subtilis</i>	<i>Pseudomonas aueroginosa</i>	<i>Escherichia coli</i>
2a	27	30	29	30
2b	25	33	25	21
2c	25	26	18	35
2d	25	35	31	31
2e	28	25	21	28
2f	29	28	21	30
2g	29	29	27	34
2h	26	26	27	34
2i	31	21	25	29
2j	25	23	20	30
Tetracycline	35	29	19	35
Pencillin	35	29	-	-
Metronidazole	22	24	-	-

Diameter of inhibition (mm)

- = no activity; Concentration used: 2mg/ml

General procedures for the synthesis of 1-aroyl-3-aryl thioureas

A solution of substituted benzoyl chloride (10 mmol) in acetone (50 ml) was added dropwise to a suspension of potassium thiocyanate (10 mmol) in acetone (30 ml) and the reaction mixture was refluxed for 30 min. After cooling to room temperature, a solution of substituted aniline (10 mmol) in acetone (10 ml) was added and the resulting mixture refluxed for 2-3 h. The reaction mixture was poured into cold water and the precipitated thioureas were recrystallized aqueous ethanol.

The physicochemical and spectral data are given in Tables 1 and 2, respectively. All compounds gave satisfactory elemental analyses.

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