Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713926081

Update survey on aroyl substituted thioureas and their applications

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To cite this Article Aly, Ashraf A. , Ahmed, Essam K. , El-Mokadem, Khaled M. and Hegazy, Mohamed El-Amir F.(2007) 'Update survey on aroyl substituted thioureas and their applications', Journal of Sulfur Chemistry, 28: 1, 73 — 93
To link to this Article: DOI: 10.1080/17415990601124691
URL: http://dx.doi.org/10.1080/17415990601124691

Journal of Sulfur Chemistry
Vol. 28, No. 1, February 2007, 73–93

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Update survey on aroyl substituted thioureas and their applications

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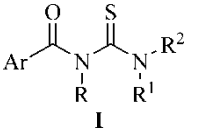
(Received 1 August 2006; in final form 12 November 2006)

The literature on synthesis and applications of aroyl substituted thioureas is updated to 2006. Emphasis is placed on the relationship of structural features of the thioureas to their applications, which are in such diverse areas as the trace analysis of metals, materials science and agriculture. The review contains 93 references.

Keywords: Benzoyl substitution; Thioureas; Metal complexation; Heterocycles; Analysis

1. Introduction

The importance of aroyl thioureas **I** are found largely in heterocyclic syntheses and many of these substrates have interesting biological activities. Aroyl thioureas have also been found to have applications in metal complexes and molecular electronics. Since a substantial amount of information about these molecules is in the patent literature, our aim in this review is to shed more light on the chemistry of aroyl thioureas and their wide variety of applications.



I

Our interest focuses on the chemistry of the readily available derivatives of aroyl-disubstituted ureas and thioureas. These compounds are a rich source of materials for development of agrochemical and pharmaceutical products [1]. The stereochemistry of the phenyl and benzoyl groups in benzoylphenylthiourea, was found to be *cis* and *trans* forms, respectively, to the S atom across the thiourea C-N bonds (**I**, Ar = R^1 = Ph). The benzoylphenyl thiourea molecules were packed as dimers, *via* N-H–S intermolecular-H bonds, and arranged

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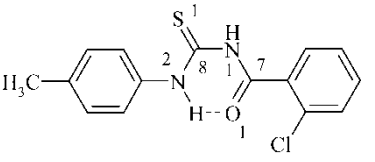
Journal of Sulfur Chemistry
ISSN 1741-5993 print/ISSN 1741-6000 online © 2007 Taylor & Francis
http://www.tandf.co.uk/journals
DOI: 10.1080/17415990601124691

parallel to the a and c axes [2]. It was reported that as in most benzoylthiourea derivatives, intramolecular hydrogen bonding N2–H2….O1 maintains the six membered ring formation of the N2/C8/N1/C7/O1 plane [2]. The relative positions of atoms in the parent molecule fragment, common to all the three analyzed compounds were discussed [3]. The intramolecular hydrogen bonds of the NH . . . O=C type were detected in the of *N*-substituted *N′*-benzoyl- and *N′*-(2-chlorobenzoyl)thioureas on the basis of IR spectral studies [4].



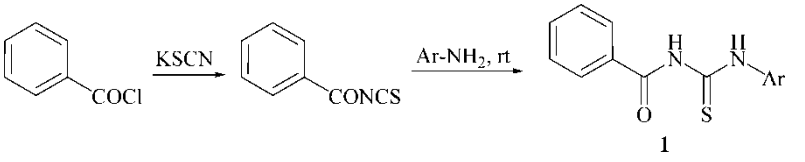
The utility of nonlinear optical (NLO) phenomena underpin many operations performed by devices in telecommunications system switching nodes and provide a means for optical signal processing in general. Therefore, the subject of aroylsubstituted thioureas is considered as a very interesting topic due to their interesting optical and electronic properties. X-ray powder diffraction was used to detect nonlinear optical activity in 1-benzoyl-3-(4-benzyl)thiourea ($C_{15}H_{14}N_2OS$) [5]. Moreover, the molecular structures for PhNHCONHAc and PhNHCSNHCOR (R = *n*-C_5H_{11}, Ph) were also deduced by X-ray diffraction and NMR spectroscopy [5].

2. Synthesis

2.1 *General methods*

Benzoyl isothiocyanate (obtained from PhCOCl and NH_4SCN) was treated with anilines to give the corresponding thioureas, ArNHCSNHCOPh (**1**, scheme 1, Ar = Ph, 3-F-C_6H_4, alkylphenyl, $PhCH_2OC_6H_4$, $O_2NC_6H_4$, $Me_2NC_6H_4$, $MeClC_6H_3$, and dimethoxyphenyl) [6]. Due to the importance of these compounds, Sarkis reported the synthesis of another thirty-six of *N*,*N′*-disubstituted thioureas $RNHCSNHR^1$ [R = benzoyl, Ph, 4-FC_6H_4; R^1 = (un)substituted Ph, pyridyl, 4-quinolyl] using the same methodology [7].

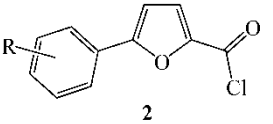
N-Aryl-*N′*-(5-aryl-2-furoyl)-thioureas **3** (R = 2-NO_2, 3-NO_2, 4-NO_2; R^1 = Ph, substituted Ph, 1-naphthyl, 2-naphthyl, 2-pyridyl and 3-pyridyl) were prepared by phase transfer reaction of acid chlorides **2** with NH_4SCN in CH_2Cl_2 in the presence of polyethylene glycol-400 (PEG-400) followed by treatment with R^1NH_2. Selected compounds **3** (R = 4-NO_2 and R^1 = 2-$O_2NC_6H_4$) demonstrated a promoting effect on wheat growth [8]. A series of furothioureas of the sort **3** having different substituents close to the sulfur atom were synthesized. Under dry conditions, the aroyl chloride (30 mmol) was added to a solution of (30 mmol) NH_4SCN in dried acetone (15 mL) with stirring, at room temperature over 10 min, after which a white precipitate of NH_4Cl appeared. Thereafter, 30 mmol of the appropriate aromatic amine in



1

SCHEME 1

acetone (20 mL) were slowly added. When the mixture reached room temperature, the mixture was briefly refluxed. The furothioureas were precipitated as a solid or an oily product by pouring the reaction mixture slowly into 400 mL ice-water with stirring [9].



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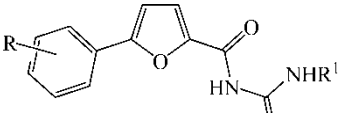
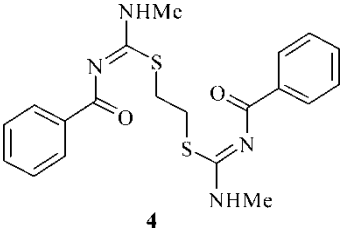


3

A process for the preparation of bis(alkylisothioureas) comprised the treatment of *N*-acyl-*N′*-aryl and *N*-acyl-*N′*-alkyl-isothioureas with bifunctional alkylating agents, such as 1,2-dihaloethane was also demonstrated [10]. Thus, 1,2-dibromoethane (5 mmol) was added to a mixture of *N*-benzoyl-*N′*-methylthiourea (10 mmol), DMF (30 mL), and sodium hydride to give ethylene-bis(*N*-benzoyl-*N′*-methylisothiourea) **4** in 55% yield [10].



4

2.2 *Synthesis of aroyl thioureas catalyzed by phase-transfer conditions*

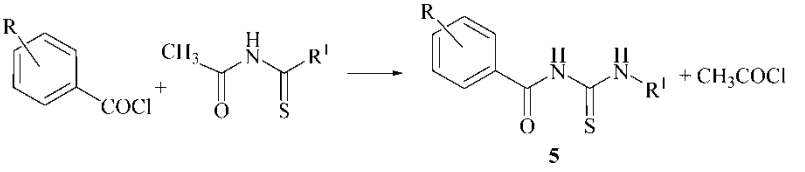
The reaction of polymethylene diamine with aroyl chloride and ammonium thiocyanate under phase-transfer conditions using PEG-400 as catalyst yielded poly-methylene-bis-aroyl thiourea derivatives, in good-to-excellent yields [11]. An efficient and clean synthesis of *N*-benzoyl-*N′*-aryl ureas PhCONHCO-NHR (R = Ph, 2-MeC_6H_4, and 4-$O_2NC_6H_4NH$) from benzoyl chloride using polymer-supported isothiocyanate or iodate as reagents and a strong acidic ion-exchange resin as scavenger was described [12]. The ureas were obtained in moderate to high yield (73–77%) [12].

2.3 *Synthesis of N-benzoyl-N′-phenylthioureas under microwave irradiation*

A simple, rapid and efficient method for the synthesis of the title compounds under microwave irradiation was reported. The effect of microwave irradiation power, reactions times and phase transfer catalyst on the reaction were also studied [13–15]. Another alternative method used to prepare 1-benzoylthioureas $RC_6H_4CONHC(=S)NHR^1$ (**5**, R^1 = Me, Ph; R = Me_2N, MeO, Me, H, Cl, NO_2, etc.) was performed by condensation of $AcNHC(S)NHR^1$ and RC_6H_4COCl (scheme 2) [16].

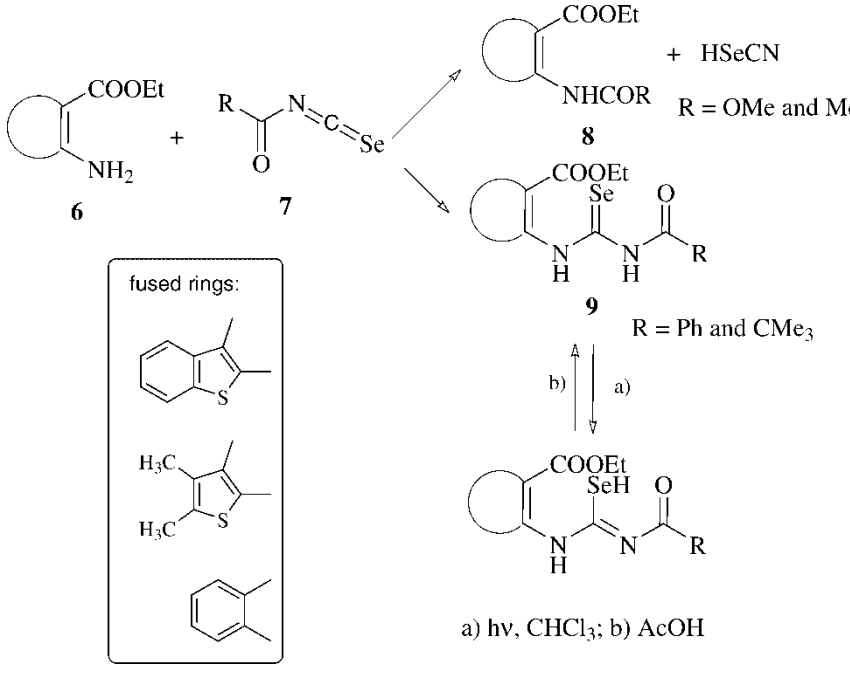
2.4 *Photoisomerization of ethyl 2-(3-acylselenoureido)thiophene-3-carboxylates*

Selenium has been shown to be a trace element essential for animals. Its importance is connected with immunobiochemical activity of enzymatic selenoproteins [17]. A successful synthesis of acylselenoureas derived from ethyl esters of 2-amino-4,5,6,7-tetrahydrobenzo-[*b*]thiophene-3-carboxylic, 2-amino-5,6-dimethylthiophene-3-carboxylic and 2-amino-benzoic acids was effected by an addition of the corresponding amines to

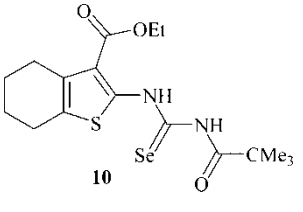


SCHEME 2

acetyl-, benzoyl-, methoxy-carbonyl- and pivaloylisoselenocyanate (scheme 3), respectively. The benzoyl- and pivaloylisoselenocyanates were obtained in good yields [17]. The others acylisoselenocyanates gave either the product of acylation of the starting aminoester, identified by acylation of the corresponding amines with acylchlorides or a mixture of this with acylselenourea. Separation of acylselenoureas by column chromatography was unsuccessful due to elemental selenium formation by conversion of selenourea to urea derivatives. Ethyl 2-(3-pivaloylselenoureido)-4,5,6,7-tetrahydrobenzo[*b*]-thiophene-3-carboxylate (**10**) was analyzed by X-ray structural analysis and one of these compounds indicated to have the skeleton of benzothiazole thioureas [17].



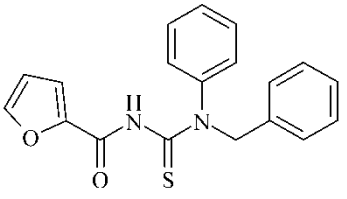
SCHEME 3



2.5 *Spectroscopic investigation N,N′-aroylthioureas*

Ion and molecular recognition materials are the subject of much study due to their practical application in the field of chemical sensors. These materials have received special attention due to simplification of the systematic control and prevention of water contamination and protection of the environment. Recent reviews about membrane ion selective electrodes (ISE) have been reported [18–20]. The main component in the membrane is the ion recognition substance (so-called ionophore). Many organic and inorganic compounds were tested as ionophores in ISE [21–29]. It has become a necessity to determine the ionophore structure as precisely as possible, since their shape and spatial fit with ions are important for good, sensible and selective ISE. Thioureas are known to be good ligands for metal ions and this property can be used in cation-selective membranes.

The effect of the intramolecular hydrogen bonding of the NH. . .O=C type that was detected in aroylthioureas derivatives, prompted many groups to investigate this effect on the absorptions in the IR and ^{1}H NMR spectra. Moreover, it is valuable to show the influence of substituents on the ^{13}C NMR chemical shift values of the carbon signals of aromatic ring and the CONH-C(=X)- groups (i.e. X = S, Se and O) of a series of *N*-aroylthioureas. A series of *N*-benzoyl-*N′*-(Y-aryl)- and -*N′*-alkylthioureas, selenoureas, ureas, thiourethanes and isothioureas 4-XC_6H_4CONH-C(=S)NHC_6H_4-Y-4, PhCONHC(=S)R (R = e.g., NHEt, OMe), PhCONHC(=Z)NHC_6H_4-Y-4 (Z = Se and O), and PhCON=C(SEt)NHC_6H_4-Y-4 was prepared. The substituents on *N*-benzoyl-*N′*-(4-Y-phenyl)thio-(seleno)ureas do not considerably influence the ^{13}C NMR chemical shifts of C=X and C=O carbons; however, there was a marked shift in the aromatic carbons due to these substituents. Differences between the benzoyl δ (CO) values of *N′*-monosubstituted and *N′*,*N′*-disubstituted thioureas indicate the existence of an intermolecular hydrogen bond in the acylthiourea grouping, namely between the benzoyl CO and the NH groups. The ^{13}C NMR chemical shift values of C=Se carbons in *N*-benzoyl-*N′*-(4-Y-phenyl)selenoureas are higher than those of the analogous C=S carbons of the corresponding thioureas [30]. The IR spectrum of 1-(furanyl-2-carbonyl)-3-benzyl-3-phenylthiourea (**11**) revealed bands at ν_{max}/cm^{-1}: 3370 (s-m, free NH), 3133 (m, assoc.-NH), 3053 (m, arom-CH), 2982 (w, asym.-CH_3), 2937 (w, asym.-CH_2), 1706 (s, C=O), 1586 (s) and 1491 (s, arom-C=C).

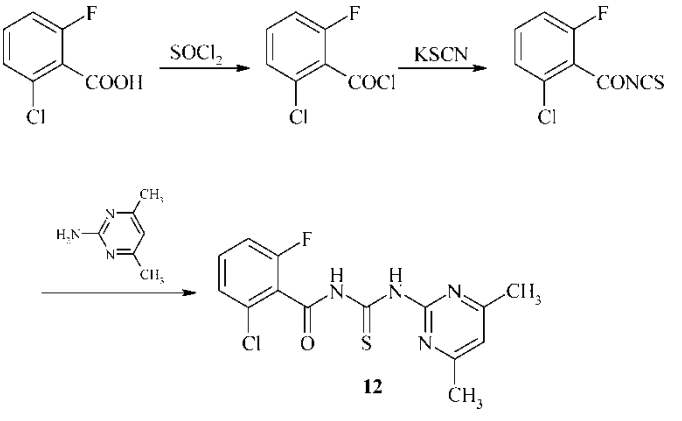


1-(Furanyl-2-carbonyl)-3-benzyl-3-phenylthiourea (**11**)

The ^{1}H NMR spectrum of **11** revealed protons at δ 5.57 (2 H, s), 6.54 (1 H, dd, H_4-furan), 7.10-7.39 (11 H, m, H_3-furan and 2 Ph), 7.77 (1 H, s, H_5-furan), 10.58 (1 NH, s, broad). The ^{13}C NMR spectrum showed the carbon signals of the CH_2-benzyl, C=O and the C=S at δ 58.9, 153.2 and 181.8, respectively [31].

2-Fluoro-6-chlorobenzoyl-thiourea containing a substituted pyrimidine ring (**12**, $C_{14}H_{12}FN_4OClS$) was synthesized by a procedure shown in scheme 4 [32].

The IR spectrum of the pyrimidinoaroylthiourea **12** revealed absorption bands at ν_{max}/cm^{-1}: 3446, 3176 (N-H), 1695 (C=O) and 1256 (C=S), whereas the ^{1}H NMR spectral data in $CDCl_3$ showed the presence of four singlets at δ 2.42 (6 H, $2CH_3$), 6.80 (1 H, Py-5′-H), 8.81 (1 H, NH) and 11.58 (1 H, NH). Also one multiplet at δ 7.12–7.43 (3 H, Ph-H) appeared [32].



SCHEME 4

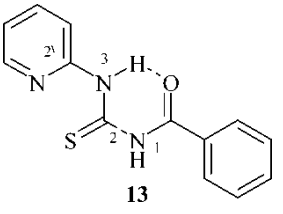


Figure 1. Intramolecular hydrogen bonding in pyridobenzoylthiourea.

The addition of amine to the C=N double bond takes place by attacking the carbon atom in the isocyanate group resulting in the formation of the desired compounds. After complete reaction, the strong band at around 2000 cm^{-1} (N=C=S) in the isocyanate disappears. Instead of the expected normal carbonyl absorption around ν_{max}/cm^{-1}: 1710 and a medium strong band (C=O) at 1672 cm^{-1} suggested a possible hydrogen bond formation between the H-atom of the NH-group in position three and the O-atom of the carbonyl group. The band around at ν_{max} 2500–2600 cm^{-1} corresponding to SH is not found. This indicates the absence of the N=CSH tautomeric form in all the compounds. A medium to strong band at ν_{max} 1262 cm^{-1} is due to the stretching vibration of the thione group. The unusual intensity of CHN-band at ν_{max} 1510 cm^{-1} compared to (C=O) suggests the possible existence of an intramolecular hydrogen bond in these compounds. That the NH between the carbonyl and thiocarbonyl resonates near 11.5 ppm at lower field and the NH between carbonyl and thiocarbonyl appears near 9 ppm at high field may be due to a deshielding effect of the intramolecular hydrogen bond [5].

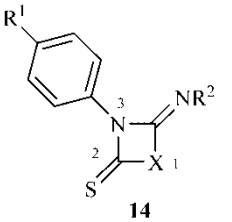
In spite of the presence of the nitrogen atom of the pyridine of pyridoaroylthiourea **13**, the intramolecular hydrogen bonds was still explained as due to NH…O=C type (figure 1) [32].

3. Aroyl thioureas in heterocyclic syntheses

The author's interest in aroyl substituted thiourea chemistry revolves around their construction in the synthesis of various heterocyclic compounds, which themselves can be expected to have prospective biological and pharmaceutical applications.

3.1 *Synthesis of heterocyclic four membered ring system*

3.1.1 Preparation of 4-benzimino-3-phenyl-1,3-selenazetidine-2-thiones. Compounds **14** [X = Se, R^1 = H, halo, R^2 = PhCO; or X = S, R^1 = H, halo, R^2 = PhCO and EtO], were prepared as fungicides, insecticides, and mycobacteriostatics. Treatment of *N′*-phenyl-*N*-benzoyl-selenourea in acetone with thiophosgene gave 4-benzimino-3-phenyl-1.3-selenazetidine-2-thiones **14** in 45% yield [33]. Whereas the reaction of *N′*-phenyl-*N*-benzoylselonurea (X = S, R = Ph and OEt) with thiophosgene in acetone gave thiazetidinethione **15** (R = Ph and OEt) in good yield [33].



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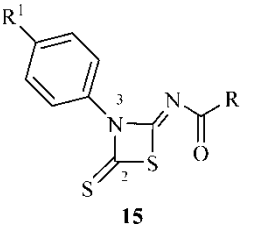


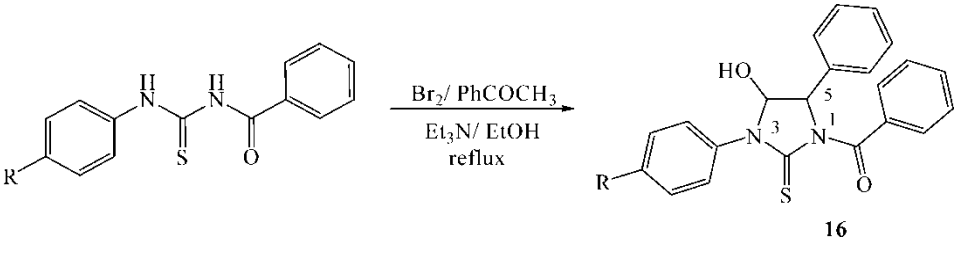
15

3.2 *Synthesis of heterocyclic five membered ring system*

3.2.1 Imidazolidin-2-thiones. (4-Hydroxy-3-aryl-5-phenyl-2-thioxo-imidazolidin-1-yl)-phenylmethanones **16** were synthesized readily from the cyclization of 1-dibenzoyl-3-arylthioureas with bromine/acetophenone in the presence of excess triethylamine (scheme 5) [34]. An efficient route to prepare 3,4-daryl-2-thioxo-2,3-dihydro-imidazol-1-yl)-aryl-methanones **17** (R = Ph, 2-Cl-C_6H_4; R^1 = Ph, 4-BrC_6H_4, PhCH_2, 3-MeC_6H_4, etc.; R^2 = H, Me, Ph), which involved the cyclization of aroyl thioureas R^1CONHCSNHR^2 with aldehydes or ketones MeCOR^3 in the presence of Br_2 and Et_3N, was developed (scheme 6) [35].

3.2.2 1,3-Thiazoles. The reaction of RNHC(S)NHR^1 (R = R^1 = 4-BrC_6H_4, R^1 = COPh, R = benzoyl, R^1 = PhCH_2, Ph; R = cinnamoyl, R^1 = Ph) with LiH or NaH and 2-propynyl bromide in DMF afforded *S*-(2-propynyl)isothioureas, which could be either isolated from the reaction mixture or cyclized *in situ* by addition of another portion of LiH or NaH to give thiazolines **18** (scheme 7) [36].

Thioureas of the structure PhCONHCSNRR^1 reacted with derivatives of ψ-bromocrotonic acid BrCH_2CH=CHR^2 (H, R^2 = CO_2Me, cyano) to give thiazoles **19**. Treatment of the target thioureas (R = H, R^1 = PhCH_2, Ph) with ClCH_2CO_2Et leads to the thiazolidines **20**



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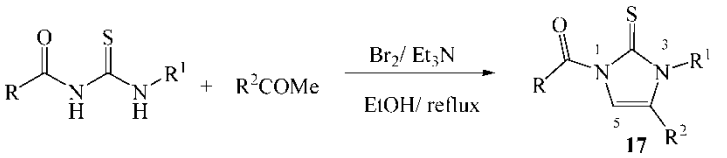
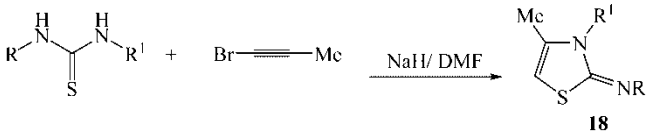
SCHEME 5

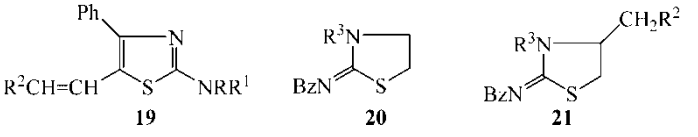


SCHEME 6

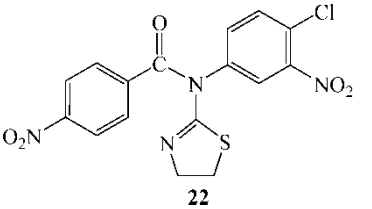


SCHEME 7

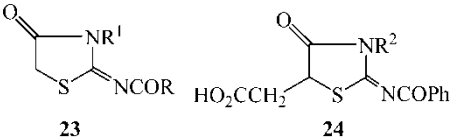
(R^3 = $PhCH_2$, Ph) or **21** (R^2 = CO_2Me, cyano, R^3 = $PhCH_2$, Ph), respectively [37].



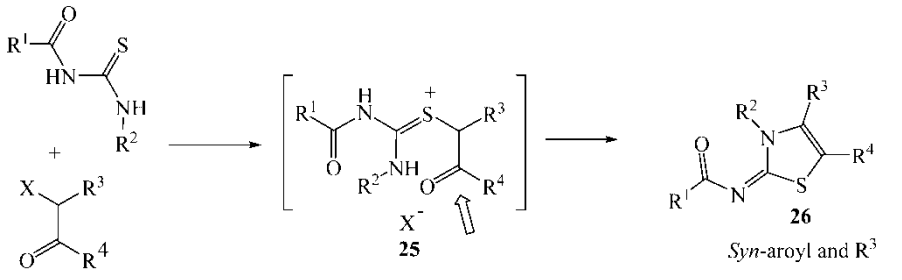
A series of 2-(*N*-aryl-*N*-aroyl)amino-4,5-dihydrothiazoles **22** was obtained *via* cyclo-condensation of *N*-aryl thioureas with 2-bromoethylamine hydrobromide followed by the reaction of the product thus obtained with aroyl chlorides. Title compounds were evaluated for their antithrombotic activity *in vivo* in mice where one of these compound **22** provided 65% protection as compared to 77% protection [38].



3-Substituted-2-acylimino-4-thiazolidones **23** (R = Ph, Me; R^1 = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$O_2NC_6H_4$, Me_3C, 2-naphthyl, cyclohexyl) were synthesized by reaction of $RCONHC(S)NHR_1$ with haloacetic acids or Et α-bromoacetate. Thiazolidone-5-acetic acid derivatives **24** (R^2 = Ph, 4-MeC_6H_4, 4-ClC_6H_4) were obtained by reaction of $PhCONHC(S)NHR_2$ with maleic anhydride [39].



Manaka *et al.* [40], reported a one-pot, three-component condensation of aroyl isothiocyanates $R^1CON{=}C{=}S$ (R^1 = (un)substituted Ph), primary amines R^2NH_2 (R^2 = (un)substituted alkyl, cycloalkyl or phenyl), and α-halocarbonyl derivatives $R^3CH(X)COR^4$ (ethyl 2-chloro-acetoacetate, 3-chloroacetylacetone, chloroacetone or ethyl bromomalonate).



SCHEME 8

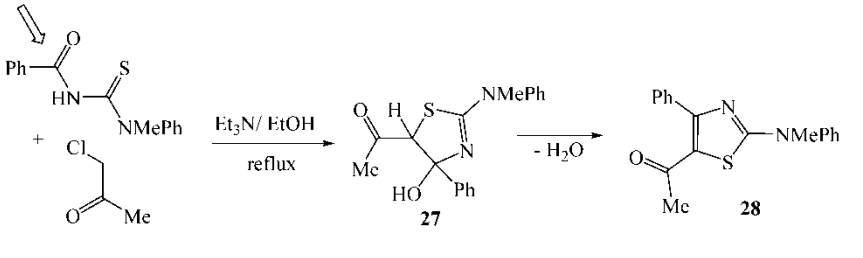
The final product was 2-(acylimino)-3-alkyl-3*H*-thiazoline derivatives **26**, with the mechanism of reaction thought to involve the intermediate formation of salt **25** (scheme 8) [40].

Prior to the Manaka *et al.* contribution, the development of convenient general synthetic procedures for preparing *N*-acyl-*N′*-mono and -*N′*,*N′*-disubstituted thioureas from acid chlorides, and related *N*-imidoyl thioureas from imidoyl chlorides was reported [41].

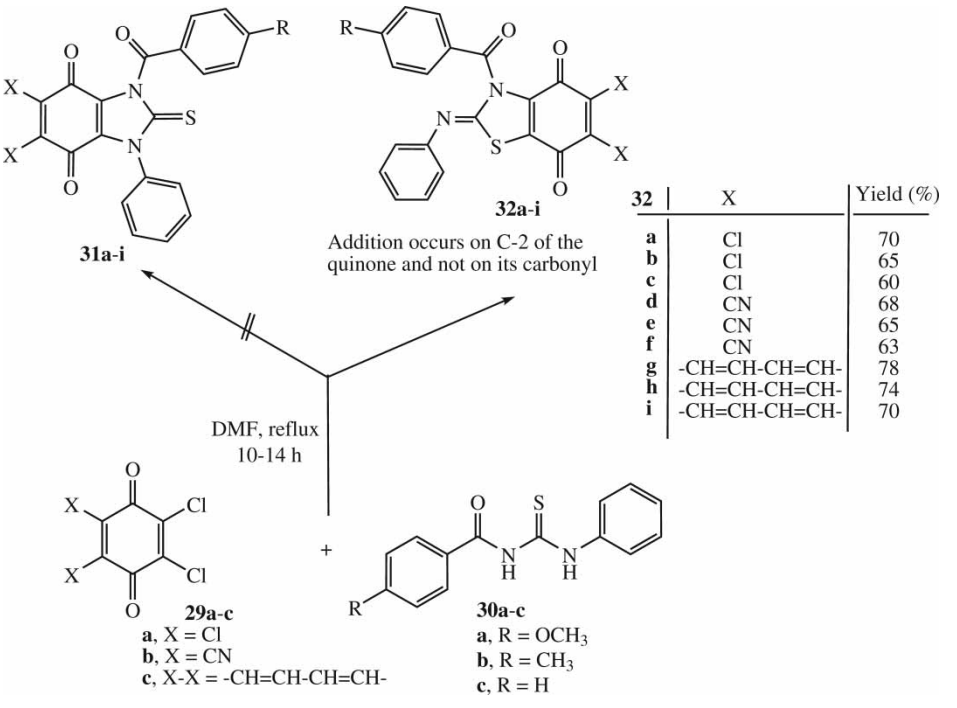
It was thought that formation of the 5-benzoyl-4-methylthiazoles involves *N*–C(4) fission of a cyclic intermediate to give an open-chain intermediate in which nucleophilic attack can occur at either the acetyl or the benzoyl group. One of the latter intermediates was generated directly from 2-acetyl-2-bromoacetophenone and *N*-methyl-*N*-phenylthiourea, and found to give the 5-benzoyl-4-methyl and 5-acetyl-4-phenyl-thiazoles as the major and minor products, respectively [41]. The mechanism proposed for the formation of **28** involved the addition of N^1 to the carbonyl group of the α-haloketone to give **27** as an intermediate, which lost water affording **28** (scheme 9) [41].

Aly *et al.* [42], reported the synthesis of a series of benzo- and naphthothiazoldiones (**32a–i**) by the reaction of *N*-substituted thioureas **30a–c** with π-deficient quinones **29a–c** (scheme 10). It was proved that the synthesized thiazoles possessed the *anti* relationship of aroyl and the phenyl groups. However, it can also be suggested that the reaction proceeds *via syn* selectivity in relation to the stereochemistry of the aroyl and R^3 groups [42]. The reaction mechanism depends on the presence of a tautomerism between the NH and the C=S into the N=C-SH groups in **30a–c** (scheme 11). Additionally, it was believed that attachment by the SH group proceeds faster compared to the aromatic amine (scheme 11) [42].

3.2.3 1,2,4-Thiadiazolidines. Compounds **34** [R = (un)substituted alkyl, aryl, alkoxy, aryloxy; R = (un)substituted (ar)alkyl, alkenyl, (hetero)aryl] were prepared for use as

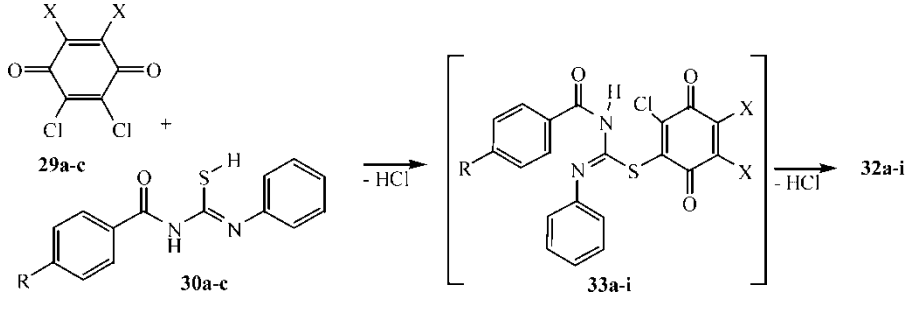


SCHEME 9



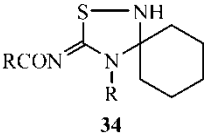
32	X	Yield (%)
a	Cl	70
b	Cl	65
c	Cl	60
d	CN	68
e	CN	65
f	CN	63
g	-CH=CH-CH=CH-	78
h	-CH=CH-CH=CH-	74
i	-CH=CH-CH=CH-	70

SCHEME 10



SCHEME 11

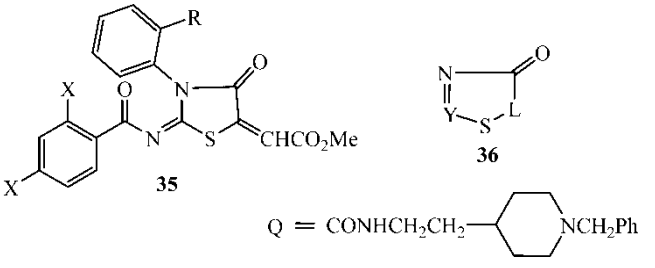
potential vulcanization regulators or fungicides by cyclocondensation of RCONHCSNHR with 3,3-pentamethylene-oxaziridine [43].



34

1,3-Thiazolidin-4-ones, **35** and **36** [44] (R^1 = alkyl-, aryl-, cycloalkyl, heterocycloyl-acylhetero-cycloyl-, (un)substituted aryl; Y = R^3R^4NC, CO; wherein L = C=CHR^5, CHR^7], were successfully prepared. These compounds were found to be useful for the treatment of the thrombin receptor-mediated diseases, e.g. thrombotic diseases, angina pectoris, heart disorder, valvular heart disease, lung infarction, Raynaud syndrome, nephritis, inflammation,

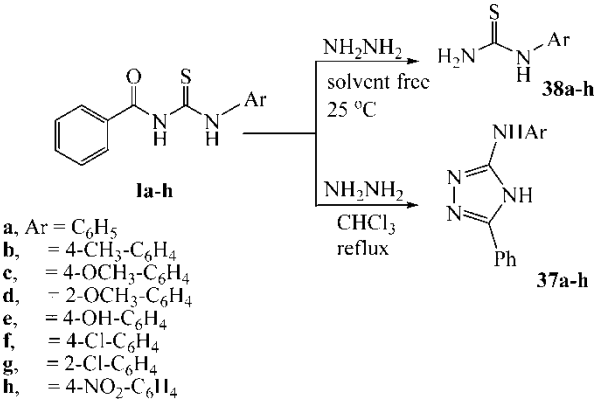
and arteriosclerosis [44]. It was reported that one derivative of compound **35**, (R = Q, X = Cl) showed an IC_{50} of 2.2×10^{-6} M for inhibiting the blood platelet aggregation of human platelet rich plasma which was induced by thrombin receptor agonist peptide.



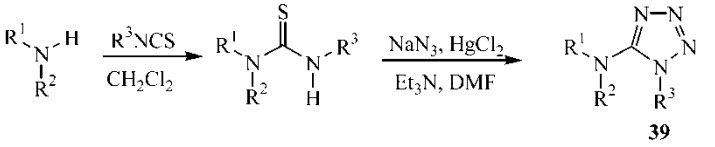
3.2.4 1*H*-1,2,4-Triazoles. It was reported [45] that the reaction of *N*-aryl-*N*-benzoylthioureas **Ia–h** with hydrazine hydrate was carried out in chloroform or without a solvent. The reactions in chloroform gave the corresponding triazoles **37a–h** in good yields. Under solvent-free conditions, debenzoylation of *N*-aryl-*N*-benzoylthioureas occurred and the corresponding *N*-arylthioureas **38a–h** were obtained in high yields. For example, *N*-phenyl-*N*-benzoylthiourea (1 mmol) was allowed to react with hydrazine hydrate (5 mmol) for 3 h in refluxing chloroform to give 3,5-diphenyl-1*H*-1,2,4-triazole in 86% yield. In contrast, the same reaction was carried out at 25 °C for 10 min under solvent-free conditions and afforded *N*-phenylthiourea in 95% yield (scheme 12) [45].

3.2.5 Tetrazoles. Primary and secondary amines were reacted with isothiocyanates to afford thioureas, which underwent mercury(II)-promoted attack of azide anion, to provide 5-aminotetrazoles **39** (scheme 13) [46]. This is considered as a general method for the synthesis of 5-aminotetrazoles (scheme 13). The reaction proceeds through a guanyl azide intermediate, which undergoes electrocyclization to the tetrazole. The method is high yielding and provides access to mono-, di-, and trisubstituted 5-aminotetrazoles, targets of potential interest for combinatorial library development [46].

3.2.6 1,2,4-Oxathiazoles. 1,2,4-Oxathiazole derivatives **40** (R^1 = H, R^2 = Ph, 3-$O_2NC_6H_4$, R^1 = Me and R^2 = Ph), **41**, and **42** were synthesized from their precursors, the



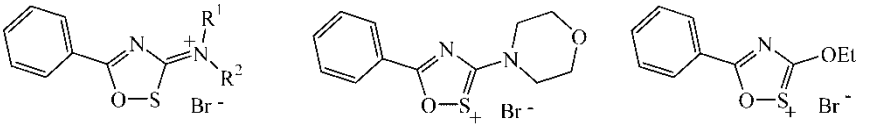
SCHEME 12



39

SCHEME 13

N-acylthioureas PhCONHC(=S)XR^2R^3 (X = N, O; XR^2R^3 = morpholino) by oxidative cyclization reaction. Ring structure and the charge distribution above the ring have also been studied [47].

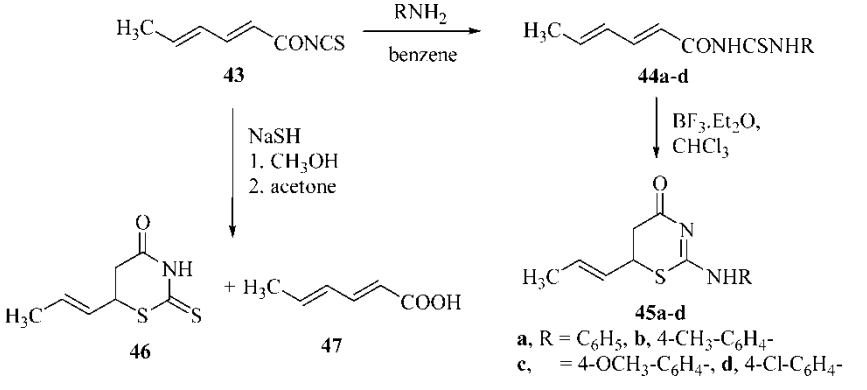


40 41 42

3.3 *Synthesis of heterocyclic six membered ring systems*

3.3.1 Synthesis of 1,3-thiazin-4-ones. Treatment of isothiocyanate **43** with aromatic amines in benzene or acetone for 15–20 min afforded the corresponding *N*-substituted-*N*-(hexa-2,4-dienoyl)thioureas **44a–d** in 79–92% yield (scheme 14) [48]. Boron trifluoride-catalyzed cyclization of thioureas **44a–d** in chloroform resulted exclusively in the formation of the 2-substituted 6-(propen-1-yl)-5,6-dihydro-4*H*-1,3-thiazin-4-ones (**45a–d**, scheme 14). The reaction was studied in methanol and acetone as solvents, with yields of thiazine at 37% and 29%, respectively. Nucleophilic addition of sodium hydrogen sulfide to hexa-2,4-dienoyl isothiocyanate **43** afforded two products, namely 6-(propen-1-yl)-2-thioxotetrahydro-4*H*-1,3-thiazin-4-one (**46**) and hexa-2,4-dienoic acid (**47**) (scheme 14) [48].

3.3.2 Synthesis of 1,3,5-oxadiazinium, 1,3,5-thiadiazinium and 1,2,4-dithiazolium salts. Treating RCONHCSNR^1R^2 [R = Ph,4-MeC_6H_4; $R^1 = R^2$ = Me; $(CH_2)_2$, $(CH_2)_4$, R^1R^2 = $(CH_2)_5$, and $(CH_2)_{20}$] with $SOCl_2$ in $ClCH_2CH_2Cl$ followed by 70% $HClO_4$ gave 31–94% diamino-aryloxadiazinium perchlorates **48**. Aminoaryldithiazolium perchlorates, e.g., **49** were

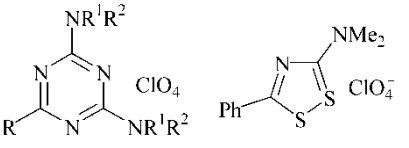


43 44a-d 46 47 45a-d

a, R = C_6H_5, **b**, 4-CH_3-C_6H_4-
c, = 4-OCH_3-C_6H_4-, **d**, 4-Cl-C_6H_4-

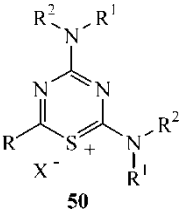
SCHEME 14

obtained by treating the target *N*-acylthioureas with HCO_2H or MeOH, and then 70% $HClO_4$, followed by 30% H_2O_2 [49].



48 **49**

3.3.3 2-Aryl-4,6-diamino-1,3,5-thiadiazinium salts. 2-Aryl-4,6-diamino-1,3,5-thiadiazinium salts (**50**; R = (un)substituted Ph or $C_{10}H_7$; $R^1 = R^2$ = alkyl; R^1R^2 = alkylene, oxalkylene, etc; X = acid anion) were prepared by cyclization of $RCONHCSNR^1R^2$ with $POCl_3$. Thus, $PhCONHCSNMe_2$ was refluxed with $POCl_3$ in ethylene chloride, followed by the addition of $HClO_4$ to give 50% **50** (R = Ph, $R^1 = R^2$ = Me, X = ClO_4) [49].



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4. Applications of aroyl thioureas in material science

A number of heterocycle preparations utilizing aroyl substituted thioureas have been carried out, with an emphasis on various aspects of electronic and biological applications. The non linear optical properties of the prepared 1-benzoyl-3-aryl(R-phenyl)-thiourea (R = nitro, H, methoxy, chloro, or methyl) were investigated and proved to have third-order nonlinear optical activity [50]. Moreover, these compounds revealed a photoinduced isomerization process [50]. *N*-Benzoyl-*N′*-*p*-substituted phenylthioureas were investigated as thermal stabilizers or co-stabilizers for rigid PVC at 180 °C in air [51]. The results revealed a higher stabilizing potency of the investigated organic stabilizers as compared with some of reference stabilizers, which is proved by their greater induction period values (Ts). During that induction period, no detectable amount of hydrogen chloride gas could be detected, but a higher dehydrochlorination rate was noted at the later stages of degradation [51].

Complexation of these materials with the chlorides of Ni^{2+} and Cd^{2+} greatly improved the induction period values, however the dehydrochlorination rate is only slightly improved. On the other hand, blending these thermal stabilizers with some of the corresponding known reference stabilizers in different proportions leads to a true synergistic effect [52].

Photosensitive lithographic plates (resin compounds) can be used as negatively chargeable electrophotographic photoreceptor plates. The former can be achieved if the chemical structure of these plates (resins) is comprised of a phthalocyanine, a thiourea, and a compound with either polynuclear quinone, bisazo-, cyanine or quinacridone skeleton in a binder resin [53]. Therefore, the prepared photoreceptor using the photosensitive resin compounds can be made into a lithographic plate using a near-IR semiconductor laser [53].

Homonuclear irradiation experiments involving correlation analysis of 3-alkyl substituted aroylthioureas have focused on the NH, CO and C=S signals in order to determine the best

way to modulate the nucleophilic character of the C=S group, as thioureas are well-known ionophore groups. The fragment -CO-NH- poorly transmits the electronic effects of substituents in the aroyl group [54]. As ionophores, some 1-furoyl-3-substituted thioureas gave the best results in Pb(II), Hg(II) and Cd(II) as ion selective electrodes (ISEs). The strong intramolecular hydrogen bond allows ligand interaction only through the C=S group. Substituents on the furan and phenyl rings give rise to low solubility in the membrane plasticizer [55].

The methods of conjugated deviations and regression analyses were used to study the substituent effects on ^{13}C and ^{15}N NMR of the chemical shifts (δ) of twelve derivatives of l-aroyl-3-phenylthiourea and l-aroyl-3-methylthiourea. The ^{13}C NMR δ values can be described by two latent variables, one correlated with Hammett substituent constants and in the other reflecting the increased shielding of the nuclei due to overlap of the adjacent bond electrons as a consequence of electron-donor or electron-acceptor character of the substituents. This effect is less pronounced with the ^{15}N nuclei [56]. Polarographic half-wave potentials were determined for acylthioureas **51a** (R = MeO, Me, H, I, Br, Cl, NO_2; R^1 = H), **51b** (R = H; R^1 = 4-NH_2, 4-OH, 3-OH, 4-Me, 3-Me, 3-OMe, H, 4-Br), and 4-$RC_6H_4CONHCSNHPh$ **51c** (R = MeO, Me and H). Hammett correlations yielded ρ values of 0.90, 0.14, and 0.70, respectively, for the above series [56].

51a-c

5. Metal complexes and their applications

The metal complexes of thioureas are neutral compounds. These chelating agents have been remarkable agents for analytical chemistry, especially for the trace analysis of metals in complex matrices. A variety of metal chelates have been described in the literature. Many transition metal complexes with such thiourea derivatives have been reported, and the structures with O,S-binding to the metal ions in alkaline media were well proposed, based on a series of physicochemical methods [57–59].

The biological activities of complexes with thiourea derivatives have been successfully screened for various biological action, and some *N*-substituted-*N′*-carbonyl thioureas have been used in commercial fungicides. *N*,*N*-Dialkyl-*N′*-benzoylthioureas have been found to be useful ligands for the determination of traces of the transition metals by means of normal phase chromatography. More significantly, these reagents have been shown to selectively extract several of the platinum group metals in the form of remarkably stable neutral metal chelates.

5.1 *Metal complexes of aroylsubstituted thioureas*

A work dealt with carrier-facilitated membrane transport of Au(III) from chloride media across a polymer-immobilized liquid membrane (FILM) using as organic reagents *N*-(thiocarbamoyl)-benzamide and *N*-benzoylthiourea derivatives [60]. In view of the performance of these carriers, *N*-benzoylthioureas were selected as a metal receptor for detailed studies of Au(III) permeation and extraction [60]. Benzoylthioureas are excellent reagents for the solvent extraction of gold. Very effective separations of gold from platinum group metals and base metals are possible due to control of the extraction parameters. The best result

defined by a fast extraction and low residual gold concentrations (<1 μ g/L) are obtained with *N*,*N*-di-*n*-hexyl-benzoylthiourea and toluene [61].

Acylthioureas inhibit the corrosion of the steel in acidic solutions even at very low concentrations. The effect of substituents of phenyl- and furyl-type was examined. The inhibition of the cathodic evolution of H_2 and anodic dissolution of steel was observed. The inhibition properties decreased with increasing temperature [62].

Benzoylthioureas are excellent reagents for solvent extraction and have a high selectivity for Pt-group metals. Very effective separations of Pt-group metals are possible due to control of the extraction parameters through variation of the ligand structure. An easy synthesis and a high chemical resistance permitted technical applications [63]. The Pt-group metals and Au are recovered from aqueous solution by precipitation with thiourea derivatives at 110 °C and pH < 7, and separated for purification. The thioureas have the general formula $R^1NHCSNHCOR^2$ or $R^1NHCSNHCO_2R^2$ (R^1 is substituted alkyl, aryl, or H; R^2 is substituted alkyl, aryl) [64].

The reaction of $[Rh(CO)_2Cl]_2$ with *N*-benzoyl-*N*′-phenylthiourea (H_2L_2) followed by PPh_3 resulted in an unprecedented tridentate bonding mode of the doubly deprotonated anion of *N*-benzoyl-*N*′-phenylthiourea to yield a binuclear compound, the structure of which was determined by X-ray crystallographic [65].

The facilitated transport of Cu(II) from chloride media through a flat-sheet supported liquid membrane (FSSLM) was studied, using thiourea derivatives. A model is presented that describes the transport mechanism, which consists of diffusion through a feed aqueous diffusion layer, a fast interfacial chemical reaction and finally diffusion of carrier and its metal complex through the organic membrane [66].

In the preparation of compounds $MLCl_2$ (M = Co, Ni, Cu, Cd; L = PhC(O)NHC(S)NHR, R = Ph, benzyl, naphthyl) and $[ML_2]Cl_2$ (M = Ni, Cu; L = PhC(O)NHC(S)NHPh), the ligands coordinated to the metal ions as neutral bidentate SO donors. The complexes were confirmed by elemental analyses, IR and electronic spectra as well as by condensation measurements. A tetrahedral or square planar geometry is proposed for the synthesized chelates [67]. The coordination properties of l-monosubstituted-3-benzoylthiourea ligands $C_6H_5C(O)NH\text{-}C(S)NHR$ towards Cu(II) were studied. The preparation of six new ligands was reported together with preparation of their copper complexes [68]. The formation of 1:1 Cu(II) complexes was observed for all ligands under study [68].

The distribution of copper(II) between aqueous solutions and cumene solutions of *N*-(thiocarbamoyl)-benzamidine and *N*-benzoylthiourea derivatives from chloride media (1 mol/L NaCl) was studied [69]. Stability constants were determined pH-potentiometrically for Pd(II), Au(III), and Hg(II) complexes of $RR^1NC(S)NHC(O)C_6H_4R^2$-*p* ($R = R^1 = Et$, $R^2 = H$, SO_3K; $R = Ph$, $R^1 = R^2 = H$). The stabilities can be arranged in the sequence Au(III) > Pd(III) > Hg(II). The complexes of Au(III) can be reduced conveniently to complexes of Au(I) [70].

5.2 *Application of palladium thiourea reagents as carriers to a solid supported liquid membrane*

N_2-Substituted N_1-phenylbenzamidines and *N*′-disubstituted *N*-benzoyl thiourea derivatives, which contain donor S, N and O atoms, were studied as carriers for the facilitated transport of Pd(II) [71]. *N*,*N*-Disubstituted thioureas possess a remarkable capacity for coordination with transition metals giving rise to highly colored chelate compounds. These chelating agents have been remarkable agents for analytical chemistry, especially for the trace analysis of metals in complex matrices [72–74]. Many transition metal complexes with such thiourea derivatives

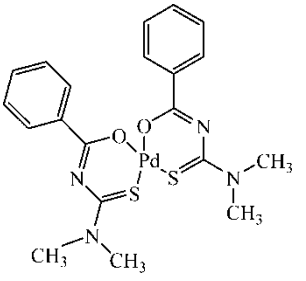

Figure 2. *cis*-Bis(*N*,*N*-dimethyl-*N*′-benzoylthioureato)palladium (**52**).

were reported, and the structures with O-, and S-binding to the metal ions in alkaline media were proposed based on a series of physicochemical methods [75–78].

A study showed that *N*,*N*-dimethyl-*N*-benzoylthiourea preferentially forms a neutral *cis*-[PdL_2] type complex (**52**). The palladium atom is bounded by two S and two O atoms in square planar coordination geometry (figure 2) [79].

5.3 *Complexation of silicon metal with benzoylthioureas*

A serious environmental threat from heavy metal ion pollution, especially mercury, has generated a great deal of attention in recent years. The harmful effect of mercury toxicity is manifested by hindering the transport processes in living cells, which is due to the high affinity of this element toward sulfur-containing biological molecules. This high affinity could be exploited for the removal of mercury ions from aqueous media, for example, by designing materials with sulfur-containing groups. The recently discovered mesoporous silica-MCM-41, having a high surface area, is a good candidate as an insoluble matrix for the attachment of sulfur containing groups, which possess the desired surface affinity toward mercury ions [80, 81].

It was reported that the proper selection of the multifunctional ligand attached to a large-pore **53** (figure 3) leads to a significant increase in the adsorption capacity of functionalized material toward mercury ions [82]. The nomenclature of the formed complex is a part of 1-benzoyl-3-(3-trimethylsilanyl-propyl)-urea.

5.4 *Some other complexes of copper aroylthioureas*

The structure the *cis*-bis[4′-chloro-*N*-(pyrrolidine-1-carbothioyl]benzamido]copper(II) complex (**54**) is depicted as in figure 4 [83].

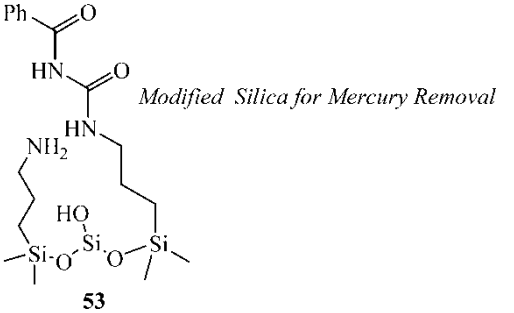

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Figure 3. Schematic illustration of the surface groups thioureas.

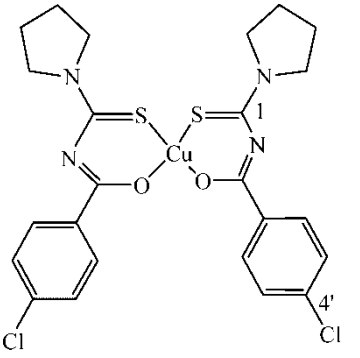


Figure 4. The structure of complex **54**.

With respect to the X-ray structure of the chelating ligands the molecule showed the *cis*-arrangement. The angles at the Cu center S11-Cu11-O12 and S12-Cu11-O11 were 168.09(7)° and 170.28(7)° respectively, whereas the dihedral angle between the S11-Cu11-O11 and S12-Cu11-O12 planes of 14.6(1)° indicates a strong distortion from square planar towards tetrahedral geometry. The copper atom lies 0.022(1) Å above the best plane through the 4 O and S atoms, but these atoms deviate by +0.205 Å and 0.207 Å from planarity [83].

A series of competitive transport experiments involving metal ligands **55** from an aqueous source phase through a chloroform membrane into an aqueous receiving phase were carried out using a series of acylthiourea ligands as the ionophore present in the organic phase [84]. It was demonstrated that the source phase contained equimolar concentrations of cobalt(II), nickel(II), copper(II), zinc(II), silver(I), cadmium(II) and lead(II) with the source and receiving phases being buffered at a number of different pHs. Transport selectivity was observed for silver(I) in all but one case. A study of the silver(I) complex of *N*,*N*-dibutyl-*N*′-benzoylthiourea **55** (figure 5) from this series was reported [84]. Two crystallographically independent molecules in the asymmetric unit were found and each molecule consists of four silver(I) ligand complex units, giving rise to $Z = 8$. In each molecule, both chelate and monodentate co-ordination modes of complexation to silver(I) are evident. Hence, each silver is co-ordinated to a sulfur and oxygen atom from one ligand and to a shared (bridging) sulfur from another ligand. Each silver atom is thus co-ordinated to three donor atoms [84].

A versatile reaction system; *N*-benzoyl-*N*′-(2-pyridyl)thiourea (L) with $CuCl_2$, was studied [85] under conditions of control of the relative concentration of the components (L or $CuCl_2$). Therefore, both converse approaches were employed: one is dropwise addition of L to $CuCl_2$ in ethanol solution, from which a dark-brown needle-like crystal, **56a**, was obtained. Product **56a** represents a chloride-bridged one-dimensional Cu(II) polynuclear complex coordinated by the oxidative cyclization product L′ generated from L (L′ = 2-benzoylimino-[1,2,4]thiadiazolo-[2,3-*a*]pyridine). The second approach was conversely dropping $CuCl_2$ into L in acetone solution; at first, a pale-yellow reduced copper(I) mononuclear complex, $[CuL_2Cl]$ (**56b**) was formed which was later found to exhibit a planar molecular configuration with a regular three coordination geometry. Subsequently, a red bis-sulfur-bridged copper(II) dinuclear complex,

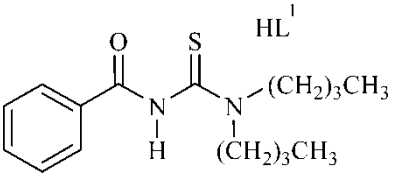
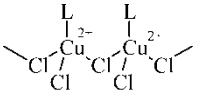


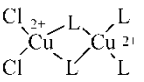
Figure 5. Structure of ligands **55**.

$[CuLCl_2]_2$ (**56c**) appeared. The crystal structures of these three products were determined by X-ray diffraction [85].



56a

56b

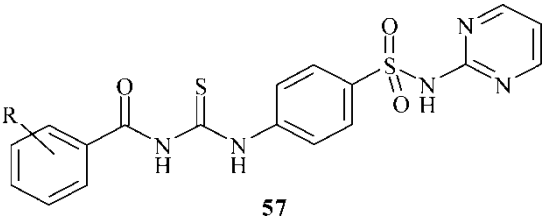


56c

6. Biological activity

N,*N*-Disubstituted thiourea derivatives exhibit a broad spectrum of biological activities including antifungal, insecticidal, fungicide, antibacterial and herbicidal properties [86]. Twenty-five $RCONHC(=NH)NR^1CSNH_3^+\ Cl^-$ (R = Ph, *p*-tolyl, 2-ClC_6H_4, benzyl, 4-$O_2NC_6H_4$; R^1 = Ph, *p*-tolyl, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-$EtOC_6H_4$) were prepared in 45–84% yield by reaction of $RCONHCSNH_2$ with $R^1NHCCl{=}NH_2^+Cl^-$. All prepared salts were potent as antifungal agents against *Alternaria alternata* and *Curvulana lunata* and as local anesthetics [87].

A series of 1-aroyl-3-(4-benzosulfonamidopyrimidine)-thioureas **57** (R = H, Me, Br, Cl and I) was obtained during the reaction of aroyl isothiocyanate with sulfadiazine in CH_3CN. Preliminary biological tests indicate that some of compounds **57** possess marked inhibiting activity against *Bacillus coli*, *Bacillus subtilis*, *Proteus*, and *Staphylococcus aureus* [88]. The biological activities of complexes with thiourea derivatives were successfully screened for various biological activities.



57

Some *N*-substituted-*N*-carbonyl thioureas have been used in commercial fungicides [89]. For example, *N*-aryl-*N*′-2,6-dichlorobenzoylureas (**58**) are recognized to have insecticidal properties. Surprisingly, it was demonstrated that the above compounds have excellent pesticidal activity while being well tolerated by plants and have low mammalian toxicity. They are particularly suitable for controlling pests that attack plants and animals. Compounds **58** are suitable for controlling insects of the orders: *Lepidoptera, Coleoptera, Homoptera, Heteroptera, Diptera, Thysanoptera, Orthoptera, Anoplura, Siphonaptera, Mallophaga, Thysanura, Isoptera, Psocoptera* and *Hymenoptera*. In addition to their very advantageous action against flies, e.g. *Musca domestica*, and *mosquito larvae*, compounds **58** were also suitable for controlling plant-destructive feeding insects in ornamentals and crops of useful plants such as cotton (e.g. against *Spodoptera littoralis* and *Heliothis virescens*) and in fruit and vegetables (e.g. against *Laspeyresia pomonella*, *Leptinotarsa decemlineata* and *Pieris brassicae*). When thioureas **58** were ingested with the feed by adult insects, then reduced oviposition and/or a reduced hatching rate is observed in many pests, especially in Coleoptera, e.g. *Anthonomus grandis* [89]. Furthermore, compounds **56** were found to be suitable for controlling ectoparasites in domestic animals and productive livestock [89].

Some other aroyl thioureas were screened and exhibited antitumor activity as on three cancer cell lines [90]. More significantly, these reagents were shown to selectively extract several of

the platinum group metals in the form of remarkably stable neutral metal chelates [91]. The Pt complexes of aroylsubstituted thioureas have been used as anti-tumor agents in chemotherapy for some types of cancer [91].

7. Thermolysis of aroylthioureas

Thermolysis of *N*-benzoyl-*N*′-phenylthiourea (BPTU) in air at 230 °C gives NH_3, H_2S, benzaldehyde, benzil, aniline, azobenzene, benzamide, benzanilide, phenyl isothiocyanate, phenylcyanamide, thiocarbanilide, and benzoyl isothiocyanate [92]. *S*-Acyl-1-phenylthioureas and their three methyl derivatives rearranged to 1-acyl derivatives of thiourea in MeOH solution. Rearrangement of the 1-acyl-1-phenyl derivatives to the thermodynamically more stable 3-acyl derivatives was subject to specific base catalysis. Rearrangement of the benzyl group is approximately two orders of magnitude faster than that of the acetyl group. The $AcN(Ph)CSNH_2$ undergoes base-catalyzed methanolysis (giving $PhNHCSNH_2$ and MeOAc) instead of the rearrangement. The methanolysis rates of 1-acyl-3-phenylthioureas and their *N*-Me derivatives were measured [93].

8. Conclusion

Although the chemistry of aroyl thioureas has exhibited promise on a number of fronts, the full evaluation of their utility in heterocyclic synthesis has not been sufficiently investigated. Therefore, more efforts are required to understand the reactivity of these simple molecules.

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