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Heterocyclization of Thiourea Derivative to Novel Azines and Azoles: Antioxidant and Antimicrobial studies

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Abstract

N,N'-disubstituted thiourea derivative 2 underwent oxidative cyclization with Br2/AcOH mixture to give thiazole 3.Thiadiazole 6 was obtained as the result of chlorination of 2 followed by amination and subsequent intramolecular cyclodehydraration. Thermal treatment of N,N'-disubstituted thiourea derivative 2 with TEA in DMF resulted in hydrolysis of 2 to furnish thiourea derivative 8. Treatment of compound 8 with semicarbazide, thiosemicarbazide, diethyl succinate, diethyl malonate / benzaldehyde or urea resulted in the formation of triazoles 11a,b, pyrrole 13, thiazine 16 and oxathiazole 19. The newly synthesized compounds were tested for their antioxidant and antimicrobial activities.

Key words: Thiazole, Triazole, Thiadiazole, Oxathiazole, Anti-oxidant.

1. Introduction

Many studies have shown that thiourea derivatives have a broad spectrum of biological effects profile including antiviral [1], anti-tubercular [2, 3], antibacterial [4], anti-fungal [5], anti-inflammatory [6], anticancer [7], antitumor [8] and anti-malarial [9] activities. Nitrogen-containing heterocycles are of great importance to both medicinal and organic chemists, and the design and synthesis of these compounds continue to represent a challenge from both an academic and industrial perspective [10]. Many of these compounds have attracted considerable attention due to the wide spectrum of their pharmacological activities such as anti-inflammatory [11], antimicrobial [12-15], antioxidant [16], anticancer [17], antihypertensive [18], antiviral [19], diuretic [20], anti-HIV [21], anticonvulsant [22], and anti-tubercular agents [23]. Accordingly, we report herein about methods for the synthesis and modification of such ring systems and evaluation of the new synthesized heterocyclic systems as antioxidant and antimicrobial agents.

2. Experimental

Melting points were measured using an Electro thermal IA 9100 apparatus with open capillary tube and are uncorrected. The IR spectrum (KBr disc) was recorded on a Pye Unicom Sp-3-300 or a Shimadzu FTIR 8101 PC infrared spectrophotometer. The (^{1}HNMR) spectrum was measured on a JEOL-JNM-LA 400 MHz spectrometer using DMSO as a solvent. All chemical shifts were expressed on the δ (ppm) scale using TMS as an internal standard reference. Analytical data were obtained from the Microanalysis Center at Cairo University, Giza, Egypt.

4-Chloro-N-(6-chlorobenzo[d]thiazol-2-yl)benzamide (3)

A mixture of compound **2** (0.01 mol), bromine (0.01 mol) in acetic acid (20ml) was heated under reflux for 8 hrs. The solid formed upon pouring onto water was collected by filtration and recrystallized from dilute ethanol to give **3** as brown crystals. Yield 73%, mp178-180 °C. IR spectrum, υ, cm^{-1}: 3334(NH), 1648 (C=O). ^{1}H NMR spectrum, δ, ppm: δ=7.99-7.4

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(m, 7H, Ar-H), 10.37(s, 1H, NH). Anal: $C_{14}H_8Cl_2N_2OS$ (323.20); Calcd, %: C, 52.03; H, 2.49; N, 8.67; Found, %: C, 52.20; H, 2.42; N, 8.69.

5-(4-Chlorobenzylidene)-3-(4-chlorophenyl)-4,5-dihydro-1,2,4-thiadiazole (6)

A mixture of compound **2** (0.01 mol), sodium hydroxide (0.01 mol), sodium hypochlorite (0.01 mol) and ammonium hydroxide (0.01 mol) in DMF (25 ml) was stirred at r.t. for 6 hours. The precipitate formed upon cooling was filtered and recrystallized from DMF to give **6** as black crystals. Yield 62%, mp159-161°C. IR spectrum, υ, cm^{-1}: 3334(NH) cm^{-1}. ^{1}H NMR spectrum, δ, ppm: 7.95-7.38 (m, 9H, Ar-H + exocyclic olefinic-H), 9.75(s, 1H, exchangeable with D_2O, NH). Anal: $C_{15}H_{10}Cl_2N_2S$ (321.23); Calcd, %: C, 56.09; H, 3.14; N, 8.72; Found, %: C, 56.12; H, 3.18; N, 8.91.

Hydrolysis method of compound 2 to 1-(4-Chlorophenyl)thiourea (8)

A mixture of compound **2** (0.01 mol), TEA (3 drops) in DMF 20 ml was heated under reflux for 2 hrs. The precipitate formed upon addition of reaction mixture to cold water was collected by filtration and recrystallized from DMF to give **8** as yellow crystals. Yield 61%, mp180-182°C (as reported). IR spectrum, υ, cm^{-1}: 3449, 3345 (NH, NH_2). ^{1}H NMR spectrum, δ, ppm: 6.58 (s, 2H, NH_2), δ= 7.43-7.96 (m, 4H, Ar-H), 10.39 (s, 1H, NH). Anal: $C_7H_7ClN_2S$ (186.66); Calcd, %: C, 45.04; H, 3.78; N, 15.01; Found, %: C, 45.13; H, 3.67; N, 15.09.

5-((4-chlorophenyl)amino)-3H-1,2,4-triazol-3-one (11a) and **5-((4-chlorophenyl)amino)-3H-1,2,4-triazole-3-thione (11b)**

General method:

A mixture of compound **(8)** (0.01 mol), semicarbazide or thiosemicarbazide (0.01 mol), and sodium carbonate (0.01 mol) in DMF (30 ml) was heated under reflux for 7hrs. The precipitate formed upon dilution with water was filtered and recrystallized from DMF to give **11a,b** as yellow crystals.

Compound (11a)

Yield 66%, mp 203-205 °C. IR spectrum, υ, cm^{-1}: 3333 (NH), 1648 (C=O). ^{1}H NMR spectrum, δ, ppm: δ=7.88-7.36 (m, 4H, Ar-H), 10.38 (s, 1H, exchangeable with D_2O, NH). Anal: $C_8H_5ClN_4O$ (210.62); Calcd, %: C, 46.06; H, 2.42; N, 26.86; Found, %: C, 46.08; H, 2.41; N, 26.84.

Compound (11b)

Yield 58%, mp180-182 °C. ^{1}H NMR spectrum, δ, ppm: 7.96-7.40 (m, 4H, Ar-H), 10.38 (s, 1H, NH). Anal: $C_8H_5ClN_4S$ (226.69); Calcd, %: C, 42.77; H, 2.24; N, 24.94; Found, %: C, 42.78; H, 2.25; N, 24.92.

2-((4-Chlorophenyl)amino)-4H-1,3-thiazine-4,6(5H)-dione (13)

A ternary mixture of compound **(8)** (0.01 mol), diethyl succinate (0.01 mol) and 3 drops of TEA in DMF (20 ml) was refluxed for 6 hrs. The precipitate formed upon concentration was collected by filtration and recrystallized from DMF to give compound **13** as yellow crystals. Yield 81%, mp188-190 °C. IR spectrum, υ, cm^{-1}: 3450 (NH), 1519(C=N), 1648 (C=O). ^{1}H NMR spectrum, δ, ppm: 7.36-7.88 (m, 6H, Ar-H + pyrrole-H), 10.45 (s, 1H, exchangeable with D_2O, NH). Anal: $C_{11}H_7ClN_2O_2S$ (266.71); Calcd, %: C, 49.54; H, 2.65; N, 10.50; Found, %: C, 49.55; H, 2.75; N, 10.41.

5-Benzylidene-2-((4-chlorophenyl)amino)-4H-1,3-thiazine-4,6(5H)-dione (16)

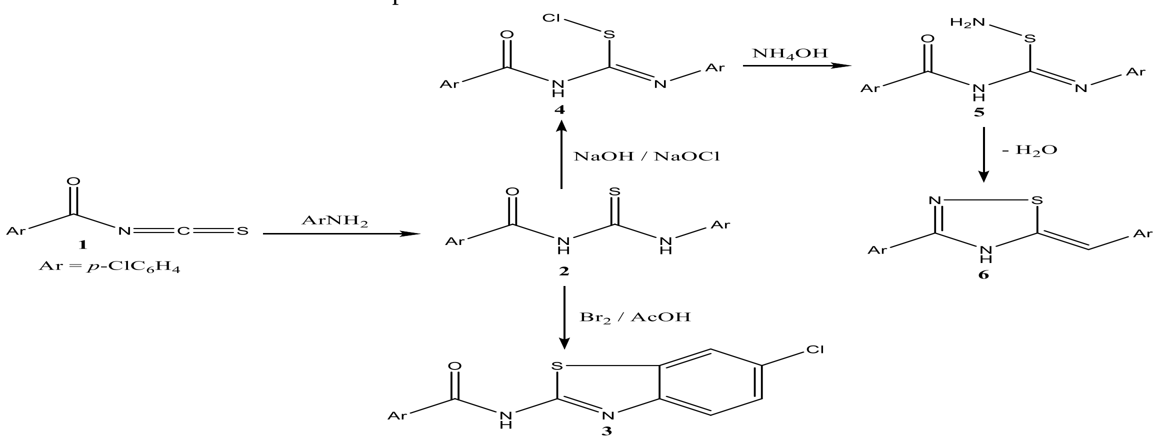
A mixture of compound **(8)** (0.01 mol), diethyl malonate (0.01 mol), 3 drops of TEA and benzaldehyde (0.01 mol) in DMF (50 ml) was refluxed for 7 hrs. The solid produced upon cooling was collected by filtration and recrystallized from DMF to give **16** as yellow crystals. Yield 61%, mp 222-224 ºC. IR spectrum, υ, cm^{-1}: 1647 (C=O), 1594 (C=N). ^{1}H NMR spectrum, δ, ppm: 7.41-7.94 (m, 10H, Ar-H + exocyclic olefinic-H), 10.38 (s, 1H, exchangeable with D_2O, NH). Anal: $C_{17}H_{11}ClN_2O_2S$ (342.81); Calcd: C, 59.56; H, 3.23; N, 8.17; Found, %: C, 59.55; H, 3.22; N, 8.16.

3-((4-Chlorophenyl)amino)-5H-1,2,4-oxathiazol-5-one (19)

A mixture of compound **(8)** (0.01 mol), urea (0.01 mol) and sodium carbonate (0.01 mol) in DMF (75 ml) was heated under reflux for 5hrs. The precipitate formed upon pouring the reaction mixture with water was collected by filtration and recrystallized from DMF to give **19** as yellow crystals. Yield 74%, mp 265-267 ºC. IR spectrum, υ, cm^{-1}: 3347 (NH), 1653 (C=O). ^{1}H NMR spectrum, δ, ppm: δ=7.96-7.41 (m, 4H, Ar-H), 10.39 (s, 1H, exchangeable with D_2O, NH). Anal: $C_8H_5ClN_2O_2S$ (228.66); Calcd: C, 42.02; H, 2.20; N, 12.25; Found: C, 42.00; H, 2.21; N, 12.24.

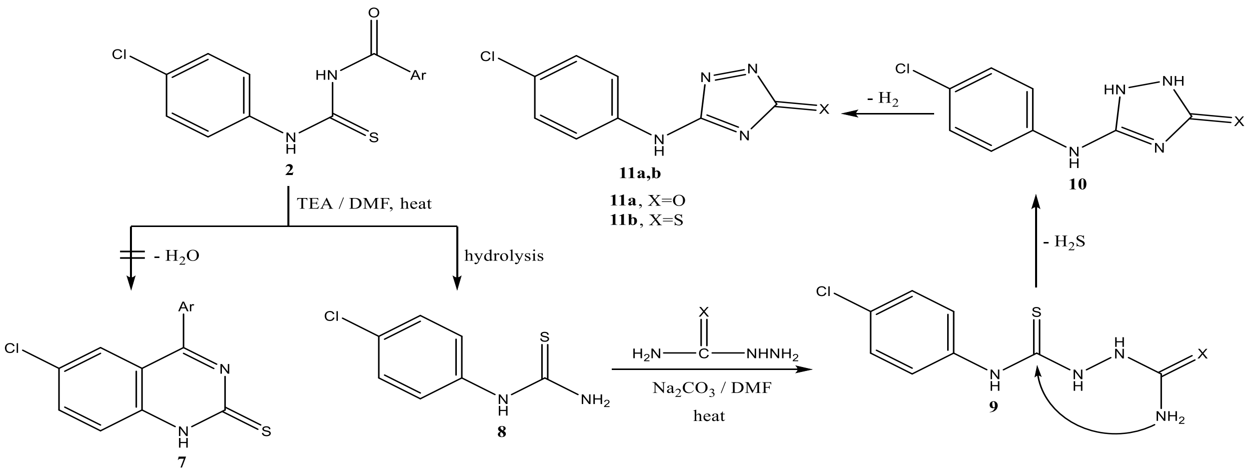
3. Results and Discussion

In the present study, *N,N'*-disubstituted thiourea derivative **2** was prepared by the addition of *p*-chloroaniline to *p*-chlorobenzoyl isothiocyantate **[**24**]**. The intramolecular oxidative cyclization of the target **2** to benzothiazole **3** was achieved by treatment of **2** with bromine/ AcOH mixture (Scheme1). The characteristic resonance NH of compound **3** was detected at δ=10.37 ppm, IR Spectrum of **3** displayed the NH and C=O function at 3334 and 1648 cm^{-1}, respectively. The thiadiazole **6** was obtained by keeping **2** in NaOCI in the presence of NaOH / NH_4OH mixture. The reaction may be started by the formation of sulphenyl chloride that underwent amination forming sulphenamide, followed by intramolecular cyclodehydration. The formation of **6** was potentiated by the absence of C=O frequency and the presence of D_2O exchangeable NH signal at 9.75 ppm (Scheme1).



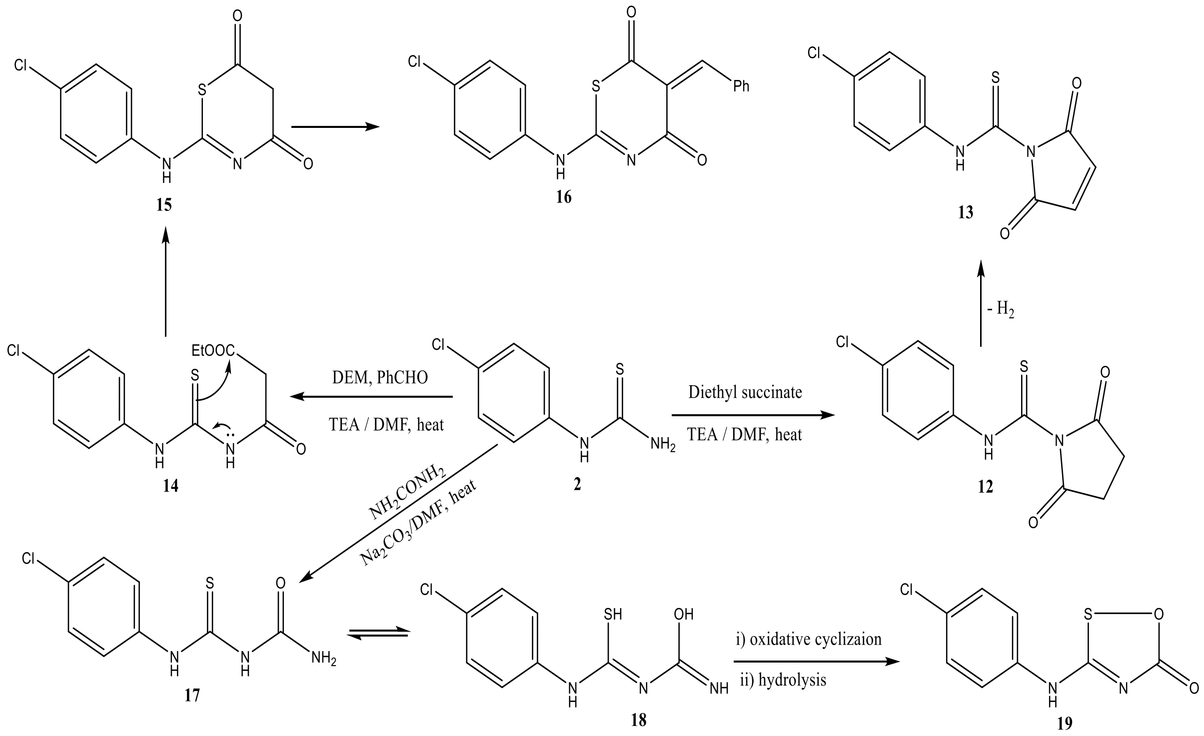
Scheme 1: Synthetic pathway for benzothiazole **3** and thiadiazole **6**

In attempt to synthesize quinazoline **7**; thiourea derivative **2** was heated in DMF in presence of TEA. However, the product was identified to be *N*-aryl thiourea **8** not the desired quinazoline **7**. Base-induced cyclization of **8** with semicarbazide and/or thiosemicarbazide yielded triazoles **11a,b** (Scheme2). The formation of the latter compounds was confirmed by their spectral data; for example, IR spectrum of triazolone **11a** clarified a C=O absorption band at 1648 cm^{-1}, whereas its 1H NMR revealed a D_2O-exchangeable signal at 10.38 ppm for NH. Treatment of compound **8** with diethyl succinate leads to condensation, followed by dehydrogenation providing pyrrole **13**. Compound **13** showed ^{1}HNMR signal at 10.45 ppm for NH function.



Scheme 2: Synthetic pathway for triazoles **11a,b**

Thermal reaction of ternary mixture of **8**, diethylmalonate and benzaldehyde in basic medium resulted in cyclocondensation followed by condensation with benzaldehyde to produce thiazine **16**. Compound **16** showed stretching frequency at 1647 cm^{-1} for C=O. The ^{1}HNMR clarified a singlet at 10.38 ppm for NH. Finally, heterocyclization of **2** with urea in refluxing DMF yielded oxathiazole **19** whose IR spectrum revealed a stretching band at 1653 cm^{-1} for C=O, and its ^{1}H NMR clarified a D_2O-exchangeable singlet at 10.39 ppm for NH (Scheme 3).



Scheme 3: Synthetic pathway for pyrrole **13** and thiazine **16** and oxathiazole **19**

Antioxidant Evaluation

The antioxidant activities of the synthesized compounds were determined and listed in Table 1.

Table 1: Antioxidant assay for the tested new compounds

compounds	Absorbance of compounds	% Inhibition
6	0.225	54.6
11a	0.136	72.8
13	0.081	83.8
16	0.062	87.6
Ascorbic acid (standard)	0.058	88.4

The results given in table (1) revealed that all compounds were found to be potent. Moreover, the results showed that compound **16** and **13** had the most potent levels of activity. Additionally, compound **11a** was found to have moderate activity. While compound **6** was found to have the lowest potent levels

Antimicrobial Evaluation

The antimicrobial activities of the newly synthesized compounds were determined *in vitro* against a group of microorganisms using disc diffusion method. Tetracycline and Econazole were used as antibacterial and antifungal agent standards, respectively. DMSO was used as solvent. The zone of inhibition of bacterial growth was observed.

Table 2: Antibacterial Activity for the tested new compounds

Bacteria	DMSO (-ve control)	Tetracycline (standard)	5	6	11a	13	16
Staphylococcus aureus	0	23	0	9.5	10.5	11	0
Bacillus cereus	0	27	0	10	0	9.5	10.5
Escherichia coli	0	25	10	11.5	0	9	11
Klebsiella pneumonia	0	25.5	0	12	12.5	9	13.5

The results given in tables (2 and 3) showed that most of the tested compounds have weak to moderate activity against the tested microorganisms.

Table 3: Antifungal Activity for the tested new compounds

Fungi	DMSO (-ve control)	Econazole (standard)	5	6	11a	13	16
Pencillium sp.	0	23.5	9.5	11	0	11	0
Aspergillusochraceus	0	23	9.5	0	12	8	9.5
Aspergillusfalvus	0	21	10	0	0	10.5	9
Aspergillusparasiticus	0	26	12.5	0	12	0	0

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