Asian Journal of Chemistry Vol. 19, No. 3 (2007), 1455-1460

Cyclization Reactions of 1-Pyrimidinyl-3-arylthiourea Derivatives with Oxalyl Dichloride

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N,N´-Disubstituted thioureas (**1a-h**) can be cyclized by use of oxalyl dichloride to the 4,5-dioxo-2-thioxo-perhydro-imidazolyl-pyrimidine-2*H*-ones(thiones) (**2a-h**) in good yields (58-80%). The structures of these compounds were determined by elemental analysis, IR, ^{1}H NMR and ^{13}C NMR spectroscopic measurements.

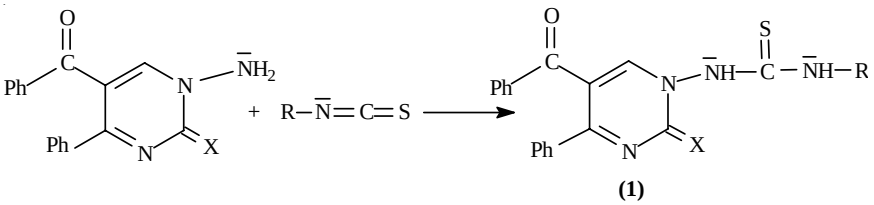
Key Words: 1-Pyrimidinyl-3-aryl-ureas, 4,5-Dioxo-2-thioxo-perhydro-imidazolyl-pyrimidine-2*H*-ones(thiones), Cyclocondensation reactions.

INTRODUCTION

The chemistry of the compounds of 2,3-dihydro-2,3-furandione attracted attention for more than a few decades due to their high reactivity, which belong to the group of γ-lactones, carbon atoms could be used for the construction of many monocyclic or condensed heterocyclic compounds upon reactions with various nucleophiles[1]. 1-Methylenaminopyrimidines were synthesized from the reaction of 4-benzoyl-5-phenyl-furan-2,3-dione with semi-/thiosemicarbazones[2,3]. There is nucleophilic attack of the NH_2-group of semi-/thiosemicarbazones at the C-5 position of the furandione ring similar to a Micheal-type addition[4]. Their hydrolysis afforded the 1-amino-pyrimidine derivatives exhibiting a free N-NH_2- moiety, which were applied to several subsequent reactions. The reactions of 1-amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-one(thione) with several anhydrides and 1,3-dicarbonyl compounds have been reported in different solvents at various temperatures[5,6]. Pyrimidines are interested in biological and medicinal properties (herbicidal, antibacterial, antifungal, antiviral)[7]. Some of them are frequently encountered in many drugs used for the treatment of hypothyroide, hypertension, cancer chemotherapy or HIV infection[8].

The aim of this study was to synthesized various pyrimidine derivatives to make notable contributions to this class of heterocyclic compounds that are generally well known for their potential biologicial activities. N,N´-Disubstituted thioureas (**1a-h**) were obtained from the reactions of the 1-amino-pyrimidine derivatives with various arylisothiocyanates

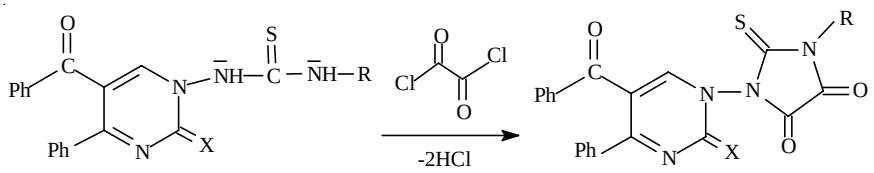
(**Scheme-1**). In the present study, we carried out the cyclization reaction between various N,N´-disubstituted thioureas (**1a-h**) and oxalyl dichloride and being prepared some new compounds of 4,5-dioxo-2-thioxo-perhydro-imidazolyl-pyrimidine-2*H*-ones(thiones) (**2a-h**) (**Scheme-2**).



(1)

X = O, S R = Ph-, *p*-$CH_3OC_6H_4$-, *p*-$NO_2C_6H_4$-, 3,4-Dichlorophenyl-

Scheme-1



(1) **(2)**

1-2	X	R
a	O	Ph-
b	S	Ph-
c	O	*p*-$CH_3OC_6H_4$-
d	S	*p*-$CH_3OC_6H_4$-
e	O	*p*-$NO_2C_6H_4$-
f	S	*p*-$NO_2C_6H_4$-
g	O	3,4-Dichlorophenyl-
h	S	3,4-Dichlorophenyl-

Scheme-2

EXPERIMENTAL

Solvents were dried by refluxing with the appropriate drying agent and distilled before use. Melting points were determined by use of Büchi melting point apparatus and not corrected. The compounds were routinely checked for their homogenity by TLC using, kieselgel $GF_{254}60$ as absorbant. Microanalyses were performed on a Carlo Erba elemental analyser, Model 1108; the results agreed favorably with the calculated values. The IR spectra were recorded on a Shimadzu Model 435 V-04 spectrometer, using potassium bromide discs. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Gemini-Varian 200 MHz instrument. The chemical shifts are reported in ppm from tetramethylsilane and are given in δ (ppm). Chemicals were from Merck and Aldrich chemicals comp.

5-Benzoyl-4-pheny-l-(4,5-dioxo-3-phenyl-2-thioxo-perhydro-imidazol-1-yl)-pyrimidine-2*H*-one (2a): To the solution of (**1a**) (0.2 g, 0.47 mmol) in 10 mL of benzene at 60-65ºC oxalyl dichloride (0.12 mL, 1.40 mmol) was added drop by drop with stirring. After few min a clear solution was obtained and the mixture was kept at this temperature for 6.3 h. Benzene was evaporated to dryness and the remaining oily residue was treated with diethyl ether to give the crude product which was recrystallized from *n*-butanol and allowed to dry on P_2O_5; yield 0.14 g (68%); m.f. $C_{26}H_{16}N_4O_4S$ m.p. 172ºC; IR (KBr, cm^{-1}): 3100-3000 ν(aromatic C-H), 1770 ν(C=O), 1720 ν(C=O), 1620 ν(C=O), 1250 ν(C=S); ^{1}H NMR ($CDCl_3$, δ ppm): 7.63-5.92 (m, 16H, ArH). Elemental analysis: Found (Calcd.): C = 64.89 (65.00), H = 3.09 (3.35), N = 11.35 (11.66), S = 6.41 (6.66).

5-Benzoyl-4-pheny-l-(4,5-dioxo-3-phenyl-2-thioxo-perhydro-imidazol-1-yl)-pyrimidine-2*H*-thione (2b): To the solution of (**1b**) (0.2 g, 0.45 mmol), in 10 mL of benzene at 60-65ºC oxalyl dichloride (0.11 mL, 1.28 mmol) was added drop by drop with stirring. The mixture was kept at this temperature for 50 min. The solvent was evaporated to dryness and the remaining oily residue was treated with diethyl ether to give the crude product which was washed with petroleum ether and allowed to dry on P_2O_5; yield 0.13 g (63%); m.f. $C_{26}H_{16}N_4O_3S_2$ m.p.157ºC; IR (KBr, cm^{-1}): 1740 ν(C=O), 1680 ν(C=O), 1620 ν(C=O), 1260-1230 ν(C=S); ^{1}H NMR ($CDCl_3$, δ ppm): 7.85-7.33 (m, 16H, ArH). Elemental analysis: Found (Calcd.): C = 62.78 (62.90), H = 3.09 (3.25), N = 11.43 (11.29), S = 12.53 (12.89).

5-Benzoyl-4-phenyl-1-(4,5-dioxo-3-*p*-methoxyphenyl-2-thioxo-perhydro-imidazol-1-yl)-pyrimidine-2*H*-one (2c): To the solution of (**1c**) (0.2 g, 0.44 mmol) in 10 mL of benzene at 60-65ºC oxalyl dichloride (0.11 mL, 1.28 mmol) was added drop by drop with stirring. The mixture was kept at this temperature for 4 h. The solvent was evaporated to dryness and the remaining oily residue was treated with diethyl ether. The formed crude product was washed in hot petroleum ether and allowed to dry on P_2O_5; yield 0.16 g (79%); m.f. $C_{27}H_{18}N_4O_5S$ m.p. 168ºC; IR (KBr, cm^{-1}): 2900-2850 ν(aliphatic C-H), 1760, 1700, 1640 ν(C=O), 1240 ν(C=S); ^{1}H NMR (DMSO): 7.60-7.02 (m, 18H, ArH), 3.90 ppm (s, 3H, CH_3O). Elemental analysis: Found (Calcd.): C = 63.10 (63.41), H = 3.84 (3.74), N = 10.87 (10.95), S = 6.41 (6.26).

5-Benzoyl-4-phenyl-1-(4,5-dioxo-3-*p*-methoxyphenyl-2-thioxo-perhydro-imidazol-1-yl)-pyrimidine-2*H*-thione (2d): To the solution of (**1d**) (0.2 g, 0.42 mmol) in 10 mL of benzene at 60-65ºC oxalyl dichloride (0.11 mL, 1.28 mmol) was added. The mixture was kept at this temperature for 1.5 h. The solvent was evaporated to dryness and the remaining oily residue was treated with diethyl ether. The formed crude product

was washed with hot butanol and allowed to dry on P_2O_5; yield 0.15 g (75%); m.f. $C_{27}H_{18}N_4O_4S_2$ m.p. 203ºC; IR (KBr, cm^{-1}): 2900 ν(aliphatic C-H), 1740 ν(C=O), 1650, 1620 ν(C=O), 1260-1235 ν(C=S); ^{1}H NMR (DMSO, δ ppm): 7.88-7.37 (m, 18H, ArH), 3.92 (s, 3H, CH_3O). Elemental analysis: Found (Calcd.): C = 61.35 (61.60), H = 3.38 (3.44), N = 10.29 (10.64), S = 11.97 (12.16).

5-Benzoyl-4-phenyl-1-(4,5-dioxo-3-*p*-nitrophenyl-2-thioxo-perhydro-imidazol-1-yl)-pyrimidine-2*H*-one (2e): To the solution of (**1e**) (0.2 g, 0.42 mmol) in 10 mL of benzene at 60-65ºC oxalyl dichloride (0.11 mL, 1.28 mmol) was added drop by drop with stirring. The mixture was kept at this temperature for 6 h. The solvent was evaporated and the remaining oily residue was treated with diethyl ether. The yellow precipitate was collected by filtration and recrystallized from toluene and allowed to dry on P_2O_5; yield 0.16 g (80%); m.f. $C_{26}H_{15}N_5O_6S$ m.p. 206ºC; IR (KBr, cm^{-1}): 1760 ν(C=O), 1700 ν(C=O), 1660 ν(C=O), 1600 ν(C=O), 1245 ν(C=S); ^{1}H NMR (DMSO, δ ppm): 8.67-7.12 (m, 15H, ArH). Elemental analysis: Found (Calcd.): C = 59.28 (59.44), H = 3.02 (2.88), N = 13.15 (13.33), S = 5.89 (6.09).

5-Benzoyl-4-phenyl-1-(4,5-dioxo-3-*p*-nitrophenyl-2-thioxo-perhydro-imidazol-1-yl)-pyrimidine-2*H*-thione (2f): To the solution of (**1f**) (0.2 g, 0.41 mmol), in 10 mL of benzene at 60-65ºC oxalyl dichloride (0.11 mL, 1.28 mmol) was added drop by drop with stirring. The mixture was kept at this temperature for 3.5 h. The mixture was evaporated. The remaining oily residue was treated with diethyl ether and stirred for 24 h to give a yellow product which was washed with hot *n*-butanol and allowed to dry on P_2O_5; yield 0.12 g (60%); m.f. $C_{26}H_{15}N_5O_5S_2$ m.p. 327ºC; IR (KBr, cm^{-1}): 1740 ν(C=O), 1680 ν(C=O), 1600 ν(C=O), 1260-1240 ν(C=S); ^{1}H NMR (DMSO, δ ppm): 8.37-7.45 (m, 15H, ArH). Elemental analysis: Found (Calcd.): C = 57.48 (57.68), H = 2.63 (2.79), N = 12.58 (12.94), S = 11.67 (11.82).

5-Benzoyl-4-phenyl-1-(4,5-dioxo-3,4-dichlorophenyl-2-thioxo-perhydro-imidazol-1-yl)-pyrimidine-2*H*-one (2g): To the solution of (**1g**) (0.2 g, 0.40 mmol), in 3 mL of benzene at 60-65ºC oxalyl dichloride (0.10 mL, 1.17 mmol) was added drop by drop with stirring. The mixture was kept at this temperature for 5 h. The mixture was evaporated and the remaining oily residue was treated with diethyl ether and stirred for 24 h. The formed crude product was washed with hot cyclohexane and allowed to dry on P_2O_5; yield 0.15 g (75%); m.f. $C_{26}H_{14}N_4O_4SCl_2$ m.p. 159ºC; IR (KBr, cm^{-1}): 1760 ν(s, C=O), 1640 ν(C=O), 1610 ν(C=O), 1255 ν(C=S); ^{1}H NMR (DMSO, δ ppm): 7.91-6.00 (m, 14H, ArH). Elemental analysis: Found (Calcd.): C = 56.50 (56.84), H = 3.01 (2.57), N = 10.35 (10.20), S = 5.65 (5.82).

5-Benzoyl-4-phenyl-1-(4,5-dioxo-3,4-dichlorophenyl-2-thioxo-perhydro-imidazol-1-yl)-pyrimidine-2*H*-thione (2h): To the solution of (**1h**) (0.2 g, 0.39 mmol), in 10 mL of benzene at 60-65ºC oxalyl dichloride (0.10 mL, 1.17 mmol) was added drop by drop. The mixture was kept at this temperature for 1 h. The mixture was evaporated to dryness and the remaining oily residue was treated with diethyl ether and stirred for 24 h. The yellow precipitate was collected by filtration and washed with hot *n*-butanol and allowed to dry on P_2O_5; yield 0.14 g (58%); m.f. $C_{26}H_{14}N_4O_2Cl_2$ m.p. 216ºC; IR (KBr, cm^{-1}): 1760 ν(C=O), 1650 ν(C=O), 1600 ν(C=O), 1250-1230 ν(C=S); ^{1}H NMR (DMSO, δ ppm): 8.13-7.34 (m, 14H, ArH). Elemental analysis: Found (Calcd.): C = 54.95 (55.23), H = 2.33 (2.49), N = 9.67 (9.91), S = 10.99 (11.32).

RESULTS AND DISCUSSION

The N,N'-disubstituted thioureas (**1a-h**) were synthesized from the reactions of 1-amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-one(thione) with arylisothiocyanates in our laboratories (**Scheme-1**). In the N,N'-disubstituted thioureas (**1a-h**), nitrogen atoms represent nucleophilic sites and could be used for the synthesis of heterocyclic compounds with oxalyl chloride, as shown in **Scheme-2**.

The cyclocondensation reactions of N,N'-disubstituted thioureas (**1a-h**) with oxalyl chloride afforded the 1-imidazolyl-pyrimidines (**2a-h**) in keeping benzene at 60-65ºC in good yields[9] (**Scheme-2**). The reaction is initiated by nucleophilic attack of the nitrogen atom of N,N'-disubstituted thioureas (**1a-h**)[5,6]. The formation of an imidazole-dione ring system is easily deduced from IR and ^{1}H NMR spectroscopic measurements. All compounds (**2a-h**) display broad (C=O) absorption bands at 1770-1740 cm^{-1} with nearly identical intensities and line shapes characteristic for thioparabanic acid derivatives[10].

Condensation of 1-(5-benzoyl-2-oxo-4-phenyl-1,2-dihydro-pyrimidine-1-yl)-3-phenyl-thiourea (**1a**) with oxalyl chloride by stirring in benzene at 60-65ºC for 6.5 h gave (**2a**), in approximately (68% yield). The structures of (**2a**) was confirmed by elemental analysis, IR and ^{1}H NMR spectroscopic techniques that supported the assigment. The formation of (**2a**) was determined by the result of spectroscopic measurements particularly by the presence of absorbtion bands characteristic for carbonyl groups (1770, 1720, 1620 cm^{-1}). The ^{1}H NMR signals were found to be at δ 7.63-5.92 ppm (m,16H, ArH) and elemental analysis data confirm the structure of (**2a**).

Product (**2b**) was obtained in (63% yield) by treating 1-(5-benzoyl-2-thioxo-4-phenyl-1,2-dihydro-pyrimidine-1-yl)-3-phenyl-thiourea (**1b**) with oxalyl chloride and keeping reaction mixture at 60-65ºC for 50 min. Im-

portant structural information about (**2b**) can be obtained from its IR and ^{1}H NMR spectrum. In the IR spectra of compound (**2b**), the (C=O) absorbtion bands were observed at 1740, 1680, 1620 cm^{-1}. ^{1}H NMR signals were found to be at δ 7.85-7.33 ppm (m, 16H, ArH).

ACKNOWLEDGEMENT

The authors would like to express our gratitude to Prof. Dr. B. Altural for critically reading the manuscript and to B. Anil for his ^{1}H NMR spectra. This research was financially supported by the Research Center of Erciyes University (Kayseri, Turkey).

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(*Received*: 17 January 2006; *Accepted*: 18 September 2006) AJC-5114