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

Zülbiye Önal*, Elif Korkusuz, İlhan Özer İlhan

Department of Chemistry, Erciyes University, 38039, Kayseri, Turkey

ABSTRACT

N,N'-Disubstituted thioureas **(1a-g)** can be cyclized by use of oxalyl dichloride to the 4,5-dioxo-2-thioxo-perhydro-imidazolyl-pyrimidine-2*(H)*-thiones **(2a-g)** in good yields (50-68%). The structures of these compounds were determined by elemental analysis, IR, ^{1}H NMR and ^{13}C NMR spectroscopic measurements.

Keywords: 1-Pyrimidinyl-3-aryl-thioureas, 4,5-Dioxo-2-thioxo-perhydro-imidazolyl-pyrimidine-2(*H*)-thiones), Cyclocondensation Reactions.

INTRODUCTION

In recent papers, reactions of aminopyrimidine derivatives have been reported to give substituted heterocyclic compounds. Pyrimidines are interested in biological and medicinal properties (herbicidal, antibacterial, antifungal, antiviral) /1-4/. Some of them are frequently encountered in many drugs used for the treatment of hypothyroidy, hypertension, cancer chemotherapy or HIV infection /5-6/.

1-Amino-5-(4-methylbenzoyl)-4-(4-methylphenyl)pyrimidine-2(1*H*)-thione is synthesized in two steps from 4-(4-methylbenzoyl)-5-(4-methylphenyl)furan-2,3-dione /7,8/. It should start with a 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 /9/. 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 aminopyrimidine derivatives with several anhydrides, 1,3-dicarbonyl compounds, isocyanates and isothiocyanates have been reported in different conditions /10-16/.

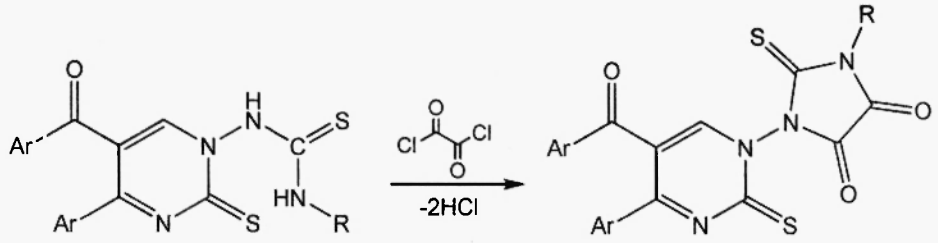
For these reasons, the aim of this study was to synthesized various pyrimidine derivatives to make notable contributions to this class of heterocyclic compounds that are generally well known for their potential biologicial activities /4/. *N,N'*-Disubstituted thioureas **(1a-g)** were obtained from the reactions of the 1-amino-pyrimidine derivatives with various arylisothiocyanates /14/. In the present study, we carried out the cyclisation reaction between various *N,N'*-disubstituted thioureas **(1a-g)** and oxalyl dichloride and being prepared some new compounds of 4,5-dioxo-2-thioxo-perhydro-imidazolyl-pyrimidine-2(*H*)-thiones **(2a-g)** as shown in **Scheme 1**.

* Corresponding author. e-mail: zulbiye@erciyes.edu.tr

RESULTS AND DISCUSSION

The *N,N'*-disubstituted thioureas **(1a-g)** were synthesized from the reactions of 1-amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-thione with arylisothiocyanates in our laboratories. The cyclocondansation reactions of *N,N'*-disubstituted thioureas **(1a-g)** with oxalyl chloride afforded the 1-imidazolyl-pyrimidines **(2a-g)** in keeping benzene at 50-68°C in good yields (see **Scheme 1**and Experimental). The reaction is initiated by nucleophilic attack of the nitrogen atom of N,N'-disubstituted thioureas **(2a-g)** /14-16/. The formation of an imidazole-dione ring system is easily deduced from IR and ^{1}H NMR spectroscopic measurements. All compounds **(2a-g)** display broad C=O absorption bands at 1770-1740 cm^{-1} with nearly identical intensities and line shapes characteristic for thioparabanic acid derivatives /17-19/.

Condensation of 1-[5-(4-methylbenzoyl)-4-(4-methylphenyl)-2-thioxo-1,2-dihydro-pyrimidine-1-yl]-3-phenyl-thiourea **(1a)** with oxalyl chloride by stirring in benzene at 60-65°C for 2 h gave **(2a)**, in approximately (63% 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 (1760, 1720, 1620 cm^{-1}). The ^{1}H NMR signals were found to be at δ 7.85-7.30 (m,14H, Ar-H), 2.39, 2.25 ppm (s, 6H, 2xCH_3) and elemental analysis data confirm the structure of **(2a)**. The result of measurements of **(2b-g)** are given in the section of experimental part.



(1a-g) Ar: *p*-$CH_3C_6H_4$- **(2a-g)**

1	R
a	Ph-
b	*p*-$CH_3OC_6H_4$-
c	*p*-$CH_3C_6H_4$-
d	3,4-Dichlorophenyl-
e	1- Naphthyl-
f	CH_3CH_2-
g	*p*-$NO_2C_6H_4$-

Scheme 1: Synthesis of the 4,5-dioxo-2-thioxo-perhydro-imidazolyl-pyrimidine-2*(H)*-thiones derivatives **2a–g**.

EXPERIMENTAL

Solvents were dried by refluxing over the appropriate drying agent and distilled before use. Melting points were determined on an Electrothermal 9200 apparatus and are uncorrected. Microanalyses were performed on a Carlo Erba elemental analyser, model 1108. The ir spectra were recorded on a Shimadzu Model 8400 FT IR spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker-400 MHz Ultra Shield istrument. The chemical shifts are

reported in ppm from tetramethylsilane as an internal standard and are given in δ (ppm). All experiments were followed by TLC using DC Alufolien Kieselgel 60 F_{254} Merck and Camag TLC lamp (254/366 nm).

5-(4-Methylbenzoyl)-4-(methylphenyl)-1-(4,5-dioxo-3-phenyl-2-thioxo-perhydro-imidazol-1-yl)-pyrimidine-2(*H*)-thione (2a).

To the solution of **(1a)** (0.2 g) in 10 mL of benzene at 60-65°C oxalyl dichloride (0.36 mL) (molar ratio 1:10) was added. The mixture was kept at this temperature for 2 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: 0.14 g (63%); m.p.: 206°C; IR: ν=2900 (aliphatic C-H), 1760 (C=O), 1720, 1620 (C=O), 1260-1240 cm^{-1} (C=S); ^1H NMR (DMSO): δ=7.85-7.30 (m, 14H, Ar-H), 2.39, 2.25 ppm (s, 6H, 2xCH_3). Anal. Cald. For $C_{28}H_{20}N_4S_2O_3$: C 64.12; H 3.84, N 10.68, S 12.20. Found C 64.22, H 3.60, N 10.48, S 12.05.

5-(4-Methylbenzoyl)-4-(methylphenyl)-1-(4,5-dioxo-3-*p*-methoxyphenyl-2-thioxo-perhydro-imidazol-1-yl)-pyrimidine-2(*H*)-thione (2b).

To the solution of **(1b)** (0.2 g), in 10 mL of benzene at 60-65°C oxalyl dichloride (0.35 mL) (molar ratio 1:10) was added drop by drop with stirring. The mixture was kept at this temperature for 3 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: 0.11 g (50%); m.p.: 337°C; IR: ν=2900 (aliphatic C-H), 1740 (C=O), 1670 (C=O), 1600 (C=O), 1260-1235 cm^{-1} (C=S); ^1H NMR (DMSO): δ= 8.30-7.43 (m, 13H, Ar-H), 3.45 (s, 3H, CH_3O), 2.39, 25 ppm (s, 6H, 2xCH_3). Anal. Cald. For $C_{29}H_{22}N_4S_2O_4$: C 62.81, H 3.99, N 10.10, S 11. 54. Found C 62.61, H 3.79, N 10.25, S 11.30.

5-(4-Methylbenzoyl)-4-(methylphenyl)-1-(4,5-dioxo-3-*p*-methylphenyl-2-thioxo-perhydro-imidazol-1-yl)-pyrimidine-2(*H*)-thione (2c).

To the solution of **(1c)** (0.2 g) in 10 mL of benzene at 60-65°C oxalyl dichloride (0.37 mL) (molar ratio 1:10) 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 (60%); m.p.: 216°C; IR: ν=2900 (aliphatic C-H), 1760 (C=O), 1655 (C=O), 1600 (C=O), 1250-1235 cm^{-1} (C=S); ^1H NMR (DMSO): δ= 8.10-7.38 (m, 13H, Ar-H), 2.36, 2.20, 2.15 ppm (s, 9H, 3xCH_3). Anal. Cald. For $C_{29}H_{22}N_4S_2O_3$: C 64.68, H 4.11, N 10.40, S 11. 88. Found C 64.58, H 4.06, N 10.25, S 11.70.

5-(4-Methylbenzoyl)-4-(methylphenyl)-1-[4,5-dioxo-3-(3,4-dichlorophenyl)-2-thioxo-perhydro-imidazol-1-yl]-pyrimidine-2(*H*)-thione (2d).

To the solution of **(1d)** (0.2 g) in 10 mL of benzene at 60-65°C oxalyl dichloride (0.33 mL) (molar ratio 1:10) was added. The mixture was kept at this temperature for 1 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: 0.14 g (60%); m.p.: 253°C; IR: ν=2900 (aliphatic C-H), 1745 (C=O), 1650, 1625 (C=O), 1260-1235 cm^{-1} (C=S); ^1H NMR (DMSO): δ =7.98-7.45 (m, 12H, Ar-H), 2.30, 2.20 ppm (s, 6H, 2xCH_3). Anal. Cald. For $C_{28}H_{18}N_4S_2Cl_2O_3$: C 56.66, H 3.05, N 9.44, S 10.78, Cl 11.96. Found C 56.55, H 3.20, N 9.30, S 10.69, Cl 11.80.

5-(4-Methylbenzoyl)-4-(methylphenyl)-1-(4,5-dioxo-3-α-napthyl)-2-thioxo-perhydro-imidazol-1-yl-pyrimidine-2(*H*)-thione (2e).

To the solution of **(1e)** (0.2 g) in 10 mL of benzene at 60-65°C oxalyl dichloride (0.35 mL) (molar ratio 1:10) was added. The mixture was kept at this temperature for 3 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 (68%); m.p.: 263°C; IR: ν=2900 (aliphatic C-H), 1745 (C=O), 1650, 1625 (C=O), 1260-1235 cm^{-1} (C=S); ^1H NMR (DMSO): δ =7.93-7.35 (m, 16H, Ar-H), 2.25, 2.18 ppm (s, 6H, 2xCH_3). Anal. Cald. For $C_{32}H_{22}N_4S_2O_3$: C 66.89, H 3.85, N 9.75, S 11.14. Found C 66.71, H 3.65, N 9.57, S 11.01.

5-(4-Methylbenzoyl)-4-(methylphenyl)-1-(4,5-dioxo-3-ethyl)-2-thioxo-perhydro-imidazol-1-yl-pyrimidine-2(*H*)-thione (2f).

To the solution of **(1f)** (0.2 g) in 10 mL of benzene at 60-65°C oxalyl dichloride (0.43 mL) (molar ratio 1:10) was added. The mixture was kept at this temperature for 3 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: 0.13 g (54%); m.p.: 255°C; IR: ν= 2900 (aliphatic C-H), 1745 (C=O), 1650, 1625 (C=O), 1260-1235 cm^{-1} (C=S); ^1H NMR (DMSO): δ = 7.93-7.45 (m, 9H, Ar-H), 3.50 (q, 2H, CH_2), 2.29, 2.20 (s, 6H, 2xCH_3), 2.14 ppm (t, 3H, CH_3). Anal. Cald. For $C_{24}H_{20}N_4S_2O_3$: C 60.50, H 4.22, N 11.76, S 13.43. Found C 60.35, H 4.05, N 11.60, S 13.32.

5-(4-Methylbenzoyl)-(4-methylpheny)-1-(4,5-dioxo-3-*p*-nitrophenyl-2-thioxo-perhydro-imidazol-1-yl)-pyrimidine-2(*H*)-thione (2g).

To the solution of **(1g)** (0.2 g), in 10 mL of benzene at 60-65°C oxalyl dichloride (0.31 mL) (molar ratio 1:10) was added drop by drop with stirring. The mixture was kept at this temperature for 40 minutes. 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: 0.12 g (60%); m.p.:187°C; IR: ν= 2900 (aliphatic C-H), 1745 (C=O), 1680 (C=O), 1630 (C=O), 1260-1230 cm^{-1} (C=S); ^1H NMR ($CDCl_3$): δ= 70-7.43 m, 13H, Ar-H), 2.25, 2.15 ppm (s, 6H, 2xCH_3). Anal. Cald. For $C_{28}H_{19}N_5S_2O_5$: C 59.05, H 3.35, N 12.30, S 11.24. Found C 59.25, H 3.05, N 12.36, S 11.18.

ACKNOWLEDGEMENTS

The authors are grateful for the financial support by Research Foundation of Erciyes University (Kayseri, Turkey).

REFERENCES

1. Varma, R.S. (1999). Solvent-free organic syntheses using supported reagents and microwave irradiation *Green Chem,* 1: 43-55.
2. Kappe, C.O. (1993). 100 Years of the Biginelli dihydropyridine synthesis. *Tetrahedron* 49: 6937-6963.
3. Xie, W., Jin Y. and Wang, P.G. (1999). Lanthanide triflates as unique catalysts: effecting organic transformations in aqueous media, *Chemtech.* 29(2): 23-29.
4. Kappe, C.O., Fabian, W.M.F., and Semones, M.A. (1997). Conformational Analysis of 4-Aryl-Dihydropyrimidine Calcium Channel Modulators. A Comparison of Ab Initio, Semiempirical and X-Ray Crystallographic Studies. *Tetrahedron* 53: 2803–2816.
5. Grover, G.J., Dzwonczyk, S., Mc Mullen, D.M., Normadinam, C.S., Sleph, P.G. and Moreland, S. (1995). Pharmacologic Profile of The Dihydropyrimidine Calcium Channel Blockers SQ 32,547 and SQ 32,946, *J. Cardiovasc. Pharmacol.,* 26: 289-294.

6. Selassie, C.D., Poe, R., Li, M. and Hansch, C. (1991). On the Optimization of Hydrophobic and Hydrophilic Substituent Interactions of 2,4-Diamino-5-(substituted-benzyl)pyrimidinews ith Dihydrofolate Reductase, *J. Med. Chem.* 34: 46-54.
7. Yıldırım, I. and Koca, I. (2005). Synthesis, Characterization and Some Reactions of Novel 4-aroyl-5-aryl-2,3-dihydro-2,3-furandiones, *Kuwait J. Sci. Eng.* 32(1): 49-60.
8. Önal, Z. and Yıldırım, I. (2007). Reactions of 4-(4-Methylbenzoyl)-5-(4-methylphenyl)-2,3-furandione with Semi-thiosemi-carbazones, *Heterocycl. Commun.* 13: 113-120.
9. Akçamur, Y., Penn, G., Ziegler, E., Sterk, H., Kollenz, G., Peters, K., Peters, E.M. and Von Schnering, H.G. (1986). Zur reaktion von 4-benzoyl-5-phenyl-furan-2,3-dion mit phenylhydrazonen bzw. Phenylhydrazin, *Monatshefte Fur Chemie,* 117: 231–245.
10. Önal, Z., Sarıpınar, E. and İlhan, İ.Ö. (2001). Reactions of 1 Amino-5- benzoyl-4-phenyl-1*H*- pyrimidine-2- one with Carboxylic Anhyrides: Experimental Data and AM1 Calculations, *J. Heterocycl. Chem.* 38: 397-402.
11. Önal, Z. and Altural, B. (1999). Reactions of N-Aminopyrimidine Derivatives, with 1,3-Dicarbonyl Compounds, *Turk J. Chem.* 23: 401-405.
12. Önal, Z., Ceran H. and Şahin, E. (2008). Synthesis of Novel Dihydropyrazolo[1,5-*c*]pyrimidin-7(3*H*)-one/-thione derivatives, *Heterocycl. Commun.* 14(4): 245-250.
13. Altural, B. and Kollenz, G. (1990). Reactions of cyclic oxalyl compounds part [30]: Some reactions with N-amino-pyrimidine derivatives, *Monatsh. Chem.* 121: 677-682.
14. Önal, Z. and Daylan, A. C. (2007). Reactions of 1-Amino-5-benzoyl-4-phenyl-1*H*-pyrimidine Derivatives with Various Isothiocyanates, *Asian J. Chem.* 19(4): 2647-2653.
15. Önal, Z., and Altural, B. (2006). Reactions of 1-Amino-5-Benzoyl-4-Phenyl-1*H*-Pyrimidine-2-thione with Various Carboxylic Anhydrides, *Asian J. Chem.* 18(2):1061-1064.
16. Önal, Z. and Daylan, A.C. (2007). Cyclization Reaction of 1-Pyrimidinyl-3-arylthiourea Derivatives with Oxalyl Dichloride, *Asian J. Chem.* 19(3): 1455-1460.
17. Schemeyers, J. and Kaupp, G. (2002). Heterocycles by cascade reactions of versatile thioureido-acetamides, *Tetrahedron 58*: 7241–7250
18. Ulrich, H. and Saying, A.A.R. (1966). Synthesis of Isocyanates and Carbodiimides, *Angew. Chem. Int. Ed. Engl.* 5(8): 704-712.
19. Ulrich, H. and Saying, A.A.R. (1966). Neuere Methoden der präparativen organischen Chemie VI Synthesen von Isocyanaten und Carbodiimiden Isocyanates and Carbodiimides, *Angew. Chem. Int. Ed. Engl.* 78(16): 761–769.