SYNTHESIS OF NOVEL DIHYDROPYRAZOLO[1,5-C]PYRIMIDIN-7(3H)-ONE/-THIONE DERIVATIVES

Zülbiye Önal*, Hacer Ceran, Eda Şahin
Department of Chemistry, Erciyes University, 38039, Kayseri, Turkey
e-mail: zulbiye@erciyes.edu.tr

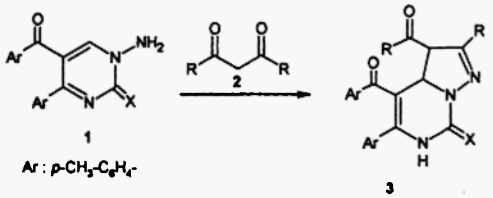
Abstract: Direct reaction of 1-amino-5-(4-methylbenzoyl)-4-(4-methylphenyl)pyrimidin-2(1H)-one/-thione (1) with various 1,3-dicarbonyl compounds (2a-h) afforded moderate to good yields of dihydropyrazolo[1,5-c]pyrimidin-7(3H)-one/-thione derivatives (3a-h) (53-67%). The newly synthesized compounds were characterized by elemental analysis, IR, ^{1}H and ^{13}C NMR spectral data. All were compared with their previous analogues.

Introduction

Pyrimidine derivatives are an important class of heterocyclic compounds because of their diverse biological activities[1-5]. They show various interesting pharmacological properties including antiviral[1], antibacterial[2,3], antitumor[4] and antiflammatory effects[5]. Some of them are frequently encountered in many drugs used for the treatment of hypothyroidy, hypertension, cancer chemotherapy or HIV infection[6-9].
Dihydro derivatives of pyrazolo[1,5-c]pyrimidines have high physiological activitiy, the most important being cardiovascular[10]. Pyrazolo[3,4-d]pyrimidine systems possess a wide spectrum of biological activities[11-15]. The antitumor activitiy and the potantialtherapeutic applications of several pyrazolo[3,4-d]pyrimidine derivatives has also promped a more through investigation of these compounds[16].

For these reasons, the aim of this study is to synthesize various pyrazolo-pyrimidine derivatives to make notable contributions to this class of heterocyclic compounds. The 1-amino-pyrimidine derivatives exhibiting a free N-NH_2 moiety, which were applied to several subsequent reactions[17,18]. Recently, the reactions of 1-amino-pyrimidine derivatives with several anhydrides, isocyanates, isothioyanates and 1,3-dicarbonyl compounds have been reported in different solvents and at various temperatures[19-23]. The reactions are generally initiated by nucleophilic attack of the nitrogen atom of 1-amino-pyrimidine derivatives.

1-Amino-5-(4-methylbenzoyl)-4-(4-methylphenyl)pyrimidin-2(1H)-one/-thione 1 were obtained from p-methylacetophenonsemicarbazone and acetophenonthiosemicarbazone with 4-(4-methylbenzoyl)-5-(4-methylphenyl)furan-2,3-dione has been reported before[17,18,24]. In the present study, we carried out the reactions of compounds 1 with some 1,3-dicarbonyl compounds 2a-h, yielding the new series of dihydropyrazolo-[1,5-c]pyrimidin-7(3H)-ones/-thiones 3a-h. The general outline of the reactions studied is shown in Scheme-1.



1-3	X	R
a	O	CH_3-
b	S	CH_3-
c	O	C_6H_5-
d	S	C_6H_5-

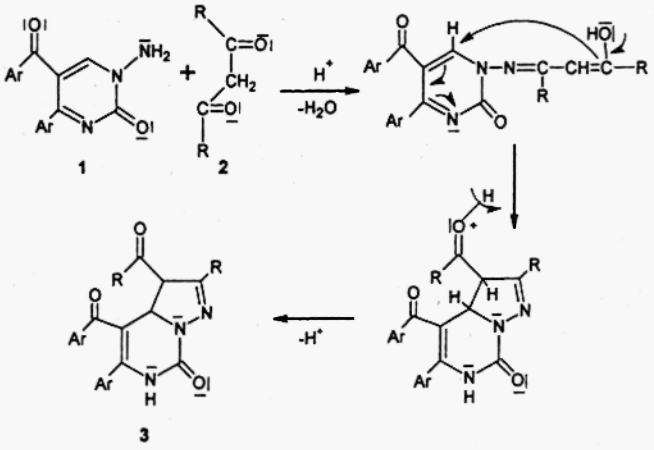
1-3	X	R
e	O	4-MeO-C_6H_4-
f	S	4-MeO-C_6H_4-
g	O	4-Me-C_6H_4-
h	S	4-Me-C_6H_4-

Scheme-1

Results and Discussion

The compounds of N-aminopyrimidine derivatives 1 with 1,3-dicarbonyl compounds 2a-h, which are used as important initial materials in the synthesis of the target heterocycles, were prepared using the literature procedures[24,25] as shown in Scheme-1. The reaction of the compounds 1 with some 1,3-dicarbonyl compounds 2a-h led to the formation of the corresponding of dihydropyrazolo[1,5-c]pyrimidin-7(3H)-ones/-thiones derivatives 3a-h in moderate yields (53-67%). All the reactions were performed by heating them without any solvent up to 110-130 °C, by the usuall chemical methods (for details see Experimental).

The reactions are generally initiated by the nucleophilic attack of the nitrogen atom of 1 directed on to the carbonyl group of the 1,3-dicarbonyl compounds 2a-h. In compounds 2 carbonyls' carbons represent electrophilic sites and could be used for the construction reaction with nucleophiles. It should start by a nucleophilic attack of the nitrogen atom lone pair electrons of 1 to the carbonyls' carbons of 2a-h. The cyclization of 1 to 3a-h, via elimination of a molecule of water occurs by heating at 110-130 °C without any solvent. In the light of this, based on the proposed reaction pathway, we showed in detail the reaction pathway of 1 with 2 as outlined in Scheme-2.



Scheme-2

The structures of the obtained dihydropyrazolo-[1,5-c]pyrimidin-7(3H)-ones/-thiones derivatives 3a-h were confirmed by interpreting their IR, ^{1}H NMR and ^{13}C NMR spectroscopic techniques, besides the elemental analyses (Experimental Section).
In the first experiment, the product (3a) 3-acetyl-4-(4-methylbenzoyl)-2-methyl-5-(4-methylphenyl)-3a,6-dihydropyrazolo[1,5-c]-pyrimidin-7(3H)-one was obtained in 54% yield by treating 1 with acetylacetone (2a) and by heating them without any solvent up to 110 °C. In the IR spectra of compound 3a, the N-H absorption band is found to be at about 3205 cm^{-1}. The C=O absorbtion bands are found to be 1718, 1696 cm^{-1}. Important structural information 3a can be obtained from its ^{1}H NMR spectrum. The ^{1}H NMR spectrum 3a, contains four singlet peaks at 2.44, 2.38, 2.14, 2.05 ppm representing the methyl groups. Chemical shift values of 3a are found to be at 5.52-5.48 and 4.04-3.99 ppm for the protons at -CH- in pyrimidine and pyrazol rings. The multiple peaks beetween 7.25-6.78 ppm are thought to represent the aromatic protons. The peak at 9.86 ppm represents the –NH. In the ^{13}C NMR spectrum of 3a, the peak at 28.51, 21.72, 20.90 ppm belong to the methyl groups, the peaks at 67.45 and 60.51 ppm the -CH- in the pyrazolo and pyrimidine ring, respectively. The peaks corresponding to 203.62 and 192.90 ppm indicate the presence of (CH_3-C=O) and (Ph-C=O) groups. In a similar way, the reaction of the 1-amino-5-(4-methylbenzoyl)-4-(4-methylphenyl) pyrimidin-2(1H)-thione with acetylacetone 2a leads to form 3-acetyl-4-(4-methylbenzoyl)-2-methyl-5-(4-methylphenyl)-3a,6-dihydropyrazolo-[1,5-c]-pyrimidin-7(3H)-thione (3b) (Scheme 1). The information about spectra of 3b is given in the experimental section and elementel analiysis data confirm the structure of 3b. The results of measurements of 3c-h were given in the experimental part.

Experimental

Solvents were dried by refluxing with 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 results agreed favorably with the calculated values. The IR spectra were recorded on a Jasco FT IR spectrometer model 460, using potassium bromide discs. ^{1}H NMR spectrum was obtained on a Gemini-Varian 200 instrument. The chemical shifts are reported in ppm from tetramethylsilane and are given in δ (ppm).

3-Acetyl-4-(4-methylbenzoyl)-2-methyl-5-(4-methylphenyl)-3a,6-dihydropyrazolo-[1,5-c]-pyrimidin-7(3H)-one (3a). Compound 1a (0.5 g), acetylacetone 2a (1.38 mL) (molar ratio 1:10 approximately) and p-toluenesulphonic acid catalyst were homogeniously mixed. The mixture was heated at 110°C and kept at this temperature for 1 h without any solvent in a calcium cloride guard tube fitted round bottom flask of 50 mL. Then, the residue was treated with dry diethyl ether and filtered and so formed crude product 3a was recrystallized from ethanol and allowed to dry on P_2O_5; yield 0.34 g (54%); m.p.: 235°C; IR (KBr): υ = 3205 (N-H), 3031 (aromatic C-H), 2913 (aliphatic C-H), 1718, 1696 (C=O), 1595-1566 cm^{-1} (C=C and C=N); ^{1}H NMR (DMSO): δ = 9.86 (s, -NH-,1H), 7.25-6.78 (m, 8H, ArH), 5.52-5.48 (d, -CH-, 1H, pyrimidine ring), 4.04-3.99 (d, -CH-, 1H, pyrazol ring), 2.44, 2.38, 2.14, 2.05 ppm (s, 12H, 4xCH_3); ^{13}C-NMR (DMSO): δ = 203.62 (CH_3-C=O), 192.90 (Ph-C=O), 146.14 (C=O, pyrimidine ring), 156.17-125.46 (aromatic carbons), 67.45 (C_3, pyrazol ring), 60.51 (C_{3a}, pyrimidine ring), 28.51 (CH_3-CO), 21.72, 20.90 (2x$CH_3C_6H_4$-), 15.64 ppm (CH_3-C=N). Anal. Cald. for $C_{24}H_{23}N_3O_3$: C 71.80, H 5.77, N 10.47. Found C 72.04, H 6.01, N 10.17.

3-Acetyl-4-(4-methylbenzoyl)-2-methyl-5-(4-methylphenyl)-3a,6-dihydropyrazolo[1,5-c]-pyrimidin-7(3H)-thione (3b). Compound 1b (0.5 g), acetylacetone 2b (1.38 mL) (molar ratio 1:10 approximately) and p-toluenesulphonic acid catalyst were homogeniously mixed. The mixture was heated at 120°C and kept at this temperature for 90 minute without any solvent in a calcium cloride guard tube fitted round bottom flask of 50 mL. Then, the residue was treated with dry diethyl ether and filtered and so formed crude product 3b was recrystallized from ethanol and allowed to dry on P_2O_5; yield 0.38 g (67%); m.p.: 249°C; IR (KBr): υ = 3250 (N-H), 3031 (aromatic C-H), 2913 (aliphatic C-H), 1720, 1665 (C=O), 1600 (C=C and C=N), 1160 cm^{-1} (C=S); ^1H NMR (DMSO): δ = 8.90 (s, 1H, -NH-), 7.33-6.99 (m, 8H, ArH), 5.43-5.37 (s,-CH-, 1H, pyrimidine ring), 4.15-4.10 (s,-CH-, 1H, pyrazol ring), 2.49, 2.35, 2.29, 2.14 ppm (s, 12H, 4xCH_3); ^{13}C-NMR (DMSO): δ = 202.50 (CH_3-C=O), 190.90 (Ph-C=O), 145.14 (C=S, pyrimidine ring), 155.17-124.40 (aromatic carbons), 66.40 (C_3, pyrazol ring), 59.50 (C_{3a}, pyrimidine ring), 27.50 (CH_3-CO), 21.70, 20.80 (2x$CH_3C_6H_4$-), 14.54 ppm (CH_3-C=N). Anal. Cald. for $C_{24}H_{23}N_3O_2S$: C 69.04, H 5.54, N 10.06, S 7.67. Found C 69.20, H 5.35, N 9.93, S 7.50.

3-Benzoyl-4-(4-methylbenzoyl)-5-(4-methylphenyl)-2-phenyl-3a,6-dihydropyrazolo[1,5-c]pyrimidin-7(3H)-one (3c). Compound 1c (0.5 g) and dibenzoylmethane 2c (1.75 g) (molar ratio 1:5 approximately) and p-toluenesulphonic acid catalyst were homogeniously mixed. The mixture was heated at 115°C and kept at this temperature for 1 h without any solvent in a calcium cloride guard tube fitted round bottom flask of 50 mL. Then, the residue was treated with dry diethyl ether and filtered and so formed crude product 3c was recrystallized from ethanol and allowed to dry on P_2O_5; yield 0.44 g (53%); m.p.: 250°C; IR (KBr): υ = 3278 (N-H), 3023 (aromatic C-H), 2940 (aliphatic C-H), 1722, 1697, 1672 s (C=O), 1592-1404 m (C=C and C=N); ^1H NMR (DMSO): δ = 8.65 (s, 1H, -NH-), 7.79-7.15 (m, 18H, ArH), 5.93-5.90 (d, -CH-, 1H, pyrimidine ring), 5.81-5.78 (d, -CH-, 1H, pyrazol ring), 2.10-2.05 ppm (s, 6H, 2xCH_3); ^{13}C-NMR (DMSO): δ = 198.20 (Ph-C=O, pyrazol ring), 192.57 (Ph-C=O, pyrimidine ring), 145.06 (C=O, pyrimidine ring), 152.41-127.86 (aromatic carbons), 64.91 (C_3, pyrazol ring), 58.64 (C_{3a}, pyrimidine ring), 22.15, 21.64 ppm (2x $CH_3C_6H_4$-). Anal. Cald. for $C_{34}H_{27}N_3O_3$: C 77.70, H 5.18, N 7.99. Found C 77.95, H 5.25, N 7.74.

3-Benzoyl-4-(4-methylbenzoyl)-5-(4-methylphenyl)-2-phenyl--3a,6-dihydropyrazolo[1,5-c]pyrimidin-7(3H)-thione (3d). Compound 1d (1) (0.5 g) and dibenzoylmethane 2d (1.52 g) (molar ratio 1:5 approximately) and p-toluenesulphonic acid catalyst were homogeniously mixed. The mixture was heated at 110°C and kept at this temperature for 1.3 h without any solvent in a calcium cloride guard tube fitted round bottom flask of 50 mL. Then, the residue was treated with dry diethyl ether and filtered and so formed crude product 3d was washed from hot ethanol and allowed to dry on P_2O_5; yield 0.48 g (65%); m.p.: 276°C; IR (KBr): υ = 3300 (N-H), 3020 (aromatic C-H), 2900 (aliphatic C-H), 1690, 1660 (C=O), 1600 (C=C and C=N), 1165 cm^{-1} (C=S); ^1H NMR (DMSO): δ = 7.79-6.66 (m, 19H, ArH), 5.89-5.85 (d, -CH, 1H, pyrazol ring), 5.76-5.71 (d, -CH-, 1H, pyrimidine ring), 2.08-2.03 ppm (s, 6H, 2xCH_3). Anal. Cald. for $C_{34}H_{27}N_3O_2S$: C 73.23, H 4.87, N 7.53, S 5.74. Found C 73.14, H 5.05, N 7.74, S 5.50.

3-(4-Methoxybenzoyl)-2-(4-methoxyphenyl)-4-(4-methylbenzoyl)-5-(4-methylphenyl)-3a,6-dihydropyrazolo[1,5-c]pyrimidin-7(3H)-one (3e). Compound 1e (0.5 g), di-p-methoxybenzoylmethane 2e (2.22 g) (molar ratio 1:5 approximately) and p-toluenesulphonic acid catalyst were homogeneously mixed. The mixture was heated at 120°C and kept at this temperature for 1 h without any solvent in a calcium

cloride guard tube fitted round bottom flask of 50 mL. Then, the residue was treated with dry diethyl ether and filtered and so formed crude product 3e was recrystallized from ethanol and allowed to dry on P_2O_5; yield 0.5 g (54%); m.p.: 285°C; IR (KBr): υ = 3223 (N-H), 3041 (aromatic C-H), 2958 (aliphatic C-H), 1712, 1650, 1640 (C=O), 1582-1463 cm^{-1} (C=C and C=N); ^{1}H NMR (DMSO): δ = 8.63 (s, 1H, -NH-), 7.45-6.83 (m, 16H, ArH), 6.92-6.88 (d, -CH-, 1H,), 6.67-6.62 (d,-CH-, 1H), 3.71-3.36 (s, 6H, 2xCH_3O-) 2.22-2.15 ppm (s, 6H, 2xCH_3); ^{13}C-NMR (DMSO): δ = 198.08 ppm (Ar-C=O, pyrimidine ring), 190.93 (Ar-C=O, pyrazol ring), 154.81 (C=O, pyrimidine ring), 161.44-109.69 (aromatic carbons), 68.50 (C_3, pyrazol ring), 60.93 (C_{3a}, pyrimidine ring), 57.10, 56.96 (s, 2XCH_3O-), 24.15, 23.64 ppm (s, CH_3, 6H, 2x $CH_3C_6H_4$-). Anal. Cald. for $C_{36}H_{31}N_3O_5$: C 73.83, H 5.33, N 7.17. Found C 73.66, H 5.54, N 7.45.

3-(4-Methoxybenzoyl)-2-(4-methoxyphenyl)-4-(4-methylbenzoyl)-5-(4-methylphenyly)-3a,6-dihydropyrazolo[1,5-c]pyrimidin-7(3H)-thione (3f). Compound 1f (0.5 g), di-p-methoxybenzoylmethane 2f (1.93 g) (molar ratio 1:5 approximately) and p-toluenesulphonic acid catalyst were homogeneously mixed. The mixture was heated at 120°C and kept at this temperature for 1 h without any solvent in a calcium cloride guard tube fitted round bottom flask of 50 mL. Then, the residue was treated with dry diethyl ether and filtered and so formed crude product 3f was recrystallized from ethanol and allowed to dry on P_2O_5; yield 0.5 g (61%); m.p.: 260°C; IR (KBr): υ = 3350 (N-H), 3050 (aromatic C-H), 2900 (aliphatic C-H), 1660 (C=O), 1530-1400 cm^{-1} (C=C and C=N); ^{1}H NMR (DMSO): δ = 8.63 (s, 1H, -NH-), 7.68-6.57(m, 16H, ArH), 5.77-5.73 (d, -CH, 1H, pyrazol ring), 5.71-5.67 (d,-CH, 1H, pyrimidine ring), 3.64-3.61 (s, 6H, 2xCH_3O-), 2.39-2.35 ppm (s, 6H, 2xCH_3). Anal. Cald. for $C_{36}H_{31}N_3O_4S$: C 71.86, H 5.18, N 6.98, S 5.32. Found C 71.66, H 5.34, N 6.71, S 5.20.

3,4-Bis(4-methylbenzoyl)-2,5-bis(4-methylphenyl)-3a,6-dihydropyrazolo[1,5-c]pyrimidin-7(3H)-one (3g). Compound 1g (0.5 g), di-p-methylbenzoylmethane 2g (1.97 g) (molar ratio 1:5 approximately) and p-toluenesulphonic acid catalyst were homogeneously mixed. The mixture was heated at 130°C and kept at this temperature for 1 h without any solvent in a calcium cloride guard tube fitted round bottom flask of 50 mL. Then, the residue was treated with dry diethyl ether and filtered and so formed crude product 3g was recrystallized from ethanol and allowed to dry on P_2O_5; yield 0.45 g (52%); m.p.: 272°C. IR (KBr): υ = 3230 (N-H), 3031 (aromatic C-H), 2968 (aliphatic C-H), 1717, 1647 (C=O), 1603-1530 (C=C and C=N); ^{1}H NMR (DMSO): δ = 9.21 (s, 1H, -NH-), 7.45-6.83 (m, 16H, ArH), 5.80-5.75 (d, -CH, 1H, pyrazol ring), 5.60-5.59 (d,-CH-, 1H, pyrimidine ring), 2.22, 2.21, 2.18, 2.15 ppm (s, 12H, 4xCH_3). Anal. Cald. for $C_{36}H_{31}N_3O_3$: C 78.10, H 5.64, N 7.59. Found C 78.23, H 5.98, N 7.35.

3,4-Bis(4-methylbenzoyl)-2,5-bis(4-methylphenyl)-3a,6-dihydropyrazolo[1,5-c]pyrimidin-7(3H)-thione (3h). Compound 1h (0.5 g), di-p-methylbenzoylmethane 2h (1.71 g) (molar ratio 1:5 approximately) and p-toluenesulphonic acid catalyst were homogeneously mixed. The mixture was heated at 120°C and kept at this temperature for 1.3 h without any solvent in a calcium cloride guard tube fitted round bottom flask of 50 mL. Then, the residue was treated with dry diethyl ether and filtered and so formed crude product 3h was recrystallized from n-butanol and allowed to dry on P_2O_5; yield 0.45 g (58%); m.p.: 278°C. IR (KBr): υ = 3280 (N-H), 3050 (aromatic C-H), 2950 (aliphatic C-H), 1660 (C=O), 1520-1450 (C=C and C=N), 1172 cm^{-1} (C=S); ^{1}H NMR (DMSO): δ = 8.63 (s, 1H, at C6), 7.80-6.85 (m, 16H, ArH), 6.40-6.35 (d,-CH, 1H, pyrazol ring), 5.85-5.83 (d,-CH, 1H, pyrimidine ring), 2.27-2.17 ppm (s,

12H, 4xCH_3). Anal. Cald. for $C_{36}H_{31}N_3O_2S$: C 75.90, H 5.47, N 7.37, S 5.62. Found: C 75.73, H 5.38, N 7.15, S 5.48.

Acknowledgements

The authors are grateful for the financial support by Research Center of Erciyes University.

References

1. Varma, R.S. Green Chem. 1999, 1, 43.
2. Kappe, C.O. Tetrahedron 1993, 46, 6937.
3. Xie, W.; Jin, Y. and Wang, P.G. Chemtech. 1999, 2, 23.
4. Kappe, C.O.; Fabian, W.M.F. and Semones, M.A. Tetrahedron 1997, 53, 2803.
5. Hardtmann, G.E.; F.G. U.S. Patent 1997, 4, 053, 600; Chem. Abstr. 1978, 88, 22970.
6. Grover, G.J.; Dzwonczyk, S.; Mc Mullen, D.M.; Normadinam, C.S.; Sleph, P.G. and Moreland, S.J. Cardiovasc. Pharmacol. 1995, 26, 289.
7. Selassie, C.D.; Poe, R. Li, M.; Hansch, C. J. Med. Chem. 1991, 34, 46.
8. Burdge, E.L. Pest Manag. Sci. 2000, 56, 245.
9. Parfitt (Ed.), K.; Martindale, 32nd Ed., Pharmaceutical Press, London, 1999.
10. Tsuda, N., Mishina, T., Obata, M., Inui, Nakamura, T., 1986., Jpn. Kokai Tokyo Koho, Jpn. Patent 61/227 584 (CI, C07D487/04).
11. Bhat, G. A.; Montero, J. G.; Panzica, R. P.; Waıting, L. L.; Towsend, L. B. J. Med. Chem. 1981, 24, 1165.
12. Petrie, C. R.; Cottam, H. B.; Mc Kernan, P. A.; Robins, R. K.; Revankar, G. R. J. Med. Chem. 1985, 28, 1010.
13. Avila, J. L.; Polegre, M. A.; Avila, A. R.; Robins, R. K. Comp. Biochem. Physiol. 1986, 83 C, 285.
14. Anderson, J. D.; Cottam, H. B.; Larson, S. B.; Nord, L. D.; Revankar, G. R.; Robins, R. K. J. He terocycl. Chem. 1990, 27, 439.
15. [15] Zaharie, C. B.; Connolly, T. P.; Rej, R.; Attardo, G.; Penney, C. L. Tetrahedron 1996, 52, 2271.
16. Youssif, S. Monatsh. Chem. 1997, 128, 493-501.
17. Akçamur,Y.; Altural, B.; Sarıpmar, E.; Kollenz, G.; Kappe, O. J. Heterocycl. Chem. 1988, 25, 1419.
18. Altural, B.; Akçamur, Y.; Sarıpınar, E.; Yıldırım, I.; Kollenz, G. Monatsh. Chem. 1989, 120, 1015.
19. Önal, Z.; Sarıpmar, E.; Ilhan, I. Ö. J. Heterocycl. Chem. 2001, 38, 397.
20. Önal, Z. And Altural, B. Asian J. Chem. 2006, 18(2), 1061.
21. Altural, B.; Kollenz, G. Monatsh. Chem. 1990, 121, 677.
22. Önal, Z. and Altural, B. Tr J. Chem. 1999, 23, 401.
23. Önal, Z. And Daylan, A. C. Asian J. Chem. 2007, 19(3),1455.
24. Yıldırım, I. and Koca, I. Kuwait J. Sci. Eng. 2005, 32(1), 49.
25. Önal, Z. and Yıldırım, I. Heterocycl Commun. 2007, 13, 113.

Received on February 21,2008