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Synthesis of Novel Pyrimidin-1(2*H*)-ethanediamide Derivatives

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Various novel pyrimidin-1(2*H*)-yl-ethanediamide derivatives (**2a-f**) have been synthesized efficiently in good yields by the treatment of 1-aminopyrimidine-2(1*H*)-one/-thione derivatives (**1a-f**) with oxalyl dichloride. Structures of these compounds **2a-f** were established on the basis of elemental analysis, IR, ^{1}H NMR and ^{13}C NMR spectral studies.

Key Words: Pyrimidine-2(1*H*)-one, Pyrimidine-2(1*H*)-thione, Nucleophilic addition-elimination.

INTRODUCTION

Pyrimidines bases are an integral part of nucleic acids and natural products. They show various interesting pharmacological properties including antiviral, antibacterial, antitumor and antiflammatory effects[1-4]. Some of them are frequently encountered in many drugs used for the treatment of hypothyroidy, hypertension, cancer chemotherapy or HIV infection[5].

There are published report about synthesis of some 1-aminopyrimidine-2(1*H*)-one/-thione derivatives (**1a-f**) from 2,3-furandiones[6-10]. 1-Aminopyrimidine-2(1*H*)-one/-thione derivatives exhibiting a free N-NH_2- moiety, which should apply to several subsequent reactions. The reactions of 1-aminopyrimidine-2(1*H*)-one/-thione derivatives with several anhydrides, 1,3-dicarbonyl compounds, isocyanates and isothiocyanates have been reported in different conditions[11-18].

In this study, the reactions of **1a-f** with oxalyl dichloride under different conditions were presented. The reactions afforded the new pyrimidin-1(2*H*)-yl-ethanediamide derivatives **2a-f** and all the compounds synthesized are original to this study (**Scheme-I**).

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 analyzer, model 1108. The ir spectra were recorded on a Shimadzu Model 8400 FT IR spectrophotometer. The ^{1}H NMR 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).

N,N'-*Bis*(5-benzoyl-4-phenyl-2-oxopyrimidin-1(2*H*)-yl)ethanediamide (2a): To the solution of 1-amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-one (**1a**) (0.5 g) in 30 mL of acetonitrile at 30 ºC oxalyl dichloride (0.15 mL) (molar ratio 1:1) was added drop by drop with constant stirring. The mixture was kept at this temperature for 5 h. The solvent was evaporated to dryness and the remaining oily residue was treated with diethyl ether. The formed crude product was recrystallized from ethanol and allowed to dry on P_2O_5; yield: 0.65 g (59 %); m.p.: 240 ºC. IR (KBr, ν_{max}, cm^{-1}): 3450 (N-H), 3066 (aromatic C-H stretching), 1708, 1676, 1668 (C=O groups), 1561-1464 (C=C and C=N aromatic rings). ^{1}H NMR (DMSO, ppm): δ = 12.80 (s, 2H, N-H), 8.76 (s, 2H, pyrimidinyl), 7.88-6.89 (m, 20H, ArH). ^{13}C NMR ($CDCl_3$, ppm) δ: 191.07 (C=O, benzoyl), 178.98 (C=O, amide), 151.20 (C=O, pyrimidinyl), 155.99-113.17 (aromatic carbons). Anal. calcd. for $C_{36}H_{24}N_6O_6$: C, 67.92; H, 3.79; N, 13.20. Found: C, 67.70; H, 3.62; N, 13.05.

N,N'-*Bis*(5-benzoyl-4-phenyl-2-thioxopyrimidin-1(2*H*)-yl)ethanediamide (2b): 1-Amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-thione (**1b**) (0.5 g) and oxalyl dichloride (0.14 mL) (molar ratio 1:1) were refluxed in 30 mL acetonitrile for 5 min. The solvent was evaporated to dryness and the remaining oily residue was treated with diethyl ether. The formed crude product was washed with hot ethanol and allowed to dry on P_2O_5; yield: 0.70 g (64 %); m.p. 350 ºC. IR

(KBr, ν_{max}, cm^{-1}): 3453 (N-H), 3058 (aromatic C-H stretching), 1701, 1668 (C=O groups), 1591-1456 (C=C and C=N aromatic rings), 1248 (C=S groups). ^{1}H NMR (DMSO, ppm) δ: 10.53 (s, 2H, N-H), 8.04 (s, 2H, pyrimidinyl), 7.80-6.78 (m, 20H, ArH). ^{13}C NMR ($CDCl_3$, ppm) δ: 190.55 (C=O, benzoyl), 177.90 (C=O, amide), 150.01 (C=O, pyrimidinyl), 154.04-116.66 (aromatic carbons). Anal. calcd. for $C_{36}H_{24}N_6O_4S_2$: C, 64.66; H, 3.61; N, 12.56; S, 9.58. Found: C, 64.35; H, 3.57; N, 12.28; S, 9.41.

N,N'-*Bis*[5-(4-methylbenzoyl)-4-(4-methylphenyl)-2-oxopyrimidin-1(2*H*)-yl]-ethanediamide (2c): To the solution of 1-amino-5-(4-methylbenzoyl)-4-(4-methylphenyl)-1*H*-pyrimidine-2-one (**1c**) (0.5 g) in 30 mL of acetonitrile at 30 ºC oxalyl dichloride (0.13 mL) (molar ratio 1:1) was added drop by drop with stirring. 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 recrystallized from ethanol and allowed to dry on P_2O_5; yield: 0.70 g (65 %); m.p.: 180 ºC. IR (KBr, ν_{max}, cm^{-1}): 3336 (N-H), 3124 (aromatic C-H stretching), 2956 (aliphatic C-H stretching), 1679, 1652, (C=O groups), 1602-1475 (C=C and C=N aromatic rings). ^{1}H NMR (DMSO, ppm) δ: 12.70 (s, 2H, N-H), 8.67 (s, 2H, pyrimidinyl), 7.81-7.16 (m, 16H, ArH), 2.35, 2.28 (s, 12H, 4×CH_3). ^{13}C NMR ($CDCl_3$, ppm) δ: 190.94 (C=O, benzoyl), 173.25 (C=O, amide), 150.01 (C=O, pyrimidinyl), 157.71-116.83 (aromatic carbons), 21.64, 21.39 (4×CH_3). Anal. calcd. for $C_{40}H_{32}N_6O_6$: C, 69.36; H, 4.65; N, 12.13. Found: C, 69.15; H, 4.54; N, 12.01.

N,N'-*Bis*[5-(4-methylbenzoyl)-4-(4-methylphenyl)-2-thioxopyrimidin-1(2*H*)-yl]-ethanediamide (2d): To the solution of 1-amino-5-(4-methylbenzoyl)-4-(4-methylphenyl)-1*H*-pyrimidine-2-thione (**1d**) (0.5 g) in 30 mL of acetonitrile at 30 ºC oxalyl dichloride (0.128 mL) (molar ratio 1:1) was added drop by drop with stirring. The mixture was kept at this temperature for 0.5 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 ethanol and allowed to dry on P_2O_5; yield: 0.70 g (64 %); m.p. 222 ºC. IR (KBr, ν_{max}, cm^{-1}): 3420 (N-H), 3040 (aromatic C-H stretching), 2920 (aliphatic C-H stretching), 1697, 1655 (C=O groups), 1606-1515 (C=C and C=N aromatic rings), 1240 (C=S groups). ^{1}H NMR (DMSO, ppm) δ: 12.50 (s, 2H, N-H), 8.61 (s, 2H, pyrimidinyl), 7.17-6.89 (m, 16H, ArH), 2.34, 2.25 (s, 12H, 4×CH_3). ^{13}C NMR ($CDCl_3$, ppm) δ: 190.55 (C=O, benzoyl), 177.90 (C=O, amide), 150.01 (C=O, pyrimidinyl), 152.04-117.46 (aromatic carbons), 28.45, 27.36 (4×CH_3). Anal. calcd. for $C_{40}H_{32}N_6O_4S_2$: C, 66.28; H, 4.44; N, 11.58; S, 8.84. Found: C, 66.19; H, 4.32; N, 11.44; S, 8.63.

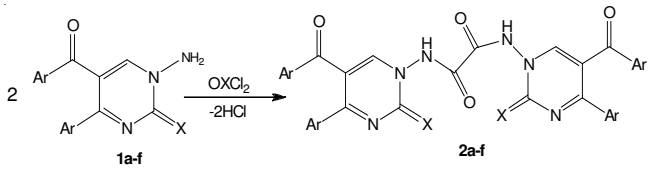
N,N'-*Bis*[5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)-2-oxopyrimidin-1(2*H*)-yl]-ethanediamide (2e): To the solution of 1-amino-5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)-1*H*-pyrimidine-2-one (**1e**) (0.5 g) in 30 mL of acetonitrile at 30 ºC oxalyl dichloride (0.122 mL) (molar ratio 1:1) was added drop by drop with stirring. 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 recrystallized from ethanol and allowed to dry on P_2O_5; yield: 0.75 g (69 %); m.p. 250 ºC. IR (KBr, ν_{max}, cm^{-1}): 3451 (N-H), 3072 (aromatic C-H stretching), 2933 (aliphatic C-H stretching), 1701, 1683, 1650 (C=O groups), 1591-1417 (C=C and C=N aromatic rings). ^{1}H NMR (DMSO, ppm) δ: 12.63 (s, 2H, N-H), 8.78 (s, 2H, pyrimidinyl), 7.92-6.94 (m, 16H, ArH), 3.83, 3.75 (s, 12H, 4×CH_3O). ^{13}C NMR ($CDCl_3$, ppm) δ: 191.17 (C=O, benzoyl), 177.88 (C=O, amide), 151.24 (C=O, pyrimidinyl), 153.04-116.72 (aromatic carbons), 57.10, 56.23 (4×CH_3O). Anal. calcd. for $C_{40}H_{32}N_6O_{10}$: C, 63.49; H, 5.25; N, 11.10. Found: C, 63.31; H, 4.13; N, 11.02.

N,N'-*Bis*[5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)-2-thioxopyrimidin-1(2*H*)-yl]ethanediamide (2f): To the solution of 1-amino-5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)-1*H*-pyrimidine-2-thione (**1f**) (0.5 g) in 30 mL of acetonitrile at 30 ºC oxalyl dichloride (0.117 mL) (molar ratio 1:1) was added drop by drop with stirring. 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 recrystallized from ethanol and allowed to dry on P_2O_5; yield: 0.62 g (57 %); m.p. 190 ºC. IR (KBr, ν_{max}, cm^{-1}): 3450 (N-H), 3072 (aromatic C-H stretching), 2970 (aliphatic C-H stretching), 1693, 1650 (C=O groups), 1591-1475 (C=C and C=N aromatic rings), 1245 (C=S groups). ^{1}H NMR (DMSO, ppm) δ: 12.41 (s, 2H, N-H), 8.43 (s, 2H, pyrimidinyl), 7.98-6.83 (m, 16H, ArH), 3.80, 3.71 (s, 12H, 4×CH_3O). ^{13}C NMR ($CDCl_3$, ppm) δ: 190.11 (C=O, benzoyl), 177.07 (C=O, amide), 154.04-118.66 (aromatic carbons), 56.06, 55.77 (4×CH_3O). Anal. calcd. for $C_{40}H_{32}N_6O_8S_2$: C, 60.92; H, 4.08; N, 10.65; S, 8.11. Found: C, 60.71; H, 4.02; N, 10.38; S, 7.98.

RESULTS AND DISCUSSION

Pyrimidin-1(2*H*)-yl-ethanediamide derivatives (**2a-f**) (**Scheme-I**) were easily obtained in good yields (59-69 %) from the reaction of 1-aminopyrimidine-2(1*H*)-one/-thione derivatives (**1a-f**) with oxalyl dichloride. The moderate yield of the reactions can be explained by the chemical behaviour of 1-aminopyrimidine-2(1*H*)-one/-thione derivatives (**1a-f**) towards oxalyl dichloride. The carbon atoms represent the electrophilic site in the molecule of the oxalyl dichloride so they can be interacted with nucleophiles[15,16]. The structures of the obtained pyrimidin-1(2*H*)-yl-ethanediamide derivatives (**2a-f**) were confirmed by interpreting their IR, ^{1}H NMR and ^{13}C NMR spectroscopic techniques, besides the elemental analysis (**2a** as examples).

The compound **2a** was obtained from the reaction of 1-amino-5-(4-benzoyl)-4-(4-phenyl)pyrimidine-2(1*H*)-one (**1a**) with oxalyl dichloride in 59 % yield. In the FT IR spectra of compound **2a**, the -NH absorbtion band was found to be at 3450 cm^{-1}. The C=O absorbtion bands were observed at 1708, 1676, 1668 cm^{-1}. The ^{1}H NMR signals were found to be at 12.80 (s, 2H, -NH) and 7.88-6.89 ppm (m, 20H, ArH). The ^{13}C NMR signals were found to be at δ 191.07 (C=O, benzoyl), 178.98 (C=O, amide), 151.20 (C=O, pyrimidinyl) and 155.99-113.17 ppm (aromatic carbons). Finally, the elemental analysis data along with spectroscopic data confirm the structure of **2a**. The results of measurements of **2a-f** were given in the experimental part.



1-2	Ar	X	m.p.(°C)	Yield (%)
a		O	240	59
b		S	350	64
c		O	180	65
d		S	222	61
e		O	250	69
f		S	190	57

Scheme-1: Synthesis of the pyrimidin-1(2*H*)-yl-ethanediamide derivatives (**2a-f**)

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