Communication

International Journal of Heterocyclic Chemistry, Vol. 4, No. 2, pp. 8-15 (2014) © Islamic Azad University, Ahvaz Branch

http://ijhc.iauahvaz.ac.ir

Aminolysis of selected methylpyrimidines in protic solvents

Hossein Eshtiagh-Hosseini, Masoud Mirzaei

Department of Chemistry, School of Sciences, Ferdowsi University of Mashhad, Mashhad, P.O. Box 917791436, Iran

Abstract – Crystallographic data analyses indicate that three types of prolinium cations, along with two types of hydrogen bonding, produce and stabilize the helical structure of triprolinium 12-phosphomolybdate. There are similarities between this organic-inorganic compound and peptides/proteins. The stronger "conventional" hydrogen bonds and the less common C-H…O attractions play critical roles in generating and stabilizing the DNA-like network.

Keywords: Proline, Hydrogen Bonding, Polyoxometallates, Molybdenum, Hybrid, Keggin, Protein, Peptide.

Recieved: 10 september 2014 Reviesed: 15 October 2014 Accepted: 9 December 2014

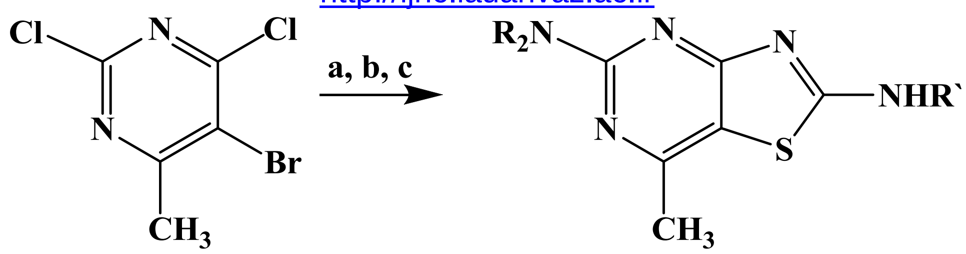
Introduction

Over the recent years, fused pyrimidines and fused pyrimidines have been the centre of attention due to their applications as anticancer, [1] antiviral, [2] antitumor [3] and anti-inflammatorial agents [4]. In recent years, our research group has reported the synthesis and 15-lipoxygenase inhibitory of pyrimido[4,5-*b*][1,4]benzothiazine derivatives [5,6]. In a previous research the synthesis of new thiazolo[4,5-*d*] pyrimidine derivatives was reported by sequential treatment of 5-bromo-2,4-dichloro-6-methylpyrimidine with ammonia, secondary amines and isothiocyanates [7] as shown in Scheme 1, with no experimental evidence for regioselective displacement of the 4-chlorine atom with ammonia.

Recently in an attempt to develop protein-targeted instead of DNA-targeted antitumor agents, some derivatives of 8H-acenaphtho[1,2-b]pyrrole have been constructed. The authors demonstrated that 8-oxo-3-thiomorpholin-4-yl-8H-acenaphtho[1,2-b]pyrrole-9-carbonitrile could serve as an apoptosis-inducing agent via interacting human B-cell lymphoma 2 (Bcl-2) protein **.** Indeed, Bcl-2 proteins have been regarded as important targets for anti-neoplastic drug development and Bcl-2 gen has been identified as over expressed in various cancers. Bcl-2 is an anti-apoptotic protein possessing an important role in various types of cancers. Bcl-2 is the member of the Bcl-2 family of apoptosis regulator proteins which is encoded by the BCL2 gene .

Various reactions of acenaphthaquinone with nucleophiles, organic and inorganic reagents have been reviewed elsewhere **.** In the frame work of our program to develop the chemistry of potentially bioactive heterocyclic compounds[13] and in connection with our ongoing interests in MCRs **,** we represent here a facile procedure for the synthesis of 9-(benzylthio)-acenaphtho[1,2-e]-1,2,4-triazines via two step condensation of thiosemicarbazide and acenaphtylene -9,10 quionone to form acenaphtho[1,2-e]-1,2,4-triazine-9(8H)-thiones and subsequent reaction with benzyl bromide derivatives. Prepared compounds were subjected to cytotoxic assay in three different cancerous cell lines. Moreover; molecular docking was used to gain further insight into the binding mode of acenaphthene derivatives with two isoforms of Bcl-2 active site.

Recieved: 10 september 2014 Reviesed: 15 October 2014 Accepted: 9 December 2014



a: EtOH, NH_3, Room Temperature
b: R_2NH, EtOH, Heat
c: DMF, $NaNH_2$, RNCS

Scheme 1. Preparation of thiazolo[4,5-*d*] pyrimidines.

In this research we show this regiselectivity by X-ray Crystallography analysis of the product and report the synthesis of some new useful 4-amino-5-bromo-2-substituted aminopyrimidines.

Exprimental

The melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu Spectrometer. The ^{1}HNMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. The mass spectra were scanned on a Varian Mat CH-7 instrument at 70 eV. Elemental analysis was obtained on a Thermo Finnigan Flash EA microanalyzer. Synthesis of 5-bromo-2,4-dichloro-6-methylpyrimidine 1 and its treatment with ammonia have been carried out according to our published method [7].

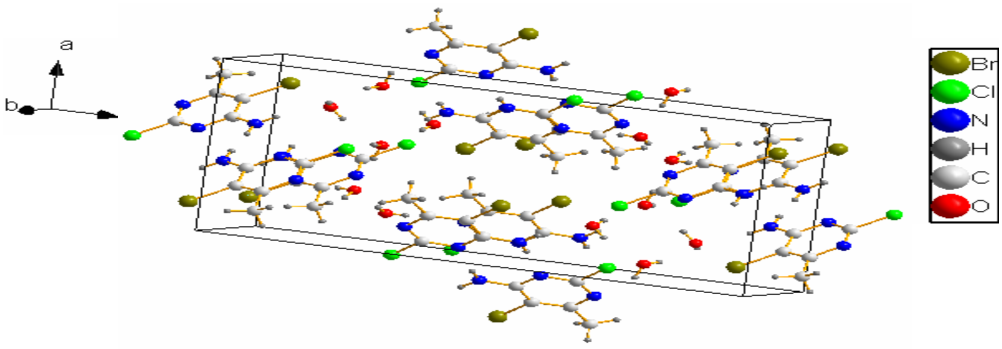
Material and methods

All of the reagents were purchased from commercial sources and were freshly used after being purified by standard procedures. Melting points were determined on the Electro-thermal Melting Point apparatus and were uncorrected. Infrared spectra were recorded on the Shimadzu-420 infrared spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in DMSO-d6 on Brucker 300 MHz spectrometer (Chemical shifts are given in parts per million or ppm). Mass spectra were recorded on a MS model 5973 Network apparatus at ionization potential of 70 eV. Elemental analyses (C, H, N) were performed by the Microanalytical Unit.

General procedure for the reaction of 5-bromo-2-chloro-6-methylpyrimidin-4-amine (1) with amines

Recieved: 10 september 2014 Reviesed: 15 October 2014 Accepted: 9 December 2014

5-Bromo-2-chloro-6-methylpyrimidin-4-amine (1) (2.22 g, 10 mmol) in ethanol (25 mL) was heated under reflux with either 1-methylpiperazin (2.0 g), 1-phenylpiperazin (2 g) or piperidine (2 g) for 4 h. Then water (20 mL) was added and the solution kept overnight, the precipitate was filtered off and washed with warm water and dried at 80 ^{0}C to give **2a, 2b** and **2c** respectively as shown in Scheme 2**.**



Scheme 2

5-Bromo-6-methyl-2-(4-methylpiperazin-1-yl)pyrimidin-4-amine (2a).

This compound was obtained as a creamy powder in 60% yield, mp 113-116 ^{o}C; IR: 3320 and 3460 cm^{-1} (NH_2); ^{1}H NMR: ($CDCl_3$): δ 2.28 (m, 7H, 2(CH_2N)-CH_3), 2.47 (s, 3H, CH_3), 3.49 (t, 4H, 2(CH_2N-Pyr.), 5.2 (s,2H, NH_2); ms: *m/z* 285 (90%), 287 (90%). *Anal*. Calcd. For $C_{10}H_{16}BrN_5$: C, 41.97; H, 5.64; N, 24.47; Found: C, 42.12; H, 5.76; N, 24.31.

5-Bromo-6-methyl-2-(4-phenylpiperazin-1-yl)pyrimidin-4-amine (2b)

This compound was obtained as a creamy powder in 80% yield, mp 125-127 ^{o}C; IR:3310 and 3440 cm^{-1} (NH_2); ^{1}H NMR: ($CDCl_3$): δ 2.32 (t, 4H, 2(CH_2N)), 2.51 (s, 3H, CH_3), 3.55 (t, 4H, 2(CH_2N-Pyr.)), 5.2 (s,2H, NH_2), 7.2-7.5(m, 5H, aromatic); ms: *m/z*, 347 (85%), 349 (85%). *Anal*. Calcd. for $C_{15}H_{18}BrN_5$: C, 51.73; H, 5.21; N, 20.11 Found : C, 51.95; H, 5.40; N, 20.31.

5-Bromo-6-methyl-2-(piperidin-1-yl)pyrimidin-4-amine (**2c**)

This compound was obtained as a creamy powder in 80% yield , mp 125-127 ^{o}C; IR: 3310 and 3440 cm^{-1} (NH_2); ^{1}H NMR: ($CDCl_3$): δ 1.2-1.7 (m, 6H, 3CH_2), 2.51 (s, 3H, CH_3), 3.41 (t, 4H,

Recieved: 10 september 2014 Reviesed: 15 October 2014 Accepted: 9 December 2014

2(CH_2N-Pyr.)), 5.2 (s,2H, NH_2), ms: *m/z*, 270 (80%), 272 (80%). *Anal*. Calcd. for $C_{10}H_{15}BrN_4$: C, 44.29; H, 5.58; N, 20.66 Found : C, 44.24; H, 5.73; N, 20.39.

X-Ray Crystallography

Crystal data and structure refinement for 5-Bromo-2-chloro-6-methylpyrimidin-4-amine·3H_2O is given in Table 1. Data were collected on a colorless prism crystal mounted on a Bruker APEX II CCD area detector diffractometer equipped with graphite monochromated MoKα radiation (λ = 0.71073 Å). The final unit cell was determined from 12645 reflections in the range of 2.3° < θ < 30.5°. The diffraction data were collected at 100(2) K with the ω-scan technique. The structure was solved by direct methods and refined by full-matrix least squares based on F^2 with weight $w=1/[\sigma^2(F_o^2)+(0.0506P)^2+0.0000P]$ where $P=(F_o^2+2F_c^2)/3$ using the SHELXTL-97 software [8]. The nonhydrogen atoms were refined anisotropically. Hydrogen atoms were placed in geometrical calculated positions and thereafter allowed to ride on their parent atoms.

X-ray crystallographic files in CIF format for the structure determination of the title compound has been deposited with the Cambridge Crystallographic Data Center. The CCDC reference number is 795507. Copy of this information may be obtained, free of charge, from The Director, CCDC, 12 Union Road, Cambridge, CB2 IEZ, UK (Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Empirical formula	$C_5H_{11}BrClN_3O_3$
Fw	276.52
Crystal system	monoclinic
Crystal size (mm^3)	0.21 × 0.25 × 0.34
space group	$P2_1/n$
a (Å)	9.7470(11)
b (Å)	4.9353(6)
c (Å)	21.154(2)
β (°)	92.553(2)
Index range	$-13\leq h\leq 13$ $-7\leq k\leq 6$ $-30\leq l\leq 30$
V (Å^3)	1016.6(3)
Z	4
D_{calcd} (Mg/m^3)	1.806
μ (mm^{-1})	4.288
θ range (°)	2.3 to 30.5

Recieved: 10 september 2014 Reviesed: 15 October 2014 Accepted: 9 December 2014

Communication
International Journal of Heterocyclic Chemistry, Vol. 4, No. 2, pp. 8-15 (2014) © Islamic Azad University, Ahvaz Branch

http://ijhc.iauahvaz.ac.ir

F(000)	552
Goodness-of-fit on F^2	1.042
Final *R* indices [I>2sigma(I)]	*R*1 = 0.0271, *wR*2 = 0.0664
Largest diff. peak and hole (e.Å^{-3})	0.77 and -0.44

Table 1: Crystal data and structure refinement for 5-bromo-2-chloro-6-methylpyrimidin-4-amine·3H_2O.

Results

The synthetic compound in this research crystallized in the monoclinic crystal system space group $P2_1/n$. In the title cocrystal, 5-bromo-2-chloro-6-methylpyrimidin-4-amine·3H_2O, the asymmetric unit contains one crystallo-graphically independent 5-bromo-2-chloro-6-methylpyrimidin-4-amine and three crystallization of water molecules. The 5-Bromo-2-chloro-6-methylpyrimidin-4-amine molecules interact with each other through N−H···N hydrogen bonds, forming a cyclic hydrogen-bonded motif $R^2_2(8)$ [9]. The pyrimidine molecules also connect them *via* water molecules. The typical intramolecular O−H···N as well as O−H···O hydrogen bond is observed in the crystalline network of the title compound. It is interesting to pointed out that the crystal structure is further stabilized by O−H···O hydrogen bonds created by $(H_2O)_\infty$ clusters. In fact, the presence of water molecules is important in establishing hydrogen bonds contributions to the total lattice energy, and is significant in the stability of the hydrated crystal structure [10]. Water is of fundamental importance for human life and plays an important role in many biological and chemical systems. It possesses polar hydrogen bonds (hereafter P-HB) which are responsible for a striking set of anomalous physical and chemical properties. Water molecules have two hydrogen atoms and two lone pairs enabling them to participate in four hydrogen bonds in a tetrahedral arrangement, but also frequently show 3-coordinate configurations. However, unlike covalent bonds, the P-HB geometry is much more flexible, Krygowski et al. describe the role of water molecules as a 'gluing factor' in organic crystals because of their readiness to deform from ideal P-HB geometry [11]. P-HBs resulted in formation of diverse structures of water/water contacts directly as called water cluster, that is, $(H_2O)_n$ clusters.

Conclusion

Recieved: 10 september 2014 Reviesed: 15 October 2014 Accepted: 9 December 2014

In conclusion X- Ray Crystallography of the product of amination of 5-bromo-2,4-dichloro-6-methylpyrimidine in ethanole, evidenced the substitutional preference of 4 position in comparison with 2 position.

Acknoledgment

The financial support of this research by Ahvaz Branch, Islamic Azad University is gratefully acknowledged.

References

[1] Petrie, C. R.; Cottam, H. B.; Mckernan, P. A.; Robins, R. K.; and Revankar, G. R., J. Med. Chem. 1985, 28, 1010.

[2] Nasr, M. N. and Gineinah, M. M., Arch. Pharm. 2002, 335, 289.

[3] Baraldi, P. G.; Pavani, M. G.; Nunez, M.; Brigidi, P.; Vitali, B.; Gambari, R. and Romagnoli, R., Bioorg. Med. Chem. 2002, 10 449.

[4] Sondhi, S. M.; Johar, M.; Rajvanshi, S.; Dastidar, S. G.; Shukla, R.; Raghubir, R. and Lown, J. W., Aust. J. Chem. 2001, 54, 69.

[5] Bakavoli, M.; Nikpour, M.; Rahimizadeh, M.; Saberi, M. R. and Sadeghian, H., Bioorg. Med. Chem. 2007, 15, 2120.

[6] Bakavoli, M.; Sadeghian, H.; Tabatabaei, Z.; Rezaei, E.; Rahimizadeh, M. and Nikpour, M., J. Mol. Model. 2008, 14, 471.

[7] Bakavoli, M.; Nikpour, M. and Rahimizadeh, M., J. Heterocycl. Chem. 2006, 43 1327.

[8] Sheldrick, G. M., SHELXS-97, Program for Crystal Structure Solution and Refinement, (University of Gottingen, 1997).

[9] Lynch, D. E. and Jones, G. D., Acta Cryst. 2004, B60, 748.

Recieved: 10 september 2014 Reviesed: 15 October 2014 Accepted: 9 December 2014

[10] Aghabozorg, H.; Eshtiagh-Hosseini, H.; Salimi, A. R. and Mirzaei, M., J. Iran. Chem. Soc. 2010, 7, 289.

[11] Krygowski, T. M.; Grabowski, S. J. and Konarski, J., Tetrahedron 1998, 54, 11311.

Recieved: 10 september 2014 Reviesed: 15 October 2014 Accepted: 9 December 2014