J. Iran. Chem. Soc., Vol. 8, No. 4, December 2011, pp. 1135-1138.

JOURNAL OF THE Iranian Chemical Society

Synthesis of Two New Heterocyclic Systems: Furo[3',2':5,6]pyrimido[2,1c][1,2,4]triazines and Furo[3,2-e][1,2,3,4]tetrazolo[1,5-a]pyrimidine

M. Rahimizadeh^{a,*}, M. Bakavoli^a, Z. Gordi^{a,b} and S.M. Seyedi^a

^aDepartment of Chemistry, Ferdowsi University of Mashhad, Mashhad 91775-1436, Iran ^bDepartment of Chemistry, Payame Noor University (PNU), Torbat-e-Heydarieh, Iran

(Received 31 August 2010, Accepted 10 June 2011)

Two novel heterocyclic triazines and tetrazole systems were synthesized through cyclization of 2-hydrazino-furo[2,3-d]pyrimidine with α -haloketones and nitrous acid respectively in high yields. The starting 2-hydrazino-pyrimidine was synthesized from 4-imino-3,6-diphenyl-furo[2,3-d]pyrimidine-2(1*H*)-thione by methylation and subsequent nucleophilic displacement of methylthio group with hydrazine hydrate.

Keywords: Furo[2,3-d]pyrimidine, α-Haloketones, Triazines, Tetrazole

INTRODUCTION

Furo[2,3-d]pyrimidines have received much attention due to their biological activities. Antifungal [1], antibacterial [2], antiviral [3], antifolate [4], antitumor [5] and anti-HCMV (human cytomegalovirus) [6] activities have been described for these compounds. Recently, some furopyrimidines were shown to be potent LCK (lymphocyte-specific kinase) [7], PI3K (phosphoinositide 3-kinase) [8], VEGFR2 (vascular endothelial growth factor receptor2) and EGFR (epidermal growth factor receptor) [9] inhibitors. Furthermore, a wide range of biological activities [10-13] has been attributed to fused triazoles, triazines and tetrazoles. In connection with our interest in the synthesis of polyheterocyclic systems [14], we recently reported [15,16] the synthesis of substituted 2-amino-3-furonitriles and 3,6-disubstituted-furo[2,3-d]pyrimidines as key-precursors for this purpose. Arising from these studies, we now report here the utility of 4-imino-3,6-diphenyl-3,4dihydrofuro[2,3-d]pyrimidine-2(1H)-thione 1 for the synthesis

of some novel tricyclic fused furo[3,2-e][1,2,3,4]tetrazolo[1,5-a]pyrimidine **4** and furo[3',2':5,6]pyrimido [2,1-c][1,2,4]triazines **5-8** as shown in Schemes 1 and 2.

EXPERIMENTAL

All melting points recorded are uncorrected open capillary measurements. IR spectra were recorded on a Shimadzu-IR 470 spectrophotometer. ¹H NMR spectra were recorded on Bruker-80 and 100 MHz instruments using tetramethylsilane (TMS) as an internal standard. Mass Spectra were scanned on a Varian Mat CH-7 instrument at 70 eV. Elemental analyses were obtained on a Thermo Finnigan Flash EA microanalyzer. 4-Imino-3,6-diphenyl-3,4-dihydrofuro[2,3-*d*]pyrimidine-2 (1*H*)-thione **1** is a known compound and was prepared according to the previously reported method [16].

Synthesis of 2-(Methylsulfanyl)-3,6-diphenylfuro[2,3*d*]pyrimidine-4(3*H*)-imine 2

To a solution of 4-imino-3,6-diphenyl-3,4-dihydrofuro[2, 3-d]pyrimidine-2(1*H*)-thione **1** (1.59 g, 5 mmol) in sodium

^{*}Corresponding author. E-mail: rahimizh@yahoo.com



Scheme 1

hydroxide solution (5%, 40 ml), methyl iodide (1.06 g, 7.5 mmol) was added and stirred for 10 min. The resulted solid was filtered, and recrystallized from ethanol to give compound **2** in 95% yields as pale yellow needles; m.p.: 230-231 °C; IR (KBr): v = 3400, 1640, 1520, 1500, 1475, 1275, 1120, 1050, 750, 700 cm⁻¹. ¹H NMR (CDCl₃, 100 MHz): $\delta = 2.50$ (s, 3H), 7.05 (s, 1H), 7.2-7.7 (m, 9H), 7.85 (dd, 2H, $J_I = 8$ Hz, $J_2 = 1.5$ Hz). MS (*m/z*): 333 (M⁺), 332, 185, 183 (base peak), 157,155, 77, 75.

Synthesis of 2-Hydrazino-3,6-diphenylfuro[2,3-*d*] pyrimidine-4(3*H*)-imine 3

A mixture of 2-(methylsulfanyl)-3,6-diphenylfuro[2,3-*d*] pyrimidine-4(3*H*)-imine **2** or 4-imino-6-phenyl-3,4dihydrofuro[2,3-*d*]pyrimidine-2(1*H*)-thione **1** (10 mmol) and hydrazine hydrate (2 or 4 mmol, respectively) in ethanol (10 ml) was heated under reflux for 24 h. The reaction mixture was cooled to room temperature and water (10 ml) was added. The resulted solid was filtered and recrystallized from ethanol to give compound **3** in 90% yields as white needles; m.p.: 280-281 °C; IR (KBr): v = 3445, 3335, 1650, 1620, 1520, 1380, 1350, 1290, 1150, 900, 820 cm⁻¹. ¹H NMR (DMSO-d₆, 100 MHz): $\delta = 4.35$ (br s, 2H), 7.1-7.35 (m, 6H), 7.4-7.6 (m, 5H), 7.7 (br s, 2H). MS (*m*/z): 317 (M⁺), 215, 213, 173, 171, 134,

Synthesis of 4,7-Diphenylfuro[3,2-*e*][1,2,3,4] tetraazolo[1,5-*a*]pyrimidine-5(4*H*)-imine 4

To a stirred cold (0-5 °C) suspension of 2-hydrazino-3,6diphenylfuro[2,3-*d*]pyrimidine-4(3*H*)-imine **3** (0.32 g, 1 mmol) in glacial acetic acid (10 ml), a solution of sodium nitrite (0.07 g, 1 mmol) in water (5 ml) was added dropwise. After stirring for 10 min. at room temperature, the resulted solid was filtered off, washed thoroughly with water and recrystallized from ethanol to give compound **4** in 85% yields as pale yellow needles; m.p.: 230-231 °C; IR (KBr): v = 3300, 2260, 2250, 1660, 1620, 1550, 1510, 1460, 1380, 1300, 1250, 750, 700 cm⁻¹. ¹H NMR (DMSO-d₆, 100 MHz): $\delta = 7.3-7.7$ (m, 5H), 7.7-8.0 (m, 6H), 8.7 (br s, 1H). MS (*m/z*): 328 (M⁺), 327, 316, 302, 283, 281, 267, 249, 235, 223, 207, 191, 183, 169, 147, 140, 121, 105, 91, 81, 71 (base peak), 57.

General Procedure for the Synthesis of Furo [3',2':5,6]pyrimido[2,1-*c*][1,2,4]triazines 5-8

A solution of 2-hydrazino-3,6-diphenylfuro[2,3-*d*] pyrimidine-4(3*H*)-imine **3** (0.32 g, 1 mmol), α -halo ketone (1 mmol), and a drop glacial acetic acid (0.1 ml) in DMF (15 ml) was heated in 90 °C for 24 h. After the completion of the reaction, water (50 ml) was added, the resulted solid filtered off, washed thoroughly with water and recrystallized from ethanol to give compounds (**5-8**) in 60-95 % yields.

2,5,9-Triphenyl-5,7-dihydro-4H-Furo[3',2':5,6] pyrimido[2,1-c][1,2,4]triazin-4-imine 5. was obtained from phenacyl bromide in 95% yield; white solids; m.p.: 257-258 °C; IR (KBr): v = 3300, 1630, 1600, 1580, 1490, 1450, 1380, 1320, 1220, 1180, 1150, 1070, 1020, 920, 750, 700 cm^{-1. 1}H NMR (DMSO-d₆, 100 MHz): $\delta = 4.95$ (br s, 1H, NH), 7.4-7.9 (m, 15H), 8.05 (d, 2H, J = 8 Hz). MS (m/z): 418, 417 (M⁺), 386, 367, 359, 344, 335, 316, 299, 288, 271 (base peak), 255, 243, 227, 213, 184, 155, 140, 127, 105, 77.

9-(4-Methoxyphenyl)-2,5-diphenyl-5,7-Dihydro-4*H*-**Furo[3',2':5,6]pyrimido[2,1-***c*]**[1,2,4]triazin-4-imine 6.** was obtained from 4-methoxy-phenacyl bromide in 90% yield; white solids; m.p.: 262-263 °C; IR (KBr): $v = 3300, 2950, 1650, 1600, 1550, 1490, 1450, 1390, 1280, 1220, 1180, 1050, 850, 800, 700 cm⁻¹. ¹H NMR (DMSO-d₆, 100 MHz): <math>\delta = 3.85$ (s, 3H), 4.90 (br s, 1H, NH), 7.1 (d, 2H, J = 8 Hz), 7.5 (m, 4H), 7.6-7.9 (m, 8H), 8.05 (d, 2H, J = 8 Hz). MS (m/z): 449, 447 (M⁺), 434, 409, 393, 378, 365, 344, 332, 319, 303, 287, 273, 261, 242, 231, 216, 204, 184, 159, 144, 135 (base peak), 116, 107, 93, 77. Anal. Calcd. for C₂₇H₂₁N5O₂: C, 72.47; H, 4.73; N, 15.65. Found: C, 72.75; H, 4.35; N, 15.56.

9-(4-Bromophenyl)-2,5-diphenyl-5,7-Dihydro-4H-Furo [3',2':5,6]pyrimido[2,1-*c*][1,2,4]triazin-4-imine 7. was obtained from 4-bromo-phenacyl bromide in 95% yield; white solids; m.p.: 207-208 °C; IR (KBr): v = 3300, 1640, 1600, 1580, 1490, 1450, 1370, 1320, 1250, 1220, 1180, 1070, 1020, 850, 750, 700 cm⁻¹. ¹H NMR (DMSO-d₆, 100 MHz): $\delta = 4.90$ (br s, 1H, NH), 7.45 (m, 4H), 7.55-8.10 (m, 12H), 9.50 (br s, 1H, NH). MS (*m*/*z*): 449, 496 (M⁺), 434, 409, 393, 378, 365, 344, 332, 319, 303, 287, 273, 261, 242, 231, 216, 204, 184, 159, 144, 135 (base peak), 116, 107, 93, 77.

9-Methyl-2,5-Diphenyl-5,7-dihydro-4H-Furo[3',2':5,6] **pyrimido**[2,1-*c*][1,2,4]triazin-4-imine 8. was obtained from chloroacetone in 60% yield; shining yellow needled; m.p.: 217-218 °C; IR (KBr): v = 3400, 3100, 2950, 1660, 1600,1510, 1480, 1450, 1370, 1250, 1150, 1050, 780, 700 cm⁻¹. ¹H-NMR (DMSO-d₆, 100 MHz): $\delta = 2.3$ (s, 3H), 4.25 (br s, 1H, NH), 7.5 (m, 4H), 7.75 (m, 8H), 8.0 (br s, 1H, NH). MS (*m*/z): 357, 355 (M⁺), 333, 332 (base peak), 273, 183, 77.

RESULTS AND DISCUSSION

4-imino-3,6-diphenyl-3,4-dihydrofuro[2,3-d] The pyrimidine-2(1H)-thione 1 reacted with methyl iodide in 5% aqueous NaOH at room temperature to produce the methylthio-pyrimidine derivative 2 in 95% yields. The 1 H NMR spectrum of compound 2 in CDCl₃ showed a singlet at 2.50 for methylthio group. Nucleophilic displacement of methylthio group with hydrazine hydrate was carried out using ethanol as solvent to afford 2-hydrazino-3,6-diphenylfuro[2,3d]pyrimidine-4(3H)-imine 3 in 90% yield. The long duration of reactions (24 h) could be explained by hindrance to nucleophilic attack in the 2-position of the 3-substituted pyrimidine rings. However, direct displacement of thione group of 1 with hydrazine hydrate was achieved in moderate yield (75%). The formation of 3 was confirmed by the presence of NH and NH₂ signals around 3400 and 3200 cm⁻¹ in the IR spectrum. The ¹H NMR spectrum of this compound in DMSO-d₆ showed D₂O-exchangable signals at 4.4 and 7.7



ppm for hydrazine and imino groups. Treatment of compound **3** with sodium nitrite in acetic acid at 0 °C, led to the formation of the furo[3,2-e][1,2,3,4]tetraazolo[1,5-a] pyrimidine **4** in 85% yield. This new ring system is in equilibrium with the 2-azido-3-substituted-furo[2,3-d] pyrimidine tautomer **4'** [17], which confirmed by a characteristic absorption of the azido group (2250 cm⁻¹) in IR spectrum. Also, the ¹H NMR spectra confirmed the assigned structure **4**.

The compounds **5-8** were obtained in good to high yields through the heterocyclization of **3** with some α -haloketones (chloroacetone and phenacyl bromide derivatives) in DMF at 90 °C. The structures of these new furo[3',2':5,6]pyrimido[2,1-c][1,2,4]triazines **5-8** were confirmed by spectral data. For example, the ¹H NMR spectrum of **6** in DMSO-d₆ showed two broad singlets (D₂O-exchangable) at 4.9 and 9.2 due to NH groups as well as two doublets at 7.1 and 8.0 corresponding to *p*-methoxy aryl hydrogens. Methoxy group protons showed a singlet at 3.85 ppm. Mass spectrum of the compound showed the molecular ion peak (M⁺) at *m*/*z* 447. Also this compound gave satisfactory elemental analysis data.

In conclusion, in this paper, the synthesis of two novel heterocyclic ring systems, furo[3',2':5,6]pyrimido[2,1-*c*] [1,2,4]triazines and furo[3,2-*e*][1,2,3,4]tetraazolo[1,5-*a*] pyrimidine, through heterocyclization of the 2-hydrazino-furo[2,3-*d*]pyrimidines with α -haloketones and nitrous acid respectively in high yields are described.

ACKNOWLEDGMENTS

We are grateful to Ferdowsi University of Mashhad Research Council for their financial support of this work.

Rahimizadeh et al.

REFERENCES

- M.M.H. Bhuiyan, K.M.M. Rahman, M.K. Hossain, M.A. Rahim, M.I. Hossain, Croat. Chem. Acta 78 (2005) 633.
- [2] C.G. Dave, R.D. Shah, Molecules 7 (2002) 554.
- a) Z. Janeba, J. Balzarini, G. Andrei, R. Snoeck, E. De Clercq, M.J. Robins, J. Med. Chem. 48 (2005) 4690; b)
 F. Amblard, V. Aucagne, P. Guenot, R.F. Schinazi, L.A. Agrofoglio, Bioorg. Med. Chem. 12 (2005) 1239.
- [4] a) A. Gangiee, Y. Zeng, J.J. McGuire, R.L. Kisliuk, J. Med. Chem. 48 (2005) 5329; b) A. Gangiee, Y. Zeng, J.J. McGuire, F. Mehraein, R.L. Kisliuk, J. Med. Chem. 47 (2004) 6893.
- [5] a) A. Gangjee, Y. Zeng, M. Ihnat, L.A. Warnke, D.W. Green, R.L. Kisliuk, F.-T. Lin, Bioorg. Med. Chem. 13 (2005) 5475; b) A. Gangiee, Y. Zeng, J.J. McGuire, R.L. Kisliuk J. Med. Chem. 43 (2000) 3125.
- [6] M.J. Robins, K. Miranda, V.K. Rajwanshi, M.A. Peterson, G. Andrei, R. Snoeck, E. De Clercq, J. Balzarini, J. Med. Chem. 49 (2006) 391.
- [7] E.F. DiMauro, J. Newcomb, J.J. Nunes, J.E. Bemis,C. Boucher, J.L. Buchanan, W.H. Buckner, A. Cheng, T. Faust, F. Hsieh, X. Huang, J.H. Lee, T.L. Marshall, M.W. Martin, D.C. McGowan, S. Schneider, S.M. Turci, R.D. White, X. Zhu, Bioorg. Med. Chem. Lett. 17 (2007) 2305.
- [8] M. Hayakawa, H. Kaizawa, H. Moritomo, T. Koizumi, T. Ohishi, M. Yamano, M. Okada, M. Ohta, S.-I. Tsukamoto, F.I. Raynaud, P. Workman, M.D.

Waterfield, P. Parker, Bioorg. Med. Chem. Lett. 17 (2007) 2438.

- [9] A. Martin-Kohler, J. Widmer, G. Bold, T. Meyer, U. Séquin, P. Traxler, Helv. Chem. Acta 87 (2004) 956.
- [10] Z.A. Hozien, A.A. Abdel-Wahab, K.M. Hassan, F.M. Atta, S.A. Ahmed, Pharmazie 52 (1997) 753.
- [11] a) E.S. Hand, D.C. Baker, Can. J. Chem. 62 (1984)
 2570; b) J.A. Montgomery, A.G. Laseter, K. Hewson, J. Heterocycl. Chem. 11 (1974) 211.
- [12] G. Franco, L. Maria, P. Giueseppe, S.H. Lee, J. Heterocycl. Chem. 26 (19890 613.
- [13] C.J. Shishoo, K.S. Jain, J. Heterocycl. Chem. 29 (1992) 883.
- [14] a) M. Rahimizadeh, M. Nikpour, M. Bakavoli, J. Heterocycl. Chem. 44 (2007) 463; b) M. Bakavoli, F.A. Sani, A. Davoodnia, M. Roshani, F. Pirouzi, Heterocyclic Commun. 13 (2007) 371; c) M. Bakavoli, B. Reihani, M. Rahimizadeh, M. Nikpour, Phosphorus Sulfur Silicon 181 (2006) 99; d) A. Davoodnia, M. Bakavoli, A. Vahedinia, M. Rahimizadeh, M. Roshani, Heterocycles 68 (2006) 801; e) M.M. Heravi, M. Bakherad, M. Rahimizadeh, M. Bakavoli, M. Ghassemzadeh, Heterocyclic Commun. 10 (2004) 335.
- [15] M. Bakavoli, M. Rahimizadeh, Z. Gordi, J. Chem. Res. (2008) 564.
- [16] M. Bakavoli, M. Rahimizadeh, Z. Gordi, Heterocycles 75 (2008) 2549.
- [17] Z.H. Khalil, A.A. Geies, Phosphorus Sulfur Silicon 60 (1991) 223.