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SYNTHESIS OF NOVEL 3,6-DISUBSTITUTED FURO[2,3-*d*]PYRIMIDINES

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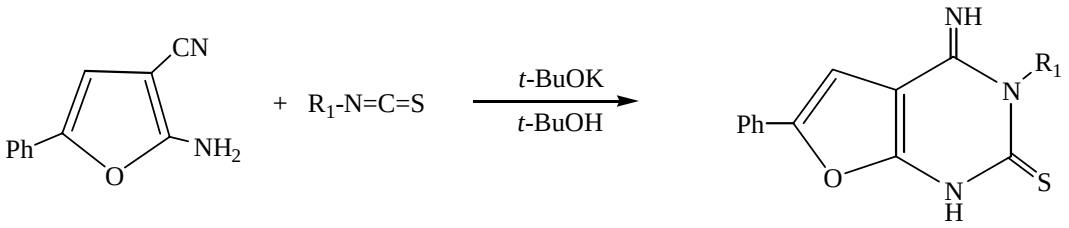
Abstract – One-pot base catalyzed heterocyclization of 2-amino-5-phenyl-3-furancarbonitrile with various isothiocyanates afforded the novel furo[2,3-*d*]pyrimidine derivatives in high yields.

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 receptor 2) and EGFR (epidermal growth factor receptor)[9] inhibitors. Various methods for the synthesis of furo[2,3-*d*]pyrimidines have been reported[10] in the literature that mainly involve cyclocondensation of 2-aminofuran derivatives with various electrophilic reagents such as formic acid,[7,11] formamide,[8,9] orthoesters,[12,13] carbon disulfide,[14] thiourea[15] and isothiocyanates.[16] In pursuing our work on the synthesis of polyheterocyclic systems,[17] we wish to report a convenient one-pot synthesis of new 3-aryl-4-imino-6-phenyl-3,4-dihydrofuro[2,3-*d*]pyrimidin-2(1*H*)-thiones (**3a-f**) as a key precursor for the synthesis of various furans polyheterocyclic compounds.

In the present work we have employed heterocyclization of 2-amino-5-phenyl-3-furancarbonitrile (**1**) with aryl- and alkyl isothiocyanates for the synthesis of new 3,6-disubstitutedfuro[2,3-*d*]pyrimidines (**3a-f**). Cyclocondensation of 2-amino-5-phenyl-3-furancarbonitrile (**1**) with aryl and alkyl isothiocyanates (**2a-f**) in the presence of potassium *t*-butoxide in *t*-butanol under reflux gave products identified as 3-aryl-4-imino-6-phenyl-3,4-dihydrofuro[2,3-*d*]pyrimidin-2(1*H*)-thiones (**3a-f**) as shown in **Scheme 1**.



1 **2a-f** **3a-f**

a) R_1= Ph

b) R_1= 4-Cl-C_6H_4

c) R_1= 4-Br-C_6H_4

d) R_1= 3-Br-C_6H_4

e) R_1= 2-Br-C_6H_4

f) R_1= Et

Scheme 1

The structures of new compounds were confirmed by spectral data. For example, the IR spectrum of **3f** was devoid of the stretching vibration bands at 3375, 3280 and 2180 cm^{-1} for NH_2 and CN absorption of the precursor but instead showed new absorption bands at 3400, 1640 and 1270 cm^{-1} for NH, C=N and C=S groups, respectively. The ^{1}H-NMR spectra in DMSO-d_6 showed two broad singlets at 4.65 and 8.6 due to NH groups as well as a triplet (1.25) and a quartet (3.5) corresponding to ethyl group and the characteristic signals at 7.2-7.7 for phenyl group. Furan proton showed a singlet at 7.05 ppm. Mass spectrum of the compound showed the molecular ion peak at *m/z* 271 and 273 corresponding to the (M^+) and (M^++2). Also this compound gave satisfactory elemental analysis data.

In conclusion, we have developed a facile method for one pot synthesis of new 3-aryl-4-imino-6-phenyl-3,4-dihydrofuro[2,3-*d*]pyrimidin-2(1*H*)-thiones through base-catalyzed cyclocondensation of 2-amino-5-phenyl-3-furancarbonitrile with aryl- and alkyl isothiocyanates. The efficiency of the present work is apparent from high yields with the lack of side product. It is noteworthy that the present method is preferred over a similar reported method because of its relative higher yields and the lack [16] of Dimroth rearrangement.

EXPERIMENTAL

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 analyses were obtained on a Thermo Finnigan Flash EA microanalyzer. 2-Amino-5-phenyl-3-furonitrile (**1**) is a known compound and was prepared according to literature.[18]

1. General procedure for the synthesis of 3-aryl-4-imino-6-phenyl-3,4-dihydrofuro[2,3-*d*] pyrimidin-2(1*H*)-thiones 3a-f

To a solution of the 2-amino-5-phenyl-3-furancarbonitrile (**1**) (1.84 g, 10 mmol) and potassium *t*-butoxide (1.68 g, 15 mmol) in *t*-butanol (40 mL), aryl or alkyl isothiocyanate (**2a-f**) (12 mmol) was added. The reaction mixture was heated under reflux for 4 h. After the completion of the reaction (monitored by TLC $CHCl_3$: MeOH 9:1), the solvent was evaporated, the residue was dissolved in water (20 mL) and subsequently neutralized by 1N HCl. The crude product was filtered, washed with water and recrystallized from EtOH to give compounds (**3a-f**) in 75-92 % yields.

1.1. 4-Imino-3,6-diphenyl-3,4-dihydrofuro[2,3-*d*]pyrimidin-2(1*H*)-thione (3a). Compound **3a** was obtained in 76 % yield; shining yellow solids; mp 220-221 ˚C; IR (KBr) : 3400, 1640, 1275 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 100 MHz) δ: 3.5 (br s, 1H, NH), 7.1-7.7 (m, 11H), 8.3 (br s, 1H, NH). MS (m/z): 319 (M^+), 194, 135, 105, 93, 77 (base peak), 65, 51. Anal. Calcd for $C_{18}H_{13}N_3OS$: C, 67.69; H, 4.10; N, 13.16; S, 10.04. Found: C, 67.57; H, 3.97; N, 13.10; S, 9.89.

1.2. 3-(4-Chlorophenyl)-4-imino-6-phenyl-3,4-dihydrofuro[2,3-*d*]pyrimidin-2(1*H*)-thione (3b). Compound **3b** was obtained in 90 % yield; white solids; mp 212-213 ˚C; IR (KBr) : 3450, 1650, 1275 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 100 MHz) δ: 4.2 (br s, 1H, NH), 7.15 (s, 1H), 7.2-8.0 (m, 9H), 8.4 (br s, 1H, NH). MS (m/z): 353 (M^+, base peak), 295, 169, 140, 127, 105, 77. Anal. Calcd for $C_{18}H_{12}ClN_3OS$: C, 61.10; H, 3.42; N, 11.88; S, 9.06. Found: C, 61.02; H, 3.28; N, 11.84; S, 8.91.

1.3. 3-(4-Bromophenyl)-4-imino-6-phenyl-3,4-dihydrofuro[2,3-*d*]pyrimidin-2(1*H*)-thione (3c). Compound **3c** was obtained in 88 % yield; white solids; mp 240-242 ˚C; IR (KBr) : 3450, 1645, 1270 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 100 MHz) δ: 4.2 (br s, 1H, NH), 7.20 (s, 1H), 7.41 (AB q, 4H, $\Delta\nu/J$ = 2.5, J = 6 Hz), 7.5-7.8 (m, 5 H), 8.6 (br s, 1H, NH). MS (m/z): 399 (M^++2), 397 (M^+, base peak), 341, 339, 260, 259, 173, 159, 140, 130, 115, 105, 77, 63. Anal. Calcd for $C_{18}H_{12}BrN_3OS$: C, 54.28; H, 3.04; N, 10.55; S, 8.05. Found: C, 54.06; H, 2.97; N, 10.35; S, 7.82.

1.4. 3-(3-Bromophenyl)-4-imino-6-phenyl-3,4-dihydrofuro[2,3-*d*]pyrimidin-2(1*H*)-thione (3d). Compound **3d** was obtained in 86 % yield; yellow solids; mp 215-216 ˚C; IR (KBr) : 3450, 1650, 1270 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 100 MHz) δ: 3.4 (br s, 1H, NH), 7.0-7.9 (m, 10 H), 8.3 (br s, 1H, NH). MS (m/z): 399 (M^++2), 397 (M^+, base peak), 340, 339, 260, 259, 171, 158, 140, 130, 116, 103, 77, 51. Anal. Calcd. for $C_{18}H_{12}BrN_3OS$: C, 54.28; H, 3.04; N, 10.55; S, 8.05. Found: C, 54.09; H, 2.98; N, 10.43; S, 7.99.

1.5. 3-(2-Bromophenyl)-4-imino-6-phenyl-3,4-dihydrofuro[2,3-*d*]pyrimidin-2(1*H*)-thione (3e). Compound **3e** was obtained in 90 % yield; yellow solids; mp 185-186 ˚C; IR (KBr) : 3450, 1650, 1270 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 100 MHz) δ: 6.75 (s, 1H), 6.7-7.7 (m, 9H), 7.7 (br s, 1H, NH), 8.7 (br s, 1H,

NH). MS (m/z): 399 (M^++2), 397 (M^+, base peak), 341, 339, 260, 259, 170, 155, 140, 130, 114, 105, 77, 63. Anal. Calcd for $C_{18}H_{12}BrN_3OS$: C, 54.28; H, 3.04; N, 10.55; S, 8.05. Found: C, 53.94; H, 2.98; N, 10.83; S, 7.92.

1.6. 3-Ethyl-4-imino-6-phenyl-3,4-dihydrofuro[2,3-*d*]pyrimidin-2(1*H*)-thione (3f). Compound **3f** was obtained in 92 % yield; white solids; mp 246-245 ˚C; IR (KBr) : 3450, 1640, 1275 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 100 MHz) δ: 1.25 (t, 3H, *J* = 8 Hz), 3.45 (q, 2H, *J* = 8 Hz), 4.6 (br s, 1H, NH), 7.05 (s, 1H), 7.2-7.7 (m, 5H), 8.6 (br s, 1H, NH). MS (m/z): 273 (M^++2), 271 (M^+, base peak), 255, 243, 227, 213, 212, 185, 184, 155, 140, 127, 105, 77, 51. Anal. Calcd for $C_{14}H_{13}N_3OS$: C, 61.97; H, 4.83; N, 15.49; S, 11.82. Found: C, 62.01; H, 4.71; N, 15.33; S, 11.64.

REFERENCES

1. M. M. H. Bhuiyan, K. M. M. Rahman, M. K. Hossain, M. A. Rahim, and M. I. Hossain, *Croat. Chem. Acta*, 2005, **78**, 633.
2. C. G. Dave and R. D. Shah, *Molecules*, 2002, **7**, 554.
3. (a) Z. Janeba, J. Balzarini, G. Andrei, R. Snoeck, E. DeClercq, and M. J. Robins, *J. Med. Chem.*, 2005, **48**, 4690. (b) F. Amblard, V. Aucagne, P. Guenot, R. F. Schinazi, and L. A. Agrofoglio, *Bioorg. Med. Chem.*, 2005, **13**, 1239.
4. (a) A. Gangiee, Y. Zeng, J. J. McGuire, and R. L. Kisliuk, *J. Med. Chem.*, 2005, **48**, 5329. (b) Gangiee, Y. Zeng, J. J. McGuire, F. Mehraein, and R. L. Kisliuk, *J. Med. Chem.*, 2004, **47**, 6893.
5. (a) A. Gangjee, Y. Zeng, M. Ihnat, L. A. Warnke, D. W. Green, R. L. Kisliuk, and F.-T. Lin, *Bioorg. Med. Chem.*, 2005, **13**, 5475. (b) A. Gangiee, Y. Zeng, J. J. McGuire, and R. L. Kisliuk, *J. Med. Chem.*, 2000, **43**, 3125.
6. M. J. Robins, K. Miranda, V. K. Rajwanshi, M. A. Peterson, G. Andrei, R. Snoeck, E. DeClercq, and J. Balzarini, *J. Med. Chem.*, 2006, **49**, 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, and X. Zhu, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 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, and P. Parker, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 2438.
9. A. Martin-Kohler, J. Widmer, G. Bold, T. Meyer, U. Séquin, and P. Traxler, *Helv. Chem. Acta*, 2004, **87**, 956.
10. (a) D. Dauzonne and A. Adam-Launay, *Tetrahedron*, 1992, **48**, 3069. (b) R. G. Melik-Ogandzhanyan, V. E. Khachatryan, and A. S. Gapoyan, *Usp. Khim.*, 1985, **54**, 450.

11. J. I. Pyo, E. J. Hwang, C. S. Cheong, S.-H. Lee, S. W. Lee, I. T. Kim, and S. H. Lee, *Synthetic Metals*, 2005, **155**, 461.
12. Y. Miyazaki, J. Tang, Y. Maeda, M. Nakano, Y. Okamoto, A. T. Truesdale, D. F. Hassler, E. N. Nartey, D. R. Patrick, M. L. Ho, and K. Ozawa, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 1773.
13. R. M. Shaker, *ARKIVOC*, 2006, part (xiv), 68.
14. M. G. Testa, G. Perrini, U. Chiacchio, and A. Corsaro, *J. Chem. Res. (S)*, 1993, 302.
15. M. Kidwai, A. D. Mishra, and S. Saxena, *Indian J. Chem.*, 2005, **44B**, 581.
16. K. R. Jyothikumari and K. N. Rajasekharan, *J. Indian Chem. Soc.*, 1991, **68**, 660.
17. (a) M. Bakavoli, F. A. Sani, A. Davoodnia, M. Roshani, and F. Pirouzi, *Heterocyclic Commun.*, 2007, **13(6)**, 371. (b) M. Bakavoli, B. Reihani, M. Rahimizadeh, and M. Nikpour, *Phosphorus Sulfur Silicon*, 2006, **181**, 99. (c) A. Davoodnia, M. Bakavoli, A. Vahedinia, M. Rahimizadeh, and M. Roshani, *Heterocycles*, 2006, **68**, 801. (d) M. M. Heravi, M. Bakherad, M. Rahimizadeh, M. Bakavoli, and M. Ghassemzadeh, *Heterocyclic Commun.*, 2004, **10**, 335.
18. X. Feng, J.-C. Lancelot, A.-C. Gillard, H. Landelle, and S. Rault, *J. Heterocycl. Chem.*, 1998, **35**, 1313.