Chemistry of Heterocyclic Compounds, Vol. 45, No. 3, 2009

REACTION OF 2-ALKYLTHIO-6-AMINO-PYRIMIDIN-4(3H)-ONES WITH ETHYL BROMOPYRUVATE. SYNTHESIS OF FURO-[2,3-*d*]-PYRIMIDINE AND FURO[3,2-*e*]IMIDAZO-[1,2-*c*]PYRIMIDINE CARBOXYLATES

V. Masevicius[1], G. Petraityte[1], S. Tumkevicius[1]*

Reaction of 2-alkylthio-6-aminopyrimidin-4(3H)-ones with ethyl bromopyruvate to give ethyl 2-alkylthio-4-aminofuro[2,3-d]pyrimidine-5-carboxylates has been shown to proceed under neutral or acidic conditions. The obtained furo[2,3-d]pyrimidines underwent further cyclocondensation reaction with ethyl bromopyruvate to afford diethyl 5-alkylthiofuro[3,2-e]imidazo[1,2-c]pyrimidine-2,9-dicarboxylates.

Keywords: furo[3,2-*e*]imidazo[1,2-*c*]pyrimidines, furo[2,3-*d*]pyrimidines, pyrimidin-4(3H)-ones, cyclization.

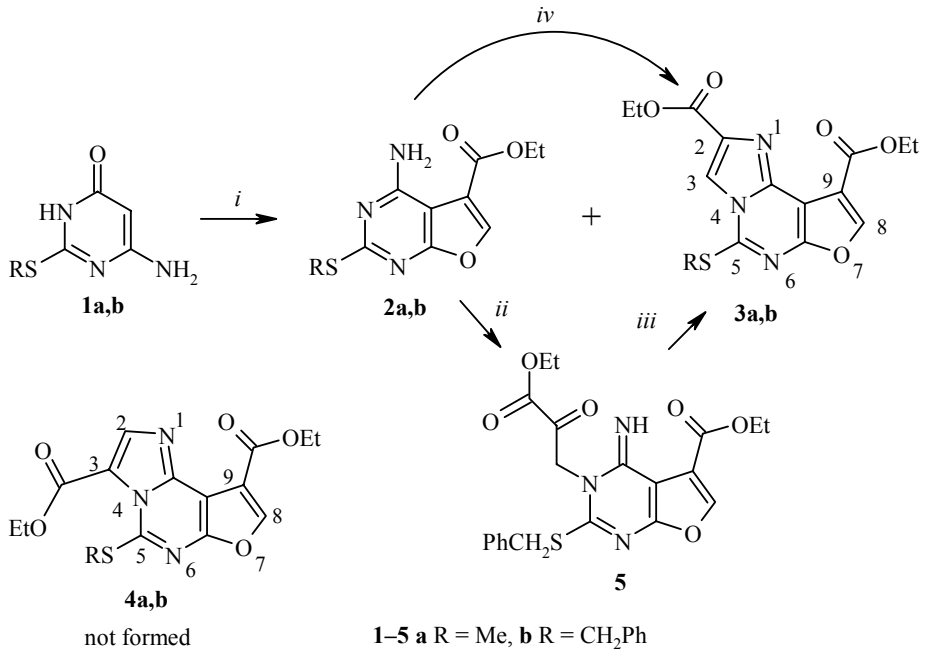
Recently we showed that esters of thieno[2,3-*d*]pyrimidine-6-carboxylic acids are useful precursors for the synthesis of analogues of folic acid and other 6-(arylamino)methylthieno[2,3-*d*]pyrimidines – potential inhibitors of dihydrofolate reductase [1, 2]. Continuing our work on the synthesis of fused heterocycles with anticipated biological and pharmaceutical activities we present herein some findings on the synthesis of 2-alkylthio-4-aminofuro[2,3-*d*]pyrimidine-5-carboxylates by the reaction of 2-alkylthio-6-aminopyrimidin-4(3H)-ones (**1**) with ethyl bromopyruvate. There are only few examples of such an approach to furo-[2,3-*d*]pyrimidine-5-carboxylates [3, 4] in the literature and they show that such a cyclocondensation reaction can be performed under basic conditions. However, attempts to apply the described procedures for the synthesis of **3a**,**b**, using triethylamine or K_2CO_3 as basic reagents, failed. Nevertheless, it was found that the cyclocondensation reaction of **1a**,**b** with an equivalent amount of ethyl bromopyruvate proceeds under neutral or acidic conditions to give furopyrimidines **2a**,**b** in good yields. Formation of the corresponding pyrrolo-[2,3-*d*]pyrimidines was not observed. When an excess of ethyl bromopyruvate was used and the reaction was carried out at room temperature together with furopyrimidines **2,** formation of furo[3,2-*e*]imidazo[1,2-*c*]pyrimidines **3** was also observed. For example, **3b** was isolated as a side product (0.4%) from the reaction of **1b** with 2 eq. of ethyl bromopyruvate.

* To whom correspondence should be addressed, e-mail: sigitas.tumkevicius@chf.vu.lt.

[1]Vilnius University Department of Organic Chemistry, Vilnius LT-03225, Lithuania.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 440-443, March, 2009. Original article received February 17, 2009.

Compounds **3a**,**b** in reasonable yields were obtained by heating **2a**,**b** with ethyl bromopyruvate in toluene or *o*-xylene. Performing reaction of **2b** with ethyl bromopyruvate at room temperature in dichloromethane allowed us to isolate a small amount of intermediate **5** which under crystallization from 2-propanol quantitatively underwent conversion to furo[3,2-*e*]imidazo[1,2-*c*]pyrimidine **3b**. Reaction of **2a**,**b**



Reagents and conditions: *i* – $BrCH_2COCO_2Et$, DMF, r.t.; *ii* – $BrCH_2COCO_2Et$, CH_2Cl_2, r.t.; *iii* – 2-propanol, Δ; *iv* – $BrCH_2COCO_2Et$, toluene or *o*-xylene, Δ

with ethyl bromopyruvate can give either compounds **3a**,**b** or their isomers **4a**,**b**. Notable difference in the NMR spectra between these compounds must be chemical shifts of imidazole carbon atoms with attached proton (C-3 in compounds **3a**,**b** and C-2 in compounds **4a**,**b**). The signal for this carbon in the ^{13}C NMR spectra of the synthesized compounds was clearly identified from ^{13}C NMR DEPT (45°) spectra. To make a choice between possible products of this reaction, calculations of the NMR spectra were performed with Gausian 98 program [5] using the DFT B3LYP method with 6-31G(d,p) basis set. Chemical shift of the calculated ^{13}C NMR spectrum for C-3 of compound **3a** was found to be 117.7 ppm. This value is in good match with δ_{exp}(C-3) = 115.2 ppm of the synthesized furo[3,2-*e*]imidazo[1,2-*c*]pyrimidine-2,9-dicarboxylate **3a**, whereas the calculated value of chemical shift for C-2 of compound **4a** is 146.7 ppm. Analogous results were also obtained for compound **3b**: δ_{exp}(C-3) = 115.3 ppm, δ_{calc}(C-3) = 118.4 ppm, while δ_{calc}(C-2) for compound **4b** is 145.9 ppm. Thus, it can be unambiguously concluded that diethyl furo[3,2-*e*]imidazo[1,2-*c*]pyrimidine-2,9-dicarboxylates **3a**,**b** are formed in the reaction of 2-alkylthio-4-aminofuro[2,3-*d*]pyrimidine-5-carboxylates **2a**,**b** with ethyl bromopyruvate.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were run on a Perkin–Elmer FT-IR spectrophotometer Spectrum BX II in nujol. ^1H and ^{13}C NMR spectra were recorded on a Varian Unity Inova spectrometer (300 and 75 MHz, respectively) in $CDCl_3$ using residual $CHCl_3$ signals (7.29 and

77.3 ppm for ^{1}H and ^{13}C NMR spectra, respectively) as internal standard. Elemental analyses were performed at the Elemental Analysis Laboratory of the Department of Organic Chemistry of Vilnius University. TLC was performed with silica gel 60 F254 aluminum plates (Merck), visualisation with UV light.

Ethyl 4-Amino-2-methylthiofuro[2,3-*d*]pyrimidine-5-carboxylate (2a). A mixture of compound **1a** [6] (9.06 g, 57.7 mmol), DMF (20 ml) and 90% ethyl bromopyruvate (8 ml, 57.38 mmol) was stirred at room temperature for 24 h. Then water was added and the resulting precipitate was filtered off, washed with diethyl ether, and recrystallized to give 11.8 g (81%) of compound **2a**; mp 167–168.5°C (benzene). IR spectrum, ν, cm^{-1}: 3370, 3295, 3142 (NH_2), 1702 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.42 (3H, t, *J* = 7.2, CH_3); 2.60 (3H, s, CH_3S); 4.41 (2H, q, *J* = 7.2, CH_2); 5.80 (1H, s, NH); 7.91 (1H, s, NH); 7.97 (1H, s, CH). ^{13}C NMR spectrum, δ, ppm: 14.4; 14.5; 61.9; 95.1; 114.2; 145.8; 158.2; 164.1; 168.3; 169.6. DEPT (45º) spectrum, δ, ppm: 14.3; 14.5; 62.0; 145.8. Found, %: C 47.61; H 4.46; N 16.79. $C_{10}H_{11}N_3O_3S$. Calculated, %: C 47.42; H 4.38; N 16.59.

Ethyl 4-Amino-2-benzylthiofuro[2,3-*d*]pyrimidine-5-carboxylate (2b) was synthesized from **1b** [7] according to the procedure described for compound **2a**. Yield 58%. When 1–2 drops of conc. H_2SO_4 were added to the reaction mixture, compound **2b** was isolated in 57% yield; mp 184–185 °C (benzene). IR spectrum, ν, cm^{-1}: 3381, 3297 (NH_2), 1708 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.34 (3H, t, *J* = 7.2, CH_3); 4.42 (2H, q, *J* = 7.2, CH_2); 4.46 (2H, s, CH_2S); 5.60 (1H, s, NH); 7.25–7.38 (3H, m, C_6H_5); 7.46–7.52 (2H, m, C_6H_5); 7.92 (1H, s, NH); 7.98 (1H, s, CH). ^{13}C NMR spectrum, δ, ppm: 14.5; 35.6; 62.0; 95.5; 114.3; 127.4; 128.7; 129.4; 137.9; 145.8; 158.4; 164.0; 168.3; 168.7. DEPT (45º) spectrum, δ, ppm: 14.5; 35.6; 62.0; 127.4; 128.7; 129.4; 145.9. Found, %: C 58.74; H 4.73; N 12.45. $C_{16}H_{15}N_3O_3S$. Calculated, %: C 58.34; H 4.59; N 12.76.

Diethyl 5-Methylthiofuro[3,2-*e*]imidazo[1,2-*c*]pyrimidine-2,9-dicarboxylate (3a). A mixture of compound **2a** (0.25 g, 0.99 mmol), toluene (50 ml), and 90% ethyl bromopyruvate (0.149 ml, 0.23 g, 1.2 mmol) was refluxed using a Dean–Stark trap for 9 h. Then toluene was evoparated to dryness and the residue recrystallized to give 0.14 g (41%) of compound **3a**; mp 215–216.5°C (benzene). IR spectrum, ν, cm^{-1}: 1712, 1703 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.49 (3H, t, *J* = 7.2, CH_3); 1.54 (3H, t, *J* = 7.2, CH_3); 2.89 (3H, s, SCH_3); 4.46–4.55 (4H, m, $2CH_2$); 8.22 (1H, s, CH); 8.28 (1H, s, CH). ^{13}C NMR spectrum, δ, ppm: 14.4; 14.5; 61.7; 61.8; 100.9; 115.2; 116.1; 138.2; 141.7; 146.8; 149.7; 157.4; 161.8; 162.9. DEPT (45º) spectrum, δ, ppm: 14.4; 14.5; 61.7; 61.8; 115.2; 146.8. Found, %: C 51.43; H 4.24; N 11.85. $C_{15}H_{15}N_3O_5S$. Calculated, %: C 51.57; H 4.33; N 12.03.

Diethyl 5-Benzylthiofuro[3,2-*e*]imidazo[1,2-*c*]pyrimidine-2,9-dicarboxylate (3b) was synthesized according to the procedure described for compound **3a**, using *o*-xylene as a solvent. Reaction time 2 h. Yield 45%; mp 154–155°C (methanol). IR spectrum, ν, cm^{-1}: 1739, 1713 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.48 (3H, t, *J* = 7.2, CH_3); 1.54 (3H, t, *J* = 7.2, CH_3); 4.42–4.56 (4H, m, $2CH_2$); 4.74 (2H, s, CH_2S); 7.35–7.42 (3H, m, C_6H_5); 7.50–7.56 (2H, m, C_6H_5); 8.24 (1H, s, CH); 8.25 (1H, s, CH). ^{13}C NMR spectrum, δ, ppm: 14.4; 14.5; 36.4; 61.7; 61.8; 101.2; 115.3; 116.1; 128.5; 129.2; 129.6; 135.1; 138.2; 141.8; 146.9; 148.7; 157.2; 161.8; 162.9. DEPT (45º) spectrum, δ, ppm: 14.4; 14.5; 36.4; 61.7; 61.8; 115.2; 128.5; 129.2; 129.6; 146.9. Found, %: C 60.05; H 4.43; N 9.82. $C_{21}H_{19}N_3O_5S$. Calculated, %: C 59.28; H 4.50; N 9.88.

Ethyl 2-Benzylthio-3-(3-ethoxy-2,3-dioxopropyl)-4-imino-3,4-dihydrofuro[2,3-*d*]pyrimidine-5-carboxylate (5) starts melting at 119ºC, then solidifies, with final mp 154–155ºC. IR spectrum, ν, cm^{-1}: 1750 (sh), 1736, 1704 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.48–1.36 (6H, m, $2CH_3$); 4.38–4.57 (4H, m, $2CH_2$); 4.60 (1H, d, *J* = 12.9, $COCH_2N$); 4.75 (1H, s, CH_2S); 4.79 (1H, s, CH_2S); 5.20 (1H, dd, *J* = 12.9, *J* = 2, $COCH_2N$); 7.36–7.42 (3H, m, C_6H_5); 7.44–7.5 (2H, m, C_6H_5); 8.15 (1H, s, CH); 9.2 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 14.3; 14.5; 37.2; 57.2; 63.2; 64.1; 90.0; 95.1; 115.3; 128.8; 129.3; 129.7; 133.7; 148.1; 153.3; 160.5; 161.9; 166.2; 166.3.

REFERENCES

1. S. Tumkevicius, M. Dailide, *J. Heterocycl. Chem*., **42**, 1305 (2005).
2. S. Tumkevicius, M. Dailide, *J. Heterocycl. Chem.*, **43**, 1629 (2006).

3. C. L. Gibson, K. Ohta, K. Paulini, C. J. Suckling, *J .Chem. Soc.*, *Perkin Trans. 1*, 3025 (1998).
4. C. L. Gibson, K. Paulini, C. J. Suckling, *Chem. Commun.*, 371 (1997).
5. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Jr. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, N. Rega, P. Salvador, J. J. Dannenberg, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, J. A. Pople, **2002** Gaussian 98, Revision A11.3. *Gaussian Inc*, Pittsburgh PA.
6. N. Zambeli, D. Kolban, *Acta Pharm. Jugoslav*., **21**, 91 (1971).
7. C. L. Gibson, S. La Rosa, K. Ohta, P. H. Boyle, F. Leurquin, A. Lemacon, C. J. Suckling, *Tetrahedron*, **60**, 943 (2004).