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New transformations of 2-methylsulfanyl-4,6-dichloropyrimidine-5-carbaldehyde involving enamines: synthesis of condensed azines

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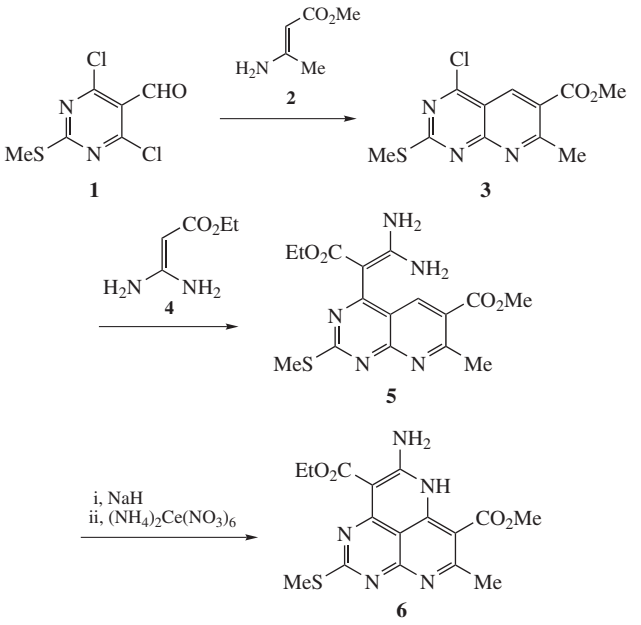
The reaction between 4,6-dichloropyrimidine-5-carbaldehyde and methyl 3-aminocrotonate leads to pyrido[2,3-*d*]pyrimidine which reacts with ethyl 3,3-diaminoacrylate to give pyrimido[4,5,6-*de*][1,6]naphthyridine derivative. The structure of the latter was confirmed by XRD analysis.

Aromatic aldehydes containing a labile halogen atom at *ortho*-position are commonly used in synthesis of condensed heterocycles.[1–9] Previously we reported the reaction of aldehyde **1**[10] (see Scheme 1) and similarly structured ketones, nitriles and esters with type **4** enediamines.[11] These transformations lead to pyrido[4,3-*d*]pyrimidines formed as a result of replacement of halogen atom by α-carbon of enediamine and binding between the nitrogen atom and carbonyl carbon atom.

In this work we determined that the reaction of aldehyde **1** and enamine **2** proceeds with another chemoselectivity. As a result, pyrido[2,3-*d*]pyrimidine **3**† is formed by replacement of halogen atom with nitrogen atom and binding between the α-carbon of enamine and formyl group (Scheme 1).

Apparently, this process is catalyzed by acid (HCl), which is produced during the reaction. Addition of catalytic amount of HCl at the beginning of the reaction increases its rate significantly. The role of acid is probably restricted to protonating of pyrimidine **1** nitrogen atom, which facilitates aromatic nucleophilic substi-



Scheme 1

† The NMR spectra were recorded on a Bruker Avance III 400 spectrometer (400.13 and 100.61 MHz for ^{1}H and ^{13}C, respectively; the residual solvent peaks were used as internal standards: 7.26 and 2.50 ppm for ^{1}H in $CDCl_3$ and DMSO-d_6, respectively, 39.7 ppm for ^{13}C in DMSO-d_6). Mass spectra were recorded on a Bruker micrOTOF spectrometer (ESI). Melting points were determined in open capillary tubes on a Stuart SMP30 instrument.

*Methyl 4-chloro-7-methyl-2-(methylsulfanyl)pyrido[2,3-*d*]pyrimidine-6-carboxylate* **3**. A mixture of aldehyde **1** (540 mg, 2.42 mmol) and methyl 3-aminocrotonate **2** (610 mg, 5.30 mmol) in absolute DMF (2 ml) was stirred at room temperature for 20 min, cooled to 0 °C, filtered, washed with water and dried to afford 363 mg (54%) of **3**, beige powder, mp 175–177 °C (CH_2Cl_2–hexane, decomp.). ^{1}H NMR ($CDCl_3$) δ: 2.76 (s, 3H, SMe), 3.08 (s, 3H, 7-Me), 4.02 (s, 3H, CO_2Me), 8.99 (s, 1H, H^5). ^{13}C NMR (DMSO-d_6) δ: 15.2 (SMe), 26.6 (7-Me), 53.2 (CO_2*Me*), 114.3 (C^{4a}), 125.3 (C^6), 139.4 (C^5), 159.5 (C^{8a}), 162.8 (C^4), 165.6 (*C*O_2Me), 169.7 (C^7), 175.5 (C^2). Signals assignment was made using fully coupled ^{13}C spectrum. The structure of pyrido[2,3-*d*]pyrimidine (rather than [4,3-*d*]) is confirmed by HOESY spectrum containing cross-peak for H^5 to C^6. HRMS (ESI), *m/z*: 284.0253 [M+H]$^+$ (calc. for $C_{11}H_{10}ClN_3O_2S$, *m/z*: 284.0255).

*Methyl 4-(1,1-diamino-3-ethoxy-3-oxoprop-1-en-2-yl)-7-methyl-2-(methylsulfanyl)pyrido[2,3-*d*]pyrimidine-6-carboxylate* **5**. A mixture of pyridopyrimidine **3** (570 mg, 2.01 mmol), ethyl 3,3-diaminoacrylate **4** (290 mg, 2.23 mmol) and triethylamine (230 mg, 2.27 mmol) in absolute DMF (4 ml) was stirred at room temperature for 1 h, poured into 50 ml of water, filtered, washed with water and dried to give 690 mg (91%) of **5**, orange powder, mp 214–215 °C (MeCN, decomp.). ^{1}H NMR (DMSO-d_6) δ: 0.82 (t, 3H, CH_2*Me*, *J* 7.1 Hz), 2.60 (s, 3H, SMe), 2.89 (s, 3H, 7-Me), 3.83 (s, 3H, CO_2Me), 3.90 (q, 2H, C*H*$_2$Me, *J* 7.1 Hz), 6.7–8.3 (br.s, 4H, NH_2), 8.51 (s, 1H, H^5). ^{13}C NMR (DMSO-d_6) δ: 14.7, 14.9 (SMe, CH_2*Me*), 26.2 (7-Me), 53.3 (CO_2*Me*), 59.1 (*C*H_2Me), 77.9 [*C*=C(NH$_2$)$_2$], 114.9 (C^{4a}), 122.0 (C^6), 142.0 (C^5), 159.3 (C^{8a}), 162.7 (C^4), 165.6 (*C*O_2Me), 166.3 (*C*O_2Et), 169.6 (C^7), 169.8 [C=*C*(NH$_2$)$_2$], 172.7 (C^2). HRMS (ESI), *m/z*: 378.1229 [M+H]$^+$ (calc. for $C_{16}H_{19}N_5O_4S$, *m/z*: 378.1230).

*9-Ethyl 6-methyl 8-amino-5-methyl-2-(methylsulfanyl)-7*H*-pyrimido[4,5,6-*de*][1,6]naphthyridine-6,9-dicarboxylate* **6**. To a suspension of sodium hydride (85 mg, 2.13 mmol) in absolute DMF (1 ml), compound **5** (400 mg, 1.06 mmol) was added portionwise and the mixture was stirred at room temperature for 20 min. Then the mixture was cooled to 0 °C and a solution of ammonium cerium(IV) nitrate (1.38 g, 2.34 mmol in 1 ml of DMF) was added dropwise. The mixture was stirred at 0 °C for additional 30 min, poured into water, filtered, dried and purified by column chromatography (silica, hexane–ethyl acetate, 1:1) to furnish 250 mg (63%) of **6**, beige powder, mp 187–190 °C (decomp.). ^{1}H NMR (DMSO-d_6) δ: 1.32 (t, 3H, CH_2*Me*, *J* 7.1 Hz), 2.33 (s, 3H, SMe), 2.54 (s, 3H, 7-Me), 3.85 (s, 3H, CO_2*Me*), 4.28 (q, 2H, C*H*$_2$Me, *J* 7.1 Hz), 7.74 (br.s, 2H, NH_2). ^{13}C NMR (DMSO-d_6, 80 °C) δ: 13.8 (SMe), 14.8 (CH_2*Me*), *18.7* (7-Me), 52.7 (CO_2*Me*), 60.5 (*C*H_2Me), 91.9 (C^9), 103.7 (C^6), *113.3* (C^{9b}), *147.8* (C^{9a}), *153.4* (C^5), 154.2 (C^{6a}), 155.8 (C^{3a}), *162.8* (C^8), 166.5 (*C*O_2Me), 168.2 (*C*O_2Et), 173.4 (C^2). The signals written in italics are significantly broadened that may indicate the existence of tautomers with proton located on different nitrogen atoms of the cyclic system. Indirectly it is confirmed by the fact that NH proton signal is not observed, probably due to substantial broadening. HRMS (ESI), *m/z*: 376.1081 [M+H]$^+$ (calc. for $C_{16}H_{17}N_5O_4S$, *m/z*: 376.1074).

tution. This protonation, as we suppose, leads to change of chemoselectivity when enamine **2** is taken instead of enediamine **4**. The protonation of pyrimidine nitrogen atom not only increases the electrophilic reactivity of pyrimidine, but also makes the electrophilic center much harder. Therefore, pyrimidine **1** reacts with enamine **2** (which is significantly less reactive than enediamine **4**). Thus, enamine **2** attacks the pyrimidine ring with its hard nucleophilic center, the nitrogen atom (rather than its softer carbon atom, like enediamine **4** does).

Pyridopyrimidine **3** does not react with the second equivalent of enamine **2** (confirmed by TLC after 72 h at room temperature and 5 h at 70 °C). However, the reaction proceeds smoothly with much more active enediamine **4** giving thus the only product **5** of replacement of chlorine atom by α-carbon atom of enediamine. When treated with sodium hydride, compound **5** undergoes a cyclization *via* addition of amino group to aromatic ring of pyridine. Stabilization of labile adduct is achieved by aromatization with ammonium cerium(IV) nitrate as an oxidant. As a result, a new *peri*-condensed structure **6** is formed. Analogous transformations of pyrido[4,3-*d*]pyrimidines were described by our group earlier.[12]

The structure of compound **6** was ultimately established by XRD of the single crystal of its dihydroperchlorate hydrate **7** (Figure 1).‡

In conclusion, described cyclocondensation of aldehyde **1** with enamine **2** can be used as a convenient synthetic method for polyfunctional pyrido[2,3-*d*]pyrimidines. Interaction of compound **3** with enediamine **4**, which finally resulted in structure **6**, represents the first example of pyrimido[4,5,6-*de*]naphthyridine system synthesis.

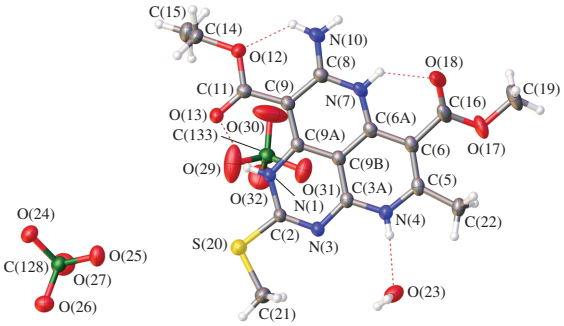


Figure 1 ORTEP representation of compound **7**. Selected interatomic distances (Å) and bond angles (°): N(4)–C(3a) 1.348(4), N(4)–C(5) 1.357(5), N(1)–C(9a) 1.358(4), N(1)–C(2) 1.364(4), N(7)–C(6a) 1.357(5), N(7)–C(8) 1.368(5), N(3)–C(2) 1.310(4), N(3)–C(3a) 1.354(4), C(3a)–C(9b) 1.388(5), C(9a)–C(9) 1.400(5), C(9a)–C(9b) 1.411(5), C(9)–C(8) 1.429(5), C(9b)–C(6a) 1.401(5), C(6)–C(6a) 1.421(5), C(9a)–C(9b)–C(6a) 120.5(3), C(6a)–C(9b)–C(3a) 120.5(3), C(9a)–C(9b)–C(3a) 118.8(3).

NMR studies were performed at the Centre for Magnetic Resonance, XRD study was carried out at the X-ray Diffraction Centre and MS analysis was performed at the Center for Chemical Analysis and Materials Research, St. Petersburg State University.

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*9-Ethyl 6-methyl 8-amino-5-methyl-2-(methylsulfanyl)-7*H*-pyrimido-[4,5,6-*de*][1,6]naphthyridine-6,9-dicarboxylate dihydroperchlorate monohydrate* **7**. To a solution of compound **6** (70 mg, 0.186 mmol) in chloroform–THF mixture (5 ml, 1:1), a solution of $HClO_4$ in THF (1:1) was added dropwise at room temperature until the precipitation completed. The suspension was stirred for additional 1 h, cooled to 0 °C, filtered and dried to give 77 mg (70%) of **7**, white powder, mp 272–275 °C (decomp.). ^{1}H NMR (DMSO-d_6) δ: 1.37 (t, 3H, CH_2Me, J 7.1 Hz), 2.68 (s, 3H, SMe); 2.75 (s, 3H, 7-Me), 3.99 (s, 3H, CO_2Me), 4.39 (q, 2H, CH_2Me, J 7.1 Hz), 8.99 (br. s, 2H, NH_2).

‡ *Crystal data for* **7**. A crystal suitable for X-ray analysis was grown by slow evaporation of methanolic solution of compound **7** at room temperature. Colourless prism, $C_{16}H_{21}Cl_2N_5O_{13}S$ (M = 594.34), monoclinic, space group $P2_1/n$, at 100(2) K: a = 8.29410(15), b = 23.9149(4) and c = 12.10785(17) Å, β = 93.6642°, V = 2396.71(7) Å^3, Z = 4, d_{calc} = = 1.647 g cm^{-3}, μ = 3.959 mm^{-1}, R_{int} = 0.0533. Agilent Technologies Supernova Atlas diffractometer, 26 400 reflections collected in the 2θ range of 7.40–153.44°, R_1 = 0.064 (wR_2 = 0.189) for 4528 unique reflections with $|F_0| \geqslant 4\sigma F$.

CCDC 957462 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2014.