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An improved synthesis of 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine

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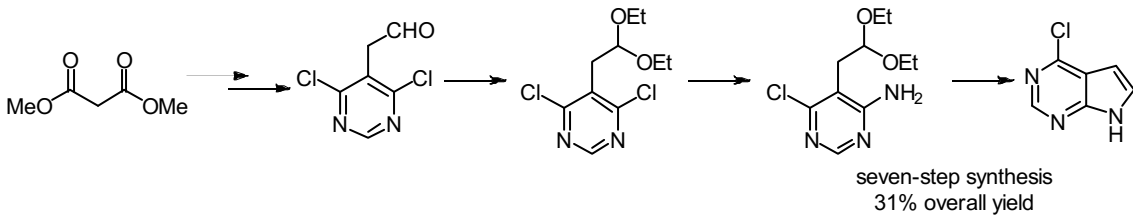


An improved seven-step synthesis of 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine from dimethyl malonate with 31% overall yield is described. The procedure is operationally simple and practical for the synthesis of the 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine building block.

Keywords: pyrimidine, Janus kinase inhibitor, ozonolysis, synthesis.

Janus kinase (JAK) inhibitors are a type of compounds that inhibit the activity of one or more of the JAK family of enzymes, thereby interfering with JAK – signal transducer and activator of transcription protein (STAT) signal pathway, which is a chain of interactions between proteins in the cell and is involved in cell division and death and in tumor formation processes. The pathway involves a chemical signal transfer from the outside into the cell nucleus, resulting in the activation of genes through a transcription process. Disrupted JAK-STAT signaling may lead to a variety of diseases affecting the immune system.[1] JAK inhibitors have therapeutic applications in the treatment of cancer and inflammatory diseases, such as rheumatoid arthritis, psoriasis, myelofibrosis, polycythemia vera, dermatitis, and others.[2] So far, three JAK inhibitors have been approved by FDA, including ruxolitinib,[3] tofacitinib,[4] and oclacitinib[5] (Fig. 1). In addition, a number of JAK inhibitors are in clinical trials, such as baricitinib,[6] filgotinib,[7] gandotinib[8] (Fig. 1). Several JAK inhibitors have a common pyrrolo[2,3-*d*]pyrimidine core. Thus, 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (**1**) might be a practical building block in the synthesis of many JAK inhibitors.

Up to now, a considerable number of synthetic routes for this heterocyclic compound have been reported, as summarized in Figure 2.[9–15] In few synthetic methods, ethyl cyanoacetate or isoxazole is employed as starting materials.

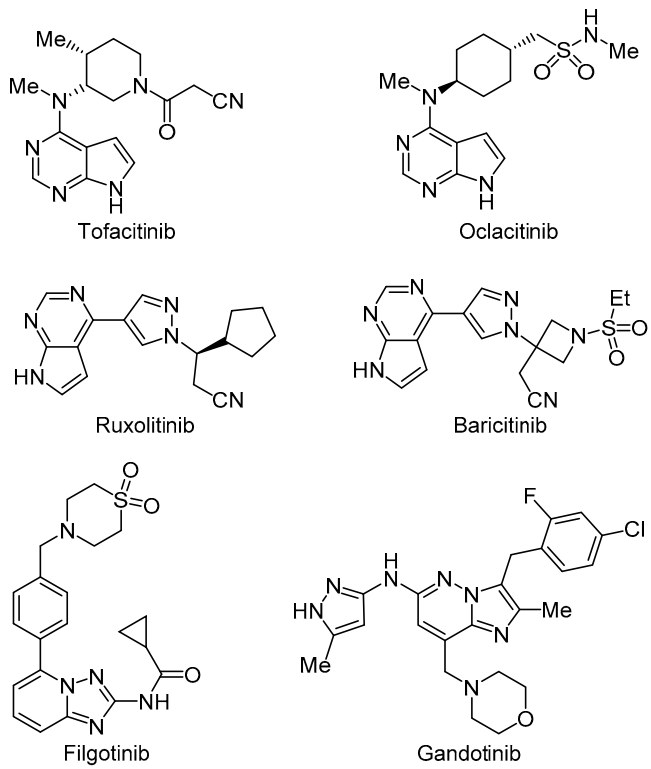


Figure 1. Chemical structures of representative JAK inhibitors.

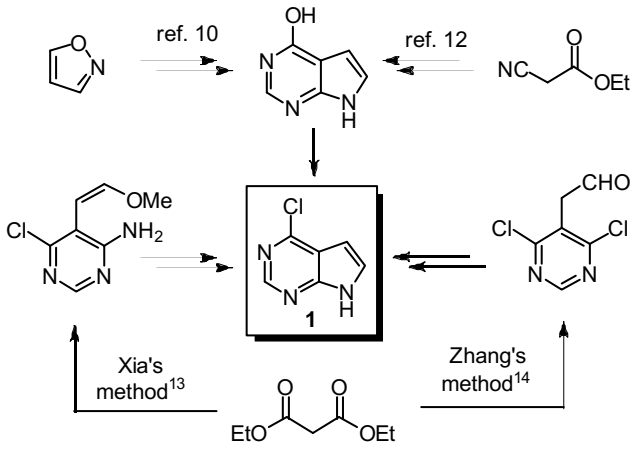
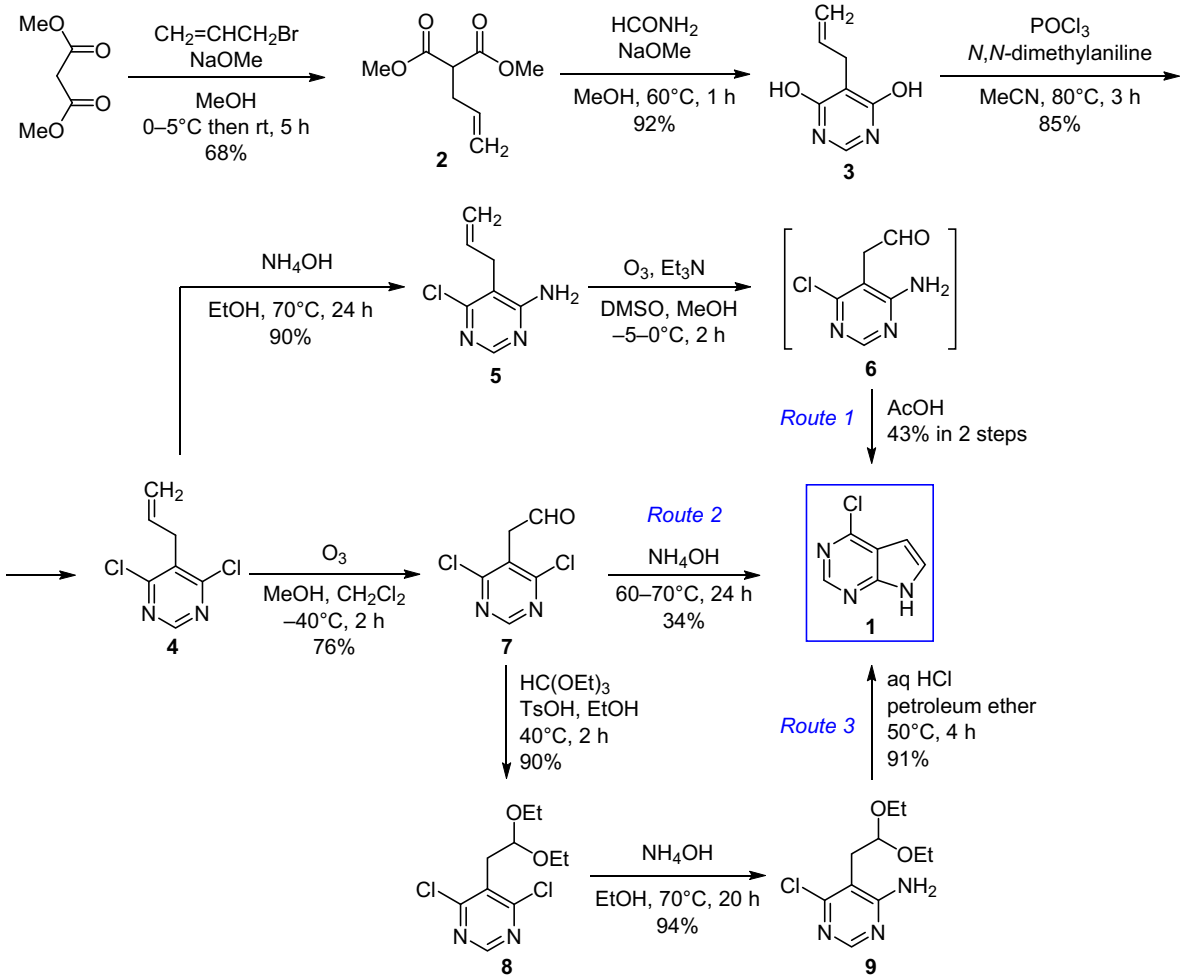


Figure 2. Literature reported routes toward building block **1**.

Although the reported methods are quite different, 4-hydroxypyrrolo[2,3-*d*]pyrimidine is used as a common intermediate in all of them, which is further converted into the target molecule. Xia and coworkers reported a synthetic route *via* vinyl ether intermediate using diethyl malonate as the starting compound.[13] Recently, Zhang and coworkers described another synthetic route, employing diethyl malonate as the starting material too, but constructing the target molecule in a different way.[14] In this method, an aldehyde is produced as an intermediate, which is directly cyclized to afford the desired compound. However, we have found that the yield of this direct cyclization is poor, probably due to the aldehyde enolization. To develop an efficient and practical synthetic protocol, we improved Zhang's method and disclosed a concise synthetic procedure in a Chinese patent.[16] Herein, we report a more detailed investigation on the synthesis of the 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine building block.

Our synthesis of building block **1** is depicted in Scheme 1. In the first step, dimethyl malonate was treated with allyl bromide under basic conditions to afford dimethyl 2-allylmalonate **2** in 68% yield. We have found that dimethyl malonate is a more convenient starting compound than diethyl malonate. The boiling point of dimethyl ester **2** is lower than that of the corresponding diethyl ester, resulting in an easier purification *via* vacuum distillation. Although the condensation of ester **2** with formamidine acetate proceeded smoothly to produce 5-allylpyrimidine-4,6-diol **3** in good yield, we found that formamide could also be used to effect this condensation and produce the desired compound in 92% yield. Since formamide is much cheaper than formamidine acetate, our protocol is more cost-efficient and convenient. Thereafter, pyrimidine **3** was

Scheme 1



treated with phosphorus oxychloride to give 5-allyl-4,6-dichloropyrimidine (**4**) in 85% yield.

With dichloride **4** in hand, three synthetic routes were investigated. First, dichloride **4** was treated with ammonium hydroxide to produce the monosubstituted amine **5** in 90% yield. Then, amine **5** was subjected to ozonolysis to afford intermediate **6**, which immediately cyclized under acidic conditions to produce the target molecule in 43% two-step yield. To dissolve compound **5**, a mixture of DMSO and MeOH was used. Even so, the temperature should not be below –10°C. Otherwise, compound **5** would precipitate from the solvent. Since the active intermediates during ozonolysis were very unstable, they might partially decompose at this temperature, resulting in low yields. Another reason for the low yield might be the deactivation of amino group, since the amino group might be protonated under the acidic conditions. Thus, more efficient synthetic routes were desired.

The second route was similar to Zhang's work, while we used ozonolysis to produce the desired aldehyde **7**, instead of oxidation by $NaIO_4/K_2OsO_4$. Since ozone is inexpensive, this protocol would be more practical.[17] Thus, dichloride **4** was treated with ozone at low temperature to produce aldehyde **7** in 76% yield. However, it was found that the direct cyclization of aldehyde **7** in concentrated ammonium hydroxide produced the target compound **1** in only 34% yield. Indeed, several conditions were screened, but the yields were still quite low. These unsatisfactory results led us to devise new strategies.

The low yield might be ascribed to the aldehyde enolization. Thus, aldehyde **7** was protected with ethanol to give acetal **8** in excellent yield. Treatment of compound **8** with ammonium hydroxide proceeded smoothly to give the monosubstituted amine **9** in 94% yield. At last, the hydrolysis and cyclization occured successively under acidic conditions to produce the desired compound **1** in 91% yield. Although the synthetic route was prolonged, the yields of the last three steps were nearly quantitative. Thus, this seven-step synthesis was more valuable and attractive.

In conclusion, we have developed a convenient seven-step synthetic approach toward 4-chloro-7*H*-pyrrolo[2,3-*d*]-pyrimidine in 31% overall yield from commercially available dimethyl malonate.

Experimental

IR spectra were obtained on a FTIR Bruker Tensor 27 apparatus in KBr pellets. ^{1}H NMR spectra were recorded on a Bruker DRX-400 (400 MHz) spectrometer. ^{13}C NMR spectra were obtained on a JNM-EX400 (100 MHz) spectrometer, using TMS as internal standard. High-resolution mass spectra (ESI) were recorded on a Bruker MicroTof II mass spectrometer. Mass spectra (EI, 70 eV) were obtained on an AGILENT 5975C mass spectrometer. Melting points were measured on a SGW X-4 (INESA) temperature apparatus and are uncorrected.

Commercial reagents were used without further purification. Petroleum ether fraction with boiling point in the range from 60 to 90°C was used in the work-up of the reaction mixtures.

Dimethyl prop-2-en-1-ylpropanedioate (2). To a solution of NaOMe (122 g, 2.27 mol) in MeOH (400 ml) in a three-necked flask at 0–5°C, dimethyl malonate (300 g, 2.27 mol) was added, and the mixture was stirred for 1 h. Then allyl bromide (174 g, 2.27 mol) was added dropwise at room temperature and stirring continued for 5 h. Water (150 ml) was added to quench the reaction. The reaction mixture was evaporated to dryness under reduced pressure to give a residue that was extracted with EtOAc (500 ml), washed with water (2×200 ml) and brine (200 ml). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product that was purified by vacuum distillation (85–90°C, 10 mmHg). Yield 266 g (68%), colorless oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 5.82–5.72 (1H, m, =CH); 5.14–5.05 (2H, m, $=CH_2$); 3.73 (6H, s, OCH_3); 3.47 (1H, t, J = 7.6, CH); 2.65 (2H, t, J = 7.1, CH_2).

5-(Prop-2-en-1-yl)pyrimidine-4,6-diol (3). A solution of NaOMe (220 g, 4.07 mol) in dry methanol (500 ml) in a three-necked flask was cooled to 0–5°C, and $HCONH_2$ (157 g, 3.49 mol) was added. The mixture was stirred at 60°C for 1 h. Compound **2** (200 g, 1.16 mol) was added to the mixture and stirring at 60°C continued for 4 h. After completion of the reaction, the solvent was removed under reduced pressure. Ice-water (400 ml) and concentrated hydrochloric acid (120 ml) were added to the residue to adjust pH to 2. The precipitate was collected and washed by ice-water to give the crude product, which was triturated with EtOAc (500 ml). Yield 162.6 g (92%), white solid, mp 238–241°C (mp 240°C[18]). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 11.30 (2H, br. s, OH); 7.94 (1H, s, H-2); 5.85–5.76 (1H, m, =CH); 4.97–4.87 (2H, m, $=CH_2$); 3.01 (2H, d, J = 6.0, CH_2). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 164.3; 147.1; 135.8; 114.3; 100.1; 26.6.

4,6-Dichloro-5-(prop-2-en-1-yl)pyrimidine (4). To a solution of compound **3** (290 g, 1.91 mol) in MeCN (600 ml), *N,N*-dimethylaniline (60 ml) was added, then the mixture was warmed to 80°C and $POCl_3$ (822 g, 5.36 mol) was added dropwise. The reaction mixture was refluxed for 3 h under nitrogen atmosphere. Then it was quenched with ice-water (500 ml) and concentrated to dryness under reduced pressure. The residue was extracted with 1,2-dichloroethane (500 ml), washed with water (3×100 ml) and aqueous Na_2CO_3 (200 ml). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude, that was purified by vacuum distillation (94–96°C, 8 mmHg). Yield 306 g (85%), light-yellow oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 8.64 (1H, s, H-2); 5.89–5.82 (1H, m, =CH); 5.17–5.09 (2H, m, $=CH_2$); 3.64 (2H, d, J = 6.2, CH_2). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 162.0; 155.8; 131.0; 130.6; 118.2; 34.0. Mass spectrum, *m/z* (I_{rel}, %): 191 [M(^{35}Cl,^{37}Cl)+H]$^+$ (61), 189 [M(^{35}Cl)+H]$^+$ (100),

6-Chloro-5-(prop-2-en-1-yl)pyrimidin-4-amine (5). A mixture of compound **4** (100.9 g, 0.53 mol) and NH_4OH (400 ml) in EtOH (300 ml) was stirred at 70°C for 24 h in a sealed flask. The solvent was removed under reduced pressure and EtOH (300 ml) was added to the residue. The precipitated ammonium chloride was filtered off. The

filtrate was concentrated under reduced pressure to give a solid product which was oven-dried and triturated with EtOAc. Yield 81.1 g (90%), white solid, mp 150–152°C. IR spectrum, ν, cm^{-1}: 3411, 3376, 3181, 1653, 1546, 901. ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 8.13 (1H, s, H-2); 7.14 (2H, br. s, NH_2); 5.89–5.79 (1H, m, =CH); 5.07 (2H, t, *J* = 8.9, $=CH_2$); 3.36 (2H, d, *J* = 5.8, CH_2). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 163.1; 157.7; 156.0; 132.7; 115.5; 111.1; 29.7. Found, *m*/*z*: 169.0406 $[M(^{35}Cl)]^+$. $C_7H_8ClN_3$. Calculated, *m*/*z*:169.0407.

(4,6-Dichloropyrimidin-5-yl)acetaldehyde (7). A solution of compound **4** (100 g, 0.53 mol) in MeOH (400 ml) and CH_2Cl_2 (150 ml) was cooled to –40°C, and ozone was bubbled through the mixture for 2 h. Then the reaction mixture was purged with nitrogen for 20 min to remove the excessive ozone. Thiocarbamide (40 g, 0.53 mol) was added to the mixture and stirred for 1 h until the starch-KI paper did not turn blue. The solvent was distilled off, the residue was extracted with CH_2Cl_2 (300 ml) and washed with water (2×100 ml). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the residue that was triturated with petroleum ether (200 ml). Yield 76.8 g (76%), white solid, mp 88–90°C (mp 89–91°C[19]). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 9.75 (1H, s, CHO); 8.89 (1H, s, H-2); 4.24 (2H, s, CH_2). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 196.9; 161.8; 157.0; 126.4; 44.5. Mass spectrum, *m*/*z* (I_{rel}, %): 192 $[M(^{35}Cl,^{37}Cl)]^+$(12), 190 $[M(^{35}Cl)]^+$ (20), 162 (100).

4,6-Dichloro-5-(2,2-diethoxyethyl)pyrimidine (8). A mixture of compound **7** (20.0 g, 0.1 mol), triethyl orthoformate (18.6 g, 0.12 mol), and TsOH (1.0 g, 5.8 mmol) in EtOH (100 ml) was stirred at 40°C for 2 h. After completion of the reaction, aqueous Na_2CO_3 was added to the mixture to adjust pH to 8. The solvent was removed under reduced pressure and the residue extracted with EtOAc (300 ml), washed with water (100 ml). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the residue that was purified by column chromatography on silica gel (eluent petroleum ether – EtOAc, 5:1). Yield 25.0 g (90%), colorless oil. IR spectrum, ν, cm^{-1}: 2987, 1546, 1518, 1123, 1068, 785. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 8.62 (1H, s, H-2); 4.80 (1H, t, *J* = 5.8, CH); 3.74–3.66 (2H, m, $C\underline{H}_2CH_3$); 3.48–3.41 (2H, m, $C\underline{H}_2CH_3$); 3.25 (2H, d, *J* = 5.7, CH_2); 1.13 (6H, t, *J* = 7.0, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 162.7; 155.8; 132.5; 129.2; 100.9; 62.9; 35.4; 15.2. Found, *m*/*z*: 287.0323 $[M(^{35}Cl)+Na]^+$. $C_{10}H_{14}Cl_2N_2NaO_2$. Calculated, *m*/*z*: 287.0325. Found, *m*/*z*: 289.0295 $[M(^{35}Cl,^{37}Cl)+Na]^+$. Calculated, *m*/*z*: 289.0296.

6-Chloro-5-(2,2-diethoxyethyl)pyrimidin-4-amine (9). A mixture of compound **8** (20.0 g, 76 mmol) and NH_4OH (100 ml) in EtOH (120 ml) was stirred at 70°C for 20 h. The solvent was removed under reduced pressure and the residue extracted with EtOAc (200 ml), washed with water (100 ml). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Yield 17.4 g (94%), yellow solid, mp 50–52°C. IR spectrum, ν, cm^{-1}: 3431, 3316, 2982, 1656, 1552, 1103, 788. ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 8.09 (1H, s, H-2); 7.01 (2H, br. s, NH_2); 4.67 (1H, t, *J* = 5.5, CH); 3.68–3.60 (2H, m, $C\underline{H}_2CH_3$); 3.47–3.39 (2H, m, $C\underline{H}_2CH_3$); 2.88 (2H, d, *J* = 5.5, CH_2); 1.06 (6H, t, *J* = 7.0, $CH_2C\underline{H}_3$).^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 164.1; 158.4; 155.9; 109.5; 101.3; 62.3; 32.4; 15.2. Found, *m*/*z*: 268.0819 $[M(^{35}Cl_2)+Na]^+$. $C_{10}H_{16}ClN_3NaO_2$. Calculated, *m*/*z*: 268.0823. Found, *m*/*z*: 270.0793 $[M(^{35}Cl,^{37}Cl)+Na]^+$. Calculated, *m*/*z*: 270.0796.

4-Chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (1). Route 1. A mixture of compound **5** (68 g, 0.41 mol), Et_3N (60.9 g, 0.6 mol), and DMSO (47 g, 0.6 mol) in MeOH (320 ml) was cooled to –5–0°C and ozone was bubbled through the mixture for 2 h. After nitrogen was bubbled through the mixture to remove the excess of ozone, thiocarbamide (61.2 g, 0.81 mol) was added and mixture stirred for 1 h, until the starch-KI paper did not turn blue. Then AcOH (120 g, 2 mol) was added and stirring at room temperature continued for 14 h. The solvent was removed under reduced pressure. The residue was extracted with EtOAc (500 ml), washed with brine (2×200 ml) and aqueous $NaHCO_3$ to neutralize the residual AcOH. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude, that was recrystallized from a mixture of petroleum ether – EtOAc, 2:1. Yield 26.1 g (43%), white solid.

Route 2. A mixture of compound **7** (10.0 g, 50 mmol) and NH_4OH (40 ml) was stirred at 60–70°C for 24 h. Then it was filtered to give the solid crude product, that was purified by column chromatography on silica gel (eluent petroleum ether – EtOAc, 5:1). Yield 2.7 g (34%), white solid.

Route 3. A mixture of compound **9** (10.0 g, 41 mmol) and 6 M HCl (30 ml) in petroleum ether (30 ml) was stirred at 50°C for 4 h. The mixture was filtered to give the solid crude, that was oven-dried and triturated with a mixture of petroleum ether – EtOAc, 1:1. Yield 5.68 g (91%), white solid, mp 189–190°C (mp 189–190°C[12]). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 12.59 (1H, s, NH); 8.58 (1H, s, H-2); 7.71 (1H, d, *J* = 3.4, H-6); 6.62 (1H, d, *J* = 3.4, H-5). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 151.8; 150.4; 150.3; 128.3; 116.5; 98.8. Found, *m*/*z*: 154.0164 $[M+H]^+$. $C_6H_5ClN_3$. Calculated, *m*/*z*: 154.0166.

Supplementary information file containing IR, ^1H and ^{13}C NMR spectra of the synthesized compounds is available at the journal website at http://link.springer.com/journal/10593.

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