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Short Note

4-Chloro-6-(chloromethyl)-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine

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Abstract: A novel 4-chloro-6-(chloromethyl)-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine was prepared by a rational and short two-step synthesis from commercially available ethyl 5-amino-1-methyl-1*H*-pyrazole-4-carboxylate via 6-(chloromethyl)-1-methyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one. The structure of the synthesized compounds was established by elemental analysis, high-resolution mass-spectrometry, ^{1}H, ^{13}C-NMR and IR spectroscopy and mass-spectrometry. 4-Chloro-6-(chloromethyl)-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine is a convenient intermediate for various disubstituted 1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidines, which may be of interest as substances with useful pharmacological properties.

Keywords: 1*H*-pyrazolo[3,4-*d*]pyrimidines; 4-chloro-6-(chloromethyl)-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine; condensation; biological activity

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1. Introduction

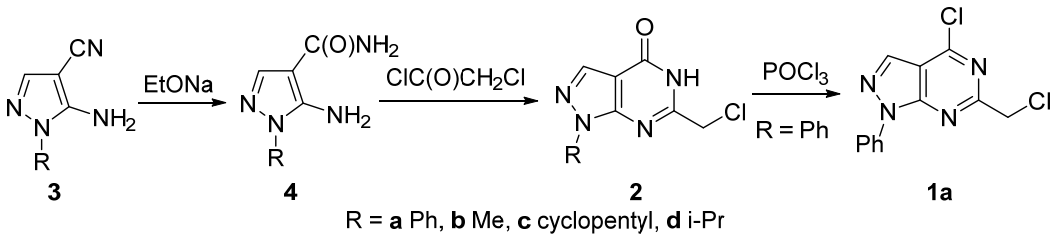
1*H*-Pyrazolo[3,4-*d*]pyrimidine is an important structural fragment present in naturally occurring nucleosides (Formycin A and Formycin B), which have significant antitumor activity [1,2]. Additionally, 1*H*-pyrazolo[3,4-*d*]pyrimidines exhibit various biological activities, including antiviral and analgesic activity, treatment of male erectile dysfunction and hyperuricemia, prevention of gout, and many others [1,3,4]. Functionally substituted 1*H*-pyrazolo[3,4-*d*]pyrimidines showed good antibacterial and antiproliferative activity [5]. Therefore, new derivatives of 1*H*-pyrazolo[3,4-*d*]pyrimidines are of great interest. 1-Substituted 4-chloro-6-(chloromethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidines can be considered important intermediates for the preparation of previously unknown disubstituted 1*H*-pyrazolo[3,4-*d*]pyrimidines. Herein, we report the synthesis of a new 4-chloro-6-(chloromethyl)-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine via its precursor 6-(chloromethyl)-1-methyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*] pyrimidin-4-one.

2. Results and Discussion

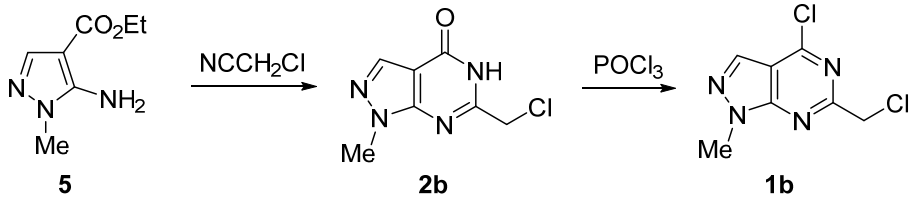
The only representative of 1-substituted 4-chloro-6-(chloromethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidines, 1-phenyl derivative **1a** was obtained by the reaction of carboxamide **2a** with $POCl_3$ [5]. Pyrimidinones **2** were prepared by a two-step synthesis, including saponification of 5-amino-1*H*-pyrazole-4-carbonitriles **3** to 5-amino-1-phenyl-1*H*-pyrazole-4-carboxamides **4** followed by reaction with choloroacetyl chloride [5–8] (Scheme 1).

We decided to carry out the synthesis of heterocycle **1b** by a shorter route from the cheaper and more accessible reagent-ester of 5-amino-1*H*-pyrazole-4-carboxylate **5**. We found that the reaction of commercially available ethyl 5-amino-1-methyl-1*H*-pyrazole-4-carboxylate **5** with chloroacetonitrile in dioxane led to the formation of pyrimidinone **2b** in high yield (83%). It should be noted that the yield of compound **2b** according to the

method described in [8] was much lower (29%). Treatment of compound **2b** with $POCl_3$ gave the target product **1b** (Scheme 2).



Scheme 1. Known synthesis of 4-chloro-6-(chloromethyl)-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine **1a**.



Scheme 2. Synthesis of 4-chloro-6-(chloromethyl)-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine **1b**.

The structure of 4-chloro-6-(chloromethyl)-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine **1b** and its precursor 6-(chloromethyl)-1-methyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one **2b** was fully confirmed by elemental analysis, high resolution mass-spectrometry, ^{1}H, ^{13}C-NMR and IR spectroscopy, and mass-spectrometry. The ^{1}H-NMR spectrum of **1b** showed characteristic singlets of Me group (4.08 ppm), $ClCH_2$ group (4.92 ppm) and C-H-pyrazole group (8.46 ppm).

In conclusion, 1*H*-pyrazolo[3,4-*d*]pyrimidine containing two reactive chlorine atoms-4-chloro-6-(chloromethyl)-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine **1b**, was obtained using a rational and short path. This compound opens up possibilities for the synthesis of various functional derivatives of disubstituted 1*H*-pyrazolo[3,4-*d*]pyrimidines, which may be of interest as compounds with useful pharmacological properties.

3. Materials and Methods

The solvents and reagents were purchased from commercial sources and used as received. Elemental analysis was performed on a 2400 Elemental Analyzer (Perkin Elmer Inc., Waltham, MA, USA). Melting point was determined on a Kofler hot-stage apparatus and is uncorrected. ^{1}H and ^{13}C-NMR spectra were taken with a Bruker AM-300 machine (Bruker AXS Handheld Inc., Kennewick, WA, USA) (at frequencies of 300 and 75 MHz) with TMS as the standard. MS spectrum (EI, 70 eV) was obtained with a Finnigan MAT INCOS 50 instrument (Hazlet, NJ, USA). IR spectrum was measured with a Bruker "Alpha-T" instrument in KBr pellet. High-resolution MS spectrum was measured on a Bruker micrOTOF II instrument (Bruker Daltonik Gmbh, Bremen, Germany) using electrospray ionization (ESI).

Synthesis of 6-(chloromethyl)-1-methyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one **2b** (Supplementary Materials).

HCl gas was passed through a solution of ethyl 5-amino-1-methyl-1*H*-pyrazole-4-carboxylate **5** (0.15 mol, 25.35 g) and chloroacetonitrile (0.15 mol, 9.5 mL) in dioxane (500 mL) at a temperature of 15–18 °C for 10 h. The volatiles were evaporated, water (300 mL) was added to the residue, and the reaction mixture was alkalized with aqueous ammonia to pH = 7. The precipitate was filtered, washed with water and dried in air. Yield 24.71 g (83%), light beige solid, mp 286–287 °C. IR spectrum (KBr), ν, cm^{-1}: 3434, 3106, 2978, 2890, 2858 (all C-H), 1727 (C=O), 1658, 1614 (C=N), 1407, 1200, 1070, 865, 849, 777, 724, 673, 616, 506. ^{1}H-NMR (DMSO-d_6, ppm): δ 3.90 (3H, s), 4.57 (2H, s), 8.05 (1H, s), 12.47

(1H, broad s). ^{13}C-NMR (DMSO-d_6, ppm): δ 34.1 (CH_3), 42.7 (CH_2Cl), 104.6, 134.2 (C-H), 151.6, 155.2, 157.6 (C=O). Mass spectrum (EI, 70 Ev), *m*/*z* (I, %): 200 (M+2, 37), 198 (M^+, 100), 163 (10), 149 (57), 136 (18), 41(15). HRMS (ESI-TOF): calcd. for $C_7H_8ClN_4O$ $[M + H]^+$ 199.0381; found m/z 199.0387, calcd. for $C_7H_7ClN_4NaO$ $[M + Na]^+$ 221.0201; found *m*/*z* 221.0203. Anal. calcd. for $C_7H_7ClN_4O$: C, 42.33; H, 3.55; Cl, 17.85; N, 28.21; found: C, 42.25; H, 3.63; Cl, 17.96; N, 28.29%.

Synthesis of 4-chloro-6-(chloromethyl)-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine **1b** (Supplementary Materials).

A mixture of 6-(chloromethyl)-1-methyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one **2b** (0.1 mol, 19.85 g), $POCl_3$ (0.2 mol, 18.6 mL) and diethylisopropylamine (0.3 mol, 52 mL) was refluxed in toluene (400 mL) for 18 h. The reaction mixture was poured into ice water (500 mL). The organic phase was separated, washed with a saturated solution of $NaHCO_3$, brine and passed through the Al_2O_3 layer on the filter. The solvent was removed. Yield 15.62 g (72%), white solid, mp 68–69 °C. IR spectrum (KBr), ν, cm^{-1}: 3434, 3125, 3030, 2977, 2950 (all C-H), 1722, 1591, 1547 (C=N), 1498, 1444, 1406, 1295, 1217, 1132, 965, 899, 844, 794, 750, 721, 666, 607, 547, 520, 424. ^{1}H-NMR (DMSO-d_6, ppm): δ 4.08 (3H, s), 4.92 (2H, s), 8.46 (1H, s). ^{13}C-NMR (DMSO-d_6, ppm): 34.4 (CH_3), 46.5 (CH_2Cl), 111.7, 132.0 (C-H), 153.2, 153.8, 161.8 (C-Cl). Mass spectrum (EI, 70 Ev), *m*/*z* (I, %): 220 (M+4, 10), 218 (M+2, 63), 216 (M^+, 100), 181 (35), 145 (13), 49 (30), 15 (35). HRMS (ESI-TOF): calcd. for $C_7H_7Cl_2N_4$ $[M + H]^+$ 217.0042; found *m*/*z* 217.0050, calcd. for $C_7H_6Cl_2N_4Na$ $[M + Na]^+$ 238.9862; found *m*/*z* 238.9870. Anal. calcd. for $C_7H_6Cl_2N_4$: C, 38.74; H, 2.79; Cl, 32.66; N, 25.81; found: C, 38.66; H, 2.85; Cl, 32.56; N, 25.93%.

Supplementary Materials: The following are available online: copies of ^{1}H, ^{13}C-NMR, IR, HRMS and mass-spectra for the compounds **1b** and **2b**.

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