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Ethyl 2-(n-Butylamino)-7-hydroxy-5-methylpyrazolo[1,5-a]pyrimidine-3-carboxylate

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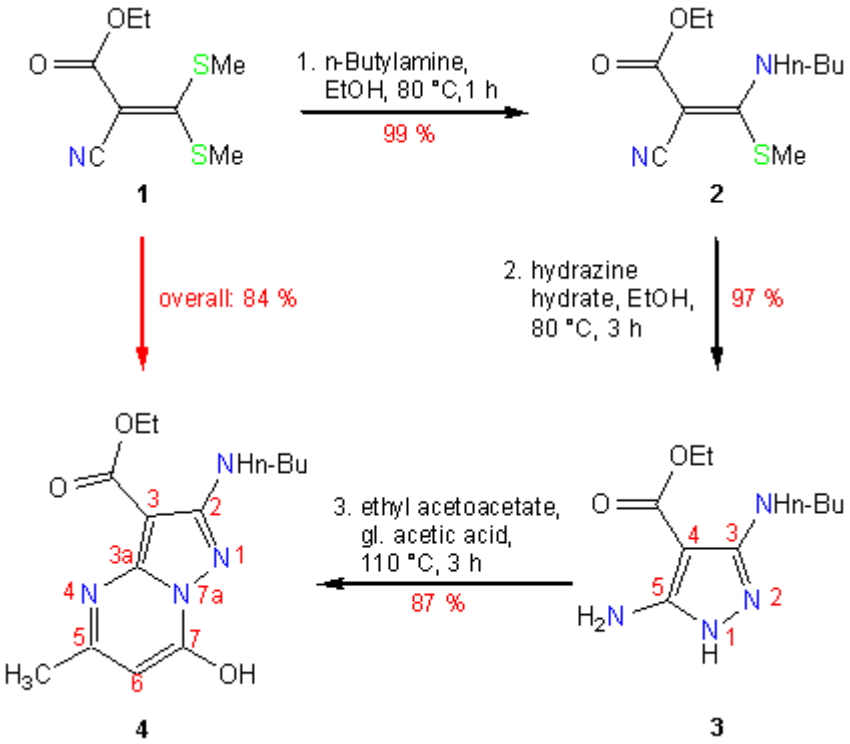

Ethyl 2-cyano-3,3-bis(methylthio)acrylate **1** [1] (3.255 g; 15.0 mmol) was dissolved in anhydrous ethanol (100 mL), n-butylamine (1.100 g; 15.0 mmol) was added and the solution was heated to reflux for 2 h in a flask equipped with a gas outlet to remove the evolving methanethiol (hood). The reaction mixture was evaporated and the product (**2**, 3.59 g, 99 %) was obtained as a yellowish oil. Tlc (light petroleum : ethyl acetate 8 : 2): single spot (R_f 0.67). ^{1}H NMR (200 MHz, $CDCl_3$): 0.97 (t, *J* 7.0 Hz, 3 H, CH_3CH_2O); 1.29-1.46 (m, 4 H, 2 x CH_2); 1.63 (t, *J* 7.4 Hz, 3 H, CH_3); 2.70 (s, 3 H, SCH_3); 3.53 (m, 2 H, CH_2); 4.23 (q, *J* 7.0 Hz, 2 H, CH_3CH_2O); 10.08 (br s, 1 H, NH). This intermediate (ethyl 2-cyano-3-n-butylamino-3-methylthioacrylate, **2**) was again dissolved in anhydrous ethanol (100 mL), hydrazine hydrate (0.74 mL; 15.0 mmol) was added and the solution was heated to reflux for 3 h (hood). The reaction mixture was evaporated and the resulting oil was triturated with hexane. After the ensuing crystallization, filtration, and washing with hexane, the product (ethyl 5-amino-3-n-butylamino-1H-pyrazole-4-carboxylate, **3**) was obtained (3.235 g; 97 %) as white crystals, mp. 103-104 °C. Tlc ($CHCl_3$: MeOH 9 : 1): single spot (R_f 0.42). Compound **3** (3.215 g, 14.21 mmol) was dissolved in glacial acetic acid (5 mL), a solution of ethyl acetoacetate (1.811 mL, 14.21 mmol) in glacial acetic acid (2 mL) was added and the reaction mixture was heated to reflux for 3 h. The solution was placed in a refrigerator for 16 h. The crystals formed were filtered off and washed with ethanol (10 mL) to give the title compound **4** (2.88 g, 69 %). From the mother liquor further crops were obtained, altogether 3.619 g (87 %).

Yield: 84 % (over 3 steps).

R_f = 0.65 (CH_2Cl_2 : MeOH = 9 : 1).

Mp. 189-190 °C.

Solubility: in water: 0.23 mg/mL (25 ˚C), 1.45 mg/mL (100 ˚C); in 40 % aq. DMF: 2.8 mg/mL (25 ˚C).

^{1}H NMR (DMSO-d_6, 500 MHz, for numbering see the figure): 0.90 (t, *J* 7.4 Hz, 3 H, CH_3); 1.30 (t, *J* 7.0 Hz, 3 H, CH_3CH_2O); 1.35 (m, 2 H, CH_2); 1.56 (m, 2 H, CH_2); 2.33 (s, 3 H, 5-CH_3); 3.25 (t, *J* 6.6 Hz, 2 H, $NHCH_2$); 4.30 (q, *J* 7.0 Hz, 2 H, CH_3CH_2O); 5.71 (s, 1 H, H-6); 5.79 (t, *J* 5.8 Hz, deut. with D_2O, 1H, NH); 11.15 (s, deut. with D_2O, 1 H, OH).

^{13}C NMR (DMSO-d_6, 125 MHz, assignment based on a HMBC experiment [2,3]): 13.93 (aliph. CH_3); 14.74 (aliph. CH_3); 18.98 (5-CH_3); 19.83 (CH_2); 31.26 (CH_2); 41.69 (NCH_2); 59.92 (OCH_2); 83.07 (C-5); 99.66 (C-6); 143.76; 149.70; 155.08; 156.86 (C-2, C-3, C-3a, C-7); 163.07 (COO).

APCI-MS (isobutane, *m/z*): 293 ($[M+H]^+$).

Anal calcd. for $C_{14}H_{20}N_4O_3$ (292.334): N, 19.17; found N 19.17 %.

References

1. Söderbäck, E. *Acta Chem. Scand.* **1963**, *17*, 362-376.
2. Bax, A.; Summers, M. F. *J. Am. Chem. Soc.* **1986**, *108*, 2093-2094.
3. Bax, A.; Marion, D. *J. Magn. Reson.***1988**, *78*, 186-191.

Sample availability: available from the authors and MDPI.