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SYNTHESIS OF ALKYL THIOETHERS OF PYRAZOLO[3,4-*d*]PYRIMIDINE

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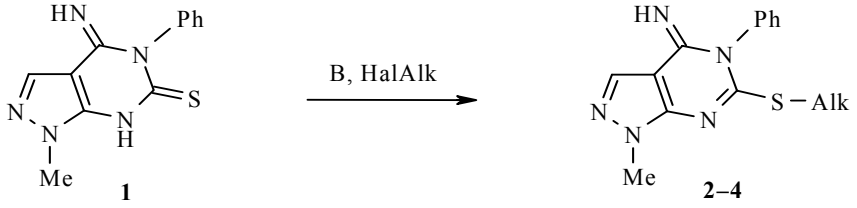
Reaction of 4-imino-1-methyl-5-phenyl-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-d]pyrimidine-6-thione with unsaturated alkyl halides gives 4-imino-6-methallylthio(cinnamylthio, allylthio)-1-methyl-5-phenyl-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidines.

Keywords: 6-allylthio-4-iminopyrazolo[3,4-*d*]pyrimidine, 4-imino-6-methallylthio-pyrazolo[3,4-*d*]pyrimidine, pyrazolo[3,4-*d*]pyrimidine, 6-cinnamylthio-4-iminopyrazolo[3,4-*d*]pyrimidine, alkylation, regioselectivity.

We have previously reported [1, 2] that alkylation of pyrazolo[3,4-*d*]pyrimidine-6-thiones using allyl and propargyl bromides gives the corresponding unsaturated thioethers which are used as substrates for studying electrophilic heterocyclization reactions. With the aim of increasing the number of unsaturated thioethers for studying the heterocyclization reaction we have carried out the alkylation of the starting 4-imino-1-methyl-5-phenyl-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-*d*]pyrimdine-6-thione (**1**) using methallyl chloride and cinnamyl bromide.

In the alkylation of the pyrazolo[3,4-*d*]pyrimidine-6-thione **1** both KOH and sodium ethylate in ethanol were used as base to give the thioethers **2-4**. It should be noted that the use of sodium ethylate gives increased yields of the reaction products.



1 **2–4**

Hal = Cl (synthesis of compound **2**), Br (preparation of compound **3**, **4**); B = KOH, EtONa;
2 Alk = $CH_2C(Me)=CH_2$, **3** Alk = $CH_2CH=CHPh$, **4** Alk = $CH_2CH=CH_2$

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To prove the regioselectivity of the alkylation process we have recorded the ^{13}C NMR spectrum for 4-imino-6-methallylthiopyrazolo[3,4-*d*]pyrimidine (**2**). A characteristic for determining the regioselectivity of the alkylation is the signal for the sp^3 hybridized methylene carbon atom in the alkyl chain which appears at 33.82 ppm and which points to the formation of thioether **2**. In the alternative variant of alkylation at the endocyclic nitrogen atom the signal for this carbon atom would appear at lower fields (~ 50-60 ppm [3]).

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Varian VXR-300 spectrometer (300 and 75 MHz respectively) using TMS as internal standard.

Preparation of Thioethers 2 and 3 (General Method). A. A solution of KOH (9.4 mmol) in water (2 ml) was added to a solution of 4-imino-1-methyl-5-phenyl-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-*d*]pyrimidine-6-thione (**1**) in ethanol (20 ml). The reaction mixture was heated to full dissolving and a 90% solution of methallyl chloride (1.06 ml, 9.4 mmol) or cinnamyl bromide (1.4 ml, 9.4 mmol) was added and heated for 1 h at 50-60ºC. The precipitate was filtered off and recrystallized from ethanol or acetic acid.

B. Compound **1** (7.8 mmol) was added to a solution of metallic sodium (7.8 mmol) in ethanol (15 ml). The reaction mixture was heated to full dissolving and a 90% solution of methallyl chloride (1.06 ml, 9.4 mmol) or cinnamyl bromide (1.4 ml, 9.4 mmol) was added and heated for 1 h at 50-60ºC. The precipitate was filtered off and recrystallized from ethanol or acetic acid.

4-Imino-6-methallylthio-1-methyl-5-phenyl-4,5-dihydro-1H-pyrazolo[3,4-*d*]pyrimidine (2). Yield 67 (method A) and 78% (method B); mp 130-132ºC. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.88 (3H, s, CH_3); 3.98 (3H, s, NCH_3); 4.01 (2H, s, SCH_2); 4.94 (1H, s, $=CH_2$); 5.08 (1H, s, $=CH_2$); 7.09, 7.25, 7.40 (5H, m, C_6H_5); 7.76 (1H, s, CH pyrazole); 7.87 (1H, s, =NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 21.65, 33.82, 34.80, 105.85, 114.85, 119.87, 122.29, 128.95, 131.77, 140.70, 141.13, 153.38, 157.35, 164.20. Found, %: N 22.19. $C_{16}H_{17}N_5S$. Calculated, %: N 22.49.

6-Cinnamylthio-4-imino-1-methyl-5-phenyl-4,5-dihydro-1H-pyrazolo[3,4-*d*]pyrimidine (3). Yield 64 (method A) and 81% (method B); mp 162-164ºC. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 3.99 (3H, s, NCH_3); 4.18 (2H, d, *J* = 5.0, SCH_2); 6.38 (1H, m, =CH); 6.64 (1H, d, *J* = 16.0, =CH); 7.08, 7.38 (10H, m, C_6H_5); 7.77 (1H, s, CH pyrazole); 7.87 (1H, s, =NH). Found, %: N 18.23. $C_{21}H_{19}N_5S$. Calculated, %: N 18.75.

6-Allylthio-4-imino-1-methyl-5-phenyl-4,5-dihydro-1H-pyrazolo[3,4-*d*]pyrimidine (4). Yield 72 (method A) and 93% (method B); mp 134-136ºC. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 4.03 (3H, s, NCH_3); 4.07 (2H, d, *J* = 5.0, SCH_2); 5.21 (1H, d, *J* = 10.0, $=CH_2$); 5.37 (1H, d, *J* = 17.0, $=CH_2$); 6.05 (1H, m, =CH); 7.11, 7.29, 7.41 (5H, m, C_6H_5); 7.76 (1H, s, CH pyrazole); 7.89 (1H, s, =NH). Found, %: N 23.15. $C_{15}H_{15}N_5S$. Calculated, %: N 23.55.

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