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SYNTHESIS AND HALOGENATION OF PROPARGYL PYRAZOLO-[3,4-*d*]PYRIMIDINE THIOETHER

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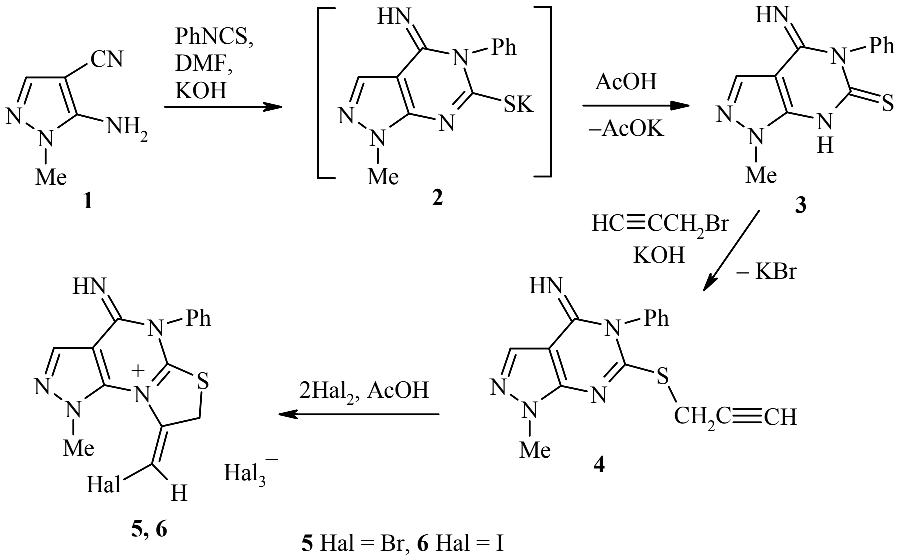
The reaction of 4-imino-1-methyl-5-phenyl-6-propargylthio-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidine with halogens leads to the formation of (Z)-8-halomethylene-4-imino-1-methyl-5-phenyl-4,5,7,8-tetrahydro-1H-pyrazolo[4,3-e][1,3]thiazolo[3,2-a]pyrimidinium trihalide.

Keywords: 4-imino-6-propargylthiopyrazolo[3,4-*d*]pyrimidine, pyrazolo[3,4-d]pyrimidine, trihalide, haloheterocyclization.

Earlier [1] it was reported that *o*-aminocyanopyrazoles condense effectively with isothiocyanates to pyrazolo[3,4-*d*]pyrimidine-6-thiones. In the present work 5-amino-4-cyano-1-methyl-1H-pyrazole (**1**) was used as initial aminopyrazole.

In [1] boiling ethanol was used as solvent for the condensation, and this was followed by cyclization with alkali. We used a mixture of DMF with potassium hydroxide for the condensation and cyclization of the pyrazole **1**. The potassium salt of pyrazolo[3,4-*d*]pyrimidine-6-thione **2** was obtained as a result of the reaction without isolation of the thiourea. The thione **3** was obtained when the salt **2** was neutralized with acetic acid.



5 Hal = Br, **6** Hal = I

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The thioether **4** was obtained by alkylation of the thione **3** with propargyl bromide in 95% ethanol in the presence of alkali. The thioether is capable of heterocyclization during halogenation in acetic acid.

We studied the halogenation of the thioether **4**. As halogens we used iodine and bromine. The reaction was carried out in acetic acid with twice the amount of halogen. The reaction was monitored by TLC (in the 1:3 acetic acid–hexane system). According to elemental analysis for nitrogen and halogen the trihalides **5** and **6** were formed as a result of the reaction.

In order to investigate the structure of the synthesized compound **6** we measured its ^{1}H and ^{13}C NMR spectra, and we also carried out heteronuclear ^{1}H^{13}C correlation experiments through one chemical bond (HMQC) and through 2-3 chemical bonds (HMBC). The assignment of the signals in the proton spectrum was not subject to doubt since the two singlets present in the spectrum in the region of the signals for the aromatic protons are separated from each other by almost 1 ppm. In order to assign the signals of the protonated carbon atoms we made use of correlations in the HMQC spectrum, indicating the presence of a chemical bond between the proton and the corresponding carbon atom. The assignment of the quaternary carbon atoms follows from the presence of correlations through 2-3 chemical bonds in the HMBC spectrum. All the found heteronuclear ^{1}H^{13}C correlations are given in Table 1.

It is possible to assign all the signals in the carbon spectrum on the basis of the obtained correlations. Thus, for example, the presence of a correlation between the signal of a proton at 8.65 ppm and the signals of the carbon atoms at 106.1 and 151.1 ppm makes it possible to assign the signals to the nodal carbon atoms. The location of the last signal is also confirmed by the presence of a correlation with the signal of the methyl protons. The assignment of the most downfield signal of a carbon atom (165.8 ppm) to the nodal carbon atom

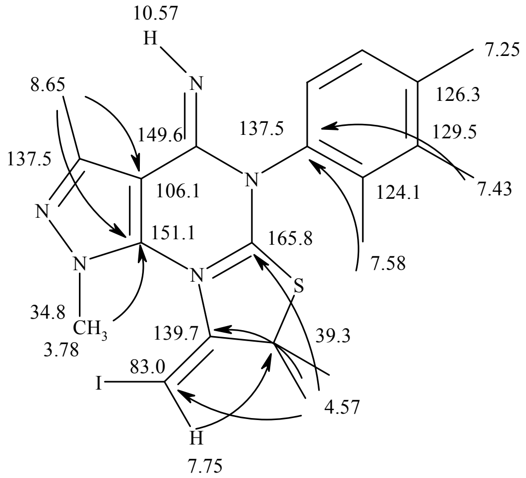

TABLE 1. The HMQC and HMBC Correlations Obtained for the Signals of the Protons in Compound **6**

δ, ppm	HMQC	HMBC
10.57	—	—
8.65	137.5	151.1, 106.1
7.75	83.0	39.3
7.58	124.1	137.5, 126.3, 124.1
7.43	129.5	137.5, 129.5, 126.3
7.25	126.3	129.5, 124.1
4.57	39.3	165.8, 83.0, 139.7
3.78	34.8	151.1

situated between the two nitrogen atoms and the sulfur atom follows from the presence of a correlation with the signal of the protons of the methylene group, the protons of which are separated from the given carbon atom by three chemical bonds. The main assignments of the signals in the proton and carbon spectra of compound **6** are shown in the scheme, and the HMBC correlations, which served as the basis for the assignments, are presented.

The only signal for which HMBC correlations were not found is the signal of the quaternary carbon atom with a chemical shift of 149.6 ppm. We assigned it by the exclusion method. Our proposed structure for compound **6** agrees well with the obtained chemical shifts.

It is not possible to determine the orientation of the iodine atom and the olefinic proton in the molecule in relation to the exocyclic double bond directly from the NMR spectra. To solve this problem we measured the ^{13}C NMR spectrum without spin–spin decoupling with the protons. For the signal of the carbon atom with a chemical shift of 39.3 ppm under these conditions a spin–spin coupling constant with the olefinic protons of $^3J_{CH}$ = 6 Hz was observed. This indicates a cisoid orientation for the olefinic proton and the carbon atom of the methylene group contained in the thiazoline ring. A further argument in favor of the given geometry of the molecule is the absence of an appreciable NOE between the signal of the protons of the methyl group and the signal of the olefinic proton in a NOESY-1D experiment.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra and HMQC and HMBC heteronuclear correlation spectra were obtained on a Varian Mercury-400 spectrometer (400 and 100 MHz respectively). All the two-dimensional experiments were performed with gradient selection of the useful signals. The mixing time in the pulse sequences corresponded to $^1J_{CH}$ = 140 in the HMQC method and $^{2\text{-}3}J_{CH}$ = 8 Hz in the HMBC method. The number of increments amounted to 128 in the HMQC spectra and 400 in the HMBC spectra. In all cases the solvent was DMSO-d$_6$ and the internal standard TMS.

4-Imino-1-methyl-5-phenyl-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-*d*]pyrimidine-6-thione (3). To a solution of 5-amino-1-methyl-1H-4-pyrazolecarbonitrile (**1**) (5 mmol) we added DMF (10 ml), phenyl isothiocyanate (0.52 ml), and potassium hydroxide (0.28 g). The mixture was heated for 2.5 h, cooled, and acidified with 85% acetic acid solution. The yellow precipitate was filtered off, washed with water, and recrystallized from acetic acid. The yield was 55%; mp 290-292°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.83 (3H, s, N–CH$_3$); 7.05, 7.36, 7.68 (5H, m, C$_6$H$_5$); 7.91 (1H, s, H-3); 9.05 (1H, s, =NH); 11.83 (1H, m, NH). Found, %: N 27.29. $C_{12}H_{11}N_5S$. Calculated, %: N 27.12.

1-Methyl-5-phenyl-6-(2-propynylthio)-4,5-dihydro-1H-pyrazolo[3,4-*d*]pyrimidine-4-imine (4). To a solution of the thione **3** (6.8 mmol) in ethanol (15 ml) we added potassium hydroxide (8 mmol) and propargyl bromide (8 mmol). The reaction mixture was heated at 60°C for 1 h and cooled. The light-yellow precipitate was filtered off and recrystallized from ethanol. The yield was 88%; mp 155-157°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.04 (1H, s, ≡CH); 3.87 (3H, s, N–CH$_3$); 4.21 (2H, s, CH$_2$); 6.96, 7.28, 7.86 (5H, m, C$_6$H$_5$); 7.90 (1H, s, H-3); 9.71 (1H, s, =NH). Found, %: N 23.27. $C_{15}H_{13}N_5S$. Calculated, %: N 23.71.

(*Z*)-8-Bromomethylene-4-imino-1-methyl-5-phenyl-4,5,7,8-tetrahydro-1H-pyrazolo[4,3-*e*][1,3]thiazolo-[3,2-*a*]pyrimidinium Tribromide (5). To a solution of the thioether **4** (10 mmol) in acetic acid (20 ml) with constant stirring we slowly added bromine (20 mmol) dissolved in acetic acid (5 ml). The reaction mixture was stirred for a further 3 h. The yellow precipitate was filtered off and recrystallized from DMF. The yield was 79%; mp 189-191°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.84 (3H, s, N–CH$_3$); 4.63 (2H, s, S–CH$_2$); 7.60 (5H, m, C$_6$H$_5$); 7.70 (1H, s, =CHBr); 8.60 (1H, s, H-3); 10.45 (1H, s, =NH). Found, %: Br 52.03; N 11.38. $C_{15}H_{13}Br_4N_5S$. Calculated, %: Br 51.32; N 11.20.

(*Z*)-8-Iodomethylene-4-imino-1-methyl-5-phenyl-4,5,7,8-tetrahydro-1H-pyrazolo[4,3-*e*][1,3]thiazolo-[3,2-*a*]pyrimidinium Triiodide (6). To a solution of the thioether **4** (10 mmol) in acetic acid (20 ml) with constant stirring we slowly added iodine (20 ml) dissolved in acetic acid (40 ml). The reaction mixture was stirred for a further 3 h. The brown precipitate was filtered off and recrystallized from DMF. The yield 74%; mp 198-200°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.78 (3H, s, N–CH_3); 4.57 (2H, s, S–CH_2); 7.25, 7.43, 7.58 (5H, m, C_6H_5); 7.75 (1H, s, =CHI); 8.65 (1H, s, H-3); 10.57 (1H, s, =NH). ^{13}C NMR spectrum, δ, ppm: 34.8, 39.3, 83.0, 106.1, 124.1, 126.3, 129.5, 137.5, 139.7, 149.6, 151.1, 165.8. Found, %: I 63.26; N 8.72. $C_{15}H_{13}I_4N_5S$. Calculated, %: I 61.79; N 8.36.

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