Synthesis of vicinal aminoiodo- and (acetylamino)iodo-1-alkylpyrazoles

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3- and 5-(Acetylamino)-4-iodo-1-alkylpyrazoles were obtained by successive acylation and iodination from 3- and 5-amino-1-alkylpyrazoles without isolating intermediate (acetylamino)pyrazoles. 3- and 5-Iodo- and 3,5-diiodo-4-amino-1-methylpyrazoles were synthesized from appropriate iodonitropyrazoles by reduction with $SnCl_2$ in HCl.

Key words: reduction, iodopyrazoles, nitropyrazoles, aminopyrazoles.

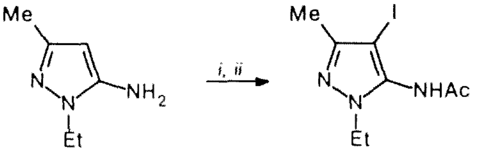
In comparative studies of the heterocyclization of diazonium salts of aryl- and hetarylacetylenes it has been shown that the behavior of 1,3-dimethyl-5-phenylethynylpyrazole-4-diazonium chloride and bromide differ from that of their benzene analogs.[1,2] Substrates with all possible variants of the arrangements of the interacting groups (C≡C, $N^+{\equiv}N/Cl^-$) are necessary for a systematic investigation of this reaction in a series of pyrazoles. This circumstance is quite significant if one takes into account the considerable difference between the electronic densities at positions 3, 4, and 5 in the pyrazole ring, which, in turn, may influence both the direction of heterocyclization and the ability of the molecule to add functional groups at the triple bond.[2,3]

In this connection, we took on the task of developing convenient methods for the synthesis of vicinal aminoiodopyrazoles and (acetylamino)iodopyrazoles, precursors of diazonium salts of acetylenylpyrazoles, which were then planned to be introduced into acetylene condensation followed by the elimination of acetyl protection and diazotization.

The choice of iodo- and not bromo- or chloroderivatives of pyrazole as the halo compound to be used in acetylene condensation was due to the excess of π-electrons in the heterocycle. Obviously, for the same reason, acylation of the amino group is also necessary in order to deactivate its donating influence and simultaneously stabilize the substrate.[4]

It should be noted that the synthesis of vicinal aminoiodo-1-alkylpyrazoles is poorly described in the literature. We found[5,6] that the oxidizing iodination of 1-methylpyrazoles with I_2—HIO_3 was effective, which induced us to study the possible application of this method to the synthesis of the target aminoiodo- and (acetylamino)iodo-1-alkylpyrazoles.

The synthesis of 5-acetylamino-1-ethyl-4-iodo-3-methylpyrazole (**2**) (yield 86%) was carried out by us *via* the acylation of amine **1** followed by iodination without isolation of the intermediate acetylamine.



1 **2**

i. Ac_2O, C_6H_6; *ii.* I_2, HIO_3, AcOH.

We studied the possibility of synthesizing 3-acetylamino-4-iodo-1-methylpyrazole (**3**) by oxidative iodination of available 1-methyl-4-nitropyrazole (**4**)[5] followed by the reduction of the 4-iodo-1-methyl-3-nitropyrazole (**5**) obtained to 3-amino-4-iodo-1-methylpyrazole with subsequent acylation of the latter. This method would have been more convenient than the alternative reduction of nitropyrazole **4** to 3-amino-1-methylpyrazole (**6**) followed by iodination, since the separation of aminopyrazole **6** from the reaction mixture is hindered by its high solubility in water.

However, the use of reducing agents of different types ($SnCl_2$, NH_2NH_2) added in direct and reverse order over a broad temperature range (20—100 °C) led to deiodination of nitroiodide **5** accompanied by its reduction to give aminopyrazole **6**. Thus, the synthesis of iodide **3** is possible only *via* the reduction of nitropyrazole **4** to amine **6** followed by its successive acylation and iodination resulting in the target product.

Significant problems emerge in the synthesis of 3- and 5-iododerivatives containing an amino- or acetylamino group at position 4 of the pyrazole ring. Attempts to directly iodinate 4-amino-1,3-dimethyl- (**7a**) and isomeric 4-amino-1,5-dimethylpyrazole (**8a**) as well as their *N*-acetyl derivatives (**7b**, **8b**) in the I_2—HIO_3 system failed. Long heating of acetylaminopyrazoles **7b** and **8b** led to the recovery of the starting compounds in 75—80% yield. Iodination of aminopyrazoles **7a** and **8a**

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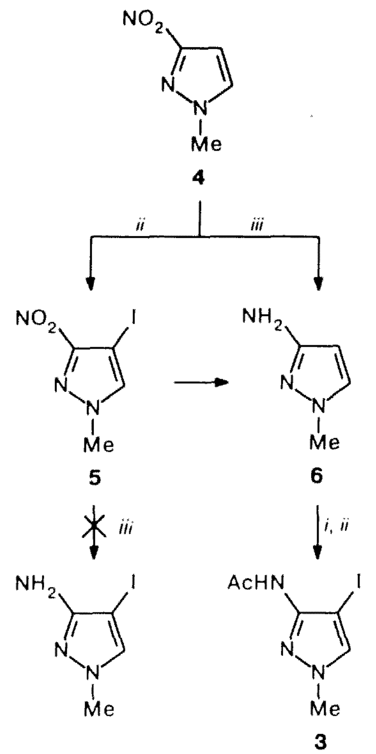
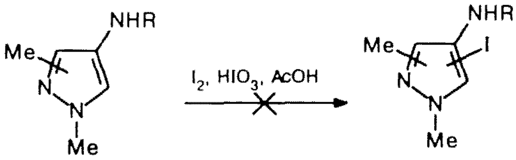


i. Ac_2O, C_6H_6; *ii.* I_2, HIO_3, AcOH; *iii.* $SnCl_2$, HCl.

is accompanied by resinification, and we could not identify any products of this reaction.

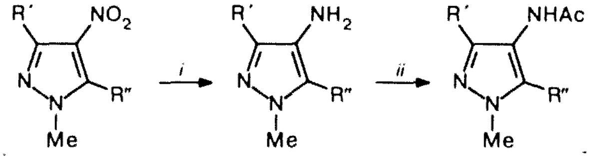


7a,b, 8a,b

7: 3-Me; **8:** 5-Me; **a:** R = H; **b:** R = Ac

The absence of iodination products was explained by us by the protonation of the amino group under the reaction conditions. A similar process seems to occur even for the acetylamino group, which occupies the most nucleophilic position of the pyrazole ring, position 4.

Another pathway for synthesizing iododerivatives of 4-(acetylamino)pyrazoles **9a—9d** is based on the use of available (owing to the nitrodeiodination of polyiododerivatives recently proposed by us[7,8]) 4-nitroiodo- and 4-diiodopyrazoles **10a—10d** as the starting compounds, which undergo reduction to amines **11a—11d** followed by acylation.



10a—d **11a—d** **9a—d**

a: R' = CH_3, R" = I; **c:** R' = I, R" = H;
b: R' = I, R" = CH_3; **d:** R' = I, R" = I

i. $SnCl_2$, HCl; *ii.* Ac_2O, C_6H_5.

It turned out that both the choice of the reagent and the order of its addition are important for the successful reduction of iodonitropyrazoles. Thus, when nitroiodides are reduced with hydrazine in boiling ethanol and *n*-butanol, only traces of amino derivatives form. The use of $SnCl_2$ in HCl at 60 °C according to the known procedure[4] allowed us to obtain aminoiodopyrazoles **11a,b** in 53 and 67% yields, respectively, whereas adding the reagents in the reverse order and a lower reaction temperature (30 °C) resulted in 86 and 90% yields of the target products. It is noteworthy that the order of addition of the reagents is of special importance when the amounts of reagents are increased. We determined that the decrease in the yields of aminoiodopyrazoles **11a,b** when reduction is carried out according to the procedure described in Ref. 4 is due to the formation of deiodination products **7a** and **8a**. Probably, this is caused by the fact that the iododerivative is in a large excess of $SnCl_2$, which leads to the reduction of not only the nitro group but also the iodine atom in aminoiodopyrazoles **11a—11c** formed.

Using a modified procedure, we also obtained rather labile 4-amino-3,5-diiodo-1-methylpyrazole (**11d**) in 64% yield.

Thus, convenient methods for the synthesis of different vicinal amino- and acetylamino-1-alkylpyrazoles have been proposed in the present work.

Experimental

^1H NMR spectra were recorded on a JEOL FX 90Q spectrometer at 25 °C (in $CDCl_3$). IR spectra were recorded on an UR-20 instrument.

5-Amino-1-ethyl-3-methylpyrazole (1) was obtained from diacetonitrile (24 g, 0.29 mol) and ethyl hydrazine (17.4 g, 0.29 mol) according to a known procedure.[9] The yield of compound **1** was 19.1 g (51.9%), m.p. 93—94 °C (from a hexane—benzene (1 : 1) mixture). Found (%): C, 57.54; H, 8.82; N, 33.35. $C_6H_{11}N_3$. Calculated (%): C, 57.57; H, 8.86; N, 33.57. IR ($CHCl_3$), ν/cm^{-1}: 3390, 3470 (NH_2).

5-Acetylamino-1-ethyl-4-iodo-3-methylpyrazole (2). Ac_2O (3 mL) was added dropwise to aminopyrazole **1** (3.14 g, 0.025 mol) in 30 mL of dry C_6H_6 and stirred at 30—40 °C for 30 min. I_2 (2.8 g, 0.011 mol), HIO_3 (1.23 g, 0.07 mol), AcOH (30 mL), and 30% H_2SO_4 (3 mL) were added to the suspension obtained and stirred at 50—60 °C for 2 h. Then the reaction mixture was diluted with 100 mL of H_2O, the mineral acid was neutralized with Na_2CO_3, and the solution was decolorized with Na_2SO_3. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (3×30 mL). The combined organic extracts were concentrated, and the residue was recrystallized from benzene. The yield of compound **2** was 6.34 g (86.2%), m.p. 156—157 °C. Found (%): C, 32.68; H, 4.01; I, 43.42. $C_8H_{12}IN_3O$. Calculated (%): C, 32.78; H, 4.13; I, 43.30. IR ($CHCl_3$), ν/cm^{-1}: 1715 (C=O); 3440 (NH). ^1H NMR ($CDCl_3$), δ: 1.35 (t, 3 H, $CH_2\underline{CH_3}$); 2.2 (s, 3 H, 3-CH_3); 2.3 (s, 3 H, CH_3CO); 4.0 (q, 2 H, $\underline{CH_2}CH_3$); 6.9 (br.s, 1 H, NH).

3-Acetylamino-4-iodo-1-methylpyrazole (3) was synthesized from 3-amino-1-methylpyrazole similarly to compound **2**,[10] yield 92.0%, m.p. 130—131 °C (from benzene). Found (%): C, 27.01; H, 3.08; I, 48.16. $C_6H_8IN_3O$. Calculated (%): C, 27.19; H, 3.04; I, 47.88. IR ($CHCl_3$), ν/cm^{-1}: 1705 (C=O); 3425 (NH). ^1H NMR ($CDCl_3$), δ: 2.35 (s, 3 H, CH_3CO); 3.86 (s, 3 H, NCH_3); 7.50 (s, 1 H, 5-H).

4-Amino-3-iodo-1,5-dimethylpyrazole (11b). A solution of $SnCl_2 \cdot 2H_2O$ (122 g, 0.54 mol) in 250 mL of conc. HCl was added with stirring to a solution of 3-iodo-1,5-dimethyl-4-nitropyrazole[7] (**10b**) (47.0 g, 0.176 mol) in 100 mL of HCl at 30 °C for 2 h. Then the HCl was removed *in vacuo*, 100 mL of H_2O was added, and the residue was neutralized with a 40% NaOH solution, extracted with $CHCl_3$ (6×100 mL), and dried with $MgSO_4$. The solvent was removed, and a residue was recrystallized from CCl_4. The yield of iodopyrazole **11b** was 37.8 g (89.9%), m.p. 69—70 °C. Found (%): C, 25.35; H, 3.50; I, 53.55. $C_5H_8IN_3$. Calculated (%): C, 25.33; H, 3.40; I, 53.54. IR ($CHCl_3$), ν/cm^{-1}: 3350, 3425 (NH_2).

4-Amino-5-iodo-1,3-dimethylpyrazole (11a) was synthesized from 5-iodo-1,3-dimethyl-4-nitropyrazole (**10a**) similarly to compound **11b**,[4] yield 86.0%, m.p. 109—111 °C[4] (from a hexane—chloroform mixture).

4-Acetylamino-3-iodo-1-methylpyrazole (9c). 3-Iodo-1-methyl-4-nitropyrazole[8] (**10c**) was reduced to 4-amino-3-iodo-1-methylpyrazole (**11c**) using procedures similar to those mentioned above. The oil obtained was acylated according to a procedure described earlier.[5] The total yield of compound **9** was 89.2%, m.p. 125—126 °C (from a benzene—ethyl acetate mixture, 2 : 1). Found (%): C, 27.40; H, 3.01; I, 49.61. $C_6H_8IN_3O$. Calculated (%): C, 27.19; H, 3.04; I, 47.88. IR ($CHCl_3$), ν/cm^{-1}: 1710 (C=O); 3395 (NH). ^1H NMR ($CDCl_3$), δ: 2.35 (s, 3 H, CH_3CO); 3.83 (s, 3 H, NCH_3); 7.54 (s, 1 H, 5-H).

4-Acetylamino-3,5-diiodo-1-methylpyrazole (9d). 3,5-Diiodo-1-methyl-4-nitropyrazole[7] (**10d**) was reduced to 4-amino-3,5-diiodo-1-methylpyrazole (**11d**) similarly to compound **10a**, yield 63.7%, m.p. 115—116 °C (from a hexane—chloroform mixture). IR ($CHCl_3$), ν/cm^{-1}: 3390, 3480 (NH_2). ^1H NMR ($CDCl_3$), δ: 3.85 (s, 3 H, NCH_3). Aminopyrazole **11d** was acylated according to a procedure described earlier.[5] The total yield of compound **9d** was 59.2%, m.p. 125—126 °C (from a benzene—ethyl acetate mixture, 2 : 1). Found (%): C, 18.62; H, 1.87; I, 65.31. $C_6H_7I_2N_3O$. Calculated (%): C, 18.43; H, 1.80; I, 64.92. IR ($CHCl_3$), ν/cm^{-1}: 1710 (C=O); 3425 (NH). ^1H NMR ($CDCl_3$), δ: 2.37 (s, 3 H, CH_3CO); 3.85 (s, 3 H, NCH_3).

The reduction of 4-iodo-1-methyl-3-nitropyrazole (5) was carried out similarly to the reduction of compounds **10a—10d**. 3-Amino-1-methylpyrazole (**6**) was isolated as the main reaction product, yield 51%, b.p. 90—92 °C (1 Torr), n_D^{20} 1.5410.[10]

4-Acetylamino-5-iodo-1,3-dimethylpyrazole (9a) was obtained from 8.2 g of aminopyrazole **11a** according to a known procedure.[5] The yield of product **9a** was 9.3 g (96.3%), m.p. 171—172 °C (from a hexane—chloroform mixture). Found (%): C, 30.27; H, 3.56; I, 45.98. $C_7H_{10}IN_3O$. Calculated (%): C, 30.13; H, 3.61; I, 45.47. IR ($CHCl_3$), ν/cm^{-1}: 1700 (C=O); 3460 (NH). ^1H NMR ($CDCl_3$), δ: 2.15 (s, 3 H, 3-CH_3); 2.20 (s, 3 H, CH_3CO); 3.80 (s, 3 H, NCH_3); 7.0 (br.s, 1 H, NH).

4-Acetylamino-3-iodo-1,5-dimethylpyrazole (9b) was obtained from 23.7 g of aminopyrazole **11b** according to a known procedure.[5] The yield of compound **9b** was 24.3 g (87.1%), m.p. 154—155 °C. Found (%): C, 30.23; H, 3.51; I, 45.60. $C_7H_{10}IN_3O$. Calculated (%): 30.13; H, 3.61; I, 45.47. IR ($CHCl_3$), ν/cm^{-1}: 1705 (C=O); 3440 (NH). ^1H NMR ($CDCl_3$), δ: 2.25 (s, 3 H, CH_3CO); 2.40 (s, 3 H, 5-CH_3); 3.81 (s, 3 H, NCH_3); 7.0 (br.s, 1 H, NH).

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