Noncyclic intermediate in the synthesis of pyrazolidinylpyrazoles

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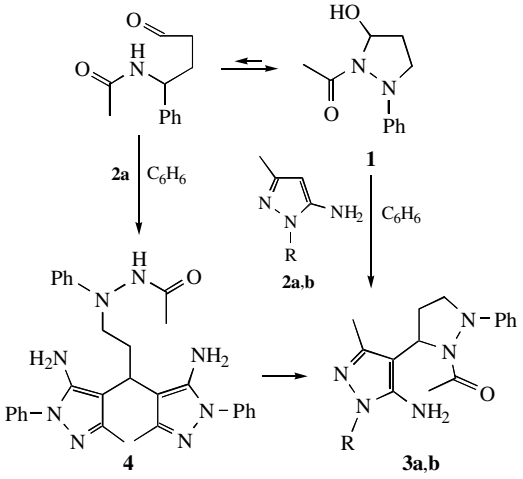
10.1070/MC2003v013n05ABEH001754

Hydroxypyrazolidine 1 reacts with 5-aminopyrazoles 2 to form selectively the products of substitution to 4 or 5-aminogroup positions; the isolated intermediate of interaction of noncyclic tautomer 1 with two molecules of aminopyrazole carried out the cyclization into 4-pyrazolidinyl-5-aminopyrazole eliminating one molecule of aminopyrazole.

The direct interaction of 5-hydroxypyrazolidine **1** with π-excess heterocycles can be a useful method for the synthesis of bis-heterocyclic molecules containing pyrazolidine. We found that the use of a solid adsorbent as a catalyst in this process leads to 4-pyrazolidinylpyrazolones-5[1] and 3-pyrazolidinyloxindoles-2[2] in considerable yields.

In this work, we introduced a pyrazolidine substituent into 5-aminopyrazoles **2**. We found that, in a boiling benzene solution, 5-aminopyrazoles react with **1** selectively at the 4-position to result in 4-pyrazolidinyl-5-aminopyrazoles **3a**,**b**.† The position of substituents in aminopyrazole products **3** can be easily determined by NMR spectroscopy. The 5′-H signal in the ^{1}H NMR spectra of these compounds is located at 5.15–5.20 ppm, and the 5′-C signal in the ^{13}C NMR spectra is located at 53.45–53.50 ppm. This suggests the C–C bond formation.

In case of aminopyrazole **2a**, product **4**† of the interaction of linear tautomer **1** with two molecules of aminopyrazole was isolated after 2 h from the reaction mixture cooled to room temperature. This intermediate **4** was converted slowly (10 h) into corresponding cyclic derivative **3a** eliminating one molecule of starting 5-aminopyrazole **2a** in solution under refluxing.



a R = Ph
b R = *p*-$NO_2C_6H_4$

† *General procedure and spectroscopic characteristics.* Starting 5-hydroxypyrazolidine **1** was prepared from 1-acetyl-2-phenylhydrazine and acroleine.[6] Aminopyrazoles **2a–c** were obtained using a published procedure.[7] ^{1}H and ^{13}C NMR spectra were measured on a VXR-400 Varian spectrometer in $CDCl_3$ solutions. Mass spectra were recorded using an MX1320A spectrometer.

Synthesis of 3-methyl-4-(1-acetyl-2-phenylpyrazolidin-5-yl)-5-aminopyrazoles **3a**,**b**. A solution of 5-hydroxypyrazolidine **1** (2.45 mmol) and 5-aminopyrazole **2a**,**b** (2.10 mmol) in benzene was refluxed for 15 h. Benzene was evaporated; the product was purified by flash chromatography (silica gel, 5–40 μm, EtOAc–hexane, 1:2 → 1:1). Yields of **3a**, 50%; **3b**, 48%.

Selected data for **3a**: ^{1}H NMR, δ: 1.74 (s, 3H, Me), 2.07 (s, 3H, Me), 2.26 (m, 1H, 4′-C*H*H′), 2.54 (m, 1H, 4′-CH*H*′), 3.35 (m, 1H, 3′-C*H*H′), 4.02 (m, 1H, 3′-CH*H*′), 4.88 (s, 2H, NH_2) 5.19 (t, 1H, 5′-H), 6.90–7.55 (m, 10H, Ph). ^{13}C NMR, δ: 13.90 (3-Me), 21.24 (*Me*CO), 29.20 (4′-C), 52.66 (3′-C), 53.51 (5′-C), 99.05 (4-C), 145.48 (3-C), 149.25 (5-C), 175.15 (Me*C*O), 115.14, 121.76, 123.67, 127.15, 128.26, 129.45, 138.72, 146.56 (Ph, Ph′).

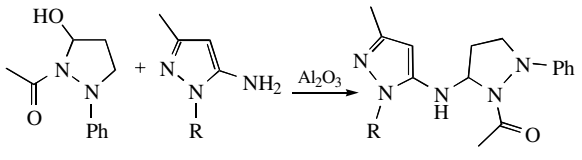
Selected data for **3b**: mp 147–149 °C. ^{1}H NMR, δ: 1.65 (s, 3H, Me), 2.04 (s, 3H, Me), 2.27 (m, 1H, 4′-C*H*H′), 2.51 (m, 1H, 4′-CH*H*′), 3.36 (m, 1H, 3′-C*H*H′), 4.02 (m, 1H, 3′-CH*H*′), 5.03 (s, 2H, NH_2) 5.15 (t, 1H, 5′-H), 6.90–7.20 (m, 10H, Ph), 7.71 (d, 2H, *p*-$NO_2C_6H_4$), 8.19 (d, 2H, *p*-$NO_2C_6H_4$). ^{13}C NMR, δ: 14.50 (3-Me), 21.25 (*Me*CO), 29.28 (4′-C), 52.40 (3′-C), 53.45 (5′-C), 101.25 (4-C), 144.15 (3-C), 146.38 (5-C), 175.60 (Me*C*O), 115.10, 121.98, 122.45, 125.10, 128.37, 129.50, 149.47, 151.30 (*p*-$NO_2C_6H_4$, Ph′). MS, *m*/*z* (%): 406 (25) [M$^+$], 365 (33), 257 (100), 255 (6), 243 (4), 211 (11), 163 (8), 146 (11), 106 (10), 104 (6), 91 (7), 77 (20).

2-Acetyl-bis-3,3-(5-amino-3-methyl-1-phenylpyrazol-4-yl)-1-phenylhydrazinopropane **4** was isolated from the reaction mixture for **3a** after refluxing for 2 h. The solution was cooled at room temperature; after 1 h, the product was filtered off and washed with benzene. Yield 68%. The conversion of **4** into **3a** was carried out in boiling benzene solution for 10 h checking by TLC-control and ^{1}H NMR spectroscopy.

Selected data for **4**: mp 165–167 °C. ^{1}H NMR, δ: 2.00 (d, 6H, 3-Me), 2.25 (s, 3H, COMe), 2.28 (m, 2H, 2-CH_2), 3.30 (m, 2H, 1-CH_2), 3.90–4.20 (m, 4H, 2-NH_2), 6.41 (m, 1H, N*H*Ac), 6.80 (m, 1H, 3-CH), 7.10–7.60 (15H, Ph). MS, *m*/*z* (%): 534 (20) [M$^+$], 361 (29), 358 (33), 319 (21), 303 (20), 212 (100).

Pyrazoles condense with aldehydes to give bispyrazolylmethane derivatives.[3] The structures similar to compound **4** were obtained in reactions of hydroxypyrazolidines with indoles.[4] We believe that the driving force of this process is the elimination of a stable aminopyrazole molecule with an attack on a new electrophilic centre. The interaction of **1** with pyrazolones[1] and oxindoles[2] evidently occurs similarly in spite of some difference in reaction conditions; however, the cyclization occurs more quickly, and such intermediates cannot be found.

In the presence of a fivefold excess of alumina, the interaction between **1** and **2** gives N-substituted derivatives **5a–c**‡ in 2 h. Compounds **3** or **4** were not detected. The 5′-H signal in the ^{1}H NMR spectra (5.85–6.00 ppm) and the 5′-C signal in the ^{13}C NMR spectra (66–69 ppm) of compounds **5** are downfield shifted in comparison with **3**. The 4-H signal of aminopyrazole was found in the same field as the 5′-H signal (5.90–5.95 ppm). The MS fragmentation of N-derivatives **5a–c** is characterised by the elimination of an acetylpyrazolinium fragment (*m*/*z* 189). Derivative **3b** does not undergo such a fragmentation, and the elimination of a hydrazine fragment from the pyrazolidine ring takes place. Note that the conversion of compounds **5** to C-isomers **3** does not occur in solution on heating.



a R = Ph
b R = *p*-$NO_2C_6H_4$
c R = CH_2Ph

The role of alumina can be related to its mild basic properties. It is well known that the base is able to activate the amino group

in 5-aminopirazoles. For instance, 1-phenyl-3-methyl-5-aminopyrazole **2a** reacts with aromatic aldehydes to result in products similar to compound **4**; in the presence of pyrrolidine, Schiff bases were obtained.[5]

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‡ *Synthesis of 5-(1-acetyl-2-phenylpyrazolidin-5-yl)amino-3-methylpyrazoles* **5a**–**c**. A fivefold excess of Al_2O_3 was added to a solution of equimolar amounts of **1** and **2a**–**c** in benzene. The mixture was stirred at 60 °C for 2 h, cooled and filtered. Alumina was washed with chloroform three times; the combined benzene solution and chloroform extracts were evaporated. The product was purified by flash chromatography (silica gel, 5–40 μm, EtOAc–hexane, 1:2 → 1:1). Yields of **5a**, 68%; **5b**, 51%; **5c**, 55%.

Selected data for **5a**: mp 145–147 °C. ^{1}H NMR, δ: 2.02 (s, 3H, Me), 2.14 (s, 3H, Me), 5.91 (s, 1H, 4-H), 1.91 (m, 1H, 4′-C*H*H′), 2.34 (m, 1H, 4′-CH*H*′), 3.48 (m, 1H, 3′-C*H*H′), 3.66 (m, 1H, 3′-CH*H*′), 3.70–3.80 (1H, NH), 5.85–5.91 (m, 1H, 5′-H), 6.90–7.55 (m, 10H, Ph). ^{13}C NMR, δ: 14.10 (3-Me), 21.18 (*Me*CO), 33.27 (4′-C), 52.23 (3′-C), 68.85 (5′-C), 90.58 (4-C), 145.03 (3-C), 149.40 (5-C), 114.10, 121.50, 124.03, 126.95, 128.00, 129.20, 138.36, 150.92 (Ph, Ph′). MS, *m*/*z* (%): 361 (16) [M$^+$], 213 (22), 190 (15), 189 (27), 173 (6), 172 (5), 147 (100), 146 (55), 104 (20), 91 (10), 77 (37).

Selected data for **5b**: mp 170–172 °C. ^{1}H NMR, δ: 2.05 (s, 3H, Me), 2.20 (s, 3H, Me), 5.95 (s, 1H, 4-H), 2.00–2.10 (m, 1H, 4′-C*H*H′), 2.39 (m, 1H, 4′-CH*H*′), 3.58 (m, 1H, 3′-C*H*H′), 3.78 (m, 1H, 3′-CH*H*′), 3.80–3.90 (1H, NH) 5.84–5.97 (m, 1H, 5′-H), 6.90–8.10 (m, 9H, Ph, *p*-$NO_2C_6H_4$). ^{13}C NMR, δ: 13.96 (3-Me), 20.96 (*Me*CO), 33.05 (4′-C), 51.96 (3′-C), 66.88 (5′-C), 92.62 (4-C), 143.93 (3-C), 146.57 (5-C), 176.0 (Me*C*O), 113.80, 121.48, 122.36, 124.51, 128.10, 129.10, 150.25, 151.25 (*p*-$NO_2C_6H_4$, Ph′). MS, *m*/*z* (%): 406 (6) [M$^+$], 257 (13), 256 (16), 189 (22), 163 (14), 147 (100), 146 (48), 104 (17), 91 (12), 77 (33).

Selected data for **5c**: mp 150–152 °C. ^{1}H NMR, δ: 2.04 (s, 3H, Me), 2.15 (s, 3H, Me), 5.90 (s, 1H, 4-H), 1.95 (m, 1H, 4′-C*H*H′), 2.28 (m, 1H, 4′-CH*H*′), 3.55–3.65 (m, 1H, 3′-C*H*H′), 3.40–3.50 (1H, NH), 3.55–3.65 (m, 1H, 3′-CH*H*′), 4.85–4.99 (m, 2H, CH_2Ph), 5.80–5.95 (m, 1H, 5′-H), 6.90–7.55 (m, 10H, Ph). ^{13}C NMR, δ: 13.85 (3-Me), 21.03 (*Me*CO), 33.0 (4′-C), 51.0 (3′-C), 67.0 (5′-C), 91.02 (4-C), 145.0 (3-C), 147.52 (5-C), 173.60 (Me*C*O), 50.94, 114.0, 121.30, 126.44, 127.20, 128.40, 128.95, 136.38, 150.75 (CH_2Ph, Ph′). MS, *m*/*z* (%): 375 (14) [M$^+$], 227 (26), 189 (25), 186 (7), 163 (16), 147 (100), 146 (63), 145 (10), 104 (25), 91 (66), 77 (31).

Received: 10th April 2003; Com. 03/2080