Synthesis of benzoylmethylpyrazolidine regioisomers on the surface of basic adsorbents: a competitive attack of crotonaldehyde at the two nitrogen atoms of 1,2-acetylphenylhydrazine

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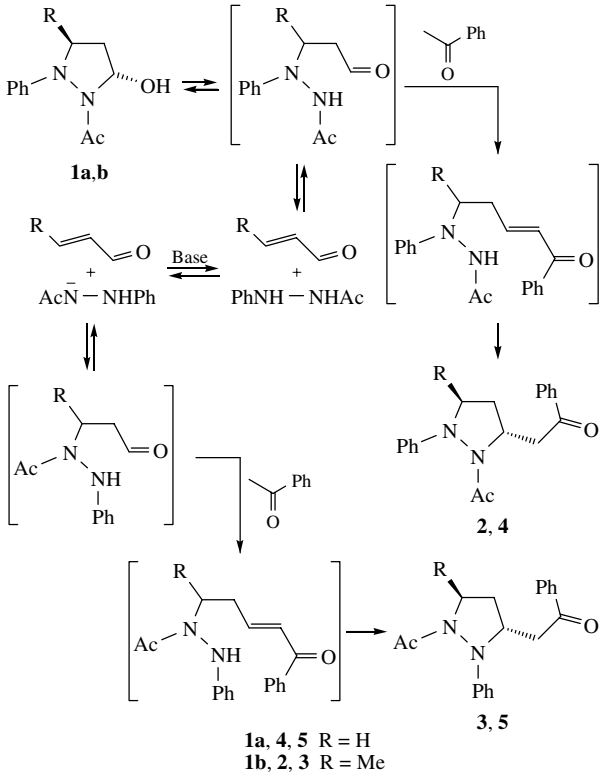
In the interaction of 5-hydroxypyrazolidines with acetophenone on the surface of basic adsorbents, regioisomeric 3-benzoylmethylpyrazolidine was formed along with expected 5-benzoylmethylpyrazolidine as a consequence of the retro-Michael degradation of the starting compounds followed by an attack of crotonaldehyde at the imide nitrogen atom.

Previously, we reported that the interaction of 1-acetyl-5-hydroxy-2-phenylpyrazolidine **1a** with various C-nucleophilic agents, including ketones, occurred at the surface of aluminium oxide with the formation of corresponding pyrazolidinyl methyl ketones.[1] We found that a homologue of compound **1a**, 1-acetyl-5-hydroxy-3-methyl-2-phenylpyrazolidine **1b**, does not react with ketones at the surface of aluminium oxide. The interaction of pyrazolidine **1b** with acetophenone occurs at the surface of potassium fluoride supported on aluminium oxide without a solvent at 80 °C. In this case, along with expected 5-benzoylmethyl derivative **2**,† its regioisomer, 3-benzoylmethyl derivative **3**, was isolated in a ratio of 1:4. Note that the formation of 3-functional pyrazolidine derivatives (regioisomers of previously prepared 5-derivatives) was not observed previously.

Taking into account the fact, which was observed previously, that pyrazolidine **1a** reacts with aminopyrazole through a linear form of hydroxypyrazolidine,[2] we assumed that the cause of the formation of regioisomer **3** also consists in the participation of linear hydroxypyrazolidine tautomer **1b**, which readily undergoes the retro-Michael degradation to a hydrazide and crotonaldehyde followed by reverse addition under conditions of basic catalysis, in the reaction.

Isomers **2** and **3** were separated on a dry column with silica gel. The IR and ^{1}H and ^{13}C NMR spectra of these isomers were almost identical. The mass-spectroscopic degradation of compounds **2** and **3** provides an opportunity to identify them: the isomeric pyrazolinium ions initially formed as a result of the removal of an acyl group ($M^+ - 43$) underwent degradation by different mechanisms.



† *Experimental procedures and spectroscopic characteristics*. Starting hydroxypyrazolidines **1a** and **1b** were prepared from 1-acetyl-2-phenylhydrazine and acroleine or crotonaldehyde, respectively.[3] The ^{1}H and ^{13}C NMR spectra were measured on a VXR-400 Varian spectrometer in $CDCl_3$ solutions.

Procedure A. A solution of 2.2 g (10 mmol) of hydroxypyrazolidine **1b** in 10 ml of benzene were mixed with 22 g of a KF/Al_2O_3 adsorbent, which was prepared in accordance with a published procedure,[4] containing 20% KF, and evaporated to dryness. A solution of 2.4 ml (15 mmol) of acetophenone was applied to 10 g of Al_2O_3 and evaporated to dryness. Both of the reagents supported on sorbents were mixed and heated in an evacuated ampule for 4 h at 80 °C. The reaction products were eluted from the support with a mixture of light petroleum and diethyl ether (1:1); the filtrate was evaporated, and the residue was separated on a dry column with silica gel (5/40) with the use of an ethyl acetate–light petroleum mixture for gradient elution from 1:10 to 1:1. The resulting reaction products were recrystallised from diethyl ether.

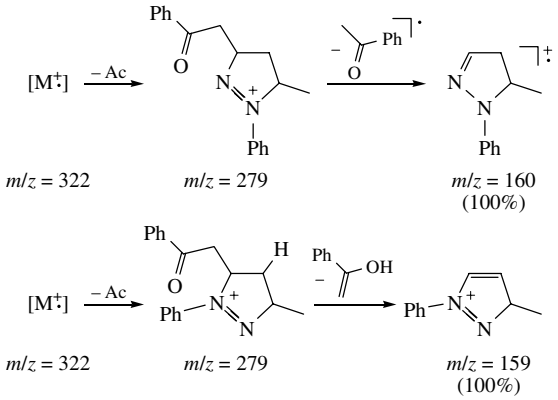
Procedure B. A mixture of 2.2 g (10 mmol) hydroxypyrazolidine **1b** and a tenfold amount (by weight) of barium hydroxide was ground in a mortar. The mixture was immediately placed in a closed vessel, and a solution of 2.4 ml (15 mmol) of acetophenone in 5 ml of light petroleum was added (70–100 °C). The reaction flask was purged with an inert gas, hermetically sealed and allowed to stand for several days at room temperature (TLC monitoring). The reaction products were isolated in accordance with *Procedure A*.

1-Acetyl-5-benzoylmethyl-3-methyl-2-phenylpyrazolidine **2**: yield 25% (*B*), mp 98–99 °C. ^{1}H NMR, δ: 1.21 (d, 3H, 3-Me), 2.02 (s, 3H, MeCO), 1.85 (m, 1H, 4-H), 2.25 (m, 1H, 4-H), 2.83 (dd, 1H, α-H), 4.10 (dd, 1H, α-H), 4.15 (m, 1H, 3-H), 4.76 (m, 1H, 5-H), 6.95–7.27 (5H, Ph), 7.40–7.90 (5H, COPh). ^{13}C NMR, δ: 19.5 (Me), 21.3 (Me), 38.2 (C^4), 44.6 (α-CH_2), 53.7 (C^3), 61.7 (C^5), 115.0 (*o*-PhN), 121.7 (*p*-PhN), 128.1 (*m*-PhN), 128.5 (*m*-PhCO), 129.2 (*o*-PhCO), 133.2 (*p*-PhCO), 136.3 (*i*-PhCO), 150.4 (*i*-PhN), 174.6 (COMe), 197.8 (COPh). IR, ν/cm^{-1}: 1650 (CO amide), 1690 (CO ketone). MS, *m*/*z* (%): 322 (29.7) [M$^+$], 279 (94.1), 160 (100), 159 (21), 145 (24.8), 133 (5), 118 (32.7).

1-Acetyl-3-benzoylmethyl-5-methyl-2-phenylpyrazolidine **3**: yield 16% (*A*), mp 124–125 °C. ^{1}H NMR, δ: 1.50 (d, 3H, 5-Me), 1.83 (s, 3H, MeCO), 1.95 (m, 1H, 4-H), 2.10 (m, 1H, 4-H), 2.83 (dd, 1H, α-H), 3.38 (dd, 1H, 4-H), 4.40 (m, 1H, 5-H), 4.70 (m, 1H, 3-H), 6.95–7.55 (10H, Ar). ^{13}C NMR, δ: 21.18 (Me), 21.25 (Me), 38.2 (C^4), 40.1 (α-C), 52.6 (C^3), 62.9 (C^5), 115.6 (*o*-PhN), 121.9 (*p*-PhN), 127.9 (*m*-PhN), 128.6 (*m*-PhCO), 128.9 (*o*-PhCO), 133.3 (*p*-PhCO), 136.6 (*i*-PhCO), 150.2 (*i*-PhN), 173.8 (COMe), 197.6 (COPh). IR, ν/cm^{-1}: 1650 (CO amide), 1690 (CO ketone). MS, *m*/*z* (%): 322 (15.9) [M$^+$], 279 (7), 159 (100), 118 (32.7), 105 (72.3).

1-Acetyl-5-benzoylmethyl-2-phenylpyrazolidine **4** (prepared in accordance with *Procedure A*): yield 5%, mp 102–103 °C. ^{1}H NMR, δ: 2.10 (s, 3H, MeCO), 1.70 (m, 1H, 4-H), 2.50 (m, 1H, 4-H), 2.88 (dd, 1H, α-H), 4.12 (dd, 1H, α-H), 3.35 (m, 1H, 3-H), 3.82 (m, 1H, 3-H), 4.75 (m, 1H, 5-H), 7.0–7.9 (10H, Ph). IR, ν/cm^{-1}: 1660 (CO amide), 1680 (CO ketone). MS, m/z (%): 308 (4.2) [M+], 265 (52.8), 146 (62.0), 145 (21.1), 105 (100).

1-Acetyl-3-benzoylmethyl-2-phenylpyrazolidine **5** (prepared in accordance with *Procedure A*): yield 3%, oil. ^{1}H NMR, δ: 1.85 (s, 3H, MeCO), 1.90 (m, 1H, 4-H), 2.25 (m, 1H, 4-H), 2.82 (dd, 1H, α-H), 3.40 (dd, 1H, α-H), 3.46 (m, 1H, 5-H), 4.10 (m, 1H, 5-H), 4.62 (m, 1H, 3-H), 7.0–7.45 (10H, Ph). IR, ν/cm^{-1}: 1660 (CO amide), 1680 (CO ketone). MS, *m*/*z* (%): 308 (4.2) [M$^+$], 265 (12.0), 145 (100), 105 (31.7).



According to NOE data, both of the compounds exhibit the *trans* structure [$\eta_{3\text{-H}}$(4-H) = 6.30%; $\eta_{5\text{-H}}$(4′-H) = 4.41% for **2** and $\eta_{3\text{-H}}$(4-H) = 4.10%; $\eta_{5\text{-H}}$(4′-H) = 3.65% for **3**], which is explained by an optimum combination of stereoelectronic factors.

If the process was performed at the surface of barium hydroxide at room temperature, the ratio between isomers changed to 2.5:1. It is likely that an elevated temperature of the process on potassium fluoride was favourable for the formation of isomer **3**.

3-Unsubstituted hydroxypyrazolidine **1a** reacts with acetophenone on neutral and acidic aluminium oxide with no regioisomer formation,[1] whereas the formation of two regioisomers **4** and **5** in a ratio of 3:2 occurred on the surface of KF/Al_2O_3 at 80 °C, as well as in the case of pyrazolidine **1b**. Here, the same mass-spectrometric degradation was observed as in compounds **2** and **3**: the formation of stable radical ions with *m/z* 146 for 5-derivative **4** and an ion with *m/z* 145 for 3-substituted compound **5**.

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