1,3-Dipolar Cycloadditions of Diazoalkanes to Pyridazine Derivatives. Thermal 1,5-Sigmatropic Rearrangement of Methyl Groups in 3,3-Dimethyl-3*H*-pyrazolo[3,4-*d*]pyridazine Derivatives

Branko Stanovnik*, Boris Jelen, Anton Štimac and Miha Tišler

Department of Chemistry, Edvard Kardelj University,
61000 Ljubljana, Yugoslavia

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Thermal 1,5-sigmatropic rearrangements of one of the methyl group attached at position 3 of 3,3-dimethyl-3*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-ones **1-3** taking place either in a clock-wise or anti-clockwise direction gave N_2-methylated products **4-6** and C_{3a}-methylated products **7-9**. The -7(6)-one derivative **10** and -4,7(5*H*,6*H*)-dione derivative **12** gave only N_2-methylated products **11** and **13** respectively, and 1,2-dihydro derivative **14** produced after elimination of methane, **15**.

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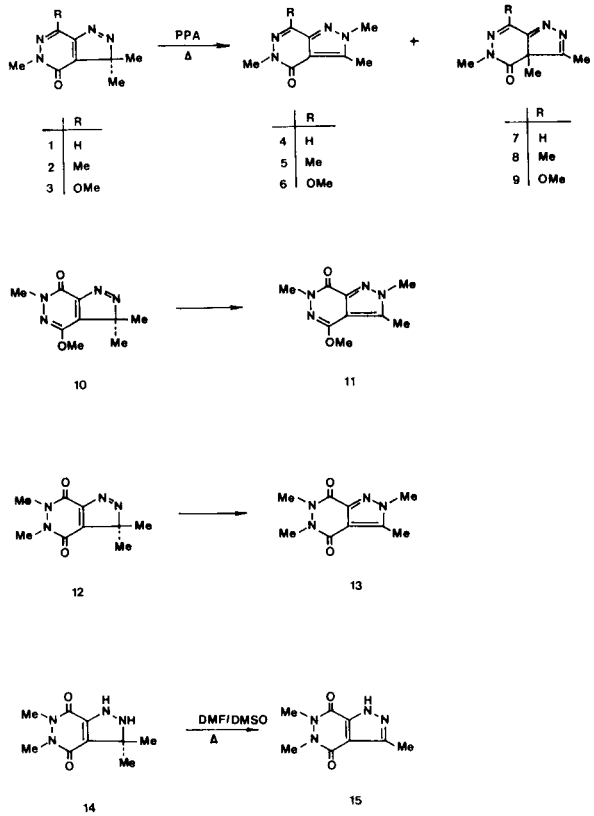
Recently, we have observed a thermal 1,5-sigmatropic rearrangement of one of the methyl groups of 7-phenyl-3,3,5-trimethyl-3*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-one in polyphosphoric acid to give two isomeric compounds [1], analogous to those reported earlier in monocyclic 3*H*-pyrazole series [2].

In this communication we report on some other examples of 1,5-sigmatropic methyl group migration. The following examples were selected: 3,3-dimethyl-3*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-ones **1**, **2**, and **3**, isomeric -7(6*H*)-one **10**, and -4,7(5*H*,6*H*)-dione **12**. The -4(5*H*)-ones **1**, **2**, and **3**, when heated in polyphosphoric acid at 120° for 30 minutes, followed after cooling, by neutralization with concentrated aqueous solution of ammonia and separation by flash chromatography, gave the isomeric N- and C-methylated products **4** and **7** in a ratio of 1:1, **5** and **8** in a ratio of 1:1, and **6** and **9** in a ratio of 3:1, respectively. The isomeric -7(6*H*)-one **10** gave only N-methylated product **11**, and similarly -4,7(5*H*,6*H*)-dione **12** produced also only the N-methylated product **13**. While the yields of isomeric pairs obtained from compounds **1-3** are practically quantitative, the yields of **11** and **13** are only 58% and 52%, respectively. The formation of the products can be explained as a thermal 1,5-sigmatropic migration of one of the methyl groups attached at position 3 either in a clockwise direction around the pyrazole ring to give N_2-methylated products or in anti-clockwise direction to give C_{3a}-methylated products (Scheme 1).

On the other hand, when the 1,2-dihydro derivative **14** was heated either in the solid state at 190° or in the mixture of DMF and DMSO at reflux temperature elimination of one methyl group from position 3 in the form of methane was observed to give trimethyl derivative **15**.

The structural assignments of rearranged products were made on the basis of ^1H and ^{13}C nmr spectra. The signals for methyl groups attached at N_{3a} in isomers **4-6**, **11** and **13** appear in the ^1H nmr spectra at lower field (δ = 3.6 to 3.9 ppm) than the signals for methyl groups attached at

Scheme 1



C_{3a} in isomers **7-9** (δ = 2.1 to 2.3 ppm). This is further confirmed by ^{13}C nmr spectra. The C_4 in C_{3a} methylated isomers **7-9** appears as a multiplet (two overlapped quartets) due to the long range couplings with the protons of methyl groups attached at C_{3a} and N_5 with coupling constants $^3J \cong 3$ Hz, while in N_2-methylated isomers it appears only as a broad singlet (narrow quartet) due to the long range coupling with the protons of the methyl group attached at N_5 with a coupling constant $^3J \cong 2$ Hz. The ^1H nmr spectrum of **15** shows three singlet for three methyl groups at δ 2.50, 3.54, and 3.56 ppm, corresponding to one methyl group at-

tached at position 3 of the pyrazole part of the molecule and two methyl groups attached at N_5 and N_6 of the pyridazine ring.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage. The ^1H and ^{13}C nmr spectra were recorded on a JEOL FX 90Q FT spectrometer with TMS as internal standard. Elemental analyses for C, H, and N were obtained on a PERKIN-ELMER CHN Analyser 240 C.

The following compounds were prepared according to the procedures described in the literature: 3,3,5-trimethyl-3*H*-pyrazolo-[3,4-*d*]pyridazin-4(5*H*)-one (**1**) [3], 3,3,5,7-tetramethyl-3*H*-pyrazolo-[3,4-*d*]pyridazin-4(5*H*)-one (**2**) [3], 7-methoxy-3,3,5-trimethyl-3*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-one (**3**) [3], 4-methoxy-3,3,6-trimethyl-3*H*-pyrazolo[3,4-*d*]pyridazin-7(6*H*)-one (**10**) [4], 3,3,-5,6-tetramethyl-3*H*-pyrazolo[3,4-*d*]pyridazine-4,7(5*H*,6*H*)-dione (**12**) [4], and 3,3,5,6-tetramethyl-1,2-dihydro-3*H*-pyrazolo[3,4-*d*]-pyridazine-4,7(5*H*,6*H*)-dione (**14**) [4].

Thermal Rearrangement of 3*H*-Pyrazolo[3,4-*d*]pyridazine Derivatives.

General Method.

A mixture of the corresponding substituted 3,3,5-trimethyl-3*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-one **1-3**, **10** or **12** (0.002 mole) in polyphosphoric acid (2 g) was heated on the oil bath at 120° for 30 minutes. After cooling, water (5 ml) was added and the mixture was neutralized with aqueous ammonia (25%) and extracted with chloroform (3 times, 15 ml each time). The combined extracts were dried with anhydrous sodium sulphate, the solvent was evaporated *in vacuo* and the residue was separated by flash chromatography (Kieselgel 60, 0.040-0.063, E. Merck). The first fraction eluted with diethyl ether, gave, after evaporation of the solvent, the isomers **4**, **5** and **6**, the second fraction gave, after elution with acetone the isomers **7**, **8**, and **9**, respectively. The compounds **10** and **12** gave only one isomer each. In this manner the following compounds were prepared:

2,3,5-Trimethyl-2*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-one (**4**).

This compound was prepared from **1** in 50% yield, mp 160-162° (from *n*-heptane); ^1H nmr (deuteriochloroform): δ 2.65 (s, 3-Me), 3.65 (s) and 3.92 (s) (2-Me and 5-Me), 7.98 (s, H_7).

Anal. Calcd. for $C_8H_{10}N_4O$: C, 53.92; H, 5.66; N, 31.44. Found: C, 53.69; H, 5.76; N, 31.52.

3,3a,5-Trimethyl-3a*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-one (**7**).

This compound was obtained from **1** in 50% yield, mp 133-134° (from *n*-heptane); ^1H nmr (deuteriochloroform): δ 2.15 (s, 3a-Me), 8.35 (s, 3-Me), 3.74 (s, 5-Me), 7.85 (s, H_7); ^{13}C nmr (deuteriochloroform): δ 154.8 (m, C_4), 144.5 (br s, C_{7a}), 133.1 (m, C_3), 128.9 (d, C_7, $^1J_{CH}$ = 191.5 Hz), 112.6 (m, C_{3a}), 39.1 (q, 5-Me, $^1J_{CH}$ = 142 Hz), 12.0 (q) and 7.5 (q) (3-Me and 3a-Me, $^1J_{CH}$ = 128 Hz).

Anal. Calcd. for $C_8H_{10}N_4O$: C, 53.92; H, 5.66; N, 31.44. Found: C, 54.20; H, 5.66; N, 31.12.

2,3,5,7-Tetramethyl-2*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-one (**5**).

This compound was prepared from **2** in 50% yield, mp 148-149° (from *n*-heptane); ^1H nmr (deuteriochloroform): δ 2.41 (s) and 2.66 (s) (3-Me and 7-Me), 3.62 (s) adn 3.91 (s) (2-Me and 5-Me); ^{13}C nmr (deuteriochloroform): δ 159.1 (q, $^3J_{C\text{-}5Me}$ = 2.0 Hz, C_4), 145.2 (q, C_{7a}, $^3J_{C\text{-}6Me}$ = 2.5 Hz), 140.0 (m, C_{3a}), 139.6 (q, C_7, $^2J_{C\text{-}Me}$ = 7 Hz), 112.2 (q, C_3, $^2J_{C\text{-}Me}$ = 2.5 Hz), 37.7 (q, 2-Me, $^1J_{CH}$ = 140.5 Hz), 37.1 (q, 5-Me, $^1J_{CH}$ = 142 Hz), 16.8 (q, 7-Me, $^1J_{CH}$ = 128 Hz), 10.5 (q, 3-Me, $^1J_{CH}$ = 130.5 Hz).

Anal. Calcd. for $C_9H_{12}N_4O$: C, 56.24; H, 6.29; N, 29.15. Found: C, 55.91; H, 6.38; N, 29.20.

3,3a,5,7-Tetramethyl-3a*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-one (**8**).

This compound was prepared from **2** in 50% yield, mp 120-122° (*n*-heptane); ^1H nmr (deuteriochloroform): δ 2.25 (s, 3a-Me), 2.33 (s) and 2.43 (s) (2-Me and 7-Me), 3.66 (s, 5-Me); ^{13}C nmr (deuteriochloroform): δ 154.7 (m, C_4), 144.5 (br s, C_{7a}), 138.4 (q, C_7, $^2J_{C\text{-}Me}$ = 7 Hz), 133.1 (m, C_3), 113.1 (m, C_{3a}), 38.5 (q, 5-Me, $^1J_{CH}$ = 141.5 Hz), 19.1 (q, 7-Me, $^1J_{CH}$ = 130 Hz), 12.1 (q, $^1J_{CH}$ = 128.5 Hz) and 8.7 (q, $^1J_{CH}$ = 129 Hz) (3-Me and 3a-Me).

Anal. Calcd. for $C_9H_{12}N_4O$: C, 56.24; H, 6.29; N, 29.15. Found: C, 56.01; H, 6.18; N, 29.29.

7-Methoxy-2,3,5-trimethyl-2*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-one (**6**).

This compound was prepared from **3** in 75% yield, mp 134-137° (from *n*-heptane); ^1H nmr (deuteriochloroform): δ 2.65 (s, 3-Me), 3.56 (s) and 3.92 (s) (2-Me, 5-Me and OMe); ^{13}C nmr (deuteriochloroform): 158.4 (q, C_4, $^3J_{C\text{-}5Me}$ = 2.0 Hz), 146.8 (q, C_7, $^3J_{C\text{-}OMe}$ = 3.5 Hz), 140.6 (m, C_{3a}), 139.0 (s, C_{7a}), 113 (m, C_3), 54.1 (q, OMe, $^1J_{CH}$ = 147 Hz), 37.4 (q, 2-Me, $^1J_{CH}$ = 140 Hz), 37.2 (q, 5-Me, $^1J_{CH}$ = 142 Hz), 10.2 (q, 3-Me, $^1J_{CH}$ = 128.5 Hz).

Anal. Calcd. for $C_9H_{12}N_4O_2$: C, 51.92; H, 5.81; N, 26.91. Found: C, 52.05; H, 5.97; N, 27.05.

7-Methoxy-3,3a,5-trimethyl-3a*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-one (**9**).

This compound was prepared from **3** in 25% yield, mp 124-127° (*n*-heptane); ^1H nmr (deuteriochloroform): δ 2.19 (s, 3a-Me), 2.24 (s, 3-Me), 3.61 (s) and 3.88 (s) (5-Me and OMe); ^{13}C nmr (deuteriochloroform): δ 154.5 (m, C_4), 147.4 (q, C_7, $^3J_{C\text{-}Me}$ = 3.5 Hz), 127.7 (br q, C_3, $^2J_{C\text{-}Me}$ = 4.5 Hz), 113.8 (m, C_{3a}), 54.4 (q, OMe, $^1J_{CH}$ = 147 Hz), 38.7 (q, 5-Me, $^1J_{CH}$ = 142.5 Hz), 12.0 (q, $^1J_{CH}$ = 128 Hz) and 8.1 (q, $^1J_{CH}$ = 129.5 Hz) (3-Me and 3a-Me).

Anal. Calcd. for $C_9H_{12}N_4O_2$: C, 51.92; H, 5.81; N, 26.91. Found: C, 52.01; H, 5.92; N, 27.29.

4-Methoxy-2,3,6-trimethyl-2*H*-pyrazolo[3,4-*d*]pyridazin-7(6*H*)-one (**11**).

This compound was prepared from **10** in 58% yield, mp 185-187° (from *n*-heptane); ^1H nmr (deuteriochloroform): δ 2.53 (s, 3-Me), 3.60 (s), 3.85 (s) and 3.95 (s) (2-Me, 6-Me, and OMe).

Anal. Calcd. for $C_9H_{12}N_4O_2$: C, 51.92; H, 5.81; N, 26.91. Found: C, 51.78; H, 5.82; N, 26.63.

2,3,5,6-Tetramethyl-2*H*-pyrazolo[3,4-*d*]pyridazine-4,7(5*H*,6*H*)-dione (**13**).

This compound was prepared from **12** in 52% yield, mp 203-205° (from ethanol); ^1H nmr (deuteriochloroform): δ 2.62 (s, 3-Me), 3.52 (s), 3.70 (s) and 3.79 (s) (2-Me, 5-Me, and 6-Me).

Anal. Calcd. for $C_9H_{12}N_4O_2$: C, 51.92; H, 5.81; N, 26.91. Found: C, 51.60; H, 5.89; N, 26.72.

3,5,6-Trimethyl-1*H*-pyrazolo[3,4-*d*]pyridazine-4,7(5*H*,6*H*)-dione (**15**).

Method A: A solution of **14** (210 mg) in a mixture of DMF (1 ml) and DMSO (0.3 ml) was heated under reflux for 3 hours. The precipitate formed after cooling was collected by filtration to give **15** (62 mg, 32%), mp >300° (from ethanol); ^{1}H nmr (DMSO-d_6): 95° δ 2.50 (s, 3-Me), 3.54 (s) and 3.56 (s) (5-Me and 7-Me), NH (exchanged).

Anal. Calcd. for $C_8H_{10}N_4O_2$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.69; H, 5.30; N, 29.21.

Method B: The solid **14** (210 mg) was heated in a test tube at 190°. The evolution of methane ceased approximately after 30 minutes of heating and the product was recrystallized from ethanol to give **15** (128 mg, 66%), mp >300°. The compound was identical in every respect with the compound obtained according to the method A.

REFERENCES AND NOTES

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