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1,4-Cycloaddition of pyrazole with mesityl oxide; solid-state structure of bicyclic [$C_6H_5Me_3N_2(OH)$]Cl

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Abstract—The synthesis of bicyclic 6-hydroxy-6,8,8-dimethyl-5-aza-1-azonia-bicyclo[3.3.0]octa-1,3-diene chloride, [$C_6H_5Me_3N_2(OH)$]Cl, (**5**) by the HCl-catalyzed 1,4-cycloaddition of pyrazole (**1**) with mesityl oxide (**4**) is described. A proposed mechanism for the formation of **5** will be given. © 2003 Elsevier Science Ltd. All rights reserved.

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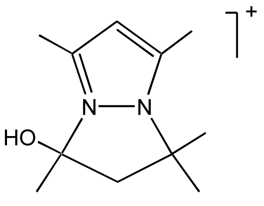
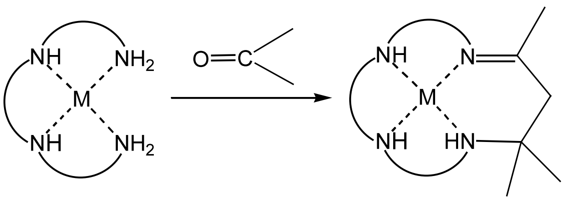
1. Introduction

The synthesis of nitrogen-containing macrocycles can be achieved by the reaction of multidentate amines with organic carbonyls.[1–3] In this respect, a wide range of macrocycles is accessible by, for example, the template aldol-like reaction of acetone with transition metal complexes of multidentate amines (Scheme 1).



A



Scheme 1. Template synthesis of nitrogen-containing macrocycles.[1,2]

Nitrogen-containing macrocycles can also be prepared by *non*-template synthetic routes. In 1981 Bailey and McCleverty reported the isolation of the bicyclic salt [$C_6H_3Me_5N_2(OH)$][$I_{1/2}(I_3)_{1/2}$] (type **A** molecule), which was obtained as a side-product in the reaction of degassed ethanol-free acetone with Mo{HB(3,5-Me_2-C_3HN_2)$_3$}(NO)I_2 (3,5-Me_2-C_3HN_2=3,5-dimethyl-pyrazole).[4]

The formation of **A** is presumably the result of the addition of mesityl oxide, derived from the aldol condensation of acetone, across the N–N bond of 3,5-dimethyl-pyrazole.[5] Nevertheless, the direct synthesis of **A** from pyrazole, mesityl oxide and traces of HI could not be achieved.

We describe now an efficient route for the preparation of a molecule of type **A**.

2. Results and discussion

In order to synthesize osmium pyrazole complexes, we reacted OsO_2 with pyrazole in a MeOH/Me_2CO mixture and in the presence of HCl (0.1 mol L^{-1}). In this reaction the title compound [$C_6H_5Me_3N_2(OH)$]Cl (**5**) could be isolated in very low yield.[6] Short reaction times (2 h) lead to the selective formation of the osmium(VI) complex [$OsO_2Cl_2(pz)_2$] (pz = pyrazole),[7] while prolonged heating produces mainly [$C_6H_5Me_3N_2(OH)$]$_2OsCl_6$.[6] Compound **5** is presumably the result of a 1,4-cycloaddition of in situ generated mesityl oxide with pyrazole.

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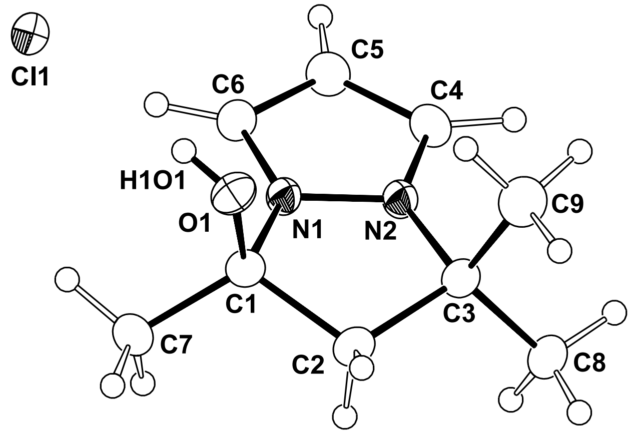


Figure 1. Molecular geometry of **5** with the atom numbering scheme. Important interatomic bond distances (Å) and angles (°) are: N1–N2 1.3360(15), N1–C1 1.4975(13), N1–C6 1.3382(14), N2–C3 1.4853(14), N2–C4 1.3373(14), C1–C2 1.5272(18), C2–C3 1.5382(16), C4–C5 1.3877(19), C5–C6 1.3866(17), N1–C1–C2 99.45(9), C1–C2–C3 108.12(9), C2–C3–N2 99.44(9), C3–N2–N1 113.28(9), N2–N1–C1 111.84(9), N1–C6–C5 103.37(11), C6–C5–C4 106.57(10), C5–C4–N2 107.30(12), N2–N1–C6 109.32(9).

In an attempt to estimate the reaction mechanism of this 1,4-cycloaddition, we reacted pyrazole with acetone in the presence of HCl. In the course of this reaction, mesityl oxide was formed in high yield as the result of an aldol condensation, as could be demonstrated by mass-spectrometry. This prompted us to study the influence of acids on this reaction. We found that on addition of traces of acid (0.001 mol L^{-1}), on a mixture of 3,5-dimethyl-pyrazole and mesityl oxide, no reaction between the respective starting materials takes place. Nevertheless, by rising the amount of acid to 0.1–0.2 mol L^{-1}, formation of **5** is observed. By addition of HCl to pyrazole and acetone in a 2:1 molar ratio, compound **5** is formed in 90% yield (elemental analysis of **5**: $C_9H_{15}ClN_2O$ (202.71); calcd C, 53.32; H, 7.47; N, 13.82. Found: C, 52.82; H, 7.14; N, 13.60%) (Eq. (1)). Crystallization of **5** from MeOH at 25°C affords colorless crystals. The structure of **5** was established by single X-ray crystal analysis (Fig. 1). Interatomic bond distances (Å) and angles (°) are summarized in the legend of Figure 1.

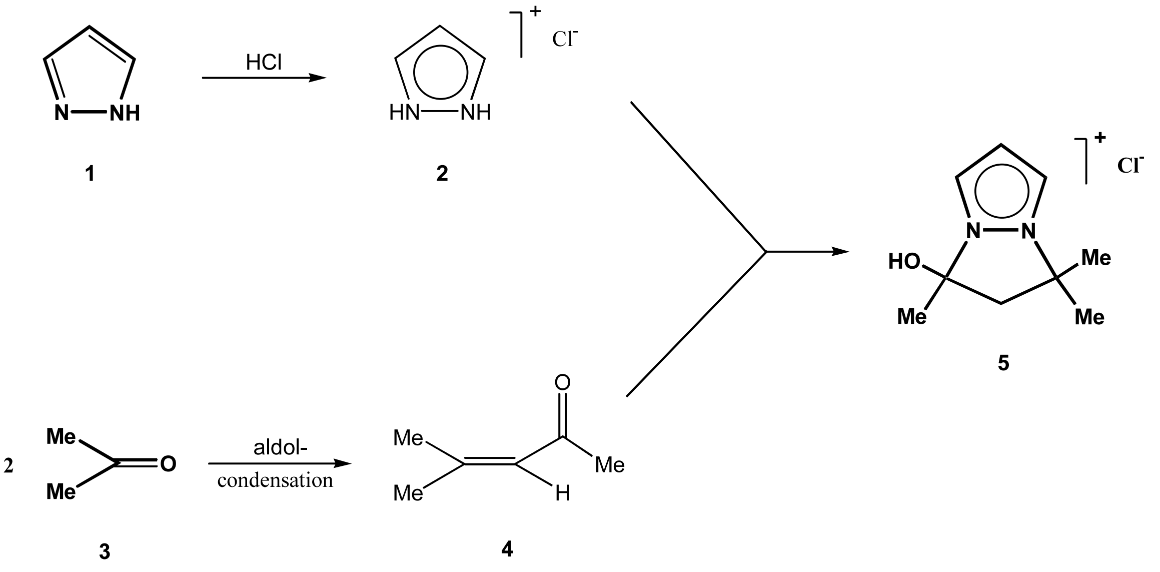
Compound **5** crystallizes in the monoclinic space group $P2(1)_n$. The π-conjugated N1–N2–C4–C5–C6 is, as expected, planar (r.m.s. deviation of fitted atoms 0.0018 Å) (Fig. 1). The saturated N1–N2–C1–C2–C3 ring is folded along the N1–N2 axis [interplanar angle 3.97(0.04)°] and adopts an envelope-like conformation, being folded along C1–C3 by 28.67(0.06)°, which results in a zig-zag overall shape (Fig. 1). The same structural motif was found for $[C_6H_3Me_5N_2(OH)][I_{1/2}(I_3)_{1/2}]$.[5]

In the ^1H NMR spectrum of **5** resonance signals are observed at 6.84 and 8.19 ppm for the CH moieties, while the protons of the CH_2 unit appear at 4.71 ppm and are, as the resonance signals for the CH_3 groups (1.69 and 1.96 ppm), compared with the CH entities, highfield shifted. The HO unit is found at 2.95 ppm as broad signal.

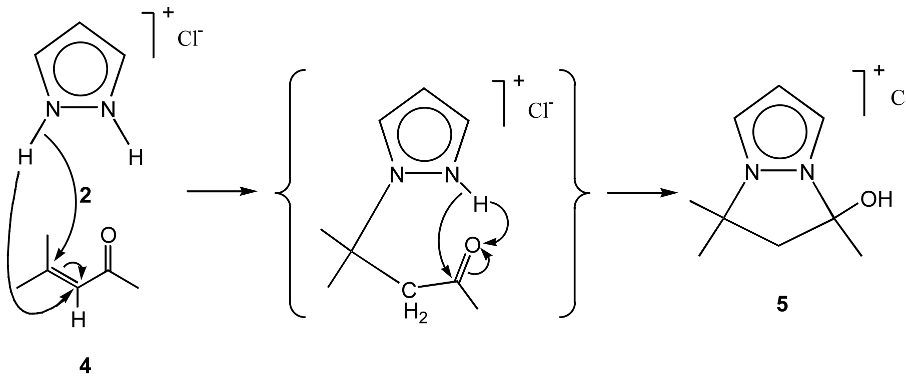
In the $^{13}C\{^1H\}$ NMR spectrum the carbon atoms of the CH units appear at 113.4, 127.5 and 129.9 ppm. The signals of the sp^3-hybridized carbon atoms are found at 54.5 ppm for the CH_2 unit, and for the CH_3 entities at 25.9, 27.3 and 28.1 ppm, while the carbon atoms of the $\underline{C}Me_2$ and $\underline{C}(Me)(OH)$ units appear at 66.9 and 93.0 ppm.

In the IR spectrum the ν_{OH} absorption is observed at 3100 cm^{-1}. Further typical bands are found at 1227 cm^{-1} [ν(C–O)] and at 1410 cm^{-1} [$\delta_{as}(CH_3)$]. The absorptions at 1508 and 1652 cm^{-1} can be assigned to the C=C and C=N stretching vibrations.

A possible mechanism for the formation of **5** is outlined in Scheme 2.[5] Based on the earlier studies of Bailey and McCleverty, **5** is formed in a similar manner. However, we were able to show that the mesityl oxide does not



(1)



Scheme 2. Proposed mechanism for the formation of **5** upon addition of **4** to **2**.

react with free pyrazole, rather it reacts with the pyrazolium chloride salt $[C_3H_5N_2]^+Cl^-$ to produce **5** (Scheme 2).

Most important for the proposed mechanism (Scheme 2) is the availability of pyrazole in its protonated form $[C_3H_5N_2]^+Cl^-$ (**2**) (reaction of **1** with HCl). This salt reacts then with the mesityl oxide **4**, formed by aldol condensation of two molecules of acetone, in a 1,4-cycloaddition to give **5**.

Acknowledgements

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