

SYNTHESIS OF α -HYDROXYDIMETHYLACETALS FROM NITROGEN HETEROCYCLIC KETONES USING HYPERVALENT IODINE OXIDATION

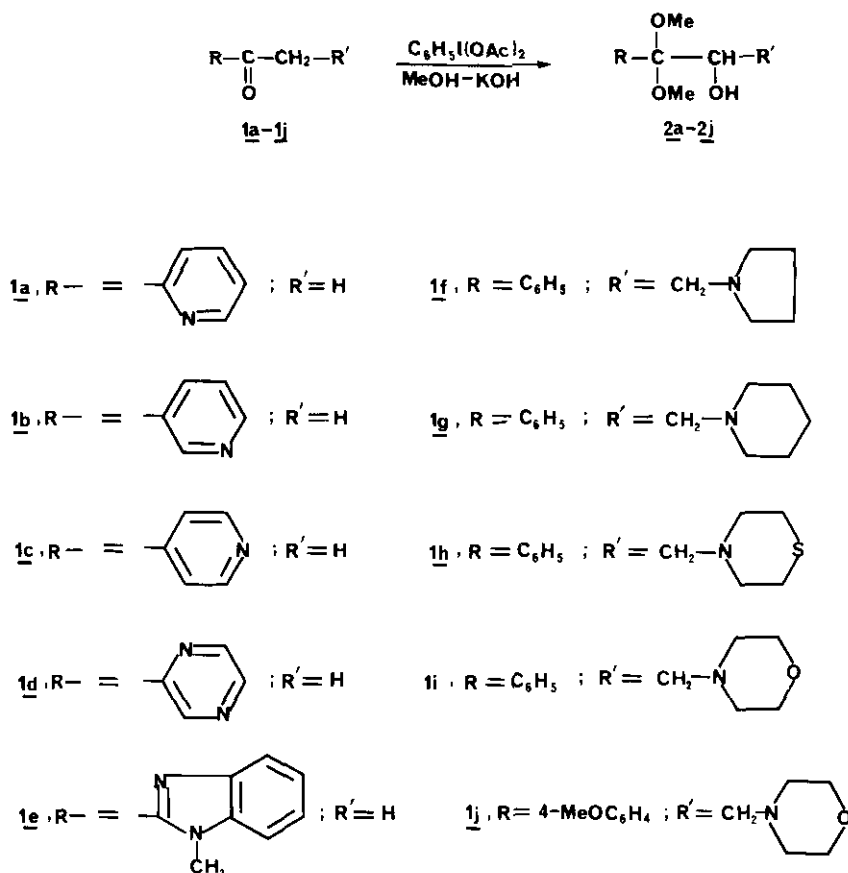
Robert M. Moriarty^{*a}, Om Prakash^a, Cyriac T. Thachet,^a and Hikmat A. Musallam^b

^aChemistry Department, University of Illinois at Chicago

^bDepartment of Army, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D.C. 20307

Abstract - The synthesis of various α -hydroxydimethylacetals (2a-2j) has been achieved by the oxidation of nitrogen containing heterocyclic ketones (1a-1j) using $C_6H_5I(OAc)_2$ -KOH-MeOH. The nmr and mass spectra of the acetals are discussed.

In a previous communication¹ we showed that various aminoketones can be converted into the corresponding α -hydroxydimethylacetal using either *o*-iodosobenzoic acid or iodobenzene diacetate (KOH/MeOH) without oxidation at the amino group. We now report the application of the hypervalent iodine oxidative method² to several nitrogen containing heterocyclic ketones, namely 2-acetyl-, 3-acetyl-, 4-acetylpyridines (1a-1c), acetylpyrazine (1d), 2-acetyl-1-methylbenzimidazole (1e) and various Mannich base aminoketones (1f-1j). The derived α -hydroxydimethylacetals (2a-2j) were obtained in good yield when aminoketones (1a-1j) were treated with 1.1 equivalents of iodobenzene diacetate and 3 equivalents of potassium hydroxide in methanol (Scheme 1). α -Hydroxydimethylacetals (2a-2j) were prepared with a view towards their conversion *via* ketones to the oxime methiodides. These compounds are potential reactivators for diisopropyl fluorophosphonate inhibited acetylcholinesterase.³ However, the hydrolysis of the acetals was not straightforward and initially either starting material or uncharacterized products were obtained in most of the cases. Acetals 2b and 2j could be hydrolysed with aqueous HCl. Results of the reactivation properties of these compounds will be published elsewhere.

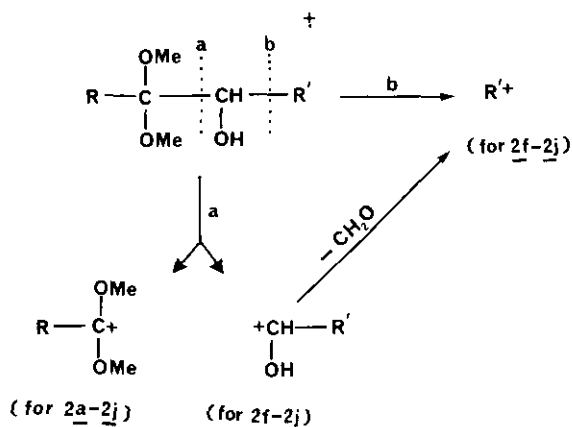


Scheme 1

The structures of these acetals are based upon correct elemental analyses and spectral properties. The two methoxy groups (in the acetals) are diastereotopic if the adjacent carbon is chiral e.g. compounds 2f-2j. The nmr spectra of 2f-2j showed two singlets (2f shows at δ 3.30 and 3.43) while other acetals (2a-2e), which do not contain chiral carbon adjacent to the acetal carbon atom, exhibit a singlet absorption peak which corresponds to six protons due to the equivalent acetal methoxy groups. In 2f-j the C₂-methine proton is unequally coupled to the C₃-diastereotopic protons, J_{2-3A} , 3Hz, J_{2-3B} , 11Hz.

The ir spectra of all acetals showed absorption due to -OH stretching ($\sim 3500 \text{ cm}^{-1}$) and no absorption peaks attributed to carbonyl groups thereby indicating the absence of starting ketone. The mass spectral data of the acetals also support the structural assignments. The most characteristic feature in the mass spectra is the loss of R'-CH-OH (pathway a) from the parent molecular ion to yield the R-C⁺

(OCH₃)₂ ions which appear as the base peak in 2a-2e. The base peak in the cases of 2f-2j results from the cleavage of the molecules via pathway b while pathway a affords two prominent ions due to R-C⁺(OCH₃)₂ and R'-C⁺H-OH. The latter ions can also furnish R'⁺ after the loss of CH₂O. The molecular ions in all these acetals have very low intensity (Scheme 2).



Scheme 2

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ir spectra were obtained using a Unicam SP1000 ir spectrophotometer and peak positions are expressed in cm⁻¹. ¹H NMR spectra were recorded at 60 MHz in CDCl₃ (2a-2j) or D₂O (1f-1h hydrochloride) with TMS as internal reference. Chemical shifts are given in ppm (δ). Hydroxyl signals were identified by deuteration. Mass spectra were measured with a Hewlett Packard GC/MS 5985 apparatus operating at 20 eV. All acetals (2a-2j) were recrystallized from hexane unless otherwise stated.

Availability of aminoketones. 2-Acetyl-, 3-acetyl-, 4-acetylpyridines and acetylpyrazine are commercially available (Aldrich). 2-Acetyl-1-methylbenzimidazole was prepared according to the literature procedure which involves three steps - (i) formation of 2-α-hydroxyethylbenzimidazole (3).⁴ (ii) Oxidation of alcohol 3 by CrO₃ to 2-acetylbenzimidazole (4).⁵ (iii) Methylation of 4 using Me₂SO₄.⁵ Mannich base ketones (1f-1j) were prepared using the procedure of Mannich and Lammering.⁶ A typical preparation is given below.

1-(Phenyl)-3-(1'-pyrrolidiny)propanone hydrochloride (1f). A mixture of 10.8 g (0.1 mole) of pyrrolidine hydrochloride, 0.25 ml of concentrated hydrochloric acid, 4.5 g (0.15 mole) of paraformaldehyde, 30 ml of absolute ethanol, and 12.0 g (0.1 mole) of acetophenone were heated to reflux. After 1 h, 3.0 g (0.1 mole) of paraformaldehyde was added to the solution and refluxing was continued for 2 h. To the hot mixture was added 250 ml of boiling acetone, and the resulting solution was cooled slowly, finally in ice water. The white crystalline product, mp 160-162°C (lit.⁷ mp 163-164°C) was collected by filtration in 66% yield. IR (nujol): 1675 (>C=O str); NMR δ : 1.92 (6 H m, O=C-CH_2 and four pyrrolidiny protons), 3.42 [(6 H m, $\text{N}^+(\text{CH}_2)_3$], 7.64 (5 H m, aromatic protons).

The following Mannich bases were prepared using the above procedure.

1-Phenyl-3-(1'-piperidiny)propanone hydrochloride (1g). Yield, 81%; mp 190-192°C (lit.⁶ mp 192-193°C); IR (Nujol): 1675 (>C=O str); NMR δ : 1.88 (8 H m, O=C-CH_2 and six piperidiny protons), 3.60 [(6 H m, $\text{N}^+(\text{CH}_2)_3$],

1-Phenyl-3-(4'-thiomorpholinyl)propanone hydrochloride (1h). Yield, 54%; mp 177-179°C (lit.⁸ mp 181.1-183°C); IR (Nujol): 1675 (C=O str); NMR δ : 2.18 [2 H m, O=C-CH_2], 3.00 [4 H m, $\text{N}^+(\text{CH}_2)_3$], 7.60 (3 H m, aromatic protons), 8.00 (2 H m, aromatic protons).

3-(4'-Morpholinyl)-1-phenylpropanone hydrochloride (1i). Yield, 78%; mp 175-178°C (lit.⁹ mp 177-179°C); IR (Nujol): 1670 (>C=O str).

1-(4-Methoxyphenyl)-3-(4'-Morpholinyl)propanone hydrochloride (1j). yield, 80%; mp 212-214°C (lit.¹⁰ mp 207.5°C); IR (Nujol): 1670 (>C=O str).

General procedure for preparation of α -hydroxydimethylacetals. Potassium hydroxide (0.15 mole for 1a-1e and 0.20 mole for 1f-1j) was dissolved in methanol (80-100ml) with ice cooling and a solution of the aminoketone (or hydrochloride of 1f-1j) (0.05 mole) in methanol was added dropwise through a pressure equalized addition funnel with stirring over a period of 30 min. Then solid iodobenzene diacetate (0.055 mole) was added in small portions during 10 min. The reaction mixture was allowed to stir at room temperature overnight. Most of the methanol was evaporated in vacuo and to the residue water (150-200ml) was added. The resulting mixture was saturated with potassium carbonate or ammonium chloride and extracted with ether (5x50ml). The combined ether extracts were dried (MgSO_4) and concentrated in vacuo to yield the crude product containing iodobenzene. Final isolation and purification were done by crystallization or chromatography. The methods of isolation, purification and properties of these acetals are given below:

2,2-Dimethoxy-2-(2'-pyridinyl)ethanol (2a). It was obtained in 61% yield from column chromatography using CH_2Cl_2 : $\text{CH}_3-\text{C}(\text{O})-\text{CH}_3$ (95:5) as eluent ($R_f=0.35$), mp 58-59°C. Anal. Calcd for $\text{C}_9\text{H}_{13}\text{NO}_3$: C, 59.02; H, 7.10; N, 7.65. Found: C, 59.23; H, 7.40; N, 7.53. NMR δ : 2.15 (1H s, -OH), 3.25 [(6H s, $\text{C}_2-(\text{OCH}_3)_2$], 3.94 (2H s, CH_2OH), 7.25 (1H m, $\text{C}_4\text{'-H}$), 7.75 (2H m, $\text{C}_3\text{'-H}$, $\text{C}_5\text{'-H}$), 8.60 (1H m, $\text{C}_6\text{'-H}$); MS: m/z 183 (M^+ , 0.5), 166(1), 152(100), 136 (5) 78 (8).

2,2-Dimethoxy-2-(3'-pyridinyl)ethanol (2b). Crude product, a brown viscous oil was dissolved in a mixture of hexane and ether (60:40) and decanted leaving some undissolved brown oil. On keeping the solution in refrigerator for 2 days, colorless crystalline product separated. Filtering, washing with cold hexane and drying gave pure 2b, mp 88-89°C, in 40-45% yield. Anal. Calcd for $\text{C}_9\text{H}_{13}\text{NO}_3$: C, 59.02; H, 7.10; N, 7.65. Found: C, 58.92; H, 7.06; N, 7.63. NMR δ : 3.26 [6H s, $\text{C}_2-(\text{OCH}_3)_2$], 3.79 (2H s, $-\text{CH}_2\text{OH}$), 7.21 (1H m, $\text{C}_4\text{'-H}$), 7.80 (1H m, $\text{C}_5\text{'-H}$), 8.33 (1H m, pyridinium proton), 8.60 (1H d, pyridinium proton); MS: m/z 183 (M^+ , 0.3) 152 (100), 122 (2), 120 (9), 106 (16), 78 (4).

2,2-Dimethoxy-2-(4'-pyridinyl)ethanol (2c). Addition of hexane to the crude product turned an oil to a crystalline solid which was recrystallized from hexane-ether (70:30) to give pure 2c as colorless crystalline solid, mp 95-96°C; in 58% yield. Anal. Calcd for $\text{C}_9\text{H}_{13}\text{NO}_3$: C, 59.02; H, 7.10; N, 7.65. Found: C, 59.31; H, 7.45; N, 7.51. NMR δ : 3.25 [(6H s, $\text{C}_2-(\text{OCH}_3)_2$], 3.75 (2H s, CH_2OH), 7.42 (2H m, $\text{C}_3\text{'-H}$ and $\text{C}_5\text{'-H}$), 8.60 (2H m, $\text{C}_2\text{'-H}$ and $\text{C}_6\text{'-H}$); MS: m/z (183, M^+ , 0.8), 166 (5), 152 (100), 137 (7), 120 (33), 106 (76), 93 (12), 92 (48), 78 (21),

2,2-Dimethoxy-2-(pyrazinyl)ethanol (2d). Crude product was purified using crystallization process as for 2c. Colorless crystalline product, mp 99-100°C, was obtained in 62% yield. Anal. Calcd for $\text{C}_8\text{H}_{12}\text{N}_2\text{O}_3$: C, 52.17; H, 6.52; N, 15.22. Found: C, 52.03; H, 6.59; N, 15.07. NMR δ : 3.33 [(6H s, $\text{C}_2-(\text{OCH}_3)_2$], 4.01 (2H s, CH_2OH), 8.58 (2H m, pyrazinium protons), 8.97 (1H m, pyrazinium proton); MS m/z 184 (M^+ , 0), 153 [($\text{M}-31$) $^+$, 100], 139(9), 129 (6), 121 (23), 107 (9), 105 (11), 93 (21), 80 (12), 79 (26).

2,2-Dimethoxy-2-(1-methyl-2-benzimidazolyl)ethanol (2e). Colorless crystalline product, mp 133-136°C, was obtained in 65% yield using procedure as described for 2c. Anal. Calcd for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_3$: C, 61.02; H, 6.78; N, 11.86. Found: C, 60.84; H, 6.81; N, 11.81. NMR δ : 3.22 [6H s, $\text{C}_2-(\text{OCH}_3)_2$], 3.83 (3H s, $-\text{N}_1\text{'-CH}_3$), 3.95 (2H s, $-\text{CH}_2\text{-OH}$); MS: 237 (1) m/z 236 (M, 1) 205 (100), 191 (43) 159 (22), 147 (6), 146 (30), 133 (9), 132 (19), 131 (21), 105 (5) 104 (8).

1,1-Dimethoxy-1-phenyl-3-(1-pyrrolidinyl)propan-2-ol (2f). Crystalline acetal, mp

77-78°C, was obtained in 25% yield by dissolving the crude oil in hexane and keeping the solution in refrigerator for 2-3 days. Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.92; H, 8.68; N, 5.28. Found C, 67.69; H, 8.73; N, 5.20. NMR: 1.73 (4H bs, C_3 -H₂ and C_4 -H₂), 2.40 (6H m, N_1 '-(CH₂)₃), 3.30 (3H s, -C₁'-OCH₃), 3.43 (3H s, -C₁-OCH₃), 3.55 (1H s, -OH), 4.12 (1H dd, C_2 -H), (J_{2-3A} = 3Hz, J_{2-3B} = 12Hz), 7.40 (5H m, aromatic protons); MS: m/z 265 (M^+ , 0.4), 235 (3), 151, (16), 114 (12), 105 (3), 84 (100) 70 (1).

1,1-Dimethoxy-1-phenyl-3-(1'-piperidiny)propan-2-ol (2g).¹ The acetal, mp 80-81°C, was obtained in 50% yield from the crude product using crystallization process as for 2f. Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.82; H, 8.96; N, 5.02. Found: C, 68.58; H, 9.03; N, 4.95. NMR δ : 1.45 (6 H m, C_3 -H₂, C_4 -H₂ and C_5 -H₂), 2.25 (6 H m, N_1 '-(CH₂)₃), 3.23 (3H s, C_1 -OCH₃), 3.38 (3H s, C_1 -OCH₃), 4.05 (1H dd, C_2 -H) (J_{2-3A} = 3Hz, J_{2-3B} = 12Hz) 7.35 (5H m, aromatic protons) MS: m/z 279 (M^+ , 0.6), 151 (46), 128 (52), 98 (100), 84 (1).

1,1-Dimethoxy-1-phenyl-3-(4'-thiomorpholinyl)propan-2-ol (2h).¹ Colorless solid separated out when water was added to the residual reaction mixture which was obtained after evaporation of methanol. Hexane (20ml) was added and the resulting mixture was stirred for 5 min. Filtering the solid under suction, washing with cold hexane and water, and then drying gave pure product (recrystallization from EtOH), mp 129-130°C, in 65% yield. Anal. Calcd for $C_{15}H_{23}NO_3S$: C, 60.61; H, 7.74; N, 4.71. Found: C, 60.45; H, 7.68; N, 4.76. NMR δ : 3.22 (3H s, C_1 -OCH₃), 3.38 (3H s, C_1 -OCH₃), 4.07 (1H dd, C_2 -H), (J_{2-3A} = 3Hz, J_{2-3B} = 11Hz) 7.35 (5H m, aromatic protons) 1.95-2.62 (10 H); MS: m/z 297 (M^+ , 1), 151 (20), 146 (6), 116 (100), 105 (11), 88 (11).

1,1-Dimethoxy-1-phenyl-3-(4'-morpholinyl)propan-2-ol (2i).¹ Colorless crystalline product, mp 75-77°C, was obtained in 60% yield by crystallization as described for 2f. Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.06; H, 8.18; N, 4.98. Found: C 63.92; H, 8.11; N, 5.02. NMR δ : 2.40 [(6H m, N_4 '-(CH₂)₃), 3.65 [(4H t, O_1 '-(CH₂)₂), 3.25 (3H s, C_1 -OCH₃), 3.40 (3H s, C_1 -OCH₃) 4.11 (1H dd, C_2 -H), (J_{2-3A} = 3Hz, J_{2-3B} = 11Hz) 7.37 (5H m, aromatic protons); MS: 281 (M^+ , 1), 251 (7), 264 (1), 232 (5), 105 (18), 100 (100) 151 (48), 130 (18).

1,1-Dimethoxy-1-(4-methoxyphenyl)-3-(4'-morpholinyl)propan-2-ol (2j). Using the same crystallization process as described for 2f, colorless crystalline acetal (2j), mp 96-97°C, was obtained in 44% yield. Anal. Calcd. for $C_{16}H_{25}NO_5$: C, 61.74; H, 8.04; N, 4.50. Found: C, 61.67; H, 8.06; N, 4.40. NMR δ : 2.34 [(6H m, N_4 '-(CH₂)₃), 3.24 (3H s, C_1 -OCH₃), 3.37 (3H s, C_1 -OCH₃), 3.65 [4H t, O_1 '-(CH₂)₂], 3.82

(3H s, 4-OCH₃-C₆H₄), 4.12 (1H dd, C₂-H) ($J_{2-3A} = 3\text{Hz}$, $J_{2-3B} = 11\text{Hz}$), 3.00 (1H s, OH), 6.90 (2H m, aromatic protons), 7.43 (2H m, aromatic protons); MS: m/z 311 (M^+ , 1), 281 (5), 266 (3), 263 (6), 181 (80), 130 (40), 100 (100).

ACKNOWLEDGEMENT

The authors thank the USAMRDC for support of this work under contract DAMD 17-83-C-3107, (contribution number 1744 to the Army Research Program on Antiparasitic Drugs) and the Petroleum Research Fund PRF-14773-AC1.

REFERENCES

1. R. M. Moriarty, O. Prakash, P. Karalis and I. Prakash, Tetrahedron Lett., 1984, 25, 4745.
2. R. M. Moriarty, H. Hu and S. C. Gupta, Tetrahedron Lett., 1981, 22, 1283; R. M. Moriarty, L. S. John and P. C. Du, J. Chem. Soc. Chem. Commun., 1981, 641; R. M. Moriarty, S. C. Gupta, H. Hu, D. R. Berenschot and K. B. White, J. Am. Chem. Soc., 1981, 103, 686; R. M. Moriarty and H. Hu, Tetrahedron Lett., 1981, 22, 2747; R. M. Moriarty and K. C. Hou, Tetrahedron Lett., 1984, 25, 691.
3. J. G. Clement, Biochem. Pharmac., 1982 31, 1283.
4. M. A. Phillips, J. Chem. Soc., 1928, 2393.
5. G. W. H. Cheeseman, J. Chem. Soc., 1964 4645.
6. C. Mannich and D. Lammering, Ber., 1922, 55B, 3510.
7. J. Mills, U. S. Patent, 1953, 2655, 509; Chem. Abstr., 1954, 48, 13726d.
8. F. Asinger, H. Offermanns, A. Saus, C. Dudeck, D. Neuray and E. Wilms, Montash. Chem., 1973 104, 118.
9. O. Takachiyo, J. Pharm. Soc. Japan, 1956 76, 1.
10. E. Profft, F. Runge and A. Jumar, J. Prakt. Chem., 1954, 1, 57; Chem. Abstr., 1956, 50, 988a.

Received, 5th November, 1984