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Regioisomeric oximes and thiosemicarbazones derived from 6-substituted pyridoxines

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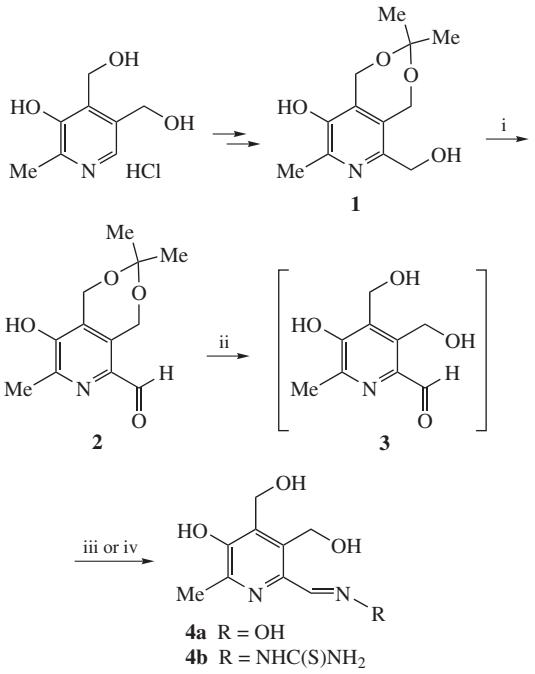
The selective oxidation of 2- and 4-positioned hydroxymethyl groups of 6-methyl-2,3,4-tris(hydroxymethyl)pyridin-5-ol was developed and the thus obtained aldehydes were converted into their oximes and thiosemicarbazones.

Thiosemicarbazones and oximes of pyridinecarboxaldehydes as well as their metal complexes are the subject of great interest in chemistry and biology,[1–4] in particular, transition metal complexes with pyridoxal thiosemicarbazone (one of the forms of vitamin B_6).[5–7]

No less interesting is the oxime of pyridoxal which has structural similarities with oxime pyridine derivatives used as antidotes against organophosphorus poisoning.[8,9] One of the major disadvantages of pyridine oximes is their high toxicity, so the oximes based on derivatives of pyridoxine which combine the structural proximity with pyridine oximes and low toxicity as derivatives of natural compounds can seem promising.

In continuation of systematic studies of the 6-hydroxymethyl pyridoxine derivatives carried out in our group[10,11] herein we developed regioselective oxidation of hydroxymethyl groups in 6-methyl-2,3,4-tris(hydroxymethyl)pyridin-5-ol to the corresponding aldehydes. The latter were converted into their oximes and thiosemicarbazones, which seem to be important precursors for a wide range of biologically active compounds.

In order to selectively oxidize 2-positioned CH_2OH group, acetonide protection could be a solution (Scheme 1). To this, seven-membered ketal **1** (prepared from pyridoxine hydrochloride[10]) was treated with activated manganese dioxide in aqueous ethanol giving the corresponding aldehyde **2** in a yield of ~65%. Removal of acetonide protection in compound **2** in acidic medium led to the product **3** which was unstable and therefore was used in subsequent transformations without isolation. Treatment of aldehyde **3** with hydroxylamine hydrochloride or thiosemicarbazide afforded oxime **4a** and thiosemicarbazone **4b**, respectively.†



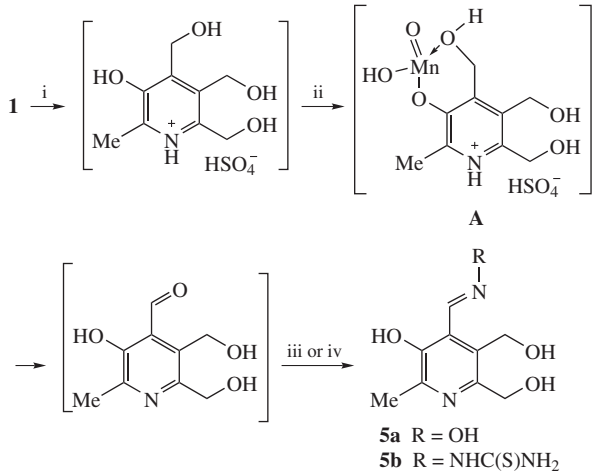
Scheme 1 *Reagents and conditions*: i, MnO_2, EtOH, H_2O, 40 °C, 6 h; ii, HCl, H_2O, EtOH, 20 °C, 8 h; iii, $NH_2OH{\cdot}HCl$, AcONa, H_2O, reflux, 5 min; iv, $NH_2NHC(S)NH_2$, EtOH, reflux, 10 h.

To access regioisomers of compounds **4a** and **4b** we used a different approach (Scheme 2) involving the initial removal of

† For synthesis and characteristics of compound **2**, see Online Supplementary Materials.

5-Hydroxy-3,4-bis(hydroxymethyl)-6-methylpyridine-2-carboxaldehyde oxime **4a**. Conc. HCl (1 ml) was added to a solution of compound **2** (0.6 g, 2.53 mmol) in 20 ml of water and the mixture was stirred for 4 h at room temperature. The solution was neutralized with aqueous K_2CO_3 and then AcONa (0.4 g, 4.88 mmol) and $NH_2OH{\cdot}HCl$ (0.26 g, 3.74 mmol) were added and the mixture was refluxed for 5 min. Then a solution was cooled to 5 °C and kept at this temperature for about 24 h. The precipitate formed was filtered off and washed with water. Yield 0.28 g (44%), brown crystals, mp 164–165 °C (decomp.). ^{1}H NMR (DMSO-d_6) δ: 2.35 (s, 3H, Me), 4.68 (d, 2H, CH_2, $^3J_{HH}$ 5.6 Hz), 4.80 (s, 2H, CH_2), 4.89 (t, 1H, OH, $^3J_{HH}$ 5.6 Hz), 8.19 (s, 1H, CH=N), 11.25 (s, 1H, N–OH). Found (%): C, 50.34; H, 5.28; N, 12.85. Calc. for $C_9H_{12}N_2O_4$ (%): C, 50.94; H, 5.70; N, 13.20.

5-Hydroxy-3,4-bis(hydroxymethyl)-6-methylpyridine-2-carboxaldehyde thiosemicarbazone **4b** *ethanol monosolvate*. Conc. HCl (1 ml) was added to a solution of compound **2** (0.67 g, 2.80 mmol) in 20 ml of water and the mixture was stirred for 4 h at room temperature. Then the solution was neutralized with aqueous potassium carbonate, the solvent was evaporated under reduced pressure, the residue was extracted with 20 ml of anhydrous ethanol and filtered. To the filtrate, thiosemicarbazide (0.26 g, 2.86 mmol) was added and the mixture was refluxed for 10 h. The precipitate was filtered off and washed with water and ethanol. Yield of ethanol monosolvate of **4b** was 0.34 g (38%), yellow crystals, mp 188–189 °C (decomp.). ^{1}H NMR (DMSO-d_6) δ: 1.12 (t, 3H, *Me*CH_2OH, $^3J_{HH}$ 7.2 Hz), 2.39 (s, 3H, Me), 3.63 (m, 2H, EtOH), 5.16 (s, 2H, CH_2), 5.28 (s, 2H, CH_2), 7.28 (s, 1H, NH_2), 8.13 (s, 1H, NH_2), 8.27 (s, 1H, CH=N), 10.19 (s, 1H, OH), 11.53 (s, 1H, NHCS). Found (%): C, 45.67; H, 5.95; N, 17.58; S, 10.84. Calc. for $C_{12}H_{20}N_4O_4S$ (%): C, 45.56; H, 6.37; N, 17.71; S, 10.14.



Scheme 2 *Reagents and conditions*: i, H_2SO_4, H_2O, 20 °C, 6 h; ii, MnO_2, 20 °C, 10 min; iii, $NH_2OH·HCl$, AcONa, H_2O, reflux, 5 min; iv, $NH_2NHC(S)NH_2$, EtOH, reflux, 4 h.

acetonide protection in compound **1** in acidic medium, the further *in situ* oxidation of the product with activated manganese dioxide, and finally interaction of the thus obtained aldehyde with hydroxylamine hydrochloride or thiosemicarbazide. In this way oxime **5a** and thiosemicarbazone **5b** were prepared.‡

Regiospecificity of these reactions should be noted: oxidation occurred on 4-positioned hydroxymethyl group. This was confirmed by the X-ray analysis of compound **5a** (Figure 1).§ In our opinion, such a regiospecificity resulted from the directing effect of the aromatic hydroxyl group, forming a donor–acceptor complex **A** with the Mn^{IV} ion (*cf.* refs. 12, 13). Obviously, due to steric shielding effect of the nitrogen atom by the *ortho*-substituents, preliminary N-coordination to the Mn^{IV} ion is less preferable.

According to the X-ray data compound **5a** is a hydrate of the 1:1 composition. The atoms of the hydroxyl group at C(3) and the oxime group at C(4) are located in the plane of the pyridine ring. Such a conformation of these substituents is stabilized by intramolecular hydrogen bond O(1)–H(1)···N(2), the interaction parameters are the following: the distances H(1)···N(2) 1.81(2) Å and O(1)···N(2) 2.623(1) Å, the angle ∠O(1)–H(1)···N(2) 149(2)°. In the crystal, there is an extensive system of intermolecular hydrogen bonds involving the hydroxyl groups of the oxime and water.

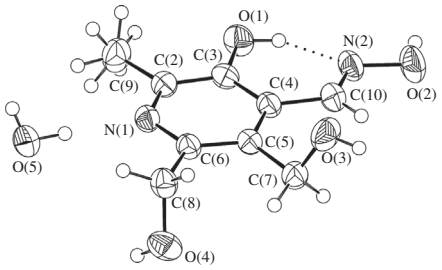


Figure 1 General view of molecule of **5a** in representation of atoms *via* thermal ellipsoids at 50% probability level. The dashed line designates intramolecular hydrogen bond. The hydrogen atoms of methyl group are disordered in two equal positions.

In conclusion, a new synthetic approach to a regioselective oxidation of hydroxymethyl groups in 6-methyl-2,3,4-tris(hydroxymethyl)-pyridin-5-ol into corresponding aldehydes was proposed, which seem promising in search for new biologically active compounds.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2012.05.021.

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‡ *3-Hydroxy-5,6-bis(hydroxymethyl)-2-methylpyridine-4-carboxaldehyde oxime* **5a** *monohydrate*. Yield 0.74 g (77%), light-green crystals, mp 162 °C (decomp.). ^{1}H NMR (DMSO-d_6) δ: 2.37 (s, 3H, Me), 3.43 (s, 2H, H_2O), 4.55 (d, 2H, CH_2, $^3J_{HH}$ 3.6 Hz), 4.64 (d, 2H, CH_2, $^3J_{HH}$ 3.6 Hz), 5.03 (t, 1H, OH, ^3J 3.6 Hz), 5.15 (t, 1H, OH, $^3J_{HH}$ 3.6 Hz), 8.65 (s, 1H, CH=N), 10.75 (s, 1H, N–OH), 12.13 (s, 1H, OH). Found (%): C, 47.87; H, 6.22; N, 12.86. Calc. for $C_9H_{14}N_2O_5$ (%): C, 46.95; H, 6.13; N, 12.17.

3-Hydroxy-5,6-bis(hydroxymethyl)-2-methylpyridine-4-carboxaldehyde thiosemicarbazone **5b** *monohydrate*. Yield 0.18 g (50%), yellow crystals, mp 217–218 °C (decomp.). ^{1}H NMR (DMSO-d_6) δ: 2.37 (s, 3H, Me), 3.35 (s, 2H, H_2O), 4.70 (d, 2H, CH_2, $^3J_{HH}$ 5.6 Hz), 4.82 (s, 2H, CH_2), 5.00 (t, 1H, OH, $^3J_{HH}$ 5.6 Hz), 5.80 (s, 1H, OH), 7.68 (s, 1H, NH_2), 8.15 (s, 1H, NH_2), 8.25 (s, 1H, CH=N), 9.69 (s, 1H, OH), 11.50 (s, 1H, NHCS). Found (%): C, 41.40; H, 5.12; N, 19.07; S, 11.16. Calc. for $C_{10}H_{16}N_4O_4S$ (%): C, 41.66; H, 5.59; N, 19.43; S, 11.12.

For syntheses of compounds **5a**,**b**, see Online Supplementary Materials.

§ *Crystallographic data.* Crystals of **5a** monohydrate ($C_9H_{12}N_2O_4·H_2O$, M = 230.22) are monoclinic, space group $P2_1/n$, at 296 K: a = 7.9819(6), b = 10.5876(7) and c = 13.5164(9) Å, β = 106.940 (1)°, V = 1092.7(1) Å^3, Z = 4 (Z' = 1), d_{calc} = 1.400 g cm^{-3}, μ(MoKα) = 1.15 cm^{-1}, F(000) = 488. Intensities of 15 106 reflections were measured with a Bruker SMART APEX II CCD diffractometer [λ(MoKα) = 0.71073 Å, ω-scans, $2\theta < 58°$] and 2613 independent reflections (R_{int} = 0.031) were used in further refinement. The structure was solved by direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. Hydrogen atoms of OH groups were located from the Fourier synthesis of the electron density and refined in the isotropic approximation. The H(C) atom positions were calculated and refined as riding atoms. The H atoms of methyl group are disordered in two equal positions. The refinement converged to wR_2 = 0.1114 and GOF = 1.10 for all independent reflections, R_1 = 0.0366 was calculated against F for 2105 observed reflections with $I > 2\sigma(I)$. All calculations were performed using SHELXL97 program.[14]

CCDC 850810 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2012.