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Regioisomeric oximes and thiosemicarbazones derived from 6-substituted pyridoxines

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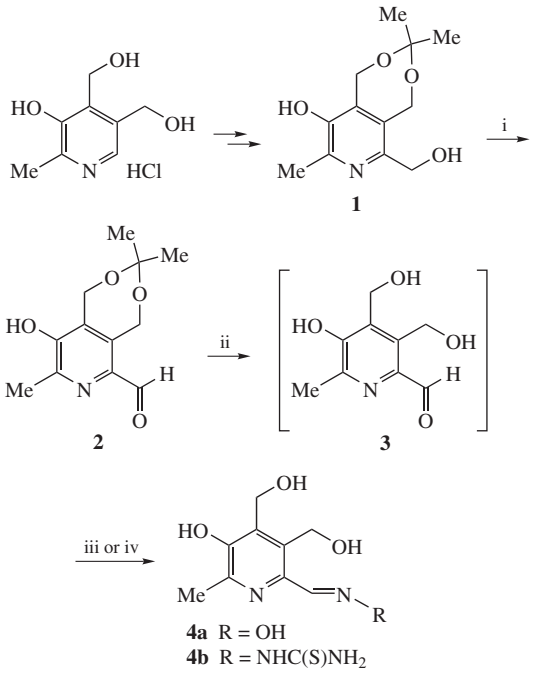
The selective oxidation of 2- and 4-positioned hydroxymethyl groups of 6-methyl-2,3,4-tris(hydroxymethyl)pyridin-5-ol was developed and the thus obtained aldehydes were converted into their oximes and thiosemicarbazones.

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.