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Directed Aminomethylation of 3-Hydroxy-2(1H)-pyridinones and 3-Hydroxy-4(1H)-pyridinones: Synthesis of iso-Deferiprone

Manojbhai K. Patel, Raymond Fox and Paul D. Taylor*

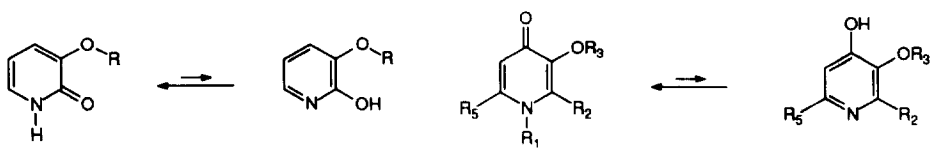
Department of Biological and Chemical Sciences, Central Campus, University of Essex, Wivenhoe Park, Colchester, CO4 3SQ, UK.

Abstract: The site of aminomethylation of N-unsubstituted 3-hydroxy-2-(1H)-pyridinones and 3-hydroxy-4(1H)-pyridinones, under Mannich reaction conditions, is directed by the hydroxyl group when this is unprotected and by the keto group when the hydroxyl is protected as an ether. This offers a convenient route to a variety of Mannich base synthons useful in the synthesis of derivatives of these clinically important, bidentate, metal-ion chelators. This is exemplified by reactions of 3-hydroxy-2-(1H)-pyridinone, 3-methoxy-2(1H)-pyridinone, 2-hydroxymethyl- 5-hydroxy- 4(1H) pyridinone and 3- benzyloxy- 2- methyl-4(1H)- pyridinone.

3-Hydroxy-2-(1H)-pyridinones and 3-hydroxy-4(1H)-pyridinones are of medicinal interest as bidentate chelators with high affinity for metal-ions in high oxidation state. [1,2,3,4] The specific chelator 1,2-dimethyl-3-hydroxy-4(1H)-pyridinone, also known as L1, is used clinically for the treatment of iron-overload under the name deferiprone although some toxic effects are now known. [5] The synthesis of less toxic derivatives and also of oligodentate chelators by covalent coupling of these moities is currently under investigation by several workers.

Both the 2- and 4-pyridinones are capable of tautomerism with the 2-hydroxy- and 4-hydroxy-pyridines respectively (Scheme 1) but the pyridinone tautomers are strongly favoured in polar solvents. In the pyridinone forms **1a** and **3a**, only one enolic hydroxy group is present and the position *ortho* to this hydroxyl group is readily subject to aminomethylation in the Mannich reaction. In the case of **1a**, a second aminomethylation occurs at the vinylogous enol, *para* to the hydroxyl group, under more vigourous conditions.

Scheme 1



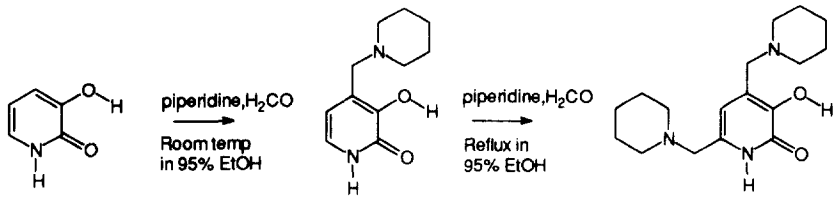
1a R = H **1b** **3a** $R_1 = CH_3$; $R_2 = R_3 = H$; $R_5 = HOCH_2$
2a R = CH_3 **2b** **4a** $R_1 = H$; $R_2 = CH_3$; $R_3 = CH_2Ph$; $R_5 = H$ **4b**

When the hydroxyl group of the pyridone tautomer is protected as an ether (**2a**, **4a**), the site of substitution in the Mannich reaction is directed *para* and *ortho* to the carbonyl group presumably in the form of the hydroxy-pyridine tautomer. The substitution patterns of the unprotected pyridinones are described initially.

Reaction of 3-hydroxy-2-(1H)-pyridinone

We have previously shown [6] that the mono-substituted Mannich base obtained from **1** is aminomethylated at C4 and not at C6 as reported by other workers [7,8] and appearing in the literature. [9] The C4 mono-substituted Mannich base **5** is formed readily even at room temperature in aqueous ethanol (Scheme 2). Further reaction with excess formaldehyde and amine, under refluxing conditions, gives the C4, C6 disubstituted Mannich base **6**, reported correctly in earlier work. [7]

Scheme 2



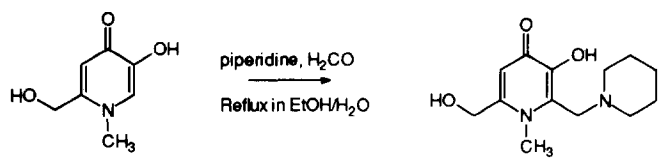
1a **5** **6**

The order of reactivity of **1** in the Mannich reaction is thus C4 > C6 rather than *vice-versa* and is in contrast to 3-hydroxy-pyridine for which C2 > C6 >> C4. [9] Compared to 3-hydroxy-pyridine, C4 of compound **1** is presumably activated to attack by electrophiles by the greater double bond character between C3 and C4.

Reaction of 5-hydroxy-2-hydroxymethyl-4(1H)-pyridinone

The 4(1H)-pyridinone **3a** is obtained from 5-hydroxy-2-hydroxymethy-pyrone (kojic acid) by reaction with methylamine. [10] Kojic acid readily undergoes the Mannich reaction *ortho* to the enolic hydroxyl group at room temperature. [11] The corresponding reaction of **3a** requires heating and although it appears not to have been reported before, it gives the expected substitution *ortho* to the enolic hydroxyl group (Scheme 3, **7**).

Scheme 3



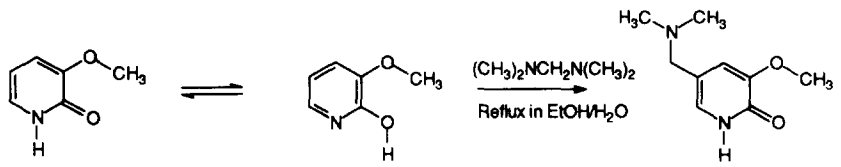
3a **7**

Reaction of 3-methoxy-2-(1H)-pyridinone

When the 3-OH group of **1** is protected as the methyl-ether **2**, no reaction at C4 or C6 takes place. Instead, reaction occurs entirely at C5 to give **8**, consistent with *para* attack on the enolic 2-hydroxy- pyridine tautomer **2b**, (Scheme 4). An indication of the phenol like nature of the 2-OH group of **2b** is given by the formation of a red complex with iron(III). An earlier report that the product is a water hydrolysable N-Mannich base product [7] occurring *via* substitution *ortho* to the carbonyl group of **2a** may be correct,

however, under the vigorous conditions we have used and in the presence of 10% water, this N-Mannich base may form in a non-productive equilibrium and could not be confirmed.

Scheme 4

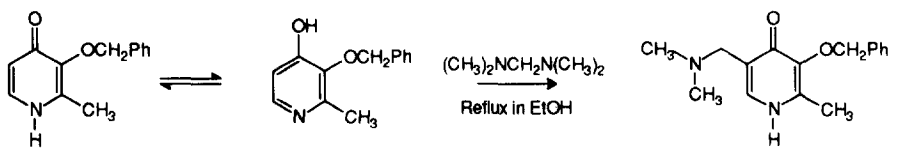


2a **2b** **8**

Reaction of 3-benzyloxy-2-methyl-4(1H)-pyridinone

A similar argument prevails with 4(1H)-pyridinones. 3-Benzyloxy-2-methyl-4(1H)-pyridinone (**4a**) undergoes aminomethylation at C5, *ortho* to the carbonyl group giving **9** in almost quantitative yield presumably *via* the 4-hydroxy-pyridine tautomer **4b**. Again, an idication of the phenol like nature of **4b** is the orange complex formed with iron(III) (the N-substituted analogue 3-benzyloxy-N-methyl-4-(1H)-pyridinone, cannot undergo this tautomerism and gives no colour with iron(III)).

Scheme 5



4a **4b** **9**

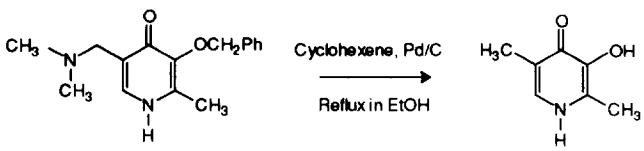
Discussion

Directed aminomethylation in a number of permutations is therefore possible by reaction of 3-hydroxy-pyridinones or their ethers. For the 2(1H)-pyridinones, substitution of **1** at C4 alone or at both C4 and C6 may be controlled by the vigour of the reaction conditions. Substitution of **1** at C5 may be achieved by first forming the 3-methoxy ether **2** followed by Mannich reaction conditions. The complete suppression of the Mannich reaction directed by the hydroxyl group in **1a**, upon ether protection, is surprising. In principle substitution could be achieved at C5 and C4 or even at C5, C4 and C6 by suitable combination of the two reactions. For the 4(1H)-pyridinones, substitution of **3**, *ortho* to the hydroxyl group or of **4** *ortho* to the carbonyl is possible.

Mannich bases are readily further transformed, conversion to the methyl group by hydrogenolysis proving to be quite straightforward. For example, under standard palladium catalysed transfer hydrogenolysis conditions, **9** can be hydrogenolysed selectively (Scheme 6) to remove the benzyl group without cleaving the Mannich

base, or with longer reaction times, to give 2,5-dimethyl-3-hydroxy-4(1H)-pyridinone, **10** an isomer of the drug deferiprone. The physical properties and biological activity of this isomer are currently being assessed.

Scheme 6



9 **10**

Experimental section

3-Hydroxy-4-piperidino-methyl-2-(1H)-pyridinone (5). Formaldehyde (37% aqueous solution, 7mL, 0.09mol) and piperidine (15.7g, 0.18mol) were stirred together in ethanol (95%, 10mL) for 30min. This solution was then added slowly to a solution of 3-hydroxy-2-(1H)-pyridinone (10g, 0.09mol) in 95% ethanol. After 12h the solution was rotary evaporated and the crude product recrystallized from acetone/ethanol. Yield 94%. Mpt 190-191°C. Mass spec 209. Elemental analysis. $C_{11}H_{16}N_2O_2$ requires: C, 63.44%; H, 7.74%; N, 13.45%. Found: C, 63.69%; H, 7.72%; N, 13.36%. ^{1}Hnmr, d_6DMSO; δ1.382m, 2H; δ1.479m, 4H; δ2.327broad, 4H; δ3.32s, 2H; δ6.087d, 1H, δ6.785d, 1H, δ8.31s, 1H.

3-Hydroxy-4,6-bis(piperidino-methyl)-2-(1H)-pyridinone (6). 3-Hydroxy-2-(1H)-pyridinone (1.1g, 0.01mol), formaldehyde (37% aqueous solution, 1.9ml, 0.025mol) and piperidine (4.3g, 0.05mol) were refluxed in 95% ethanol for 24h. Chloroform (100mL) was added to dissolve the product and the mixture filtered under vacuum. The filtrate was rotary evaporated to a solid which was recrystallized from acetone/ethanol/water (2.5:2.5:1). Yield 29%. Mpt 166-168°C. Mass spec 306. Elemental analysis. $C_{17}H_{27}N_3O_2$ requires: C, 66.85%; H, 8.91%; N, 13.76%. Found: C, 66.89%; H, 8.97%; N, 13.67%. ^{1}Hnmr $CDCl_3$; δ1.41m, 4H; δ1.526m, 4H; δ1.601m, 4H; δ2.3broad, 4H; δ2.5broad, 4H; δ3.199s, 2H; δ3.44s, 2H; δ5.679s, 1H; δ7.240s, 1H.

3-Hydroxy-6-hydroxymethyl-1-methyl-2-piperidinomethyl-4(1H)-pyridinone (7).

5-Hydroxy-2-hydroxymethyl-4(1H)-pyrone (kojic acid) was reacted with methylamine to give 5-hydroxy- 2-hydroxymethyl- 4(1H)- pyridinone using established procedures. [10] Formaldehyde (37% aqueous solution, 1.05g, 12.9mmol) and piperidine (1.1g, 12.9mmol) were added to a solution of 5- hydroxy- 2-hydroxymethyl- 1-methyl-4(1H)-pyridinone (1g, 6.45mmol) in aqueous ethanol (80%,10mL). The mixture was refluxed for 24h and then cooled and refrigerated. The resulting precipitate was collected by filtration and combined with the solid obtained upon evaporation of the filtrate under reduced pressure to afford a crystalline solid which was recrystallized from aqueous ethanol. Yield 47%. Mpt 195-197°C. Mass spec 253. Elemental analysis. $C_{13}H_{20}O_3N_2.H_2O$ requires: C, 58.76%; H, 8.20%, N, 10.36%. Found: C, 58.33%; H,

7.88%; N, 10.19%. ^{1}Hnmr d_6DMSO; δ1.37m, 2H; δ1.44m, 4H; δ2.36m, 4H; δ3.52s, 2H; δ3.68s, 3H; δ4.41s, 2H; δ6.25s, 1H.

5-Dimethylamino-methyl-3-methoxy-2-(1H)-pyridinone (8). 3-Methoxy-2-(1H)-pyridinone (1.25g, 0.01mol) and *N,N,N',N'*-tetramethyl-diaminomethane, (10.2g, 0.1mol) were refluxed in ethanol/water (10:1, 50mL) for 72h. The reaction mixture was then rotary evaporated to an oil which crystallized on standing. The solid was washed with acetone and recrystallized from acetone/ethanol. Yield 24%. Mpt 152-153°C. Mass spec. 182. Elemental analysis. $C_9H_{14}O_2N_2$ requires: C, 59.32%; H, 7.74%; N 15.37%. Found: C, 59.53%; H, 7.46%; N 15.33%. ^{1}Hnmr d_6DMSO; δ2.099s, 6H; δ3.082s, 2H; δ3.671s, 3H, δ6.705d(2.01Hz), 1H; δ6.778d(2.01Hz), 1H; δ11.4 broad, 1H.

3-Benzyloxy-5-(dimethylaminomethyl)-2-methyl-4(1H)-pyridinone (9).

Maltol (3-hydroxy-2-methyl-4-pyrone) and benzyl chloride were reacted to give 3-benzyloxy-2-methyl-4-pyrone which was then reacted with ammonia to give 3-benzyloxy-2-methyl-4(1H)-pyridinone using established procedures. [12] To a solution of 3-benzyloxy-2-methyl-4(1H)-pyridinone (1.74g, 8mmol) in ethanol (40mL absolute) was added *N,N,N',N'*-tetramethyl-diaminomethane (16.5g, 0.161mol). The mixture was refluxed for 20h and then rotary evaporated to an oil which crystallized on standing. The crude solid was recrystallized from acetone/ethanol. Yield 98%. Mpt 131-132°C. Mass spec 273. Elemental analysis. $C_{16}H_{20}O_2N_2$ requires: C, 70.56%; H, 7.40%; N, 10.29%. Found: C, 70.57%; H, 7.40%; N, 10.29%. ^{1}Hnmr d_6DMSO δ2.051s, 3H, δ2.140s, 6H, δ3.242s, 2H, δ5.014s, 2H, δ7.39s, 1H, δ7.32m,5H.

2,5-Dimethyl-3-hydroxy-4(1H)-pyridinone (10).

To 3-benzyloxy-5-(dimethylaminomethyl)-2-methyl-4(1H)-pyridinone (**9**) (1g, 3.7mmol), dissolved in absolute ethanol (30mL) and cyclohexene (40mL) was added palladium hydroxide on carbon (1g). The mixture was then refluxed for 4 days with further additions of cyclohexene (40mL) and palladium hydroxide (2g) at intervals and then cooled. The precipitate removed by filtration was resuspended in ethanol and filtered twice more to recover product and the combined filtrates evaporated to dryness under vacuum. The crude solid was recrystallized from acetone/ethanol. Yield 87%. Mpt 278°C. Mass spec 139. Elemental analysis. requires: C, 60.42%; H, 6.52%; N, 10.07%. Found: C, 60.14%; H, 6.35%; N 9.89%. ^{1}Hnmr d_6DMSO δ1.908s, 3H, δ2.171s, 3H, 7.372s, 1H.

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