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Short communication

Synthesis of 3-hydroxypyrid-2-ones from furfural for treatment against iron overload and iron deficiency

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Abstract

Derivatives of 3-hydroxypyrid-2-ones, which posses very high affinity for iron and have anomalous applications in iron overload and iron deficiency, were prepared from furfural in simple reaction conditions.

Keywords: 3-Hydroxypyrid-2-ones; Iron overload; Iron deficiency; Furfural

1. Introduction

Iron overload is the most undesirable since, following saturation of the ferritin and transferrin in the body, deposition of iron can occur and many tissues can be adversely affected, particular toxic effects being degenerative changes in the myocardium, liver and endocrine organs [1]. Certain pathological conditions such as thalassaemia, sickle cell anaemia, idiopathic haemochromatosis and aplastic anaemia are treated by regular blood transfusions [2]. It is commonly found that such transfusions lead to a widespread iron overload, which can also arise through increased iron absorption by the body under certain other circumstances. Such iron overload is most often treated by the use of desferrioxamine [3]. However, this compound is an expensive natural product obtained from the culture of *Streptomyces* [4] and, as it is susceptible to acid hydrolysis, it cannot be administered orally to the patient and has to be given by a parenteral route. Since relatively large amounts of desferrioxamine may be required daily over an extended period, these disadvantages are particularly relevant and an extensive amount of research has been directed towards the development of alternative drugs. However, work has been concentrated on three major classes of iron chelating agents or siderophores, namely hydroxamates [5], ethylenediamine tetra-acetic acid (EDTA) analogues [6] and catechols [7]. The hydroxamates generally suffer from the same defects as desferrioxamine, being expensive and acid labile [8], whilst the other two classes are ineffective at removing iron from intracellular sites. Moreover, some catechol derivatives are retained by the liver and spleen and EDTA analogues possess a high affinity for calcium and so are also likely to have associated toxicity problems. Hence, convenient iron chelating agents which are easy to synthesize, stable at wide range of pH, nontoxic and selective for iron are always appealing.

The purpose of this letter is to describe a useful one-pot preparation of 3-hydroxypyrid-2-ones, which are extensively used in the treatment against iron overload and iron deficiency. 3-Hydroxypyrid-2-ones possess a high affinity for iron(III). In addition to the use described hereinbefore for the treatment of general iron overload, 3-hydroxypyridones are also of interest for use in certain pathological conditions where there may be an excess of iron deposited at certain sites even though the patient does not exhibit a general iron overload, this being the case, for example, in certain arthritic and cancerous conditions [9]. Thus, a mixture of an iron complex of a 3-hydroxypyridone together with one of the 3-hydroxypyridones in metal-free form will have the effects of remedying the overall anaemia through the action of the iron complex whilst the metal-free compound will act to

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remove iron from pathological to physiological sites [10]. On the other hand, 3-hydroxypyrid-2-ones were used in pharmaceutical compositions for the treatment of iron deficiency anaemia. An adequate supply of iron to the body is an essential requirement for tissue growth in both humans and animals. Although there is normally an ample amount of iron in the diet [11], the level of absorption of iron from food is generally low so that the supply of iron to the body can easily become critical under a variety of conditions. Iron deficiency anaemia is commonly encountered in pregnancy [12] and may also present a problem in the newly born [13], particularly in certain animal species such as the pig [14] and horse [15]. Moreover, in certain pathological conditions there is a maldistribution of body iron leading to a state of chronic anaemia. This is seen in chronic diseases [16] such as rheumatoid arthritis, certain haemolytic diseases and cancer.

2. Results and discussion

Though 3-hydroxypyrid-2-ones are very useful in treatment against iron overload and iron deficiency, the synthesis routes [10,17–19] for these compounds are not studied so extensively. These synthesis methods which are described in literature for synthesis of derivatives of 3-hydroxypyrid-2-ones suffer from issues such as non-availability of starting materials, tedious product isolation and competing side reactions. Due to this, the use of 3-hydroxypyrid-2-ones in treatment against iron overload and iron deficiency is limited. In this letter I am describing a synthesis method with mechanism for different derivatives of 3-hydroxypyrid-2-ones from furfural. Furfural is very easily available; economically and ecologically viable raw material. 3-Hydroxypyrid-2-ones were prepared by oxidation of furfural with sodium hypochloride in aqueous medium followed by treatment with different amines (Scheme 1). Mechanism involved in this process is similar to Chichibabin pyridine synthesis [20]. Sodium hypochloride as oxidizing agent opens the ring of furfural to give intermediate (OCHCH:CH–COCHO) by addition of one oxygen. This intermediate can be stored at 268 K temperature. Dropwise addition of different amines to this intermediate solution gave temperature rise in the range of 273–288 K. The temperature of the reacting mixture was restricted below 290 K to prevent the formation of sticky polymer-like substance. The control on pH range was essential in this process. The pH of the intermediate solution became 8 after the addition of amines. The solution was maintained at the prevailing pH by addition of 40% sodium hydroxide solution. This mixture was then heated to 348 K for 20 min to get different 3-hydroxypyrid-2-ones. In the mechanism, one hydrogen atom which came from amine was removed as a water molecule in the subsequent step. The formation of six-membered aromatic ring takes place due to the shifting of lone pair of electrons from nitrogen to aldehyde. Thus, five-membered ring structure of furfural was converted into six-membered ring structure of 3-hydroxypyrid-2-ones. Product was extracted by diethyl ether and subjected to rotary evaporation to yield 3-hydroxypyrid-2-ones in crystalline form. The reaction progress was analyzed by gas chromatography. The formation of products was confirmed by IR and NMR studies.

Scheme 2 describes the mechanism of formation of *N*-alkyl carbamoyl alkyl amines by Ritter reaction. These *N*-alkyl carbamoyl alkyl amines were used as reactant in Scheme 1 to form different derivatives of 3-hydroxypyrid-2-ones. Conditions for Ritter reaction are very simple and yield is very high [21]. In this process, mixture of alcohol and methyl cyanide was mixed with acetic acid and cooled to 273 K. Sulfuric acid was added dropwise, keeping temperature below 283 K. The reaction mixture was allowed to reach room temperature, stirred for 5 h and poured in ice water. Precipitate was filtered and retentate was washed with sodium bicarbonate solution. It was found that the rate of conversion of the nitriles to the corresponding amides was highly dependent on the concentration of sulfuric acid and the amount of water present in reaction mixture. Conversion increased with increasing concentration of sulfuric acid and decreased with increasing water content in the reaction mixture. Table 1 provides % yields of *N*-alkyl carbamoyl alkyl amines. It was observed that % yield of *N*-alkyl carbamoyl alkyl amines increased with the increasing alkyl chain length. This is because the increasing alkyl chain length shows more electron-donating ability, which in turn increases the rate of reaction.

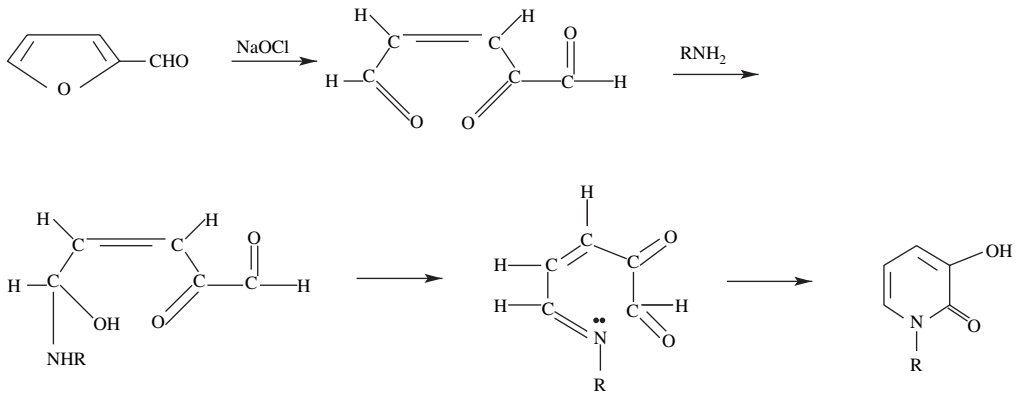
3. Conclusion

3-Hydroxypyrid-2-ones, which are very important chemical compounds in medicinal science, can be prepared from furfural as starting material. The high availability of starting compound (i.e., furfural), satisfactory yields of 3-hydroxypyrid-2-ones derivatives and the easy reaction conditions are salutary features of this synthesis method.

4. Experimental

4.1. General

The reactions were monitored by GC (Chemito 8610) with flame ionization detector (FID). A 4 m long and 0.37×10^{-2} m internal diameter S.S. column packed with 10% SE-30 on chromosorb WHP was employed for the analysis. Nitrogen at the flow rate of 0.5×10^{-7} m^3 sec^{-1} was used as carrier gas. Injector and detector (FID) temperatures were maintained at 573 K. The oven temperature program was as follows: starting at 423 K hold for 5 min rise of temperature 276 K min^{-1} up to 553 K and hold for 5 min. Samples (1 μl) were injected in split-less mode. Melting points are uncorrected. The products were purified by flash chromatography on Merck silica gel 60 (230400 mesh ASTM). Products were confirmed using ^{1}H NMR spectra (Varian Gemini 300 MHz) instrument. IR spectra in Nujol mulls were recorded on a Perkin Elmer Spectrum BX FTIR spectrometer. UV spectra were detrmined by using Chemito 2100 UV spectrophotometer. Mass spectra of compound **2** was obtained by using Agilent 5975C gas chromatography/mass spectrophotometer.



1. R = H
2. R = $COCH_3$
3. R = CH_2 COOH
4. R = OCH_2 $COCH_3$
5. R = OCH_2 CH_2 $COCH_3$
6. R = CH_2 $CONHCH_3$
7. R = CH_2 CH_2 $CONHCH_3$
8. R = CH_2 CH_2 CH_2 $CONHCH_3$
9. R = CH_2 CH_2 CH_2 CH_2 $CONHCH_3$
10. R = CH_2 $CH(CH_3)$–$CONHCH_3$

Scheme 1. Mechanism of preparation of 3-hydroxypyrid-2-ones from furfural.

4.2. Procedure to prepare intermediate (OCHCH:CH−COCHO)

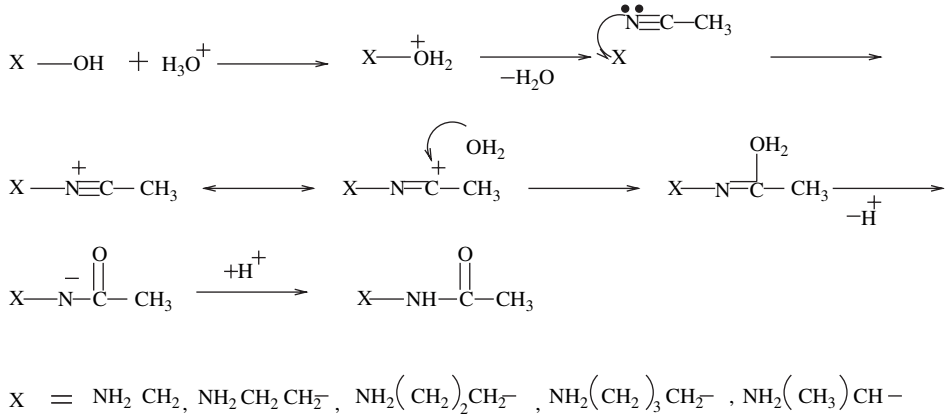
Emulsion of 96.1 g of furfural in 700 ml water was formed. Then dropwise addition of 74 g of sodium hypochloride was performed at 273 K in 30 min to give intermediate solution.

*4.2.1. 3-Hydroxypyrid-2-one (**1**)*

Intermediate solution was treated with 20 g of liqueur ammonia. Addition of liqueur ammonia was done dropwise, it gives rise in temperature from 273 to 288 K. The pH of this mixture was 8 and held at this pH by addition of 40% sodium hydroxide solution for 40 min. This mixture was then heated to 348 K for 20 min to give **1** as product. Product was extracted by diethyl ether in 400, 200, 200 ml fractions and isolated by flash column chromatography in 30% isolated yield.

*4.2.2. 1-Acetyl-3-hydroxypyrid-2-one (**2**)*

Intermediate solution was treated with NH_2COCH_3. Dropwise addition of 60 g NH_2COCH_3 gave rise in temperature from 273 to 290 K. The pH of this mixture was above 8.



Scheme 2. Mechanism of formation of *N*-alkyl carbamoyl alkyl amines.

Table 1
% yields of *N*-alkyl carbamoyl alkyl amines

Entry	X	% Yield of $XNHCOCH_3$
1	NH_2CH_2-	25
2	$NH_2CH_2CH_2-$	35
3	$NH_2(CH_2)_2CH_2-$	32
4	$NH_2(CH_2)_3CH_2-$	33
5	$NH_2(CH_3)CH-$	30

This mixture was then heated to 348 K for 20 min to give **2** as product. Product was extracted by diethyl ether and subjected to rotary evaporation at 323 K to yield 1-acetyl-3-hydroxypyrid-2-one as white crystals (42.8 g), m.p. 413–414 K. UV (EtOH): 313 nm (pyridone ring). IR (KBr) ν_{max} cm^{-1} (Nujol): 3120 (−OH), 1715 (C=O from aromatic ring), 1686 (C=O from side chain). ^1H NMR (DMSO-d_6) (δ): 7.20 (s, 1H, −OH), 6.10–6.50 (m, 4H, aromatic), 2.20 (s, 3H, $-COCH_3$). Mass spectra ($M^{+\bullet}$) at *m/z* 585, 472 (M, side chain), 399 (M, $C_9H_4N_3S$), 384 (M, $C_9H_5N_4S$).

*4.2.3. 1-Carboxymethyl-3-hydroxypyrid-2-one (**3**)*

Intermediate solution was treated with NH_2CH_2COOH. Dropwise addition of 75 g NH_2CH_2CO gave rise in temperature from 273 to 288 K. The pH of this mixture was above 8. This mixture was then heated to 348 K for 20 min to give **3** as product. Product was extracted by diethyl ether and subjected to rotary evaporation at 323 K to yield yellow solid. This solid is recrystallised from water to yield white crystals (49 g), m.p. 476–478 K. UV (EtOH): 309 nm (pyridone ring). IR (KBr) ν_{max} cm^{-1} (Nujol): 3240 (−OH), 1695 (C=O from COOH), 1640 (C=O at 2nd position in pyridone ring), 1540 (substituted pyridone). ^1H NMR (DMSO-d_6) (δ): 10.20 (s, 1H, −COOH), 7.00 (s, 1H, −OH), 5.95–6.60 (m, 3H, aromatic), 3.35 (s, 2H, $-CH_2CO-$).

*4.2.4. 3-Hydroxy-1-methoxycarbonylmethylpyrid-2-one (**4**)*

Intermediate solution was treated with $NH_2OCH_2COCH_3$. Dropwise addition of 90 g $NH_2OCH_2COCH_3$ gave rise in temperature from 273 to 288 K. The pH of this mixture was above 8. This mixture was then heated to 348 K for 20 min to give **4** as product. Product was extracted by diethyl ether and subjected to rotary evaporation at 323 K to yield yellow solid. This solid is recrystallised from water to give 51 g of 3-hydroxy-1-methoxycarbonylmethylpyrid-2-one (**4**), m.p. 414–416 K. UV (EtOH): 316 nm (pyridone ring). IR (KBr) ν_{max} cm^{-1} (Nujol): 3220 (O–H), 1730 (C=O at 2nd position in pyridone ring), 1700 (O–CH_2), 1645 (C=O from side chain), 1560 (substituted pyridone). ^1H NMR (DMSO-d_6) (δ): 9.20 (s, 1H, −OH), 6.05–7.10 (m, 3H, aromatic), 4.65 (s, 2H, $-OCH_2CO$), 1.55 (s, 3H, $-COCH_3$).

*4.2.5. 1-Ethoxycarbonylmethyl-3-hydroxypyrid-2-one (**5**)*

Intermediate solution was treated with $NH_2OCH_2CH_2COCH_3$. Dropwise addition of 105 g $NH_2OCH_2CH_2COCH_3$ gave rise in temperature from 273 to 288 K. The pH of this mixture was above 8. This mixture was then heated to 348 K for 20 min to give **5** as product. Product was extracted by diethyl ether and subjected to rotary evaporation at 323 K to yield yellow solid. Recrystallisation of this solid from water yields 51 g of 1-ethoxycarbonylmethyl-3-hydroxypyrid-2-one (**5**) as white crystals, m.p. 414–424 K. UV (EtOH): 313 nm (pyridone ring). IR (KBr) ν_{max} cm^{-1} (Nujol): 3270 (O–H), 1720 (C=O at 2nd position in pyridone ring), 1645 (C=O from side chain). ^1H NMR (DMSO-d_6) (δ): 7.05 (s, 1H, −OH), 5.95–6.60 (m, 3H, aromatic), 4.55 (t, 2H, $-OCH_2$), 2.00 (t, 2H, $-CH_2CO$), 1.95 (s, 3H, $-COCH_3$).

*4.2.6. 3-Hydroxy-1-(N-methylcarbamoylmethyl)pyrid-2-one (**6**)*

Intermediate solution was treated with $NHCH_2CONHCH_3$. Dropwise addition of 88 g $NHCH_2CONHCH_3$ gave rise in temperature from 273 to 285 K. The pH of this mixture was above 8. This mixture was then heated to 348 K for 20 min to give **6** as product. Product was extracted by diethyl ether and subjected to rotary evaporation at 323 K to yield yellow solid. This solid is recrystallised from ethanol to give 50 g of 3-hydroxy-(*N*-methylcarbamoylmethyl)-pyrid-2-one (**6**), m.p. 477–479 K. UV (EtOH): 310 nm (pyridone ring). IR (KBr) ν_{max} cm^{-1} (Nujol): 3275 (O–H), 2950 (N–H), 1685 (C=O at 2nd position in pyridone ring), 1645 (C=O from CONH), 1585 (amide), 1560 (substituted pyridone). ^1H NMR (DMSO-d_6) (δ): 8.60 (s, 1H, −OH), 7.95 (s, 1H, −NH), 6.55–6.95 (m, 3H, aromatic), 3.35 (s, 2H, $-NCH_2CO$), 2.80 (s, 3H, $-CONHCH_3$).

*4.2.7. 1-(N-Ethylcarbamoylmethyl)-3-hydroxypyrid-2-one (**7**)*

Intermediate solution was treated with $NH_2CH_2CH_2CONHCH_3$. Dropwise addition of 102 g $NH_2CH_2CH_2CONHCH_3$ gave rise in temperature from 273 to 285 K. The pH of this mixture was above 8. This mixture was then heated to 348 K for 20 min to give **7** as product. Product was extracted by diethyl ether and subjected to rotary evaporation at 323 K to yield yellow solid. This solid is recrystallised from ethanol to give 49 g of 1-(*N*-ethylcarbamoylmethyl)-3-hydroxypyrid-2-one (**7**), m.p. 487–489 K. UV (EtOH): 307 nm (pyridone ring). IR (KBr) ν_{max} cm^{-1} (Nujol): 3400 (O–H), 3260 (N–H), 1675 (C=O at 2nd position in pyridone ring), 1645 (C=O from CONH), 1580 (amide), 1555 (substituted pyridone). ^1H NMR (DMSO-d_6) (δ): 8.20 (s, 1H, −OH), 7.05 (s, 1H, NH), 6.05–6.70 (m, 3H, aromatic), 3.10 (t, 2H, $-NCH_2$), 2.5 (s, 3H, $-CONHCH_3$), 1.80 (t, 2H, $-CH_2CO$).

*4.2.8. 3-Hydroxy-1-(N-propylcarbamoylmethyl)-pyrid-2-one (**8**)*

To prepare, intermediate solution was treated with $NH_2CH_2CH_2CH_2CONHCH_3$. Dropwise addition of 116 g $NH_2CH_2CH_2CH_2CONHCH_3$ gave rise in temperature from 273 to 285 K. The pH of this mixture was above 8. This mixture was then heated to 348 K for 20 min to give **8** as product. Product was extracted by diethyl ether and subjected to rotary evaporation at 323 K to yield yellow solid. This solid is recrystallised from ethanol to give 48 g of 3-hydroxy-1-(*N*-

propylcarbamoylmethyl)-pyrid-2-one (**8**), m.p. 477–478 K. UV (EtOH): 315 nm (pyridone ring). IR (KBr) ν_{max} cm^{-1} (Nujol): 3200 (O–H), 3050 (N–H), 1695 (C=O at 2nd position in pyridone ring), 1640 (C=O from CONH), 1580 (amide), 1560 (substituted pyridone). ^{1}H NMR (DMSO-d_6) (δ): 8.95 (s, 1H, –OH), 8.10 (s, 1H, –NH), 6.70–7.05 (m, 3H, aromatic), 3.85 (t, 2H, $-CH_2$), 3.00 (s, 3H, $-CONHCH_3$), 1.95 (t, 2H, $-CH_2CO$), 0.85 (q, 2H, $-CH_2$).

*4.2.9. 1-(N-Butylcarbamoylmethyl)-3-hydroxypyrid-2-one (**9**)*

Intermediate solution was treated with $NH_2CH_2CH_2CH_2CH_2CONHCH_3$. Dropwise addition of 130 g $NH_2CH_2CH_2CH_2CH_2CONHCH_3$ gave rise in temperature from 273 to 285 K. The pH of this mixture was above 8. This mixture was then heated to 348 K for 20 min to give **9** as product. Product was extracted by diethyl ether and subjected to rotary evaporation at 323 K to yield yellow solid. This solid is recrystallised from ethanol to give 45 g of 1-(*N*-butylcarbamoylmethyl)-3-hydroxypyrid-2-one (**9**) as colourless needles, m.p. 472–473 K. UV (EtOH): 309 nm (pyridone ring). IR (KBr) ν_{max} cm^{-1} (Nujol): 3270 (O–H), 3100 (N–H), 1680 (C=O at 2nd position in pyridone ring), 1650 (C=O from CONH), 1595 (amide), 1565 (substituted pyridone). ^{1}H NMR (DMSO-d_6) (δ): 8.86 (s, 1H, –OH), 8.00 (s, 1H, –NH), 6.63–6.96 (m, 3H, aromatic), 2.95 (t, 2H, $-NCH_2$), 2.20 (s, 3H, $CONHCH_3$), 1.95 (m, 2H, $-CH_2CO$), 1.30 (q, 2H, $-CH_2$), 0.95 (m, 2H, $-CH_2$).

*4.2.10. 3-Hydroxy-1-[N-(2′-methylethyl)carbamoylmethyl]-pyrid-2-one (**10**)*

Intermediate solution was treated with $NH_2CH_2CH(CH_3)CONHCH_3$. Dropwise addition of 116 g $NH_2CH_2CH(CH_3)CONHCH_3$ gave rise in temperature from 273 to 285 K. The pH of this mixture was above 8. This mixture was then heated to 348 K for 20 min to give **10** as product. Product was extracted by diethyl ether and subjected to rotary evaporation at 323 K to yield solid. This solid is recrystallised from ethanol to give 42 g of 3-hydroxy-1-[*N*-(2′-methylethyl)carbamoylmethyl]-pyrid-2-one (**10**) in a form of silvery powder, m.p. 511–514 K. UV (EtOH): 318 nm (pyridone ring). IR (KBr) ν_{max} cm^{-1} (Nujol): 3270 (O–H, N–H), 1650 (C=O at 2nd position in pyridone ring), 1645 (C=O from CONH), 1595 (amide), 1570 (substituted pyridone). ^{1}H NMR (DMSO-d_6) (δ): 8.85 (s, 1H, –OH), 7.96 (s, 1H, –NH), 5.95–6.98 (m, 3H, aromatic), 3.50 (d, 2H, $-CH_2$), 2.95 (s, 3H, $CONH-CH_3$), 2.30 (m, 1H, –CHCO), 0.95 (m, 3H, $-CH_3$).

4.3. General procedure for preparation of N-alkyl carbamoyl alkyl amines

Mixture of alcohol (5 mmol) and methyl cyanide (10 mmol) was mixed with acetic acid (0.8 ml) and cooled to 273 K. Sulfuric acid (0.80 ml, 15 mmol) was added dropwise keeping temperature below 283 K. The reaction mixture was allowed to reach room temperature, stirred for 5 h and poured in ice water. Precipitate was filtered and retentate was washed with sodium bicarbonate solution to give *N*-alkyl carbamoyl alkyl amines as a product.

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