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Oxidation of Polyhydroxyalkyl - Heterocycles by Cerium (IV). A Convenient Route to Pyrrole-2,5-Dicarbaldehydes.

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Abstract: The synthesis of 3-ethoxycarbonyl-2,5-diformylpyrrole (**2**) from 3-ethoxycarbonyl-2-methyl-5-D-(*arabino*-tetritol-1-yl)pyrrole (**1**) by oxidation with ceric ammonium nitrate is described. When the reaction was applied to related furan derivatives, ethyl (5*S*,6*R*,7*R*)-2-acetyl-5,6,7,8-tetrabenzyloxyoct-2-enoate (**8**) was obtained as an *E/Z* mixture.

Pyrrole-2,5-dicarbaldehydes are sought after precursors for the synthesis of biologically active compounds[1,2] and several macrocycles[2-6] displaying unusual chemical[2], coordination[6] or physical properties[7]. Among these, porphyrins represent one of the most extensively studied groups of compounds, especially β-substituted porphyrins. The β-substituents not only exert much greater steric and electronic effects on the porphyrin ring than do substituents at the *meso*-aryl positions, but also induce the porphyrin ring into a non-planar conformation which may control the biological properties in tetrapyrrole systems,[1,8] for example photosynthesis, electron transfer, vitamin B_{12} biosynthesis, and so on. In addition to these important areas, β-substituted porphyrins have been found to be promising for treating hollow-organ cancers.[9]

In spite of the growing interest over recent years in 3-substituted and 3,4-disubstituted pyrrole-2,5-dicarbaldehydes, few procedures for the synthesis of these compounds have been reported.[10,11] A well-known method for formylation of pyrroles is the Vilsmeier-Haack reaction,[10] but this method is not applicable for the synthesis of pyrrole-2,5-dicarbaldehydes[3] owing to the fact that the first formyl group, introduced at position 2, deactivates position 5 and directs the next formylation to position 4 leading to less than 1% yield of the pyrrole-2,5-dicarbaldehydes.[3] This difficulty has been overcome by multiple step sequences[3,12] that involve protection and deprotection of the formyl groups or by the use[13] of pyrroles with substituents that are masked formyl groups. Recently Guilard *et al.*[11] have described a one-step pathway to 3,4-disubstituted pyrrole-2,5-dicarbaldehydes in 22-65% yield starting from pyrrole-2-carboxylic acid derivatives. 3,4-Disubstituted pyrrole-2,5-dicarbaldehydes have also been obtained from the corresponding 2,5-dimethyl derivatives in 8% yield by oxidation with $Pb(OAc)_4$ - PbO_2 in acetic acid at room temperature for 72 h.[14]

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Other five-membered heterocycles bearing two formyl groups at 2,5-positions are also of interest. For example, pyrrole-, thiophene- or furan-2,5-dicarbaldehydes are used for the synthesis of analogs of the well--known organic conductor TTF (tetrathiafulvalene) system.[7] Also several polyazamacrocycles[6] include 2,5-joined furan rings in their structure.

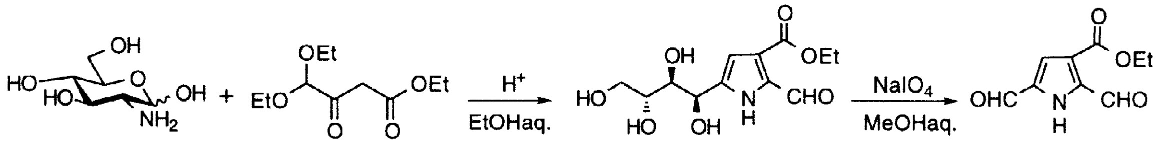
Ceric ammonium nitrate (CAN) is a widely used reagent for the oxidation of numerous compounds including alcohols, carbonyl compounds, carboxylic acids and derivatives, organosulfur or organonitrogen compounds and hydrocarbons.[15] The oxidation of benzylic positions in arenes[15b] to alcohols and aldehydes and the oxidative cleavage of alcohols,[16a,b] benzoins[16c] and glycols[15b,16d] have also been reported. Its broad applicability is owed to its mild reaction conditions, fast conversions and convenient working-up procedures. The use of this reagent in heterocyclic chemistry is scarce and, to the best of our knowledge, is limited to the oxidation of furoin to furoic acid[16c] and of a polyhydroxyalkyl triazole to the corresponding triazole-4-carboxylic acid[16e] when treated at 60 - 100 °C with ceric ammonium nitrate.

In this paper we report the action of ceric ammonium nitrate on polyhydroxyalkyl pyrroles and furans, presenting an easy route to 3-substituted-2,5-diformylpyrroles which are key intermediates in porphyrin syntheses based on "3+1" condensation.[17]

The products of the reaction of readily accessible[10,18] 3-ethoxycarbonyl-2-methyl-5-(D-*arabino*-tetritol-1-yl)pyrrole **1** (68% from D-glucosamine in one step) with CAN in acetonitrile-water at room temperature are shown in the Scheme. Ceric ammonium nitrate is able to provoke the oxidative cleavage of the polyhydroxyalkyl-side chain and the concomitant oxidation of the 2-methyl group on the pyrrole ring. In this way 3-ethoxycarbonyl-2,5-pyrrole-dicarbaldehyde **2**[19] is obtained in moderate-to-good yield depending on the rate of addition of the oxidising reagent. The optimal yield (66%) was observed when 11 equiv. of CAN was added slowly (1 equiv. each 15 min); the rapid addition of all the reagent to the starting material gave a complex mixture of decomposition products and **2** was isolated only in 10% yield. This was probably due to the high initial Lewis acid concentration, since it is known that aqueous CAN solutions are acidic. Compound **2** can also be obtained in 58% yield from aldehyde **3**[18] by reaction with 6.5 equiv. of CAN. Compound **3** was readily obtained in 91 % yield after treatment of **1** with $NaIO_4$. When the oxidation of **3** was carried out with 4.2 equiv. of CAN, the partially oxidized intermediate 3-ethoxycarbonyl-5-formyl-2-hydroxymethylpyrrole (**4**)[20] was obtained in 23% yield together with **2** in 40 % yield.

The same reaction conditions applied to commercially available 2,5-dimethylpyrrole lead to a complex mixture of decomposition products. Thus, the presence of an electron-withdrawing substituent, such as ethoxycarbonyl, in the pyrrole system seems to be necessary for the success of the reaction.

Another pathway for the synthesis of compound **2** is the reaction of D-glucosamine with ethyl 4,4-diethoxy-3-oxobutanoate followed by oxidative degradation of the polyhydroxyalkyl side-chain; however, the low yield in the first step makes this procedure of little preparative value.[21]

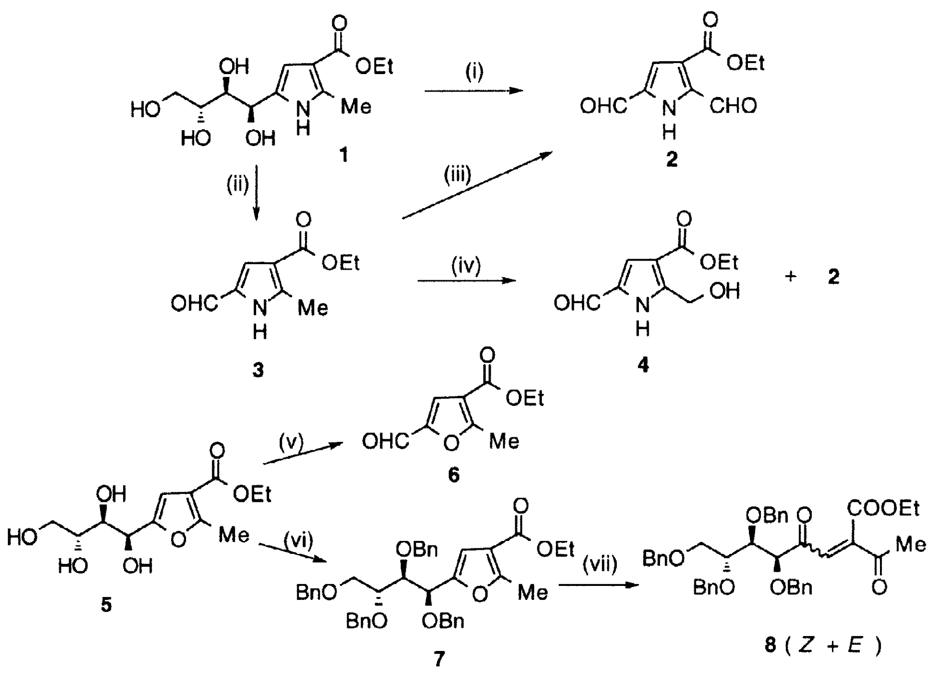


2

The same reaction conditions were applied to furan derivatives, and different results were obtained. Thus, the slow addition of CAN (5.0 and 11.0 equiv.) to compound **5** produced the oxidative cleavage of the polyhydroxyalkyl chain, no oxidation of the 2-methyl group was observed and compound **6** was obtained in 38 - 48% yield. As in the case of pyrrole **1**, the rapid addition of CAN caused decomposition of the starting material.

The difficulty in the oxidation of the 2-methyl group of the furan ring seems to be related to the electron density of the heterocyclic ring. Therefore, the first formyl group introduced in **6** could deactivate the later 2-methyl oxidation. In order to favour this oxidation, the oxidative glycol cleavage was avoided by carrying out the reaction on the tetra-*O*-benzyl derivative 7.[22] However, both slow and rapid addition of 5 equiv. of CAN caused oxidative furan ring opening and a mixture of the two acyclic isomers **8**[23] (*Z*+*E*) in a ratio 1:1.3 (measured by integration of signals in the ^{1}H-NMR spectra) was formed. No products of the 2-methyl oxidation were detected. The structure of **8** was in agreement with IR, NMR and MS data.

Scheme



Reaction Conditions

(i) CAN, 11 equiv., MeCN-H_2O (5:1), 2 h 45 min, **2**: 66%. (ii) $NaIO_4$, MeOH-H_2O, **3**: 91%. (iii) CAN, 6.5 equiv., MeCN-H_2O (9:1), 15 min, **2**: 58%. (iv) CAN, 4.2 equiv., MeCN-H_2O (9:1), 15 min, **2**: 40% yield + **4**: 23%. (v) CAN, 5 equiv., MeCN-H_2O (5:1), 1 h 15 min, **6**: 38% yield; 11 equiv., 2 h 45 min, **6**: 48%. (vi) BnBr, NaH, DMF, **7**: 70%. (vii) CAN, 5 equiv., MeCN-H_2O (9:1), 1h 15 min, **8**: 34%

Typical Procedure for Oxidation with Ceric Ammonium Nitrate: To a stirred solution of the starting material (1.0 mmol) in MeCN-H_2O (40 mL) at r.t., ceric ammonium nitrate was added over a period of time (by adding 1 equiv. each 15 min). After the total reaction time the reaction mixture was diluted with ether, washed with water (3 x 25 mL), dried (Na_2SO_4) and evaporated to give the crude product that was purified by crystallisation from EtOH-H_2O or by column chromatography (dichloromethane-acetone, 40:1 → 10:1).

In conclusion, a new and efficient one-pot synthesis of pyrrole-2,5-dicarbaldehydes is described. The method is applicable to a pyrrole ring having an electron-withdrawing substituent and appears to be dependent on the π-electron density of the heterocyclic ring. The scope and limitations of this method are currently under study in our laboratory.

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19. Selected data for **2**: m. p. 130-132 °C, Lit[21] 128-129 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): 10.17 (s, 1H, N*H*), 10.40, 9.76 (2s, 2H, 2C*H*O), 7.40 (s, 1H, H-4), 4.41 (q, 2H, $J_{H,H}$ = 7.1, C*H*$_2$CH$_3$), 1.41 (t, 3H, $J_{H,H}$ = 7.1, CH$_2$C*H*$_3$); ^{13}C-NMR (75.5 MHz): 183.87, 180.66 (2*C*HO), 162.46 (*C*OOEt), 135.12, 133.32 (C-2, C-5), 120.89 (C-4), 112.57 (C-3), 61.23 (*C*H$_2$CH$_3$), 14.18 (CH$_2$*C*H$_3$).
20. Selected data for **4**: 136-138 °C, Lit[21] 138-139.5 °C ^{1}H-NMR (300 MHz, $CDCl_3$): 10.22 (bs, 1H, N*H*), 9.49 (s, 1H, C*H*O), 7.37 (d, 1H, $J_{4,CHO}$ = 2.7, H-4), 5.03 (d, 2H, $J_{H,OH}$ = 5.3, C*H*$_2$), 4.33 (q, 2H, $J_{H,H}$ = 7.1, C*H*$_2$CH$_3$), 3.73 (bs, 1H, OH), 1.37 (t, 3H, $J_{H,H}$ = 7.1, CH$_2$C*H*$_3$); ^{13}C-NMR (75.5 MHz): 179.54 (*C*HO), 164.23 (*C*OOEt), 145.33 (C-5), 130.47 (C-2), 123.49 (C-4), 114.41 (C-3), 60.43 (*C*H$_2$CH$_3$), 14.27 (CH$_2$*C*H$_3$).
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22. Selected data for **7**: IR, 1717 cm^{-1} (C=O); $[\alpha]_D^{25}$ -30.9° (*c* 1.0, CH_2Cl_2); ^{1}H-NMR (300 MHz, $CDCl_3$): 7.20 - 7.34 (m, 20H, aromatic), 6.54 (s, 1H, H-4), 4.64 (d, 1H, $J_{1',2'}$ = 5.3, H-1'), 4.59, 4.52 (2d, 1H each, $^2J_{H,H}$ = 11.2, C*H*$_2$Ph),), 4.57, 4.32 (2d, 1H each, $^2J_{H,H}$ = 11.8Hz, C*H*$_2$Ph),), 4.53, 4.35 (2d, 1H each, $^2J_{H,H}$ = 11.7, C*H*$_2$Ph),), 4.49, 4.42 (2d, 1H each, $^2J_{H,H}$ = 12.1Hz, C*H*$_2$Ph), 4.29 (q, 2H, $J_{H,H}$ = 7.1, C*H*$_2$CH$_3$), 4.02 (t, 1H, $J_{2',3'}$ = 5.30, H-2'), 3.58 - 3.70 (m, 3H, H-3', H-4'a, H-4'b), 2.50 (s, 3H, C*H*$_3$), 1.35 (t, 3H, $J_{H,H}$ = 7.1, CH$_2$C*H*$_3$); ^{13}C-NMR (75.5 MHz): 163.86 (*C*OOEt), 158.96, 149.79 (C-2, C-5), 138.34, 138.26, 138.15, 137.73 (C-1 of Ph), 128.22 - 127.35 (20C of Ph), 114.05 (C-3), 109.95 (C-4), 80.45 (C-2'), 77.96 (C-3'), 74.49 (C-1'), 74.79, 73.15, 71.84, 71.11 (*C*H$_2$Ph), 68.89 (C-4'), 60.02 (*C*H$_2$CH$_3$), 14.27 (*C*H$_3$), 13.76 (CH$_2$*C*H$_3$).
23. Selected data for **8**: $[\alpha]_D^{25}$ -31.8° (*c* 1.0, CH_2Cl_2); ^{13}C-NMR (125.7 MHz, $CDCl_3$), 201.05 (2C), 200.89, 194.69 (4 C=O), 165.72, 163.01 (2*C*OOEt), 144.02, 141.11 (2C-2), 138.08 (2C), 137.98, 137.98, 137.47, 137,41, 136.79, 136.72 (8C-1 of Ph), 132.17, 131.91 (2C-3), 128.40-127.50 (40C of Ph), 85.45, 85.13 (2C-5), 80.11, 79.79 (2C-6), 77.56, 77.37 (2C-7), 74.71, 74.52, 73.47(2C), 73.31(2C), 71.69, 71.61 (8*C*H$_2$Ph), 68.05, 67.90 (2C-8), 61.92, 61.67 (2*C*H$_2$CH$_3$), 29.84, 27.27 (2CO*C*H$_3$), 13.88, 13.79 (2CH$_2$*C*H$_3$). FABMS: *m/z* 673(100%, M+Na).