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Preparation of pyrrolin-2-ones and 4,5-dihydrodipyrrin-1-ones by oxidation of α-formylpyrroles and α-formyldipyrromethanes with hydrogen peroxide

Clotilde Pichon-Santander and A. Ian Scott *

Center for Biological NMR, Department of Chemistry, Texas A&M University, PO Box 30012, College Station, TX 77842-3012, USA

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Abstract

Various substituted α-formylpyrroles and -dipyrromethanes have been oxidized by hydrogen peroxide under mild conditions to give pyrrolin-2-ones (**2**) and 4,5-dihydrodipyrrin-1-ones (**4**) with concomitant loss of the formyl substituent, thus extending the scope of this oxidation to dipyrromethanes. This makes the reaction especially useful for the preparation of bile pigments, for which the pyrrolinones and 4,5-dihydrodipyrrinones constitute important synthons.

Keywords: pyrroles; oxidation; pyrrolinones; pigments.

The oxidation of pyrroles to pyrrolin-2-ones is well known, as pyrrolin-2-ones form the terminal rings of bile pigments.[1a] Several studies on their formation by auto- and photo-oxygenation have been reported[2–5] and a variety of preparative methods developed for the syntheses of bile pigments and other biologically important natural products.[1b] However, very few accounts concerning the oxidation of the parent dipyrromethanes to 4,5-dihydrodipyrrin-1-ones can be found; these products are usually obtained by a coupling of pyrrolin-2-ones with α-formylpyrroles followed by reduction of the methine bridge.[1c] We chose to focus on oxidation by hydrogen peroxide (H_2O_2), a reaction which has been known for some time[6] and where the yields and products are very dependent on the pH of the reaction and the pyrrole substitution.[7,8]

When carrying out the oxidation of α-free pyrroles (**1**, R_2=H) with H_2O_2 under different conditions, a mixture of products is always obtained, from which pyrrolin-2-ones (**2**) constitute the main product. Noteworthy, with α-formylpyrroles only pyrrolin-2-ones, with concomitant loss of the formyl substituent, were detected. Table 1 shows the results for the oxidation of a variety of α-formylpyrroles. The conditions used and the yields obtained are close to the ones described by Lightner for the oxidation of kryptopyrrole (**1**, R_1=R_2=H, R_3=R_5=Me, R_4=Et) toward the synthesis of xanthobilirubic acid methyl

* Corresponding author. Fax: 409 845 5992; e-mail: scott@mail.chem.tamu.edu (A. I. Scott)

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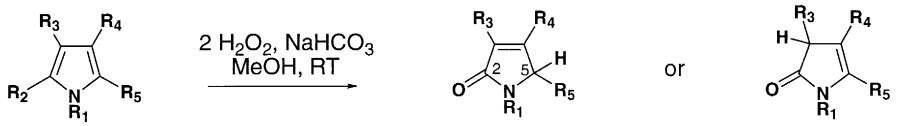
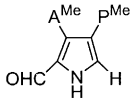
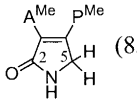
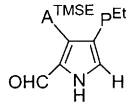
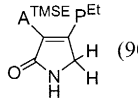
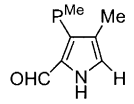
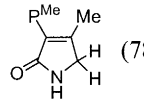
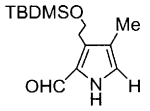
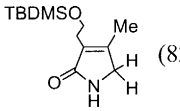
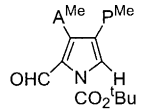
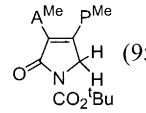
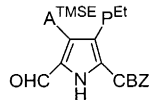
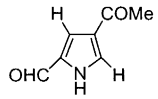
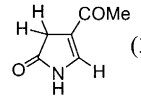
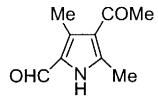
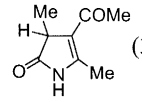
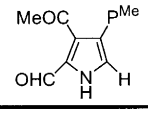
Table 1
Oxidation of α-formylpyrroles



1
R_2=H or CHO

2
Δ^3 with R_4=P^R, Me

2
Δ^4 with R_4=CO Me

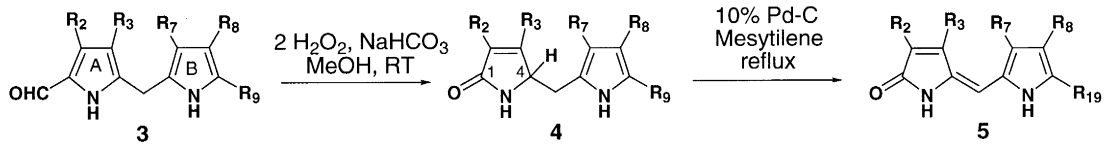
Entry	Starting pyrrole **1**	Time[a] in days	Pyrrolin-2-ones **2** (yield, %)	Main **NMR** characteristics of the products in $CDCl_3$[b] ^{1}H(ppm)	^{13}C(ppm)
1		3	 (85)	3.76, s, H-5	170.21, C-2 48.44, C-5
2		3	 (90)	3.85, s, H-5	170.12, C-2 48.63, C-5
3		3	 (78)	3.71, s, H-5	175.79, C-2 50.16, C-5
4		4	 (82)	3.74, s, H-5	176.17, C-2 50.20, C-5
5		3	 (95)	4.12, s, H-5	168.37, C-2 51.17, C-5
6		7	no oxidation		
7		4	 (37)	3.30, s, H-3 6.53, s, H-5	181.94, C-2 46.48, C-3
8		4	 (39)	3.29, q, H-3 2.26, s, Me-5 1.39, d, Me-3	182.04, C-2 42.98, C-3
9		2	no oxidation		

A^R=CH_2CO_2R; TMSE=$CH_2CH_2SiMe_3$; P^R=$CH_2CH_2CO_2R$; CBZ=CO_2CH_2Ph; TBDMS=^{t}$BuMe_2Si$

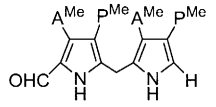
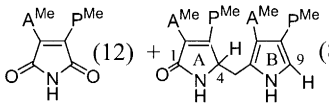
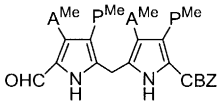
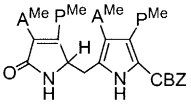
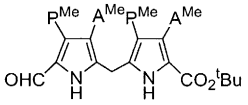
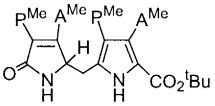
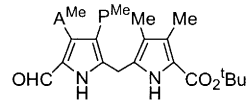
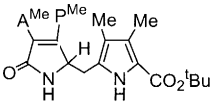
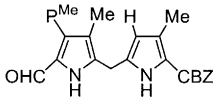
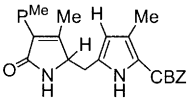
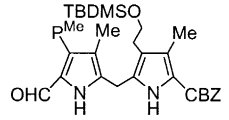
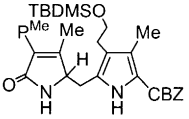
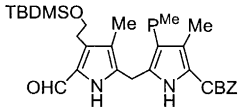
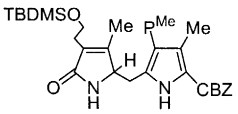
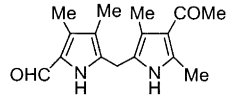
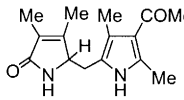
a) conditions: MeOH, 1 eq. $NaHCO_3$, 2 eq. H_2O_2, RT.

b) ^{1}H- and ^{13}C-NMR were recorded on a Brüker AM-500 (500 MHz).

Table 2
Oxidation of α-formyldipyrromethanes



3 4 5

Entry	Starting dipyrromethane 3	Time[a] in days	Product 4 (yield, %)	Main NMR characteristics of the products in $CDCl_3$[b] ^{1}H(ppm)	^{13}C(ppm)
10		4	 (12) + (8)	6.44, d, H-9 4.19, m, H-4	170.91, C-1 59.33, C-4
11		2	 (62)	4.15, dd, H-4	170.46, C-1 59.12, C-4
12		3	 (56)	4.37, dd, H-4	169.98, C-1 58.88, C-4
13		3	 (61)	4.22, d, H-4	170.50, C-1 58.88, C-4
14		3	 (80)	4.04, dd, H-4	173.29, C-1 59.95, C-4
15		3	 (77)	4.07, dd, H-4	173.32, C-1 60.29, C-4
16		3	 (66)	4.06, dd, H-4	173.34, C-1 60.26, C-4
17		3	 (33)	3.97, dd, H-4	175.70, C-1 61.39, C-4

A^R=CH_2CO_2R; TMSE=$CH_2CH_2SiMe_3$; P^R=$CH_2CH_2CO_2R$; CBZ=CO_2CH_2Ph; TBDMS=^{t}$BuMe_2Si$

a) conditions: MeOH, 1 eq. $NaHCO_3$, 2 eq. H_2O_2, RT.

b) ^{1}H- and ^{13}C-NMR were recorded on a Brüker AM-500 (500 MHz).

ester,[9] which itself represents a substantial improvement over previously used conditions, affording only moderate yields of **2** (30–40%).[7,10,11] As already observed,[8] the presence of electron-withdrawing group (EWG) influences the product of reaction. If no EWG is present (entries 1 to 4) or is attached to the pyrrolic nitrogen (entry 5), very good yields of Δ^3-pyrrolin-2-ones are obtained. If the EWG is at the

other α-position (entry 6), no oxidation takes place. If the EWG is at a β-position and opposite to the formyl group (entries 7 and 8), moderate yields of Δ^4-pyrrolin-2-one can be isolated; when the two EWGs are adjacent (entry 9), no oxidation is detected. The structural assignments as Δ^3 and Δ^4 have been made in correlation with previous works on the subject,[7,8,12] showing H-3 of the Δ^4 form to be at higher field than H-5 of the Δ^3 form. The Δ^3 structure was confirmed by the equivalence of the two H-5s (entries 1 to 5) and the Δ^4 by unambiguous NMR structure assignment of a parent compound.[13] These mild conditions allow the reaction to be carried out with pyrroles bearing a wide variety of substituents, thus making it particularly interesting for the synthesis of bile pigments, which often bear alkyl, propionic acid or vinyl side-chains, the latter being easily generated from the protected 2-hydroxyethyl group (as in entry 4).[14]

Only one example of α-free dipyrromethane oxidation with H_2O_2, giving a moderate yield (45%) of the 4,5-dihydrodipyrrin-1-one (**4**), has been reported.[8] Dipyrromethanes behave similarly to monopyrroles. Table 2 shows the results for α-formyldipyrromethanes (**3**), which are oxidized with concomitant loss of the formyl group; if the second α-position is free, low yields of products are obtained (entry 10), while with a larger excess of H_2O_2 the α-free pyrrole ring (B) is also oxidized (39%, not shown). With α-formyldipyrromethanes bearing an EWG at the α′-position, only 4,5-dihydrodipyrrin-1-ones are obtained in good yields, the NMR exhibiting a new sp^3 carbon (C-4) bearing a proton (entries 11 to 17). This is of special interest for bile pigment synthesis, as 4,5-dihydrodipyrrinones can only be prepared through reduction by sodium amalgam or sodium dithionite of their dipyrrinones formed by condensation of pyrrolin-2-ones with α-formylpyrroles, often in variable yields and with side-product formation.[1b] 4,5-Dihydrodipyrrinones are also smoothly dehydrogenated in excellent yields to the corresponding dipyrrinones (**5**) with 10% Pd–C in mesitylene at reflux. As mentioned above, the vinyl side-chain, often present in bile pigments, can be easily generated from the protected 2-hydroxyethyl group (as in entries 15 and 16).[14]

In summary, a variety of substituted α-formylpyrroles and -dipyrromethanes have been oxidized by H_2O_2 under very mild conditions, giving good to excellent yields of pyrrolin-2-ones and 4,5-dihydrodipyrrin-1-ones, thus showing a substantial improvement over most of the other methods described in the literature. This represents the first report of H_2O_2 oxidation of α-formyldipyrromethanes. The compatibility of the reaction conditions with diverse functional groups present in bile pigments further demonstrates its usefulness for preparative purposes. Indeed, this oxidation provides an alternative route for bile pigment synthesis and especially, should lead to improved yields for the preparation of urobilins and coprobilins.[14,15]

Acknowledgements

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13. ^{1}H NMR of **2** (R_1=H, R_3=P^{Me}, R_4=COMe, R_5=Me) showed a singlet at 2.26 ppm for Me-5 and a multiplet at 3.38 ppm for H-3 and ^{13}C NMR a peak for C-3 at 46.73 ppm and for C-2 at 180.79 ppm.
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