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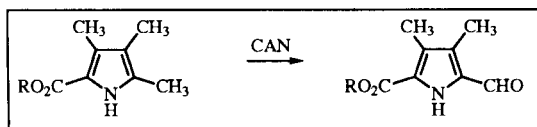
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Dipyrrylmethanes are smoothly and efficiently oxidized to dipyrryl ketones by ceric ammonium nitrate in water-tetrahydrofuran-acetic acid solvent at room temperature.

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Although the synthetic utility of ceric ammonium nitrate (CAN) for benzylic oxidations has been repeatedly if not frequently demonstrated [1,2], until recently there had been very few reported oxidations of pyrroles [3,4]. Benzylic methyls are converted to aldehydes; benzylic methylenes to ketones – both in high yield. When multiple potential oxidation sites are present, the reaction normally stops at the monocarbonyl stage, as in the oxidation of mesitylene to 3,5-dimethylbenzaldehyde in 100% yield [1]. Nearly 20 years ago the reaction was extended to aromatics with the relatively more sensitive pyrrole nucleus [3].



Thus, while the oxidation of ethyl and benzyl esters of 3,4,5-trimethylpyrrole-2-carboxylic acid gave the corresponding 5-formyl analogs in 66 and 42% yields, respectively, a complicating factor was the production of a by-product in 8% yield, the symmetrical dipyrryl ketone, 5,5'-dicarbobenzyloxy-3,3',4,4'-tetramethyl-2,2'-dipyrryl ketone, which could also be formed more directly in 45% yield by CAN oxidation of the corresponding dipyrrylmethane. The authors [3] concluded that conversions of pyrrolmethyl to pyrrolaldehyde using CAN was uneconomical since the yields were only fair, and by-products were formed, but it was shown more recently that conversion of a pyrrole α -methyl to α -formyl by CAN depends considerably on the choice of solvents and reaction conditions, and on the presence of a carboxylic acid (ester) group at the pyrrole α' position. In the absence of, for example, a carboethoxy group at the α' position, the reaction is much less smooth. An α' -carboxylic acid ester group uniquely

activates an α -methyl group toward CAN oxidation, and it has been shown that CAN can be used to oxidize pyrrole such as α -methyls to α -formyls in high yield in α' -carboethoxypyrroles with a wide variety of β substituents [4].

In the following we describe how CAN may be used to oxidize dipyrrylmethanes smoothly to dipyrryl ketones under mild conditions, yielding analytically pure product in high yield. Thus, dipyrrylmethanes with carboethoxy groups at the α' positions and simple alkyl groups at the β positions can be oxidized efficiently to their corresponding dipyrryl ketones **1** and **2**. More interestingly, the reaction also succeeds when pyrrole β -positions are substituted by propionic acid esters to form dipyrryl ketone **3**. Work is currently underway to convert **3** into 10-oxomesobilirubin-XIII α , an interesting analog of a potential bilirubin metabolite, 10-oxobilirubin [5].

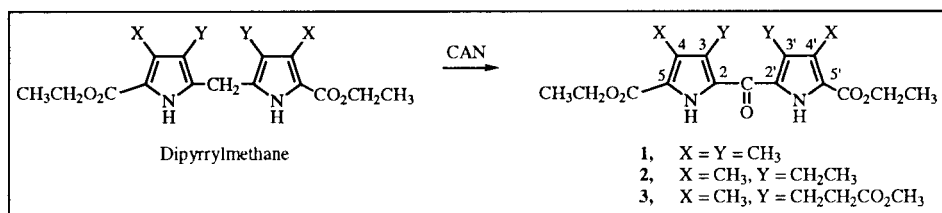
EXPERIMENTAL

General.

All nmr spectra were run on a Varian Aspect 500 MHz or GE QE-300 FT spectrometer in dimethyl sulfoxide-*d*₆ (99.9% *d*₆) from Aldrich. Ceric ammonium nitrate, acetic acid and tetrahydrofuran were from Fisher. Combustion microanalyses were performed by Desert Analytics, Tucson, AZ.

5,5'-Biscarboethoxy-3,3',-4,4'-tetramethyl-2,2'-dipyrryl Ketone (**1**).

To a stirred solution of 5,5'-biscarboethoxy-3,3',4,4'-tetramethyl-2,2'-dipyrrylmethane [6] (50 mg, 0.144 mmole) in acetic acid (12 ml), tetrahydrofuran (12 ml) and water (5 ml) was added ceric ammonium nitrate (332 mg, 0.606 mmole). The solution was stirred for 2.5 hours at room temperature, and the resulting slurry was poured into 50 ml of water, cooled to 5° and filtered. The yield of dried, white dipyrryl ketone **1** was 42 mg (81%). It had mp 212-213° (lit [3] mp 212-214°); ¹H-nmr:



δ 1.28 (t, 6H, J = 7.0 Hz), 1.92 (s, 6H), 2.20 (s, 6H) 4.23 (q, 4H, J = 7.0 Hz), 11.67 (s, 2H, NH) ppm; ^{13}C -nmr: δ 9.31 (q), 9.62 (q), 13.99 (q), 59.53 (t), 121.5 (s), 124.5 (s), 125.7 (s), 131.3 (s), 160.5 (s), 177.8 (s) ppm.

5,5'-Biscarboethoxy-3,3'-diethyl-4,4'-dimethyl-2,2'-dipyrryl Ketone (2).

This ketone was prepared from 5,5'-biscarboethoxy-3,3'-diethyl-4,4'-dimethyl-2,2'-dipyrrylmethane [7] exactly as described for 1 above in 58% yield. It had mp 183-185° (lit [8] mp 190-191°); ^1H -nmr: δ 0.97 (t, 6H, J = 7.2 Hz), 1.27 (s, 6H, J = 6.9 Hz), 2.23 (s, 6H), 2.39 (q, 4H, J = 7.2 Hz), 4.23 (q, 4H, J = 6.9 Hz), 11.64 (s, 2H, NH) ppm; ^{13}C -nmr: δ 9.85 (q), 14.29 (q), 15.23 (q), 17.15 (t), 59.78 (t), 121.5 (s), 125.3 (s), 131.2 (s), 160.8 (s), 178.4 (s) ppm.

5,5'-Biscarboethoxy-3,3'-bis(2-methoxycarbonylethyl)-4,4'-dimethyl-2,2'-dipyrryl Ketone (3).

To a stirred mixture of 5,5'-biscarboethoxy-4,4'-dimethyl-3,3'-bis(2-ethoxycarbonylethyl)-4,4'-dimethyl-2,2'-dipyrrylmethane [9] (30 mg, 0.0612 mmole) in acetic acid (3 ml) and water (3 ml) was added 130 mg (0.237 mmole) of ceric ammonium nitrate. After stirring for 2.5 hours, the reaction was quenched by adding 10 ml of water, cooled to -20° and filtered to remove dipyrrol ketone product 3. The yield of pure, dried product is 23 mg (75%). It had mp 129-131°; ^1H -nmr: δ 1.24 (t, 6H, J = 6.9 Hz), 2.20 (s, 6H), 2.42 (t, 4H, J = 6.9 Hz), 3.49 (s, 6H), 4.21 (q, 4H, J = 7.2 Hz), 11.72 (s, 2H, NH) ppm; ^{13}C -nmr: δ 9.86

(q), 14.28 (q), 19.52 (t), 34.20 (t), 51.20 (q), 59.84 (t), 121.6 (s), 125.8 (s), 128.0 (s), 131.5 (s), 160.7 (s), 172.6 (s), 178.2 (s) ppm.

Anal. Calcd. for $\text{C}_{25}\text{H}_{32}\text{N}_2\text{O}_9$ (504.53): C, 59.52; H, 6.35; N, 5.55. Found: C, 59.35; H, 6.54; N, 5.14.

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