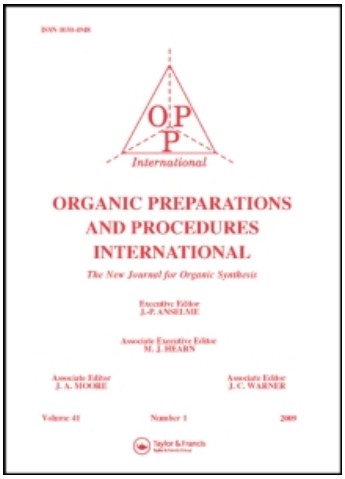

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IMPROVED SYNTHESIS OF SYMMETRICAL DIPYRROMETHENES

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IMPROVED SYNTHESIS OF SYMMETRICAL DIPYRROMETHENES

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(03/08/99)

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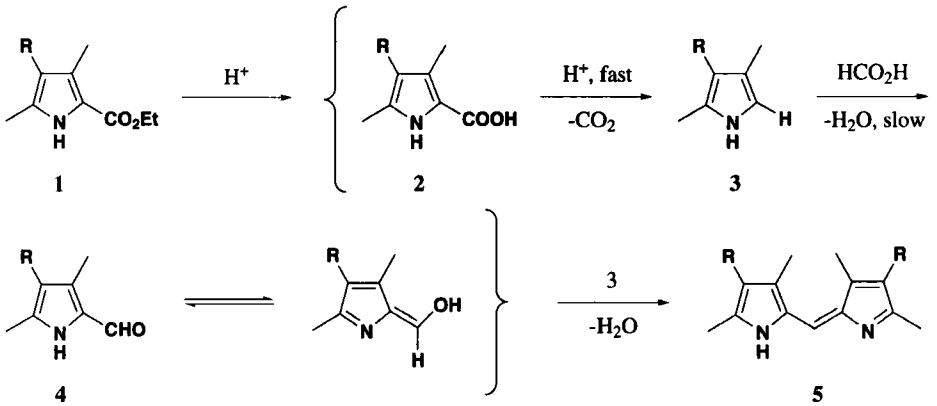
Numerous dipyrromethenes bearing symmetrical substitutents, such as 5,5'-dibromo, 5,5'-dibromomethyl, 5,5'-dicarboxy, 5,5'-diformyl, non-symmetrical substitutents such as 5-methyl-5'-bromomethyl, and unsubstituted dipyrromethenes are necessary intermediates in the synthesis of symmetrical porphyrins,[1,2] and some symmetrical bile pigments. All these derivatives can be obtained from 5,5'-dimethyl-dipyrromethenes (**5**). The following reactions have usually been used to yield symmetrical dipyrromethenes:[3] a) condensation of pyrrole-2-carboxaldehydes (**4**) with an α-unsubstituted pyrrole, *e. g.* cryptopyrrole (**3e**); b) condensation of two equivalents of an α-unsubstituted pyrrole, *e. g.* cryptopyrrole (**3e**) in formic acid or 2,3,4-trimethylpyrrole in chloromethyl methyl ether; c) acid-catalyzed self-condensation of pyrrole-2-carboxaldehydes (*e. g.* **4**) in hydrobromic acid and ethanol; d) acid-catalyzed condensation of pyrrole-2-carboxylic acids (**2**) in mineral acids (*e. g.* $HClO_4$, HBr, HCl) and formic acid.[4] We now report that symmetrical 5,5'-dimethyldipyrromethenes (**5**) are obtained in high yield and short time *via* self-condensation of pyrrole-2-carboxylates (**1**) in formic acid containing catalytic conc. HCl at reflux temperature. The carboxylates (**1**) are easily prepared by the Knorr reaction. Thus the use of unstable and toxic $HClO_4$ or HBr[5] is avoided.



a) R = $CH_2CH_2CH_2OH$ b) R = $CH_2CH_2CO_2C_2H_5$ c) R = $CH_2CH_2CH_2Cl$
d) R = $CH_2CH_2CO_2CH_3$ e) R = CH_2CH_3

An intermediate from the conversion of ethyl 4-(3-chloropropyl)-3,5-dimethylpyrrole-2-carboxylate (**1c**) to the 4,4'-(3-chloropropyl)-3,3',5,5'-tetramethyldipyrromethene hydrochloride (**5c**) was isolated and identified as 4-(3-chloropropyl)-3,5-dimethylpyrrole-2-carboxaldehyde (**4c**, MS: m/e 201, 199, 187, 185, 173, 171, 158, 148, 136, 122, 108, 94). When the reaction temperature was lowered to 60-70°, an unstable oil (which turned red in air) separated and was identified as 4-(3-

chloropropyl)-3,5-dimethylpyrrole (**3c**, IR: 3377, 1689, 1644cm^{-1}). This probably constitutes the first isolation of a reactive intermediate suggested earlier.[4] A reasonable reaction mechanism may proceed as follows: initial hydrolysis of pyrrole-2-carboxylates (**1**) to pyrrole-2-carboxylic acids (**2**) is followed by decarboxylation to give the α-unsubstituted pyrroles (**3**). This occurs more rapidly than the next step in which the pyrrole undergoes acylation by formic acid with subsequent elimination of H_2O to form the pyrrole-2-carboxaldehydes (**4**). The final step, condensation of pyrrole-2-carboxaldehydes (**4**) with α-unsubstituted pyrroles (**3**) to give dipyrromethenes (**5**), is rapid. The dipyrromethene product usually separates as a salt of the mineral acid used.

EXPERIMENTAL SECTION

IR spectra (cm^{-1}) were recorded on BIO-RAD FT-165 IR spectrophotometer as KBr pellets. ^{1}H NMR spectra (δ downfield from internal TMS) were recorded on a Varian Gemini-300 MHz instrument. UV-Vis spectra were recorded on Hitachi U-2001 spectrophotometer. MS were run on VG TR10-200 spectrometer. Elemental analyses were done on Carlo Erba-120 instrument. The melting points are not corrected.

Ethyl 4-(3-Hydroxypropyl)-3,5-dimethylpyrrole-2-carboxylate (1a).- A mixture of ethyl 4-(ethoxycarbonylethyl)-3,5-dimethylpyrrole-2-carboxylate (**1b**, 16g, 0.06mol) obtained by the Knorr reaction,[6] $NaBH_4$ (12g) and dried THF (120 mL) was placed in a 500 mL flask cooled in an ice/NaCl bath. After dropwise addition of BF_3•Et_2O (100 mL) below 10°, the reaction mixture was stirred continuously for 1h, then water was dripped in until effervescence ceased. The mixture was filtered to remove salts and the filtrate was extracted with chloroform (3x150 mL). The chloroform extract was washed with water (3x60 mL), dried (Na_2SO_4), and evaporated to dryness. Crystallization of the residue from 80% ethanol gave 13g (97%) of **1a** as a colorless crystalline solid, mp. 120-124°.
^{1}H NMR ($CDCl_3$): δ 1.34 (t, 3H), 1.71 (m, 2H), 2.20 (s, 3H), 2.30 (s, 3H), 2.45 (t, 2H), 3.64 (t, 2H), 4.30 (q, 2H), 9.01 (s, 1H); IR: 3290, 1664, 1441, 1272, 1099, 902, 769cm^{-1}.
Anal. Calcd. For $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 64.25; H, 8.37; N, 6.10

Ethyl 4-(3-Chloropropyl)-3,5-dimethylpyrrole-2-carboxylate (1c).- To a solution of ethyl 4-(3-hydroxypropyl)-3,5-dimethylpyrrole-2-carboxylate (**1a,** 4.5g, 0.02mol) in 20 mL dichloromethane and 1.6 mL pyridine, thionyl chloride (1.43 mL) was dripped in rapidly with stirring at 50°. The mixture was stirred and purged continuously with dried nitrogen for 1h, then diluted with dichloromethane and washed with 2N HCl, saturated aqueous $NaHCO_3$, and water, dried over anhydrous sodium sulfate and evaporated. The residue was redissolved in benzene and filtered through a short alumina column. After removal of the solvent from the filtrate the residue was crystallized from dichloromethane and *n*-hexane to give 4.4g (91%) of **1c** as light yellow needle crystals, mp. 88-91°.
^{1}H NMR($CDCl_3$): δ 1.35 (t, 3H), 1.90 (m, 2H), 2.23 (s, 3H), 2.27 (s, 3H), 2.54 (t, 2H), 3.51 (t, 2H), 4.30 (q, 2H), 8.68 (s, 1H); IR: 3313, 1673, 1454, 1171, 1029, 769, 708cm^{-1}.
Anal. Calcd. for $C_{12}H_{18}ClNO_2$: C, 59.14; H, 7.44; N,5.75. Found: C, 59.33; H, 7.28; N, 5.72

4,4'-(3-Chloropropyl)-3,3',5,5'-tetramethyldipyrromethene Hydrochloride (5c).- Ethyl 4-(3-

chloropropyl)-3,5-dimethylpyrrole-2-carboxylate (**1c,** 1g, 0.004mol) was dissolved in 98% formic acid (30 mL) containing conc. HCl (0.5 mL). The mixture was heated to 120° and refluxed for 1h with a color change from colorless to golden-yellow, then cooled to room temperature. The solution was evaporated to dryness and crystallized from hot methanol to give 0.77g (96%) of **5c** as red-yellow needle crystals with a metallic sheen, mp.186-188°.

^{1}H NMR($CDCl_3$): δ 1.920 (m, 4H), 2.29 (s, 6H), 2.61 (t, 4H), 2.64 (s, 6H), 3.52 (t, 4H), 7.04 (s, 1H); IR: 3415, 1613, 1522, 1248, 944, 772 cm^{-1}; MS: (m/e) 352, 337, 317, 289, 171, 108; UV-Vis: λ_{max} ($CHCl_3$) 279.5, 365.0, 486.5 nm (ε 1,700 5,900 93,700); fluorescence: λ_{max} ($CHCl_3$) 514.4 nm.

*Anal.*Calcd.for $C_{19}H_{28}Cl_2N_2$·HCl: C, 58.26; H, 7.46; N, 7.15. Found: C, 58.50; H, 7.22; N, 7.03

4,4'-Dimethylcarbonylethyl-3,3',5,5'-tetramethyldipyrromethene Hydrochloride (5d).- Ethyl 4-(methylcarbonylethyl)-3,5-dimethylpyrrole-2-carboxylate (**1d,** 1g, 0.004mol), prepared as described in reference[6] for ethyl 4-(ethoxycarbonylethyl)-3,5-dimethylpyrrole-2-carboxylate using methyl 4-acetyl-5-oxohexanoate, was dissolved in 98% formic acid (30 mL) containing 0.5 mL conc. HCl. The mixture was refluxed for 1h with a color change from colorless to golden-yellow, then cooled. After evaporation of the solvent, the residue was washed with cold methanol to afford 4,4'-dipropionic acid-3,3',5,5'-tetramethyldipyrromethene hydrochloride (IR: 3439, 1721, 1612, 1255, 936, 676 cm^{-1}) as a red powder. A portion of the dipropionic acid derivative of dipyrromethene (0.5g, 1.3mmol) was methylated in anhydrous methanol (20 mL) and conc. HCl (2 mL) at reflux temperature for 1h, then cooled in refrigerator. The product was collected by filtration and crystallized from hot methanol to give 0.52g (93%) of **5d** as yellow-red needle crystals with a metallic sheen, mp. 204-208°.

^{1}H NMR($CDCl_3$): δ 2.29 (s, 6H), 2.46 (t, 4H), 2.64 (s, 6H), 2.76 (t, 4H), 3.77 (s, 6H), 7.04 (s, 1H); IR: 3415, 1735, 1612, 1534, 1248, 1172, 949 cm^{-1}; MS: (m/e) 372, 357, 299, 283, 251, 225, 211, 112; UV-Vis: λ_{max} ($CHCl_3$) 365, 484.5 nm (ε 7,700 92,400); fluorescence: λmax ($CHCl_3$) 511.2 nm.

Anal. Calcd. For $C_{21}H_{28}N_2O_4$·HCl: C, 61.69; H, 7.15; N, 6.85. Found: C, 61.31; H, 7.13; N, 6.89

4,4'-Diethyl-3,3',5,5'-tetramethyldipyrromethene Hydrochloride (5e).- Ethyl 4-ethyl-3,5-dimethylpyrrole-2-carboxylate (**1e,** 3g, 0.015mol) was synthesized as described in reference.[7] The following procedure was the same as compound **5c**, and gave 2.2g (98%) of **5e** as yellow-red needle crystals with a metallic sheen, mp. 254-256°.

^{1}H NMR ($CDCl_3$): δ 1.10 (t, 6H), 2.29 (s, 6H), 2.45 (q, 4H), 2.65 (s, 4H), 7.04 (s, 1H); MS: (m/e) 256, 241, 212, 197; IR: 3415, 1615, 1523, 1246, 955cm^{-1}; UV-Vis: λ_{max} ($CHCl_3$) 280, 365, 486 nm (ε 1,600 4,900 92,400); fluorescence: λ_{max} ($CHCl_3$) 511 nm.

Anal. Calcd. For $C_{17}H_{24}N_2$·HCl: C, 69.72; H, 8.60; N, 9.56. Found: C, 69.37; H, 8.19; N, 9.45

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TRANSFORMATION OF 6-HALOPENICILLANATES INTO 3-HALO-4-OXOAZETIDINE DERIVATIVES

Submitted by Irena Lukić
(04/27/99)

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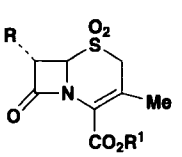
Azetidin-2-ones are of interest as precursors for the elaboration of new β-lactam analogues **A**[1] or for the stereocontrolled synthesis of thienamycin **B**.[2] Since readily obtained[3] penicillanic acid 1,1-dioxides may be degraded to azetidin-2-ones by reaction with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN),[4] we became interested in studying this reaction with 6,6-dibromo- and 6-bromopenicillanate 1,1-dioxides **1, 4** and **5** as substrates.



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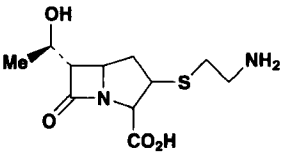

B