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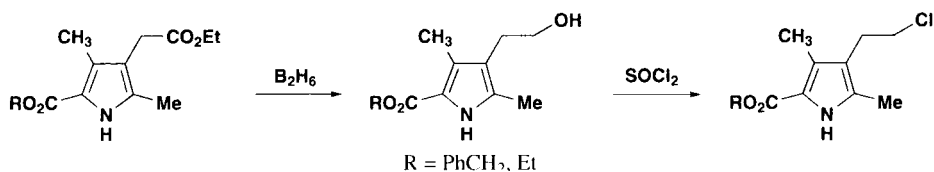
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NEW METHOD FOR SYNTHESIS OF (ω -CHLOROALKYL) PYRROLES

Submitted by Bin Tu, Changqi Wang and Jinshi Ma*
(05/02/00)

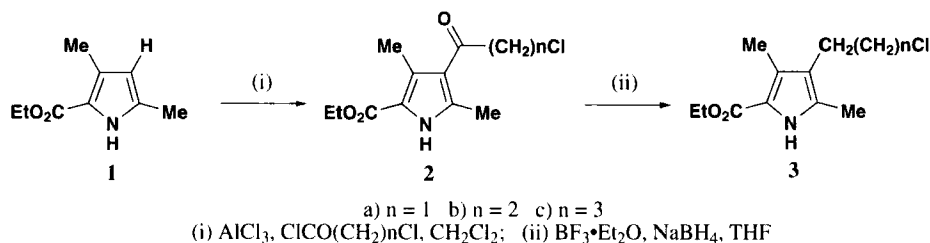
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In the total synthesis of some biologically important bile pigments and porphyrins, such as bilirubin IX α and protoporphyrin IX, a key step involves obtaining a vinyl side-chain. A method successfully used to obtain vinyl residues is dehydrochlorination of 2-chloroethyl residues using sodium hydroxide in boiling pyridine.^{1,5} The 2-chloroethyl moieties may themselves play an important role in the synthesis of biliverdins with stable extended conformations,^{6,7} during which intramolecular substitution reactions take place between the 2-chloroethyl portions and the basic pyrroline or pyrrolinone nitrogens. (2-Chloroethyl) pyrroles have usually been prepared by the reduction of carboethoxymethylpyrroles with diborane to the (2-hydroxyethyl) pyrroles, followed by treatment with thionyl chloride in pyridine (*Scheme 1*)^{1,8}. Herein, we report a novel way to synthesize (2-chloroethyl) pyrroles which reduces the synthetic effort to three high-yielding steps.



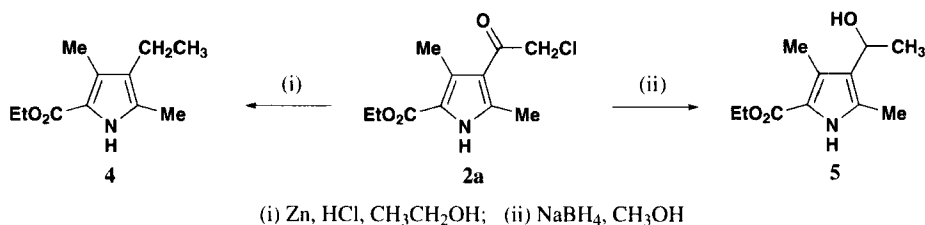
Scheme 1

2-(Ethoxycarbonyl)-3,5-dimethylpyrrole **1** (prepared in one step from 2,4-pentanedione and diethyl aminomalonate⁹ or diethyl oximinomalonate¹⁰), which incorporates a free β -position, was chosen as starting material. As shown in *Scheme 2*, pyrrole **1** treated with chloroacetyl chloride *via* the Friedel-Crafts reaction^{11,12} gives chloroacetylpyrrole **2a**. The optimal conditions were found to



Scheme 2

involve the use of anhydrous AlCl_3 as catalyst in dried CH_2Cl_2 . Two factors are important to enhance the yield: (i) The solvent must be absolutely dry, since even a little water will reduce the yield greatly; (ii) A 2-3 fold excess of the catalyst and chloroacetyl chloride should be used to ensure completeness of the reaction. It was difficult to select an appropriate reducing agent to convert **2a** to **3a**. In earlier articles,¹¹⁻¹³ diborane had been applied as reducing reagent (a procedure developed by Whitlock and Hanaure¹⁴) for the reduction of carbonyl to methylene or ethoxycarbonyl to hydroxymethyl on pyrroles, but it was not clear whether the chloro group would be affected during this process. However, no satisfactory results were obtained with several other reducing agents. Clemmensen reduction using zinc and hydrochloric acid or treatment with NaBH_4 in methanol gave pyrroles **4** and **5** respectively (Scheme 3). Thus, we turned our attention back to diborane: NaBH_4 was first added to a



Scheme 3

solution of pyrrole **2a** in dried THF, followed by the slow addition of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in 30 min and the temperature was kept under 10° ; after stirring for an additional 2h at room temperature, the product obtained was shown to be pyrrole **3a** in nearly quantitative yield.

It should be noted that (3-chloropropyl) pyrrole (**3b**) and (4-chlorobutyl) pyrrole (**3c**) were also obtained from **2b** and **2c** respectively under the same conditions, which indicated that diborane has no influence on the chloro group regardless of its position. The chloroalkyl side-chains afford wide possibilities for the synthesis of complex and interesting bile pigments or porphyrins.

EXPERIMENTAL SECTION

IR spectra (cm^{-1}) were recorded on BIO-RAD FT-165 IR spectrophotometer as KBr pellets. ^1H NMR spectra (δ downfield from internal TMS) were obtained on a Varian Gemini-300 MHz instrument. Elemental analyses were carried out on a Carlo Erba-120 instrument. The melting points are not corrected.

Ethyl 4-(2-Chloroacetyl)-3,5-dimethyl-1H-pyrrole-2-carboxylate (2a).- To a 150 mL 3-neck round-bottomed flask fitted with a reflux condenser and a drying tube, was added pyrrole **1** (5g, 0.03mol) in 100 mL CH₂Cl₂ (dried over P₂O₅). After addition of anhydrous AlCl₃ (10g, 0.075mol), the mixture was stirred at room temperature until it became homogeneous, then chloroacetyl chloride (8.5g, 0.075mol) was added quickly. The mixture was stirred and heated slowly at reflux for 2 h. After cooling to room temperature, the reaction mixture was poured into H₂O (300mL) and extracted with CH₂Cl₂ (3x50mL). The combined organic solution was washed with saturated sodium chloride (2x100mL) and dried over anhydrous Na₂SO₄. The solvent was removed (roto-vap) to give a pinkish white product. The crude material was recrystallized from 95% ethanol to afford 6.84g (94%) of beautiful white needles, mp 179-181°. ¹H NMR (CDCl₃): δ 1.39 (t, 3H), 2.55 (s, 3H), 2.61 (s, 3H), 4.35 (q, 2H), 4.49 (s, 2H), 9.38 (s, 1H); IR: 3276.8, 1674.2, 1652.2, 1515.5, 1419.3, 1275.7, 979.1, 731.9 cm⁻¹. *Anal.* Calcd. for C₁₁H₁₄ClNO₃; C, 54.21; H, 5.79; N, 5.74. Found: C, 54.23; H, 5.76; N, 5.72

Ethyl 4-(3-Chloropropionyl)-3,5-dimethyl-1H-pyrrole-2-carboxylate (2b).- Pyrrole **1** (5g, 0.03mol) reacted with 3-chloropropionyl chloride (9.5g, 0.075mol) under the same conditions described above to give 7.08g (92%) of white needles, mp 140-142°. ¹H NMR (CDCl₃): δ 1.39 (t, 3H), 2.55 (s, 3H), 2.61 (s, 3H), 3.32 (t, 2H), 3.91(t, 2H), 4.34 (q, 2H), 9.04 (s, 1H); IR: 3293.0, 1665.7, 1633.1, 1420.9, 1281.6, cm⁻¹.

Anal. Calcd. for C₁₂H₁₆ClNO₃; C, 55.92; H, 6.25; N, 5.43. Found: C, 55.88; H, 6.32; N, 5.40

Ethyl 4-(4-Chlorobutyryl)-3,5-dimethyl-1H-pyrrole-2-carboxylate (2c).- Pyrrole **1** (5g, 0.03mol) reacted with 4-chlorobutyryl chloride (10.6g, 0.075mol) under the same conditions described above to give 7.38g (91%) of white needles, mp 106-108°. ¹H NMR (CDCl₃): δ 1.38 (t, 3H), 2.20 (m, 2H), 2.54 (s, 3H), 2.62 (s, 3H), 2.94 (t, 2H), 3.68 (t, 2H), 4.33 (q, 2H), 8.90 (s, 1H); IR: 3290.8, 1669.3, 1646.8, 1443.6 cm⁻¹.

Anal. Calcd. for C₁₃H₁₈ClNO₃; C, 57.46; H, 6.67; N, 5.15. Found: C, 57.43; H, 6.72; N, 5.15

Ethyl 4-(2-Chloroethyl)-3,5-dimethyl-1H-pyrrole-2-carboxylate (3a).- To a 500 mL 3-neck round-bottomed flask fitted with a dropping funnel, thermometer and a drying tube, was added pyrrole **2a** (10g, 0.04mol) in 250 mL THF (dried over LiAlH₄). The mixture was cooled in an ice-salt bath to about 0°. After complete addition of NaBH₄ (3.04g, 0.08mol) in portions, BF₃•Et₂O (11.36g, 0.08mol) was added dropwise during 30 min. During the procedure, the temperature was controlled below 10° and the effervescence was not too vigorous. The solution was then warmed slowly to room temperature and stirred for an additional 2h, after which, 5% HCl was dripped in slowly to decompose the unreacted NaBH₄. The mixture was poured into H₂O (200mL) and extracted with CH₂Cl₂ (3x100mL), the organic layer was washed with H₂O (3x200mL), and saturated sodium chloride (2x100mL) and dried over anhydrous Na₂SO₄. The solvent was removed to give a white product. The residue was recrystallized from 95% ethanol to give 9.33g (99%) of fine white needles, mp 134-136°. ¹H NMR (CDCl₃): δ 1.35 (t, 3H), 2.23 (s, 3H), 2.28 (s, 3H), 2.83 (t, 2H), 3.51 (t, 2H), 4.21 (s, 2H), 8.61 (s, 1H); IR: 3311.6, 1672.3, 1453.6, 1281.7, 1093.6, 769.5 cm⁻¹.

Anal. Calcd. for C₁₁H₁₆ClNO₂; C, 57.52; H, 7.02; N, 6.10. Found: C, 57.80; H, 7.02; N, 6.35

Ethyl 4-(3-Chloropropyl)-3,5-dimethyl-1H-pyrrole-2-carboxylate (3b).- Pyrrole **2b** (10g, 0.039mol) treated with NaBH₄ (2.96g, 0.078mol) and BF₃•Et₂O (11.07g, 0.078mol) under the conditions described above give 9.27g (98%) of white needles, mp 88-90°. ¹H NMR (CDCl₃): 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), 4.29 (s, 2H), 8.72 (s, 1H); IR: 3258.6, 1669.2, 1440.7, 1279.7, 1097.1, 773.8 cm⁻¹.

Anal. Calcd. for C₁₂H₁₈ClNO₂: C, 59.13; H, 7.44; N, 5.74. Found: C, 59.33; H, 7.28; N, 5.72

Ethyl 4-(4-Chlorobutyl)-3,5-dimethyl-1H-pyrrole-2-carboxylate (3c).- Pyrrole **2c** (10g, 0.037mol) treated with NaBH₄ (2.81g, 0.074mol) and BF₃•Et₂O (10.51g, 0.074mol) under the conditions described above give 9.10g (96%) of white needles, mp 76-78°. ¹H NMR (CDCl₃): δ 1.35 (t, 3H), 1.61(m, 2H), 1.78 (m, 2H), 2.20 (s, 3H), 2.26 (s, 3H), 2.38 (t, 2H), 3.53 (t, 2H), 4.27 (s, 2H), 8.50 (s, 1H); IR: 3313.6, 1672.4, 1442.7, 1274.2, 1173.2, 723.3 cm⁻¹.

Anal. Calcd. for C₁₃H₂₀ClNO₂: C, 60.57; H, 7.82; N, 5.43. Found: C, 60.43; H, 7.78; N, 5.39

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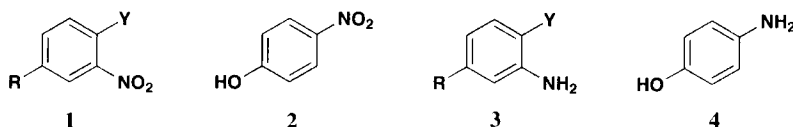
EFFICIENCY OF THE URUSHIBARA NICKEL CATALYZED ATMOSPHERIC HYDROGENATION IN THE SYNTHESIS OF ANILINE DERIVATIVES

Submitted by X. Liu, T. Jia, J. Chen[†], Z. Jiang*, H. Zhang and X. Huang*
(05/10/00)

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Although Urushibara catalysts can be used for the same catalytic reactions as Raney nickel catalysts,¹ their application have not been illustrated in the literature over the past twenty-five years except for two papers about their characterization.² Since Urushibara catalysts are prepared by a simple method and are not pyrophoric like Raney nickel catalysts, the exploitation of their practical uses would be significant for organic synthesis. We now report that some 4-substituted-2-nitroanilines (**1a-d**), 4-substituted-2-nitrophenols (**1e**) and nitrophenols (**1f**, **2**) are reduced to corresponding aniline derivatives in 80-90% yields by the atmospheric pressure catalytic hydrogenation using Urushibara nickel catalyst (U-Ni-A).



a) R = CH₃, Y = NH₂ b) R = F, Y = NH₂ c) Cl, Y = NH₂
d) R = Br, Y = NH₂ e) R = CF₃, Y = OH f) R = H, Y = OH