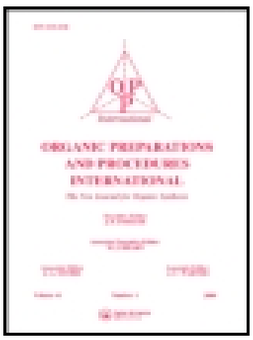

Organic Preparations and Procedures International

ISSN: 0030-4948 (Print) 1945-5453 (Online) Journal homepage: http://www.tandfonline.com/loi/uopp20

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To cite this article: Bin Tu , Changqi Wang & Jinshi Ma (2000) NEW METHOD FOR SYNTHESIS OF (ω-CHLOROALKYL) PYRROLES, Organic Preparations and Procedures International, 32:5, 481-485, DOI: 10.1080/00304940009356762

To link to this article: http://dx.doi.org/10.1080/00304940009356762

ORGANIC PREPARATIONS AND PROCEDURES INT., 32 (5), 481-504 (2000)

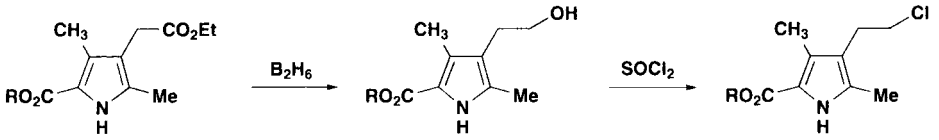
OPPI BRIEFS

NEW METHOD FOR SYNTHESIS OF (ω–CHLOROALKYL) PYRROLES

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

Center for Molecular Science, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100080, P. R. CHINA

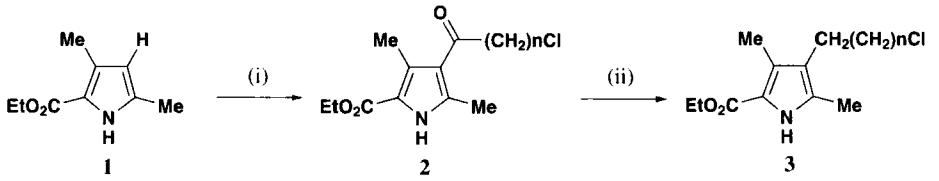
In the total synthesis of some biologically important bile pigments and porphyrins, such as bilirubin IXα and protoporphyrin IX, a key step involves obtaining a vinyl side-chain. A method successfully used to obtain vinyl residues is dehydrochlorination of 2-chloroethyl residues using sodium hydroxide 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 pyrrolenine or pyrrolinone nitrogens. (2-Chloroethyl) pyrroles have usually been prepared by the reduction of carbethoxymethylpyrroles 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.



R = $PhCH_2$, Et

Scheme 1

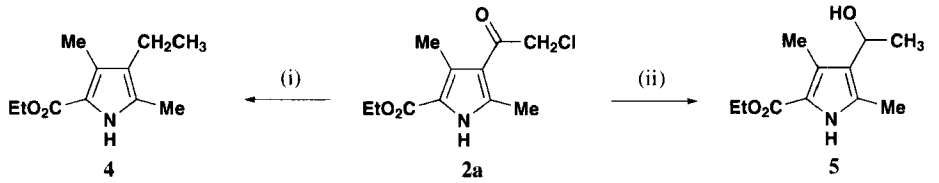
2-(Ethoxycarbonyl)-3,5-dimethylpyrrole **1** (prepared in one step from 2,4-pentanedione and diethyl aminomalonate[9] or diethyl oximinomalonate[10]), which incorporates a free β-position, was chosen as starting material. As shown in *Scheme 2*, pyrrole **1** treated with chloroacetyl chloride *via* the Friedel-Crafts reaction[11,12] gives chloroacetylpyrrole **2a**. The optimal conditions were found to



a) n = 1 b) n = 2 c) n = 3
(i) $AlCl_3$, $ClCO(CH_2)nCl$, CH_2Cl_2; (ii) BF_3•Et_2O, $NaBH_4$, THF

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 Hanaure[14]) 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



(i) Zn, HCl, CH_3CH_2OH; (ii) $NaBH_4$, CH_3OH

Scheme 3

solution of pyrrole **2a** in dried THF, followed by the slow addition of BF_3•Et_2O 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 CH_2Cl_2 (dried over P_2O_5). After addition of anhydrous $AlCl_3$ (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 H_2O (300mL) and extracted with CH_2Cl_2 (3x50mL). The combined organic solution was washed with saturated sodium chloride (2x100mL) and dried over anhydrous Na_2SO_4. 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°. ^{1}H NMR ($CDCl_3$): 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 $C_{11}H_{14}ClNO_3$: 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°. ^{1}H NMR ($CDCl_3$): 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 $C_{12}H_{16}ClNO_3$: 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°. ^{1}H NMR ($CDCl_3$): 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 $C_{13}H_{18}ClNO_3$: 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 $LiAlH_4$). The mixture was cooled in an ice-salt bath to about 0°. After complete addition of $NaBH_4$ (3.04g, 0.08mol) in portions, BF_3•Et_2O (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 $NaBH_4$. The mixture was poured into H_2O (200mL) and extracted with CH_2Cl_2 (3x100mL), the organic layer was washed with H_2O (3x200mL), and saturated sodium chloride (2x100mL) and dried over anhydrous Na_2SO_4. 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°. ^{1}H NMR ($CDCl_3$): 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 $C_{11}H_{16}ClNO_2$: 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 $NaBH_4$ (2.96g, 0.078mol) and BF_3•Et_2O (11.07g, 0.078mol) under the conditions described above give 9.27g (98%) of white needles, mp 88-90°. ^1H 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), 4.29 (s, 2H), 8.72 (s, 1H); IR: 3258.6, 1669.2, 1440.7, 1279.7, 1097.1, 773.8 cm^{-1}.

Anal. Calcd. for $C_{12}H_{18}ClNO_2$: 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 $NaBH_4$ (2.81g, 0.074mol) and BF_3•Et_2O (10.51g, 0.074mol) under the conditions described above give 9.10g (96%) of white needles, mp 76-78°. ^1H NMR ($CDCl_3$): 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 $C_{13}H_{20}ClNO_2$: C, 60.57; H, 7.82; N, 5.43. Found: C, 60.43; H, 7.78; N, 5.39

Acknowledgements.- The authors are grateful to Professor J.-P. Anselme, Department of Chemistry, University of Massachusetts, for critically reading the preliminary draft and giving helpful comments. The National Natural Science Foundation of China (29572071, 39830090), Ministry of Science and Technology of China (1995-043) and the National Key Laboratory for Structural chemistry of Unstable and Stable Species supported this work.

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* To whom correspondence should be addressed. At Institute of Photographic Chemistry, Chinese Academy of Sciences, Beijing, 100101, P. R. China. Email: jsma@ipc.ac.cn

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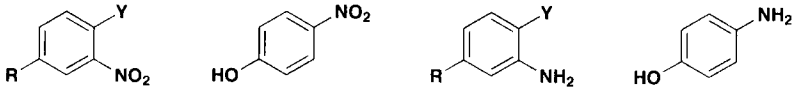
EFFICIENCY OF THE URUSHIBARA NICKEL CATALYZED ATMOSPHERIC HYDROGENATION IN THE SYNTHESIS OF ANILINE DERIVATIVES

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

Department of Chemistry, Wuhan University, Wuhan 430072, P. R. CHINA

† *Department of Fine Chemicals, Wuhan Institute of Chemical Technology, Wuhan 430074, P. R. CHINA*

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).



1 **2** **3** **4**

a) R = CH_3, Y = NH_2 b) R = F, Y = NH_2 c) Cl, Y = NH_2
d) R = Br, Y = NH_2 e) R = CF_3, Y = OH f) R = H, Y = OH