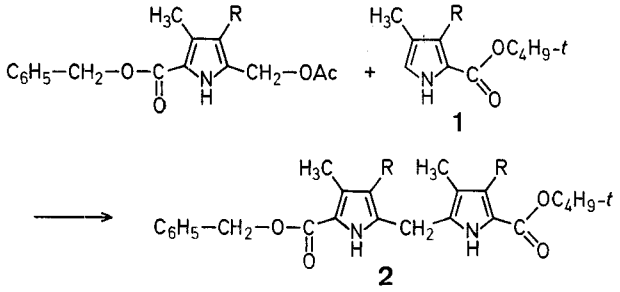
Convenient Synthesis of *t*-Butyl Pyrrole-2-carboxylates from 2-Methylpyrroles

Kevin M. SMITH*, G. Wayne CRAIG, Fahimeh EIVAZI, Zoya MARTYNENKO

Department of Chemistry, University of California at Davis, Davis, California 95616, U.S.A.

5-Unsubstituted *t*-butyl pyrrole-2-carboxylates **1** are important precursors for unsymmetrically substituted dipyrrylmethanes (e.g. **2**[1]) which are in turn key intermediates in general syntheses of complex porphyrins[2].



1

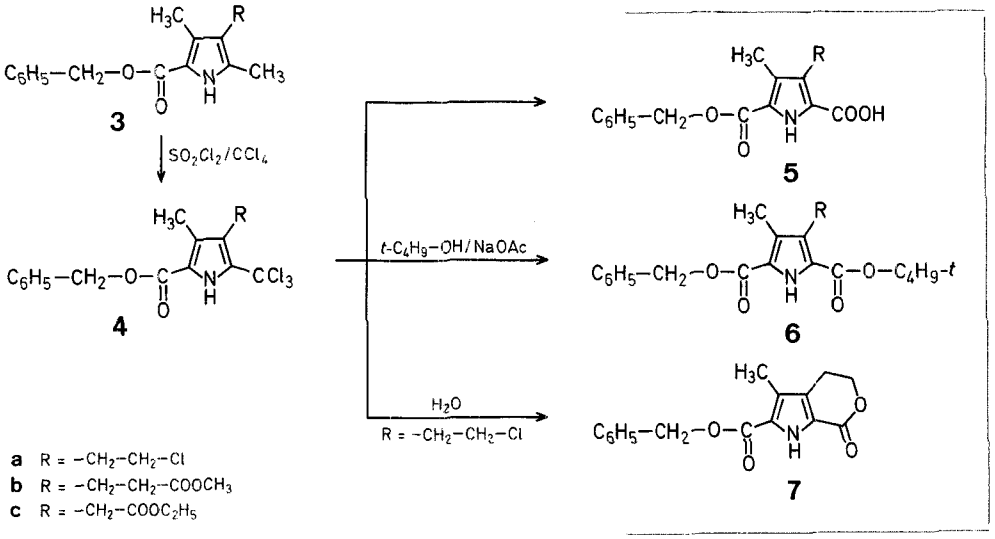
2

The pyrroles **1** cannot be synthesized directly from acyclic intermediates. Instead, they are obtained by a multi-step procedure in which the 2-methylpyrrole **3** (readily available) is trichlorinated with sulfuryl chloride (to give **4**), then hydrolyzed (to give **5**), and converted into the pyrrole

0039-7881/80/0632-0493 $ 03.00

mixed ester **6** by treatment with isobutylene and mineral acid. Hydrogenolysis and iodinative decarboxylation then gives **1**. Unfortunately, a major problem arises in the formation of the pyrrole-2-carboxylic acid **5** from **4**, and large quantities of pyrrocoll (by self-condensation) are obtained[3]. A procedure in which the trichloromethylpyrrole **4** is hydrolyzed in aqueous acetone has been devised[4], and on many occasions this decreases the yield of pyrrocoll. In the case of pyrrole **4a**, this method produces the pyrrole lactone **7**[5] along with a little pyrrocoll and virtually no pyrrole-5-carboxylic acid.

Since 2-chloroethyl-substituted compounds have been employed in many recent approaches[6] to vinyl-substituted porphyrins, we have developed an efficient general method for synthesis of *t*-butyl pyrrole-2-carboxylates from 2-methylpyrroles; the method hinges on the ready and high-yield alcoholysis of trichloromethylpyrroles **4**. The trichloromethylpyrroles **4** were prepared by treatment of the methylpyrroles **3** with sulfuryl chloride in carbon tetrachloride [when this solvent is used the reaction mixture can be monitored directly for disappearance of the resonances at $\delta \approx 4.6$ ($C\underline{H}_2Cl$) and 6.6 ppm ($C\underline{H}Cl_2$)]. The solvent was then removed by evaporation under vacuum and the oily (occasionally crystalline[7]) residue was dissolved in dichloromethane and filtered through a small column of silica-gel. [This step is essential in order to remove excess sulfuryl chloride and its derivatives. If it is omitted, the subsequent reaction with *t*-butyl alcohol produces di-*t*-butyl sulfate, which is chromatographically similar to the mixed ester **6**, and completely inhibits the subsequent hydrogenolysis of the benzyl ester. Heating at 100 °C under vacuum is partially effective for removal of the sulfate]. After evaporation once more, the residue was treated at 60 °C for 24 h with a stirred suspension of anhydrous sodium acetate in *t*-butyl alcohol to give, after appropriate work-up, the required mixed ester **6**. If the pyrrole-2-carboxylic acid **5** is required, it can be obtained in quantitative yield by treatment of **6** with trifluoroacetic acid.



a R = $-CH_2-CH_2-Cl$
b R = $-CH_2-CH_2-COOCH_3$
c R = $-CH_2-COOC_2H_5$

Melting points were measured on a hot stage apparatus, and are uncorrected.

***t*-Butyl 5-Benzyloxycarbonyl-3-(2-chloroethyl)-4-methylpyrrole-2-carboxylate (6a):**

To a solution of benzyl 3-(2-chloroethyl)-2,4-dimethylpyrrole-5-carboxylate[1] (**3a**; 5.45 g) in dry carbon tetrachloride (300 ml) is added, dropwise, sulfuryl chloride (5.5 ml). The solution is stirred overnight at room temperature and ^{1}H-N.M.R. sampling of the crude reaction mixture [disappearance of the signals of $C\underline{H}_2Cl$ and $C\underline{H}Cl_2$ at $\delta \approx 4.6$ and 6.6 ppm, respectively] indicates that the reaction is complete. After evaporation under vacuum and re-evaporation of toluene (100 ml) (as a chaser), the oily residue is dissolved in a minimum amount of dichloromethane and applied to a column of silica gel (15 g) in a sintered glass funnel. The trichloromethylpyrrole **4a** is washed through the silica gel with dichloromethane, and the combined eluates are evaporated under vacuum to give an oily residue which is dissolved in dry *t*-butyl alcohol (100 ml) containing anhydrous sodium acetate (8 g) in suspension. After stirring under nitrogen for 24 h at 60 °C, the cooled solution is diluted with dichloromethane and washed with water. The organic phase is evaporated under vacuum and the crude product is chromatographed on alumina (Brockmann Grade III; elution with dichloromethane). Evaporation of the eluates from the major yellowish band gives product **6a** which is recrystallized from ether to give long prisms; yield: 5.53 g (78%); m. p. 58.5–59.5 °C (Ref.[1], yield: 28%; m. p. 59.5–60.5 °C).

Similarly prepared:

t-*Butyl 5-Benzyloxycarbonyl-3-(2-methoxycarbonylethyl)-4-methylpyrrole-2-carboxylate* **(6b)**; yield: 80%; m. p. 92 °C (Ref.[8,9], yield: 63%; m. p. 91–92 °C).

t-*Butyl 5-Benzyloxycarbonyl-3-ethoxycarbonylmethyl-4-methylpyrrole-2-carboxylate* **(6c)**; yield: 71%; m. p. 63–65 °C (Ref.[7], yield: 47%; m. p. 64–65 °C).

5-Benzyloxycarbonyl-3-(2-chloroethyl)-4-methylpyrrole-2-carboxylic Acid (5a):

A solution of *t*-butyl-5-benzyloxycarbonyl-3-(2-chloroethyl)-4-methylpyrrole-2-carboxylate (**6a**; 100 mg) in dichloromethane (1.0 ml) is stirred with trifluoroacetic acid (1.0 ml) for 5 min at room temperature under nitrogen. The mixture is then diluted with dichloromethane (100 ml), the solution washed with water several times, and dried with sodium sulfate. The solvent is evaporated and the residual colorless product recrystallized from dichloromethane/hexane; yield: 84 mg (99%); m. p. 178–181 °C (Ref.[1], m. p. 178–182 °C).

This study was supported by the National Institutes of Health (HL 22252) and the National Science Foundation (CHE 78-25557).

Received: August 8, 1979
(Revised form: October 18, 1979)

* Address for correspondence.

[1] J. A. S. Cavaleiro, A. M. d'A. Rocha Gonsalves, G. W. Kenner K. M. Smith, *J. Chem. Soc. Perkin Trans. 1* **1973**, 2471.

[2] For a review, see: A. H. Jackson, K. M. Smith, in: *Total Synthesis of Natural Products*. J. W. ApSimon, ed., Vol., 1, John Wiley & Sons, New York, 1973, p. 143.
[3] For a review, see: J. B. Paine, in: *The Porphyrins*, D. Dolphin, ed., Vol. 1, Academic Press, New York, 1978, pp. 159–163.
[4] A. R. Battersby, E. Hunt, E. McDonald, J. B. Paine, *J. Chem. Soc. Perkin Trans. 1* **1976,** 1008.
[5] R. P. Carr, A. H. Jackson, G. W. Kenner, G. S. Sach, *J. Chem. Soc.* [C] **1971,** 487.
[6] E. g. K. M. Smith et al., *Bioorg. Chem.* **8**, 485 (1979).
J. A. P. Baptista de Ameida, G. W. Kenner, J. Rimmer, K. M. Smith, *Tetrahedron* **32,** 1793 (1976).
A. R. Battersby, G. L. Hodgson, E. McDonald, J. Saunders, *J. Chem. Soc. Perkin Trans. 1* **1973,** 2923.
P. S. Clezy, C. J. R. Fookes, *Aust. J. Chem.* **31,** 2491 (1978).
[7] M. T. Cox, A. H. Jackson, G. W. Kenner, K. M. Smith, *J. Chem. Soc. Perkin Trans. 1* **1974,** 516.
[8] A. H. Jackson, G. W. Kenner, K. M. Smith, *J. Chem. Soc.* [C] **1971,** 502.
[9] J. A. S. Cavaleiro, G. W. Kenner, K. M. Smith, *J. Chem. Soc. Perkin Trans. 1* **1973,** 2478.

0039-7881/80/0632-0495 $ 03.00