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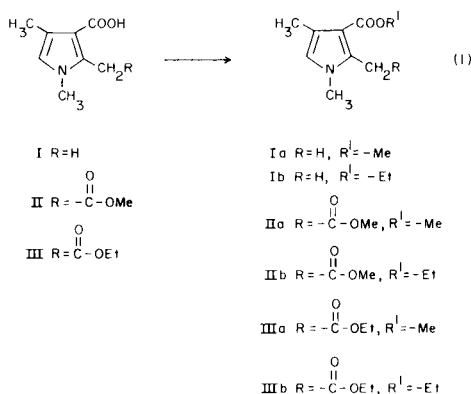
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A simple and efficient method for the esterification of sterically hindered pyrrole carboxylic acids using dialkylsulfate and anhydrous potassium carbonate is described.

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In connection with another investigation it became necessary for us to synthesize the sterically hindered pyrrole carboxylic acid esters Ia-b from the corresponding acid I (Equation 1). A literature survey indicated that the



esterification of pyrrole carboxylic acids most commonly is carried out with diazomethane and diazoethane (1) or with an alcoholic hydrogen chloride and alcohol-sulfuric acid mixture (2). The esterification with diazo compounds gives very good yields of methyl and ethyl esters, but its inapplicability to esterification on a preparative scale is an important disadvantage. The acid catalyzed esterification method has been applied to the preparation of sterically hindered pyrrole carboxylic acid esters. However, this method has a drawback due to the formation of side products and the yields are moderate. Our attempt to esterify I with a methanol-sulfuric acid mixture under reflux for 26 hours resulted in the formation of Ia in trace amounts. In addition, the starting material I was found to decompose under the reaction conditions. This observation introduced the necessity of selecting a basic esterification method.

Esterification of pyrrole carboxylic acids under basic conditions using a combination of silver oxide and methyl iodide (3) and potassium carbonate and methyl iodide (4) are known, but the yields are not satisfactory. Less frequently, pyrrole carboxylic acid esters are prepared by employing dimethyl sulfate (DMS) and diethyl sulfate (DES) under aqueous or alcoholic basic conditions (5) and the yields are moderate or not reported.

Recently, Grundy, *et al.*(6), and Hallas and Hepworth (7) reported that hindered benzoic acids could easily be esterified in excellent yields by dimethyl sulfate-anhydrous potassium carbonate under mild basic conditions. This prompted us to reinvestigate the use of dimethyl sulfate and diethyl sulfate in the esterification of hindered pyrrole carboxylic acids I. We wish to report our results in this article.

Table I summarizes our yields of isolated and purified products. The efficiency of this simple procedure in the preparation of hindered pyrrole carboxylic acid esters is quite evident from Table I. In addition to the preparation of hindered esters, this method provides another excellent choice of synthesizing methyl and ethyl esters of unhindered as well as acid sensitive pyrrole carboxylic acids. The significance of the very mild basic conditions of this procedure is clearly demonstrated in the conversion of acids II-III to the esters IIa-b and IIIa-b without affecting the primary ester functions, which are very susceptible to hydrolysis under aqueous basic conditions.

In light of these observations, the use of dimethyl sulfate or diethyl sulfate with anhydrous potassium carbonate in the esterification of pyrrole carboxylic acid is highly recommended in spite of the limitation that only methyl and ethyl esters could be prepared.

EXPERIMENTAL

Melting points were taken on a Hoover-Thomas Uni-melt Apparatus and are uncorrected. Nmr spectra were recorded on a Varian A-60 Spectrometer and ir spectra were obtained on a Perkin-Elmer 621 spectrophotometer. Micro analysis were performed by Industrial Testing Laboratories, Inc., St. Louis, Missouri.

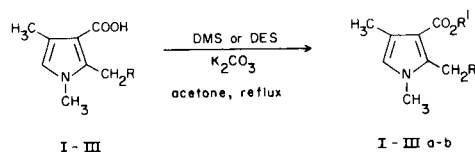
A representative procedure for the preparation of esters listed in Table I is as follows:

3-Carboxy-1,2,4-trimethylpyrrole (Ib).

1,2,4-Trimethylpyrrole-3-carboxylic acid, I (1.53 g., 0.01 mole), diethyl sulfate (1.7 g., 1.45 ml., 0.011 mole) and anhydrous potassium carbonate (1.7 g., 0.012 mole) are mixed in 30 ml. of acetone and refluxed for 5 hours. Then the reaction mixture is poured into plenty of cold water and extracted with ethylene dichloride. The organic layer was dried and the solvent stripped off to give the crude ester Ib in > 95% yield. The crude ester was recrystallized from hexane to yield 1.65 g. (91%) of pure Ib, m.p. 60-61° (lit. (9) 60-61°) ir (potassium bromide): 1685 cm⁻¹ (s); nmr (deuteriochloroform): δ 1.2-1.5 (t, 3, J_{AB} = 7 Hz), 2.23 (s, 3, C₄-methyl), 2.5 (s, 3, C₂-methyl), 3.45 (s, 3, N-methyl), 4.08-4.50 (q, 2, J_{AB} = 7 Hz), 6.25 (s, 1, C₅-H).

Table I

Esterification of Hindered Pyrrole Carboxylic Acids Using Dimethyl and Diethyl Sulfate Under Mild Basic Conditions



Compound No.	Starting Material (a)	Product	Isolated % Yield	M.p. or B.p., °C	Spectral Data
I	R = H	R = H R' = -CH ₃	85-88	85.5-86°, Lit. (8) 85-86°	Ir (potassium bromide): 1680 cm ⁻¹ (s); nmr (deuteriochloroform): δ 2.2 (s, 3, C ₄ -methyl), 2.45 (s, 3, C ₂ -methyl), 3.45 (s, 3, N-methyl), 3.8 (s, 3, O-methyl), 6.26 (s, 1, C ₅ -H)
		R = H R' = -CH ₂ CH ₃	91	60-61°, Lit. (9) 60-61°	Ir (potassium bromide): 1685 cm ⁻¹ (s); nmr (deuteriochloroform): δ 1.2-1.5 (t, 3, J _{AB} = 7 Hz), 2.23 (s, 3, C ₄ -methyl), 2.5 (s, 3, C ₂ -methyl), 3.45 (s, 3, N-methyl), 4.08-4.50 (q, 2, J _{AB} = 7 Hz), 6.25 (s, 1, C ₅ -H)
II	R = -CO ₂ Me	R = -CO ₂ Me R' = -CH ₃	85	72-73°	Ir (potassium bromide): 1675, 1740 cm ⁻¹ (s); nmr (deuteriochloroform): δ 2.18 (s, 3, C ₄ -methyl), 3.46 (s, 3, N-methyl), 3.66-3.74 (s, 6, O-methyl), 4.01 (s, 2, C ₂ -methylene), 6.28 (s, 1, C ₅ -H)
		R = -CO ₂ Me R' = -CH ₂ CH ₃	92	91-92°	Ir (potassium bromide): 1700, 1740 cm ⁻¹ (s); nmr (deuteriochloroform): δ 1.2-1.43 (t, 3, J _{AB} = 7 Hz), 2.2 (s, 3, C ₄ -methyl) 3.49 (s, 3, N-methyl), 3.69 (s, 3, O-methyl), 4.04 (s, 2, C ₂ -methylene), 4.04-4.42 (q, 2, J _{AB} = 7 Hz), 6.31 (s, 1, C ₅ -H)
III	R = -CO ₂ Et	R = -CO ₂ Et R' = CH ₃	94	69-70°	Ir (potassium bromide): 1680, 1725 cm ⁻¹ (s); nmr (deuteriochloroform): δ 1.14-1.38 (t, 3, J _{AB} = 7 Hz), 2.2 (s, 3, C ₄ -methyl), 3.5 (s, 3, N-methyl), 3.77 (s, 3, O-methyl), 4.05 (s, 2, C ₂ -methylene), 4.0-4.35 (q, 2, J _{AB} = 7 Hz), 6.35 (s, 1, C ₅ -H)
		R = -CO ₂ Et R' = -CH ₂ CH ₃	96	73-74°, Lit. (10) 71-73°	Ir (potassium bromide): 1670, 1725 cm ⁻¹ (s); nmr (deuteriochloroform): δ 1.1-1.45 (m, 6), 2.2 (s, 3, C ₄ -methyl), 3.48 (s, 3, N-methyl), 4.04 (s, 2, C ₂ -methylene), 3.95-4.45 (m, 4), 6.34 (s, 1, C ₅ -H)
IV	A	R' = -CH ₃	90	44.5-46°/ 0.8 mm, Lit. (4) 95-98°/28 mm	Ir (neat): 1710 cm ⁻¹ (s); nmr (deuteriochloroform): δ 3.8 (s, 3, N-methyl), 3.9 (s, 3, O-methyl), 6.03-6.15 (m, 1, C ₄ -H), 6.72-6.8 (m, 1, C ₃ -H), 6.9-7.0 (m, 1, C ₅ -H)

(a) A = *N*-Methylpyrrole-2-carboxylic acid.

Table II

Elemental Analysis for New Compounds IIa, IIb and IIIa

Compound No.	Molecular Formula	Analysis					
		Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIa	C ₁₁ H ₁₅ NO ₄	58.66	6.71	6.21	58.77	6.78	6.19
IIb	C ₁₂ H ₁₇ NO ₄	60.24	7.16	5.85	59.97	6.91	5.74
IIIa	C ₁₂ H ₁₇ NO ₄	60.24	7.16	5.85	60.25	7.27	5.78

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