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4-CHLOROMETHYLATION OF 1-METHYL-2-PYRRYL KETONES

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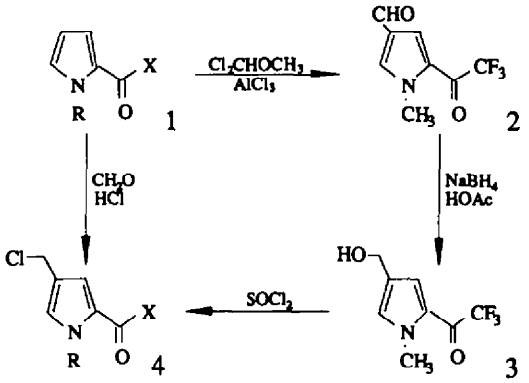
Abstract *A novel chloromethylation of pyrroles containing certain electron-withdrawing groups at the 2-position has been observed, which is of synthetic utility. Specifically, 2-(trichloro)- and (trifluoro)- acetyl-1-methyl pyrroles and ethyl 1-methylpyrrole-2-oxoacetate yield, when treated with paraformaldehyde and hydrogen chloride, and in the absence of any Friedel-Crafts catalyst, the corresponding 4-chloromethyl compounds in high yield and with high regiospecificity. These chloromethylpyrroles are versatile intermediates and offer access to some known and some new pyrrole compounds.*

The chloromethyl group is a versatile functionality, readily converted to methyl, hydroxymethyl, cyanomethyl, formyl, dialkylaminomethyl, and other groups. It is possible to obtain in this way many compounds otherwise difficult to synthesize. We desired a straightforward method for preparing 4-chloromethylpyrrole-2-esters and -ketones; however, a literature search revealed no useful method for the regiospecific introduction of a 4-chloromethyl group into pyrrole- 2-esters or -ketones. While chloromethylpyrroles are well known, they are most often prepared by the chlorination of methyl pyrroles[1]. Chloromethylation of 2,4-dimethyl-5-carbethoxy-pyrrole has been achieved using paraformaldehyde and hydrogen chloride in acetic acid[2], but with only one open ring position in the starting material the question of regioselectivity was not addressed. Mannich amino-methylation of 2-acetylpyrrole, which can serve as an alternative to chloromethylation, reportedly gives 2-acetyl-5-dimethylaminomethylpyrrole exclusively[3], with none of the 4-dimethylaminomethyl isomer. Pyrrolidonium perchlorates of 2-formylpyrrole undergo electrophilic substitutions regiospecifically at the 4-position, but chloromethylation of such compounds has not been reported and the utility of this approach is diminished by the difficulty of the subsequent conversion of the 4-substituted-pyrrolidonium perchlorate to the corresponding ester[4]. Finally, in the related thiophene series, the hydrogen chloride catalysed chloromethylation of 2-acetylthiophene with formaldehyde produces an undesirable equimolar mixture of the 4- and 5-chloromethylated thiophenes[5]. We were surprised and gratified therefore that treatment of 1-methyl-2-trifluoroacetylpyrrole with paraformaldehyde and anhydrous hydrogen chloride gave the 4-chloromethyl derivative in high yield and with no detectable 5-isomer (Scheme I).

Aprotic Lewis acid catalysed acylations[6] and alkylations[7] of pyrrole compounds with electron-withdrawing groups in the 2-position, such as esters and ketones, are known to generally go into the 4-position of the pyrrole. 2-Trichloroacetylpyrrole has been cited as a useful intermediate for the preparation of 2,4-disubstituted pyrroles, but only when a Lewis acid catalyst is employed or with radical-mediated halogenations[8]. In contrast, electrophilic substitutions on pyrrole esters and ketones not catalysed by metal halides, such as nitrations[9a,b] and Vilsmeier-Haack formylation[10], generally give indiscriminate substitution in the 4- and 5-positions. The Lewis acid catalyst (e.g., $AlCl_3$) is thus necessary for directing the incoming electrophile to the 4-position of the pyrrole. We therefore assume that the hydrogen chloride in our reaction not only activates the formaldehyde for electrophilic attack, but also complexes with the ketone and directs 4-substitution, thus behaving as a Lewis acid catalyst. In light of the previous reports of HCl mediated chloromethylations, the observed regioselectivity of our reaction appears unprecedented.

In order to prove the structures of our chloromethylated products, beyond the characteristic proton NMR signals of the 3,4-hydrogens versus the 3,5-hydrogens[11], **4a** was synthesized unambiguously via another route (see Scheme I). Thus, formylation of 1-methyl-2-trifluoroacetylpyrrole gave the 4-aldehyde[6]. Selective reduction[12] of the pyrrole aldehyde **2a** followed by treatment with thionyl chloride gave material identical by IR, NMR, tlc, and melting point to the same product obtained by direct chloromethylation.

Scheme I



1,4	R	X
a	CH_3	CF_3
b	CH_3	CCl_3
c	CH_3	$CO_2C_2H_5$
d	CH_3	CH_3

The chloromethylation procedure is facile for pyrrole ketones **1a-c**; 1-methyl-2-acetylpyrrole (**1d**) decomposed under the reaction conditions. The chloromethylated derivatives **4a-c** provide access to a number of synthetically useful pyrroles. For example, complete methanolysis of **4b** (X=CCl_3) gives the ether/ester **5** which yields the 1,4-dimethylpyrrole ester **6** upon hydrogenolysis (Scheme II). This represents a significant improvement over previous syntheses of the pyrrole[13a,b]. Hydrogenation of **4b** gives 2-acetyl-1,4-dimethylpyrrole (**7**), again an improvement over previous methods[14].

The chloromethylpyrrole **4a** (X=CF_3) undergoes displacement by a variety of nucleophiles. Thus, the acetoxymethyl- (**8**), aryl ether (**9**), and phosphonium salt (**10**) derivatives are all prepared in high yields. Catalytic reduction of **4a** gives the 1,4-dimethylpyrrole ketone **11**, which upon saponification and esterification yields **6**.

The pyrrole oxoacetate **1c**, potentially useful in the synthesis of medicinally interesting pyrrole acetic acids[15], proved difficult to derivatize by conventional means. Treatment with dichloromethyl methyl ether/aluminum chloride gave only starting material, and Vilsmeier-Haack formylation gave a low yield (26%) of the pyrrole aldehyde (substitution position unknown). However, chloromethylation with a tenfold excess of paraformaldehyde affords **4c** in high yield. Hydrogenation of **4c** gives the 1,4-dimethylpyrrole-2-oxoacetate **13**. Direct permanganate oxidation of **4c** yields the corresponding 4-carboxylate **14**.

In summary, the directed chloromethylation of 1-methyl-2-pyrryl ketones is a novel method for the regiospecific synthesis of 2,4-disubstituted pyrroles. While limited to pyrrole ketones which are stable to anhydrous hydrogen chloride, this method gives easy access to useful pyrrole derivatives, some of which are prepared with difficulty by other approaches. The use of other aldehydes to give (alkyl)chloromethyl- and (aryl)chloromethylpyrroles is currently being investigated.

Experimental Section

All melting points were determined on a Thomas apparatus and are uncorrected. ^1H NMR spectra were recorded with a Varian EM-390 with tetramethylsilane as internal standard and deuterochloroform (unless otherwise noted).

4-Chloromethyl-1-methyl-2-trifluoroacetylpyrrole (**4a**).

(*Method A*). A solution of 1-methyl-2-trifluoroacetylpyrrole[16] (6.63 g, 37.4 mmol) and paraformaldehyde (1.35 g) in 100 mL of dichloromethane was cooled with an ice bath while anhydrous hydrogen chloride was bubbled through for 15 min. After stirring for an additional 30 min. the solution was washed with water and brine and dried (magnesium sulfate). Filtration and evaporation of the solvent gave 7.68 g of a pink solid (no detectable 5-isomer by ^1H NMR or tlc) which was Kugelrohr distilled (80°/2 mm) to give 7.41 g (32.9 mmol, 88% yield) of a colorless crystalline solid, mp 52-54°. ^1H NMR: 7.1 (m, 2H), 4.5 (s, 2H), 3.9 (s, 3H). Anal. calc. for $C_8H_{11}ClF_3NO$: C 42.59, H 6.21, N, 3.13, Cl 15.71. Found: C 42.61, H 6.38, N 3.06, Cl 15.57.

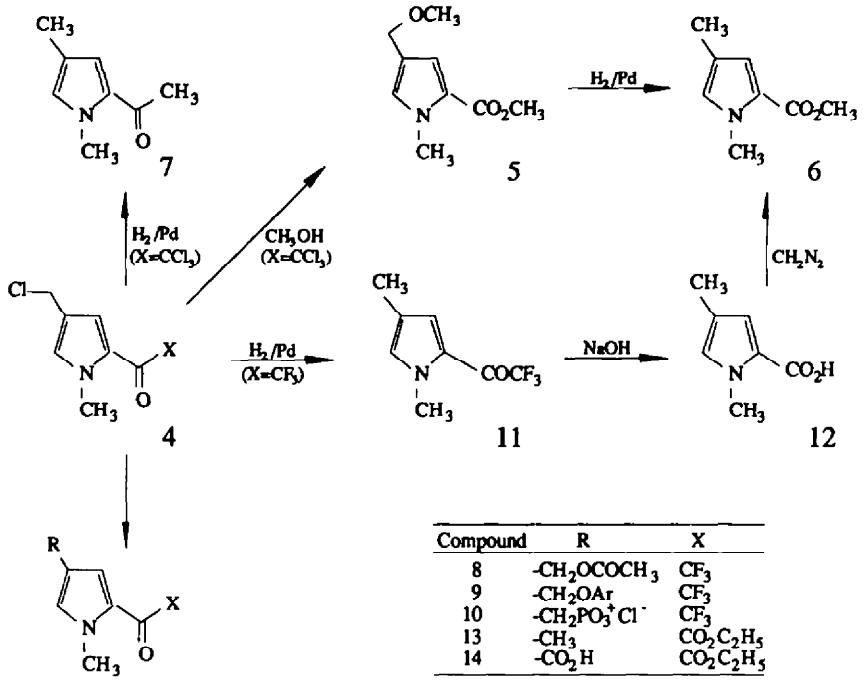
4-Chloromethyl-1-methyl-2-trichloroacetylpyrrole (**4b**).

Compound **4b** was prepared by Method A from 1-methyl-2-trichloroacetylpyrrole and isolated in 88% yield. ^1H NMR: 7.4 (d, J=2, 1H), 7.05 (d, J=2, 1H), 4.5 (s, 2H), 3.95 (s, 3H). HRMS calc: 272.9282; found: 272.9284. Anal. calc. for $C_8H_7Cl_4NO$: C 34.95, H 2.57, N 5.09, Cl 51.57. Found: C 33.92, H 2.62, N 4.64, Cl 49.97.

Ethyl 4-chloromethyl-1-methylpyrrole-2-oxoacetate (**4c**).

Compound **4c** was prepared by Method A from ethyl 1-methylpyrrole-2-oxoacetate[17] and isolated in 93% yield. ^1H NMR: 7.5 (d, J=2, 1H), 7.0 (d, J=2, 1H), 4.45 (s, 2H), 4.3 (q, J=7, 2H), 3.85 (s, 3H), 1.35 (t, J=7, 3H).

Scheme II



Compound	R	X
8	$-CH_2OCOCH_3$	CF_3
9	$-CH_2OAr$	CF_3
10	$-CH_2PO_3^+Cl^-$	CF_3
13	$-CH_3$	$CO_2C_2H_5$
14	$-CO_2H$	$CO_2C_2H_5$

4-Formyl-1-methyl-2-trifluoroacetylpyrrole (**2a**).

Compound **2a** was prepared by the literature method for 4-formyl-1-methyl-2-trichloroacetylpyrrole[6] and recrystallized from diethyl ether/hexane (mp 80-82°). ^{1}H NMR: 9.8 (s, 1H), 7.65 (br s, 2H), 4.1 (s, 3H).

4-Hydroxymethyl-1-methyl-2-trifluoroacetylpyrrole (**3a**).

In 50 mL of benzene was combined 550 mg (14.6 mmol) of sodium borohydride and 2.71 mL (47.5 mmol) of glacial acetic acid and the mixture was heated to reflux for 15 min. **2a** (750 mg, 3.65 mmol) was then added and the solution was further refluxed for one hour. The solution was cooled to room temperature, water (100 mL) was added and the layers were separated. The aqueous phase was extracted with ether (2 x 50mL) and the combined organic extracts were washed with brine and dried (sodium sulfate); filtration and evaporation gave 715 mg (3.45 mmol, 95% yield) of **3a**. ^{1}H NMR: 7.2 (m, 2H), 4.7 (s, 3H), 4.1 (s, 3H).

4-Chloromethyl-1-methyl-2-trifluoroacetylpyrrole (**4a**).

(*Method B*). Compound **3a** (715 mg, 3.45 mmol) was combined with 2.5 mL (35 mmol) of thionyl chloride in 50 mL of benzene, and the solution was heated to reflux for 30 min. The solvent was then evaporated and the residue was recrystallized from hexane yielding material identical by tlc, mp, IR, and 1H NMR to **4a** from method A.

1,4-Dimethyl-2-methoxycarbonylpyrrole (**6**).

To a solution of 57.3 g (208 mmol) of **4b** in 500 mL of anhydrous methanol was added 100 mL of triethylamine, and the resulting solution was stirred at ambient temp. for 24 hr. The solvent was then evaporated and the residue was partitioned between 500 mL of ether and 300 ml if 1N HCl. The ether phase was washed with brine, dried (sodium sulfate), filtered and concentrated to a white amorphous solid (22.8 g, 125 mmol) of **5**. ^{1}H NMR 6.8 (d, J=2, 1H), 6.65 (d, J=2, 1H), 4.2 (s, 2H), 3.8 (s, 3H), 3.7 (s, 3H), 3.25 (s, 3H).

A solution of 22.6 g (123 mmol) of **5** in 400 mL of ethyl acetate was hydrogenated at 40 psi over 7.5 g of 10% Pd/C in a Parr hydrogenation apparatus. The catalyst was removed by filtration and the solvent was evaporated yielding 16.9 g (110 mmol) of solid (mp 37°). ^{1}H NMR 6.7 (d, J=1 1H), 6.55 (d, J=1, 1H), 3.8 (s, 3H), 3.75 (s, 3H), 2.05 (s, 3H). Anal. calc. for $C_8H_{11}NO_2$: C 62.73, H 7.24, N 9.14. Found: C 62.50, H 7.25, N 9.09.

2-Acetyl-1,4-dimethylpyrrole (**7**).

A mixture of 4.5 g (16 mmol) of **4b** and 4.5 mL of triethylamine in 70 mL of ethyl acetate was hydrogenated at 40 psi over 1.2 g of 10% Pd/C. After 24 hr four equivalents of hydrogen had been consumed. The catalyst was removed by filtration and the filtrate was washed with cold 1N HCl and brine and dried (sodium sulfate). Filtration and evaporation yielded 1.8 g (13 mmol) of slightly impure product. Chromatography on silica gel yielded pure **7**. ^{1}H NMR: 6.6 (br s, 1H), 6.45 (br s, 1H), 3.7 (s, 3H), 2.3 s, 3H), 2.0 (s, 3H). This material was identical to that obtained by catalytic reduction of 2-acetyl-4-formyl-1-methylpyrrole[18].

1,4-Dimethyl-2-trifluoroacetylpyrrole (11).

A solution of 2.5 g (11.1 mmol) of **4a** and 2.5 mL of triethylamine in 50 mL of ethyl acetate was hydrogenated at 40 psi over 0.5 g of 10% Pd/C in a Parr hydrogenation apparatus. The catalyst was removed by filtration and the filtrate was washed with cold 1N HCl and brine, and dried (sodium sulfate). Filtration and evaporation gave 1.9 g of pure liquid **11**. ^{1}H NMR: 6.9 (br s, 1H), 6.75 (br s, 1H), 3.85 (s, 3H), 2.1 (s, 3H).

2-Carboxy-1,4-dimethylpyrrole (12).

To a solution of 1.9 g (10 mol) of **11** in 50 mL of methanol was added 20 mL of 2.5 N NaOH and the solution was heated to reflux for 6 hr. The solution was then cooled and poured into 150 mL of ice cold 1N HCl. The precipitated product was collected by suction filtration, rinsed thoroughly with water and air-dried yielding 860 mg (5.2 mmol) of **12**, (mp 150-151°). ^{1}H NMR (acetone d 6): 6.6 (s, 2H), 3.75 (s, 3H), 2.0 (s, 3H). Anal calcd for $C_7H_9NO_2$: C 60.42, H 6.42, N 10.07. Found: C60.85, H 6.37, N 10.10.

Ethyl 1,4-dimethylpyrrole-2-oxoacetate (13).

A solution of 2.9 g (12.5 mmol) of **4c**, 1.73 mL of triethylamine, and 0.2 g of 10% Pd/C in 100 mL of ethyl acetate was reduced at 40 psi in Parr hydrogenation apparatus. After 12.5 mmol of hydrogen had been consumed the solution was filtered and washed with cold 1 N HCl and brine, and dried (sodium sulfate). Filtration and evaporation gave 2.25 g of an amber oil which crystallized upon standing (mp 36-38°). ^{1}H NMR: 6.9 (br s, 1H), 6.65 (br s, 1H), 4.3 (q, J=7, 2H), 3.8 (s, 3H), 2.05 (s, 3H), 1.35 (t, J=7, 3H). Anal. calc. for $C_{10}H_{13}NO_3$: C 61.03, H 6.71, N 7.17. Found: C 61.68, H 6.66, N 7.14.

Ethyl-4-carboxy-1-methylpyrrole-2-oxoacetate (14).

A solution of 6.95 g (44 mmol) of potassium permanganate and 5 g of potassium carbonate in 50 mL of water was diluted with 50 mL of acetone and added over 30 min to a solution of 2.43 g (10.6 mmol) of **4c** in 50 mL of acetone. After 1 hr the reaction mixture was poured into 250 mL of a solution of 10% $NaHSO_3$ in 1N HCl and extracted with chloroform (3 x 100 mL). The combined chloroform extracts were washed with water (100 mL) and 5% $NaHCO_3$ (3 x 100 mL). The bicarbonate washes were carefully acidified to pH 3 and extracted with chloroform (3 x 100 mL), which was washed with brine, dried (sodium sulfate), filtered and evaporated to give 1.0 g of **14**. Recrystallization from chloroform/hexane gave mp 199-201°. ^{1}H NMR (acetone d-6): 7.75 (d, J=2, 1H), 7.45 (d, J=2, 1H), 4.3 (q, J=7, 2H), 3.9 (s, 3H), 1.35 (t, J=7, 3H).

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18. Hydrogenation of pyrrole aldehydes gives the corresponding methylpyrroles, e.g. ref. 13a.