A Convenient Synthesis of Trifluoromethylated Pyrroles and Porphyrins

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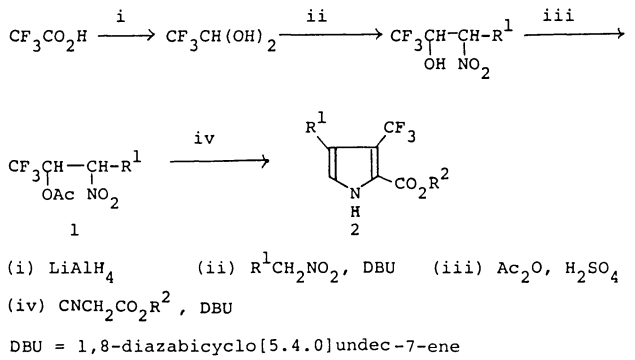
(Received June 9, 1989)

Synopsis. 4-Alkyl-3-trifluoromethyl-2-pyrrolecarboxylic acid esters (**2**) were conveniently prepared by the reaction of trifluoromethylated β-nitro acetates (**1**) with ethyl isocyanoacetate. The pyrroles were converted into the corresponding porphyrins via tetramerization of 2-(hydroxymethyl)pyrroles.

Over past several years organofluorine compounds obtained considerable interest due to the enhanced biological activity.[1] A number of fluorine-containing heterocyclic compounds have been prepared so far. As pyrroles are basic components in various biologically active substances such as porphyrins and related compounds, the preparation of trifluoromethylated pyrroles is very important. Recently, Ogoshi and his co-workers have reported the first synthesis of 3-(trifluoromethyl)pyrroles[2] and their conversion into the corresponding porphyrins.[3] These porphyrins are useful probes for clarifying the structure of enzymes and the interaction between substrates and enzymes by use of ^{19}F NMR spectroscopy.[4] The first method to get trifluoromethylpyrroles is based on the Knorr reaction of ethyl trifluoroacetate,[2] and later the method is modified by the reaction of β-trifluoromethyl α,β-unsaturated ketones with *p*-tolylsulfonylmethyl isocyanide.[5] However, much difficulty still exists in the preparation of trifluoromethylpyrroles. In this paper we wish to report a simple and general method to get 4-alkyl-3-trifluromethyl-2-pyrrolecarboxylic acid exters (**2**), which are good precursors to the corresponding porphyrins. Our method is summarized in Scheme 1.

As shown in Scheme 1, the requisite materials to prepare **2** are all readily available and the procedures are very simple.

Reduction of perfluoroacetic acid with $LiAlH_4$ afforded 2,2,2-trifluoro-1,1-ethanediol (bp 105 °C),[6] which was directly converted into nitro alcohols on treatment with nitroalkanes in the presence of DBU. Thus, the tedious procedure for handling perfluoroacetaldehyde (bp −18 °C) is not required. The nitro alcohols were acetylated with acetic anhydride to give the corresponding β-nitro acetates (**1**) in good yields. The reaction of **1** with ethyl isocyanoacetate or *t*-butyl isocyanoacetate in the presence of DBU (2 equiv) gave 4-alkyl-3-trifluoromethyl-2-pyrrolecarboxylic acid (**2**).[7] The results are summarized in Table 1.



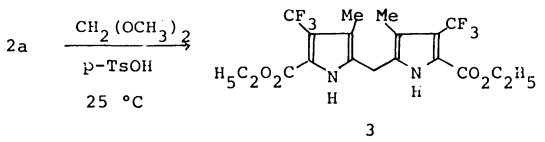
Scheme 1. Preparation of pyrroles (**2**).

Table 1 Preparation of 4-Alkyl-3-trifluoromethyl-2-pyrrolecarboxylic Acid Esters (**2**)

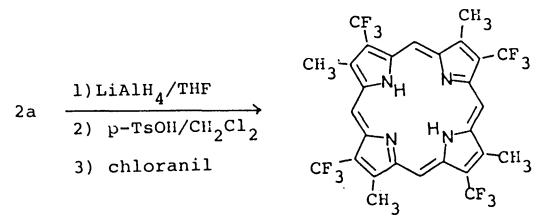
R^1	R^2	**2**, Yield/%
CH_3	C_2H_5	**2a**, 60
CH_3	*t*-C_4H_9	**2b**, 57
C_2H_5	C_2H_5	**2c**, 65
C_2H_5	*t*-C_4H_9	**2d**, 57
$CH_2CH_2CO_2CH_3$	C_2H_5	**2e**, 60

Thus, trifluoromethylated pyrroles are readily prepared starting from CF_3CO_2H and nitroalkanes. Other perfluoroalkylated pyrroles may be also prepared by the similar procedure as shown in Scheme 1 if appropriate perfluoro carboxylic acids are used.

Trifluoromethylpyrroles **2** are less reactive toward electrophiles than the corresponding alkyl derivatives. For example, **2a** reacts with methylal in the presence of *p*-toluenesulfonic acid (*p*-TsOH) to give dipyrromethane **3** in 60% yield. However, it takes about 7 days to complete the reaction, while the corresponding alkyl derivatives react with methylal very quickly under the same conditions.[8]



Pyrroles **2** are ideally functionalized for porphyrin synthesis. For example, pyrrole **2a** was converted into porphyrin **4a** via reduction with $LiAlH_4$ followed by treatment with *p*-TsOH and oxidation with chloranil, where type I porphyrin was formed selectively.[8] Other types of porphyrins are prepared via pyrromethanes such as **3**, which is well documented.[9]



Absorption maxima in electronic spectra and redox potentials of **4a** and Zn complex of **4a** (Zn**4a**) are

Table 2 Absorption Maxima in Electronic Spectra and Redox Potentials of porphyrins

Porphyrins	λ_{max}/nm	Redox potentials[a] E^1/V	E^2/V
4a	407, 504, 539, 580, 635	0.84	1.22
OEP	396, 497, 532, 565, 619	0.60	1.02
Zn**4a**	404, 532, 568	0.78	1.02
ZnOEP	405, 532, 568	0.45	0.79

a) Redox potentials were determined by cyclic voltammetry. Measurements were made on platinum electrode in 0.1 M tetrabutylammonium perchlorate in CH_2Cl_2 at 25 °C. Reversible oxidation was observed, and E^1 and E^2 are the first and second oxidation peak potentials, respectively. Reference is Ag-$AgClO_4$.

compared with those of octaethylporphyrin (OEP) and Zn complex of OEP (ZnOEP). The results are summarized in Table 2. Each absorption maxima of **4a** shows red shift by about 10 nm compared with that of OEP. The redox potentials are dramatically changed by the introduction of the trifluoromethyl group at the β-position. The ring oxidation of **4a** and Zn**4a** occurs at about 200—300 mV higher than for OEP and ZnOEP, respectively.

Experimental

2,2,2-Trifluoro-1,1-ethanediol was prepared according to the procedure of the literature.[6] To a solution of perfluoroacetic acid (0.333 mol) in 300 ml of anhydrous diethyl ether was added slowly a slurry of $LiAlH_4$ (0.19 mol) in 250 ml of anhydrous diethyl ether at −5 °C to 0 °C during 1.5 h. Stirring was continued at −5 °C for 1 h. The reaction mixture was hydrolyzed with 15 ml of water followed by 30 ml of concd H_2SO_4 in 70 ml of water. The ether was decantated, and the solids remaining in the flask were dissolved in 300 ml of water. The aqueous solution was extracted with diethyl ether, and the extracts were combined and dried with anhydrous magnesium sulfate. After the removal of the solvent, the residue was distilled to give 2,2,2-trifluoro-1,1-ethanediol in 70—80% yield, bp 105 °C. This material was used for the next step without further purification.

3-Nitro-1,1,1-trifluoro-2-butanol. A mixture of 2,2,2-trifluoro-1,1-ethanediol (10 g, 0.086 mol), nitroethane (13 g, 0.17 mol), and DBU (2.6 g, 0.12 mol) was stirred at room temperature for 24 h. The resultant solution was poured into 1 M-HCl (100 ml) (1M=1 mol dm^{-3}) and extracted with ethyl acetate. The extracts were washed with water and dried with anhydrous magnesium sulfate. The solvent was removed and the residue was distilled to give the alcohol, 8.7 g (67% yield). Bp 85—87 °C/25 mmHg; 1 mmHg=133.32 Pa. ^{1}H NMR ($CDCl_3$) δ=1.90 (d, 3H), 3.70 (s, 1H), 4.62 (m, 1H), 5.10 (m, 1H). IR (neat) 3400, 1560, 1380, 1260, 1180 cm^{-1}. This compound was acetylated on treatment with acetic anhydride in the presence of H_2SO_4. Yield 90%, bp 57 °C/5 mmHg. ^{1}H NMR ($CDCl_3$) δ=1.75 (d, 3H, J=7 Hz), 2.28 (s, 4H), 4.46—4.84 (m, 1H), 5.85 (m, 1H).

Following nitro alcohols and their acetates were prepared in the same way as described above.

3-Nitro-1,1,1-trifluoro-2-pentanol. Yield 65%, bp 57—58 °C/4 mmHg. ^{1}H NMR ($CDCl_3$) δ=1.02 (t, 3H, J=7 Hz), 2.05 (m, 2H), 3.5 (br s, 1H), 4.45 (m, 1H), 4.75 (m, 1H), IR (neat) 3400, 1560, 1380, 1260, 1180 cm^{-1}. Acetyl Derivative: bp 62 °C/5 mmHg. ^{1}H NMR ($CDCl_3$) δ=1.05 (t, 3H, J=7 Hz), 1.97—2.08 (m, 2H), 2.21 (s, 3H), 4.70—4.83 (m, 1H), 5.75—5.96 (m, 1H).

Methyl 5-Hydroxy-4-nitro-6,6,6-triflurohexanoate. Yield 60%, bp 80 °C/2 mmHg. ^{1}H NMR ($CDCl_3$) δ=2.0—2.2 (m, 4H), 3.4 (br s, 1H), 3.65 (s, 3H), 4.70 (m, 2H), 5.22 (m, 1H). IR (neat) 3400, 1720, 1560, 1380, 1260, 1200 cm^{-1}. Acetyl Derivative: bp 95 °C/2 mmHg.

Preparation of Pyrroles. Ethyl 4-Methyl-3-trifluoromethyl-2-pyrrolecarboxylate (Typical Procedure). To a stirred solution of ethyl isocyanoacetate (2.5 g, 22 mmol) and 2-acetoxy-3-nitro-1,1,1-trifluorobutane (4.0 g, 19 mmol) in tetrahydrofuran (20 ml) was added DBU (5.5 g, 36 mmol) at 0 °C. The resulting mixture was stirred at 25 °C for 12 h. The reaction mixture was poured into water (100 ml) containing 1 M-HCl (10 ml) and extracted with ethyl acetate. The extracts were combined and washed with water. After drying with anhydrous magnesium sulfate and removal of the solvent, the residue was subjected to column chromatography (silica gel/benzene) to give the desired pyrrole (**2a**), 2.5 g (60% yield). Mp 73—75 °C. ^{1}H NMR ($CDCl_3$) δ=1.31 (t, 3H, J=7 Hz), 2.19 (s, 3H), 4.38 (q, 2H, J=7 Hz), 6.65 (d, 1H, J=4 Hz), 9.28 (s, 1H). IR (KBr) 3280, 1670, 1290, 1260, 1140 cm^{-1}. Found: C, 48.97; H, 4.47; N, 6.38; F, 25.60%. Calcd for $C_9H_{10}NO_2F_3$: C, 48.87; H, 4.56; N, 6.33; F, 25.77%.

***t*-Butyl 4-Methyl-3-trifluoromethyl-2-pyrrolecarboxylate (2b).** This pyrrole was prepared by the same procedure as the preparation of **2a**, but *t*-butyl isocyanoacetate was used instead of ethyl isocyanoacetate. Mp 103—105 °C. ^{1}H NMR ($CDCl_3$) δ=1.55 (s, 9H), 2.18 (s, 3H), 6.65 (d, 1H, J=4 Hz), 9.16 (s, 1H). IR (KBr) 3280, 1660, 1290, 1260, 1140 cm^{-1}. Found: C, 53.08; H, 5.60; N, 5.68%. Calcd for $C_{11}H_{14}NO_2F_3$: C, 53.01; H, 5.66; N, 5.62; F, 22.87%. Following pyrroles were prepared by the same procedure.

2c: oil, ^{1}H NMR ($CDCl_3$) δ=1.33 (t, 3H, J=7 Hz), 1.38 (t, 3H, J=7 Hz), 4.32 (q, 2H, J=7 Hz), 6.70 (d, 1H, J=4 Hz), 9.63 (s, 1H). IR (neat) 3300, 1670, 1290, 1260, 1150 cm^{-1}. Found: C, 50.92; H, 5.07; N, 5.67%. Calcd for $C_{12}H_{12}NO_2F_3$: C, 51.06; H, 5.14; N, 5.96%.

2d: mp 93—94 °C. ^{1}H NMR ($CDCl_3$) δ=1.39 (t, 3H, J=7 Hz), 1.59 (s, 9H), 2.63 (q, 2H, J=7 Hz), 6.71 (d, 1H, J=4 Hz), 9.25 (s, 1H). IR (KBr) 3280, 1660, 1290, 1260, 1140 cm^{-1}. Found; C, 54.43; H, 6.07; N, 5.51%. Calcd for $C_{12}H_{16}NO_2F_3$: C, 54.75; H, 6.08; N, 5.31%.

2r: oil ^{1}H NMR ($CDCl_3$) δ=1.32 (t, 3H, J=7 Hz), 2.50—2.72 (m, 4H), 3.72 (s, 3H), 4.26 (q, 2H, J=7 Hz), 6.65 (q, 1H, J=4 Hz), 9.90 (s, 1H). IR (neat) 3300, 1670, 1700, 1290, 1260, 1150 cm^{-1}. Found: C, 49.02; H, 4.72; N, 4.52%. Calcd for $C_{12}H_{14}NO_4F_3$: C, 49.15; H, 4.80; N, 4.78%.

Preparation of Dipyrromethane 3. A mixture of **2a** (0.22 g, 1 mmol), methylal (0.38 g, 5 mmol), and *p*-TsOH (0.1 g) in CH_2Cl_2 (10 ml) was stirred at room temperature for 7 days. The reaction mixture was poured into water, extracted with CH_2Cl_2, and washed with aqueous $NaHCO_3$. The organic layer was dried with anhydrous $MgSO_4$, and the solvent was removed. The residue was subjected to column chromatography (silica gel/CH_2Cl_2) to give **3**, 0.13 g (60% yield). Mp 166—168 °C. ^{1}H NMR ($CDCl_3$) δ=1.31 (t, 3H, J=7 Hz), 2.16 (s, 6H), 3.94 (s, 2H), 4.21 (q, 4H, J=7 Hz), 10.12 (s, 2 H). IR (KBr) 3280, 1680, 1290, 1260, 1140 cm^{-1}. Found: C, 50.15; H, 4.44; N, 6.17%. Calcd for $C_{20}H_{20}N_2O_4F_6$: C, 50.22; H, 4.43; N, 6.16%.

Preparation of Porphyrin 4. To a stirred mixture of $LiAlH_4$ (0.08 g, 2 mmol) in 30 ml of THF was added a solution of **2a** (0.50 g, 2.26 mmol) in 10 ml of THF. The mixture was stirred at 0 °C for 2 h and to the mixture was added 1 ml of ethyl acetate. The reaction mixture was poured into water containing dilute HCl and extracted with CH_2Cl_2. The organic layer was dried with anhydrous $MgSO_4$ and *p*-TsOH (0.1 g) was added to the organic layer

(ca. 100 ml). The resulting solution was stirred at room temperature for 12 h, and then chloranil (0.28 g, 1.1 mmol) was added to the resulting reaction mixture. After stirring at room temperature for 8 h, the reaction mixture was washed with 5%-$NaHCO_3$ and dried with anhydrous Na_2SO_4. The solvent was removed and the residue was subjected to column chromatography (silica gel/$CHCl_3$) to give **4**, 51 mg (14% yield). ^1H NMR ($CDCl_3$) δ=−3.48 (s, 2H, NH), 3.65 (s, 12H, CH_3), 10.40 (s, 4H, meso H). IR (KBr) 1120, 1050 cm^{-1}. Absorption maxima and redox potentials are summarized in Table 2. All these data are in good agreement with those reported by Ogoshi.[3,5]

References

1) T. Fuchikami, *Yuki Gosei Kagaku Kyokai Shi*, **42**, 775 (1984); "Biomedicinal Aspects of Fluorine Chemistry," ed by R. Filler and Y. Kobayashi, Elsevier, New York (1982); R. J. Linderman and M. S. Lonikan, *J. Org. Chem.*, **53**, 6013 (1988); T. Ishihara, Y. Okada, M. Kuroboshi, T. Shinozaki, and T. Ando, *Chem. Lett.*, **1988**, 819 and references therein.

2) H. Ogoshi, M. Homma, K. Yokota, H. Toi, and Y. Yokota, *Tetrahedron Lett.*, **24**, 929 (1983).

3) M. Homma, K. Aoyagi, Y. Aoyama, and H. Ogoshi, *Tetrahedron Lett.*, **24**, 4343 (1983).

4) H. Toi, A. Sudzuki, M. Homma, and H. Ogoshi, *J. Chem. Soc., Chem. Commun.*, **1985**, 1791.

5) K. Aoyagi, H. Toi, Y. Aoyama, and H. Ogoshi, *Chem. Lett.*, **1988**, 1891.

6) D. R. Husted and A. H. Ahlbrecht, *J. Am. Chem. Soc.*, **74**, 5422 (1952).

7) D. H. R. Barton and S. Z. Zard, *J. Chem. Soc., Chem. Commun.*, **1985**, 1098 where simple nitroalkenes are used.

8) N. Ono and K. Maruyama, *Chem. Lett.*, **1988**, 1511.

9) "Porphyrins and Metalloporphyrins," ed by K. M. Smith, Elsevier, Amsterdam (1975).