Synthesis of 3,4-Bis[trifluoromethyl]-1H-pyrole

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In the course of a physical study on symmetrical 3,4-disubstituted-1H-pyrroles, the 3,4-bis[trifluoromethyl]-1H-pyrole (1) was needed. For the synthesis of this compound two methods were explored.

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\begin{align*}
\text{F}_3\text{C} & \text{CF}_3 \\
\text{1} \\
\end{align*}
\]

The first approach is based on a thermal opening of an alkyl-oxy carbonylaziridine and cycloaddition of the generated ylid with 2-perfluorobutene. This method has been successfully used for the synthesis of 1-alkyl-2-methoxycarbonyl-3,4-bis[trifluoromethyl]pyroles. The 2-methoxycarbonyl analogue of 1 was also accidentally obtained but the synthesis was not reproducible.

The thermal [2 + 3]-cycloaddition of 2-(t-butoxycarbonyl)-aziridine (2) with 2-perfluorobutene was ineffective. This result is not surprising considering the thermal instability of aziridines. Moreover, secondary amines add easily to 2-perfluorobutene. The N-trimethylsilyl protecting group appeared to be suitable since it is easily introduced on a nitrogen atom and can be easily removed. Thus, a mixture of N-trimethylsilyl-2-(t-butoxycarbonyl)-aziridine (3) and excess of 2-perfluorobutene in benzene was heated at 160°C for 12 h in an autoclave. The diastereoisomeric pyrrolidines 4 were obtained as well as the aziridine (3). Treatment of the reaction mixture with potassium t-butoxide in t-butanol produced 2-(t-butoxycarbonyl)-3,4-bis[trifluoromethyl]-1H-pyrole (5; 40% from 3) (Scheme A).

Scheme A
The cleavage of the ester group was performed with trimethylsilyl iodide\(^1\), affording the 2-carboxy-3,4-bis(trifluoromethyl)-1H-pyrole (6) in 80% yield. Unfortunately, the decarboxylation of pyrole 6 was unsuccessful. The failure of the copper-assisted thermal decomposition of this acid is not surprising since electron-withdrawing substituents are known to stabilize pyrrole-carboxylic acids.\(^1\)

Another approach for the preparation of pyrrole 1 was therefore developed. The synthesis involves, as a first step, clean 4+2 cycloaddition of hexafluorobutyne to N-(t-butoxycarbonyl)-pyrrole (7) (Scheme B). The t-butoxycarbonyl group was selected as an easily removable protecting group.\(^2\)

Such a reaction is closely related to the condensation of 1-methylpyrrole with hexafluorobutyne.\(^3\) However, at the condensation temperature (100 °C), no reverse Diels-Alder reaction of 8 to give pyroles 7 or 9, nor Michael addition of 8 on hexafluorobutyne was observed. The retro Diels-Alder reaction has been widely used in organic synthesis to produce a variety of carbocyclic compounds.\(^4\) In our case, heating of the bicyclic derivative 8 (160 °C, 30 min) afforded a complex mixture from which the expected pyrrole 9 could not be detected.

It has been shown that the cycloaddition of 2,4,6-trimethylbenzonitrile oxide (10) to bicyclic adducts of type 15 allows mild cycloversion of the adduct, through extrusion of 3-(2,4,6-trimethylphenyl)-isoxazoles.\(^5\) Thus, when an ethereal suspension of 10 is gently heated (30 °C) with adduct 8, smooth cycloversion occurs (Scheme C) and a mixture of the des 3,4-bis(trifluoromethyl)-N-(t-butoxycarbonyl)pyrrole (9) and of pyrrole 7 is obtained in a ratio 9:7 = 6:1. The corresponding isoxazoles 13 and 14 could not be separated and 14 was identified by \(^1\)H-NMR spectroscopy (\(\delta = 61.18\) vs 166.7 ppm (CF\(_3\), J\(_{1H} = 7\) Hz)).

Addition of the nitrile oxide 10 to the bicyclic adduct 8 appears to be highly regioselective as compared to the case of the homologue 15 in which the ratio 16:17 is 1:2 (Scheme D).

The dealkoxycarbonylation of the \(N\)-(t-butoxycarbonyl)-3,4-bis(trifluoromethyl)-1H-pyrole (1) was performed by simple heating of the product at 160 °C. The expected 3,4-bis(trifluoromethyl)-1H-pyrole (1) is obtained in a 80% yield by this procedure (Scheme E).

The fluorinated pyrrole 1 prepared by this procedure is a water soluble, low-melting solid, with high vapor pressure. This synthetic method was efficient owing to the high regioselectivity of the nitrile oxide addition to the bicyclic adduct 8 and also to the easy removal of the t-butoxycarbonyl protecting group.

2-(t-Butoxycarbonyl)-azidine (2): Prepared from t-butylic 2,3-dibromopropanoate and ammonia in dimethyl sulfoxide according to Refs.\(^11\),\(^12\); yield: 50%; b.p. 66 °C/12 torr.

2-(t-Butoxycarbonyl)-azidine (3): Prepared from isobutyric acid and ammonia in dimethyl sulfoxide (84 g, 8.17 mmol) at 90 °C/12 torr.

2-(t-Butoxycarbonyl)-azidine (3): Prepared from isobutyric acid and ammonia in dimethyl sulfoxide (84 g, 8.17 mmol) at 90 °C/12 torr.
4.3-Bis[bis(trifluoromethyl)-2-carbonyl]pyrrole (6): To a hot solution (70°C) of 2-(4-butoxyphenyl)-3,4-bis[bis(trifluoromethyl)-1H-pyrrole (5; 1.8 g, 6 mmol) in anhydrous carbon tetrachloride (20 ml), is added dropwise, under nitrogen, iodotrimethylsilane (6.4 ml, 33.7 mmol). The mixture is heated with stirring for about 44 h at 70°C. After cooling, the mixture is poured into water (150 ml), then extracted with diethyl ether (3 x 50 ml). The combined extracts are washed with an aqueous solution of sodium thiosulfate then with water and dried with magnesium sulfate. Evaporation of the solvents gives a solid contaminated by sulfur. Extraction with acetone, filtration and evaporation of the solvent gives crude 2-carboxy-3,4-bis[bis(trifluoromethyl)-1H-pyrrole (6). Sublimation (100°C/0.01 torr) affords the acid 6; yield: 1.2 g (80%); insubfusible, dec.

C₆H₄F₃NO₂ calc. C 34.03 H 1.22 N 5.67 (247.1) found 34.11 1.34 5.64

4.3-H.N.M.R. (CDCl₃/TMS, 60 MHz): δ = 7.43 (d, J_HH = 3.2 Hz, 1H); 10.5 ppm (s, -COOH).

4-F.N.M.R. (CDCl₃/CFCI₃, 60 MHz): δ = 52 ppm (q, J_HH = 7.8 Hz, -CF₃); 54.5 ppm (q, J_HH = 7.8 Hz, -CF₃).

N-(4-Butoxybenzyl)-2,3-bis[bis(trifluoromethyl)-7-azabicyle[2.2.2]hepta-2,5-diene (8): A 50 ml stainless steel autoclave charged with N-(4-butoxybenzyl)-1H-pyrole (7; 3.8 g, 18 mmol) and hexafluoroisobutane (0.8 g, 16 mmol) is heated at 100°C for 15 h. After cooling, sublimation of the crude product (70°C/0.05 torr) affords N-(4-butoxybenzyl)-2,3-bis[bis(trifluoromethyl)-7-azabicyle[2.2.2]hepta-2,5-diene (8); yield: 5.65 g (96%); m.p. 59°C.

C₆H₆F₃NO₂ calc. C 24.72 H 4.38 F 34.62 N 1.25 (329.2) found 24.72 4.37 34.62 4.25

4.3-H.N.M.R. (CDCl₃/TMS, 60 MHz): δ = 1.37 ppm (q, J-HH = 1.5 Hz, 2H).

4-F.N.M.R. (CDCl₃/CFCI₃, 60 MHz): δ = 52 ppm (s, -CF₃).

N-(4-Butoxybenzyl)-3,4-bis[bis(trifluoromethyl)-1H-pyrrole (9): To a solution of N-(4-butoxybenzyl)-2,3-bis[bis(trifluoromethyl)-7-azabicyle[2.2.2]hepta-2,5-diene (8; 5.4 g, 16.4 mmol) in diethyl ether (60 ml) is added 2,4,6-trimethylbenzonitrile oxide (10; 2.96 g, 18.3 mmol). The stirred suspension is heated at 30°C for 24 h (a clear solution is observed after about 2 h) then evaporated. The solid residue is submitted to a bulb-to-bulb distillation (bath temperature 90°C/0.1 torr; compounds 10 and 14 as residue), then the semi-solid distillate is liquefied by heating and allowed to recrystallize at room temperature. The mixture is filtered by suction on a Büchner funnel to eliminate 7, the cake rinsed with small portions of cold methanol, then dried under vacuum affording 2 g of N-(4-butoxybenzyl)-3,4-bis[bis(trifluoromethyl)-1H-pyrrole (9). A second crop is obtained from the filtrate to give additional 0.6 g of pyrrole 9; total yield: 52%. An analytical sample is obtained by sublimation (bath temperature 80°C/0.1 torr); m.p. 59°C.

C₆H₆F₃NO₂ calc. C 34.57 H 3.66 F 37.6 N 4.62 (303.2) found 34.68 3.71 37.4 4.60

4.3-H.N.M.R. (CDCl₃/TMS, 60 MHz): δ = 1.58 ppm (s, 9 H); 7.53 ppm (s, 2 H).

4-F.N.M.R. (CDCl₃/CFCI₃, 60 MHz): δ = 60.0 ppm (s, -CF₃).

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