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IMPROVED SYNTHESIS OF 3-(TRIFLUOROMETHYL)PYRROLE

J. LEROY

CNRS-CERCOA, 2, rue H. Dunant, 94320 Thiais (France)

SUMMARY

This paper describes a synthesis of 3-(trifluoromethyl)pyrrole from *t*-butyl (*E*)-4,4,4-trifluorobutenoate and tosylmethylisocyanide *via* decarboxylation in 45% yield of 4-(trifluoromethyl) pyrrole-3-carboxylic acid over barium-promoted copper chromite in quinoline.

INTRODUCTION

Since β-substituted pyrroles are present in electron-conducting polypyrroles [1], porphyrins [2] and other naturally occurring compounds [3], the search for efficient methods of synthesis of these compounds continues [4].

Although some pyrroles bearing a perfluoroalkyl group have been prepared by classical methods such as the Knorr condensation [5], more specific approaches have also been developed owing to the ability of perfluoroalkylhalides to give radicals, either thermally [6] or photochemically [7]. While pyrrole itself gave only tars when heated at 165°C with trifluoromethyl iodide [6], Kobayashi *et al.* obtained 2-trifluoromethylpyrrole in 33% yield under irradiation [7]. More recently, Wakselman *et al.* [8] reported the trifluoromethylation of pyrrole at the 2-position (47% yield) induced by the sulphur dioxide radical anion.

In 1982, we reported the first synthesis of the previously unknown 3,4-bis(trifluoromethyl)pyrrole (**1**) [9]. The successful approach was based on a smooth,

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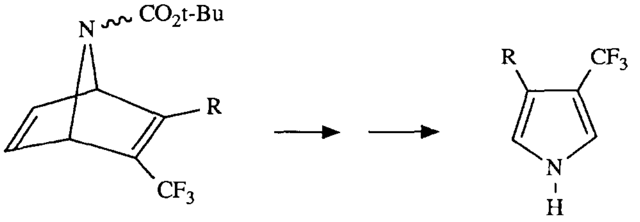
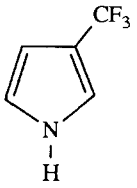
controlled cycloreversion of the Diels-Alder adduct 2a obtained from the condensation of perfluorobut-2-yne with *N*-(*t*-butoxycarbonyl)pyrrole.



2a, R = CF_3
b, R = CO_2Et

1, R = CF_3
[5a, R = CO_2Et]

We thought to apply this strategy to the synthesis of the, at that time unknown, 3-(trifluoromethyl)pyrrole 3 and we examined the condensation of 3,3,3-trifluoropropyne with *N*-(*t*-butoxycarbonyl)pyrrole at 100 and 150°C. Only unreacted material was recovered.



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On the other hand, the adduct 2b was obtained (62% yield) by condensation of the same *N*-protected pyrrole and ethyl 3,3,3-trifluoropropynoate [10]. Attempted smooth cycloreversion of this adduct under the same conditions as used for 2a *i.e.* in the presence of 2,4,6-trimethylbenzonitrile oxide [11], essentially gave back the starting pyrrole. By analogy with thiophene [12], a copper-mediated coupling between *N*-(triisopropylsilyl)-3-bromo pyrrole [13] and trifluoromethyl iodide was attempted without success.

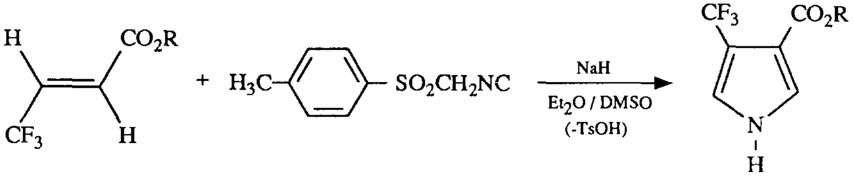
Some classical routes to substituted pyrroles involve the thermal decarboxylation of a pyrrole carboxylic acid at the final step, either by simple heating or in the presence of a copper catalyst and in a solvent [14]. Thus, 3-methylpyrrole was obtained by simple heating of 3-carboxy-4-methylpyrrole [15] and *N*-(*t*-butyl)-3,4-difluoropyrrole was prepared by refluxing *N*-(*t*-butyl)-2-carboxy-3,4-difluoropyrrole at 160°C [16].

Despite the well known propensity of pyrrole carboxylic acids bearing additional electron-withdrawing groups to be particularly resistant to decarboxylation (we failed to decarboxylate 2-carboxy-3,4-bis(trifluoromethyl)pyrrole [9]), a new route to 4-(trifluoro methyl)-3-pyrrolecarboxylic acid (6) was devised.

Although a recent Japanese patent [17] described the synthesis of 3-(trifluoromethyl)pyrrole (3) by essentially the same strategy that we have independently developed, we report our own results, giving more details on the procedures used and a more complete characterization of this pyrrole.

RESULTS AND DISCUSSION

A one-step formation of the pyrrole ring from Michael acceptors and tosylmethyl isocyanide (TosMIC) under basic conditions was reported by van Leusen et al. [18]. The application of this procedure to the readily available ethyl (*E*)-4,4,4-trifluorobutenoate (4a) [19] led to the pyrrole 5a in 68% yield, using sodium hydride as the base in a mixture of diethyl ether and dimethylsulfoxide. Recently, Ogoshi et al. also applied this procedure to the preparation of 3-acetyl-4-(trifluoromethyl) and 4-(heptafluoropropyl)pyrrole in somewhat lower yields, 44 and 39% respectively [20].



4a, R = Et
b, R = *t*-Bu

5a, R = Et
b, R = *t*-Bu

The reaction of 5a with refluxing ethanolic potassium hydroxide led to hydrolysis of both the ester functionality and the trifluoromethyl group, giving pyrrole-3,4-dicarboxylic acid [21]. On the other hand, attempts to effect acidic hydrolysis-decarboxylation [22] failed, and ester cleavage with trimethylsilyl iodide (Me_3SiI) [23] was unsatisfactory. Following the Japanese patent [17], this ester could be cleaved with a mixture of sodium iodide and trimethylsilyl chloride in acetonitrile, a *in situ* source of Me_3SiI [24]. Nevertheless, this reaction is slow since it needed three days of heating at 80-85°C for a 78.7% yield. Since we previously observed the very easy cleavage of a *t*-butyl pyrrole-2-carboxylic ester [9] with Me_3SiI, *t*-butyl (*E*)-4,4,4-trifluorobutenoate 4b was prepared from (*E*)-4,4,4-trifluorobutenoic acid and acidic isobutene / *t*-butanol (55% yield)*. Then, 4b was allowed to react with TosMIC, giving the pyrrole 5b in 65% yield after sublimation of an essentially pure crude. The cleavage of the ester moiety of 5b to the acid 6 was readily achieved with Me_3SiI in chloroform, at room temperature within 15-20 min and in nearly quantitative yield.

The decarboxylation step was decisive for the usefulness of the whole sequence. Attempts at dry decarboxylation of the acid 6 by simple heating with or without copper bronze powder as catalyst resulted in decomposition.

The report in 1987 by Anderson et al. [25] of improved conditions for the decarboxylation of pyrrole-2-carboxylic acids, substituted at the 4-position by electron withdrawing groups, prompted us to re-investigate this crucial step.

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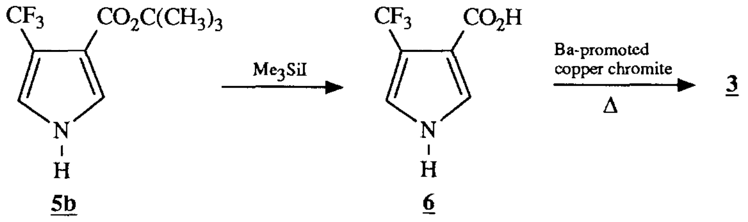
* In an alternative procedure, 4b was also prepared by a Wittig reaction between trifluoroacetaldehyde and (*t*-butoxycarbonyl)methylenetriphenylphosphorane.

When the acid 6 was added to a preheated mixture of quinoline with barium-promoted copper chromite catalyst at 200°C, rapid evolution of carbon dioxide took place. As indicated by Anderson, monitoring of this evolution with an eudiometer was useful to avoid prolonged heating and hence, decomposition of the desired product. The theoretical volume of carbon dioxide was collected but lowering the inner temperature of the reaction mixture from 200 to 180-185°C appreciably reduced the decarboxylation rate and lowered the yield.



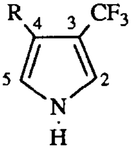
The conditions required for decarboxylation of 6, as briefly reported by the Japanese patent [17], are similar to that which we used. Nevertheless, the use of barium-promoted copper chromite instead of simple copper powder in quinoline, under carefully controlled conditions, increases the yield in the decarboxylation step from 16% (Japanese patent) up to 45%.

In the 200 MHz ^1H spectrum of 3-(trifluoromethyl)pyrrole (3), the ^{14}N-^1H triplet was remarkably well observed although much broadened by the ^{14}N quadrupolar relaxation. The resonance signals of the three nuclear protons appeared as intricate multiplets, resulting from a first order, seven spin system. As no coupling constant could be determined, the assignments are doubtful, except for H-4 which was assumed to be the least deshielded.

We attempted to solve the ambiguous H-2 and H-5 assignements *via* a heterocorrelated ^1H-^{13}C NMR 2D spectrum. Once again, the discrimination between C-2 and C-5 ($\Delta\delta$ = 1.44 ppm) was critical, owing to the lack of reliable literature data for such simple pyrroles, whereas the C-4 carbon was unambiguously located at 106.21 ppm *vs*. 107.6 for pyrrole [26]. An attempted comparison was made with the pyrrole 5b and 3,4-bis(trifluoromethyl)pyrrole (1) (**Table 1**). For the latter, α-carbons appeared as a broad singlet ($W_{1/2}$ ~10.8 Hz). As for 3, the most shielded α-carbon of 5b was coupled with the three fluorine nuclei giving rise to a quartet. Such a situation was found in (trifluoromethyl)benzene [27] for which δ (C-2,6) < δ (C-3,5) and ^3J(C,F)= 3.9 Hz whereas C-3 and C-5 (a ^4J coupling is then involved) were not coupled with the fluorine nuclei. By analogy, the C-2 carbon in 3-(trifluoromethyl)pyrrole (3) can be considered as occupying a pseudo *ortho* position *vs*. the C-3 carbon bearing the trifluoromethyl group, and C-5 a *meta* position. We may assume, therefore, that amongst the two α carbons in 3, the most deshielded is C-5.

TABLE 1

^{13}C NMR data for β-trifluoromethylpyrroles[a]



Compound	R	C-2	C-3	C-4	C-5	CF_3
5b	CO_2t-Bu	120.71[b]	114.41	115.53	126.28	123.01
		[q, 6.4]	[q, 37.1]	[q, 1.8]	[s]	[q, 266.3]
1	CF_3	120.74	112.49	112.49	120.74	122.65
		[br s]	[q, 39.5]	[q, 39.5]	[br s]	[q, 266.8]
3	H	117.59	115.05	106.21	119.03	124.05
		[q, 4.7]	[q, 36.8]	[q, 2.7]	[s]	[q, 265.6]

[a] In $CDCl_3$ at 50.3 MHz. [b] δ ppm (δ $CDCl_3/Me_4Si$ 77.0 ppm) and [multiplicity, J(C,F) Hz]

The ^1H-^{13}C correlation plane gave three connecting peaks corresponding to the three nuclear protons. Protons H-2 and H-5 connected to C-2 and C-5, were thus found to be unambiguously located at 7.09 and 6.79 ppm respectively, and H-4 at 6.42 ppm.

Proton homonuclear decoupling experiments were performed without decisive success. Nevertheless, irradiation of the intricate multiplet of H-2 gave rise to two triplets for H-4 and H-5, giving access to $J(4,5) \approx J(4,1) \sim 2.6$ Hz and $J(2,5) = 1.7$ Hz as a disappearing coupling. These values are in good accord with that given for pyrrolic structures [28]. Small couplings with fluorine (*ca.* 0.8 Hz for H-5) were observed by careful recording at 300 MHz but we failed to obtain more information. The ^{19}F NMR spectrum of 3 was still more deceptive since it exhibits a narrow unresolved singlet ($W_{1/2}$ ~3.8 Hz).

EXPERIMENTAL

'Ether' means diethyl ether. 'Brine' is a saturated aqueous sodium chloride solution. M.p.s. were determined on a Mettler FP-61 apparatus. NMR chemical shifts (δ) are reported in ppm, positive downfield from Me_4Si for the ^1H and ^{13}C nuclei and negative upfield from $CFCl_3$ for the ^{19}F nucleus. ^1H and ^{19}F NMR spectra were recorded on a Varian EM 360L spectrometer (respectively at 60 and 56.4 MHz) or on a Bruker AC 200e Fourier transform spectrometer at 200.13 MHz for the proton. ^{13}C NMR spectra were recorded at 50.32 MHz on the Bruker apparatus. Heterocorrelated ^1H-^{13}C NMR experiments were performed on a Bruker AM-300 FT spectrometer at 300.12 and 75.47 MHz respectively. IR spectra were obtained on a Perkin-Elmer 1420 spectrophotometer. Exact mass measurements were performed on a VG ZABHSQ mass spectrometer, by the Service de Microanalyse, Université P. & M. Curie, Paris. Elemental analyses were performed either by the Service Central d'Analyse du CNRS, Vernaison or Gif-sur-Yvette, ICSN (France). Copper chromite barium promoted was purchased from Chemalog, Chemical Dynamic Corporation, South Plainfield, N. J., USA. Preparative GLC were performed on a Shimadzu GC-8A gas chromatograph equipped with a 2.5 m x 7 mm stainless-steel column packed with 30% SE-30 on Chromosorb WAW.

t-Butyl (*E*)-4,4,4-trifluorobutenoate (4b)

A pre-cooled (-70°C) mixture of (*E*)-4,4,4-trifluorobutenoic acid [29] (20 g, 0.143 mol) and *t*-butyl alcohol (11.0 ml) was placed in a thick-walled glass pressure vessel, concentrated (d 1.83) sulphuric acid (2.9 ml) was introduced and then, isobutene was condensed in (*ca.* 35 g, 0.625 mol). After stoppering, the mixture was stirred at room temperature for 15 hr, cooled again to -70°C and excess isobutene allowed to boil off on warming to room temperature. After neutralization with saturated aqueous sodium hydrogen carbonate, the mixture was extracted with ether. The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* (rotary evaporator, water-pump pressure) at room temperature to give an oil. Careful distillation afforded the *ester* 4b as a colourless liquid (15.4 g, 55%), b.p. 130-131°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.50 (s, 9 H, *t*-Bu), 6.40 (dq, 1 H, $J_{2,3}$ 15.8 and $J_{2,F}$ 1.8 Hz, H-2), 6.68 (dq, 1 H, $J_{3,2}$ 15.8 and $J_{3,F}$ 6.4 Hz, H-3); ^{19}F NMR ($CDCl_3$, 56.4 MHz) δ -66.2 (distorted d, *J* ~4.5 Hz). The *Z isomer* was prepared from (*Z*)-4,4,4-trifluorobutenoic acid [30] by the same procedure and in comparable yield, b.p. 150-154°C. ^{1}H NMR ($CDCl_3$, 90MHz) δ 1.51 (s, 9 H, *t*-Bu), 5.93 (dq, 1 H, $J_{3,2}$ 12.4 and $J_{3,F}$ 7.5 Hz, H-3), 6.22 (d, 1 H, $J_{2,3}$ 12.4 Hz, H-2); ^{19}F NMR ($CDCl_3$, 56.4 MHz) δ -60.8 (d, $J_{F,3}$ 7.5 Hz).

t-Butyl 4-(trifluoromethyl)pyrrole-3-carboxylate (5b)

To a stirred slurry of sodium hydride (55% in mineral oil, 1.34g, 30.6 mmol, partially freed of its oil by washing with *ca.* 10 ml of dry ether) under argon (or nitrogen), in dry ether (50 ml) was added a mixture of the ester 4b (5.0 g, 25.5 mmol) and tosylmethyl isocyanide (4.98 g, 25.5 mmol) in a 2:1 mixture (125 ml) of dry ether and dry dimethylsulfoxide. The mixture came to gentle reflux. After addition was complete, stirring was maintained for 15-30 min and then the mixture was quenched with water (*ca.* 50 ml) and extracted with ether (4x25 ml). The combined organic extracts were washed with water (50 ml) then with brine (30 ml). After drying ($MgSO_4$), concentration under reduced pressure gave a brownish solid. Sublimation at 100°C (0.05 mmHg) afforded the *pyrrole* 5b as an off-white powdery solid

(3.9 g, 65%), m.p. 130°C. ^{1}H NMR (acetone-d_6, 60 MHz) δ 1.53 (s, 9 H, *t*-Bu), 7.36 [br m (W1/2 ~6 Hz), 1 H, H-5], 7.58 [br t~q (W1/2 ~6 Hz), 1 H, $J_{2,1} \approx J_{2,5}$ 2.3 and $J_{2,F}$ ~0.6 Hz, H-2], 11.05 (vbr s, NH). ^{19}F NMR (acetone-d_6, 56.4 MHz) δ -57.0 (distorted dd, $J_{F,5}$ ~1.0 and $J_{F,2}$ ~0.7 Hz). Anal. Cald. for $C_{10}H_{12}F_3NO_2$: C, 51.06; H, 5.14; F, 24.23; N, 5.96. Found: C, 51.05; H, 5.28; F, 24.25; N, 5.88.

4-(Trifluoromethyl)pyrrole-3-carboxylic acid (6)

To a stirred solution of the pyrrole 5b (1.38 g, 5.87 mmol) in dry chloroform under argon (or nitrogen) was added at room temperature iodotrimethylsilane (0.93 ml, 6.53 mmol). After 15 min, TLC monitoring [dichloromethane/ethyl acetate (90:10) as eluant, UV (254 nm) monitoring, R_f of 5b ~0.64] indicated total disappearance of the ester 5b. After 30 min, water (20 ml) then brine (10 ml) were added and the mixture was extracted with ether (40 then 2x20 ml). The combined organic extracts were successively washed with a 10% aqueous sodium thiosulfate solution (10 ml), water (10 ml) and brine (10 ml). After drying ($MgSO_4$), removal of the ether *in vacuo* afforded the *acid* 6 (1.05 g, 100%). An analytical sample was obtained by sublimation at 130°C (0.05 mmHg), m.p. dec..^{1}H NMR (acetone-d_6, 60 MHz) δ 7.4 [br m (W1/2~6 Hz), H-5], 7.67 [br t~q (W1/2 ~6 Hz), $J_{2,1} \approx J_{2,5}$ 2.4 and $J_{2,F}$ 0.7 Hz, H-2], 10.2 (vbr s, NH/CO_2H). ^{19}F NMR (acetone-d_6, 56.4 MHz) δ -57.3 [dd (unsymetrical t), $J_{F,5}$ 1.1 and $J_{F,2}$ 0.7 Hz]. ^{13}C NMR, see Table 1. Anal. Calcd. for $C_6H_4F_3NO_2$: C, 40.24; H, 2.25; F, 31.82; N, 7.82. Found: C, 40.43; H, 2.24; F, 31.50; N, 7.66.

3-(Trifluoromethyl)pyrrole (3)

According to the general procedure of Anderson *et al.* [25], a mixture of quinoline (5.0 ml) and barium-promoted copper chromite (0.30 g) was placed in a 50 ml two (or three)-necked flask equipped with a condenser connected to a gas outlet leading to a eudiometer and a thermometer. The flask was heated at 200-205°C (internal temperature) by means of a metallic bath. When the temperature had stabilized, the acid 6 (0.58 g, 3.24 mmol) was added quickly and the flask connected to the eudiometer. Rapid carbon dioxide evolution took place, helped by occasional careful manual shaking. The theoretical volume of gas (*ca.* 72 ml) was collected within *ca.* 5 min. The dark oil was then poured onto ice and the mixture acidified with concentrated hydrochloric acid (5 ml) with stirring. The suspension was filtered through a pad of Celite and the solid residue thoroughly washed with ether and water. The organic phase was separated and the water layer extracted with ether (4 x 15 ml). The combined organic extracts were washed with water then with a saturated aqueous sodium hydrogen carbonate solution (10 ml) and stirred for 30 min with a spatula of decolorizing charcoal. After filtration and drying over anhydrous K_2CO_3, the ether was distilled off in a Vigreux column. Last traces were briefly removed under water-pump pressure at room temperature and the oily brownish residue was bulb to bulb distilled with light heating (air gun) under 0.05 mmHg to give *3-(trifluoromethyl)pyrrole* (3) as a colourless oil (0.197 g, 45%). An analytical sample was obtained by preparative GLC at 170°C (SE-30 column), b.p. 168-170°C (Sivoloboff's method); high-resolution mass spectrum, *m/e* 135.0298 ($C_5H_4F_3N$ requires 135.0296); IR (CCl_4) ν_{max} 3475, 1573, 1492, 1357, 1150, 1128, 1118, 920 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.41 (br ~q, 1 H, H-4), 6.79 (~qd, 1 H, H-5), 7.09 (m, 1 H, H-2). ^{19}F NMR ($CDCl_3$, 56.4 MHz) -57.6 (s). ^{13}C NMR, see Table 1. Anal. Calcd. for $C_5H_4F_3N$: C, 44.46; H, 2.98; N, 10.37. Found: C, 44.60; H, 3.28; N, 10.07.

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