*Journal of Fluorine Chemistry*, *26* (1984) 499–506

Received: April 12, 1984; accepted: June 20, 1984

# FLUOROCARBON DERIVATIVES OF NITROGEN. PART 11. SYNTHESIS OF SOME 2-(TRIFLUOROMETHYL)IMIDAZO[1,2-a]PYRIDINES FROM TRIFLUOROACETONITRILE

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## SUMMARY

3-(t-Butoxycarbonyl)-2-(trifluoromethyl)imidazo[1,2-a]pyridine, prepared from trifluoroacetonitrile and pyridinium t-butoxycarbonylmethylide, reacts smoothly with trifluoroacetic acid to provide 2-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxylic acid, which gives 2-(trifluoromethyl)imidazo[1,2-a]pyridine when heated. 3-Cyano-2-(trifluoromethyl)imidazo[1,2-a]pyridine can be obtained *via* treatment of trifluoroacetonitrile with pyridinium cyanomethylide, which is sufficiently reactive to effect nucleophilic displacement of fluorine from pentafluoropyridine under mild conditions [$\longrightarrow$ pyridinium cyano(tetrafluoro-4-pyridyl)methylide].

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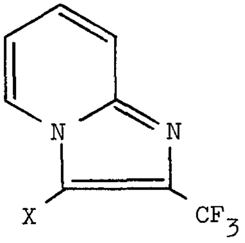
## INTRODUCTION

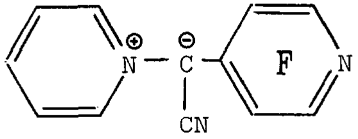
Having decided to extend our researches on reactions between fluorinated substrates and heteroaromatic _N_-oxides and -imines [1] to include work on _N_-ylides, we chose to start with pyridinium t-butoxycarbonylmethylide rather than pyridiniu methylide itself because it is easier to generate and more stable [2]; also, it was argued [3], replacement of product t-butoxycarbonyl groups by hydrogen ought to be possible _via_ pyrolysis, or protonolysis followed by pyrolysis. The latter approach is exemplified here.

## RESULTS AND DISCUSSION



(1) $X = CO_2Bu^t$ (3) X = H

(2) $X = CO_2H$ (4) X = CN



(5)

3-(t-Butoxycarbonyl)-2-(trifluoromethyl)imidazo[1,2-_a_]-pyridine (1) was converted smoothly to its parent acid (2; 82% yield[*]) _via_ alkyl-oxygen cleavage ($\underline{A_{AL}1}$ mechanism) when treated with trifluoroacetic acid [_cf_. 4] at ambient temperature; evolution of carbon dioxide occurred when the acid was heated to a temperature just above its melting point (200-201 °C), giving 2-(trifluoromethyl)imidazo[1,2-_a_]pyridine (3) in 95%

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[*] Not optimized.

yield. The overall yield of the final product (3) was therefore only 25% since the best yield of the t-butoxycarbonyl-compound (1) yet achieved is but 32% [5] owing to by-product formation [5,6]. In a single reaction, the nitrile (4) corresponding to 2-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxylic acid (2) was obtained in 37% yield by generating pyridinium cyanomethylide (from N-cyanomethylpyridinium chloride and triethylamine) in the presence of an excess of trifluoroacetonitrile, but no attempt was made to hydrolyse the cyano function.

Since, like pyridinium t-butoxycarbonylmethylide [3], pyridinium cyanomethylide is sufficiently active as a nucleophile to effect nucleophilic displacement of fluorine from pentafluoropyridine under mild conditions [eventually giving the new ylide (5)], we suspect that formation of 3-cyano-2-(trifluoromethyl)imidazo[1,2-a]pyridine (4) proceeds via a stepwise rather than a concerted 1,3-dipolar cycloaddition mechanism. By contrast with the case of the pyridinium t-butoxycarbonylmethylide—trifluoroacetonitrile reaction, we have not sought to throw further light on the mechanism by identifying the by-products which accompany the desired cycloadduct (4).

2-(Trifluoromethyl)imidazo[1,2-a]pyridine (3) and the related carboxylic acid (2) have been mentioned in a report [7] dealing with fluorescence, u.v. and i.r. spectra of some imidazo[1,2-a]pyridines; all the compounds examined were said to have been prepared via condensation of aminopyridines with appropriately substituted acetones, but no details whatsoever were given.

## EXPERIMENTAL

### Spectroscopic Analyses

I.r. and mass spectra were recorded on Perkin-Elmer 298 or 720 spectrophotometers and a Kratos MS45 spectrometer (electron beam energy 70 eV), respectively. N.m.r. spectra were obtained with Perkin-Elmer R32 ($^{19}F$, 84.6; $^{1}H$, 90 MHz) and R34 ($^{1}H$ at 220 MHz), and Bruker WP80 ($^{13}C$, 20.1 MHz) instruments [references: int. $Me_4Si$ ($^{1}H$); ext. $CF_3CO_2H$ ($^{19}F$); int. $Me_4Si$, $CDCl_3$ lock ($^{13}C$); positive chemical shift values assigned to low-field absorptions]. For information on the analysis of $^{1}H$ n.m.r. spectra of imidazo[1,2-a]pyridines, see reference 8.

### Starting Materials

Trifluoroacetonitrile was prepared from commercial (FluoroChem) trifluoroacetic acid by standard procedures ($CF_3CO_2H \longrightarrow CF_3CO_2Et \longrightarrow CF_3CONH_2 \longrightarrow CF_3CN$ [9]) and converted to 3-(t-butoxycarbonyl)-2-(trifluoromethyl)imidazo-[1,2-a]pyridine (1) via treatment with pyridinium t-butoxycarbonylmethylide [5,6]. N-Cyanomethylpyridinium chloride, m.p. 179-180 °C (lit. [10], 178 °C), with a correct elemental composition (C,H,Cl,N), was prepared from pyridine and chloroacetonitrile [10]; and pentafluoropyridine was used as received from Bristol Organics Ltd.

### Reaction of 3-(t-Butoxycarbonyl)-2-(trifluoromethyl)imidazo[1,2-a]pyridine with Trifluoroacetic Acid.

A mixture of the imidazopyridine (1.43 g, 5.0 mmol) and trifluoroacetic acid (10 $cm^3$) was stirred at ambient temperature for 1 day (probably an excessive reaction period). Removal of volatile material, *in vacuo*, followed by trituration of the white residue (1.73 g) with hot acetonitrile provided crystalline 2-(trifluoromethyl)imidazo[1,2-*a*]pyridine-3-carboxylic acid (2 ) (0.95 g, 4.1 mmol, 82%) (Found: C, 47.0; H, 2.0; F, 24.5; N, 12.4. Calc. for $C_9H_5F_3N_2O_2$: C, 46.95; H, 2.2; F, 24.8; N, 12.2%), m.p. 200-201 °C, $\lambda_{max.}$ (mull) 2850 (vbr., O-H str.), 1710 (C=O str.) $cm^{-1}$, $\delta_F$ [20% soln. in $(CD_3)_2SO$] 18.5 (s) p.p.m., $\delta_H$ (same soln.) 7.38 (td, 6-H), 7.71 (ddd, 7-H), 7.93 (ddd, 8-H), 9.39 (dt, 5-H) p.p.m. ($J_{78}$ 9.2, $J_{56} \approx J_{67} \approx$ 7, $J_{68} \approx J_{57} \approx$ 1.5, $J_{58} \approx$ 1 Hz), *m/z* 230 ($M^{+\cdot}$, 100%), 213 (*M*-OH , 69%), 186 (*M*-$CO_2$, 51%), 185(*M*-$CO_2H$, 19%).

## Decarboxylation of 2-(Trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxylic Acid

The acid (0.92 g, 4.0 mmol) was heated slowly to *ca*. 20 °C (oil bath) in a flask (50 $cm^3$) fitted with a water-cooled condenser and silica-gel guard tube. The sample melted and evolved bubbles of a gas for a few minutes, leaving a slightly charred white residue that was sublimed *in vacuo* (bath temp. 60-70 °C) to provide fine white crystals of 2-(trifluoromethyl)-imidazo[1,2-*a*]pyridine( 3 )(0.70 g, 3.8 mmol, 95%) (Found: C, 51.8; H, 2.5; F, 31.0; N, 15.3. Calc. for $C_8H_5F_3N_2$ : C, 51.6; H, 2.7; F, 30.6; N, 15.05%), m.p. 91-92 °C, $\delta_F$ (20% soln. in $CDCl_3$) 15.6 (s) p.p.m., $\delta_H$ (same soln.) 6.91 (td, 6-H), 7.30 (ddd, 7-H), 7.65 (br.dt, 8-H), 7.92 (br.d, 3-H), 8.18 (dt, 5-H) p.p.m. ($J_{78}$ 9.2, $J_{56} \approx J_{67} \approx 7$, $J_{58} \approx J_{57} \approx J_{35} \approx 1.5$, $J_{68} \approx 1$ Hz), $\delta_C$ (30% soln. in $CDCl_3$) 111.4 (q, $^3J_{CF}$ 3.7 Hz; C-3), 113.7 (s; C-6 or -8), 118.1 (s; C-8 or -6), 121.6 (q, $^1J_{CF}$ 269 Hz; $CF_3$), 126.3 (s; C-7), 126.4 (s; C-5), 135.5 (q, ${}^2\underline{J}_{CF}$ 38 Hz; C-2), 145.2 (s; C-8a) p.p.m., m/z 186 ($\underline{M}^{+\cdot}$, 100%), 167 (M-F, 29%), 78 ($C_5H_4N^+$, 9%).

Reactions of Pyridinium Cyanomethylide

(a) With trifluoroacetonitrile

Triethylamine (1.01 g, 10 mmol) and then trifluoroacetonitrile (1.9 g, 20 mmol) were condensed into a cold (-196 °C), evacuated Pyrex Rotaflo tube (300 $cm^3$) containing a degassed suspension of N-cyanomethylpyridinium chloride (1.55 g, 10 mmol) in dry acetonitrile (50 $cm^3$) and a PTFE-coated magnetic stirrer follower. The tube was sealed, allowed to warm to room temperature (a bright yellow solution containing solid material formed) then stored for 2 days with the stirrer in motion. Gaseous material was removed from the tube and found by i.r. spectroscopy to be unreacted trifluoroacetonitrile (7.0 mmol); filtration of the liquid product to remove triethylammonium chloride (0.34 g, 2.5 mmol) followed by evaporation of the filtrate to remove acetonitrile provided an orange-red solid (3.21 g), shown by t.l.c. analysis to comprise at least four components and residual material. More triethylammonium chloride (0.87 g, 6.3 mmol, total yield 88%) was recovered when the solid product was dissolved in acetone for absorption on silica prior to work-up by dry column 'flash' chromatography [4.0 x 50 mm silica; $CH_2Cl_2$ - light petroleum (b.p. 40-60 °C)]; this technique provided 3-cyano-2-(trifluoromethyl)imidazo[1,2-a]pyridine (4 ;nc) [0.79 g (after a final recrystallization from petroleum ether, b.p. 80-100 °C), 3.7 mmol, 37% based on N-cyanomethylpyridinium chloride] (Found: C, 51.4; H, 1.6; N, 20.2. $C_9H_4F_3N_3$ requires

C, 51.2; H, 1.9; N, 19.9%), m.p. 101-102 °C, $\lambda_{max}$ (mull) 2214 (C≡N str.) cm$^{-1}$, $\delta_F$ (20% soln. in $CDCl_3$) 15.4 (s) p.p.m., $\delta_H$ (same soln.) 7.35 (td; 6-H), 7.69 (ddd; 7-H), 7.91 (dt; 8-H), 8.48 (dt; 5-H) p.p.m. ($J_{78}$ 9.2, $J_{56} \approx J_{67} \approx 7$, all other couplings *ca*. 1 Hz), $\delta_C$ (30% soln. in $CDCl_3$) 94.6 (s; C-3), 108.2 (s; CN), 116.5 (s; C-6 or -8), 118.9 (s; C-8 or -6), 119.7 (q; $CF_3$), 125.8 (s; C-7), 130.1 (s; C-5), 142.0 (q; C-2), 146.0 (s; C-8*a*) p.p.m. ($^1J_{CF}$ 270.6, $^2J_{CF}$ 39.0 Hz), *m/z* 211 ($M^{+\cdot}$, 100%), 192 (*M*-F, 22%), 78 ($C_5H_4N^+$, 13%).

### (b) With pentafluoropyridine

Triethylamine (1.0 g, 10 mmol) and then pentafluoropyridine (1.69 g, 10 mmol) were condensed, *in vacuo*, into a cold (-196 °C) Pyrex tube (300 cm$^3$) containing a magnetic stirrer follower and a frozen, de-gassed suspension of *N*-cyanomethylpyridinium chloride (1.55 g, 10 mmol) in dry acetonitrile (35 cm$^3$). The tube was sealed (PTFE-glass Rotaflo valve) and allowed to warm to room temperature; as it did so, the reaction mixture turned yellow, then orange, and finally bright red. After the reaction mixture (now containing a white precipitate) had been stirred for 2 days, the tube was opened and the product was filtered to remove triethylammonium chloride (0.23 g, 1.7 mmol; identified by i.r. spectroscopy and m.p. determination). Addition of water to the filtrate caused the precipitation of orange pyridinium cyano(2,3,5,6-tetrafluoro-4-pyridyl)methylide (5; nc) (2.01 g, 7.5 mmol, 75%) (Found: C, 53.9; H, 1.6; F, 28.6; N, 15.6. $C_{12}H_5F_4N_3$ requires C, 53.9; H, 1.9; F, 28.5; N, 15.7%), m.p. 171-172 °C (decomp.), $\lambda_{max.}$ (mull) 2153 (C≡N str.) cm$^{-1}$, $\delta_F$ [10% soln. in $(CD_3)_2CO$] -20.7 (m; 2-,6-F), -71.4

(m; 3-,5-F) p.p.m., $\delta_H$ (same soln.) 8.03 (t; 3-,5-H), 8.28 (t; 4-H), 8.87 (d; 2-,6-H) p.p.m., m/z 267 ($M^{+\cdot}$, 100%), 248 (M-F, 12%), 79 ($C_5H_5N^+$ 6%).

ACKNOWLEDGEMENTS

We are indebted to the SERC for the award of a Studentship (to J.T.), and to David M. Rackham (Lilly Research Centre Ltd., Surrey, U.K.) for a copy of the 60 MHz $^1H$ n.m.r. spectrum of 2-(trifluoromethyl)imidazo[1,2-a]pyridine (3), which corresponded well with the spectrum of the material synthesised by the method described here.

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