1,8-Naphthyridines. Part I. Synthesis of Some Trifluoromethyl-1,8-naphthyridine Derivatives

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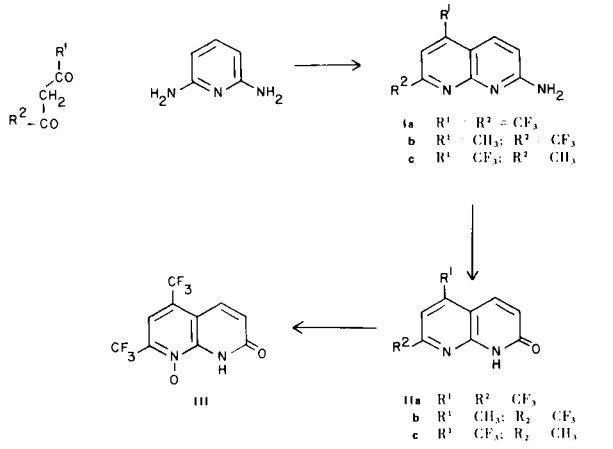
Received August 27, 1975

The synthesis of some 2-amino-1,8-naphthyridine derivatives substituted in the 5- and/or 7-positions with trifluoromethyl is described along with their conversions to the corresponding 1,8-naphthyridin-2(1*H*)ones. A modified procedure for oxidizing electron-deficient heterocyclic compounds to their *N*-oxides is presented.

As part of a program of synthesizing naphthyridines with bronchial dilator activity, it was decided to make 5,7-di(trifluourmethyl)-1,8-naphthyridin-2(1*H*)one. Condensation of 1,1,1,5,5,5-hexafluoropentan-2,4-dione with 2,6-diaminopyridine in 85% phosphoric acid took place in the expected manner (2) to give 2-amino-5,7-di(trifluoromethyl)-1,8-naphthyridine (Ia). The usual method of converting a 2-amino-1,8-naphthyridine to a 1,8-naphthyridin-2(1*H*)one is by treatment of the compound in dilute hydrochloric acid with sodium nitrite. This conversion failed to take place with the aforementioned compound; nor did reaction occur in 40% sulfuric acid. However, the amino compound dissolved readily in trifluoroacetic acid and treatment of the solution with about 2.2 equivalents of sodium nitrite gave a 60% yield of the desired naphthyridone.

When 2,6-diaminopyridine was condensed with 1,1,1-trifluoropentan-2,4-dione, both Ib and Ic were formed. These compounds were separated by chromatography and the structures assigned on the basis of their pmr spectra: the proton in the 4-position of the naphthyridine nucleus in Ic shows long-range coupling of about 1½-2 Hz with the fluorine atoms of the 5-trifluoromethyl substituent. This splitting of the 4-proton signal is seen in all of the compounds having this structural feature, *i.e.*, Ia, Ic, IIa, IIc and III, but in some cases the outer signals of the quartets appeared as shoulders on the inner signals instead of as clearly resolved quartets. Although the geometry of these molecules, with an H F interatomic distance of about 1.6 Å, raises the possibility of "through-space" coupling (3), the low value of $J_{CF_3,H}$ does not preclude a normal σ-π polarization mechanism.

As an electron-deficient heterocyclic system, one would not expect 5,7-di(trifluoromethyl)-1,8-naphthyridin-2(1*H*)one to *N*-oxidize very easily. Chivers and Suschitzsky (4) have developed a procedure for oxidizing such compounds using 90% hydrogen peroxide in a mixture of trifluoroacetic and sulfuric acids. Wishing to avoid the use of 90% hydrogen peroxide if possible, we tried the stable, solid adduct of urea and hydrogen peroxide in its place. The adduct dissolved in the mixed acids without appreciable exotherm (on a 14 mmolar scale) and the solution evolved oxygen only slowly. Excess of the oxidant was needed to take the reaction to completion but the yield was satisfactory. The scope of this reagent has not been investigated further, but it may have utility in other reactions in which concentrated hydrogen peroxide is used, provided the presence of urea in the reaction mixture is not objectionable.



EXPERIMENTAL

Nmr spectra were recorded by Mr. S.-C. Ho and his co-workers of these Laboratories in a Varian A60A spectrometer, the chemical shifts are in ppm (δ) DMSO-d_6 with TMS as the standard. Ir spectra were recorded by a Perkin Elmer 257 spectrophotometer.

Melting points (uncorrected) were determined in a Thomas Hoover capillary apparatus.

2-Amino-5,7-di(trifluoromethyl)-1,8-naphthyridine (Ia).

A mixture of 2,6-diaminopyridine (5.20 g., 47.6 mmoles), 1,1,1,5,5,5-hexafluoropentane-2,4-dione (10.0 g., 48.0 mmoles) and 85% phosphoric acid (50 ml.) was stirred in an oil bath at 90-95° for 6 hours, and then allowed to stand at room temperature overnight. The reaction mixture was poured into ice water and the mixture neutralized with ammonium hydroxide to *p*H 7. The solid was collected, washed with water and dried to afford Ia (9.0 g., 67%), m.p. 198-204°. Upon recrystallization from benzene, the solid separates in the form of pale yellow needles, m.p. 204-206°; ir ν max (potassium bromide): 1657, 1275, 1160; nmr: δ 8.21 (d of q, 1H, J = 9 Hz, J' = 2 Hz, H-4), 7.83 (s, 1H, H-6), 7.57 (bs, 2H, NH_2), 7.22 (d, 1H, J = 9 Hz).

Anal. Calcd. for $C_{10}H_5F_6N_3$: C, 42.72; H, 1.79; F, 40.54; N, 14.94. Found: C, 42.77; H, 2.13; F, 40.33; N, 15.23.

5,7-Di(trifluoromethyl)-1,8-naphthyridin-2(1*H*)one (IIa).

To a solution of Ia (5.60 g., 20 mmoles) in trifluoroacetic acid (40 ml.) cooled in an ice bath was added finely powdered sodium nitrite (3.00 g., 43.5 mmoles) in small portions with stirring. The mixture was stirred for 1 hour, then poured into ice water (500 ml.). The crude product was collected, washed with water and dried at 60° in air to yield 4.2 g. (75%) of solid, which upon recrystallization from diisopropyl ether gave IIa (3.4 g., 60%), m.p. 182-184°, ir ν max (potassium bromide): 1675 br, 1210, 1140; nmr: δ 13 (bs, 1H, NH), 8.26 (d of q, 1H, J = 10 Hz, J' = ~ 1-3/4 Hz, H-4) (5), 7.97 (s, 1H, H-6), 6.97 (d, 1H, J = 10 Hz, H-3).

Anal. Calcd. for $C_{10}H_4F_6N_2O$: C, 42.57; H, 1.43; F, 40.40; N, 9.92. Found: C, 43.02; H, 1.66; F, 40.75; N, 10.22.

2-Amino-5-methyl-7-trifluoromethyl-1,8-naphthyridine (Ib) and 2-Amino-7-methyl-5-trifluoromethylnaphthyridine (Ic).

A mixture of 2,6-diaminopyridine (7.15 g., 65.5 mmoles), 1,1,1-trifluoropentane-2,4-dione (10.0 g., 64.9 mmoles) and 85% phosphoric acid (65 ml.) was stirred at 90° for 6 hours and then left at ambient temperature overnight. The reaction mixture was poured into ice water and basified with ammonium hydroxide. The solid was collected and washed with water to remove ammonium phosphate. A mixture (12.8 g., 86%) of Ib and Ic was obtained. The yield of crude product was consistently 86-89% and appeared to be only two compounds by tlc. However, separation of the compounds by column chromatography gave variable amounts of the two isomers. The crude material, absorbed on 5 parts by weight of Baker 3405 silica gel, was placed on top of a dry column of 100 parts by weight of silica gel, and the column was developed with ethyl acetate. 2-Amino-5-methyl-7-trifluoromethyl-1,8-naphthyridine (Ib) was eluted first in yields of 29-42%, m.p. 255-257° (from toluene); ir ν max (potassium bromide): 1632, 1418, 1262, 1121; nmr: δ 8.23 (d, 1H, J = 9 Hz, H-4), 7.47 (s, 1H, H-6), 7.05 (bs, 2H, NH_2), 6.99 (d, 1H, J = 9 Hz, H-3), 2.63 (s, 3H, CH_3).

Anal. Calcd. for $C_{10}H_8F_3N_3$: C, 52.87; H, 3.55; F, 25.08; N, 18.50. Found: C, 52.69; H, 3.75; F, 25.41; N, 18.77.

2-Amino-7-methyl-5-trifluoromethyl-1,8-naphthyridine (Ic) was obtained in 10-23% yield, m.p. 195-197° dec. (from benzene); ir ν max (potassium bromide): 1598, 1262, 1156, 1125; nmr: δ 8.02 (d of q, 1H, J = 9 Hz, J' = ~ 1-3/4 Hz, H-4), 7.41 (s, 1H, H-6), 7.04 (bs, 2H, NH_2), 6.97 (d, 1H, J = 9 Hz, H-3), 2.62 (s, 3H, CH_3).

Anal. Calcd. for $C_{10}H_8F_3N_3$: C, 52.87; H, 3.55; F, 25.08; N, 18.50. Found: C, 52.99; H, 3.75; F, 25.18; N, 18.79.

5-Methyl-7-trifluoromethyl-1,8-naphthyridin-2(1*H*)one (IIb).

Treatment of the amino compound Ib, with sodium nitrite in trifluoroacetic acid as described for IIa, afforded 5-methyl-7-trifluoromethyl-1,8-naphthyridin-2(1*H*)one (IIb) in 69% yield, m.p. 200-202° (from 2-propanol, ir ν max (potassium bromide): 1660, 1182, 1145, 1112; nmr: δ 12.3 (bs, 1H, NH), 8.14 (d, 1H, J = 9 Hz, H-4), 7.60 (s, 1H, H-6), 6.73 (d, 1H, J = 9 Hz, H-3), 2.67 (s, 3H, CH_3).

Anal. Calcd. for $C_{10}H_7F_3N_2O$: C, 52.64; H, 3.09; F, 24.97; N, 12.27. Found: C, 52.39; H, 3.52; F, 25.10; N, 12.36.

7-Methyl-5-trifluoromethyl-1,8-naphthyridin-2(1*H*)one (IIc).

Treatment of the amino compound Ic with sodium nitrite in trifluoroacetic acid gave 35% of 7-methyl-5-trifluoromethyl-1,8-naphthyridin-2(1*H*)one (IIc), m.p. 165-167° (from ethyl acetate); ir ν max (potassium bromide): 1690, 1162, 1133; nmr: δ 12.6 (bs, 1H, NH), 7.92 (d of q, 1H, J = 10 Hz, J' = ~ 2 Hz, H-4), 6.51 (s, 1H, H-6). 6.70 (d, 1H, J = 10 Hz, H-3), 2.62 (s, 3H, CH_3).

Anal. Calcd. for $C_{10}H_7F_3N_2O$: C, 52.64; H, 3.09; F, 24.97; N, 12.27. Found: C, 52.70; H, 3.21; F, 25.32; N, 12.47.

5,7-Di(trifluoromethyl)-1,8-naphthyridin-2(1*H*)one 8-Oxide (III).

5,7-Di(trifluoromethyl)-1,8-naphthyridin-2(1*H*)one (4.02 g., 14.25 mmoles) was dissolved in trifluoroacetic acid (20 ml.). Concentrated sulfuric acid (24 ml.) was added, and after a few minutes, urea-hydrogen peroxide adduct (6) (2.0 g.) was added. The mixture was stirred in the ice bath for 15 minutes and then at room temperature. Urea-hydrogen peroxide (1 g.) was added at hourly intervals without cooling until a further 5.0 g. had been added and the reaction mixture was allowed to stand over the weekend. Tlc showed the absence of starting material. The mixture was poured onto ice (150 g.) and extracted with chloroform (2 x 50 ml.). The extract was washed with water (20 ml.) to which 10% sodium carbonate solution was added to bring the *p*H to 4-4.5. Some yellow solid crystallized during this process and more product was obtained by evaporating the chloroform layer. After air drying at 60° 3.03 g. (71%) of product, m.p. 171-176°, was obtained. The solid was dissolved in hot 1,1,1-trichloroethane (70 ml.) and the filtered solution was evaporated to ~ 25 ml. giving 2.56 g. (60%) of 5,7-di(trifluoromethyl)-1,8-naphthyridin-2(1*H*)one 8-oxide (III), m.p. 177-180°. Further recrystallization of the solid, followed by drying at 100°/0.005 Torr gave pure III as pale yellow needles, m.p. 180.5-181°; ir ν max (potassium bromide): 1698, 1300, 1285, 1173; nmr: δ 8.24 (d of q, 1H, J = 10 Hz, J' = ~ 2 Hz, H-4), 8.13 (s, 1H, H-6), 7.23 (d, 1H, J = 10 Hz, H-3). The NH was not detected.

Anal. Calcd. for $C_{10}H_4F_6N_2O_2$: C, 40.29; H, 1.35; F, 38.23; N, 9.40; O, 10.73. Found: C, 40.00; H, 1.17; F, 38.37; N, 9.52; O, 10.48.

REFERENCES AND NOTES

(1) Request for reprints to this author.

(2) *c.f.*, E. Ochiai and K. Miyaki, *Chem. Ber.*, **74**, 1115 (1941).

(3) G. W. Gribble and J. R. Douglas, Jr., *J. Am. Chem. Soc.*, **92**, 5764 (1970) and reference therein.

(4) G. E. Chivers and H. Suschitzsky, *J. Chem. Soc.* (C), 2867 (1971).

(5) A 220 MHz spectrum recorded at Canadian 220 MHz NMR Centre, Ontario Research Foundation, Sheridan Park, Mississauga, Ont. L5K 1B3, shows $J_{CF_3,H}$ as ~ 1.9 Hz.

(6) Urea-hydrogen peroxide (BDH) contains 33-35% hydrogen peroxide. The tablets were crushed to give a coarse powder just before use.