

1,8-Naphthyridines. Part II. Synthesis of Some 3-Pyridyl-5,7-di(trifluoromethyl)-1,8-naphthyridin-2(1H)ones

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Received August 27, 1975

Ethyl 2-amino-4,6-di(trifluoromethyl)nicotinate was prepared and its use as an intermediate in the synthesis of two 3-pyridyl-5,7-di(trifluoromethyl)-1,8-naphthyridin-2(1H)ones is presented. A dimer of 2-amino-4,6-di(trifluoromethyl)nicotinaldehyde is described.

As part of a medicinal chemical program, it was desired to make some 5,7-di(trifluoromethyl)-1,8-naphthyridin-2(1H)ones substituted in the 3-position with pyridyl. Hawes and Wilberley (2) have developed a route to 3-substituted-1,8-naphthyridin-2(1H)ones based on the condensation of 2-aminonicotinaldehydes with esters containing a moderately activated α -methylene group. Accordingly, 1,1,1,5,5,5-hexafluoropentane-2,4-dione was condensed with ethyl ethoxycarbonylacetimide after the method of Dornow and Karlson (3) for the preparation of ethyl 2-amino-4,6-dimethylnicotinate. The resulting di(trifluoromethyl)nicotinic ester (1) was converted to the hydrazide (2) and the latter was benzenesulfonated to give 3. When 3 was subjected to a McFadyen-Stevens reaction under the conditions employed by Albert and Reich (4) to prepare 2-aminonicotinaldehyde, the product was a dimer (5) of the required aminoaldehyde (4).

However, it was found possible to carry out the McFadyen-Stevens reaction in the presence of a pyridylacetic ester and hence obtain compounds 6a and 6b.

The "dimeric" aminoaldehyde actually does analyze as the dimer $C_{16}H_8F_{12}N_4O_2$, but structure 5 monohydrate is supported by a mass spectral ion $M^+ = 498$, and is corroborated by a signal for exchangeable protons in the nmr spectrum at the position at which water protons are usually seen in DMSO- d_6 , i.e., at about 3 ppm. While neither piece of evidence is conclusive in itself, the two together are indicative of structure 5. A similar compound derived from another aminonicotinaldehyde will be reported later.

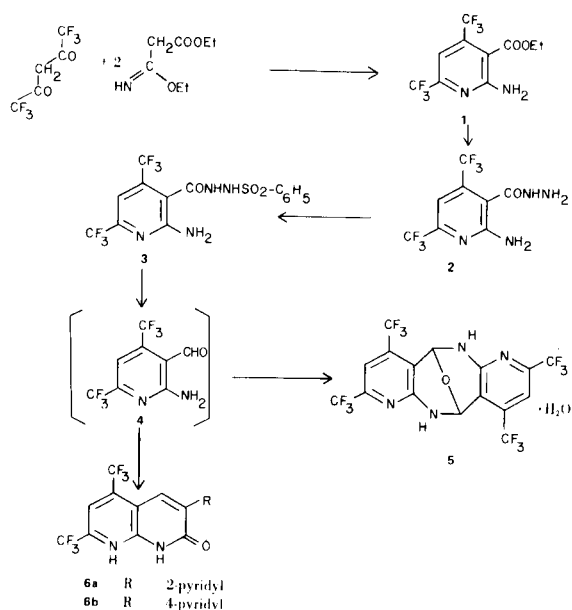
EXPERIMENTAL

Nmr spectra were recorded on a Varian A60A spectrometer and ir spectra on a Perkin Elmer 257 spectrophotometer. Melting points are uncorrected. Microanalyses were obtained from Organic Microanalyses, Dr. C. Daessle, and a mass spectrum from Morgan Schaffer Corporation, both of Montreal.

Ethyl 2-Amino-4,6-di(trifluoromethyl)nicotinate (1).

1,1,1,5,5,5-Hexafluoropentane-2,4-dione (39.0 g., 0.188 mole) was added slowly over 15 minutes to ethyl ethoxycarbonylacetimide (5) (59.6 g., 0.375 mole) with stirring and cooling (ice bath). The mixture was stirred for 15 minutes at room temperature and then for 20 hours in an oil bath at 105-110°. The reaction mixture was distilled and the fraction, b.p. 65-88°/0.05 Torr was collected. The distillate crystallized partially and the solid was filtered off and washed on the filter with a little cold alcohol to give 1, 10.44 g., (18.6%), m.p. 84-86°. By chilling the filtrate (oil and alcohol washings combined) a further 1.60 g. (2.8%) was obtained. Pure ethyl 2-amino-4,6-di(trifluoromethyl)nicotinate, m.p. 87-88°, was obtained by recrystallization of the product from 2:1 methanol/water followed by sublimation at 45°/0.005 Torr; ν_{max} (potassium bromide): 3465, 3325, 1703, 1272, 1140, 862; nmr δ (DMSO- d_6): 7.24 (bs, 2H, NH_2), 7.18 (1H, s, pyridyl-H), 4.40 (q, 2H, J = 7 Hz, CH_2), 1.28 (t, 3H, J = 7 Hz, CH_3).

Anal. Calcd. for $C_{10}H_8F_6N_2O_2$: C, 39.75; H, 2.67; F, 37.72; N, 9.27. Found: C, 39.61; H, 2.96; F, 37.80; N, 9.66.



2-Amino-4,6-di(trifluoromethyl)nicotinic Acid Hydrazide (2).

A mixture of **1** (2.55 g., 8.45 moles), 85% hydrazine hydrate (5 ml.) and 2-propanol (5 ml.) was stirred in an oil bath at 110° for 3 hours. On cooling, the dark red solution deposited colourless crystals, which were filtered off and washed with a little 2-propanol. A second crop of solid was obtained from the mother liquors giving a total of 1.45 g. (59.6%) of product, m.p. 240-243° dec., which upon recrystallization from 2-propanol (25 ml.) afforded 1.05 g. (42.8%) of 2-amino-4,6-di(trifluoromethyl)nicotinic acid hydrazide, m.p. 244-245° dec.; ν max (potassium bromide): 3410, 3295, 1658, 1265, 1135, 860; nmr δ (DMSO- d_6): 9.65 (bs, 1H, NH), 7.09 (s, 1H, pyridyl H), 6.97 (bs, 2H, NH₂), 4.37 (bs, 2H, NH₂).

Anal. Calcd. for C₈H₆F₆N₄O: C, 33.35; H, 2.10; F, 39.56; N, 19.44. Found: C, 33.27; H, 2.20; F, 39.48; N, 19.53.

N'-(2-Amino-4,6-di(trifluoromethyl)nicotinoyl)-*N*²-benzenesulfonylhydrazine (3).

2-Amino-4,6-di(trifluoromethyl)nicotinic acid hydrazide (4.35 g., 15.1 mmoles) was stirred in *N* sodium hydroxide solution (36.3 ml.) until a clear solution was obtained. Benzenesulfonyl chloride (2.94 g., 16.6 mmoles) was added in one portion and the mixture was stirred rapidly until solution was complete. The solution was poured into a stirred solution of acetic acid (0.90 g., 15 mmoles) in water (40 ml.) and the pH of the suspension was adjusted to ~6.5 by the addition of a few drops of acetic acid. The solid was collected, washed with water and dried to give **3**, 6.52 g. (100%) sintering at \approx 230°, m.p. 235-238° dec. *N'*-(2-Amino-4,6-di(trifluoromethyl)nicotinoyl)-*N*²-benzenesulfonylhydrazine was purified by diluting a filtered solution of the solid in ethyl acetate (4 ml./g.) with chloroform (10 ml./g.), and then had m.p. 243-245° dec.; ν max (potassium bromide): 3445, 3327, 1694, 1662, 850; nmr δ (deuterioethanenitrile): ~7.9 (bm, 2H, aryl H), ~7.65 (bm, 3H, aryl H), 7.18 (s, 1H, pyridyl H), 6.2-5.5 (bm, ~4H, 2NH and NH₂).

Anal. Calcd. for C₁₄H₁₀F₆N₄O₃S: C, 39.26; H, 2.35; N, 13.08; S, 7.49. Found: C, 39.72; H, 2.78; N, 13.20; S, 7.55.

2,4,8,10-Tetra(trifluoromethyl)-5,11-epoxy-5,6,11,12-tetrahydro-dipyrido[2,3-*b*:2',3'-*f'*]diazocine Monohydrate (5).

A mixture of **3** (1.00 g., 2.33 mmoles) and ethylene glycol (10 ml.) was heated in an oil bath at 170-175° and to the hot solution was added anhydrous sodium carbonate (650 mg., 6.13 mmoles) with efficient stirring. After 1 minute the mixture was allowed to cool and then it was poured into water (50 ml.). The pale yellow solid (280 mg.) was collected and dried at 60° in air. Recrystallization of the crude product from acetonitrile (7 ml.) gave 212 mg. of **5**; the solid begins to shrink at ~280° with formation of a sublimate, m.p. 316-317° with slight darkening; ν max (potassium bromide): 3250 (broad), 1621, 1599, 1271, 1192-1125 (sm), 864, nmr δ

(DMSO- d_6): 8.78 (bs, 2H, NH), 7.40 (s, 2H, pyridyl-H), 6.77 (s, 2H, OCHN), 3.25 (s, ~2H, H₂O).

Anal. Calcd. for C₁₆H₆F₁₂N₄O·H₂O: C, 37.23; H, 1.56; F, 44.16; N, 10.85. Found: C, 38.16; H, 1.72; F, 44.56; N, 10.87.

Changing the reaction conditions to 10 seconds at 165° reduced the crude yield to 210 mg. and about 30% of unreacted **3** was recovered from the aqueous solution by continuous extraction with methylene chloride.

3-(2-Pyridyl)-5,7-di(trifluoromethyl)-1,8-naphthyridin-2(1*H*)one (6a).

To ethylene glycol (10 ml.) heated in an oil bath at 175° was added with stirring **3** (428 mg., 1 mmole), a solution of ethyl 2-pyridylacetate (165 mg., 1 mmole) and 1,4-diazobicyclo-[2,2,2]octane (112 mg., 1 mmole) in ethylene glycol (2 ml.), and then after a short pause to allow the temperature to rise to 175° again, anhydrous sodium carbonate (300 mg.) was added. The mixture was stirred for 1 minute and then allowed to cool before pouring it into water (50 ml.). The crude product (183 mg.) was recrystallized from acetonitrile (18 ml.) to afford **6a**, 111 mg. (31%), m.p. 298-300°; ν max (potassium bromide): 1671, 1272, 1197; nmr δ (deuteriotrifluoroacetic acid): ~8.67-8.0 (m, 4H, H-4 and pyridyl H-6, H-4 and H-3), ~7.75-7.4 (m, 1H, pyridyl H-5), 7.53 (s, 1H, H-6). (Chemical shifts are approximate because the TMS signal was not evident.)

Anal. Calcd. for C₁₅H₇F₆N₃O: C, 50.15; H, 1.96; N, 11.69. Found: C, 49.88; H, 2.15; N, 11.48.

3-(4-Pyridyl)-5,7-di(trifluoromethyl)-1,8-naphthyridin-2(1*H*)one (6b).

Use of ethyl 4-pyridylacetate in place of ethyl 2-pyridylacetate in the above reaction gave **6b**, m.p. 283-286°, in 30% yield after purification by Soxhlet extraction with acetonitrile; ν max (potassium bromide): 1686, 1280, 1205; nmr δ (deuteriotrifluoroacetic acid): 8.63 (d, 2H, J = 6.5 Hz, α -pyridyl H's), 8.43 (d, 1H, J_{HF} = 1 Hz, H-4), 8.22 (d, 2H, J = 6.5 Hz, β -pyridyl H's), 7.73 (s, 1H, H-6). (Chemical shifts approximate because the TMS signal was not evident.)

Anal. Calcd. for C₁₅H₇F₆N₃O: C, 50.15; H, 1.96; N, 11.69. Found: C, 49.61; H, 2.19; N, 11.87.

REFERENCES AND NOTES

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