

Fluorinated Nitrogen Heterocycles *via* Cyclization. III.
3-Trifluoromethyl-1-(4-trifluoromethyl-2-pyridyl)-pyrazoles
from Fluorinated 1,3-Diketones and 4-Trifluoromethyl-2-hydrazinopyridines.

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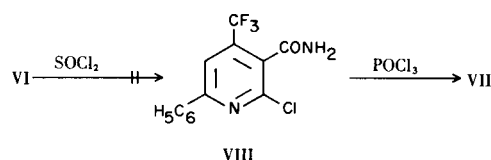
Fluorinated 1,3-diketone compounds having the general structure $\text{CF}_3\text{COCH}_2\text{COR}_1$ underwent cyclization with 4-trifluoromethyl-2-hydrazinopyridines (IV) to give a series of 3-trifluoromethyl-1-(4-trifluoromethyl-2-pyridyl)-pyrazoles (V). The hydrazinopyridine intermediates (IV) were prepared by conversion of 4-trifluoromethyl-2-pyridones (II) to the chloropyridines (III) followed by treatment of the latter with hydrazine hydrate.

The preparation of trifluoromethylpyrazoles from hydrazine and fluorinated 1,3-diketones has been sparsely reported (1,2). In continuation of work on the preparation of new fluorinated nitrogen heterocycles (3,4), this laboratory has extended this reaction to the fluorinated hydrazinopyridines. It was found that when 4-trifluoromethyl-2-hydrazinopyridines (IV, Table III) were reacted with fluorinated 1,3-diketones having the general structure $\text{CF}_3\text{COCH}_2\text{COR}_1$, where $\text{R}_1 = \text{CH}_3, \text{C}_6\text{H}_5, 2\text{-C}_4\text{H}_3\text{S}(2\text{-thienyl})$ or $2\text{-C}_4\text{H}_3\text{O}(2\text{-furyl})$, cyclizations occurred giving, in most cases, the desired pyrazole compounds (Va-j, Table IV).

The reaction of 1,1,1-trifluoro-4-(2-thienyl)-2,4-butanedione with IVc, on the other hand, did not result in the expected pyrazole product (V_k), but gave instead the partially dehydrated product, 3-(2-thienyl)-1-[6-(2-thienyl)-4-trifluoromethyl-2-pyridyl]-5-trifluoromethyl-5-hydroxypyrazoline. Similar results were obtained using 1,1,1-trifluoro-4-(2-furyl)-2,4-butanedione. Instead of the pyrazole compound (VI), 3-(2-furyl)-1-[6-(2-thienyl-4-trifluoromethyl-2-pyridyl)-5-trifluoromethyl-5-hydroxypyrazoline was isolated. These reactions are presently being investigated and will be reported, along with analogous reactions, in a forthcoming paper.

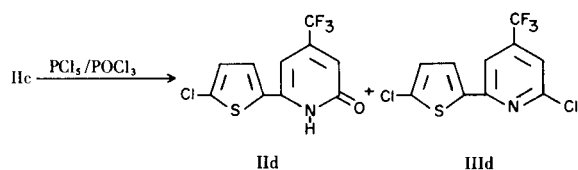
The hydrazinopyridine intermediates (IV) were prepared from previously synthesized 3-cyano-4-trifluoromethyl-2-pyridones (I) (3). This was accomplished by treatment of I with 50-55% sulfuric acid, conversion of the resulting decyanated pyridones (II, Table I) to the chloropyridine product (III, Table II) by phosphorus pentachloride and phosphorus oxychloride or phenylphosphonic dichloride, and finally conversion of III to IV with hydrazine hydrate.

Contrary to the literature concerning related compounds (5-7), treatment of 3-cyano-6-phenyl-4-trifluoromethyl-2(1*H*)-pyridone (Ia) with phosphorus pentachloride and phosphorus oxychloride under a variety of reaction conditions did not give the expected chloropyridine product (VII). An attempt to prepare VII from VI was equally unsuccessful (8). In contrast to what is reported elsewhere in an analogous situation (9), reaction of VI with thionyl chloride does not give the chloropyridine with the acid amide group intact (VIII) but results only in dehydration of the acid amide.



It was found that the chloropyridines could be prepared only from the decyanated pyridones (II). Accordingly, successive treatment of Ia and Ib with 50-55% sulfuric acid and phosphorus pentachloride/phosphorus oxychloride gave IIIa and IIIb.

In the case of IIc, treatment with phosphorus pentachloride/phosphorus oxychloride gave the monochloro product, 6-(5-chloro-2-thienyl)-4-trifluoromethyl-2(1*H*)-pyridone (II_d). In addition, the dichloro product, 6-(5-chloro-2-thienyl)-4-trifluoromethyl-2-chloropyridine (III_d), was also isolated.



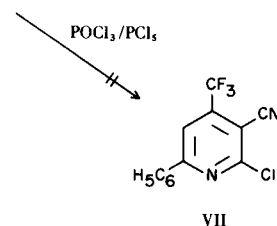
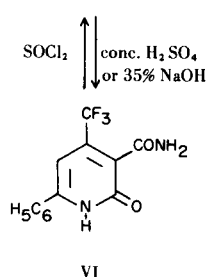
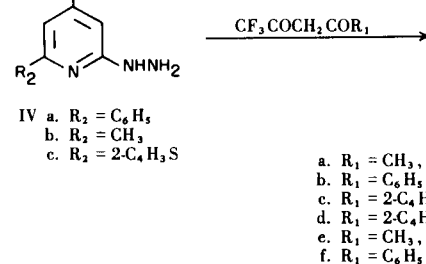
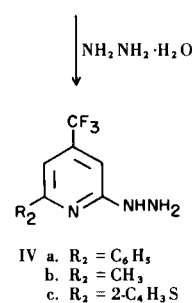
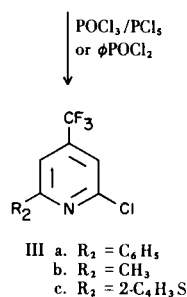
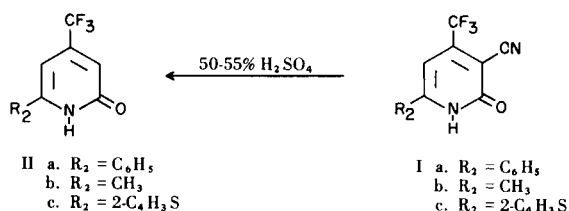
The desired chloropyridine (IIc) was synthesized via use of phenylphosphonic dichloride (11).

EXPERIMENTAL (12)

Preparation of 4-Trifluoromethyl-2-pyridones (II).

6-Phenyl-4-trifluoromethyl-2(1H)-pyridone (IIa).

Compound Ia (10.0 g., 0.038 mole) was slowly added to 150 ml. of 50% sulfuric acid. The mixture was heated with stirring for 10 hours at 148° and the crude product crystallized upon standing.



6-Methyl-4-trifluoromethyl-2(1H)-pyridone (IIb).

The reaction was performed initially in the same manner as above, employing Ib (60.6 g., 0.3 mole) and 500 ml. of 50% sulfuric acid. The initially non-crystalline product was isolated when the mixture was concentrated (in an air stream), basified with concentrated aqueous sodium hydroxide (pH 8), filtered, and washed with cold water.

6-(2-Thienyl)-4-trifluoromethyl-2(1H)-pyridone (IIc).

The reaction was carried out in the same manner as that for IIa, using Ic (1.9 g., 0.007 mole) and 70 ml. of 55% sulfuric acid. On cooling, the yellow-tan crude product was precipitated by addition of (50 ml.) water.

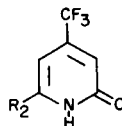
Preparation of 4-Trifluoromethyl-2-chloropyridines (III).

6-Phenyl-4-trifluoromethyl-2-chloropyridine (IIIa).

To a flask fitted with stirrer, condenser and drying tube were added IIa (4.7 g., 0.02 mole) and 11.0 g. of phosphorus pentachloride. Phosphorus oxychloride (25 ml.) was then added over a period of 15 minutes, the mixture was mildly refluxed for 13 hours, and the excess phosphorus oxychloride was removed by distillation. After cooling (ice-bath), the addition of 30 ml. of cold water (13) resulted in a grey crude product which was collected by filtration.

TABLE I

4-Trifluoromethyl-2-pyridones (II)



Compound	Recrystallization	M.P. (°C)	Yield %	Formula	Analysis	
					Calcd.	Found
IIa	white needles from 50% HOAc	188.5-189.0	86	C ₁₂ H ₈ F ₃ NO	C, 60.26 H, 3.37 N, 5.86	C, 59.84 H, 3.25 N, 5.79
IIb	white needles from pet. ether (10)	133.8-135.2	77	C ₇ H ₆ F ₃ NO	C, 47.47 H, 3.42 N, 7.91	C, 47.33 H, 3.21 N, 7.71
IIc	pale-yellow needles from EtOH	201.6-202.7	85	C ₁₀ H ₆ F ₃ NOS	C, 48.98 H, 2.47 N, 5.71	C, 49.20 H, 2.40 N, 5.98
II d	yellow powder from CHCl ₃	234.7-236.3	25	C ₁₀ H ₅ ClF ₃ NOS	C, 42.95 H, 1.80 Cl, 12.68 F, 20.38 N, 5.01	C, 42.59 H, 1.77 Cl, 12.90 F, 20.57 N, 4.72

6-Methyl-4-trifluoromethyl-2-chloropyridine (IIIb).

A mixture of IIb (10.6 g., 0.06 mole) and 18.0 g. phosphorus pentachloride was chilled in an ice-bath and 45 ml. of cold phosphorus oxychloride was added slowly over a period of 45 minutes. The mixture, after mildly refluxing with stirring for 6 hours, was freed from excess phosphorus oxychloride by distillation, neutralized with concentrated aqueous sodium hydroxide and extracted with ether. The ether extracts were dried over anhydrous sodium sulfate and the ether was removed by distillation. Vacuum distillation through a 3-in. Vigreux column gave a fraction from 78-79° at 25 mm.; 58-59° at 13 mm.

6-(2-Thienyl)-4-trifluoromethyl-2-chloropyridine (IIIc).

Compound IIc (4.9 g., 0.02 mole) and phenylphosphonic dichloride (11.7 g., 0.06 mole) were mixed in a moisture protected flask and heated at 180-190° for 3.5 hours. Upon cooling, the contents were added to 45 ml. of water. The crude product was isolated when the mixture was basified with a saturated solution of potassium carbonate (pH 8) and filtered.

Preparation of 4-Trifluoromethyl-2-hydrazinopyridines (IV).
General Method.

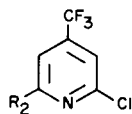
The appropriate 4-trifluoromethyl-2-chloropyridine (III) (0.01 mole) and 13 ml. of hydrazine hydrate were mildly refluxed for 17 hours, after which, the immiscible oil usually crystallized on standing. If crystallization did not occur the mixture was extracted with ether, the ether solution was dried over anhydrous sodium sulfate and evaporated with a stream of clean-dry air until a viscous oil remained. The mixture was cooled and shaken, if necessary, to initiate crystallization.

Preparation of 3-Trifluoromethyl-1-(4-trifluoromethyl-2-pyridyl)-pyrazoles (V). General Method.

The 4-trifluoromethyl-2-hydrazinopyridine (IV) (0.004 mole) was added slowly to a very slight excess of the 1,3-diketone intermediate. After solution (14), 10 drops of concentrated hydrochloric acid (37%) were added. The mixture was then heated at 90-100° for 2 hours (15), freed from water by distillation at 35°/20 mm., dissolved in acetone, filtered, and the acetone

TABLE II

4-Trifluoromethyl-2-chloropyridines (III)

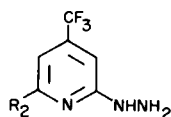


Compound	Recrystallization	M.P. (°C)	Yield %	Formula	Analysis	
					Calcd.	Found
IIIa	white clusters from MeOH-H ₂ O	49.6-50.6	88	C ₁₂ H ₇ ClF ₃ N	C, 55.94 H, 2.74 N, 5.44	C, 55.85 H, 2.77 N, 5.10
IIIb	—	162.0-162.5 (a)	66	C ₇ H ₅ ClF ₃ N	C, 42.99 H, 2.58 Cl, 18.13 N, 7.16	C, 43.10 H, 2.57 Cl, 18.30 N, 7.23
IIIc	white needles from EtOH-H ₂ O	54.8-56.1	80	C ₁₀ H ₅ ClF ₃ NS	C, 45.55 H, 1.91 Cl, 13.44 N, 5.31	C, 45.86 H, 1.78 Cl, 13.74 N, 5.18
III d	white clusters from EtOH-H ₂ O (3:1)	63.0-65.0	18	C ₁₀ H ₄ Cl ₂ F ₃ NS	C, 40.29 H, 1.35 Cl, 23.78 F, 19.12 N, 4.70	C, 39.93 H, 1.26 Cl, 24.07 F, 19.23 N, 4.50

(a) B.P. at 764 mm; $n_D^{25} = 1.45084$

TABLE III

4-Trifluoromethyl-2-hydrazinopyridines (IV)

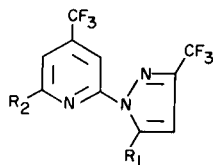


Compound	Recrystallization	M.P. (°C)	Yield %	Formula	Analysis	
					Calcd.	Found
IVa	white needles from pet. ether	88.3-89.5	89	C ₁₂ H ₁₀ F ₃ N ₃	C, 56.92 H, 3.98 N, 16.59	C, 57.27 H, 3.85 N, 16.57
IVb	white needles from pet. ether	82.0-83.5	94	C ₇ H ₈ F ₃ N ₃	C, 43.98 H, 4.22 N, 21.98	C, 43.54 H, 4.12 N, 21.76
IVc	faintly yellow needles from pet. ether	96.5-97.7 (a)	86	C ₁₀ H ₈ F ₃ N ₃ S	C, 46.33 H, 3.11 N, 16.21	C, 46.16 H, 2.97 N, 16.09

(a) Turned yellow on melting.

TABLE IV

3-Trifluoromethyl-1-(4-trifluoromethyl-2-pyridyl)-pyrazoles (V)



Compound	Recrystallization	M.P. (°C)	Yield %	Formula	Analysis	
					Calcd.	Found
Va	white needle clusters from MeOH-H ₂ O	79.8-81.2	63	C ₁₇ H ₁₁ F ₆ N ₃	C, 54.99 H, 2.99 F, 30.70 N, 11.32	C, 55.12 H, 2.69 F, 30.91 N, 11.10
Vb	white needle clusters from pet. ether	117.0-119.2	48	C ₂₂ H ₁₃ F ₆ N ₃	C, 60.97 H, 3.02 F, 26.31 N, 9.70	C, 60.71 H, 3.10 F, 26.69 N, 9.39
Vc	white needles from MeOH-H ₂ O	105.3-106.7	63	C ₂₀ H ₁₁ F ₆ N ₃ S	C, 54.67 H, 2.52 N, 9.56	C, 54.34 H, 2.49 N, 9.49
Vd	white powder from MeOH	81.0-82.2	35	C ₂₀ H ₁₁ F ₆ N ₃ O	C, 56.75 H, 2.62 N, 9.93	C, 56.88 H, 2.73 N, 9.78
Ve	white needles from pet. ether	48.5-50.0	71	C ₁₂ H ₉ F ₆ N ₃	C, 46.61 H, 2.93 N, 13.59	C, 46.87 H, 2.98 N, 13.55
Vf	white needles from MeOH	125.4-127.0	82	C ₁₇ H ₁₁ F ₆ N ₃	C, 54.99 H, 2.99 N, 11.32	C, 54.64 H, 3.05 N, 11.10
Vg	white needles from MeOH-H ₂ O	107.0-108.3	20	C ₁₅ H ₉ F ₆ N ₃ S	C, 47.75 H, 2.40 N, 11.14	C, 47.84 H, 2.45 N, 11.19
Vh	white needles from MeOH-H ₂ O	90.5-92.0	31	C ₁₅ H ₉ F ₆ N ₃ O	C, 49.87 H, 2.51 N, 11.63	C, 49.59 H, 2.67 N, 11.91
Vi	white needles from pet. ether	103.5-105.0	62	C ₁₅ H ₉ F ₆ N ₃ S	C, 47.75 H, 2.40 N, 11.14	C, 47.79 H, 2.42 N, 11.23
Vj	white powder from MeOH	107.0-110.0	55	C ₂₀ H ₁₁ F ₆ N ₃ S	C, 54.67 H, 2.52 N, 9.56	C, 54.87 H, 2.66 N, 9.57

solution was evaporated with clean-dry air. The mixture was cooled and shaken, if necessary, to initiate crystallization.

Reaction of IVc with 1,1,1-trifluoro-4-(2-thienyl)-2,4-butanedione.

Compound IVc when reacted with 1,1,1-trifluoro-4-(2-thienyl)-2,4-butanedione by the above procedure gave 3-(2-thienyl)-1-[6-(2-thienyl)-4-trifluoromethyl-2-pyridyl]-5-trifluoromethyl-5-hydroxypyrazoline as a cream-colored powder from methanol, m.p. 164.9-166.7°, 50%.

Anal. Calcd. for $C_{18}H_{11}F_6N_3OS_2$: C, 46.65; H, 2.39; N, 9.07. Found: C, 46.48; H, 2.16; N, 8.96.

Reaction of IVc with 1,1,1-trifluoro-4-(2-furyl)-2,4-butanedione.

Compound IVc when reacted with 1,1,1-trifluoro-4-(2-furyl)-2,4-butanedione by the above procedure gave 3-(2-furyl)-1-[6-(2-thienyl)-4-trifluoromethyl-2-pyridyl]-5-trifluoromethyl-5-hydroxypyrazoline as a pale yellow powder from methanol, m.p. 166.2-167.3°, 45%.

Anal. Calcd. for $C_{18}H_{11}F_6N_3O_2S$: C, 48.33; H, 2.48; N, 9.39. Found: C, 48.11; H, 2.17; N, 9.20.

Preparation of 3-Carboxamide-6-phenyl-4-trifluoromethyl-2(1H)-pyridone (VI).

Compound Ia (5.3 g., 0.02 mole) was added slowly with stirring to 8.5 ml. of concentrated sulfuric acid. The mixture was heated at 125-135° for 30 minutes and then cooled to 0°. The light tan crude product precipitated on addition of 60 g. of ice-water, white needles from ethanol, m.p. 326.0-327.0° dec., 95%.

Anal. Calcd. for $C_{13}H_9F_3N_2O_2$: C, 55.32; H, 3.21; N, 9.93. Found: C, 55.35; H, 3.15; N, 10.04.

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(3) S. Portnoy, *J. Org. Chem.*, 30, 3377 (1965).

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(8) Reaction of Ic with concentrated sulfuric acid resulted in sulfonation of the thiophene ring in addition to the expected conversion of the pyridone nitrile to the acid amide, and was characterized as the *p*-toluidine salt, yellow needles from minimum H_2O , m.p. 276.5-277.4° dec.

Anal. Calcd. for $C_{18}H_{16}F_3N_3O_5S_2$: C, 45.47; H, 3.39; F, 11.99; N, 8.84; S, 13.49. Found: C, 45.24; H, 3.49; F, 12.44; N, 8.57; S, 13.71.

(9) H. E. Mertel, "Pyridine and Its Derivatives", Part 2, E. Klingsberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1961, p. 332.

(10) Petroleum ether, b.p. range 38-53°, used throughout this work.

(11) M. M. Robison, *J. Am. Chem. Soc.*, 80, 5481 (1958).

(12) All melting points are uncorrected; analyses by this laboratory and Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.

(13) The application of heat and the addition of a small quantity of ethanol aids in breaking-up the solid.

(14) Heat is applied if solution fails to occur.

(15) Reaction temperature range for preparation of Vc, 110-120°; Vh, 80-90°.

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