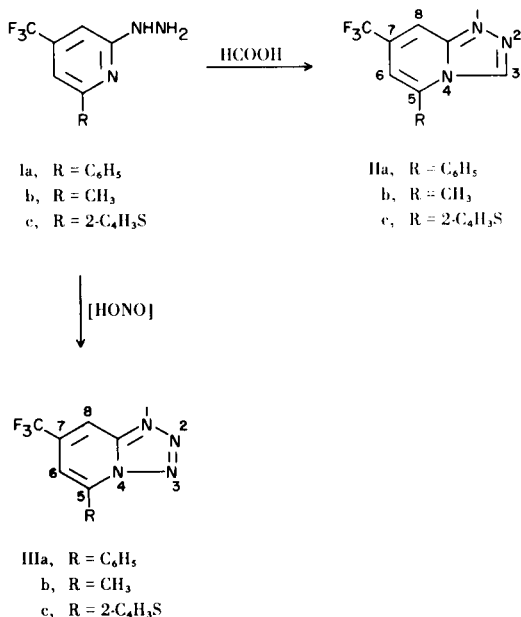


Fluorinated Nitrogen Heterocycles *via* Cyclization. IV. *s*-Triazolo[4,3-*a*]pyridines and Tetrazolo[1,5-*a*]pyridines from 4-Trifluoromethyl-2-hydrazinopyridines.

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The preparation of 3-trifluoromethyl-1-(4-trifluoromethyl-2-pyridyl)pyrazoles from fluorinated 1,3-diketones and 4-trifluoromethyl-2-hydrazinopyridines (I) was investigated recently in this laboratory (1). Continuation of work on the cyclization reactions of I has led to the syntheses of two series of fused heterocyclic ring compounds.



7-Trifluoromethyl-*s*-triazolo[4,3-*a*]pyridines (II, Table I) were readily prepared in high yields by the reaction of I with 97-100% formic acid. Potts and coworkers have recently investigated this condensed ring system (2,3) and summarized previous work by others (4).

Similarly, treatment of I with nitrous acid afforded good yields of the 7-trifluoromethyltetrazolo[1,5-*a*]pyridines (III, Table I). Relatively little has been reported on this fused ring system (5-11).

The possibility of the *s*-triazolo[4,3-*a*]pyridines (II) undergoing Dimroth rearrangement under acidic reaction conditions to the isomeric *s*-triazolo[1,5-*a*]pyridines (3), aided by the electron-withdrawing effect of the 7-trifluoromethyl substituent on the C-5 position of the nucleus (site of hydrolytic attack), was considered unlikely because

of the steric effect of the 5-substituent (12). That compounds IIa-c are *s*-triazolo[4,3-*a*]pyridines is strongly supported by a NMR study of the two isomeric systems by Potts and coworkers (13). They have reported that *s*-triazolo[4,3-*a*]pyridines, unsubstituted in the 3-position, exhibit low-field peaks at *ca.* τ 1.14; whereas, in the isomeric [1,5-*a*] system, the corresponding proton in the 2-position occurs at higher field (*ca.* τ 1.65). In this work, the 3-proton of the [4,3-*a*] system is shown by absorptions (Table II) at τ 1.10 (IIa), τ 1.17 (IIb) and τ 0.78 (IIc). The downfield shift of IIc by 0.32-0.39 ppm results from the deshielding influence of sulfur (14).

The intermediate 4-trifluoromethyl-2-hydrazinopyridines (I) were prepared by the action of hydrazine hydrate on the appropriate 2-chloropyridine compound (1), themselves obtained from the respective 2-pyridone (15).

Weak absorptions of the -C=N- grouping of the ring system are shown by both series of compounds in the 1640-1660 cm⁻¹ region (Table II) (3). Bands characteristic of pyridine ring stretching (16) appear in the region 1410-1600 cm⁻¹. No assignments could be made for the tetrazole ring in the 1000-1110 cm⁻¹ region (17).

Strong blue fluorescence in alcohol and acetone under ultraviolet illumination is exhibited by IIa, IIc and IIIc. Weak fluorescence is shown by IIb and IIIa, and none is displayed by IIIb.

EXPERIMENTAL (18)

Preparation of 7-Trifluoromethyl-*s*-triazolo[4,3-*a*]pyridines (II). General Method.

The appropriate 4-trifluoromethyl-2-hydrazinopyridine (I) (0.004 mole) and 5.0 g. of formic acid (97-100%) were refluxed for 2 hours. Upon cooling, the mixture was freed from excess formic acid by distillation at 35°/20 mm., neutralized with a saturated solution of sodium bicarbonate and dried at 35°/20 mm. Several recrystallizations, from ether, using carbon black, gave the desired product (19).

Preparation of 7-Trifluoromethyltetrazolo[1,5-*a*]pyridines (III). General Method.

The 4-trifluoromethyl-2-hydrazinopyridine (I) (0.004 mole) was dissolved in a solution of 5 ml. of 38% hydrochloric acid and 3 ml. of water (20). To the stirred mixture, cooled by an ice-water bath, was added a solution of 1.2 g. sodium nitrite and 3.5 ml.

TABLE I

7-Trifluoromethyl-*s*-triazolo[4,3-*a*]pyridines (II) and 7-Trifluoromethyltetrazolo[1,5-*a*]pyridines (III)

Compound	Recrystallization	M.p. (°C)	Yield %	Formula	Analysis			
					Calcd.		Found	
IIa	white needles from ether	117.0-118.7	89	C ₁₃ H ₈ F ₃ N ₃	C,	59.32	C,	59.54
					H,	3.06	H,	2.83
					N,	15.96	N,	15.80
IIb	white needles from ether	135.5-136.9	87	C ₈ H ₆ F ₃ N ₃	C,	47.77	C,	47.94
					H,	3.01	H,	2.82
					N,	20.89	N,	20.90
IIc	pale-yellow powder from ether	111.3-112.7	92	C ₁₁ H ₆ F ₃ N ₃ S	C,	49.07	C,	49.29
					H,	2.25	H,	2.25
					N,	15.61	N,	15.41
IIIa	white needles from pet. ether (a)	97.8-99.0	94	C ₁₂ H ₇ F ₃ N ₄	C,	54.55	C,	54.20
					H,	2.67	H,	2.46
					N,	21.21	N,	20.77
IIIb	white needles from pet. ether (a)	108.7-109.9	81	C ₇ H ₅ F ₃ N ₄	C,	41.59	C,	41.42
					H,	2.49	H,	2.18
					N,	27.72	N,	27.84
IIIc	pale-yellow needles from methanol-water	121.8-122.7 (b)	85	C ₁₀ H ₅ F ₃ N ₄ S	C,	44.45	C,	44.53
					H,	1.87	H,	1.79
					N,	20.73	N,	20.63

(a) Petroleum ether, b.p. range 30-75°. (b) Turned deep yellow on melting.

TABLE II

Spectral Data

Compound	IR Absorption Frequencies (cm ⁻¹) (a)			NMR Chemical Shifts, τ (ppm) (b)			
	CH	C=N	Aromatic	3H	6H	8H	5-R
IIa	3090	1651	1562, 1514, 1496, 1430	1.10	3.09	1.93	2.40 (c)
IIb	3170, 3052	1660	1601, 1561, 1460, 1420	1.17	3.19	2.02	7.25 (d)
IIc	3045	1644	1545, 1507, 1448 (e), 1430	0.78	2.95	1.92	2.34, 2.42, 2.67-2.77 (f)
IIIa	3050	1651	1561, 1518, 1498, 1418				
IIIb	3053	1653	1563, 1507, 1411				
IIIc	3062	1639	1549, 1525, 1496, 1428				

(a) Nujol mull. (b) Sample concentration in deuteriochloroform is 20 mg. to 0.5 ml. solution. (c) R = C₆H₅. (d) R = CH₃. (e) Shoulder. (f) R = 2-C₄H₃S.

water over a period of 15 minutes. Stirring was continued for 1 hour at 0° followed by an additional hour at room temperature. The contents of the reaction flask were transferred with a minimum amount of acetone and neutralized with a saturated solution of sodium bicarbonate. Evaporation of acetone with a stream of clean air resulted in the precipitation of the crude product (21). Products were recrystallized from appropriate solvents (Table I).

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- (18) All melting points are uncorrected; analyses by this laboratory and Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. Infrared spectra were obtained on a Perkin-Elmer Model 21 spectrophotometer. The NMR spectra were determined at 60 Mc. on a Model A-60 spectrometer (Varian Associates, Palo Alto, Calif.) at 37°. Chemical shifts were measured in cps from tetramethylsilane which was used as an internal standard.
- (19) In some cases, cooling with shaking was found necessary to initiate crystallization.
- (20) In the case of 5-(2-thienyl)-7-trifluoromethyltetrazolo-[1,5-a]pyridine (IIIc), the 2-hydrazinopyridine intermediate (Ic) is insoluble in the hydrochloric acid solution. Consequently, a solution of 2.2 g. sodium nitrite and 6.5 ml. water was added over a period of 30 minutes to a slurry of Ic (0.004 mole), 9 ml. 38% hydrochloric acid and 5.5 ml. water and stirred at 0° and room temperature for 1.5 and 2 hours, respectively.
- (21) Crude IIIc was washed with cold water prior to crystallization.

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