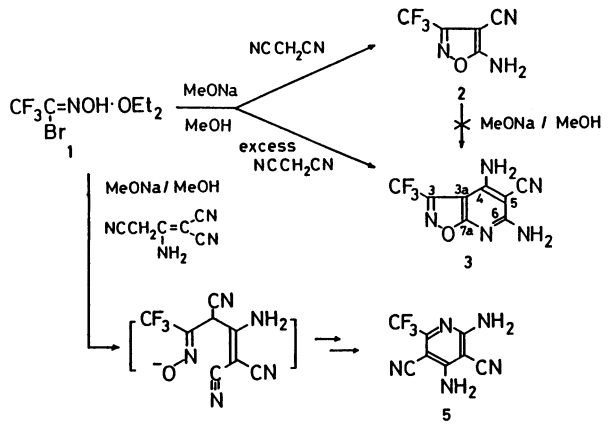
An Unusual Cyclization of Trifluoroacetohydroximoyl and -hydrazonoyl Bromides with Malononitrile[1)]

Kiyoshi TANAKA,* Takashi SUZUKI, Seiji MAENO, and Keiryo MITSUHASHI
Department of Industrial Chemistry, College of Technology, Seikei University, Musashino, Tokyo 180
(Received June 23, 1987)

Synopsis. Trifluoroacetohydroximoyl bromide etherate (**1**) reacted with an excess of malononitrile in the presence of sodium methoxide, giving a fused isoxazolopyridine **3**, participated by two molecules of malononitrile, along with the conventional isoxazole **2**. Similar concomitant formation of **7** and the fused pyrazolopyridines **8** was also recognized from the hydrazonoyl bromides **6** and their product ratio was found to depend on the reaction conditions, particularly on the concentration of malononitrile used.

It has been well explored that nitrile oxides and nitrilimines offer a wide variey of isoxazoles and pyrazoles, respectively, through the reaction with the doubly activated methylene compounds.[2-4)] So far, we have demonstrated the successful synthetic routes to 3-trifluoromethylisoxazoles and -pyrazoles by the reactions of trifluoroacetohydroximoyl bromide etherate (**1**) and *N*-aryltrifluoroacetohydrazonoyl bromides (**6**), respectively, with various active methylene compounds such as β-keto esters,[5)] β-diketones, and cyanoacetates.[6)] As an extension of this study, we now wish to describe an unusual cyclization of **1** and **6** with two molecules of malononitrile other than the conventional cyclization giving 5-amino-4-cyanoazole derivatives.



Scheme 1.

The bromide **1** reacted with an equimolar malononitrile in the presence of sodium methoxide to give 5-amino-4-cyano-3-trifluoromethylisoxazole (**2**) in 45% yield (Table 1). The orientation of the cycloaddition was deduced by the chemical shifts of its 4-and 5-carbons compared with those of 4-methoxycarbonyl analogue **2'**[6)] (Table 2). However, the treatment with an excess of malononitrile resulted in the formation of brown tarry matter, from which 4,6-diamino-5-cyano-3-trifluoromethylisoxazolo[5,4-*b*]pyridine (**3**) could be isolated in 18% yield. Thus obtained bicyclic product **3** was converted into the 6-chloro analogue, 4-amino-6-chloro-5-cyano-3-trifluoromethylisoxazolo[5,4-*b*]pyridine (**4**), by diazotization followed by chlorination with hydrochloric acid. The structure of **3** and **4** was supported by their elemental analysis and spectral data, particularly by ^{13}C NMR analysis (Table 2). The similar behavior producing the fused pyridine was also recognized in case of the hydrazonoyl bromides **6**. Thus, the reaction of **6a** with three times of malononitrile afforded a mixture of 5-amino-4-cyano-1-phenyl-3-trifluoromethylpyrazole (**7a**) (38%) and 4,6-diamino-

Table 1. Analytical and Spectral Data of Products

Compound	Formula	Calcd (Found)/% C	H	N	IR ν/cm^{-1}	^1H NMR δ
2	$C_5H_2F_3N_3O$	33.91	1.14	23.73	3340, 3250, 3200, 3160 (NH_2)	7.5 (br. s)
		(33.70)	(1.12)	(23.83)	2240 (C≡N), 1660 (C=N)	
3	$C_8H_4F_3N_5O$	39.52	1.66	28.80	3442, 3330, 3220 (NH_2)	6.7 (br. s, 2H)
		(39.70)	(1.57)	(28.71)	2199 (C≡N), 1638 (C=N)	7.1 (br. s, 2H)
4	$C_8H_2F_3N_4OCl$	36.59	0.77	21.34	3475, 3330, 3225 (NH_2)	3.2 (br. s)
		(36.77)	(0.68)	(21.38)	2230 (C≡N), 1655 (C=N)	
7a	$C_{11}H_7F_3N_4$	52.39	2.80	22.22	3458, 3368, 3312, 3212, 3190	5.65 (br. s, 2H)
		(52.05)	(2.74)	(22.56)	(NH_2), 2224 (C≡N), 1642 (C=N)	7.5 (s, 5H)[a)]
7b	$C_{11}H_6F_3N_5O_2$	44.46	2.03	23.56	3405, 3309, 3219, 3195 (NH_2)	7.5 (br. s, 2H)
		(44.69)	(1.99)	(23.76)	2205 (C≡N), 1640 (C=N)	8.15 (A_2X_2, 4H)
8a	$C_{14}H_9F_3N_6$	52.84	2.85	26.41	3505, 3461, 3323, 3231, 3209	6.6 (br. s, 2H), 6.85 (br. s, 2H)
		(52.90)	(2.76)	(26.70)	(NH_2), 2200 (C≡N), 1661, 1640 (C=N)	7.1—8.3 (m, 5H)
8b	$C_{14}H_8F_3N_7O_2$	46.29	2.22	26.99	3464, 3372, 3332, 3239 (NH_2)	6.8 (br. s, 2H), 7.1 (br. s, 2H)
		(46.08)	(2.18)	(26.84)	2199 (C≡N), 1661 (C=N)	8.5 (A_2X_2, 4H)
10	$C_{14}H_7F_3N_5OCl$	49.80	2.09	20.74	3480, 3325, 3220 (NH_2)	3.3 (br. s, 2H)
		(50.29)	(2.07)	(20.27)	2230 (C≡N), 1660 (C=N)	7.4—8.0 (m, 5H)

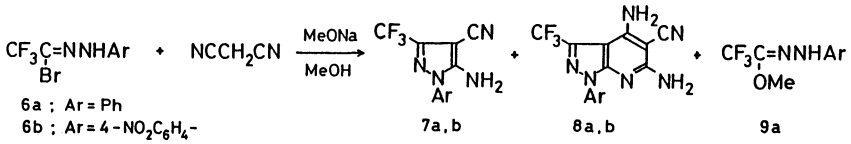
a) Measured in deuteriochloroform.

Table 2. ^{13}C NMR Data of Products

Isoxazole and pyrazole Compound	^{13}C chemical shifts (coupling constants with fluorine)							
	3-C	4-C	5-C	CF_3	C≡N	C=O	CH_3	Ar
2	152.8	61.3	172.6	117.3	108.9			
	(37.2)			(271.9)				
2'	151.9	82.5	172.6	118.5		160.9	50.7	
	(37.2)			(271.9)				
7a	142.7	74.0	151.2	119.7	111.4			135.9, 130.2
	(39.1)			(270.9)				129.9, 124.6[a]
7a'	141.0	92.5	151.0	120.4		163.6	51.4	136.4, 129.9
	(38.2)			(270.0)				129.2, 124.4[a]
7b	141.0	70.5	151.7	118.1	109.9			145.0, 140.0
	(38.1)			(270.0)				123.4, 123.2

Fused isoxazolo- and pyrazolopyridine Compound	^{13}C chemical shifts (coupling constants with fluorine)								
	3-C	3a-C	4-C	5-C	6-C	7a-C	CF_3	C≡N	Ar
3	146.3	70.2	151.1	86.0	161.4	172.5	118.0	113.7	
	(39.1)						(270.9)		
4	147.6	89.3	151.8	93.7	156.1	170.4	118.1	112.3	
	(39.1)						(271.9)		
8a	131.9	69.9	150.4	93.7	159.4	151.7	124.7	114.6	136.8, 127.2
	(38.1)		or 151.7			or 150.4	(269.0)		125.3, 120.7
10	132.2	85.4	150.7	98.5	152.1	148.8	119.2	112.8	135.8, 127.7
	(39.1)		or 148.8			or 150.7	(270.9)		126.6, 121.1

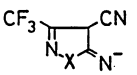
a) Measured in deuteriochloroform.



Scheme 2.

5-cyano-1-phenyl-3-trifluoromethylpyrazolo[5,4-*b*]-pyridine (**8a**) (3%) along with 20% of methyl *N*-phenyltrifluoroacetohydrazonate (**9a**).[7] The structure of **7a** was confirmed by a comparison of its ^{13}C NMR spectra with those of 4-methoxycarbonyl analogue **7a'**[6] (Table 2). The pyrazolopyridine **8a** was similarly converted into 4-amino-6-chloro-5-cyano-1-phenyl-3-trifluoromethylpyrazolo[5,4-*b*]pyridine (**10**). *N*-(4-Nitrophenyl)hydrazonoyl bromide **6b** also afforded a mixture of **7b** and **8b** in 64 and 7% yields, respectively, with no appreciable formation of the corresponding hydrazonate **9b**. It should be noted that the product ratio of **8a** increased remarkably with increase in malononitrile used.

The formation of the fused pyridines **3** and **8** is characteristic of the trifluoromethylated bromides **1** and **6** and three plausible reaction paths could be considered. These paths involve 1) the process where the initially formed **2** and **7** cyclized subsequently with another molecule of malononitrile, 2) the reaction of **1** and **6** with dimeric malononitrile, formed under the used reaction conditions, as reported in the literature on the formation of an isoxazolopyridine analogue from benzohydroximoyl chloride and dimeric malononitrile,[8] or 3) the cycloaddition of a certain reactive intermediate with another molecule of malononitrile. Out of these, the paths 1) and 2) can be both ruled out from the following results. First, the isolated **2** and **7** were subjected to the further reaction with malononitrile under similar conditions, the former giving a tarry matter with no appreciable amount of **3** and the latter being recovered almost. Second, the treatment of **6a** with the commercially available dimeric malononitrile did not give **8a**, resulting in substitution into **9a**, whereas that of **1** afforded an unexpected product, 2,4-diamino-3,5-dicyano-6-trifluoromethylpyridine (**5**) in 9% yield. Elemental analysis and MS spectra of **5** strongly support the absence of oxygen, and ^1H NMR and IR spectra features the characteristic pattern of diaminodicyanopyridine.[9] From the fact that the product ratio of **8a** depends on the reaction conditions, particularly on the concentration of malononitrile, the intervention of the reactive anions **3'** and **8'** seems to be reasonable, where the anions attack another molecule of malononitrile to give **3** and **8**, respectively.



3' ; X = O

8' ; X = NAr

Experimental

The IR spectra were recorded on a JASCO A-100 spectrometer. Samples were run as potassium bromide pellets. The ^1H and ^{13}C NMR spectra were measured with a JEOL

JNM-GX270 spectrometer using tetramethylsilane as an internal standard, the chemical shifts being given in δppm downfield. Samples were prepared by dissolving in deuteriochloroform-bis(deuteriomethyl) sulfoxide unless otherwise noted. The UV spectra were observed with a Hitachi 340 spectrometer. The MS spectra were obtained on a Finnigan 4023 GC-MS DS spectrometer. The bromides **1** and **6** were prepared by the methods reported in our previous paper.[6]

Reaction of 1 with Malononitrile. (A) A solution of **1** (3.65 g, 13.7 mmol) in 20 cm^3 of methanol was rapidly added dropwise to a solution of malononitrile (0.91 g, 13.8 mmol) and sodium methoxide (0.75 g, 13.9 mmol) in 25 cm^3 of methanol. After stirring at room temperature for 2 h, the solvent was removed to leave a residue which was extracted with diethyl ether. The extracts were washed with water and brine, dried over magnesium sulfate, and evaporated. The resulting residue was chromatographed on silica gel with chloroform to give 1.10 g (45%) of the isoxazole **2**, mp 149—150 °C (recrystallized from hexane-chloroform).

(B) Three times of malononitrile was reacted on a similar procedure to the above and the solvent was removed. The resulting mixture was washed with chloroform and extracted with acetone. The extracts were evaporated and the residual solid was sublimed, giving 0.60 g (18%) of **3** which was further purified by recrystallization from chloroform-acetone (sublimed at around 200 °C).

Reaction of 6a with Malononitrile. (A) To a solution of malononitrile (0.89 g, 13.5 mmol) and sodium methoxide (0.73 g, 13.5 mmol) in 20 cm^3 of methanol was added a solution of **6a** (1.20 g, 4.5 mmol) in 10 cm^3 of methanol. After the mixture was refluxed for 2 h, the solvent was removed to leave a residue which was extracted with diethyl ether. The extracts were dried over magnesium sulfate and evaporated under reduced pressure. To the residue was added excess hexane and the deposited solid was collected on a filter to give 0.05 g (3%) of **8a** which was recrystallized from acetone-methanol, mp 249.5—250.5 °C. On the other hand, hexane-extracts were evaporated and the resulting mixture was chromatographed (silica gel, hexane-chloroform, 4:1) to give 0.43 g (38%) of **7a**, which was further purified by recrystallization from hexane-chloroform, mp 115—116 °C, along with 0.20 g (20%) of oily **9a**. The spectral data of **9a** are consistent with those of our authentic sample.[7]

(B) A solution of **6a** (4.80 g, 18.0 mmol) in 20 cm^3 of methanol was added to a solution of malononitrile (3.56 g, 53.9 mmol) and sodium methoxide (2.92 g, 54.1 mmol) in 40 cm^3 of methanol and the mixture was heated under reflux for 2 h. Usual work-up yielded 1.01 g (22%) of **7a** and 2.27 g (40%) of **8a**.

Reaction of 6b with Malononitrile. A mixture of malononitrile (0.76 g, 11.5 mmol), sodium methoxide (0.62 g, 11.5 mmol), and **6b** (1.20 g, 3.8 mmol) in 30 cm^3 of methanol was stirred at room temperature for 15 h. The formed solid was collected on a filter, washed with water, and dried at the pump to give 0.10 g (7%) of **8b** which was recrystallized from chloroform-ethyl acetate, mp 309 °C (decomp). On the other hand, the filtrate was concentrated and chromatographed (silica gel, hexane-ethyl acetate, 1:1) to give 0.72 g (64%) of **7b** which was further purified by recrystallization from chloroform-ethyl acetate, mp 213—214 °C.

Chlorination of 3 into 4. Isoxazolopyridine **3** (0.40 g, 1.6 mmol) was dissolved in 50 cm^3 of 6 mol dm^{-3} hydrochloric acid under reflux. To this solution was added dropwise a solution of 0.40 g of sodium nitrite in 5 cm^3 of water at the same temperature. The mixture was refluxed for 2 h and cooled overnight in a refrigerator. The deposited solid was collected on a filter and passed through a short column (silica gel, hexane-ethyl acetate, 3:1) to give 0.09 g (21%) of **4**, which was recrystallized from hexane-diethyl ether, mp 165—166 °C.

Chlorination of 8a into 10. In a similar manner to the above, diazotization of 0.25 g of **8a** was carried out at the same temperature for 10 min, giving 0.13 g (49%) of **10**, mp 221—222 °C (recrystallized from hexane-ethanol).

Reaction of 1 with Dimeric Malononitrile. A mixture of 2.40 g (18.2 mmol) of dimeric malononitrile and 1.00 g (18.5 mmol) of sodium methoxide in 30 cm^3 of methanol was stirred for 40 min. And to this mixture was added dropwise a solution of 4.00 g (15.0 mmol) of **1** in 10 cm^3 of methanol over a period of 30 min. After stirring at room temperature for 25 h, the solvent was removed to leave a residue which was extracted with acetone and evaporated under reduced pressure. The resulting mixture was chromatographed (silica gel, hexane-ethyl acetate, 4:1) to give 0.32 g (9%) of **5** which was further purified by recrystallization from hexane-ethanol, mp 290—291.5 °C (decomp), IR 3460, 3330, 3230, 3160 (NH_2), 2210 (C≡N), 1630 cm^{-1} (C=N, C=C), ^1H NMR δ=7.1 (br.s, 2H), 7.4 (br.s, 2H), ^{13}C NMR δ=159.6, 157.3, 150.8 (J_{CCF}=33.3 Hz), 118.5 (J_{CF}=277.8 Hz), 112.4, 111.4, 78.5, 72.2, MS (CI, *m/z*) 228 $(M+H)^+$, 208 $(M+H-HF)^+$, UV λ_{max}^{EtOH} (ε) 238 (4.143×10⁴), 324 (5.516×10³), 328 (5.600×10³).

Found: C, 42.19; H, 1.49; N, 30.64%. Calcd for $C_8H_4F_3N_5$: C, 42.30; H, 1.77; N, 30.83%.

References

1) Part XIII in "Applications of the fluorinated 1,3-dipolar compounds as the building blocks of the heterocycles with fluorine groups." Part XII: K. Tanaka, M. Ohsuga, Y. Sugimoto, Y. Okafuji, and K. Mitsuhashi, J. Fluorine Chem., in press.

2) S. A. Lang, Jr. and Y. -i Lin, "Isoxazoles and their Benzo Derivatives," in "Comprehensive Heterocyclic Chemistry," ed by A. Katritzky and C. W. Rees, Pergamon Press, Oxford (1984); A. S. Shawali and C. Párkányi, *J. Heterocyclic Chem.*, **17**, 833 (1980).

3) C. Grundmann and S. K. Datta, *J. Org. Chem.*, **34**, 2016 (1969).

4) A. O. Abdehamid, C. Párkányi, A. S. Shawali, and M. A. Abdalla, *J. Heterocyclic Chem.*, **21**, 1049 (1984).

5) K. Tanaka, M. Kishida, S. Maeno, and K. Mitsuhashi, *Bull. Chem. Soc. Jpn.*, **59**, 2631 (1986).

6) K. Tanaka, T. Suzuki, S. Maeno, and K. Mitsuhashi, *J. Heterocyclic Chem.*, **23**, 1535 (1986).

7) For the formation of **9a** in the reaction of **6a** with sodium methoxide in methanol, see K. Tanaka, S. Maeno, and K. Mitsuhashi, *Bull. Chem. Soc. Jpn.*, **58**, 1841 (1985).

8) H. Junek, B. Thierrichter, and G. Lukas, *Chem. Ber.*, **113**, 1195 (1980).

9) H. Junek, M. Mittelbach, and B. Thierrichter, *Monatsh. Chem.*, **110**, 1279 (1979); A. Sakurai and H. Midorikawa, *Bull. Chem. Soc. Jpn.*, **41**, 430 (1968).