Reaction of Hydroxylamine with 5-Aminooxazoles. A New Route to Isoxazoles.

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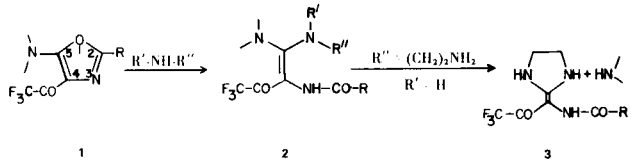
The nucleophilic attack of hydroxylamine at the 5 position of 2-aryl-4-trifluoroacetyl-5-aminooxazoles leads to a mixture of stereoisomeric isoxazolines. Dehydration of these isomeric isoxazolines in the presence of trifluoroacetic anhydride gives 3-amino-4-acylamino-5-trifluoromethylisoxazoles. The structures and spectroscopic data of these compounds are discussed.

J. Heterocyclic Chem., 13, 825 (1976).

We have previously reported the synthesis of 2-aryl-4-trifluoroacetyl-5-aminooxazoles (**1**) and their reactions with various amines (2,3). Thus, primary and secondary amines gave triaminoethylenes (**2**) while ethylenediamine afforded 2-methylene imidazolidine derivatives (**3**) (Scheme I). Formation of these compounds can be explained by a nucleophilic attack of the amine at the 5 position of **1** followed by ring opening (C_5-O bond breaking). In the case of ethylenediamine, subsequent intramolecular transamination reaction led to **3**.

Scheme I



1 2 3

We now wish to report the reaction of 5-aminooxazoles (**1**) with hydroxylamine.

Results and Discussion.

When 5-aminooxazole (**1a**) was reacted with hydroxylamine in boiling ethanol, a product $C_{13}H_{14}F_3N_3O_3$ was obtained in almost quantitative yield. The empirical formula, deduced from the elemental analysis suggested that one mole of **1a** had reacted with one mole of hydroxylamine. This result excluded the formation of an oxime arising from the condensation of hydroxylamine with the trifluoromethylketone.

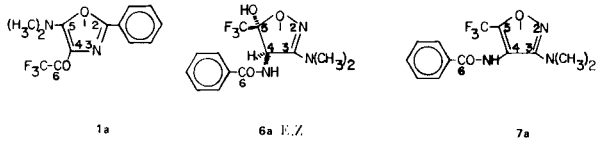
Thus, it seemed likely that the reaction had proceeded by a nucleophilic attack at the 5-position of the oxazole ring as already shown for amines (3); acyclic or cyclic structures **4a**, **5a** and **6a** were therefore possible (see Scheme II).

The infrared spectrum revealed major peaks at 3360 and 1645 cm^{-1} indicating the presence of an amide function, a 3200 cm^{-1} broad band which is characteristic of an associated hydroxyl group and a strong absorption at 1620 cm^{-1} which could correspond to the conjugated trifluoromethylketone of **4a** already reported for compounds **2** (3) or to the C, N double bond of **5a** and **6a**. However, structure **5a** was ruled out since no absorption occurred near 1780 cm^{-1} as expected for an unconjugated trifluoromethylketone (4).

The ^1H nmr spectrum recorded in DMSO excluded definitively the acyclic structure **4a** and showed the presence of two stereoisomeric compounds of structure **6a** E and Z (Scheme II). Thus, the hydroxy protons appeared as two exchangeable singlets at 8.13 and 8.17 ppm and the two different CH-NH groups at 5.75 and 9.32 ppm (^3J = 9 Hz) and 5.89 and 8.95 ppm (^3J = 10 Hz) respectively. The ratio in DMSO solution which was about 2:3 immediately after dissolution and became 1:3 after 12 hours and 1:5 after 24 hours, indicated that the two isomers interconverted in solution probably *via* **5a**. The methyl and aromatic protons appeared, respectively, as a unique singlet at 2.77 ppm and two multiplets between 7.47 and 8.08 ppm.

Table I

^{13}C Chemical Shifts of **1a**, **6a** (E + Z) and **7a**



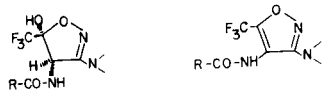
1a 6a E,Z 7a

Carbons	δ (ppm) (a) **1a**	**6a** (E + Z)	**7a**
2	149.5	----	----
3	----	160.3 (b) 159.9	163.4
4	111.2	61.5; $^{1}J_{CH}$ = 150 Hz (b) 55.5; $^{1}J_{CH}$ = 145 Hz	110.1; $^{3}J_{CF}$ = 2 Hz
5	162.5	100.6; $^{2}J_{CF}$ = 33 Hz	153.4; $^{2}J_{CF}$ = 39.5 Hz
6	170.7; $^{2}J_{CF}$ = 33 Hz	166.0 (b) 165.8	168.1

(a) All compounds show methyl carbons near 40 ppm, aromatic carbons between 126 and 133 ppm and trifluoromethylcarbons toward 115 ppm. (b) These peaks belong to the predominant isomer.

Table II

Synthesis and Physical Properties of Isoxazolines **6** and Isoxazoles **7**



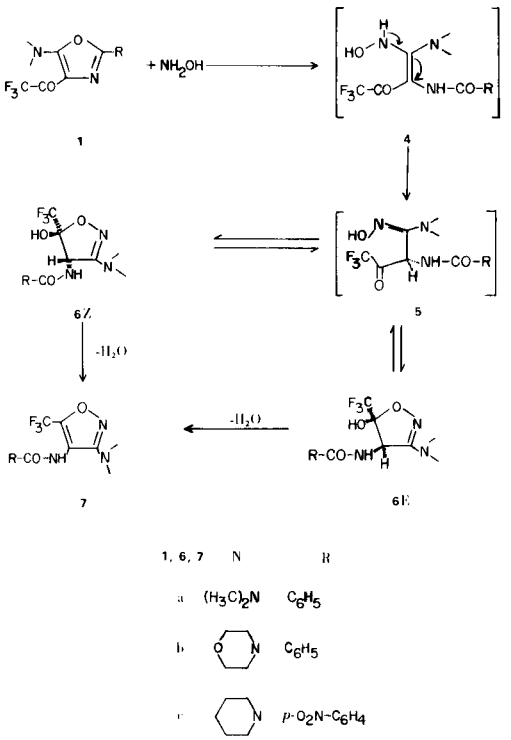
6 7

No.	M.p. °C	Yield (%)	Recrystallization solvents	Empirical Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
6a	207-208 dec.	92	water-ethanol	$C_{13}H_{14}F_3N_3O_3$	49.21	4.42	13.25	49.46	4.50	13.38
6b	216-217 dec.	95	96% ethanol	$C_{15}H_{16}F_3N_3O_4$	50.14	4.46	11.70	50.13	4.82	11.56
6c	233-235 dec.	85	96% ethanol	$C_{16}H_{17}F_3N_4O_5$	47.76	4.23	13.93	47.80	4.23	13.96
7a	132-133	85	chloroform-heptane	$C_{13}H_{12}F_3N_3O_2$	52.11	4.01	14.05	52.15	3.99	13.96
7b	186-187	78	chloroform	$C_{15}H_{14}F_3N_3O_3$	52.79	4.11	12.32	52.77	4.35	12.09
7c	187-188	83	chloroform	$C_{16}H_{15}F_3N_4O_4$	50.00	3.91	14.58	50.14	4.01	14.59

The ^{13}C nmr spectrum showed also the presence of two isomers and provided further support of the structure (Table I). ^{13}C nmr spectra of **1a** and **6a** (E + Z) were recorded in the Fourier mode at 25.2 MHz with and without proton noise decoupling. Complete assignment of the signals was achieved by consideration of chemical shifts and ^{13}C,H and ^{13}C,F coupling constants (5). The assignment of the signals due to the quaternary carbons

C_2, C_4 and C_5 of **1a** was made by comparison with results obtained previously (6) and by assuming C_5 conjugated with the electron withdrawing trifluoroacetyl group (deshielding effect) and C_2 with the lone pair of the exocyclic nitrogen (shielding effect). The electrophilic character of the 5 position also suggested that it should be somewhat deshielded. For compound **6a** (E + Z) the C_4 carbons were identified by the large ^1J CH coupling constants while C_3 and C_6 appeared near 160 and 165 ppm as expected from the reported structures. Comparison of **1a** and **6a** spectra revealed that the carbonyl carbon C_6 which

Scheme II

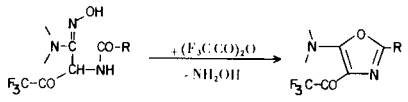


appeared at 170.7 ppm in **1a** has been shifted to 100.6 ppm in **6a** ($^3J_{C,F}$ = 33 Hz in both compounds) and this indicates the carbonyl function of **1a** to be deeply implicated in the rearrangement.

No attempt was made to assign the ^1H and ^{13}C nmr resonances of the corresponding isomer **6a** E or Z.

Oxazoles (**1b** and **c**) reacted in the same way as **1a** with hydroxylamine but the ^1H nmr spectra of isoxazolines (**6b** and **c**) showed the presence of only one isomer E or Z.

Isoxazolines (**6a-c**) were found to be stable to dehydration even in strong acid media such as concentrated sulfuric acid or trifluoroacetic acid. These results are in agreement with the stability of α-trifluoromethylalcohols reported in the literature several years ago (7). However, treatment of **6a-c** with a mixture of trifluoroacetic acid and its anhydride led to the expected isoxazoles (**7a-c**) readily identified from the ir and ^1H nmr spectra (see Experimental) and the ^{13}C nmr spectrum of **7a**. Assignment of ^{13}C resonances of **7a** was made as previously described for **1a** and **6a** and by comparison with the chemical shifts reported for **6a** (see Table I). On the other hand, 5-aminooxazoles (**1a-c**) were formed as by-products (about 10%) during the dehydration reactions and these compounds may result from the cyclization of the acyclic compounds **5a-c**, present to a small extent in the reaction mixture, as already shown for α-acylaminoamides (2b). However, the mechanisms of the dehydration and cyclization reactions are not well established but one may expect the formation of trifluoroacetylated intermediates, to be involved in both reactions.



From these results, 5-aminooxazoles (**1**) appear as very useful reagents for the synthesis of 3,4-diamino-5-trifluoromethylisoxazole derivatives and an extension of this method to the reaction of **1** with other nitrogen bases is under investigation.

Acknowledgment.

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EXPERIMENTAL

Melting points were taken in capillaries using a Büchi apparatus. Spectral characteristics were determined on the following instrumentation: ir, Perkin-Elmer Model 21 spectrophotometer; ^1H nmr, Varian T-60 and Varian A-60-A spectrometers using TMS as internal standard; ^{13}C nmr, Varian XL-100/15 Fourier Transform spectrometer operating at 25.15 MHz with solution *ca.* 200 mg. of compound per ml. of solvent and using TMS as the internal standard.

Elemental analysis were performed by the department of Microanalysis, Centre National de la Recherche Scientifique, Strasbourg, France.

2-Aryl-4-trifluoroacetyl-5-aminooxazoles (**1**) were prepared as previously described (2a).

3-Amino-4-acylamino-5-trifluoromethyl-5-hydroxy-Δ^2-isoxazolines (**6** E and Z).

Hydroxylamine, hydrochloride (2.8 g., 40 mmoles), 10 ml. of absolute ethanol and 4 g. (40 mmoles) of dry triethylamine were stirred at room temperature for 10 minutes. Triethylamine hydrochloride which precipitated, was filtered off and the filtrate added to 10 mmoles of 5-aminooxazole (**1**) in 50 ml. of ethanol. The mixture was heated under reflux until **1** had disappeared (1-2 hours). The solvent was evaporated and the oil treated with cold water until a solid product was obtained. It was crystallized from the appropriate solvent (see Table II).

3-Dimethylamino-4-benzoylamino-5-trifluoromethyl-5-hydroxy-Δ^2-isoxazoline (**6a** E, Z).

This compound had ir (potassium bromide): 3360, 3200, 1645 (NH-CO; OH), 1620 (C=N), 1195-1172 (C-F) cm^{-1}; nmr (DMSO-d_6): 2.77 (s, $N(CH_3)_2$), 5.75, 5.89 (d, CH), 7.47-7.61, 7.84-8.08 (m, aromatic), 8.13, 8.17 (s, OH), 8.95, 9.32 (d, NH) ppm.

3-Morpholino-4-benzoylamino-5-trifluoromethyl-5-hydroxy-Δ^2-isoxazoline (**6b** E or Z).

This compound had ir (potassium bromide): 3320, 3160, 1640 (NH-CO; OH), 1604 (C=N), 1190-1160 (C-F) cm^{-1}; nmr (DMSO-d_6): 3.39 (m, $NC_4H_{10}O$), 5.87 (d, $^3J_{CH-NH}$ = 9 Hz, CH), 7.49-7.59, 7.88-8.05 (m, aromatic), 8.2 (s, OH), 9.7 (d, NH) ppm.

3-Piperidino-4-*p*-nitrobenzoylamino-5-trifluoromethyl-5-hydroxy-Δ^2-isoxazoline (**6c** E or Z).

This compound had ir (potassium bromide): 3470, 3150, 1680 (NH-CO; OH), 1612 (C=N), 1540, 1350 (NO_2), 1167 (C-F) cm^{-1}; nmr (DMSO-d_6): 1.5 (m, $(CH_2)_3$), 3.1 (m, $(CH_2)_2N$), 5.78 (d, $^3J_{CH-NH}$ = 9.5 Hz, CH), 8.19 (s, OH), 8.23 (q, aromatic), 9.35 (d, NH) ppm.

3-Amino-4-acylamino-5-trifluoromethylisoxazoles (**7**).

A mixture of isoxazolines **6** (5 mmoles), dry chloroform (20 ml.), trifluoroacetic anhydride (4.2 g., 20 mmoles) and trifluoroacetic acid (0.5 ml.) was stirred at room temperature until **6** had disappeared (about 15 minutes). The solvent was removed *in vacuo* and the solid residue washed with cold water and filtered. Tlc (silica) showed the presence of **1**. ^1H nmr spectra of the crude reaction products indicated the fraction of 5-aminooxazoles (**1**) to be about 10%. Crystallization from the appropriate solvent yielded **7** (see Table II).

3-Dimethyl-4-benzoylamino-5-trifluoromethylisoxazole (**7a**).

This compound had ir (potassium bromide): 3230 (NH), 1667, 1600 (C=N, C=C), 1650 (CO), 1180, 1140 (C-F) cm^{-1}; nmr (deuteriochloroform): 2.90 (s, $N(CH_3)_2$), 7.40-7.57, 7.74-7.91 (m, aromatic), 7.8 (m, NH) ppm.

3-Morpholino-4-benzoylamino-5-trifluoromethylisoxazole (**7b**).

This compound had ir (potassium bromide): 3250 (NH), 1670, 1600 (C=N, C=C), 1650 (CO), 1185, 1175, 1140 (C-F) cm^{-1}; nmr (acetone-d_6): 3.43 (m, $NC_4H_{10}O$), 7.43-7.56, 7.86-8.04 (m, aromatic), 9.3 (m, NH) ppm.

3-Piperidino-4-*p*-nitrobenzoylamino-5-trifluoromethylisoxazole (**7c**).

This compound had ir (potassium bromide): 3280 (NH), 1680, 1605 (C=N, C=C), 1655 (CO), 1530, 1340 (NO_2), 1178, 1160 (C-F) cm^{-1}; nmr (acetone-d_6): 1.6 (m, $(CH_2)_3$), 3.3 (m, $(CH_2)_2N$), 8.23 (q, aromatic), 9.4 (m, NH) ppm.

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