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Received July 25, 1997

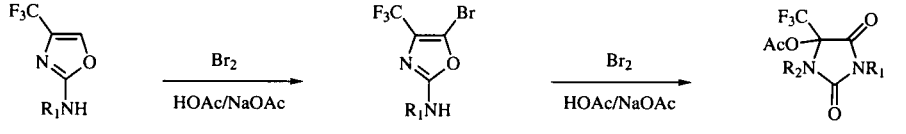
Reaction of 2-amino-4-trifluoromethyloxazoles with excess bromine in acetic acid/sodium acetate gives 5-acetoxyhydantoins. The 5-bromooxazoles are intermediates in the reaction.

J. Heterocyclic Chem., **36**, 283 (1999).

Halogenation of 2-aminooxazoles normally yields the 5-halooxazole derivatives [1]. We find that although bromination of 2-amino-4-trifluoromethyloxazoles in acetic acid/sodium acetate proceeds initially to furnish 5-bromooxazoles, the products were further transformed under the reaction conditions to give 5-acetoxyhydantoins. The rearrangement took place as a major side reaction during 5-halogenation of the oxazoles when one equivalent of bromine was used and proceeded in high yield with two equivalents of bromine.

Attempts to examine the scope of the rearrangement were thwarted by difficulties encountered in the synthesis of the starting aminooxazoles. When higher homologs (R_1 = Et, *i*-Pr, *i*-Bu) were prepared using the method described for **2b** (3-bromo-1,1,1-trifluoroacetone/*tert*-butyl alcohol/reflux), complicated mixtures were obtained. In addition to the desired 5-H oxazoles and uncharacterized materials, the reaction mixtures contained the corresponding 5-bromooxazoles as indicated by gc-ms.

Scheme 1



1
a: R_1 = H
b: R_1 = CH_3

2
a: R_1 = H
b: R_1 = CH_3

3
a: R_1 = H, R_2 = Ac
b: R_1 = CH_3, R_2 = H

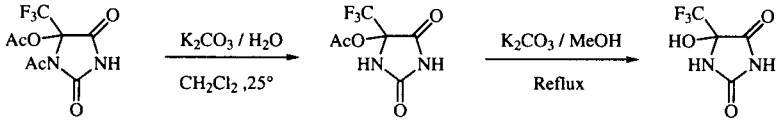
Aminooxazole **1a** [2] gave a hydantoin containing two acetyl groups. The position of the acetyl groups was determined by single crystal X-ray diffraction [3] to be as shown in **3a.** Although the *N*-methyl analog **1b** gave rise to the 1-unsubstituted hydantoin **3b**, it was not clear whether **3b** was the initial product of the rearrangement or whether it was formed from a labile 1-acyl derivative during isolation. Similarly the diacetyl derivative **3a** may be the product of a secondary acylation in the reaction medium. Hydantoin **3a** was readily hydrolysed to the 1*H*-analog **4** with aqueous potassium carbonate under mild two phase conditions. Conversion of **4** to 5-hydroxy-5-trifluoromethylhydantoin **5** [4] was readily accomplished with potassium carbonate in methanol at reflux.

EXPERIMENTAL

General.

Melting points were taken in open capillaries in a Thomas UNI-Melt apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Varian T-60A, Varian EM-360L, Bruker AM360 or Varian XL-400 spectrometer. Thin layer chromatography was performed on E. Merck 60 F-254 TLC plates, 0.25 mm with visualization by ultraviolet light and iodine staining. E. Merck Silica Gel 60, 0.040-0.063 mm, was used for preliminary purifications and for flash chromatography. Gas chromatography was performed on a Hewlett Packard model 5790A chromatograph equipped with a flame ionization detector and a 2 mm x 6 ft. glass column containing 10% OV-101 on

Scheme 2



3a **4** **5**

WHP (80/100) and was typically used to monitor the progress of reactions. Analysis (gc-ms) was on a Hewlett Packard system 5790A chromatograph and Mass Selective Detector employing an HP Ultra 1 column (12 meter x 0.2 mm) with a 0.33 micron film thickness. Kugelrohr distillation was conducted with equipment obtained form Aldrich Chemical Co. and boiling ranges represent the temperature of the air bath. Combustion analyses were performed by Midwest Microlab, Indianapolis, Indiana.

2-Methylamino-4-(trifluoromethyl)oxazole (**1b**).

To 276 g (1.45 moles) of 1-bromo-3,3,3-trifluoropropanone was added 300 ml of *tert*-butyl alcohol and 265 g (3.58 moles) of *N*-methylurea. The suspension was heated to reflux. The reaction was somewhat exothermic and evolved a gas. After 18 hours the dark mixture was partially concentrated and highly crystalline aminooxazole sublimed from the melt, mp 81-83°. The residue was kugelrohr distilled (75°, 0.05 mm) to give a total of 110 g (46%) of white crystalline **1a**; ^{1}H nmr (60 MHz, deuteriochloroform): δ 3.0 (d, J = 5, 3H), 5.4-6.1 (1H, NH), 7.45 (q, J_{HF} = 2, 1H).

Anal. Calcd. for $C_5H_5N_2OF_3$: C, 36.15; H, 3.03; N, 16.86. Found: C, 36.03; H, 3.03; N, 17.02.

2-Amino-4-trifluoromethyl-5-bromooxazole (**2a**).

To 11.8 g (144 mmoles) of sodium acetate suspended in 100 ml of acetic acid at 25° was added 5.0 g (32.9 mmoles) of 2-amino-4-trifluoromethyloxazole **1a** [3]. The suspension was stirred at ambient and a solution of 5.0 g (31.3 mmoles) of bromine in 110 ml of acetic acid was added dropwise over about 5 hours. The mixture was stirred a total of 21 hours and was poured into 1500 ml of ether. The precipitated salts were removed by filtration and the filtrate was passed through a pad of silica gel. After concentration the residue was partitioned between ether and a *p*H 6.4 buffer solution. The organic phase was washed with 3 x 100 ml of *p*H 6.4 buffer and two 100 ml portions of saturated aqueous sodium chloride. The organic phase was dried (sodium sulfate), filtered through silica gel and concentrated to give 4.6 g of a light yellow solid. Recrystallization from cyclohexane gave 4.0 g (55%) of off-white crystals, mp 98-100.5°; ^{1}H nmr (60 MHz, deuteriochloroform): δ 5.2-6.4 (br s, 2H).

Anal. Calcd. for $C_4H_2N_2O_1F_3Br$: C, 20.80; H 0.87; N, 12.13. Found: C, 20.79; H, 0.88; N, 12.05.

2-Methylamino-4-trifluoromethyl-5-bromooxazole (**2b**) [5].

To 4.7 g (28.3 mmoles) of **1b** in 35 ml of acetonitrile was added 5.3 g (29.7 mmoles) of *N*-bromosuccinimide. The solution quickly became yellow and the reaction was somewhat exothermic. The temperature reached about 45° and the mixture was stirred at ambient for 18 hours. Analysis (tlc) showed a trace of remaining starting material and an additional 500 mg (32.5 mmoles total) of *N*-bromosuccinimide was added. After stirring 4 days the mixture was concentrated. The residue was triturated with ether and succinimide was removed by filtration. The filtrate was washed with two portions of saturated aqueous sodium chloride and was dried over magnesium sulfate. Concentration gave 6 g (87%) of **2b** [5] as yellow solid. An analytical sample was obtained by trituration of the crude product with petroleum ether (bp 30-60°), filtration of the mixture through a pad of silica gel, elution with hexane/ether (9:1), and concentration to give a white solid, mp 77-79°; ^{13}C nmr (90 MHz, deuteriochloroform): δ 29 (s, NMe), 111.5 (q, J_{CF} = 4 Hz, C5), 119 (q, J_{CF} = 267 Hz, CF_3), 129 (q, J_{CF} = 40 Hz, C4), 162.1 (s, C2).

Anal. Calcd. for $C_5H_4N_2F_3BrO$: C, 24.51; H, 1.65; N, 11.43. Found: C, 24.35; H, 1.51; N, 11.52.

1-Acetyl-5-acetoxy-5-(trifluoromethyl)imidazolidine-2,4-dione (**3a**).

To 27 g (329 mmoles) of sodium acetate suspended in 250 ml of acetic acid at 25° was added 10 g (65.8 mmoles) of 2-amino-4-trifluoromethyloxazole **1a**. The mixture was stirred and a solution of 21.1 g (131.6 mmoles) of bromine in 20 ml of acetic acid was added dropwise over 15 minutes. The mixture became homogeneous during the first half of the addition as the temperature rose to 38°. A solid precipitated from solution during the latter half of the addition. The mixture was stirred for 2.25 hours and excess bromine was destroyed by the addition of 6 ml of a saturated aqueous solution of sodium thiosulfate. The mixture was poured into 700 ml of ether and filtered. The filtrate was concentrated and the residue was partitioned between ether and water. The organic phase was washed with 2 x 100 ml of a *p*H 6.4 aqueous buffer solution, 2 x 100 ml of saturated aqueous sodium chloride, dried (sodium sulfate), filtered through silica gel, and concentrated to give 12 g of a yellow oil. Kugelrohr distillation (80-85°, 0.03 torr) removed a volatile impurity leaving 9 g of a semisolid residue. Preparative chromatography on silica gel (ethyl acetate/hexane, 1:9) gave 4.2 g of a white solid. Recrystallization from ethyl acetate/hexane gave 3.45 g (20%) of **3a** as white crystals, mp 110-110.5°; ^{1}H nmr (400 MHz, deuteriochloroform): δ 2.2 (s, 3H), 2.5 (s, 3H), 8.9 (br s, 1H); ^{13}C nmr (90 MHz, deuteriochloroform): δ 19.9 (s), 26.2 (s), 84.5 (q, J_{CF} = 36.1,C5), 120 (q, J_{CF} = 287.5, CF_3), 151.7 (s), 162.0 (s), 168.2 (s), 168.6 (s).

Anal. Calcd. for $C_8H_7F_3N_2O_5$: C, 35.83; H, 2.63; N, 10.45. Found: C, 35.61; H, 2.78; N, 10.28.

5-Acetoxy-5-(trifluoromethyl)imidazolidine-2,4-dione (**4**).

To a solution of 77.3 g of potassium carbonate in 250 ml of water at 25° was added a solution of 30.0 g of the diacetoxyhydantoin in 250 ml of dichloromethane. The mixture was stirred at room temperature for 1 hour, cooled to 0°, and slowly acidified (*p*H about 1) with concentrated hydrochloric acid and partitioned with 500 ml of ether. The organic phase was washed with saturated aqueous sodium chloride, dried (sodium sulfate), filtered through silica gel and concentrated to give 26 g of a light yellow oil. Crystallization from hexane gave 20.5 g of a white solid. Recrystallization from ethyl acetate/hexane gave 16.8 g (66%) of **4** as a white crystalline solid, mp 144-144.5°; ^{1}H nmr (400 MHz, deuteriodimethyl sulfoxide): δ 2.47 (s, 3H), 8.84 (br s, 1H), 12.45 (br s, 1H), ^{13}C nmr (100.6 MHz, deuteriodimethyl sulfoxide): δ 26.7 (s), 85.8 (q, J_{CF} = 34, C5), 121.7 (q, J_{CF} = 289, CF_3), 153.3 (s), 166.6 (s), 168.2 (s).

Anal.. Calcd. for $C_6H_5N_2F_3O_4$: C, 31.87; H, 2.23; N, 12.39. Found: C, 32.26; H, 2.23; N, 12.20.

5-Hydroxy-5-(trifluoromethyl)imidazolidine-2,4-dione (**5**).

To 3.0 g (13.3 mmoles) of **4** in 40 ml of methanol was added 2.75 g (19.9 mmoles) of anhydrous potassium carbonate. The mixture was heated at reflux for 2 hours 20 minutes and was concentrated. The residue was acidified (*p*H < 2) with concentrated hydrochloric acid and the solution was extracted with three portions of ether. The organic phases were combined and washed with saturated aqueous sodium chloride, dried (magnesium sulfate) and concentrated to give a white solid. Recrystallization from ethyl acetate/hexane gave 2.0 g (83%) of white crystalline **5**, mp 178-181° (lit [4] 180-181°).

3-Methyl-5-acetoxy-5-(trifluoromethyl)imidazolidine-2,4-dione (**3b**).

To 350 ml of glacial acetic acid was added 79 g (960 mmoles) of anhydrous sodium acetate. The temperature rose to 45°. When the temperature had fallen to 40°, 20 g (120 mmoles) of **1b** was added. To the resulting suspension was added dropwise 12.7 ml (247 mmoles) of bromine over about 30 minutes. The temperature remained at 40° during the first half of the addition then rose to 53° during the latter half. The bromine was rapidly consumed until the addition was more than 90% complete at which time the suspension became yellow. The mixture was stirred at 25° for 16 hours and the excess bromine was reduced with the addition of a small amount of aqueous sodium thiosulfate. The white suspension was poured into two liters of anhydrous ether and was filtered. The filtrate was concentrated and the residue was dissolved in ether and filtered through silica gel. The filtrate was washed with 10% aqueous citric acid, saturated aqueous sodium chloride, dried (magnesium sulfate), and concentrated to give 23.7 g of a solid residue. The mixture was dissolved in ether and filtered through silica gel to remove a trace of sodium acetate present in the crude product. The filtrate was concentrated and the residue recrystallized from ethyl acetate/hexane/ether to give 15.5 g (54%) of **3b** as a white crystalline solid in two crops, mp 91-93°; ^{1}H nmr (400 MHz, deuteriodimethyl sulfoxide): δ 2.19 (s, 3H); 2.94 (s, 3H); 10.26 (br, 1H); ^{13}C nmr (100.6 MHz, deuteriodimethyl sulfoxide): δ 20.7 (s), 25.3 (s), 82.9 (q, J_{CF} = 34 Hz), 121 (q, J_{CF} = 284 Hz), 156 (s), 165 (s), 169 (s).

Anal. Calcd. for $C_7H_7F_3N_2O_4$: C, 35.01; H, 2.94; N, 11.67. Found: C, 34.96; H, 2.90; N, 11.59.

REFERENCES AND NOTES

[1] B. K Pattanayak, D. N. Rout and G. N. Mahapatra, *Indian J. Chem.*, Sect. B, **16B**, 1030 (1978).

[2] George Crank and Michael J. Foulis, *J. Med. Chem.*, **14**, 1075 (1971).

[3] Although the preliminary X-ray crystal structure of **3a** unambiguously defined the relative positions of the acetyl groups, further refinement did not yield a structure which met typical criteria for publication. The authors are indebted to Michael R. Thompson for his efforts with this structure.

[4] El-Said M. Mustafa, Akio Takaoka and Nobuo Ishikawa, *Bull Soc. Chim. France,* 944 (1986).

[5] Bromooxazole **2b** was observed by tlc as an intermediate in the conversion **1b** to **3b** but was characterized following preparation *via* the *N*-bromosuccinimide method described in the experimental section.