Syntheses and Characterization of Some 2-Trihalogeno-Methyl-s-Triazolo [1,5-a]Pyridine

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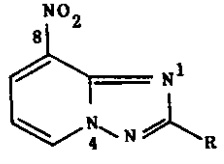
Summary: Some novel 2-trihalogenomethyl-8-nitro-s-triazolo[1,5-a]pyridines of potential interest as radiosensitizer have been prepared from 2-hydrazino-3-nitropyridine in condensation with trifluoroacetic anhydride, trichloroacetic and tribromoacetic acids respectively. These compounds are characterized by spectral techniques.

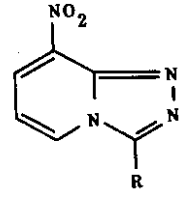
Results and Discussion

Literature survey revealed that no work has been reported on the preparation of 2-trihalogenomethyl-8-nitro-s-tirazolo[1,5-a]pyridine. However, the preparation of other derivatives such as methyl (**1**), phenyl (**2**) and benzyl (**3**) at the 2-position of 8-nitro -s-triazolo [1,5-a] have been described [1-3]. It was therefore, of interest to prepared 2-trihalogenomethyl-8-nitro-s-triazolo [1,5-a]pyridines since these compounds would be expected to show radiosensitizing properties [4] becuase of the presence of both nitro and trihalogenomethyl substituents.



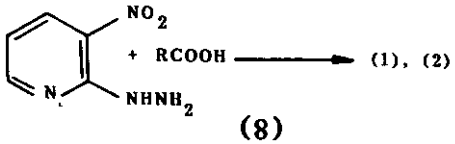
(1) R = CH_3 (5) R=CCl_3
(2) R=C_6H_5 (6) R=CBr_3
(3) R=$CH_2C_6H_5$ (7) R=H
(4) R=CF_3

We have successfully prepared 2-trifluoromethyl-8-nitro-s-triazolo [1,5-a]pyridine (**4**), 2-trichloromethyl-8-nitro-s-triazolo [1,5-a]pyridine (**5**) and 2-tribromomethyl-8-nitro-s-triazolo [1,5-a]pyridine (**6**) from the condensation reaction of 2-hydrazino-3-nitropyridine (**8**) with trifluoroacetic anhydride, trichloroacetic and tribromoacetic acids respectively.



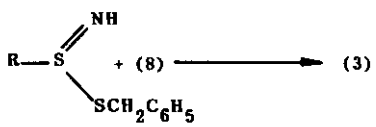
(9) R=H,CH_3,C_6H_5

The preparation of s-triazolo [1,5-a]pyridine can be achieved from the isomerization of s-triazolo [4,3-a]pyridine (**9**) in the presence of either acid or base or by heat. It was found that isomerization is greatly facilitated by electron-withdrawing nitro substituent in the pyridine ring and retarded by electron-donating amino substituent [5]. 2-Hydrazino-3-nitro-pyridine (**8**) was prepared from 2-chloro-3-nitropyridine according to the method of Potts et al. [5]. When (**8**) was treated with acetic or benzoic acid, 2-methyl-8-nitro-s-triazolo [1,5-a[pyridine (**1**) or 2-phenyl-8-nitro-s-triazolo [1,5-a]



(8)

pyridine (2) was formed respectively. However, the 2-benzyl derivative (3) was prepared from (8) and benzyl thioacetimidate in pyridine [3].

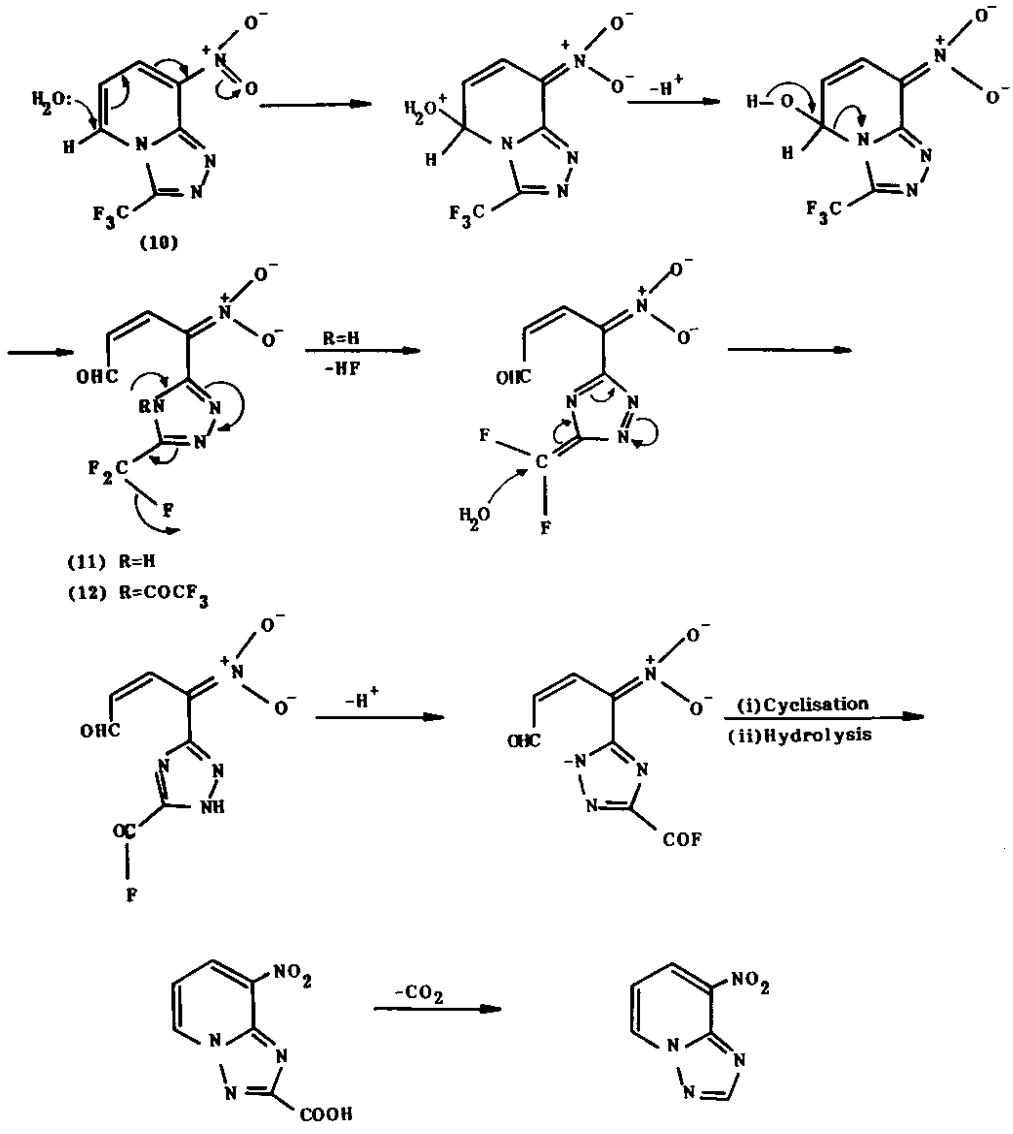


In an attempt to modify the reaction by replacement of formic, acetic or benzoic acid by trifluoroacetic acid, it was discovered that the expected 2-trifluoromethyl-8-nitro-s-triazolo [1,5-a]pyridine (4) was not obtained but a solid was isolated which was assigned the structure (7) on the basis of comparison of its melting point and infrared and proton magnetic resonance spectra with that of an authentic sample of (7) prepared from (8) and formic acid. The confirmation of the structure was further supported by the results of the elemental analysis and the mass spectrum. Generally trifluoromethyl substituents on a benzenoid nucleus are extremely stable to hydrolysis but some examples are known where basic hydrolysis of a trifluoromethyl group on a heteroaromatic nucleus occurs readily [6]. Hydrolytic reactivity has been reported for 2-trifluoromethylimidazole and some 4-trifluoromethylimidazoles. These examples and others have an acidic hydrogen atom in the molecule and the formation of the anion is an initiating step in the hydrolysis process [6]. This mechanism is not possible from the expected product (4). However, the first formed product in the reaction of an aliphatic acid with 2-hydrazino-3-nitropyridine is an s-triazolo [4,3-a]pyridine (10) (Figure 1) which then rearranges by fission of the six-membered ring to yield N-unsubstituted triazole intermediate (11). It is possible that it is at this stage, prior to rearrangment that hydrolysis (or solvolysis) of the trifluoromethyl group occurs. Presumably, decarboxylation occurs after rearrangement to the s-triazolo [1,5-a]pyridine and during the work-up procedure. The formation of the 2-trifluoromethyl derivative (4) when trifluoroacetic anhydride is used as a reactant and not when trifluoroacetic acid is employed may reflect the greater acylating power of the former. Thus, formation of the anion from the triazole intermediate may be prevented by N-trifluoroacetylation to give (12), through the trifluoroacetyl group would have to leave in the cyclization-rearrangement step. Surprisingly, the starting material (8) was recovered when the reaction mixture was not basified. This result was totally unexpected and no immediate explanation is presentable to account for this failure.

However, the preparation of (4) was achieved when trifluoroacetic acid was replaced by trifluoroacetic anhydride. The mixture was refluxed for 12 hours and extracted with ether to give a dark brown residual gum. Purification of the product was achieved by crystallization from ethanol after a brief treatment with charcoal. Characterization of the product was based on the results of elemental analysis, infrared, proton magnetic resonance and mass spectra. The proton magnetic resonance spectrum of the product showed two doublets at δ 8.83 and δ 8.52 due to the 5-H and 7-H proton and a triplet due to 6-H proton of the triazolopyridine occured at δ 7.42.

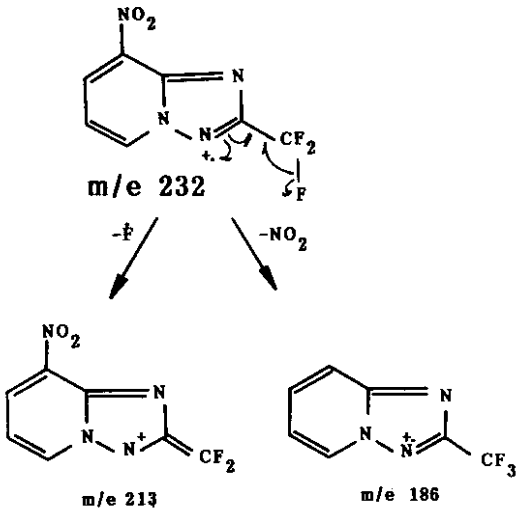
The mass spectroscopic data of the product is recorded as follows: m/e (relative abundance) 232 (80), 214 (15), 202 (34), 145(4), 107(6), 91

FIGURE - 1



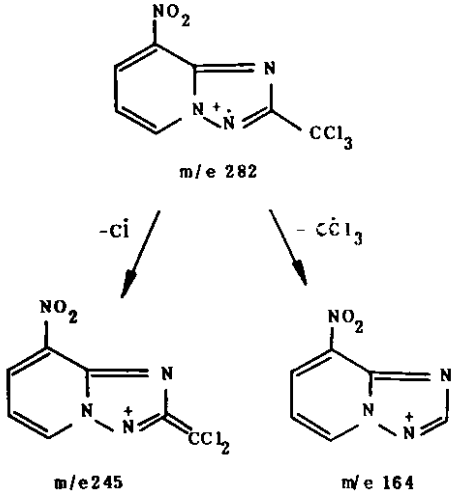
(100), 80(8), 69(25), 64(53), 63(33), 62(11), 53(13), 52(15), 40(13), 52 (15), 40(13), and 39(32). The mass spectrum of the product showed an intense molecular ion. The presence of metastable ions at 176 (calculated 175.87) and 149 (calculated 149.10) probably indicates the formation of the species m/e 213 and m/e 186 due to the loss of the F atom and NO_2 molecule from the molecular ion.

The preparation of 2-trichloromethyl -8-nitro-s-triazolo [1,5-a]pyridine (**5**) was accomplished in a similar way from the reaction of (**8**) and trichloroacetic acid. Extraction of the solution with ether gave an oil which latter yielded a solid. The structure of the product was characterized by elemental analysis, infrared, proton magnetic resonance and mass spectra. The two doublets due to 5-H and 7-H proton



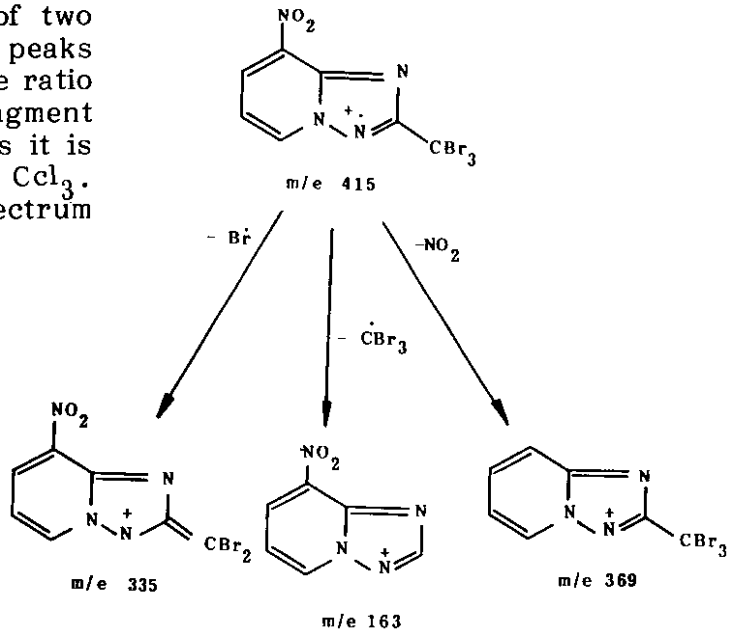
occured at δ 8.66 and δ 9.32 respectively. The triplet at δ 7.46 was assigned to the 6-H proton of (**5**).

The spectroscopic fragmentation of the product recorded as follows: m/e (relative abundance) 282(39), 249(33), 247(67), 245(100), 200(11), 164(44), 108(61), 91(17), 76(11), 75(17), 64 (22), 50(17), 39(22), 35(50). The most abundant fragment in the spectrum of the product showed at m/e 245 because of the presence of two chlorine atom is complimented by peaks at M+2(247) and M+4(249) in the ratio of M:M+2:M+4 of 3:2:1. The fragment at m/z 164 is not noteworthy as it is probably formed by the loss of CCl_3. A tentative rationale for the spectrum of (**5**) is shown below:



2-Tribromomethyl-8-nitro-s-tirazolo [1,5-a]pyridine(**6**) was similarly prepared from (**8**) and tribromoacetic acid in the presence of absolute ethanol. The solution was refluxed for 18 hours and gave after extraction with ether a residual gum which was then treated several times with petroleum-ether (b.p. 40-60°C) to give yellow solid. The confirmation of the structure was based on the results of elemental analysis, infrared, proton magnetic resonance spectra. Proton magnetic resonance spectrum showed two doublets at δ 9.15 and δ 8.55 due to the 5-H and 7-H protons and a triplet at δ 7.45 equivalent to one proton was assigned to the 6-H proton.

In addition to spectral evidence in support of the product, it was subjected to mass spectral analysis as follows: m/e (relative abundance) 415 (86), 369 (47), 335 (33), 310(19), 290(61), 252(44), 206(72), 163(70), 91(80), 90(8), 76(12), 63(54), 59(15), 54(16), 45(10), 39(43). The rationale can only be regarded as tentative.



Experimental

The proton magnetic resonance (PMR) spectra were obtained on Varian

T-60 instrument operating at 60MHz (tetramethylsilane as internal reference). The melting points were determined on Gallenkamp melting point apparatus and are uncorrected. Infrared spectra (IR) in KBr were recorded on Unicam SP-200 spectrometer.

2-Hydrazino-3-nitropyridine (**8**) was prepared from 2-chloro-3-nitropyridine according to the method of Potts et al. [5].

2-Trifluoromethyl-8-nitro-s-triazolo [1,5-a]pyridine (4)

In a two necked flask fitted with a double surface condenser (protected by a guard-tube containing anhydrous calcium chloride) and a dropping funnel, was placed 2-hydrazino-3-nitropyridine (1.54 gm, 0.01 mole). Trifluoroacetic anhydride (25 ml) was added dropwise over a period of 30 minutes. The mixture was then gently refluxed for 12 hours. It was cooled and poured into water (50 ml). The mixture was extracted with ether (3x50ml) and the ether layer was dried ($MgSO_4$). Evaporation of ether gave a residual gum which was then treated several times with petroleum ether (b.p. 40-60°C) to give a brown solid. Crystallization from ethanol (charcoal) gave yellow crystals (0.7 gm, 35%) m.p. 155-56°C (decomp.), (Found: C, 32.87; H, 1.23; N, 24.15; F, 24.40 $C_7H_3N_4O_2F_3$ requires: C, 32.03; H, 1.29; N, 24.13; F, 24.56%), (Found: M^+ 232 $C_7H_3N_4O_2F_3$ requires: M^+ 232.06), $\nu_{max.}$ (KBr) 3150, 1650, 1540, 1440, 1360, 1300, 1200, 1140, 990, 900, 820, 770, 750 cm^{-1}. PMR ($CDCl_3$): δ 8.83 (1H, d, J 7Hz, 7-H), 8.52 (1H, d, J 7Hz, 5-H) and 7.43 (1H, t, J, 6Hz, 6-H).

2-Trichloromethyl-8-nitro-s-triazolo[1,5-a]pyridine (5)

2-Hydrazino-3-nitropyridine (1.54 gm, 0.01 mole) and trichloroacetic acid (3.38 gm, 0.02 mole) were gently refluxed for 8 hours. The cooled reaction mixture was then poured into water (50 ml) and extracted with ether (3x50ml). The ether layer was dried ($MgSO_4$) and evaporated to give a dark brown viscous oil. Several treatments of the oil with petroleum ether (b.p. 40-60°C) finally gave a solid which was crystallized from ethanol (charcoal) to give slightly yellow crystals of the product (1 gm, 35%) m.p. 224-26°C (decomp.), (Found: C, 29.70; H, 1.10; N, 19.75; Cl, 37.53 $C_7H_3N_4O_2Cl_3$ requires: C, 29.89; H, 1.06; N, 19.92; Cl,37.72%) Found: M^+ 282 $C_7H_3N_4O_2Cl_3$ requires: M^+ 281.44), $\nu_{max.}$ (KBr) 3120, 1645, 1540, 1390, 1350, 1310, 1080, 1000, 900, 860, 830, 800, 740, 700 cm^{-1}. PMR (d_6-DMSO): δ 9.32 (1H, d, J, 6Hz, 5-H), 8.55 (1H, d, J, 6Hz, 7-H) and 7.45 (1H, t, J, 7Hz, 6-H).

2-Tribromomethyl-8-nitro-s-triazolo [1,5-a]pyridine (6)

A solution of 2-hydrazino-3-nitropyrdine (1.54gm, 0.01 mole) and tribromoacetic acid (5.94 gm, 0.02 mole) in absolute ethanol (75 ml) was refluxed for 18 hours. It was allowed to cool and then poured into water (50 ml). The mixture was then extracted with ether (3x50ml) and the ether layer was dried ($MgSO_4$). Evaporation of ether gave dark brown residual gum. This on several treatment with petroleum ether (b.p. 40-60°C) gave a solid. Crystallization from ethanol (charcoal) gave slightly brown crys-

tals (2 gm, 49%) m.p. 175-77°C (decomp.), (Found: C, 20.18; H, 0.63; N, 13.09; Br, 57.63; $C_7H_3N_4O_2Br_3$ requires: C, 20.24; H, 0.68; N, 13.49; Br, 57.83%) (Found: M^+ 415 $C_7H_3N_4O_2Br_3$ requires: M^+ 414.79; $\nu_{max.}$ (KBr) 3140, 1660, 1542, 1410, 1350, 1310, 1145, 1050, 980, 840, 820, 740, 710. PMR (d_6-DMSO):δ 9.15 (1H, d, J, 6Hz, 5-H), 8.55(1H, d, J, 6Hz, 7-H) and 7.45 (1H, t, J, 7Hz, 6-H).

8-Nitro-s-triazolo[1,5-a]pyridine (7)

In a two necked round bottom flask fitted with a double surface condenser (protected by guard-tube containing anhydrous calcium chloride) and a dropping funnel was placed 2-hydrazine-3-nitropyridine (1.54 gm, 0.01 mole). Trifluoroacetic acid (25 ml) was added dropwise over a period of 30 minutes. It was then gently refluxed for 12 hours. The mixture was allowed to cool, evaporation of solvent gave a gum which was basified with aqueous ammonium hydroxide. It was extracted with ether (3x25 ml) and the ether layer was dried ($MgSO_4$). Evaporation of ether gave a solid which was crystallized from ethanol (charcoal) to give slightly yellow crystals (1.25 gm, 76%) m.p. 180-82°C (Found: C, 43.80; H, 2.35; N, 33.95 $C_6H_4N_4O_2$ requires: C, 43.90; H, 2.43; N, 34.10%). $\nu_{max.}$ (KBr) 3155, 1630, 1625, 1450, 1410, 1395, 1320, 1210, 1130, 970, 830 and 710 cm^{-1}. PMR (d_6-DMSO):δ 9.75 (1H, d, J, 7Hz, 7-H), 9.45 (1H, s, 2-H), 9.20(1H, d, J, 7Hz, 5-H), 8.55 (1H, d, J, 6Hz, 6-H).

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