The Reactions of 1,2,3-Triazolo[1,5-*a*]pyridine with Electrophiles

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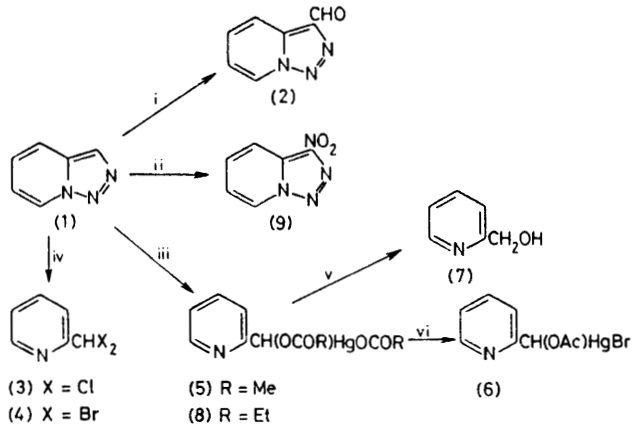
On treatment with chlorine, bromine, or mercuric acetate triazolo[1,5-*a*]pyridine (1) gives dichloromethyl-, dibromomethyl-, and alkoxy(alkoxymercurio)methyl-pyridines (3), (4), (5), and (8) with loss of nitrogen. Nitration gives 3-nitrotriazolopyridine (9), which on reduction gives 3-(2-pyridyl)imidazo[1,5-*a*]pyridine (11). The mechanism of formation of these compounds is discussed.

We have published a report [1] of the Vilsmeier reaction on 1,2,3-triazolo[1,5-*a*]pyridine (1), giving 3-formyltriazolopyridine (2). With this exception, no simple substitutions have been reported; the triazolopyridine (1) is easily prepared from pyridine-2-carbaldehyde [2,3] and we report here a number of reactions between triazolopyridine (1) and electrophiles.

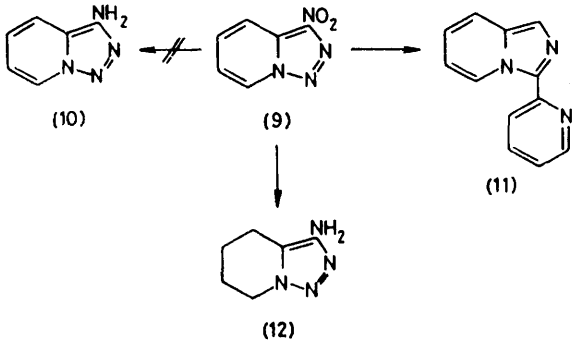


Reagents: i, $POCl_3$–DMF; ii, HNO_3–Ac_2O; iii, $Hg(OAc)_2$–RCO_2H; iv, Cl_2 or Br_2; v, $NaBH_4$–OH^-; vi, KBr

Treatment of a solution of triazolopyridine (1) in carbon tetrachloride with chlorine in carbon tetrachloride, at a temperature of 0—5 °C was accompanied by a vigorous evolution of gas. Evaporation of the solution gave an oil, shown to be substantially one compound. The mass spectrum of the distilled product showed a molecular ion at 161 m.u. with an isotope peak at 163 m.u. The analysis on the recrystallised material gave a formula of $C_6H_5Cl_2N$ and the ^1H n.m.r. spectrum showed a singlet at δ 6.62 p.p.m., with a characteristic α-substituted pyridine pattern downfield. The obvious structure for the product, 2-dichloromethylpyridine (3), was confirmed by a comparison of the melting point of the picrate with literature values. A similar reaction between triazolopyridine (1) and an equimolar amount of bromine gave 2-dibromomethylpyridine (4) in a yield of 75—77%. Again, the ^1H n.m.r. spectrum showed a 1 H singlet (6.66 p.p.m.) and an α-pyridyl pattern. The dibromomethylpyridine was obtained in similar yield when triazolopyridine (1) was treated with *N*-bromosuccinimide, and a comparison sample was prepared by the action of *N*-bromosuccinimide on α-picoline. Attempts to perform the reaction with mixed halogens, (for example iodine chloride) gave mixtures of pyridines. Novinson, Dea, and Okabe [4] have reported that 1,2,3-triazolo[1,5-*a*]pyrimidine reacts similarly with halogens, giving 2-dihalogenomethylpyrimidines, and were successful with chlorine bromide, which is surprising in view of the instability of this compound above 25 °C. Mercuric acetate was found to react with triazolopyridine (1) in glacial acetic acid at temperatures between 5 and 10 °C with evolution of nitrogen and formation of the substituted mercuriacetate (5). The ^1H n.m.r. spectrum showed two 3 H singlets at δ 1.95 and δ 2.1 p.p.m., a 1 H singlet at δ 6.0 p.p.m., and an α-pyridyl pattern at δ 7.0—8.5 p.p.m.; the ^{13}C n.m.r. spectrum confirmed two methyl carbon signals, a signal at δ 75.82 p.p.m. (d in off-resonance), pyridine CH signals at δ 126.11, 126.98, 141.96, and 149.67 p.p.m., a quaternary carbon at δ 156.31 p.p.m. (C-2), and two carbonyl signals at δ 175.52 and 183.37 p.p.m. When the diacetate (5) was stirred with an aqueous solution of potassium bromide the mercuribromide (6) was obtained; the ^1H n.m.r. spectrum was very similar to that of compound (5), lacking the 3 H singlet at δ 1.95 p.p.m. The structure of compound (5) was finally established by sodium borohydride reduction in alkaline medium. Mercury was desposited, and 2-pyridylmethanol (7) was obtained, identical with a specimen prepared from pyridine *N*-oxide by treatment with acetic anhydride, followed by acid hydrolysis of the 2-acetoxymethylpyridine.[5] An attempt to produce a mercury derivative with two different acyloxy-residues, in which mercuric acetate in propionic acid was used as the reagent, gave instead the dipropionyloxy-derivative (8).

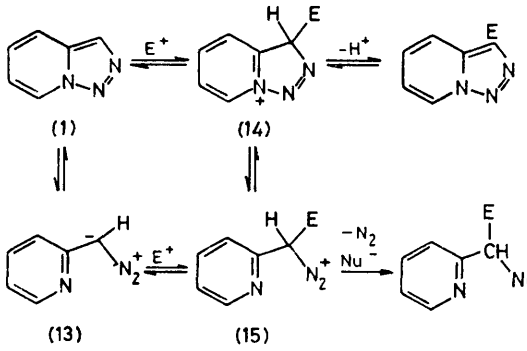
By contrast with these reactions in which ring-opening and nitrogen extrusion were characteristic, nitration gave 3-nitrotriazolopyridine (9). The reagent was a mixture of fuming nitric acid with acetic anhydride and the temperature was kept below 10 °C. The position of the nitro-substituent is easily established by the ^1H n.m.r. spectrum, which shows only four signals at δ 7.4 (dd, *J* 6.5 and 7 Hz, H-6), 7.9 (dd, *J* 7 and 9 Hz, H-5), 8.5 (d, *J* 9 Hz, H-4), and 8.95 p.p.m. (d, *J* 6.5 Hz, H-7). These coupling constants compare well with those recorded for the parent triazolopyridine (1).[6] Attempts to reduce the 3-nitrotriazolopyridine (9) to 3-aminotriazolopyridine (10) were unsuccessful. The most abundant product from transfer hydrogenation was a

colourless compound of molecular weight 195, and molecular formula $C_{12}H_9N_3$. In the ^1H n.m.r. spectrum all nine protons could be distinguished, and by selective decoupling separated into three groups. Most prominent was a singlet (1 H) at 7.58 p.p.m. One series of four protons at δ 8.62 (H^A), 7.16 (H^B), 7.75 (H^C), and 8.33 p.p.m. (H^D) represented a sequence with coupling constants $J_{A,B} = 5.1$ Hz, $J_{B,C} = 7.6$ Hz, $J_{C,D} = 8.0$ Hz, characteristic of an α-substituted pyridine. The remaining four protons showed a similar sequence δ 9.94 (H^E),



6.70 (H^F), 6.86 (H^G), and 7.48 (H^H) p.p.m., with $J_{E,F} = 6.8$ Hz, $J_{F,G} = 7.1$ Hz, and $J_{G,H} = 6.9$ Hz). The structure which best fits these data is that of 3-(2-pyridyl)imidazo[1,5-*a*]pyridine (11); a search of the literature revealed that this compound had been prepared from pyridine-2-carbaldehyde,[7] and that the melting point and physical data agreed reasonably well with those of our reduction product. A sample provided by Professor Abushunab showed no depression in a mixed melting point with our specimen.

Attempts to establish a radical mechanism for the halogen reactions were unsuccessful; methyl radicals

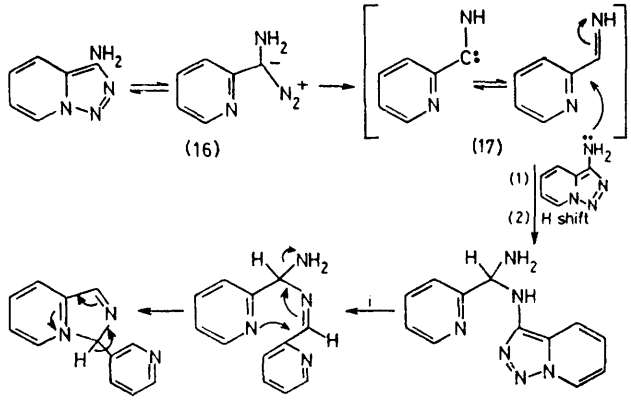


failed to react with triazolopyridine at ambient temperatures.

On catalytic hydrogenation the nitro-compound (9) gave some imidazopyridine (11) and a compound identified by spectroscopy as the tetrahydro-derivative (12); by analogy with indolizine the pyridine ring should be easily reduced.[8]

The mode of formation of the pyridine derivatives (3), (4), (5), and (8), and of the imidazopyridine (11) are best discussed together. The formation of pyridine derivatives with loss of nitrogen must be attributed to the tautomerism (1) ⇌ (13), or, more likely, to the tautomerism (14) ⇌ (15) of the intermediate in electrophilic substitution.

If the electrophile E is an electron-withdrawing group, the intermediate (15) will be longer-lived and deprotonation of the cyclic form competes successfully with loss of nitrogen. If the electrophile E is only weakly stabilizing to the diazonium intermediate (15), nucleophilic attack with loss of nitrogen is the favoured process. This hypothesis has as a corollary the extreme instability of the tautomer (13) when the hydrogen atom is replaced by an electron donor such as the amino-group. Loss of nitrogen from the tautomeric form (16) in 3-aminotriazolopyridine gives a reactive intermediate (17) similar to that proposed in the reaction between pyridine-2-carbaldehyde and ammonium chloride. The intermediate (17) can attack unchanged 3-aminotriazolopyridine to produce 3-(2-pyridyl)imidazopyridine (11) as shown in the Scheme.



i *Via* carbene as in production of (17)

SCHEME

EXPERIMENTAL

Chromatography was on Woelm alumina, activity thus (4); or on Merck Silicagel PF_{254} plates.

Triazolo[1,5-a]*pyridine* (1).—Prepared as described by Bower and Ramage,[2] or from the tosylhydrazone of pyridinecarbaldehyde by heating in morpholine, precipitation of morpholine toluene-*p*-sulphonate with ether, and evaporation,[3] the triazolopyridine had b.p. 106—109 °C/0.6 mmHg, and solidified with time. All samples were kept at 0—5 °C.

2-(*Dichloromethyl*)*pyridine* (3).—To a stirred mixture of triazolopyridine (1) (4.3 g), calcium carbonate (3 g), and carbon tetrachloride (100 ml) at 5 °C, was added a solution of chlorine (2.3 g) in carbon tetrachloride (100 ml); a gas was evolved. After the addition the mixture was filtered, and the solid washed with chloroform. The combined organic extracts were washed with sodium hydrogencarbonate solution and then water, dried (Na_2SO_4) and evaporated, to give almost pure 2-dichloromethylpyridine (3) (3.46 g, 67%). A sample was distilled, b.p. 88—90 °C/11 mmHg (lit.,[9] b.p. 90—92 °C/15 mmHg); picrate m.p. 115—116 °C (from ethanol) (lit.,[10] m.p. 117—118 °C), δ($CDCl_3$) 6.62 (1 H, s, $CHCl_2$), 7.1—7.3 (1 H, m, H-5), 7.7—

7.9 (2 H, m, H-3, and H-4), and 8.55 br p.p.m. (1 H, d, J 6 Hz, H-6).

2-*Dibromomethylpyridine* (4).—(*a*) A solution of bromine (6.8 g) in carbon tetrachloride (50 ml) was added slowly to a stirred solution of triazolopyridine (1) (5 g) in carbon tetrachloride (90 ml) at 0—5 °C. A gas was evolved and a small amount of black gum separated. After addition was complete stirring was continued (1 h) and the mixture was then treated with aqueous sodium hydrogencarbonate. The organic layer was separated, dried ($MgSO_4$), and evaporated to give 2-dibromomethylpyridine (4) (7.8—8.2 g, 75—77%), almost pure. The picrate had m.p. 137—139 °C (lit.,[11] m.p. 144—145 °C). A mixed m.p. with a sample prepared by procedure (*b*) showed no depression.

(*b*) A mixture of 2-picoline (2.3 g), *N*-bromosuccinimide (8 g), benzoyl peroxide (0.33 g), and carbon tetrachloride (100 ml) was boiled over a 100-W tungsten bulb (3 h). Filtration, and evaporation of the filtrate gave almost pure 2-dibromomethylpyridine (4); the picrate had m.p. 137—139 °C.

(*c*) A mixture of triazolopyridine (1) (1.2 g), *N*-bromosuccinimide (3.5 g), and carbon tetrachloride (50 ml), was boiled over a 100-W tungsten lamp (1 h). Work-up as in (*b*) gave dibromomethylpyridine (1.2 g, 79%).

2-*Acetoxymethylpyridylmercuric Acetate* (5).—A hot solution of mercuric acetate (13.3 g) in glacial acetic acid (30 ml) was added to a solution of triazolopyridine (1) (5 g) in glacial acetic acid (50 ml). Much gas was evolved; the mixture was stirred at room temperature (3 h) while more gas evolved. Filtration from unchanged mercuric acetate (*ca.* 1 g) was followed by evaporation of the filtrate. The solid residue was suspended in ether and filtered. The crude solid (14.6 g) was recrystallized from benzene to give the *pyridylmethylmercuric acetate* (5), m.p. 138—139 °C (10.3 g, 60%). (Found C, 28.9; H, 2.4; N, 3.55. $C_{10}H_{11}HgNO_4$ requires C, 29.3; H, 2.7; N, 3.4%); ^{1}H n.m.r. δ($CDCl_3$) 1.95 (3 H, s), 2.1 (3 H, s), 6.0 (1 H, s), 6.9—7.9 (3 H, m), and 8.35br p.p.m. (1 H, d); $\nu_{max.}$ (Nujol) 1 725s, 1 630, 1 600, 1 380s, and 1 250s cm^{-1}; ^{13}C n.m.r. δ (TFA) 21.2 (q), 21.3 (q), 75.8 (d), 126.1 (d), 127.0 (d), 141.9 (d), 149.1 (d), 156.3 (s), 175.5 (s, C=O), and 182.4 p.p.m. (s, C=O). (Multiplicities refer to off-resonance decoupling). The *mercuribromide* (6) was obtained from a solution of the mercuriacetate (5) (2 g) and potassium bromide (3 g) in a mixture of tetrahydrofuran (50 ml) and water (10 ml). Evaporation after 3 h gave a solid; recrystallized from benzene the *salt* (6) had m.p. 160—162 °C (1 g, 47%) (Found: C, 22.65; H, 1.8; N, 3.5. $C_8H_8BrHgNO_2$ requires C, 22.3; H, 1.85; N, 3.25%); δ($CDCl_3$) 2.08 (3 H, s), 5.88 (1 H, s), 6.9—7.3 (d over m, H-3 and H-5), 7.6 (dd, H-4), and 8.4br (d, H-6) p.p.m.; $\nu_{max.}$ (Nujol) 1 740 cm^{-1}; m/e 438 − 430 (7 peaks, M^+), 387—395 (M − 43), 359—367 [M − (43 + 28)], and 43 m.u.

2-*Propionyloxymethylpyridylmercuric Propionate* (8).—This compound was prepared as for compound (5) in propionic acid as solvent. Dilution of the reaction mixture gave no precipitate; evaporation *in vacuo* gave a solid, soluble in benzene. Precipitation with light petroleum (b.p. 60—80 °C) gave the crude *salt* (8) which was recrystallized from benzene–cyclohexane, m.p. 122—123 °C (41%) (Found: C, 32.75; H, 3.25; N, 3.35. $C_{12}H_{15}HgNO_4$ requires C, 32.9; H, 3.45; N, 3.2%); δ($CDCl_3$) 1.1 (3 H, t), 1.18 (3 H, t), 2.0—2.7 (4 H, overlapping q), 6.0 (1 H, s), 7.0 (1 H, t of d, H-5), 7.2 (1 H, d, H-3), 7.6 (1 H, t of d, H-4), 8.35 p.p.m. (1 H, d, H-6); $\nu_{max.}$ (Nujol) 1 730s, 1 620s, 1 260s, and 1 180s cm^{-1}.

2-*Hydroxymethylpyridine* (7).—(*a*) The mercuriacetate (5) (3.1 g) was added to a mixture of 3M-sodium hydroxide (20 ml), 0.2M in sodium borohydride and the mixture was stirred (1 h), during which time metallic mercury precipitated. The filtered solution was saturated with salt, extracted with dichloromethane, and the organic extract dried, and evaporated. The products were separated by p.l.c.; two major bands (50 : 50, ethyl acetate–toluene) R_F 0.42 and 0.11 were respectively 2-acetoxymethylpyridine and 2-hydroxymethylpyridine (7) (total yield 30%); the picrate of compound (7) had m.p. 157—158 °C. A mixed m.p. with a sample prepared as in (*b*) showed no depression.

(*b*) From 2-picoline *N*-oxide by treatment with acetic anhydride,[12] 2-acetoxymethylpyridine was obtained. Hydrolysis with aqueous acid gave 2-hydroxymethylpyridine the spectra of which were identical with those of a sample from (*a*); a melting point of the mixed picrates showed no depression.

3-*Nitrotriazolo*[1,5-a]*pyridine* (9).—Triazolopyridine (1) (5 g) was added in small portions to a cooled (0—5 °C), stirred solution of fuming nitric acid (5 ml) in acetic anhydride (50 ml) and stirring was continued for 1 h. The mixture was poured into ice–water giving a precipitate. Extraction of the precipitate with several quantities of boiling benzene, followed by concentration of the benzene solutions, gave the *nitrotriazolopyridine* (9), m.p. 165—167 °C; on recrystallization, m.p. 167—169 °C (Found: C, 43.8; H, 2.4; N, 34.4. $C_6H_4N_4O_2$ requires C, 43.9; H, 2.45; N, 34.15%). Further material was obtained from the benzene filtrate, and by p.l.c. from the benzene-insoluble material; total yield 1.5—1.7 g (20—25%); $\nu_{max.}$ (Nujol) 1 640, 1 515, 1 350, 1 240, 1 070, 830, and 772 cm^{-1}; ^{1}H n.m.r. δ[$(CD_3)_2SO$] 7.62 (1 H, td, J 1 and 7 Hz, H-6), 8.0 (1 H, dd, H-5), 8.28br (1 H, d, J 8.5 Hz, H-4), and 9.35 p.p.m. (1 H, d, J 7 Hz, H-7); ^{13}C n.m.r. [$(CD_3)_2SO$] δ 118.0 (d), 118.8 (d), 127.8 (d), 129.4 (s), 134.3 (d), and 142.9 (s) p.p.m.; m/e 164 (M^+), 118 (M − 46), 90 [M − (46 + 28)], and 78 m.u.; $\lambda_{max.}$ (95% EtOH) 280, 287, and 335 nm ($\log_{10}$ ε 3.34, 3.39, and 3.88).

Reduction of Nitrotriazolopyridine (9)—(*a*) A solution of the nitro-compound (9) (1 g) and cyclohexene (6 ml) in 95% ethanol (50 ml) was boiled with palladium-on-charcoal (1 g, 10%) for 4 h. The cooled mixture was filtered, the filtrate evaporated, and the residue separated by p.l.c. (ethyl acetate–toluene, 1 : 4). The band of R_F 0.345 was extracted and identified as 3-(2-pyridyl)imidazo-[1,5-*a*]pyridine (11), m.p. 119—120 °C (from cyclohexane) (120 mg, 20%). The ^{1}H n.m.r. is given in the Discussion. A mixed m.p. with a sample provided by Professor Abushanab showed no depression.

(*b*) A solution of the nitro-compound (9) (1.37 g) in dimethoxyethane (50 ml) was hydrogenated at atmospheric temperature and pressure over palladium-on-charcoal catalyst (1 g) until three equivalents of hydrogen were absorbed. Filtration, and evaporation of the filtrate gave a mixture, separated by p.l.c. (ethyl acetate–toluene, 1 : 4). The slowest band was extracted and was shown to be the 3-aminotetrahydrotriazolopyridine (12); m/e 138 (M^+, $C_6H_{10}N_4$); $\nu_{max.}$ 3 400 cm^{-1}; ^{1}H n.m.r. δ($CDCl_3$) 1.8—2.1 (4 H, m), 2.5—2.9 (2 H, t, H-4), 3.1br (2 H, NH_2, exch. D_2O), and 4.1—4.4 (2 H, t, H-7) p.p.m. A band of higher R_F gave a small quantity of the imidazopyridine (11).

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