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TRIAZOLOPYRIDINES. PART 9.[1] THE SYNTHESIS OF 7-AMINO(1,2,3)TRIAZOLO(1,5-a)PYRIDINES

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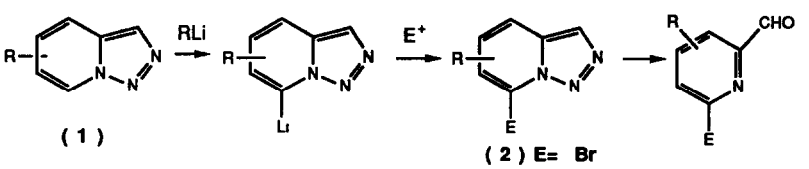
Abstract - Regiospecific lithiation of (1,2,3)triazolo(1,5-a)pyridines (1) and (4) with subsequent reaction with styryl azide gave small yields of the 7-aminotriazolopyridines (6) and (7). A longer larger scale synthesis of compounds (6) and (7) is described giving overall yields of 17 and 25%, starting from 2-amino-6-methyl (9) or 2-amino-6-ethyl pyridine (19).

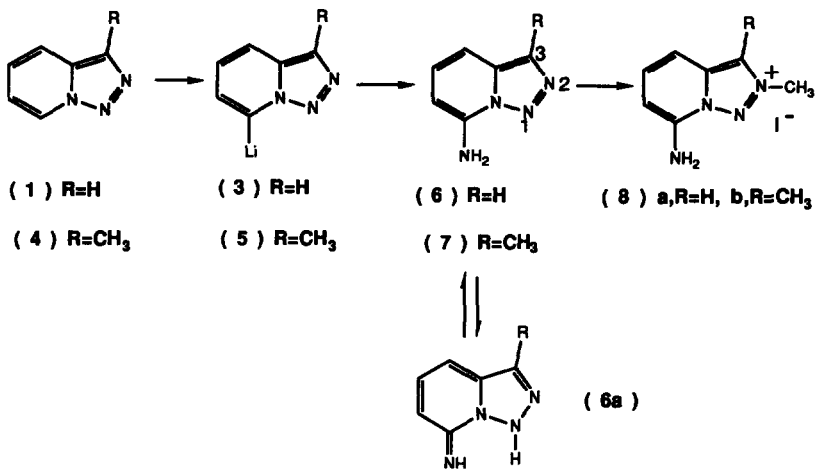
We have described the use of (1,2,3)triazolo(1,5-a)pyridine (1) as a synthon for 2,6-disubstituted pyridines, making use of the regioselective lithiation at position 7 as shown in equation (1).[2,3] The lithiation procedure allows the synthesis of 7-bromo-triazolopyridine (2, E=Br),[4] and the bromine in these derivatives is readily replaced by nucleophiles.[1] We have now begun a programme aimed at the synthesis of triazolopyridines containing other, potentially reactive; substituents. Already known are the 3-acyl and 3-aroyl derivatives reported by Regitz,[5,6] the 3-cyanotriazolopyridine,[7] the 5-methoxy derivative,[3] and various carboxylic acid derivatives, also prepared by us.[3] Here we report the synthesis of the first aminotriazolopyridines.



Eq. 1

We have prepared 3-nitrotriazolopyridine by direct nitration of compound (1) but we were unable to reduce the nitro group to an amine without extensive rearrangement.[8] Attack by an electrophile on the unsubstituted six membered ring of triazolopyridine (1) is unlikely, but there are a number of 'electrophilic nitrogen' reagents which have been reported to react with aryllithiums or aryl Grignard reagents, and we sought to use these with the readily obtainable 7-lithiotriazolopyridines. The reaction between 7-lithiotriazolopyridine (3) and lithium methoxyamine[9] failed, as did the reaction between compound (3) and tosyl azide[10,11] with subsequent reduction with nickel-alumuinium alloy.[12] A reaction between the lithium derivative (5) of 3-methyltriazolopyridine (4) and magnesium bromide was followed by treatment with phenylthiomethyl azide[13] but no amine was formed (the Grignard reagent was successfully prepared by another route but still failed to react with phenylthiomethyl azide). The only success was with Hassner's styryl azide,[14] which reacted with 7-lithiotriazolopyridine (3) to give a small (~4%) yield of a crystalline compound giving the correct microanalysis and mass spectrum for 7-aminotriazolopyridine (6). By a similar procedure from 3-methyltriazolopyridine (4) via the lithium derivative (5) we obtained an equally small yield of the amine (7). The ^{1}H n.m.r. spectra of the amines showed the characteristic upfield signal for the proton on C6 (δ6.05-6.2, dd, J=6 and 2 Hz) which we have observed in the spectra of triazolopyridines bearing a tertiary amine at position 7.[1] The infrared spectrum of compound (6) showed absorptions at 3400 and 3500 cm^{-1}, but the observation that there was no change in ultraviolet absorption from neutral to acid solution led to some doubt as to the predominant tautomeric form, (6) or (6a). A determination of the ^{15}N shifts for compound (6) showed four signals at δ56.8, 245.4, 320.6, and 346.5 p.p.m. (from nitromethane as standard at 380 p.p.m.) assigned respectively to N1, N2, N7a, and the NH_2. Imine absorption as expected for structure (6a) should be in the region >δ300 p.p.m. The 3-methyl derivative (7) showed four signals at δ56.2, 246.3, 316.8, and 350.0, in good agreement with those of the parent. Hence in solution the amino forms (6) and (7) predominate. The amines (6) and (7) reacted with methyl iodide to give, in each case, only one quaternary salt;[15] difference NOE spectra with irradiation of the quaternary N-methyl signal in the methiodides showed enhancement of the signal respectively due to H3 and to the 3-methyl group, thus establishing the general structure as (8). Armarego[16] has suggested[1] that triazolopyridine (1) should protonate on N2; the combination of greater basicity on N2 and steric hindrance to N1 must combine to ensure alkylation on N2 only. To confirm the position of protonation, for each amine (6) and (7) we have determined the ^{1}H n.m.r. spectrum in TFA, and compared the spectrum with that of the corresponding methiodide (8a) or (8b), also determined in TFA. The amine (7) serves as an example. The spectrum in TFA showed signals at δ2.85 (CH_3), 6.95 (1H, d, J=7.1 Hz, H6), 7.5 (1H, d, J=8.2, H4) and 7.78 (1H, t, H5) while that of the methiodide (8b) showed signals at δ2.84 (CH_3), 4.46 (CH_3N^+), 6.93 (1H, d), 7.46 (1H, d), and 7.75 (1H, t), the two spectra, in the

aromatic region, being almost identical. When considered alongside the n.m.r. spectrum of the methiodide (8b) in DMSO, which is very similar to that in TFA, the conclusion must be that amine (7) is predominantly protonated on N2, with little, if any, protonation of the external amine group.



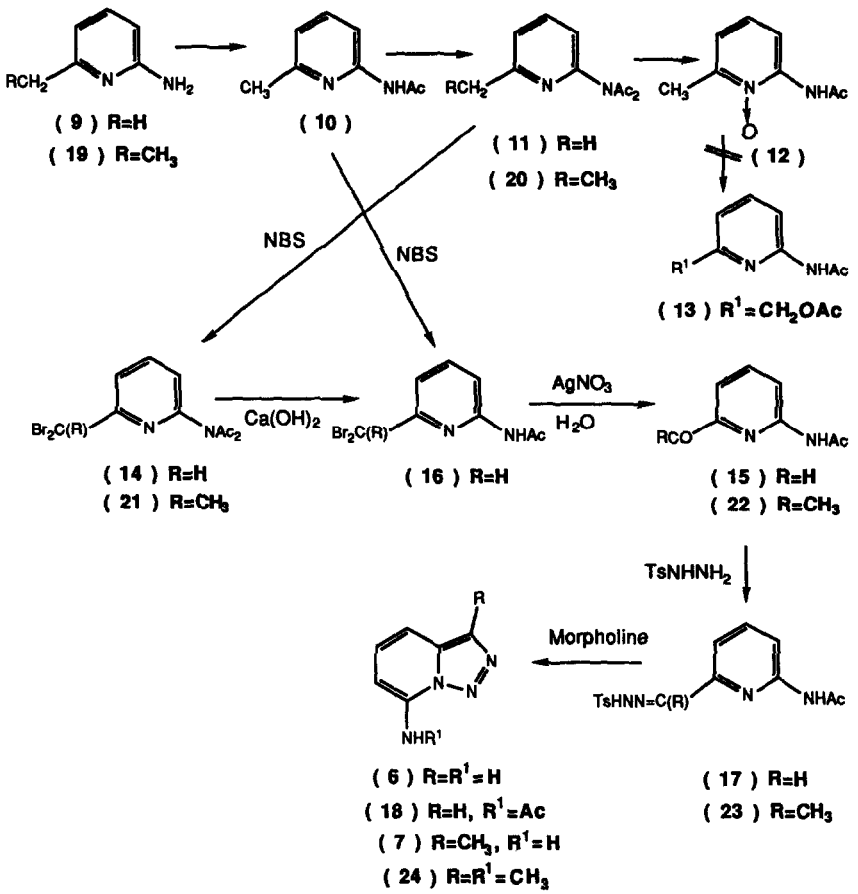
(1) R=H (3) R=H (6) R=H (8) a,R=H, b,R=CH_3

(4) R=CH_3 (5) R=CH_3 (7) R=CH_3

(6a)

The quantity of 7-amino compound available via the lithiation procedure was small and we have developed a longer synthesis which allows the production of larger quantities of amine. Our starting material was 6-amino-2-methylpyridine (9), available in kilogramme quantities. First attempts to use the N-oxide to produce a functionalized methyl group involved a preliminary protection of the amino group as the mono- (10) or di-acetyl (11) derivative. Oxidation of either amide with hydrogen peroxide in acetic acid gave the same monoacetylaminopicoline N-oxide (12).[17] Attempts to rearrange the compound (12) with acetic anydride failed to give any acetoxymethyl derivative (13). Attempts at direct oxidation of the methyl group in compound (11) with selenium dioxide in pyridine or in chlorobenzene, or of the N-oxide (12) with selenium dioxide in pyridine failed to give any aldehyde. The successful route from the N,N-diacetyl derivative (11) involved bromination with N-bromosuccinimide (2 equivalents) to give the dibromo derivative (14), characterized spectroscopically, and converted by treatment with silver nitrate in aqueous ethanol into 6-acetamidopyridine-2-carboxaldehyde (15). Hydrolysis of the dibromo compound (14) using aqueous calcium carbonate gave 2-acetamido-6-dibromomethylpyridine (16) which could be further hydrolyzed to the aldehyde (15) by silver nitrate in aqueous ethanol. Bromination of the monoacetyl derivative (10) using N-bromosuccinimide also gave compound (16).

The aldehyde (15) gave a crystalline tosylhydrazone (17), converted by treatment with morpholine into a mixture of the aminotriazolopyridine (6) and its monoacetyl derivative (18). Hydrolysis of the mixture by aqueous sodium hydroxide removed the acetyl substituent to give the pure amine (6). The overall yield was 17%.



With the experience gained, the homologous aminopyridine (19) was converted via the diacetyl derivative (20), the dibromodiacetyl derivative (21), the ketone (22) and the tosylhydrazone (23), to the 7-amino-3-methyltriazolopyridine (7) in an over-all yield of 25%.

EXPERIMENTAL

M.p.s. were determined on a Kofler hot stage and are uncorrected. In purification by Chromatotron (2 mm plates) and for p.l.c. silica (Merck PF_{254}) was used. N.m.r. spectra were determined for solutions in $CDCl_3$ unless otherwise stated.

7-Amino(1,2,3)triazolo(1,5-a)pyridine (6). (a) From triazolopyridine; treatment of a solution of triazolopyridine (1) (2.1 g, 17.76 mmol) in THF (15 ml) with n-butyllithium (10.8 ml, 1.9 M in hexane) at -40°C under argon, gave the lithioderivative (3) (complete exchange was monitored by D_2O quench of a sample and inspection of the ^1H n.m.r. spectrum of the isolated triazolopyridine for removal of the H7 doublet at δ8.5). Addition of styryl azide[14] (2.32 g, 16 mmol) to the solution at -78°C was followed by slow raising of the temperature to ambient, and then the solution was left overnight. Work up by addition of a saturated solution of ammonium chloride in ammonia (0.880 s.g.) was followed by extraction (CH_2Cl_2), drying ($MgSO_4$), and evaporation to give crude product (4.2 g). Purification via a Florisil column, eluting with mixtures of petroleum with increasing amounts of ethyl acetate gave amine (6) (0.6 g), further purified by Chromatotron and finally by short path distillation gave pure amine (6) (0.1 g, 4.2%), m.p. 137°C. Specimens were obtained by route (b).

(b). A solution of 6-acetamidopyridine-2-carboxaldehyde tosylhydrazone (17) (see below), (8.1 g, 24 mmol), in morpholine (25 ml) was heated at 95°C (1 h). Evaporation (oil pump) gave a residue, treated with anhydrous ether to precipitate morphine sulphinate. The ethereal filtrate was evaporated and the residue (5.2 g) shown to be a mixture of amine (6) and its acetyl derivative (18). The crude product was hydrolysed by 10% aqueous sodium hydroxide (60°C, 2 h), the cooled solution saturated with salt and extracted with dichloromethane. The dried ($MgSO_4$) solution was evaporated, and the crude amine (6) (3.6 g) crystallized from dichloromethane as yellowish crystals, m.p. 137°C (1.6 g, 49%). Sublimation for analysis gave colourless material . (Found: C, 53.7; H, 4.45; N, 41.65. $C_6H_6N_4$ requires C, 53.7; H, 4.5; N, 41.75%). ν_{max} 3400, 3500 cm^{-1}: λ_{max} 212.8 ($\log_{10}\epsilon$ 3.59), 303.6 nm ($\log_{10}\epsilon$ 3.41). δ(^1H) 5.5 (2H, brs, NH_2), 6.13 (1H, dd, H6), 7.0 (2H, m, H4 and H5), 7.93 (1H, s, H3). δ(^{13}C) 92.83 (d, C6), 104.35 (d, C4), 125.2 (d, C3), 128.5 (d, C5), 135.54 (s, C3a) 142.35 (s, C7). M/z 135, 134 (M^+, 84%), 106 (M -28, 100%), 105 (M-29, 54%), 79 (80%).

7-Amino-3-methyltriazolopyridine (7). (a) A solution of the lithiotriazolopyridine (5) from 3-methyltriazolopyridine (4) (2.34 g, 17.6 mmol) in THF at -78°C, was treated with styryl azide (2.32 g, 16 mmol), then allowed to reach room temperature and stood overnight. Work up was as described for compound (6) except that the first chromatography was on alumina (activity IV). Thus was obtained the amine (7), distilled for analysis in a bulb tube at 110°C/0.03 mm Hg, m.p. 109°C (O.1 g, 4%). (Found: C, 56.9; H, 5.4; N, 37.6. $C_7H_8N_4$ requires C, 56.75; H, 5.4; N, 37.85%). ν_{max} 3400, 3510 cm^{-1}. δ(^1H) 2.6 (3H, s), 5.33 (2H, brs, NH_2), 6.13 (1H, m, H6), 6.95-7.2 (2H, m, H4 and H5), δ(^{13}C) 10.58 (q, CH_3), 93.09 (d, C6), 104.78 (d, C4), 126.12

(d, C5), 132.6 (s, C3) 133.92 (s, C3a), 140.07 (s, 7C). M/z 148 (M^+, 57%), 120 (m-28, 100%), 119 (M-29, 65%), 105 (50%).

(b). The tosylhydrazone (23) in morpholine was cyclized as described for compound (18), to give, after hydrolysis, the amine (7) in 88% yield, as a solid, crystallized from dichloromethane, m.p. 109-110°C. A sample of the crude product from cyclization was separated on an alumina (a) column (eluant ethyl acetate/petroleum, 60-80°, 56.65), to give a pure sample of the 7-acetylamino-3-methyltriazolopyridine (24), m.p. 125-125.5°C (from petroleum/ethyl acetate). (Found: C, 56.66; H, 5.15; N, 29.2. $C_9H_{10}N_4O$ requires C, 56.85; H, 5.25; N, 29.45%). M/z 190 (M^+, 38%), 162 (M-28, 23%), 120 (100%), $\delta(^1H)$, 2.4 (3H, s), 2.6 (3H, s), 7.1-7.3 (2H, m), 7.7-7.85 (1H, dd, H4), 9.4 (1H, brs, N4).

2-Acetamido-6-methylpyridine (10) was prepared by the method of Zeide[18] in 74% yield, m.p. 89°C (lit.[18] m.p. 90°C). The N-oxide (12) was prepared form compound (10) by peracetic acid oxidation,[17] in 64% yield, m.p. 124-125°C (lit.[17] m.p. 130-131°C); oxidation of compound (11) gave the same N-oxide (12) in 74% yield.

2-Diacetamido-6-methylpyridine (11) was prepared by the general method of Lalonde and Davis[19] in 73% yield, m.p. 82°C.

2-Diacetamido-6-ethylpyridine (20). - Prepared from 2-amino-6-ethylpyridine, acetyl chloride, and 2,6-dimethylpyridine by the same procedure[19] in 74% yield. Recrystallized from cyclohexane the diacetamido derivative (20) had m.p. 45-46°C. (Found: C, 64.2; H, 6.8; N, 13.7. $C_{11}H_{14}N_2O_2$ requires C, 64.1; H, 6.8; N, 13.6%). ν_{max} 3430, 1700 cm^{-1}, $\delta(^1H)$ 1.15 (3H, t, CH_3 CH_2), 2.1 (6H, s, 2 x $COCH_3$), 2.7 (2H, q, CH_2 CH_3), 6.8-7.1 (2H, m), 7.6 (1H, t, J 8 Hz, H4). M/z 206 (M^+, 1.6%), 164 (M-42, 25%), 149 (63%), 43 (100%).

2-Diacetamido-6-dibromomethylpyridine (14) and 2-Acetamido-6-dibromomethylpyridine (16). - A solution of the diacetamide (11) (14.5 g, 0.076 mol) in carbon tetrachloride (200 ml) with added N-bromosuccinimide (32.26 g, 0.181 mol) was boiled under a nitrogen atmosphere for 19 h (the reaction was monitored by ^1H n.m.r. spectroscopy). The insoluble material was removed by filtration, the solution evaporated in vacuo, to give the crude dibromomethylpyridine (14) as an orange solid (30 g) used directly for the next stage. $\delta(^1H)$ 2.1 (6H, s, 2 x $COCH_3$), 6.5 (1H, s, $CHBr_2$), 7.0-7.15 (1H, dd, H3), 7.7-7.9 (2H, m, H4 and H5). M/z 348, 350, 352 (M^+).

The crude compound (14) (41.2 g, 0.118 mol), was dissolved in methanol (60 ml) and powdered calcium carbonate (25.6 g) and then water (44 ml) added. The mixture was heated at 65°C (24 h), solid filtered off, and the filtrate evaporated in vacuo to give almost pure monoacetamidodibromomethylpyridine (16) (25.1 g, 70%), m.p. 142-143°C (from cyclohexane). (Found: C, 31.25; H, 2.55; N, 9.1. $C_8H_8Br_2N_2O$ requires C, 31.15; H, 2.6; N, 9.1%). ν_{max} 3420, 1700, 1500 cm^{-1}; $\delta(^1H)$ 2.24 (3H, s, $COCH_3$), 6.52 (1H, s, $CHBr_2$), 7.36 (1H, dd, J=7.6 and 1.5 Hz, H5), 7.76 (1H, dd, 7.6 and 8.5 Hz, H4), 8.16 (1H, dd, J=8.5 and 1.5 Hz, H3), 8.25 (1H, brs, NH). M/z 306, 308, 310 (M^+).

2-Diacetamido-6-(α,α-dibromoethyl)pyridine (21) - Prepared as described for compound (14) from diacetamide (20) in virtually quantitative crude yield (suitable for conversion into compound (22)). After purification by chromatography and recrystallization from cyclohexane a sample of the diacetamido dibromoethylpyridine (21) had m.p. 141-142°C. (Found: C, 35.45; H, 3.35; N, 7.7. $C_{11}H_{12}Br_2N_2O_2$ requires C, 36.25; H, 3.3; N, 7.7%). ν_{max} 3420, 1720 cm^{-1}; $\delta(^1H)$, 2.29 (6H, s, 2 x $COCH_3$), 2.95 (3H, s, CH_3CBr_2), 7.19 (1H, d, J=7.9 Hz, H5), 7.9 (1H, t, J=7.9 Hz, H4), 8.07 (1H, d, J=7.9 Hz). M/z 362, 364, 366 (M^+).

6-Acetamidopyridine-2-carboxaldehyde (15). - (a) A solution of the crude dibromocompound (14) (30 g 0.086 mol) in ethanol (750 ml) was mixed with a hot aqueous (210 ml) solution of silver nitrate (29.2 g, 0.172 mol). After brief boiling (15 min) the cooled mixture was treated with concentrated hydrochloricacid (222 ml) and the precipitated silver salts removed by filtration. The filtrate was evaporated in vacuo, the residue treated with a saturated aqueous solution of sodium bicarbonate and extracted (CH_2Cl_2, 3 x 200 ml). The organic extracts were dried ($MgSO_4$) and evaporated to give crude product (12.2 g). Purification on a silica gel column (eluted with ethyl acetate/petroleum, 7:3) gave the acetamidoaldehyde (15), m.p. 124°C (4 g, 32%). $\delta(^1H)$ 2.0 (3H, s, $COCH_3$), 7.3 (1H, dd, J=7 and 2 Hz, H5), 7.7 (1H, t, J=7.5 Hz, H4), 8.15 (1H, dd, J=8 and 2 Hz, H3), 9.5 (1H, s, CHO). M/z 164 (M^+, 34%), 122 (M-42, 77%), 94 (100%).

(b) A similar hydrolysis of compound (16) gave a crude yield of compound (15) of 89%.

The tosylhydrazone (17), prepared in methanol solution from the aldehyde (15) (1.6 g, 9.75 mmol) and tosylhydrazone (1.8 g, 9.75 mmol) crystallized on cooling and was filtered off (1.8 g, 55.5%), m.p. 144-145°C from acetone/dichloromethane. (Found: C, 53.95; H, 4.6; N, 16.8. $C_{15}H_{16}N_4O_3S$ requires C, 54.2; H, 4.8; N, 16.85%). $\delta(^1H)$ (acetone - d_6) 2.1 (3H, s, CH_3), 2.39 (3H, s, CH_3CO), 7.4 (1H, brd, J=8 Hz, H5), 7.5 (1H, t, J=8 Hz, H4), 7.7 (1H, s, CH=N), 7.78-7.9 (4H, m), 8.15 (1H, dd, J=8 and 1 Hz, H3) 9.5 (1H, brs, NH).

6-Acetamido-2-acetylpyridine (22) - Prepared as described for compound (15) method (a) from dibromoderivative (21) in 76% yield, the 2-acetylpyridine (22) had m.p. 141-142°C (from benzene). (Found: C, 60.95; H, 5.5; N, 15.85. $C_9H_{10}N_2O_2$ requires C, 60.65; H, 5.65; N, 15.7%). ν_{max} 3440, 1700, 1540 cm^{-1}; $\delta(^1H)$ 2.29 (3H, s, $NHCOCH_3$), 2.62 (3H, s, $COCH_3$), 7.77 (1H, t, J=7.8 Hz, H4), 7.84 (1H, d, J=7.5 Hz, H5), 8.41 (1H, d, J=7.8 Hz. H3), 8.46 (1H, brs, NH). M/z 178 (M^+, 37%), 136 (M-62, 59%), 43 (100%).

The tosylhydrazone, prepared as for compound (17) in 75% yield, had m.p. 181-182°C (from acetone/dichloromethane). (Found: C, 55.25; H 5.2; N, 16.3. $C_{16}H_{18}N_4O_3S$ requires C, 55.5; H, 5.2; N, 16.2%). ν_{max} 3430, 1700 cm^{-1}; $\delta(^1H)$ 2.17 (3H, s), 2.23 (3H, s), 2.39 (3H, s), 3.23 (1H, brs, NH), 7.4 (2H, d, J=8.5 Hz), 7.65 (1H, d, J=7.8 Hz, H5), 7.75 (1H, t, J=7.8 Hz, H4), 7.87 (2H, d, J=8.5 Hz), 8.16 (1H, d, J=8 Hz, H5), 9.61 (1H brs, NHCO).

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