Pyrrolization Processes of Vinyl Substituted Imidazo[1,2-*a*]pyridine, Pyrimidine and 1,8-Naphthyridine

O. Chavignon, J. C. Teulade* and M. Madesclaire

Laboratoire de Chimie Organique Pharmaceutique,
Groupe de Recherche en Pharmacochimie,
UFR de Pharmacie, 28 Place Henri Dunant,
B.P. 38, 63001 Clermont-Ferrand, France

A. Gueiffier, Y. Blache, H. Viols and J. P. Chapat

Laboratoire de Chimie Organique Pharmaceutique, URA-CNRS 1111,
15 Avenue Charles Flahault, Faculté de Pharmacie,
34000 Montpellier, France

G. Dauphin

Laboratoire de Chimie Organique Biologique, URA 485 CNRS,
63170 Aubière, France

Received April 10, 1991

A general synthesis for the preparation of a series of *N*-bridgehead compounds: pyrroloimidazopyridine, pyrimidine and naphthyridine has been developed beginning with azidovinyl compounds with thermolytic or photochemical methods.

J. Heterocyclic Chem., **29**, 691 (1992).

Introduction.

The imidazo[1,2-*a*]azine skeleton, when selectively bifunctionalized, is a building block for the preparation of tri and tetracyclic compounds with pronounced biological activities [1].

Recent synthetically attractive variants of the indolization process have been published [2], involving the construction of 2-vinyl compounds. On the other hand, thermolysis of azidoacrylates can be successfully used in the synthesis of pharmacologically important indoles and β-carbolines [3]. In the course of our extensive studies on the reactivity of heterocycles with a bridgehead nitrogen atom, we were interested in the intramolecular reaction of azidovinyls. The methods of preparation and the comparative results of thermolysis or photolysis are described here.

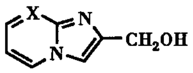
Results and Discussion.

An approach for the preparation of an unsubstituted compound involving aminovinylation in the imidazopyridine series fail [4]. The new approach for the preparation of the pyrrolization process involves the condensation of heteroaromatic aldehydes with ethyl azidoacetate.

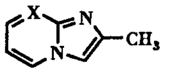
The hydride reduction route was very attractive to convert the esters **1a-c** to the corresponding methyl alcohols with subsequent oxidation to generate the aldehydes. In particular, from **1a** lithium aluminium hydride (LAH) gave the alcohol **2** [5]. However, no ester reduction was obtained from **1b,c**. When diisobutylaluminium hydride (DIBAL) was employed as the reducing agent according to the general procedure of Davey [6], we observed no ester and ring reduction. In attempting to obtain higher yields of the alcohols, we also investigated lithium borohydride reduction of the corresponding ethyl ester, consistent with the work of Kaminski [7]. The only side products observed when **1b,c** were treated with an excess of lithium borohydride in dioxane at 60° for 20 minutes were **3a,b** with 90 and 95% yields, respectively. Saturation of the 5,6,7,8 double bonds was the only reductive process observed (Scheme 1). Oxidation of 2-methylimidazo[1,2-*a*]pyridine (**4**) in nitrobenzene with selenium dioxide proceeded smoothly to give the aldehyde **10** in negligible yield.

1a X = CH Y = CH
1b X = N Y = CH
1c X = CH Y = N

3a X = NH Y = CH$_2$
3b X = CH$_2$ Y = NH



2

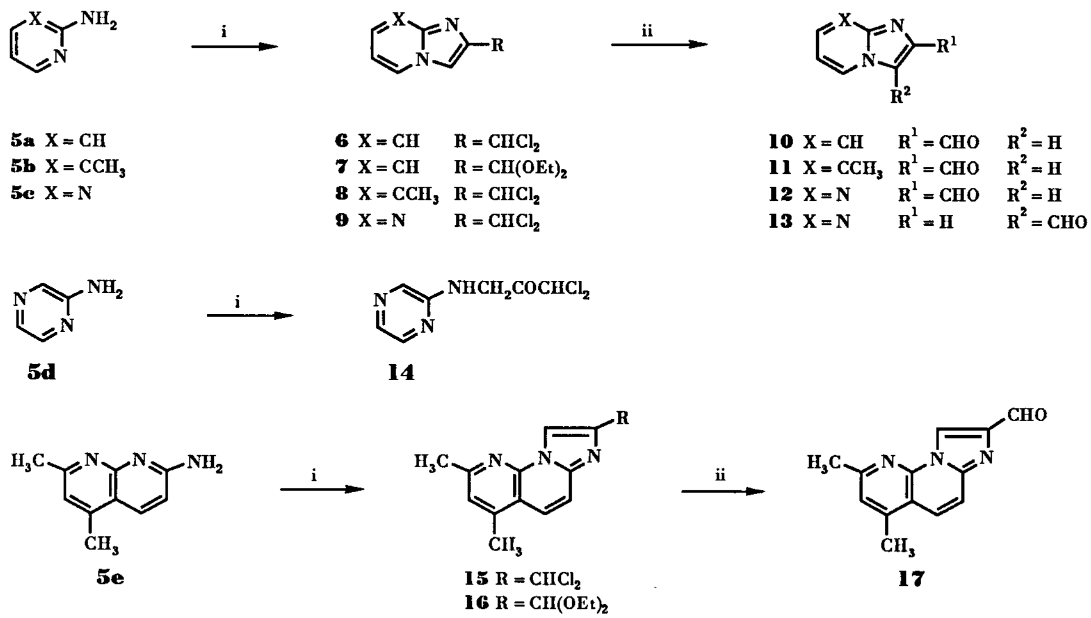


4

The reaction of salts derived from 2-nitropropane react with halogenomethyl aromatic compounds by a S_{N^2}-S_{RN^1} competitive mechanism to give aldehydes resulting of a *O*-alkylation [8a]. However, it has not been possible to prove the formation of aldehydes in the imidazopyridine series [8b].

Finally, our synthesis of the aldehydes **10-12** was carried out by a two-step procedure beginning with the condensation of 2-aminopyridines **5a,b**, pyrimidine **5c** and naphthyridine **5e** with 1,1,3-trichloroacetone. Treatment of **5a** with 1,1,3-trichloroacetone in 1,2-dimethoxyethane (DME) under the usual conditions generated a salt which upon heating in ethanol gave three products identified as

Scheme 1



Reagents: i, $ClCH_2COCHCl_2$; ii, $CaCO_3$, H_2O (compounds 6,8,9,15)

dichloromethyl compound **6** (90%), acetal **7** (5%) and aldehyde **10** (5% yield). Aqueous carbonate treatment of **6** provided **10** with a 90% yield. Similarly, **8** and **11** were obtained from **5b**. Compared to the pyridinic ring, the condensation of 2-aminopyrimidine with 1,1,3-trichloroacetone was less reactive at 0°, yielding 20% salt after 5 hours (*cf.* with the 80% conversion after 3 hours in the former case). In this case, only one product was isolated, *i.e.* dichloromethyl compound **9** readily identified through ^1H nmr and ms data. Conversion of **9** gave, after aqueous calcium carbonate treatment, partial Dimroth rearrangement of the aldehyde **12** to **13**. The ^1H nmr spectrum of compound **13** was characterized by a low field doublet (δ 9.78) suggesting a peri effect of 3-CHO group to H5. In contrast, this proton absorbed at $\delta = 8.65$ for the 2-isomer derivative **12** (38%). Attempts to cyclize 2-aminopyrazine (**5d**) and 1,1,3-trichloroacetone under various reaction conditions failed to produce the desired aldehyde. In fact, the only condensation product of **5d** with 1,1,3-trichloroacetone was **14** with a 47% yield.

Condensation of 7-amino-2,4-dimethyl-1,8-naphthyridine (**5e**) with 1,1,3-trichloroacetone in boiling ethanol, yielded the desired tricyclic structure at 60% (of consumed material). No reaction occured in DME. The main product was the dichloromethyl compound **15** (33% yield) while the two others were separated and characterized as the acetal **16** and the aldehyde **17**, with 10 and 17% yields, respectively. Conversion of **15** with calcium carbonate treatment, gave **17** in quantitative yield.

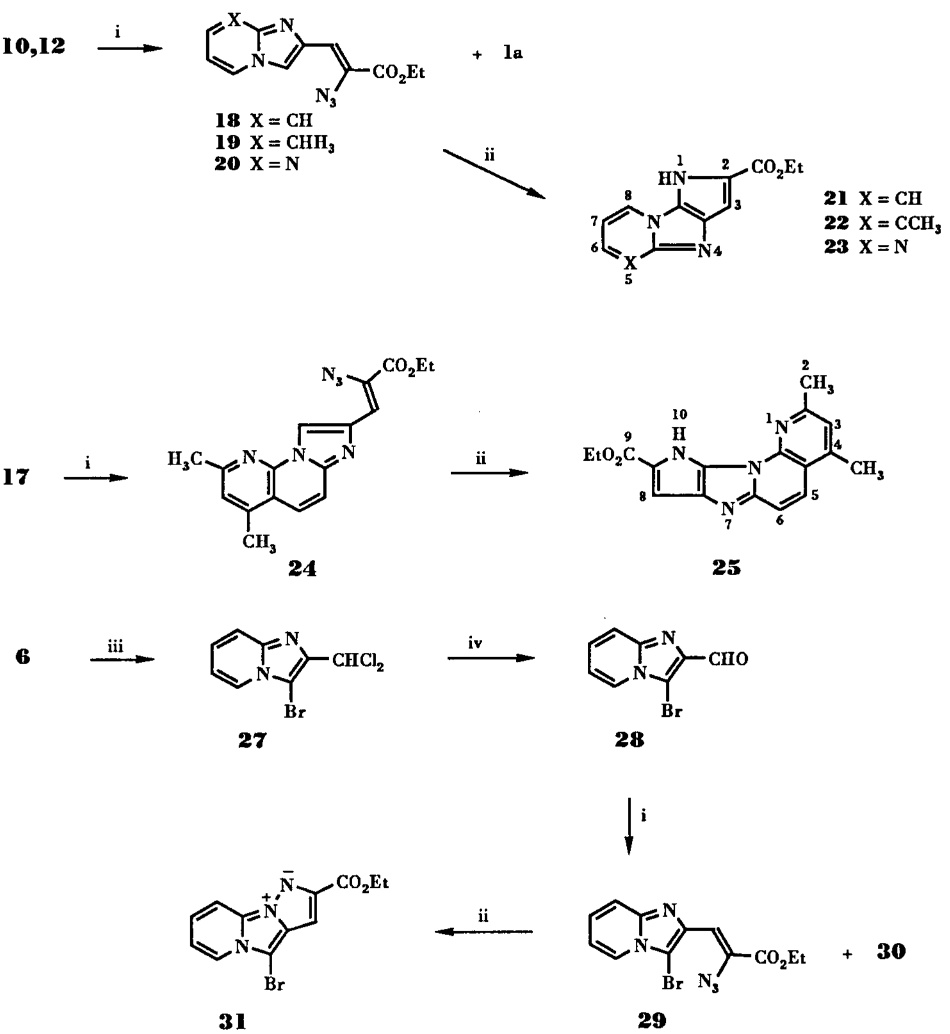
Condensation of the aldehyde **10** with ethyl azidoacetate in ethanolic sodium ethoxide at -30° gave the vinyl azide **18** and a by-product **1a** with 28 and 10% yields, respectively (Scheme 2). The mass spectrum ($M^{+\cdot}$: 190) and ^1H, ^{13}C nmr spectra obtained from the literature [9] were superimposable for **1a**, presumably formed from a crossed Tishchenko reaction. The aldehydes **11** and **12** behaved similarly to **19**, **20** with 35 and 36% yields, respectively. Such substrates are susceptible to two distinct cyclization pathways. An attack of the nitrene group of vinyl azide on the 3-carbon of the imidazole ring would lead to substituted pyrrole, while attack on the lone 1-nitrogen atom pair could provide a pyrazole structure.

Thermolysis of Azides.

Decomposition of the azides **18** and **19** was performed at 160° in dilute solution of halogenobenzene. From the azide **18** was isolated the tricyclic ester **21** in 52% yield. Examination of the mass spectral fragmentation patterns of **21** gave the molecular weight ($M^{+\cdot}$ 229) with a loss of C_2H_5 (M^+-29) and a peak at m/z 183 (100). Similarly, the azide **19** was converted into the tricyclic ester **22** with 46% yield as white crystalline solid, m/z 243 ($M^{+\cdot}$), 214 (M^+-Et) and 197 (100). The COSY spectrum gave H3 (7.05), H6 (7.0), H7 (6.68), H8 (8.31) connectivities and lacked an imidazolic signal consistent with results obtained in a ^{13}C-^1H correlation experiment.

The azide **20** totally decomposed within 8 minutes upon heating in refluxing trichlorobenzene. The resulting tricy-

Scheme 2



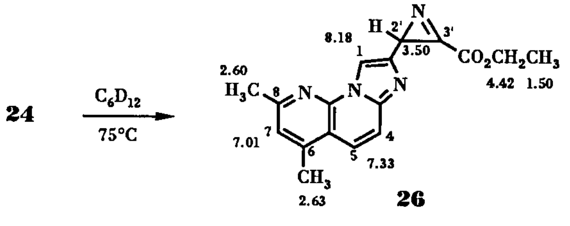
Reagents: i, $EtO_2CCH_2N_3$, NaOEt; ii, C_6H_5Br, Δ, (or CH_2Cl_2, hν); iii, Br_2, CH_3CO_2H; iv, $CaCO_3$, H_2O

clic ester **23** was isolated in 70% yield and characterized by m/z: 230 and ^1H and ^{13}C spectra.

Photolysis of the azide **18** in dry dichloromethane gave the same product **21** as from thermolysis of **18** with lowest yield (12%).

Finally, to explore the promotion of an N^+-N^- bond, the 3-position of **18** was blocked with a bromine substituent. In contrast to the reactivity of the azaindolizinic structures, imidazo[1,2-*a*][1,8]naphthyridines had a low reactivity toward electrophiles at the imidazolic 1-C carbon [10]. With few exceptions [11] the nitrene intermediate prefers to attack electron rich nitrogen atom, rather than a C insertion at the ortho position. Thus, thermolysis of the azides **24** and **29** appears attractive. The bromo derivative **27** was obtained by treatment of the dichloromethyl **6** with bromine in acetic acid. Conversion of **27** gave after calcium carbonate aqueous treatment the aldehyde **28** with 97% yield. Condensation of **17** and **28** with ethyl azidoacetate gave the vinyl azides **24** and **29** with 32 and 40% yields, respectively. From **28** was also obtained and characterized the ester **30**.

When compound **29** was thermolyzed in refluxing bromobenzene, $\overset{+}{N}$-$\overline{N}$ bond formed product **31**. Structure **31** was tentatively assigned to this product on the basis of its ms spectrum, but it could not be purified from the reaction mixture: m/z: 307-309.



Thermolysis of the azide **24** in bromobenzene gave a crystalline compound with in its mass spectrum a m/z: 308 ($M^{+\cdot}$). The novel pyrroloimidazonaphthyridine structure was established by ^1H and ^{13}C nmr. The ^1H nmr spectrum of the ester **25** showed the ethyl ester, methyl signals, characteristic H8 proton at δ 7.12, a H3 proton at δ 7.19 (J = 0.6 Hz) and two AB doublets at δ 7.54 and 7.58 corresponding to H5 and H6, respectively. The ^{13}C nmr spectrum of **25** showed four methines and nine quaternary carbon resonances, confirming that ring cyclization occurred at C10a (see Experimental). The intermediate azirine **26** can be observed by nmr when the thermolysis of **24** in perdeuteriocyclohexane was carried out at 75°.

EXPERIMENTAL

General Details.

Melting points were determined on a Büchi capillary apparatus and are not corrected. Elemental analyses were performed by Microanalytical Center, ENSCM, Montpellier. The ^1H nmr spectra were recorded with Varian EM 360 (60 MHz) or Brüker MSL 300; ^{13}C nmr spectra were performed on a Brüker MSL 300 instrument operating at 75 MHz. The ^{13}C chemical shifts are reported in ppm from TMS with the center resonance of deuteriochloroform as an internal reference for ^{13}C (77 ppm) and with the small amount of residual chloroform as an internal reference from the ^1H spectrum (7.24 ppm). Support for the assignments have been obtained by two-dimensional chemical shift correlation spectroscopy (2D COSY). The ir spectra were obtained on a Beckman AccuLab 2 spectrometer. Mass spectra were recorded on a LKB 2091 spectrometer at 70eV [(θ_{source}) = 180°]. Compounds were purified by high-performance liquid chromatography (hplc), Waters M 590 on a preparative alumina column. When necessary, solvents and reagents were dried prior to use. Dichloromethane was dried over activated alumina and distilled from calcium hydride. Thin layer chromatography (tlc) was performed on 0.25 mm E. Merck precoated neutral alumina plates. The photolysis solution was irradiated internally using a 100 W medium-pressure mercury lamp (Hanovia) with a Pyrex filter.

Ethyl 5,6,7,8-Tetrahydroimidazo[1,2-*a*]pyrimidine-2-carboxylate (**3a**).

To a well-stirred suspension of ethyl imidazo[1,2-*a*]pyrimidine-2-carboxylate (**1b**) (1 g, 5.2 mmoles) in dioxane (45 ml) was added portionwise powdered lithium borohydride (0.22 g, 10 mmoles). The resulting suspension was stirred for 10 minutes at room temperature and then gradually raised to 60°. Heating was continued for 20 minutes. The reaction mixture was cooled to room temperature and treated with dropwise addition of 1*N* hydrochloric acid. Dioxane was evaporated under reduced pressure. The residue was taken up in water and the suspension made alkaline with sodium carbonate and extracted with dichloromethane. The dichloromethane extracts were dried over anhydrous sodium sulfate, filtered and the filtrate was evaporated under reduced pressure to give **3a** (0.92 g, 90%), mp 164-166°; ^1H nmr (deuteriochloroform): 60 MHz, δ 1.3 (t, CH_3), 2.1 (m, H6 and 6'), 3.45 (m, H7 and 7'), 3.9 (m, H5 and 5'), 4.30 (q, CH_2-CH_3), 5.82 (s, NH), 7.2 (s, H3).

The following ester was prepared similarly:

Ethyl 5,6,7,8-Tetrahydroimidazo[1,2-*a*]pyrazine-2-carboxylate (**3b**).

This compound was obtained as a yellow oil (95%); ^1H nmr (deuteriochloroform): 60 MHz, δ 1.37 (t, CH_3), 3.22 (m, 2H), 4.06 (m, 4H), 4.32 (q, 2H), 7.51 (s, H3).

Anal. Calcd. for $C_9H_{13}N_3O_2$: C, 55.38; H, 6.67; N, 21.54. Found: C, 55.4; H, 6.5; N, 21.6.

Condensation of 2-Aminopyridine (**5a**) with 1,1,3-trichloroacetone.

To a stirred solution of 2-aminopyridine (**5a**) (25 g, 0.266 mole) in 1,2-dimethoxyethane (DME) (300 ml) was added dropwise a solution of 1,1,3-trichloroacetone (66 g, 0.408 mole) in 50 ml of DME. The mixture was stirred at room temperature for 4 hours. Filtration gave a solid which was poured into ethanol (200 ml) and heated under reflux for 3 hours. The cooled solution was evaporated, the suspension made alkaline with sodium carbonate and the solution extracted with dichloromethane. The dichloromethane extracts were dried (magnesium sulfate), and evaporated. The residue was chromatographed on silica gel. Elution with dichloromethane yielded dichloromethyl compound **6** in 90% yield, mp 127-129°; ^1H nmr (deuteriochloroform): 60 MHz, δ 6.85 (t, H6), 7.00 (s, CH), 7.27 (t, H7), 7.65 (dd, H8), 7.87 (s, H3), 8.16 (dd, H5); ms: (EI) 204, 202, 200, 167 (35%), 65 (100).

Anal. Calcd. for $C_8H_6Cl_2N_2$: C, 47.76; H, 2.99; N, 13.93. Found: C, 47.7; H, 2.8; N, 14.0.

Further elution gave the acetal **7** (5%) as a white liquid; ^1H nmr (deuteriochloroform): 60 MHz, δ 1.27 (t, CH_3), 3.72 (q, CH_2), 5.73 (s, CH), 6.73 (t, H6), 7.13 (t, H7), 7.58 (d, H8), 7.67 (s, H3), 8.10 (dd, H5).

Anal. Calcd. for $C_{12}H_{16}N_2O_2$: C, 65.45; H, 7.27; N, 12.73. Found: C, 67.3; H, 7.2; N, 12.8.

Further elution from the column, using dichloromethane-methanol (99:1 v/v) gave the aldehyde **10** (5%), mp 94-96°; ^1H nmr (deuteriochloroform): 60 MHz, δ 6.90 (t, H6), 7.30 (t, H7), 7.68 (dd, H8), 8.20 (s, H3), 8.23 (dd, H5), 10.17 (s, CHO).

Anal. Calcd. for $C_8H_6N_2O$: C, 65.75; H, 4.11; N, 19.18. Found: C, 65.8; H, 4.0; N, 19.2.

From 2-dichloromethylimidazo[1,2-*a*]pyridine (**6**) (5.0 g) with a calcium carbonate suspension in water, a white solid was obtained after a 1 hour reflux. Chromatography (silica gel-dichloromethane-methanol: 99/1 v/v) gave **10** with 90% yield, identical to that described above.

To a clear solution of 1 g of 2-methylimidazo[1,2-*a*]pyridine in 15 ml of freshly distilled nitrobenzene, 2 g of selenium dioxide was gradually added with stirring and heated under reflux for 2 hours. The hot solution was filtered and the filtrate was distilled to remove nitrobenzene. The residue was chromatographed on neutral alumina. Elution with dichloromethane yielded the aldehyde **10** in 2% yield.

2-Dichloromethyl-8-methylimidazo[1,2-*a*]pyridine (**8**) and 8-Methylimidazo[1,2-*a*]pyridine-2-carbaldehyde (**11**).

Prepared as described above from 2-amino-3-methylpyridine (**5b**) and 1,1,3-trichloroacetone. Severe foaming was observed when 1,1,3-trichloroacetone was added. Work-up as above gave two chromatographically inseparable crystalline products identified by ms as dichloromethyl compound **8** and aldehyde **11**.

From this mixture the dichloromethyl derivative was then converted into the aldehyde **11** by reflux in a suspension of calcium carbonate in water. The organic material was extracted with methylene chloride, the extracts dried (sodium sulfate) and evaporated to give the crude aldehyde **11**. This compound was purified by chromatography on an alumina column, eluted with dichloromethane. The aldehyde **11** (1.2 g, 52%) had mp 129-131°; ^{1}H nmr (deuteriochloroform): 60 MHz, δ 2.64 (s, 8-CH_3), 6.81 (t, H6), 7.12 (dd, H7), 8.10 (dd, H5), 8.20 (s, H3), 10.22 (s, CHO).

Anal. Calcd. for $C_9H_8N_2O$: C, 67.5; H, 5.0; N, 17.5. Found: C, 67.3; H, 5.1; N, 17.6.

Condensation of 2-Aminopyrimidine (**5c**) with 1,1,3-Trichloroacetone.

The reaction was conducted as described for the preparation of the dichloromethyl compound **6**. Work-up as before gave the dichloromethyl compound **9**, mp 179-181° dec; ^{1}H nmr (deuteriochloroform): 60 MHz, δ 6.98 (m, 2H), 7.83 (s, H3), 8.60 (m, 2H); ms: (EI) 205, 203, 201.

Anal. Calcd. for $C_7H_5Cl_2N_3$: C, 41.58; H, 2.48. Found: C, 41.7; H, 2.3.

The dichloromethyl **9** (1 g) was converted into the aldehyde by reflux in a suspension of calcium carbonate in water (5 g, 30 ml). Work-up as above yielded a residue (0.9 g). Chromatography on silica gel (eluent:dichloromethane) gave the aldehyde **12** (0.3 g, 38%), mp 209-211°; ^{1}H nmr (deuteriochloroform): 60 MHz, δ 7.01 (m, H6), 8.15 (s, H3), 8.65 (m, H5 and 7), 10.24 (s, CHO).

Anal. Calcd. for $C_7H_5N_3O$: C, 57.14; H, 3.40. Found: C, 57.0; H, 3.5.

Further elution gave the aldehyde **13** (0.4 g, 51%), mp 169-171°; ^{1}H nmr (deuteriochloroform): 60 MHz, δ 7.22 (m, H6), 8.56 (s, H2), 8.86 (m, H7), 9.78 (dd, H5), 10.02 (s, CHO).

Anal. Calcd. for $C_7H_5N_3O$: C, 57.14; H, 3.40. Found: C, 57.0; H, 3.6.

Condensation of 2-Aminopyrazine (**5d**) with 1,1,3-Trichloroacetone.

The reaction was conducted as described for **5a** except that the amino compound was dissolved in ethanol. The mixture was boiled under reflux (3 hours), cooled, filtered and the filtrate evaporated. The solid residue was chromatographed on silica gel, eluting with dichloromethane-methanol (95:5 v/v) to yield **14** (2 g, 47%), mp 146-148° dec; ^{1}H nmr (DMSO-d_6): 60 MHz, δ 5.01 (s, NH), 7.70 (s, 1H), 7.99 (d, 1H), 8.48 (s, 2H), 8.71 (d, 1H), 9.18 (s, 1H).

Condensation of 7-Amino-2,4-dimethyl-1,8-naphthyridine (**5e**) with 1,1,3-Trichloroacetone.

Reaction of 7-amino-2,4-dimethyl-1,8-naphthyridine (**5e**) (5 g, 28.3 mmoles) with 1,1,3-trichloroacetone (7 g, 43.3 mmoles) in ethanol (200 ml) under reflux for 4 hours gave after cooling, filtration of the unreacted **5e** and evaporation of solvent, 4 g of a brown mixture. To the residual mass aqueous sodium carbonate solution (10%, 50 ml) was added and the mixture was extracted with methylene chloride. The dichloromethane portion was dried (sodium sulfate) and evaporated under reduced pressure to yield the following compounds (alumina column, dichloromethane as eluent): 2-dichloromethyl-6,8-dimethylimidazo[1,2-*a*][1,8]naphthyridine (**15**) (2.6 g, 33%), mp 121-123°; ^{1}H nmr (deuteriochloroform): 60 MHz, δ 2.63 (s, CH_3), 2.67 (s, CH_3), 6.80 (s, $CHCl_2$), 7.19 (s, H7), 7.62 (m, H4 and 5), 8.52 (s, H1).

Anal. Calcd. for $C_{13}H_{11}Cl_2N_3$: C, 55.73; H, 3.96. Found: C, 55.5; H, 4.1.

Further elution gave 2-(diethoxymethyl)-6,8-dimethylimidazo[1,2-*a*][1,8]naphthyridine (**16**) (0.8 g, 10%), mp 197-199°; ^{1}H nmr (deuteriochloroform): 60 MHz, δ 1.32 (t, CH_3), 2.45 (s, CH_3), 2.62 (s, CH_3), 3.80 (q, CH_2), 5.85 (s, CH), 6.92 (s, H7), 7.40 (s, H5 and 4), 8.45 (s, H1).

Anal. Calcd. for $C_{17}H_{21}N_3O_2$: C, 68.3; H, 7.0; N, 14.0. Found: C, 68.1; H, 7.1; N, 13.9.

Further elution from the column, using dichloromethane-methanol (95:5 v/v) gave 6,8-dimethylimidazo[1,2-*a*][1,8]naphthyridine-2-carboxaldehyde (**17**) (1.1 g, 17%), mp 206-208°; ^{1}H nmr (deuteriochloroform): 60 MHz, δ 2.60 (s, CH_3), 2.70 (s, CH_3), 7.20 (s, H7), 7.56 (s, H5), 7.65 (s, H4), 9.01 (s, H1), 10.20 (s, CHO).

Anal. Calcd. for $C_{13}H_{11}N_3O$: C, 69.33; H, 4.89; N, 18.67. Found: C, 69.3; H, 4.8; N, 18.8.

A stirred suspension of the dichloromethyl compound **15** (2 g, 7.1 mmoles) and calcium carbonate (5 g) in water (50 ml) was boiled under reflux (1 hour). The mixture was basified to *p*H 8 and the aldehyde **17** extracted with methylene chloride. The dichloromethane solution was dried (sodium sulfate) and evaporated under reduced pressure. Chromatography on alumina (eluent dichloromethane) gave **17** in 99% yield.

Ethyl 2-Azido-3-(imidazo[1,2-*a*]pyridin-2-yl)propenoate (**18**).

A mixture of the ethyl azidoacetate (10.36 g, 0.08 mole) and aldehyde **10** (1.17 g, 8 mmoles) in ethanol (3 ml) was added dropwise over 3 hours to a stirred solution of sodium (0.8 g, 35 mg-atom) in ethanol (22 ml) at -30°. The mixture was stirred at this temperature for 1 hour, at -15° for 2 hours and then allowed to warm to room temperature and then stirred for a further 30 minutes. It was poured onto aqueous saturated ammonium chloride, and extracted with ether. The ether extracts were dried (sodium sulfate), evaporated under reduced pressure and the residue chromatographed on neutral alumina. Elution with dichloromethane gave ethyl imidazo[1,2-*a*]pyridine-2-carboxylate (**1a**) (150 mg, 10%), mp 56-58° (from carbon tetrachloride) [lit 57-59°].

Further elution gave the azide **18** (576 mg) in 28% yield, mp 146-148°; ir (potassium bromide): ν cm^{-1}, 2121 (N_3), 1683 (CO), 1185 (COC), 743 (arom); ^{1}H nmr (deuteriochloroform): 60 MHz, δ 1.33 (t, CH_3), 4.32 (q, CH_2), 6.81 (t, H6), 7.19 (s, CH_{vinyl}), 7.20 (t, H7), 7.55 (d, H8), 8.11 (d, H5), 8.26 (s, H3).

Anal. Calcd. for $C_{12}H_{11}N_5O_2$: C, 56.0; H, 4.28. Found: C, 56.1; H, 4.3.

Ethyl 2-Azido-3-(8-methylimidazo[1,2-*a*]pyridin-2-yl)propenoate (**19**).

A solution of ethyl azidoacetate (10.36 g, 0.08 mole) and aldehyde **11** (1.28 g, 8 mmoles) in ethanol (5 ml) was added dropwise over 6 hours to a stirred solution of sodium (0.8 g, 25 mg-atom) in ethanol (22 ml) at -30°. Work-up as above gave the azide **19** (720 mg, 35%), mp 139-141°; ir (potassium bromide): ν cm^{-1} 2120 (N_3); ^{1}H nmr (deuteriochloroform): 60 MHz, δ 1.32 (t, CH_3), 2.52 (s, CH_3), 4.32 (q, CH_2), 6.64 (t, H6), 6.92 (d, H7), 7.25 (s, CH_{vinyl}), 7.97 (d, H5), 8.25 (s, H3).

Anal. Calcd. for $C_{13}H_{13}N_5O_2$: C, 57.56; H, 4.8; N, 25.83. Found: C, 57.6; H, 4.7; N, 25.8.

Ethyl 2-Azido-3-(imidazo[1,2-*a*]pyrimidin-2-yl)propenoate (**20**).

This compound was obtained in 36% yield, mp 145-147°; ir (potassium bromide): ν cm^{-1}, 2117 (N_3), 1713 (CO), 1263 (COC), 766 (arom); ^{1}H nmr (deuteriochloroform): 60 MHz, δ 1.37 (t, CH_3), 4.39 (q, CH_2), 6.92 (m, H6), 7.24 (s, CH_{vinyl}), 8.33 (s, H3), 8.50 (m, H5 and 7).

Ethyl 2-Azido-3-(6,8-dimethylimidazo[1,2-*a*][1,8]naphthyridin-2-yl)propenoate (**24**).

This compound was obtained in 32% yield, mp 154-156°; ir (potassium bromide): ν cm^{-1}, 2125 (N_3); ^{1}H nmr (deuteriochloroform): 60 MHz, δ 1.42 (t, CH_3), 2.57 (s, CH_3), 2.65 (s, CH_3), 4.40 (q, CH_2), 7.08 (s, H7), 7.20 (s, CH_{vinyl}), 7.40 (s, H5), 7.45 (s, H4), 8.96 (s, H1).

3-Bromo-2-dichloromethylimidazo[1,2-*a*]pyridine (**27**).

To a stirred solution of **6** (2 g, 9.9 mmoles) in 20 ml of acetic acid was added dropwise a slight molar excess of bromine. After complete addition, the solution was stirred for 1 hour, made basic with 10% aqueous sodium carbonate solution and then extracted with dichloromethane. The combined dichloromethane extracts were dried (sodium sulfate) and filtered. The dichloromethane was removed *in vacuo* and the residue was purified by chromatography on neutral alumina. Elution with dichloromethane yielded 2.5 g of **27**, mp 100-102°; ^{1}H nmr (deuteriochloroform): 60 MHz, δ 6.96 (t, H6), 7.02 (s, $C\mathit{H}Cl_2$), 7.32 (t, H7), 7.69 (dd, H8), 8.09 (d, H5).

3-Bromoimidazo[1,2-*a*]pyridine-2-carboxaldehyde (**28**).

A stirred suspension of **27** (1 g, 44 mmoles) and calcium carbonate (5 g) suspended in water (60 ml) was heated under reflux for 1 hour. The mixture was made basic with 10% aqueous sodium carbonate solution and extracted with dichloromethane. The combined extracts were dried (sodium sulfate), filtered and evaporated under reduced pressure. Chromatography on neutral alumina (eluent dichloromethane) gave **28** in 97% yield, mp 123-125°; ^{1}H nmr (deuteriochloroform): 60 MHz, δ 7.09 (t, H6), 7.38 (t, H7), 7.73 (d, H8), 8.27 (d, H5), 10.25 (s, CHO).

Ethyl 2-Azido-3-(3-bromoimidazo[1,2-*a*]pyridin-2-yl)propenoate (**29**).

A solution of ethyl azidoacetate (7.7 g, 0.06 mole) and aldehyde **28** (0.87 g, 3.9 mmoles) in ethanol (1 ml) was added dropwise over 5 hours to a stirred solution of sodium (0.6 g, 26 mg-atom) in ethanol (25 ml) at -35°. Work up as **21** gave ethyl 3-bromoimidazo[1,2-*a*]pyridine-2-carboxylate (**30**) (5%), mp 57-59°; ^{1}H nmr (deuteriochloroform): 60 MHz, δ 1.47 (t, CH_3), 4.55 (q, CH_2), 7.04 (t, H6), 7.37 (t, H7), 7.74 (d, H8), 8.26 (d, H5); ms: (EI) 268-270° ($M^{+\cdot}$).

Further elution gave the azide **29** in 40% yield, mp 121-123°; ir (potassium bromide): ν cm^{-1}, 2122 (N_3); ^{1}H nmr (deuteriochloroform): 60 MHz, δ 1.41 (t, CH_3), 4.42 (q, CH_2), 6.93 (t, H6), 7.05 (s, H_{vinyl}), 7.26 (t, H7), 7.73 (d, H8), 8.10 (d, H5).

Anal. Calcd. for $C_{12}H_{10}BrN_5O_2$: C, 42.86; H, 2.97. Found: C, 42.8; H, 3.2.

Thermolysis of the Azide **18**.

A solution of the azide **18** (100 mg) in 1,2,4-trichlorobenzene (10 ml) was added under reflux dropwise over 10 minutes to 1,2,4-trichlorobenzene (70 ml). Evaporation of the solvent under reduced pressure, and chromatography of the residue gave **21** with a 52% yield; ^{1}H nmr (deuteriochloroform): 300 MHz, δ 1.35 (t, CH_3), 4.32 (q, CH_2), 6.74 (t, H7), 7.10 (s, H3), 7.15 (td, H6), 7.26 (s, NH), 7.58 (d, H5), 8.22 (d, H8); ms: (EI) 229 ($M^{+\cdot}$, 27%), 183 (100), 155 (25), 78 (25).

Photolysis of the Azide **18**.

Using the apparatus described at the beginning of the Experimental, with water cooling for an ambient temperature reaction, pure nitrogen was passed through the solution of **18** (0.5 g) in dichloromethane (200 ml). The reaction was monitored by following the disappearance of the azide ir absorption (2 hours). After removal of the solvent, the residue was chromatographed on neutral alumina to give **21** with a 12% yield.

Thermolysis of the Azide **19**.

A solution of the azide **19** (100 mg) in bromobenzene (10 ml) was added under reflux dropwise over 10 minutes to bromobenzene (60 ml). Evaporation of the solvent under reduced pressure, and chromatography of the residue gave **22**, mp 225-227°; ir (potassium bromide): ν cm^{-1} 3263 (NH), 1673 (CO), 1200 (COC), 755 (arom); ^{1}H nmr (deuteriochloroform): 300 MHz, δ 1.42 (t, CH_3), 2.63 (s, CH_3), 4.40 (q, CH_2), 6.68 (t, H7), 7.00 (d, H6), 7.05 (s, H3), 8.31 (d, H8); ^{13}C nmr (perdeuteriomethanol): 75.4 MHz, δ 14.79 (CH_3), 17.40 (5–CH_3), 61.66 (CH_2), 102.57 (C6), 111.90 (C7), 122.75 (C8), 125.38 (C3), 126.17, 128.05, 130.40, 136.05, 149.50, 163.40; ms: (EI) 243 ($M^{+\cdot}$, 26%), 198 (22), 197 (100), 169 (19), 168 (13).

Thermolysis of the Azide **20**.

A solution of the azide **20** (100 mg) in 1,2,4-trichlorobenzene (5 ml) was added under reflux dropwise over 8 minutes to 1,2,4-trichlorobenzene (60 ml). Evaporation of the solvent under reduced pressure and chromatography on neutral alumina with dichloromethane as eluent gave (**23**), mp 273-275°; ir (potassium bromide): ν cm^{-1}, 1690 (CO), 1201 (COC), 762 (arom); ^{1}H nmr (perdeuteriomethanol): 300 MHz, δ 1.52 (t, CH_3), 4.5 (q, CH_2), 7.14 (s, H3), 7.16 (m, H7), 8.63 (dd, H6), 8.91 (dd, H8); ^{13}C nmr (perdeuteriomethanol): 75.4 MHz, δ_{CH} 14.76, 61.96, 102.58, 108.44, 133.16, 151.45; ms: (EI) 230 ($M^{+\cdot}$, 29%), 185 (23), 184 (100), 157 (9), 156 (19).

Thermolysis of the Azide **24**.

A solution of the azide **24** (100 mg) in bromobenzene (10 ml) was added under reflux dropwise over 10 minutes to bromobenzene (60 ml). Evaporation of the solvent under reduced pressure, and chromatography of the yellow residue gave **25**, mp 232-234°; ir (potassium bromide): ν cm^{-1}, 3180 (NH), 1704 (CO), 1190 (COC), 763 (arom); ^{1}H nmr (deuteriochloroform): 300 MHz, δ 1.48 (t, $CH_2C\mathit{H}_3$), 2.65 (s, CH_3), 2.74 (s, CH_3), 4.47 (q, CH_2), 7.12 (s, H8), 7.19 (d, H3, $J_{3,CH3}$ = 0.6 Hz), 7.54 (d, H5, AB system), 7.58 (d, H6), 9.65 (s, NH); ^{13}C nmr (deuteriochloroform): 75.4 MHz, δ 14.62, 18.69, 24.87, 60.85, 103.37 (CH), 114.21, 117.36 (CH), 121.57 (CH), 121.95 (CH), 124.67, 129.42, 135.47, 143.27, 146.12, 146.77, 158.34, 162.34; ms: (EI) 308 ($M^{+\cdot}$, 49%), 263 (28), 262 (100), 234 (28), 157 (18).

Thermolysis of the Azide (**29**).

The reaction was conducted as described for **24** with the azide **29** (100 mg). Evaporation of the solvent under reduced pressure gave the impure **31**; ms: m/z 307, 309 ($M^{+\cdot}$), 263, 265.

REFERENCES AND NOTES

[1a] T. Yamamoto, K. Tsuji, T. Kosuge, T. Okamoto, K. Shudo, K. Takeda, Y. Itaka, K. Yamaguchi, Y. Seino, T. Yahagi, M. Nagao and T. Sugimara, *Proc. Japan Acad.*, **54**, 248 (1978); [b] D. J. Blythin, J. J. Kaminsky, M. S. Domalski, J. Spitler, D. M. Salomon, D. J. Conn, S. C. Wong, L. L. Verbiar, L. A. Bober, P. J. S. Chin, A. S. Watnick, M. I. Siegel, M. J. Hilbert and A. T. Mc Phail, *J. Med. Chem.*, **29**, 1099 (1986); J. Boryski, B. Golankiewicz and E. De Clercq, *J. Med. Chem.*, **31**, 1351 (1988).

[2] V. Pindur and R. Adams, *J. Heterocyclic Chem.*, **25**, 1 (1988).

[3a] L. Henn, D. M. B. Hickey, C. J. Moody and C. W. Rees, *J. Chem. Soc., Perkin Trans. I*, 2189 (1984); [b] C. J. Moody and J. G. Ward, *ibid.*, 2895 (1984).

[4] Reductive cyclization [12] of the *N,N*-dimethyl-2-[3-nitroimidazo-[1,2-*a*]pyridine]ethenamine, mp 133-135°; ^{1}H nmr (deuteriochloroform): 60 MHz, δ 3.13 (s, N(CH$_3$)$_2$), 6.23 (s, CH$_{vinyl}$), 6.93 (dd, H6), 7.40 (m, H7 and 8), 8.03 (s, CH$_{vinyl}$), 9.43 (d, H5); ^{13}C nmr (deuteriochloroform): 75.4 MHz, δ 41.15, 88.01, 113.25, 115.53, 128.94, 131.86, 147.33, 151.54, 153.54.

Anal. Calcd. for $C_{11}H_{12}N_4O_2$: C, 56.89; N, 24.13. Found: C, 56.8; N, 24.1, gave an unidentified dimeric structure, mp 240-242°; ms: (EI) 310 ($M^{+\cdot}$, 100%), 155.

[5] T. B. Alminger, A. Braendstroem, S. Carlsson, P. Lindberg, P. Nordberg and G. Sunden, PCT WO 8705021 A1.

[6] D. D. Davey and W. C. Lumma, Jr., *J. Org. Chem.*, **54**, 3211 (1989).

[7] D. J. Conn, J. K. Kaminski, D. M. Salomon and A. T. McPhail, *J. Org. Chem.*, **53**, 3265 (1988).

[8a] M. P. Crozet, O. Jentzer and P. Vanelle, *Tetrahedron Letters*, **28**, 5531 (1987); [b] P. Vanelle, J. Maldonado, N. Madadi, A. Gueiffier, J. C. Teulade, J. P. Chapat and M. P. Crozet, *ibid.*, **31**, 3013 (1990).

[9a] J. G. Lomdardino, *J. Org. Chem.*, **30**, 2403 (1965); [b] J. C. Teulade, R. Escale, G. Grassy, J. P. Girard and J. P. Chapat, *Bull. Soc. Bull. Chim. France*, **II**, 530 (1979).

[10] A. Gueiffier, Y. Blache, H. Viols, J. C. Teulade, O. Chavignon, G. Dauphin and J. P. Chapat, *Heterocycles*, 1990, submitted.

[11a] R. Y. Ning, P. B. Madan and L. A. Sternbach, *J. Org. Chem.*, **38**, 3995 (1973); [b] I. M. Robbie, O. Meth-Cohn and H. Suschitzky, *Tetrahedron Letters*, 925 (1976); [c] *Ibid*, 929 (1976);[d] K. T. Potts and J. L. Marshall, *J. Org. Chem.*, **48**, 129 (1976).

[12a] M. Kawase, A. K. Sinhababu and R. T. Borchardtr, *J. Heterocyclic Chem.*, **24**, 1499 (1987); [b] J. Harley-Mason, *J. Chem. Soc.*, 200 (1953); [c] L. I. Kruse, *Heterocycles*, **19**, 1119 (1981).