# Synthesis of Fused Pyridines under Neutral Conditions

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*Summary* Thermal decomposition of vinyl azides prepared by condensation of ethyl azidoacetate with aromatic and heteroaromatic aldehydes bearing *ortho* methyl groups provides a simple and general synthesis of *c*-fused pyridines under neutral conditions.

THE fusion of pyridine rings on to aromatic systems usually requires vigorous acidic conditions so that in the synthesis of polyfunctional compounds the ring system often has to be constructed at an early stage, leaving much subsequent manipulation of substituents. We now report a simple and apparently general procedure for pyrido-annulation under completely neutral conditions, based on the ready synthesis and thermal decomposition of vinyl azides.[1]

Mesitaldehyde condensed with ethyl azidoacetate in ethanolic sodium ethoxide at 0 °C to give the azidocinnamate (**1**) (40%) as an oil. This azide was decomposed by boiling in toluene or bromobenzene for 2 h with the reflux condenser open to the atmosphere to give, by layer chromatography, ethyl 5,7-dimethylisoquinoline 3-carboxylate (**2**) (45—50%), m.p. 83—84 °C. The decomposition was less clean and the yield much reduced if the thermolysis was performed with exclusion of oxygen. Hydrolysis of (**2**) with sodium hydroxide in methanol–tetrahydrofuran gave 5,7-dimethylisoquinoline 3-carboxylic acid (86%), m.p. 230—232 °C, which was decarboxylated by distillation from copper and copper sulphate at 270 °C to give 5,7-dimethylisoquinoline (100%) as an oil, picrate m.p. 260—262 °C (lit.[2] m.p. 261—262 °C).

Similar condensation of 1,3,5-trimethylpyrazole-4-carbaldehyde[3] with ethyl azidoacetate gave the azidoacrylate (**3**) as a yellow oil (60%) which decomposed in boiling bromobenzene (2 h) to give ethyl 1,3-dimethylpyrazolo-[3,4-*c*]pyridine-5-carboxylate (**4**) (48%), m.p. 176—177 °C.

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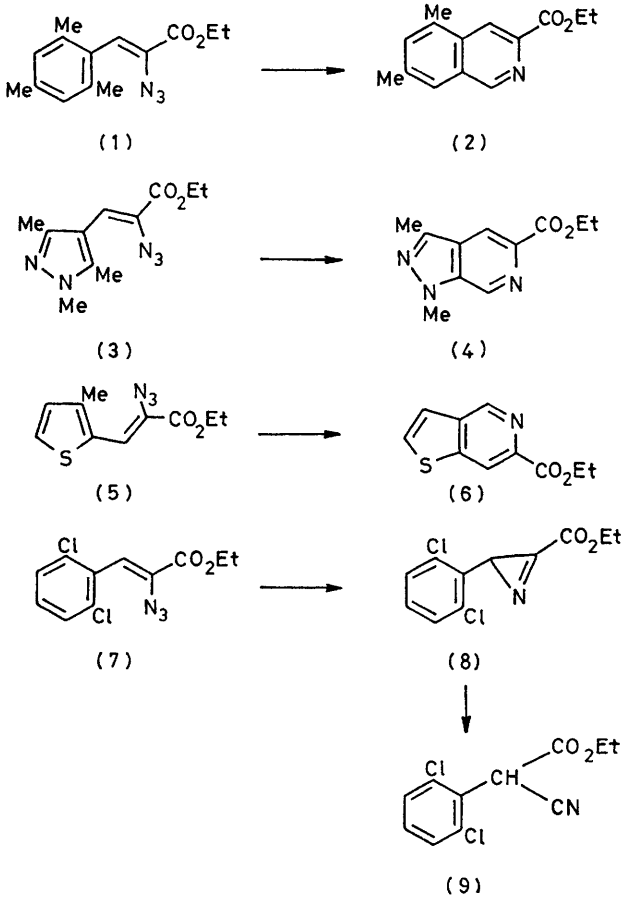
That the product was (**4**) rather than the 2,3-dimethyl isomer was clear from a comparison of its u.v. and n.m.r. spectra with those of 1- and 2-methylindazoles. The thiophen azidoacrylate (**5**), m.p. 73 °C (lit.[4] m.p. 68 °C), was similarly prepared and thermolysed to give ethyl thieno[3,2-*c*]pyridine-6-carboxylate (**6**) (45%), m.p. 65 °C (lit.[5] m.p. 65 °C).




In the decomposition of these vinyl azides loss of nitrogen is expected to give the corresponding azirine, in equilibrium with the vinyl nitrene; the nitrene could insert into the adjacent methyl group leading to the 1,2-dihydroisoquinoline which is dehydrogenated, possibly by more nitrene, to give the product isolated. In agreement with this, when the azide (**1**) was decomposed in toluene in the presence of iodine (2 mol) and potassium acetate (2 mol), the yield of the pure isoquinoline (**2**) isolated rose to 92%. Iodine did not, however, have a similar beneficial effect on the decomposition of the azides (**3**) and (**5**).

Evidence for azirine intermediates was provided by decomposition of the dichloro azidocinnamate (**7**),[6] an oil, in toluene (5 h) when the azirine (**8**), m.p. 94 °C, was isolated (82%; quantitative yield estimated by n.m.r.). On more vigorous heating (flash vacuum pyrolysis, 450 °C and $10^{-3}$ Torr) this azirine isomerised quantitatively to the cyanide (**9**), m.p. 245—247 °C, probably by a mechanism similar to that proposed for the rearrangement of analogous azidoketones.[7]

Styryl azides with an adjacent unsubstituted *ortho* position are known to cyclise, with loss of nitrogen, to give indoles, though higher decomposition temperatures have generally been employed.[1,8] Under our conditions, *o*-tolualdehyde gave ethyl 4-methylindole 2-carboxylate, m.p. 140—141 °C (lit.[9] m.p. 140·5 °C), in good overall yield.

Structures of all new compounds are supported by full spectroscopic data and, except for the azides, by combustion analysis. Although yields have not yet been optimised, the ready formation and decomposition of these vinyl azides provides a simple and probably very general route to [*c*]pyrido-compounds from *ortho*-alkylated aromatic and heteroaromatic aldehydes, under mild conditions.

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