Pyridazine *N*-Imides. Simple Precursors for Pyrazolo[2,3-*b*]pyridazines

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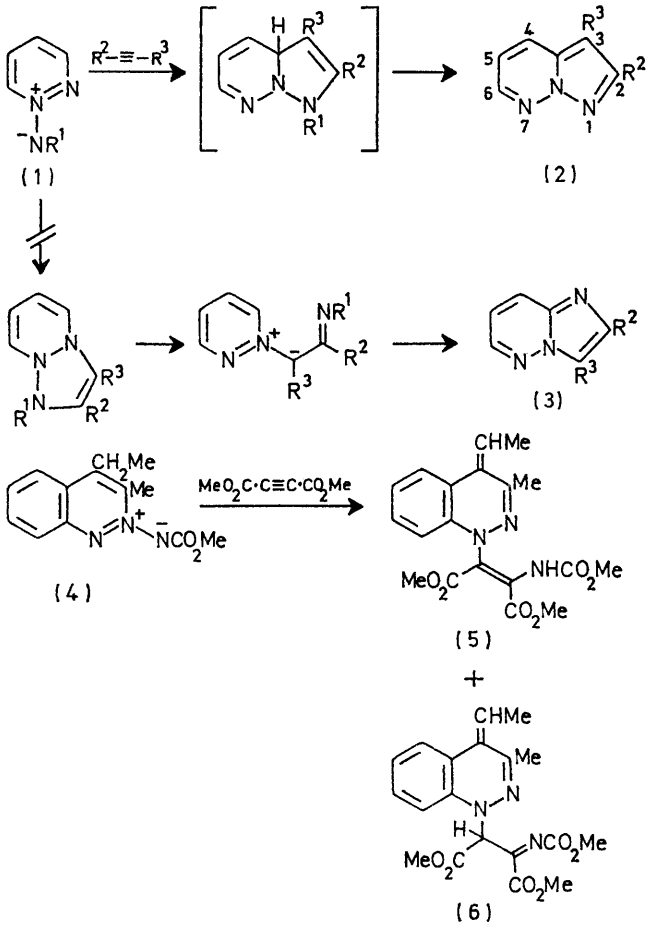
Summary Pyridazine *N*-imides (**1**) react with acetylenic esters as azomethine imines, rather than azimines; spontaneous aromatisation of the initial cycloadducts gives the pyrazolo[2,3-*b*]pyridazine ring system (**2**).

BENZOCINNOLINE *N*-IMIDES have recently provided the first examples of 1,3-dipolar cycloaddition of the three nitrogen azimine system.[1] The parent pyridazine *N*-imides (**1**) are of interest since in principle they can react as azimines or as azomethine imines. Azomethine imine reactivity is implied in the reaction of *N*-unsubstituted pyridazine imides with dimethyl acetylenedicarboxylate to give pyrazolo[2,3-*b*]-pyridazines, but the mechanism of this reaction and the possibility of competing azimine reactivity has not been considered.[2]



Liberation of the imide (**1**, R^1 = H) from its mesitylene-sulphonate salt[3] with pyridine in the presence of two equivalents of dimethyl acetylenedicarboxylate in dimethylformamide gave the pyrazolo[2,3-*b*]pyridazine (**2**, R^2 = R^3 = CO_2Me) (50%).[2] Similarly, diethyl acetylenedicarboxylate gave the corresponding diethyl ester (47%), m.p. 114—115°, and ethyl propiolate gave the mono ester (**2**, R^2 = H, R^3 = CO_2Et) (45%), m.p. 74—75°.† The parent of this new heterocyclic system, pyrazolo[2,3-*b*]pyridazine (**2**, R^2 = R^3 = H) was obtained (62%) as a colourless oil, b.p. 270°, λ_{max} 224 (ϵ, 37,100), 276 (1200), 283(sh) (1080), and 317 nm (1420), τ ($CDCl_3$) 1·75 [1H, q, *J* 4·8 and 2 Hz, H(6)], 1·98 [1H, d, 3 Hz, H(2)], 2·05 [1H, q, *J* 10 and 2 Hz, H(4)], 3·05 [1H, q, *J* 10 and 4·8 Hz, H(5)], and 3·38 [1H, d, *J* 3 Hz, H(3)], from the mono ester by hydrolysis with methanolic potassium hydroxide and decarboxylation with hot 57% hydriodic acid.

The acetyl, benzoyl, and ethoxycarbonyl derivatives (**1**, R^1 = COMe, COPh, and CO_2Et) with dimethyl acetylenedicarboxylate also gave the pyrazolopyridazine (**2**, R^2 = R^3 = CO_2Me) though, not surprisingly, the reactions are slower and the yields lower since the final aromatisation does not simply involve dehydrogenation. An analogous reaction has been reported for substituted pyridine imides[4] and as in that reaction the addition of tetracyanoethylene was found to improve the rate and yield.

These pyrazolopyridazines most reasonably arise by 1,3-dipolar cycloaddition, with the imides acting as azomethine imines, followed by aromatisation. No products resulting from cycloaddition as an azimine were isolated. In particular the isomeric imidazo[1,2-*b*]pyridazine (**3**, R^2 = R^3 = CO_2Et), synthesised from 3-amino-6-chloropyridazine and diethyl α-bromooxalacetate, was not detected in the cycloaddition to diethyl acetylenedicarboxylate. It was anticipated that this isomer would arise from an initial azimine adduct by ring opening[1] followed by 1,5-dipolar cyclisation and aromatisation.[5] Pyridazine imides therefore resemble the isoelectronic pyridine imides[4] rather than the dibenzopyridazine (benzocinnoline) imides[1] where azomethine imine reactivity is precluded. This periselectivity is expected if these dipolar cycloadditions are controlled by the dipole HOMO and dipolarophile LUMO. Incorporation of the additional electronegative N atom in the azimine system should lower the orbital energies relative to those of the azomethine imine and so reduce the dominant FMO interaction.[6]

Azomethine imine and azimine reactivity appears to be reasonably finely balanced, however, and can be controlled for example by appropriate benzo-fusion. Thus the cinnoline 2-imide (**4**), where the initial azomethine imine cycloadduct would be *o*-quinonoid, gave the interconvertible adducts (**5**) (60%), m.p. 125—127° and (**6**) (22%), m.p. 139—140°, with dimethyl acetylenedicarboxylate in methylene chloride at room temperature. Their formation can be readily explained by ring opening of the initial azimine cycloadduct (*cf.* benzocinnoline *N*-imides[1]) followed by hydrogen migration from the 4-ethyl group.

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† That this adduct is the expected regioisomer is confirmed by its ^1H n.m.r. spectrum: H(4) in (**2**, R^2 = H, R^3 = CO_2Et) absorbs at τ 1·54; *cf.* τ 1·46 for (**2**, R^2 = R^3 = CO_2Me) and τ 2·05 for (**2**, R^2 = R^3 = H).

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