Reaction of 1,2,4-Triazolo[4,3-*a*]pyridine with Dimethyl Acetylenedicarboxylate: New Structures and Mechanisms

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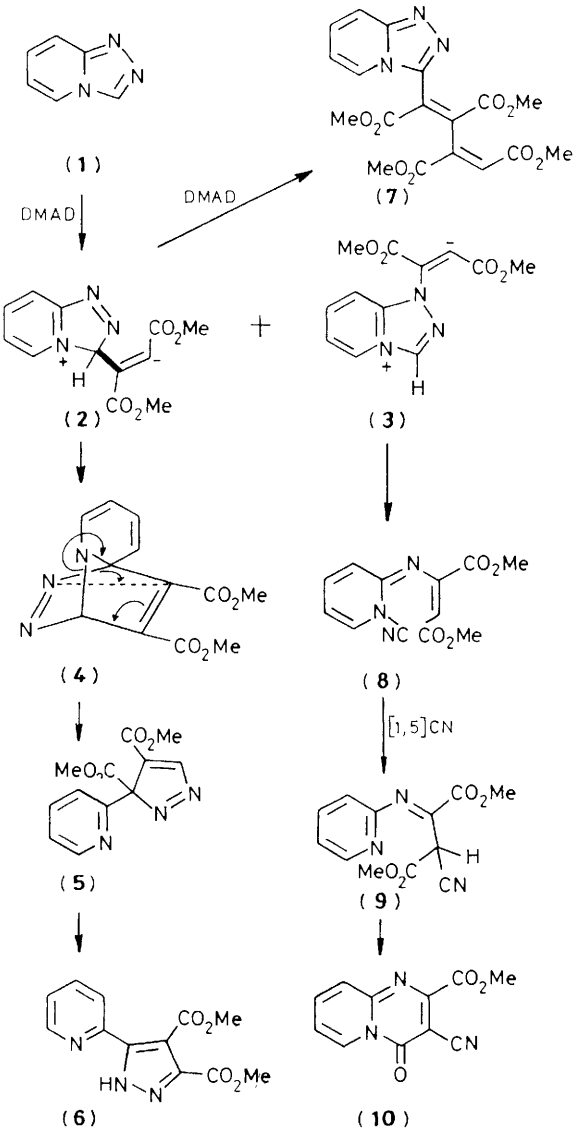
Reaction of 1,2,4-triazolo[4,3-*a*]pyridine (**1**) with dimethyl acetylenedicarboxylate gives the pyrimidone (**10**), the pyrazole (**6**), and the 1 : 2-adduct (**7**); reaction mechanisms, which include a [1,5] CN shift from nitrogen to carbon, are proposed, and two earlier structures for products of this reaction are corrected.

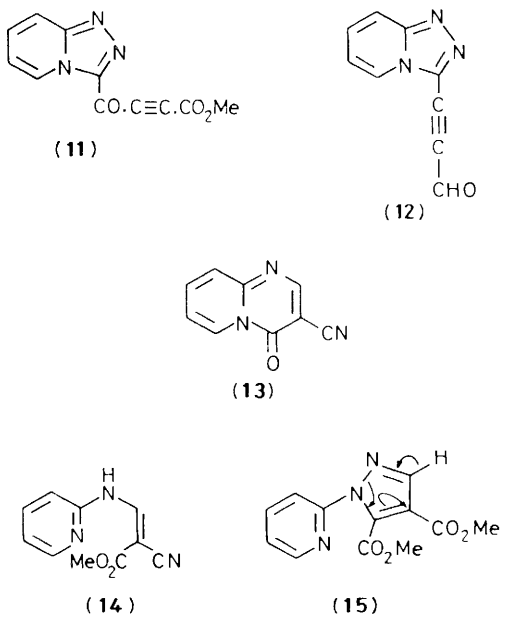
The cycl[3.2.2]azine ring system was elegantly synthesised by Boekelheide and co-workers[1] several years ago by cycloaddition of dimethyl acetylenedicarboxylate (DMAD) to indolizine, in the presence of 5% palladium-on-charcoal to dehydrogenate the initial cycloadduct. By analogy 1,2,4-triazolo[4,3-*a*]pyridine (1,2-diazaindolizine) (**1**) could give the



Scheme 1

unknown 1,2-diazacycl[3.2.2]azine system, though a very different course for this reaction in the absence of palladium-on-charcoal has been reported by Potts and co-workers.[2] When the triazolopyridine (**1**) was treated with DMAD in boiling benzene a yellow product, $C_{11}H_7N_3O_3$, m.p. 242—243 °C decomp. (35%) was isolated and assigned structure (**11**).[2]

Recently, the reaction of triazolopyridine (**1**) with DMAD in boiling toluene (24 h) in the presence of 5% palladium-on-charcoal (Boekelheide's conditions) has been reported[3] to give a different product, $C_9H_5N_3O$, m.p. 207 °C (23%); this was assigned the somewhat unlikely structure (**12**), together with an even less likely mechanism for its formation. The spectroscopic properties of (**11**) and (**12**) suggest that they are closely related, are not 1,2,4-triazolo[4,3-*a*]pyridines, and could be cyanides rather than acetylenes. On spectroscopic and mechanistic grounds, we considered the pyridopyrimidone structures (**10**) and (**13**), respectively, to be more reasonable than (**11**) and (**12**). Cyanide (**13**) has been described in the literature[4] and its properties coincide with those reported for the product of the DMAD reaction.



We have repeated the reaction of 1,2,4-triazolo[4,3-*a*]-pyridine (**1**) with DMAD (2 equiv.) in benzene and in toluene, under reflux, in the presence and absence of 5% palladium-on-charcoal, and under all sets of conditions we isolate the same three compounds (**10**), m.p. 242—245 °C (20%), (**6**), m.p. 148—150 °C (20%), and (**7**), (stereochemistry unknown), m.p. 234—237 °C (1%) from a complex mixture.† Compound (**10**) is clearly that previously assigned structure (**11**), but compounds (**6**) and (**7**) were not mentioned by the earlier workers.[2,3] Furthermore, we have been unable to isolate any of the product (**13**) or even to detect it by t.l.c. comparison with an authentic specimen. This product could possibly have arisen from the ester (**10**) by hydrolysis and decarboxylation, but we have also been unable to effect this transformation under the conditions reported[3] or in the presence of possible contaminants, such as water.

We believe that the formation of our three products, (**10**), (**6**), and (**7**) can be rationalised most simply by the mechanism outlined in Scheme 1.‡ Michael addition to DMAD of the triazolopyridine (**1**) *via* its two nucleophilic centres, C(3) and N(1), gives the zwitterionic intermediates (**2**) and (**3**); (**2**) can react with a second mole of DMAD to give product (**7**), or collapse to the cycloadduct (**4**). Rearrangement of (**4**) to (**5**), as shown,§ followed by ester migration leads to the second product (**6**). The rearrangement of (**4**) to (**5**), favoured by formation of the pyridine ring, must presumably be very fast to compete with nitrogen extrusion. The other zwitterionic intermediate (**3**) has an acidic proton on the triazolium ring and a strongly basic carbanionic centre. Intermolecular proton transfer can proceed with opening of the triazole ring to form the *N*-cyano-compound (**8**),¶ which can undergo a

† New compounds, including (**10**), were characterised by full analytical and spectroscopic data; structure (**10**) was further supported by direct spectroscopic comparison with authentic compound (**13**).

‡ Other possibilities which have been suggested to us, particularly by a Referee to whom we are grateful, are under consideration.

§ This may be an example of a more general ring opening rearrangement of bridged bicyclic systems (*cf.* ref. 5).

¶ A related base-catalysed ring opening of a 1,2,4-triazole to form an *N*-cyano-compound has been reported (ref. 6).

highly favoured [1,5] shift of cyanide from nitrogen to carbon, to give (**9**). This intermediate can then cyclise to (**10**) with elimination of methanol, possibly *via* a ketene, proton loss being facilitated by the ester, cyano-, and imino-groups. Some evidence for this pathway is provided by the treatment of triazolopyridine (**1**) with methyl propiolate in benzene at room temperature when compound (**14**), m.p. 171—173 °C, slowly crystallises over several weeks. Furthermore, when triazolopyridine (**1**) was treated with DMAD in the protic solvent methanol, product (**10**) was formed more cleanly, rapidly, and in higher yield (70%), but products (**6**) and (**7**) were not formed. This accords with the mechanistic scheme in which protonation of (**2**) would be expected to suppress the subsequent transformations, but protonation of (**3**) would not.

A possible alternative mechanism for the formation of cyano-ester (**9**), and hence (**10**), was discounted; either of the initial adducts (**2**) or (**3**) could conceivably collapse to give the pyridopyrazole (**15**), base-catalysed ring opening[7] of which could, as shown, give (**9**). Pyridopyrazole (**15**), m.p. 95—98 °C, was therefore synthesised by condensation of 2-pyridylhydrazine with diethyl ethoxymethyleneoxaloacetate followed by transesterification with sodium methoxide in methanol; however, (**15**) was completely inert under the original, and more vigorous, conditions.

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