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A SYNTHESIS OF ANNULATED PYRIDAZINES BY CYCLOADDITION OF AZODICARBOXYLATES TO VINYLPYRIDINES

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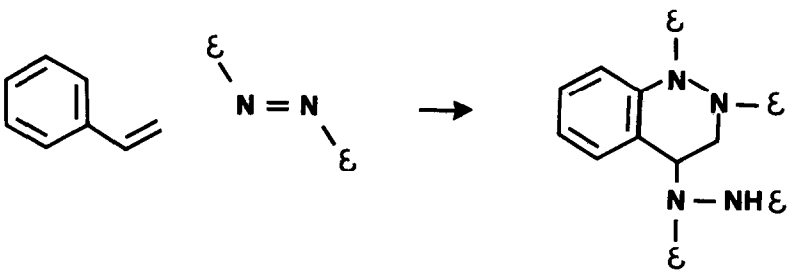
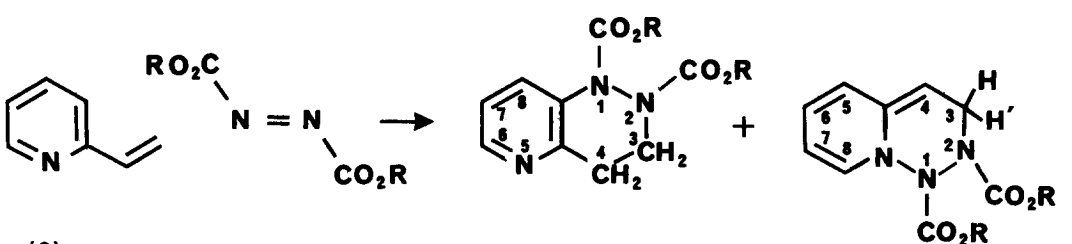
Cycloaddition of azodicarboxylates to dienes has been used to prepare a number of tetrahydropyridazines; attempts to form tetrahydrocinnolines from azodicarboxylates and styrene gave diadducts (1), no monoadducts being obtained.[1-4] Reaction between vinylpyridines and N-phenylmaleimide gave tetrahydro-quinoline and -isoquinoline derivatives,[5] but no reactions have been reported between vinyl heterocycles and azodicarboxylates, possibly because of the discouraging experience with styrene. We have now shown that azodicarboxylates react with a variety of vinylheterocycles to give annulated pyridazines. As examples of this moderate yield but simple synthesis we report here the preparation of pyrido[3,2-c]pyridazine (10) and pyrido[3,4-c]pyridazine (11) from 2-vinyl and 4-vinyl-pyridine.



(1) ε = CO_2Me or CO_2Et

Reaction between 2-vinylpyridine (2) and diethyl azodicarboxylate (3) (equimolar amounts in boiling benzene for 26 h) gave a mixture from which two isomeric 1:1 adducts could be isolated by chromatography. The major component (13%) was the tetrahydropyrido[3,2-c]pyridazine diester (4), b.p. 140°/5 x 10^{-4}mm Hg. (Found: C, 56.35; H, 6.3: N, 15.3. $C_{13}H_{17}N_3O_4$ requires C 55.9; H, 6.1; N, 15.05%.)(λ_{max} EtOH, 95%) 233 (log ε 3.9) and 269 nm (log ε 3.58). ν_{max} ($CHCl_3$) 1710, 1320 cm^{-1} δ($CDCl_3$) 1.0-1.5 (6H, m, CH_3CH_2O), 2.5-5.0 (8H, m, CH_3CH_2O and CH_2CH_2), 7.1 (1H, q, J 8 and 4Hz, H7), 8.05 (1H, d of d, J 8 and 2Hz, H8), and 8 25 p.p.m. (1H, d of d, J 4 and 2Hz, H6). The minor component was the 3H-pyrido[1,2-c]-1,2,3-triazine diester (5) (1.5%) m.p. 95°. (Found: C, 56.25; H, 6.05; N, 15.45%). λ_{max} (EtOH, 95%) 211 (log ε 4.17) and 260 nm (log ε 3.5); ν_{max} ($CHCl_3$) 1661 and 1300 cm^{-1}. δ($CDCl_3$) 1.1-1.6 (6H, m, CH_3CH_2O), 3.5 (1H, d of d, J 13 and 8Hz, H3) 4.0-4.6 (5H, m, CH_3CH_2O and H3'), 5.35 (1H, d of d, J] 8 and 3Hz, H4). 7.1-7.9 (3H, m), and 8.5 p.p.m. (1H, br d of d, J] 4 and 2Hz, H8).

Reaction between (2) and (3) was much more rapid (6.5 h) in boiling acetonitrile giving diester (4) (18.2%) with virtually no pyridotriazine (5). Reaction between 2-vinylpyridine and di-t-butyl azodicarboxylate (6) in boiling benzene was complete in 8 days, giving the di-t-butyl ester (7) (23.1%) and the pyrido triazine diester (8) (2.7%).



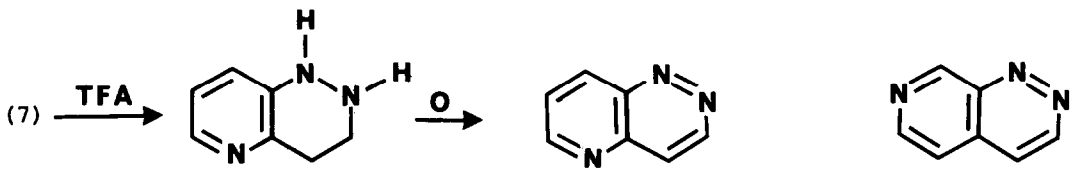
(2)

(3) R = C_2H_5 (4) R = C_2H_5 (5) R = C_2H_5

(6) R = t-C_4H_9 (7) R = t-C_4H_9 (8) R = t-C_4H_9

Hydrolysis of the diethyl ester (4) gave mixtures; by warming the di-t-butyl ester (7) in trifluoroacetic acid an unstable product was

obtained and identified from its ^1H n.m.r. spectrum as 1,2,3,4-tetrahydropyrido[3,2-c]pyridazine (9) (94% yield). Oxidation of this tetrahydro derivative was best achieved in two stages; mercuric oxide gave a dihydropyridopyridazine and this was treated, in chloroform solution, with gaseous oxygen to give pyrido[3,2-c]pyridazine (10), m.p. 89-91° (yellow crystals from cyclohexane) (37%). (Found: C, 64.4; H, 3.95; N, 31.65. $C_7H_5N_3$ requires C, 64.1; H, 3.8; N, 32.05%.) λ_{max} (EtOH, 95%) 208 (log ε 4.62), 263 (log ε 3.59), 306 (log ε 3.62), and 318 nm (log ε 3.65). δ($CDCl_3$) 7.8 (1H, d of d, J 8 and 4Hz, H7), 8.15 (1H, d of d, J 6 and 1Hz, H4), 8.85 (1H, q of d, J 8, 2, and 1Hz, H8), 9.2 (1H, d of d, J 4 and 2Hz, H6) and 9.55 p.p.m. (1H, d, J 6Hz, H3).



(9) (10) (11)

By a similar sequence from 4-vinylpyridine pyrido[3,4-c]pyridazine (11), m.p. 138° (yellow crystals from cyclohexane) was obtained. (Found: C, 63.8; H, 3.7; N, 32.35%). λ_{max} (EtOH, 95%) 209 (log ε 4.46) and 284 nm (log ε 3.58); δ($CDCl_3$) 7.6 (1H, d, J 5Hz, H5), 7.8 (1H, d, J 6Hz, H4), 8.7 (1H, d, J 5Hz, H6), 9.35 (1H, d, J 6Hz, H3), and 9.85 p.p.m. (1H, s, H8).

We believe that the initial cycloaddition reaction is concerted; further work on the mechanism, and on the synthesis of other condensed pyridazines is in progress.

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