1,3-Dipolar Cycloaddition of 2-Diazopropane to Imidazo[1,2-*b*]pyridazine Derivatives. The Synthesis of Imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazines, Derivatives of a Novel Heterocyclic System

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Facile cycloadditions of 2-diazopropane (**2**) to the imidazo[1,2-*b*]pyridazines (**1a—c**), derivatives of a 10 π-electron heteroaromatic bicyclic system, give the imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazines (**4a—d**) in 69—84% yields.

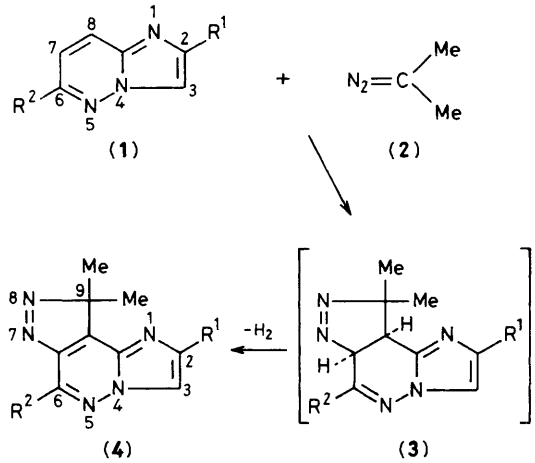
There is little known about the addition of diazoalkanes to heteroaromatic systems. The only examples described have been cycloadditions to a pyridine[1] and to a pyridazinone, which were followed by elimination of nitrogen to give a mixture of *C*-alkylated and ring-expanded products.[2] Recently, the cycloadditions of diazomethane to *N*-methylpyridazin-3(2*H*)-ones, 6-hydroxypyridazin-3(2*H*)-ones, and 1,2-dimethylpyridazin-3,6(1*H*,2*H*)-dione,[3,4] and the cycloadditions of diazoacetates to 4-nitro- and 5-nitrobenzofurazanes[5] were reported.

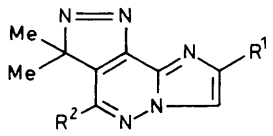
We report now an interesting reaction of the 6-substituted derivatives (**1a—c**) of a fully aromatic 10 π-electron heterocyclic bicyclic system with a bridgehead nitrogen atom, imidazo[1,2-*b*]pyridazine (**1d**) with 2-diazopropane (**2**), in which cycloaddition occurs across the C(7)–C(8) double bond to produce derivatives of a novel heterocyclic system 9*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine (**4a—c**).

To a solution of 6-chloroimidazo[1,2-*b*]pyridazine (**1a**) in ethanol (10 ml), 2-diazopropane (**2**),[6] prepared from 1.5 g of acetone hydrazone, in diethyl ether was added. After 12 h, the same amount of 2-diazopropane was added and the mixture was left at room temperature for another 12 h, when t.l.c. showed that all the starting material was consumed Evaporation of the reaction mixture *in vacuo* gave (**4a**) [from cyclohexane : toluene (5 : 1), m.p. 178 °C, 72% yield; ^{1}H n.m.r. (60 MHz, $CDCl_3$): δ 7.93 (1H, d, 2-H), 8.12 (1H, d, 3-H, $J_{2,3}$ 1.2 Hz), 1.83 (6H, s, 9,9-di-Me); *m/z* 221 (28%) (M^+)]. Analogously, 6-methoxyimidazo[1,2-*b*]pyridazine (**1b**) gave (**4b**) [from methanol, m.p. 203—205 °C, 69% yield; ^{1}H n.m.r. (60 MHz, $CDCl_3$): δ 7.70 (1H, d, 2-H), 7.88 (1H, d, 3-H, $J_{2,3}$ 1.2 Hz), 4.20 (3H, s, OMe), 1.77 (6H, s, 9,9-di-Me); *m/z* 217 (32%) (M^+)], and 6-chloro-2-phenylimidazo[1,2-*b*]-pyridazine (**1c**) gave (**4c**) [from ethanol; m.p. 221—222 °C, 84% yield; ^{1}H n.m.r. (60 MHz, $CDCl_3$): δ 8.41 (1H, s, 3-H), 8.10—7.80 and 7.60—7.25 (both m, 5H, 2-Ph), 1.84 (6H, s, 9,9-di-Me); *m/z* 297 (30%) (M^+)]. Catalytic hydrogenation (10% Pd/C) of (**4a**) in methanol followed by neutralization of the hydrochloride of (**4d**), extraction with chloroform, and purification gave (**4d**) [from cyclohexane : toluene (5 : 1), m.p. 215—220 °C, 48% yield; ^{1}H n.m.r. (60 MHz, $CDCl_3$): δ 9.15 (1H, s, 6-H), 8.15 (1H, d, 3-H), 7.92 (1H, d, 2-H, $J_{2,3}$ 1.0 Hz), 1.80 (6H, s, 9,9-di-Me); *m/z* 187 (26%) (M^+)]. All products gave correct elemental analyses for C, H, and N.

The reaction between imidazo[1,2-*b*]pyridazine dervatives (**1a—c**) and 2-diazopropane (**2**) is assumed to proceed as a 1,3-dipolar cycloaddition of (**2**) to the C(7)–C(8) double bond of the pyridazine part of the molecule followed by loss of H_2 from the primary cycloproducts (**3a—c**) to give the stable products (**4**) (Scheme 1).

The structural assignments of the products (**4**) are based on ^{1}H n.m.r. spectral data, since the chemical shift of the two methyl groups at position 9 (δ 1.77—1.84) is independent of the nature of the substituent at position 6. This is supported also by the formation of a pseudocontact complex with $Eu(fod)_3$ (fod = 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-octane-4,6-dionate). Namely, the addition of 20, 40, or 60 mg





(5)

a; R^1 = H, R^2 = Cl
b; R^1 = H, R^2 = OMe
c; R^1 = Ph, R^2 = Cl
d; R^1 = R^2 = H

Scheme 1

of $Eu(fod)_3$ to a solution of (**4a**) (55 mg in 0.5 ml $CDCl_3$) moves the signal for 2-H from δ 7.93 to 8.03, 8.30, or 8.62, respectively, and the signal for the methyl groups from δ 1.83 to 2.03, 2.30, or 2.68, respectively. This indicates that the pseudocontact complex is formed at N(1), thus strongly suggesting the structure (**4a**) and excluding the alternative structure (**5a**). The structure of (**4a**) was confirmed by an *X*-ray analysis.[7]

The reaction described here was very surprising, since it is well documented that the pyridazine part of azolo-pyridazine systems is extremely unreactive.[8]

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