Reaction of Diazoalkanes on the Activated C(4)–C(5) Isoxazole Double Bond: a New Entry to the 2-Oxa-3-azabicyclo[3.1.0]hex-3-ene Ring System

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The nitroester (**1**) was shown to give rise to 1,3-dipolar cycloadditions with diazomethane and 2-diazopropane, affording the bicyclic derivatives (**4**) and (**5**) *via* the unstable primary cycloadducts (**2**) and (**3**), respectively.

A number of cycloaddition reactions of different heterocycles with diazoalkanes have been reported,[1] but nothing is known about the reactivity of the isoxazole system with these reagents. Furthermore, whereas several dihydroisoxazoles have been successfully treated with other 1,3-dipoles such as nitrile oxides[2,3] and nitrones,[4] the possibility of using 'aromatic' isoxazoles as dipolarophiles has not been explored.

Having recently shown that the ester (**1**) cyclized with 2,3-dimethylbuta-1,3-diene into a tetrahydro-1,2-benzisoxazole *via* a [2 + 4] Diels–Alder cycloaddition,[5] we decided to investigate the behaviour of the same product towards diazoalkanes in an effort to expand the scope of this new annellation.

Preliminary studies of the reaction of compounds (**7**) and (**8**) with both diazomethane and 2-diazopropane, in diethyl ether at room temperature, were unsuccessful and the starting materials were recovered unchanged. By contrast, reaction of (**1**) with diazomethane (molar ratio 1 : 1,† overnight) under the same conditions afforded the oxa-azabicyclo[3.1.0]hexene (**4**), which was easily isolated as a pure product by flash chromatography [40%, based on the recovered nitroester (**1**)].

The formation of (**4**) could be accounted for by a cycloaddition of diazomethane on the activated C(4)–C(5) isoxazole double bond, followed by nitrogen extrusion from the

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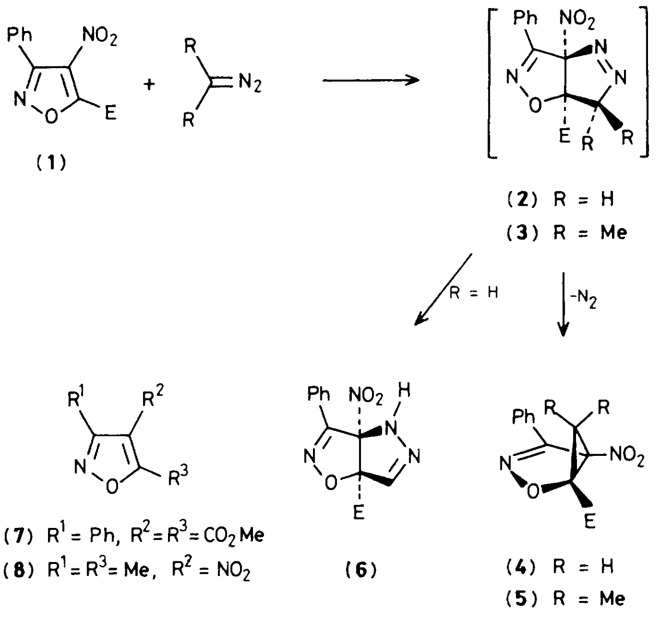
† When an excess of diazomethane was employed, a much more complex reaction mixture was obtained, probably owing to subsequent cycloaddition processes on compound (**6**) or its transformation products.



(1)

(2) R = H
(3) R = Me

(7) R1 = Ph, R2 = R3 = CO2Me
(8) R1 = R3 = Me, R2 = NO2

(6)

(4) R = H
(5) R = Me

E = CO_2Et

thermally unstable bicyclic pyrazoline (**2**).‡ ^1H N.m.r. analysis clearly showed that the original mixture contained, in addition to (**4**), a nearly equimolecular amount of a second product, which was rather unstable and escaped isolation; the spectral data were in agreement with the structure of the pyrazolo-isoxazole derivative (**6**), which could arise from the same primary cycloadduct (**2**) *via* an intramolecular hydrogen shift.

This competitive rearrangement lowered the yield of (**4**), but it was prevented when 2-diazopropane was used; in fact, the reaction of (**1**) under the above conditions with an excess of 2-diazopropane[8] (molar ratio *ca.* 1:2) gave the dimethyl derivative (**5**) in 73% yield, presumably *via* the corresponding pyrazoline (**3**).‡

The reaction of the nitroester (**1**) with diazoalkanes represents an alternative route to the 2-oxa-3-azabicyclo-[3.1.0]hex-3-ene ring system, which has previously been synthesized by cycloaddition of nitrile oxides with cyclopropenes[9] and by cyclization of 5-halogenomethyl-4,5-dihydro-isoxazoles with strong bases.[10] The requisite particular activation of the starting isoxazole severely limits this method; in spite of this the presence of the NO_2 and CO_2Et groups at the 4- and 5-positions, respectively, is sufficient to ensure a valuable entry into the new class of 1,5-difunctionalized derivatives of the above bicyclic system, which appear attractive for synthetic purposes.

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‡ The preferential formation of (**2**) and (**3**), respectively, was suggested on the basis of the regiochemical control exerted by the NO_2 group in the cycloadditions of the same diazoalkanes with nitroheterocycles[6] and variously substituted nitroalkenes.[7]