A Simple Synthesis of Aaptamine, a 1*H*-Benzo[de][1,6]-naphthyridine Alkaloid

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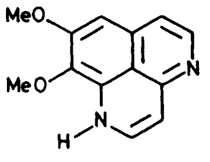
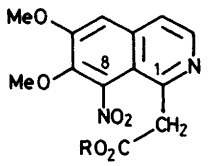
Aaptamine, a 1*H*-benzo[de][1,6]-naphthyridine alkaloid, is prepared by the triphenylphosphite reduction of a vinylic nitro derivative.

Aaptamine (**1**)[1] occurs in the okinawan sea sponge *Aaptos aaptos* and is of interest both for its remarkable α-adrenoceptor blocking properties[2] and for its novel 1*H*-benzo[de][1,6]-naphthyridine skeleton.

The first synthesis of aaptamine was reported by Cava *et al.* and consisted of the reduction of an 8-nitro-6,7-dimethoxy-3,4-dihydroisoquinoline (**2**) bearing a $-CH_2-CO_2R$ group in position 1.[3] This was followed by cyclisation. Both C-1 and C-8 functionalisation were needed for this preparation. Here we report a new synthesis of this compound requiring functionalisation only at C-1, and based on the generation of a 1-vinylnitrene (**3**) which attacks position 8 of a suitable 3,4-dihydroisoquinoline nucleus (**4**) giving aaptamine simply and selectively.



(1)



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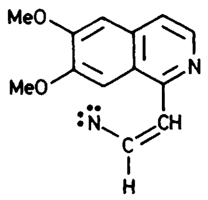

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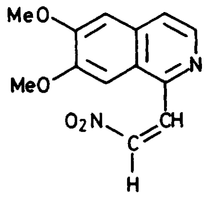

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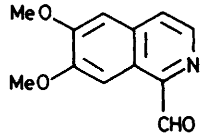

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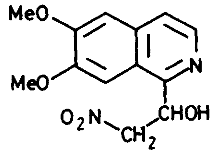

(6)

Nitromethane was condensed with 6,7-dimethoxyisoquinoline-1-carboxaldehyde (**5**)[4] operating in diethylamine at 0 °C for 1 h to obtain the alcohol (**6**) which was immediately dehydrated with pyridine and acetic anhydride at 0 °C for 14 h to give an 85% yield of the unsaturated nitro compound (**4**), m.p. 165—166 °C, ^{1}H n.m.r. signals in deuteriochloroform at δ 4.05 (3H, s); 4.10 (3H, s); 7.09 (1H, s); 7.32 (1H, s); 7.59 (1H, d, J 8 Hz); 8.16 (1H, d, J 12 Hz); 8.45 (1H, d, J 8 Hz); and 8.65 (1H, d, J 12 Hz).

Vinylnitrene generation is generally obtained by thermolysis of vinylazides[5] or by Neber rearrangement of oxime tosylates.[6] Insertion reactions are seldom obtained[7] since vinylnitrenes prefer to rearrange to give ketenimines, azirines, and nitriles and the products therefrom.[8] In one case, 2-phenylazirine rearranged to give indole *via* an electrocyclic insertion reaction.[9] Nitrene generation from aromatic nitro groups is generally performed by reflux in triethylphosphite.[10]

When the triethylphosphite reduction of the vinylic nitro derivative (**4**) was performed at reflux temperature for 150 min, a 58% yield of aptamine (**1**) was obtained. The (*Z*)-form (**4**) suitable for the cyclisation reaction is probably derived from a thermal (*E*)-(*Z*) isomerisation.

This synthetic procedure seems to be more selective than most vinylnitrene reactions, probably because conjugation stabilises the nitrene and prevents rearrangement.

All new compounds gave satisfactory mass spectral and analytical data. This work was supported by a CNR grant.

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