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REGIOSELECTIVITY IN THE [4+2] CYCLOADDITION OF BENZYNE.SYNTHESIS OF 11-SUBSTITUTED APORPHINES

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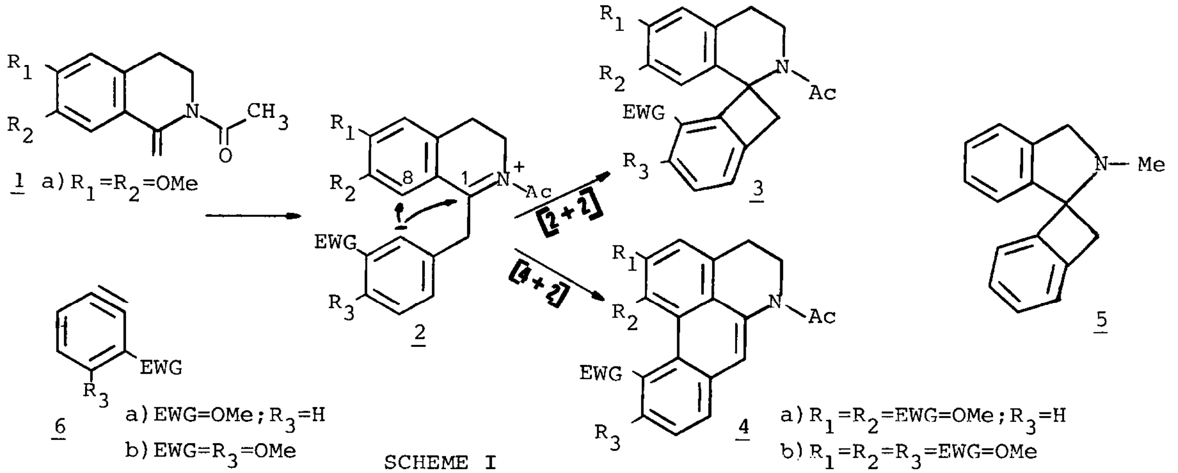
Abstract:The regioselectivity in intermolecular cyclization between unsymmetrically substituted benzynes and 1-methylene-isoquinolines is described. This route has been successfully applied to the synthesis of 11- and 10-11-substituted aporphines.

In connection with our studies on the synthesis of aporphine alkaloids, we have recently reported[2] the application of the intermolecular Diels-Alder reaction for unsubstituted benzynes to several 1-methylene-isoquinolines to give aporphine alkaloid derivatives.

In the present communication we wish to report the high degree of regioselectivity found when using unsymmetrically substituted benzynes and the degree of competition between the [4+2] and [2+2] cycloaddition pathways.

In view of the electrophilic nature of benzyne[3], and taking into consideration inductive and steric effects , one would expect that in a hypothetical non-syncronous mechanism the reaction of N-acetyl-1-methylene-isoquinolines with benzynes substituted with electron-withdrawing groups (EWG) should follow scheme I:



SCHEME I

Initial attack by the more nucleophilic site of the diene at the less hindered and more electrophilic site of the dienophile should give intermediate 2. This possesses two electrophilic positions (1 and 8) which would lead to the [4+2] and [2+2][4] cycloaddition products (4 and 3, respectively).

In fact, when 6,7-dimethoxy-1-methylene-N-acetyl-isoquinoline (1a)[2] was reacted with 3-methoxy-benzyne (6a)[5], the only adduct isolated was the 1,2,11-trimethoxy-aporphine derivative (4a)[6] in 30 % yield. In the PMR spectrum of the reaction mixture the absence of the other regioisomer, the 1,2,8-substituted aporphine,was indicated by the lack of a downfield proton corresponding to H-11[7].The absence of a pair of doublets (J=14 Hz) around 3.7 ppm demonstrated that the [2+2] cycloadduct was not present.

Analogous results were obtained when the reaction was carried out with 3,4-dimethoxy benzyne (6b)[5]. As expected, only N-acetyl dehydro-O,O-dimethyl-norcorituberine (4b)[6] was found. The above results showing the lack of competitiveness of the [2+2] process are very encouraging from a synthetic point of view. In only one instance did the [2+2] compete with the [4+2] cycloaddition, when reaction of N-methyl-3-methylene-phtalimidine with benzyne gave the [4+2] adduct[2] together with a second product (18% yield) whose structure was assigned to the cyclobutene derivative (5)[6] on the basis of spectroscopic evidence. The mass spectrum of 5 revealed the incorporation of the benzyne unit (m/e 235 M^+, 55%), and its PMR spectrum showed an ABq at δ_A=3.67 and δ_B=3.72(J=14 Hz) ppm assigned to the methylene group in the benzocyclobutene system.

The above results suggest that the [2+2] pathway competes with the favoured [4+2] process only when geometrical restraints impose severe limitations on achieving the necessary overlapping[3] of the benzyne and diene.

The regioselectivity observed in the Diels-Alder cycloaddition described represents one of the few examples of successful synthesis of 11- and 10-11-substituted aporphines[9].

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