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THE REACTION OF 1-ALKYLDIHYDROISOQUINOLINES WITH BENZYNE. AN UNEXPECTED ENTRY TO DIBENZINDOLIZINES.

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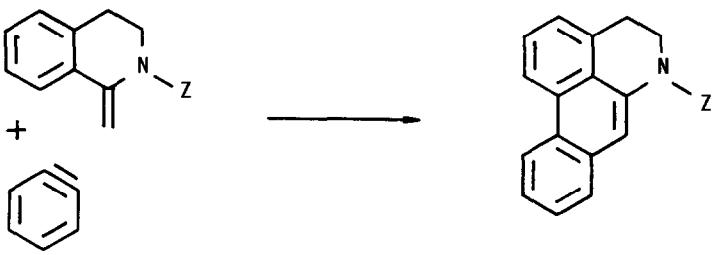
Abstract: The reaction of 1-ethylidene-2-formyl-1,2,3,4-tetrahydroisoquinolines 4a and 4b, or 1-ethyl-3,4-dihydroisoquinolines 3a and 3b, with benzyne led, by a formal 3+2 cycloaddition, to dibenzindolizines 5a and 5b, respectively. Compound 5b was also synthesized by photocyclization of enamine 6.

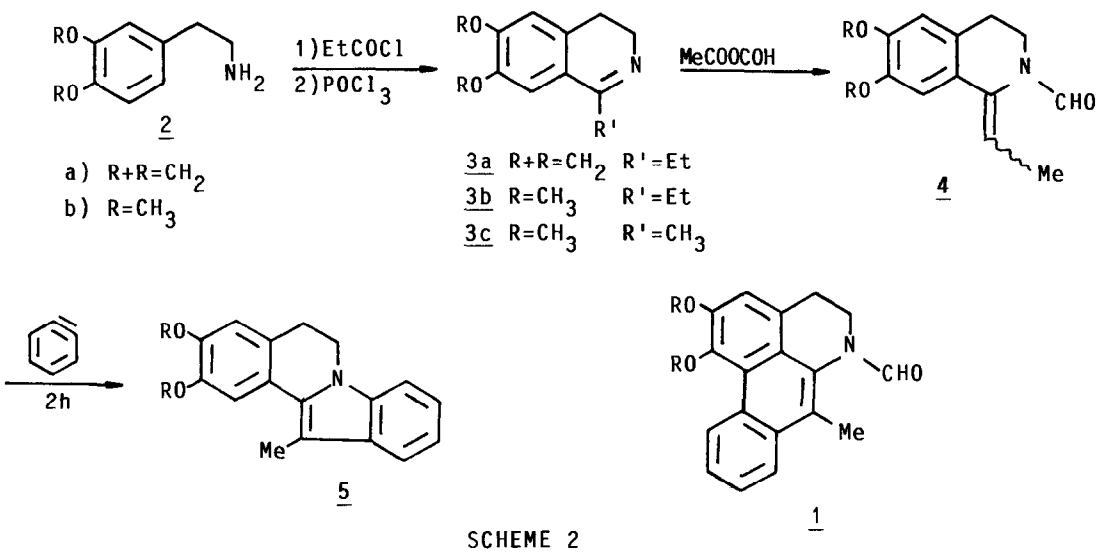
For the past few years we have been involved in a program whose main objective is the design and development of new approaches to the synthesis of the various classes of isoquinoline alkaloids[1,2]. In particular, our recently developed intermolecular benzyne cycloaddition (IBC) approach has proved to be a highly convergent, regioselective and versatile method for the synthesis of dehydroaporphines, dioxoaporphines and aristolactams[3,4], noraporphines and oxoaporphines[5], and, most recently, 13-substituted protoberberines[6]. The crucial step of the simplest and most characteristic version of the IBC approach (Scheme 1), involves the formal (4+2) cycloaddition of benzyne and an N-protected alkylidene isoquinoline (as the 4π electron moiety). This directly provides the oxidized skeleton of a phenanthrene.



SCHEME 1

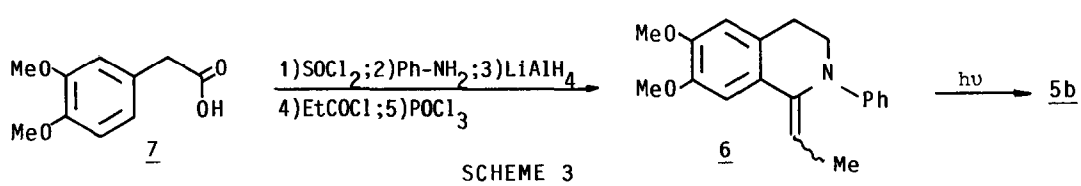
The recent isolation of trichoguattine[7], a Guatteria alkaloid, led us to attempt an IBC synthesis of 1a, the structure ascribed to this alkaloid[7]. The results were unexpected. The required 1-ethylidene-2-formyl-3,4-dihydroisoquinoline 4a[8] was prepared uneventfully from the phenethylamine 2a in good yield as a mixture of E and Z isomers, but when this precursor was reacted with benzyne (generated by thermal decomposition of benzenediazonium-2-carboxylate[9]) the main product isolated (26%) was a white crystalline solid, mp

178-180ºC (MeOH), whose spectroscopic data were consistent with its being the 12-methyl-dibenzindolizines 5a. Besides the molecular ion peak at m/z 277 (100%), significant features of these data included signals in the PMR (2.58 (s, 3H, Me), no signals above 7.6 ppm) and a UV absorption pattern (λ_{max}: 238, 262, 270, 333, 348 sh) analogous to that of some synthetic dibenzindolizines.



SCHEME 2

A similar result was obtained when 4b was reacted with benzyne: the main product was 5b, as was confirmed by comparison (mp, UV, IR, NMR) with authentic 5b synthesized in 11% yield using the method of Ninomiya et al.[10] by photochemical electrocyclization of precursor 6, itself prepared from commercially available 3,4-dimethoxyphenylacetic acid 7 through the sequence of steps outlined in Scheme 3.



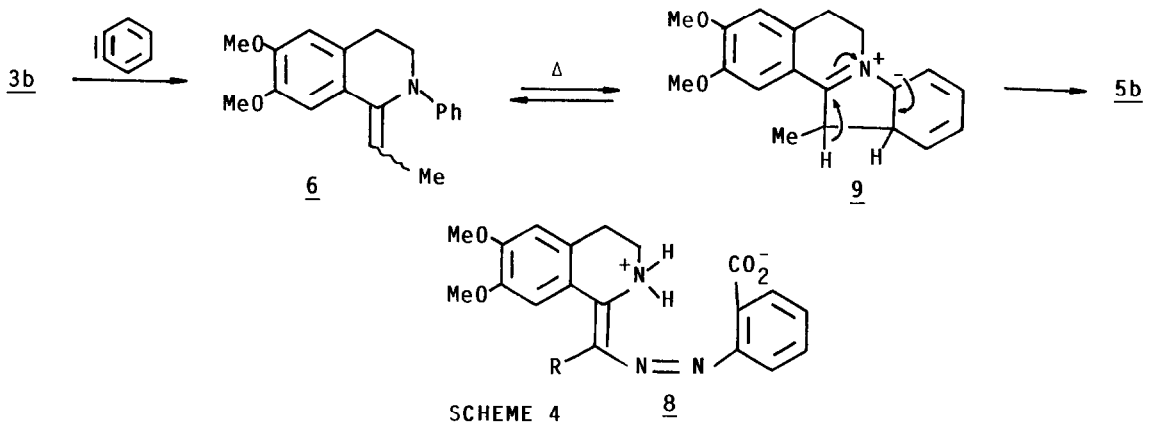
SCHEME 3

The puzzling formation of the N-aryl bond of 5 with concomitant loss of the formyl group of 4 suggested the possibility of a hydrolytic conversion of 4 into imine 3 promoted by residual water and trichloroacetic acid (TCA) present in benzenediazonium-2-carboxylate preparations. As Table 1 shows, hydrolisis of 4 is only partial after 2 h reflux in DME, so that the direct formation of 5 from 4 cannot be definitely ruled out. We nevertheless decided to investigate the reactivity of 1-alkyl-3,4-dihydroisoquinolines 3 with benzyne. At the time, the very few reports in the literature described (2+2) cycloaddition as the most usual reaction between imines and benzyne[11,12,13]. As expected,

reaction of imine 3b with benzyne generated as usual, yielded 5b in 38% yield together with a highly insoluble amorphous yellow material identified tentatively as the azocompound 8 (R=Me)[14], probably produced by benzenediazonium-2-carboxylate being trapped by the enamine tautomer of 3b. The formation of the byproduct 8 (R=Me) was finally avoided by thoroughly washing the diazonium salt with dry DME before its addition to the reaction mixture.

TABLE 1

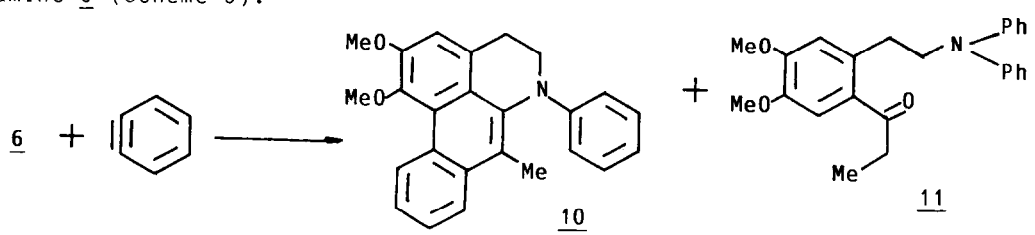
		T	t	
4b	DME + H_2O (2%)	Δ	2h	No reaction
"	DME + TCA(trace)	Δ	2h	3b + 4b
"	DME + H_2O + TCA	Δ	2h	3b + 4b



SCHEME 4

As a worthwhile working hypothesis for the reaction (3b + benzyne -----► 5b) we thought that nitrogen attack on benzyne followed by subsequent β hydrogen abstraction might lead to intermediate 6. This could then suffer a thermal disrotatory 6π electron electrocyclization to an intermediate such as 9 capable of producing the final product 5b by way of a benzyne-promoted dehydrogenation. Analogous dehydrogenations have been noticed by ourselves[3-5] and other workers (Scheme 4)[15,16].

Unfortunately, the reaction of 6 with benzyne under the usual conditions yielded dehydroaporphine 10 together with N,N-diarylaminoketone 11, a product possibly derived from reaction of benzyne with the hydrolysed product of enamine 6 (Scheme 5).



SCHEME 5

The mechanism for the formation of 5b shown in Scheme 4 must accordingly be rejected, neither 10 nor 11 having been detected in the reaction of 3b with benzyne.

Finally, another puzzling result was obtained when the above (3+2), cycloaddition was applied to 1-methyl-3,4-dihydroisoquinoline 3c in an attempt to synthesize the plane dibenzindolizine skeleton present in some naturally occurring alkaloids. All attempts to react 3c with benzyne under the usual conditions were frustrated by the exclusive formation of the yellow azo compound 8 (R=H)[14], which precipitated from the reaction mixture even when carefully washed benzenediazonium-2-carboxylate was used.

It is now clear to us that subtle factors not yet understood operate in the above formal (3+2) cycloaddition reaction of imines with benzyne. Further work in progress will try to offer a mechanistic rationale for the results reported here.

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14. Compound 8 (R=H): mp 252-254ºC(MeOH); IR(KBr)ν_{max}: 3400-2200, 1640, 1600, 1560 cm^{-1}; PMR(250 MHz, $CDCl_3$+TFA, δ): 3.12(t,J=7.5Hz,2H,CH_2), 3.89(t,J=7.5Hz,2H,CH_2N), 3.93(s,3H,OMe), 4.04(s,3H, OMe), 6.90(s,1H,Ar), 7.07(t,J=7.5Hz,1H,Ar), 7.40(s,1H,Ar), 7.55(d,J=8.2Hz,1H,Ar), 7.81(d,J=8.4 Hz,1H,Ar), 7.96(d,J=7.9Hz,1H,Ar), 8.09(s,1H,vinyl), 8.96(s,broad); MS(FAB) m/z(%): 353.1375(M^+, 72); $C_{19}H_{19}N_3O_4$.
Compound 8 (R=Me): mp 240-242ºC(MeOH); IR(KBr) ν_{max}: 3400-2200, 1640, 1600, 1580 cm^{-1}; PMR(250 MHz, $CDCl_3$+TFA, δ): 2.38(s,3H,Me), 3.12(t,J=7.4Hz,2H,CH_2), 3.89(s,3H,OMe), 3.92(t,J=7.4Hz,2H, CH_2N), 4.07(s,3H,OMe), 6.97(s,1H,Ar), 7.18(t,J=6.9Hz,1H,Ar), 7.42(s,1H,Ar), 7.4-7.7(m,2H,Ar), 8.16(d,J=8Hz,1H,Ar).
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