

Radical Cation Diels-Alder Reaction of Indoles and Exocyclic Dienes

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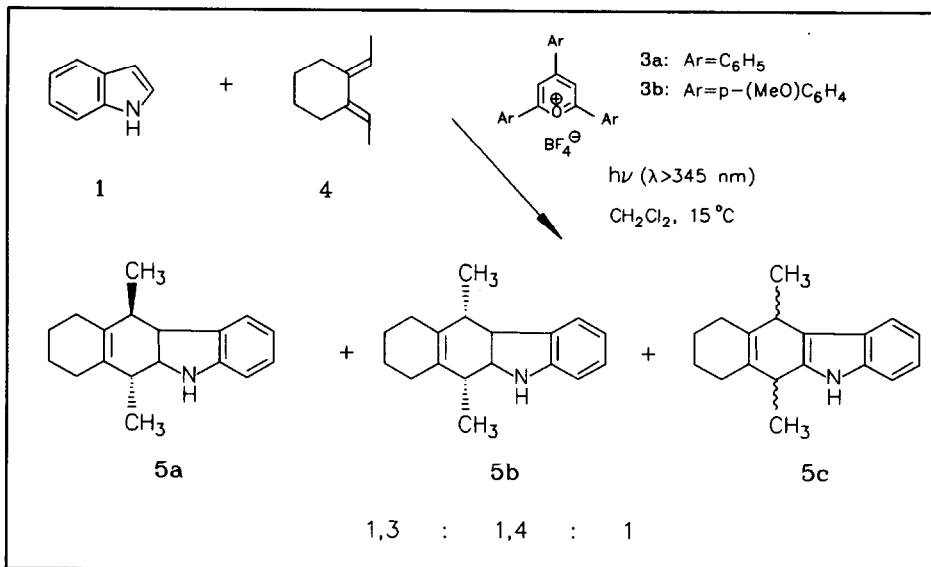
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Abstract: A convergent synthesis of [b]-annelated tetrahydrocarbazoles through a radical cation Diels-Alder reaction is described. The reaction is induced by photo electron transfer (PET). The previously predicted stepwise mechanism of this reaction type is proved by stereochemical analysis of the products.

The use of electron transfer as the most simple method for a redox umpolung has shown to be useful for a variety of reactions, including such important reactions as [4+2] and [2+2] cycloadditions^[1]. At the early stages of research in this field, interest focused mainly on the cycloadditions of simple hydrocarbon compounds such as the dimerization of 1,3-cyclohexadiene. More recently, synthetic applications involving heterosubstituted compounds have been studied extensively^[2]. With regard to the mechanistic interpretation, the most simple radical cation Diels-Alder reaction of 1,3-butadiene with ethene has been classified as nonsynchronous-concerted by ab initio calculations at different levels of theory in the [3+2] as well as in the [4+1] case^[3]. There is, however, spectroscopic evidence for intermediates in the reactions of more complex molecules^[4].

We showed recently, that indole 1^[5] and 2-vinylindoles as 2^[6] can be used as heterosubstituted dienophiles, respectively dienes in radical cation Diels-Alder reactions with electron rich 1,3-cyclohexadienes as dienes and dienophiles or styrenes as dienophiles using photoinduced electron transfer (PET). Triarylpyrylium salts 3, excited by visible light proved to be efficient electron transfer sensitizers. Semiempirical studies of the reaction^[7] gave evidence for a long bond intermediate, stabilized by the formation of a distonic radical cation with an immonium structure. The activation barrier from that intermediate to the product was found to be 15 - 20 kcal mol⁻¹, depending on the type of diene under investigation. Hence, a nonsynchronous-nonconcerted path is assumed.

If the intermediate is as stable as predicted, rotation of a C-C single bond should be possible at the stage of the intermediate. Therefore, the *cis*-stereoselectivity of a concerted cycloaddition can be used as a mechanistic probe. Product studies of appropriate systems should be able to test this prediction and give further insight into the mechanism of the radical cation Diels-Alder reaction. The formation of the *cis*- as well as the *trans*-product in the reaction of an exocyclic diene of known configuration indicates a nonconcerted mechanism.

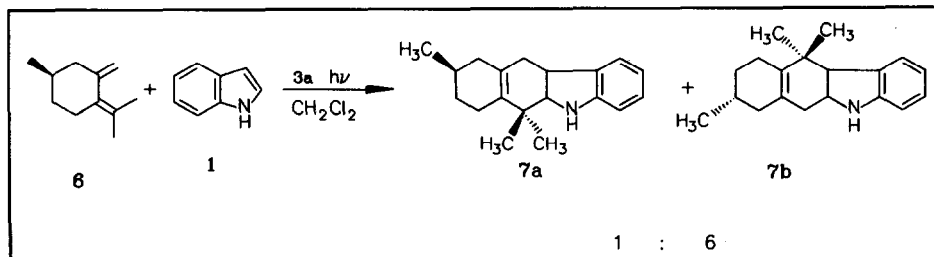


Scheme 1: PET-catalyzed reaction of an exocyclic diene with indole

The exocyclic diene **4**[8] was allowed to react with **1** under PET conditions (3 mol% **3b** as sensitizer) to give **5a-c** in 52% total yield (not optimized). The isomers were separated by preparative RP-HPLC[9]. The structures shown in scheme 1 have been proved by analysis of the ³J_{H-H} coupling constants in connection with MM2-force field calculations and by NOE-experiments[10]. The stereochemistry of the methyl groups in the aromatized product **5c** could not be determined since there are no β-hydrogens. Control experiments showed, that neither **4** nor **5** isomerize under the reaction conditions. Thus, the occurrence of **5a** as a reaction product can only be explained by a nonconcerted mechanism as predicted by the semiempirical calculations.

In addition to these mechanistic results, the [b]-annelated carbazole derivatives are of interest because of their DNA intercalating properties[11]. Several compounds of this structure type such as ellipticines have been studied extensively due to their antitumor activity. Since the radical cation Diels-Alder reaction represents a convergent synthesis of this structure type, further studies were carried out.

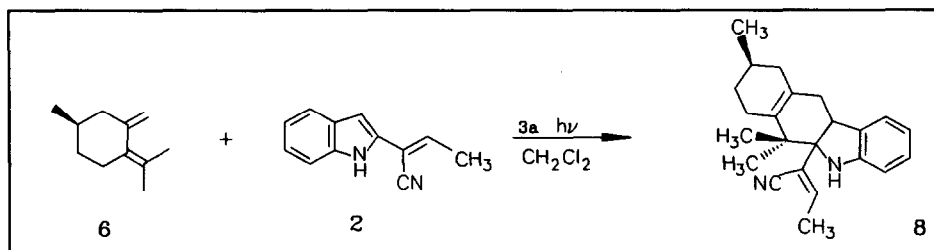
Although the reaction of the parent compound of the exocyclic dienes, 1,2-dimethylcyclohexane, failed because of an unsuitable oxidation potential[12], the easily accessible[13] chiral diene **6** gave the two isomers **7a,b** in 19% yield (not optimized). Other isomers could be detected by GC/MS in low (< 2%) yield. Hence, the reaction proceeds with almost complete diastereoselectivity and high regioselectivity, leading to chiral and enantiomeric pure benzo[b]carbazoles.



Scheme 2: PET-catalyzed reaction of indole with a chiral exocyclic diene

Surprisingly, this reaction is only possible using 3a as sensitizer, whereas the use of 3b leads to a unselective formation of several isomers of 7 as well as dimerization of 6. This behavior is not completely understood yet and can not be explained with a simple electron transfer step. Alternative mechanisms involving partial charge transfer (e.g. exciplexes or Lewis acid catalysis) must be considered in the case of 6 as a diene.

This is supported by our findings, that 6 reacts with the 2,3-double bond of 2-vinylindole 2^[14] as the dienophile in 15% yield. This is in sharp contrast to our previous studies on radical cation Diels-Alder reactions, where 2-substituted indoles showed no Diels-Alder reactivity as dienophiles at all and to the studies of some thermal Diels-Alder reactions^[15] where the vinylic double bond of 2-vinylindoles is more reactive as a dienophile. Hence, an alternative mechanism has to be assumed.



Scheme 3: PET-catalyzed reaction of a 2-vinylindole with a chiral diene

This reaction opens, however, a new synthetic pathway to [b]-annulated carbazoles with an unusual substitution pattern. The DNA intercalating properties of the resulting structures such as benzo[b]carbazoles or pyrrolo[b]carbazoles will make this convergent synthesis of these compounds an attractive topic for further studies.

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- [9] LiChroSpher100 RP18-5, 125*8 mm, gradient acetonitrile/water 40:60 to 80:20 at 10 min., flow 3.5 ml/min.
- [10] Selected spectroscopic data for 5a: $M^+(C_{18}H_{23}N)$: meas. 253.1826, calc. 253.183; 1H -NMR (400 MHz, $CDCl_3$): δ = 7.13 (1H, dddd, $J=7.2, 1.4, 0.9$ and 0.8 Hz, H-1), 7.01 (1H, tdd, $J=7.6, 1.4$ and 0.6 Hz, H-3), 6.71 (1H, td, $J=7.4, 1$ Hz, H-2), 6.64 (1H, ddd, $J=7.6, 1, 0.9$ Hz, H-4), 3.69 (1H, dd, $J=7.4, 3.2$ Hz, H-5a), 3.45 (1H, br, H-5), 2.91 (1H, ddd, $J=7.4, 5.6, 0.8$ Hz, H-11a), 2.05 (1H, m, H-6), 2.01 (1H, m, H-11), 1.95 - 2.1 and 1.67 - 1.85 (4H, m, H-7, H-10), 1.45 - 1.65 (4, m, H-8, H-9), 1.17 (3H, d, $J=7.2$ Hz, H-13), 1.11 (3H, d, $J=7.2$ Hz, H-12). Irradiation on H-12 shows a NOE on H-11a, whereas irradiation on H-13 shows a NOE-effect on H-1, but not on H-5a.
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