Radical cation Diels–Alder reaction between indoles and exocyclic 1,3-dienes with incorporated intentional cleaving points

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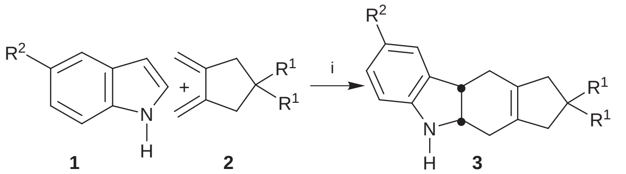
A photoinduced electron transfer catalyzed radical cation Diels–Alder reaction between exocyclic dienes, containing an N–O or N–N bond as an intentional cleaving point in the ring moiety, and indoles yields, after cleavage of the N–O or N–N bond, highly functionalized tetrahydrocarbazole derivatives, products of a formal Diels–Alder reaction between indole and open chain 1,3-dienes.

The indole skeleton is a fundamental structural unit of numerous alkaloids and biologically active compounds.[1] Since indole could prove to be an appropriate starting material for further alkaloid synthesis if suitable chemistry can be developed from this parent skeleton, attempts have been made to use the 2,3-double bond of indole in Diels–Alder cycloaddition reactions. However, the electron-rich indole shows only a low tendency to act as a dienophile. Its use mainly has been limited to Diels–Alder reactions with inverse electron demand under application of electron-poor heterodienes such as tetrazine derivatives or tetrachlorothiophene 1,1-dioxide.[2] In bimolecular Diels–Alder reactions with normal electron demand, indole can act as a dienophile if electron-withdrawing groups are present in the 1- and 3-position, but long reaction times and high temperatures are necessary.[3]

In contrast, we demonstrated the very efficient application of electron-rich indole in radical cation Diels–Alder reactions with electron-rich dienes under mild reaction conditions using photoinduced electron transfer (PET).[4,5] However, so far only a few, mainly unfunctionalized simple *endo*- and *exo*-cyclic dienes, *e.g.* cyclohexa-1,3-diene[4] and 1,2-dimethylidenecyclohexane derivatives[5] have been employed, leading to carbocyclic ring-anellated and bridged tetrahydrocarbazole derivatives, respectively. Open-chain 1,3-dienes without a rigid s-*cis*-conformation of the double bonds failed to undergo this PET-catalyzed cycloaddition reaction.

In order to broaden the synthetic scope of this reaction, we focused our investigations on the application of readily accessible functionalized exocyclic dienes, especially those which contain an intentional cleavage point in the ring moiety, thus representing the equivalents of open-chain 1,3-dienes. The rapid construction of multi-functionalized carbazoles according to this approach should be of interest with respect to indole alkaloid synthesis. In the following, our preliminary results are reported.

We started our studies with the five-membered exocyclic diene **2**[6] as a representative functionalized diene (Scheme 1). Due to the ease of preparation of a wide variety of these exocyclic dienes *via* an enyne cyclisation reaction,[7] these compounds are promising starting materials for the anticipated carbazole synthesis. Indeed, irradiation of diene **2**, indoles **1** and catalytic amounts of the photosensitizer triphenylpyrylium tetrafluoroborate (TPP) or tris(4-methoxyphenyl)pyrylium tetrafluoroborate (TAP) at $\lambda \geqslant 345$ nm gave good yields of Diels–Alder products **3**. Only the *cis*-fused tetrahydrocarbazoles were obtained (Scheme 1, Table 1, entries 1 and 2).



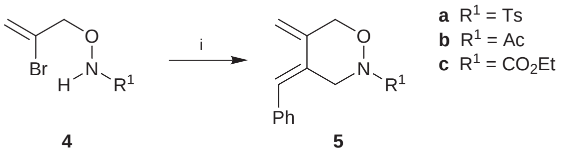
Scheme 1 *Reagents and conditions:* i, 5 mol% photosensitizer, CH_2Cl_2, $\lambda \geqslant 345$ nm, 1000 W, 20 ° C, 1.5 h.

Encouraged by these results, we turned our interest to exocyclic dienes with an intentional cleavage point in the ring moiety. As potentially ring-cleavable groups we selected the N–O and N–N bonds in compounds **5** and **10** (Schemes 2 and 3). For the rapid synthesis of the hydroxylamine-derived exocyclic dienes **5** we developed a tandem-reaction initiated by a palladium-mediated allylic amination of **4** and followed by a Heck reaction (Scheme 2). The phenyl group attached to the diene moiety was chosen to stabilize the intermediate **7** and should control the regiochemistry of the anticipated cycloaddition reaction with these asymmetrical dienes (Scheme 3).[5]

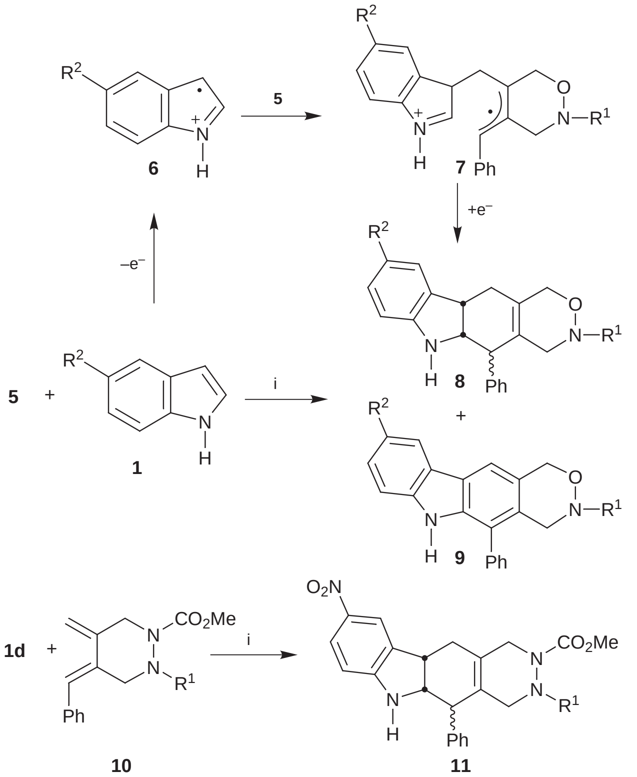
Irradiation at $\lambda \geqslant 345$nm of dienes **5**, indoles **1** and catalytic amounts of either TPP or TAP gave good to moderate yields of Diels–Alder products **8** and **9** under complete regiocontrol (Scheme 3, Table 1, entries 3–9). The somewhat lower yields obtained with dienes **5** as compared to the five-membered diene **2** might be rationalized by an increased steric demand of these phenyl substituted dienes **5**. As above, in all cases the bridge is *cis*-configured, but, due to the stereogenic carbon bearing the phenyl group, 1:1 mixtures of diastereomers were obtained. An

Table 1 Reaction of dienes **2**, **5** and **10** with indoles **1**

Entry	Diene	R¹	Indole	R²	Cycloadduct (% yield)	Photo-sensitizer
1	**2**	CO_2Et	**1b**	CO_2Me	**3a** (61)	TPP
2	**2**	CO_2Et	**1d**	NO_2	**3b** (80)	TAP
3	**5a**	Ts	**1a**	H	**8a** (15), **9** (13)	TPP
4	**5a**	Ts	**1a**	H	**9** (39)	TAP
5	**5a**	Ts	**1b**	CO_2Me	**8b** (50)	TPP
6	**5a**	Ts	**1c**	CN	**8c** (61)	TPP
7	**5a**	Ts	**1d**	NO_2	**8d** (61)	TAP
8	**5b**	Ac	**1d**	NO_2	**8e** (63)	TAP
9	**5c**	CO_2Et	**1d**	NO_2	**8f** (60)	TAP
10	**10a**	Ac	**1d**	NO_2	**11a** (58)	TAP
11	**10b**	COPh	**1d**	NO_2	**11b** (60)	TAP



Scheme 2 *Reagents and conditions:* i, $PhCH{=}CHCH_2OCO_2Me$ (1 equiv.), K_2CO_3 (2 equiv.), 5 mol% $Pd(OAc)_2$, 30 mol% PPh_3, MeCN, 20 °C, 2 h, then heated to 80 °C, 16 h, 60–70%.

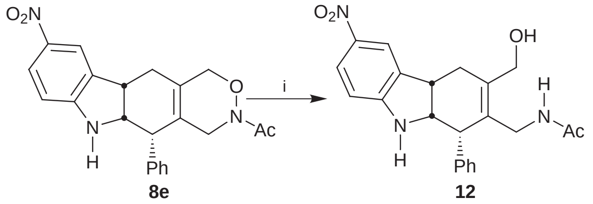


Scheme 3 *Reagents and conditions:* i, 5 mol% photosensitizer, CH_2Cl_2, $\lambda \geqslant 345$ nm, 1000 W, 20 ° C, 1.5 h.

exception is the diastereoselective (> 20 : 1) formation of **8a**, where the hydrogens at the bridge are *cis* relative to the phenyl group, probably owing to a selective aromatization of the other diastereomer giving **9**. Except for reactions with indole **1d**, this aromatization is a major follow-up reaction when TAP is used as sensitizer, but it can be completely suppressed when switching to TPP (except for indole **1a**, see Table 1, entry 3). A further feature of this reaction is the strong dependence of the yields upon the difference between the electronic character of the starting materials: the smaller the difference of the HOMO energies of the starting materials (decreasing from **1a** to **1c**/**d** in reaction with dienes **2** and **5**) the higher the obtained yield of the cycloadduct (see Table 1, entries 1–7).[8]

Variation of the electron-withdrawing group attached to the hydroxylamine component showed no effect on the cycloaddition reaction (Table 1, entries 7–9) and the yields obtained with the hydrazide-derived dienes **10**[9] are comparable to those received with the hydroxylamine derivatives **5** (Scheme 3, Table 1, entries 10 and 11). This was quite surprising because hitherto the incorporation of carbamate and amide groups in the diene was crucial to PET catalyzed reactions with indoles.[10]

As expected, the weak N–O bond of the cycloadducts is easily reductively cleaved with sodium amalgam[11] giving tetrahydrocarbazole **12** in almost quantitative yield (Scheme 4). The nitro group on the indole skeleton remained unchanged under these reaction conditions.Thus, in only four steps a highly functionalized tetrahydrocarbazole derivative is obtained in reasonable yield for further synthesis. Further experiments to explore the synthetic potential of this PET-catalyzed cycloaddition reaction are being continued in our laboratories.



Scheme 4 *Reagents and conditions:* i, Na_2HPO_4 (4.7 equiv.), 15× by weight Na(Hg), EtOH, 0 → 20 °C, 20 h, 94%.

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Notes and references

1 M. Hesse, *Indolalkaloide*, Verlag Chemie, Weinheim, 1974; R. J. Sundberg, *The Chemistry of Indoles*, Academic Press, New York, 1970; W. A. Remers, in *The Chemistry of Heterocyclic Compounds*, ed. W. J. Houlihan, Wiley-Interscience, New York, 1973, vol. 25, part I, ch. 1; R. A. Jones, in *Comprehensive Heterocyclic Chemistry*, ed. R. A. Katritzky and C. W. Reese, Pergamon, New York, 1984, vol. 4, p. 201.

2 M. S. Raasch, *J. Org. Chem.*, 1980, **45**, 856; A. Padwa, Y. Gareau, B. Harrison and A. Rodriguez, *J. Org. Chem.*, 1992, **57**, 3540; G. Seitz and T. Kaempchen, *Arch. Pharm.*, 1976, **309**, 679; M. Takahashi, H. Ishida and M. Kohmoto, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 1725; G. Seitz and R. Mohr, *Chem. Ztg.*, 1987, **111**, 81; S. C. Benson, C. A. Palabrica and J. K. Snyder, *J. Org. Chem.*, 1987, **52**, 4610; D. L. Boger and S. M. Sakya, *J. Org. Chem.*, 1988, **53**, 1415; S. C. Benson, J. L. Gross and J. K. Snyder, *J. Org. Chem.*, 1990, **55**, 3257; S. C. Benson, J.-H. Li and J. K. Snyder, *J. Org. Chem.*, 1992, **57**, 5285.

3 F. Wenkert, P. D. R. Moeller and S. R. Piettre, *J. Am. Chem. Soc.*, 1988, **110**, 7188; G. A. Kraus, J. Raggon, P. J. Thomas and D. Bougie, *Tetrahedron Lett.*, 1988, **44**, 5605; G. A. Kraus, D. Bougie, R. A. Jacobsen and Y. Su, *J. Org. Chem.*, 1989, **54**, 2425.

4 A. Gieseler, E. Steckhan, O. Wiest and F. Knoch, *J. Org. Chem.*, 1991, **56**, 1405; O. Wiest, E. Steckhan and F. Grein, *J. Org. Chem.*, 1992, **57**, 4034.

5 O. Wiest and E. Steckhan, *Tetrahedron Lett.*, 1993, **34**, 6391; U. Haberl and E. Steckhan, *Diplomarbeit*, Universität Bonn, 1995; U. Haberl, E. Steckhan and S. Blechert, *Int. Symposium of the VW-Stiftung on Intra- and Intermolecular Electron Transfer*, October 1996, Abstract Poster 16.

6 R. Grigg, P. Stevenson and T. Worakun, *Tetrahedron*, 1988, **44**, 4967.

7 For a review, see: B. M. Trost, *Acc. Chem. Res.*, 1990, **23**, 34.

8 It has been previously shown that for an efficient radical cation Diels–Alder reaction, the oxidation potentials, which correspond to the HOMO energies, of diene and dienophile should not differ by much more than 500 mV; a smaller difference normally results in higher yields; J. Mlcoch and E. Steckhan, *Angew. Chem.*, 1985, **97**, 429; J. Mlcoch and E. Steckhan, *Tetrahedron Lett.*, 1987, **28**, 1081; M. Martiny, E. Steckhan and T. Esch, *Chem Ber.*, 1993, **126**, 1671.

9 Prepared *via* a Heck reaction analogous to dienes **5**.

10 S. Blechert and E. Steckhan, unpublished results.

11 G. E. Keck, S. Fleming, D. Nickell and P. Weider, *Synth. Commun.*, 1979, **9**, 281.

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