DIELS-ALDER REACTIONS UNDER MOLECULAR SIEVE CATALYSIS: ENHANCEMENT OF REACTIVITY IN CYCLIZATION REACTIONS WITH *N*-BENZOYLINDOLE-2,3-QUINODIMETHANE TO FUNCTIONALIZED CARBAZOLES

Ulf Pindur* and Manfred Haber

Department of Chemistry and Pharmacy, University of Mainz,
Saarstraße 21, D-6500 Mainz 1, Federal Republic of Germany

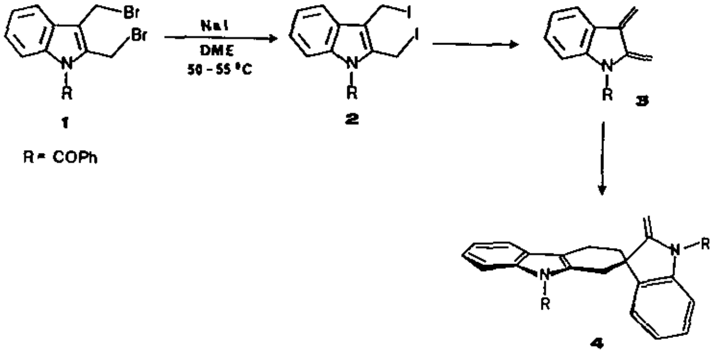
Abstract —— In the presence of highly activated molecular sieves (4 Å), the Diels-Alder reactivity of *in situ* generated *N*-benzoylindole-2,3-quinodimethane is enhanced considerably. Reactions of this species with a variety of carbodienophiles give rise to novel functionalized and [*b*]annelated carbazole derivatives in a one-pot procedure.

In addition to the established physical modes of enhancement (such as, e.g., elevated reaction temperatures, high pressures,[1] ultrasound[2]), Diels-Alder reactions can also be accelerated by a variety of catalysts: Lewis acids,[3] Brönsted acids (e.g., Nafion-H),[4] aluminum oxide,[5] silica gel,[6] florisil,[6] montmorrilonite,[7] zeolites[8], lithium perchlorate,[9] ethylammonium perchlorate,[10] and bovine albumin.[11] Furthermore, special molecular aggregation effects (e.g., generation of micelles or formation of hydrophobic packings) by performing the reactions in ethylene glycol[12] or by addition of water[13] to organic solvents have been employed for the same purpose. Similarly, the addition of β-cyclodextrin[14] or detergents[15] exerts an enormous positive effect on the acceleration of numerous Diels-Alder reactions. The use of non-acidic clays as catalysts is particularly attractive from a synthetic point of view because of their very mild character and their simple separation from the reaction mixture during work-up. In this context, it should be mentioned that highly activated molecular sieves on a zeolite basis have not previously been employed widely as catalysts for pericyclic reactions.[8]

We now report that addition of highly activated molecular sieves to reaction mixtures considerably expands the synthetic potential of Diels-Alder reactions of *N*-benzoylindole-2,3-quinodimethane (**3**). The [4 + 2]cycloaddition reactions of indole-2,3-quinodimethanes in general are of synthetic interest because they give rise to highly functionalized [*b*]-annelated indoles and functionalized hydrocarbazoles in a one-pot procedure. These products, in turn, represent useful building blocks for the synthesis of natural products possessing pronounced physiological activities.[16]

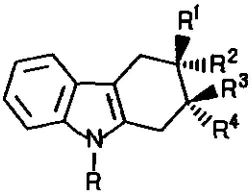
The required diene (**3**) was generated *in situ* from **1** following the established procedure[17] with the addition of sodium iodide (Scheme 1). The bis(iodomethyl) derivative (**2**) is probably the direct precursor of the generated species (**3**) (^{1}H-nmr analysis). The transient diene (**3**) can be captured by sufficiently reactive carbo- and heterodienophiles at 50-60 °C in the absence of a catalyst to furnish [*b*]annelated indoles.[17] However, the synthetic utility of this procedure is limited to the use of less reactive or less selective dienophiles. Thus, in most cases, the dimerization product (**4**) is formed regiospecifically in 30-90% yield and the yield of the desired cycloadduct is reduced accordingly (Scheme 1).

Scheme 1



On the other hand, Diels-Alder reactions of indole-2,3-quinodimethanes (**3**) with dienophiles such as tetracyanoethene, fumaric dinitrile, dimethyl fumarate, 2-chloropropenenitrile, phenyl vinyl sulfone, divinyl sulfone, propenenitrile, and methyl vinyl ketone occur smoothly in the presence of highly activated (4 Å) molecular sieves, thus considerably extending the scope of the method. The functionalized 1,2,3,4-tetrahydrocarbazoles (**5a-n**) are formed by these reactions in yields ranging from 10 to 63% (Table 1)[18] although the regioselectivities of the reactions with mono-acceptor substituted carbodienophiles vary from low to high.

Table 1. Diels-Alder adducts **5a-n** from reactions of **3** with acyclic carbodienophiles.



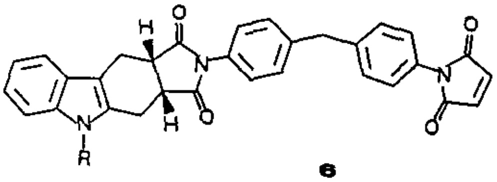
5	R^1	R^2	R^3	R^4	Yield [%]
a	CN	CN	CN	CN	19
b	CN	H	H	CN	13
c	CO_2Et	H	H	CO_2Et	63
d	CN	Cl	H	H	$51^{a,b}$
e	H	H	CN	Cl	
f	SO_2Ph	H	H	H	$10^{a,c}$
g	H	H	SO_2Ph	H	
h	$SO_2CH=CH_2$	H	H	H	$14^{a,d}$
i	H	H	$SO_2CH=CH_2$	H	
k	CN	H	H	H	$45^{a,e}$
l	H	H	CN	H	
m	COMe	H	H	H	$59^{a,f}$
n	H	H	COMe	H	

[a] Combined yield of the regioisomers.

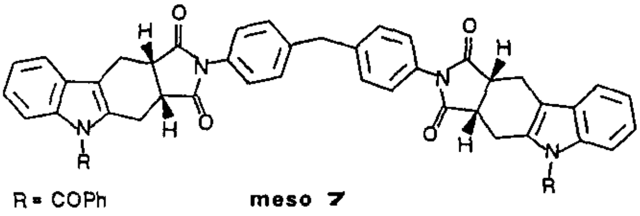
[b-f] Ratio of isomers by ^1H-nmr: b) 8:1; c) 2.3:1; d) other regioisomer < 3%; e) 4:1; f) 4:1.

The formation of a single product possessing the *trans*-configuration (**5c**) in the reaction of **3** with diethyl fumarate confirms the occurrence of a stereoselective process. The overall results of these [4 + 2]cyclo-

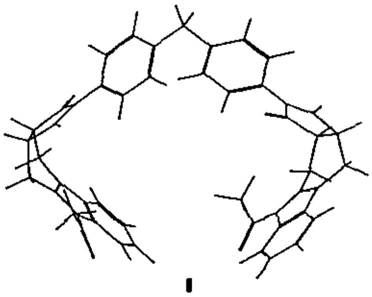
additions are fully in accord with the prediction of a HOMO(diene)-LUMO(dienophile) interaction of the reactants in the transition state.[17]
In the case of cyclic carbodienophiles, the transient species (3) reacts with *N*-phenylmaleimide in the absence of a catalyst to furnish the corresponding [4 + 2]cycloadduct.[17] On the other hand, the interesting bis(4-maleimidophenyl)methane does not react with 3 under analogous conditions. However, in the presence of molecular sieves, the cyclic bis-dienophile does react with **3** to furnish the mono- and bis[4 + 2]cycloadducts (**6**) and (**7**). Four stereocenters have been built up in the formation of the stereochemically homogeneous product (**7**) (^{1}H- and ^{13}C-nmr, hplc). On the basis of the *cis*-selectivity in the repetitive Diels-Alder step, a total of three stereoisomers would be expected: a (C_s-symmetrical) meso-form and a pair of (C_1-symmetrical) enantiomers.



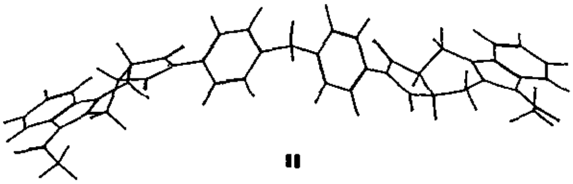
6



meso 7
(or C_1 diastereomer)



I



II

For the sake of structural clarity and for the analysis of the molecular shapes of these relatively large molecules, however, MMX molecular mechanics calculations have been carried out[19] on the *N,N'*-bisacetyl analog of **7** (molecular structures I and II). Both molecules adopt at their centers the diarylmethane propeller conformation which is linked with the "long" succinimide moiety at the molecular periphery in a slightly twisted orientation to the central rings of the diarylmethane unit. These calculations revealed that the "meso" isomer I is more stable than the "C_1" isomer II in steric energy by about 2.00 kcal • mol^{-1}. In addition, the 400 MHz ^1H- and 100.6 MHz ^{13}C-nmr spectra exhibit only one set of signals for **7**.

In conclusion, we can suggest that the exclusively formed product (**7**) possesses the stereochemistry of the meso-isomer I. The double Diels-Alder product (**7**) is of potential interest as a building block for the synthesis of polymeric compounds with probable semiconducting properties.[20] All compounds prepared were characterized by ^1H-, ^{13}C-nmr, ir, and mass spectroscopy as well as by elemental analysis.[21]

ACKNOWLEDGEMENTS

This work was supported by the *Deutsche Forschungsgemeinschaft* (Bonn) and the *Fonds der Chemischen Industrie* (FRG).

REFERENCES AND NOTES

1. K. Matsumoto and A. Sera, *Synthesis*, 1985, 999.
2. J. Lee and J. K. Snyder, *J. Org. Chem.*, 1990, **55**, 4995.
3. V. D. Kiselev and A. J. Konovalov, *Russ. Chem. Rev.*, 1989, **58**, 230.
4. G. A. Olah, P. S. Iyer, and G. K. S. Prakash, *Synthesis*, 1986, 513.
5. G. Hondogiannis, R. M. Pagni, G. W. Kabalka, P. Anosike, and R. Kurt, *Tetrahedron Lett.*, 1990, **31**, 5433.
6. V. V. Veselovsky, A. S. Gybin, A. V. Lozanowa, A. M. Mioseenkov, W. A. Smit, and R. Caple, *Tetrahedron Lett.*, 1988, **29**, 175; M. Eitel and U. Pindur, *Heterocycles*, 1989, **27**, 2353.
7. P. Laszlo and J. Lucchetti, *Tetrahedron Lett.*, 1984, **25**, 2147; P. Laszlo and H. Moison, *Chemistry Lett.*, 1989, 1031.

8. R. M. Dessau, *J. Chem. Soc., Chem. Commun.*, 1986, 1167; P. H. Götz, J. W. Bats, and H. Fritz, *Liebigs Ann. Chem.*, 1986, 2065; W. H. Flank and T. E. Whyte, Jr., *"Perspectives in Molecular Sieve Science"*, ACS Symposium Series, 368, American Chemical Society, Washington, DC, 1988, pp. 1-630.

9. P. A. Grieco, J. H. Nunes, and M. D. Gaul, *J. Am. Chem. Soc.*, 1990, **112**, 4599.

10. D. A. Jaeger and C. E. Tucker, *Tetrahedron Lett.*, 1989, **30**, 1785.

11. S. Colonna, A. Manfredi, and R. Annunziata, *Tetrahedron Lett.*, 1988, **29**, 3347.

12. T. Dunams, W. Hoekstra, M. Pentaleri, and D. Liotta, *Tetrahedron Lett.*, 1988, **29**, 3745.

13. R. Breslow and D. J. Rideout, *J. Am. Chem. Soc.*, 1980, **102**, 7816.

14. R. Breslow and T. Guo, *J. Am. Chem. Soc.*, 1988, **110**, 5613.

15. R. Braun, F. Schuster, and J. Sauer, *Tetrahedron Lett.*, 1986, **27**, 1285; B. Jursic, *Tetrahedron*, 1988, **44**, 6677.

16. U. Pindur and H. Erfanian-Abdoust, *Chem. Rev.*, 1989, **89**, 1681.

17. U. Pindur and M. Haber, *Tetrahedron*, 1991, **47**, 1925.

18. **General Procedure:** 2,3-Bis(bromomethyl)indole (**1**; 2 mmol) and the dienophile (2 mmol; or 10-20 mmol in the cases of phenyl vinyl sulfone, divinyl sulfone, bis(4-maleimidophenyl)methane) are dissolved in dimethoxyethane (30 ml). Highly activated molecular sieve (4 Å; 6 g) and powdered sodium iodide (10 mg) are added and the mixture is warmed to 50-55 °C. After the mixture has been stirred for 30 min at this temperature, the solid is filtered off, and the residue from the organic layer is purified by flash chromatography (Merck 60 silica gel, 0.04-0.063 mm; 40-60 °C petroleum ether/AcOEt, variable ratios). All products are recrystallized from AcOEt.

Preparation of Activated Molecular Sieve: The molecular sieve (100 g, Merck, 4 Å) was activated in a vacuum-dried apparatus for 24 h at 200 °C and 1 torr.

19. The MMX molecular mechanics program from Serena Software Ltd., Bloomington, IN, was used; this program was established by K. E. Gilbert and J. J. Gajewski and is based on Allinger's MM2 program (QCPE 395 and 318).

20. P. W. Kenny and L. L. Miller, *J. Chem. Soc., Chem. Commun.*, 1988, 84.

21. Selected 400 MHz ^{1}H-nmr data (in the cases of inseparable mixtures of regioisomers, A = major isomer and B = minor isomer).

5b: (DMSO-d_6): δ = 3.11 (m, 2H, C1-CH$_2$ or C4-CH$_2$), 3.17 (dd, ^2J = 16.30 Hz, ^3J = 5.7 Hz, C4-H or C1-H), 3.26 (dd, ^2J = 16.5 Hz, ^3J = 5.7 Hz, C1-H or C4-H), 3.83 (m, 1H, C2-H or C3-H), 3.91 (m, 1H, C3-H or C2-H), 6.93 (d, ^3J = 8.3 Hz, 1H, C8-H), 7.13 (ddd, ^3J = 8.3 and 7.3 Hz, ^4J = 1.15 Hz, 1H, C6-H or C7-H), 7.22 (ddd, ^3J = 7.22 and 7.41 Hz, ^4J = 0.77 Hz, C7-H or C6-H), 7.58 (m, 3H, C3'-H, C5'-H, C8-H), 7.67 (dd, ^3J = 7.66 Hz, ^4J = 1.45 Hz, 2H, C2'-H, C6'-H), 7.73 (m, 1H, C4'-H).

5d,e (8:1 mixture of regioisomers; DMSO-d_6): δ = 2.55 (m, 2H, C2-H of A, C3-H of B), 2.68 (m, 2H, C2-H of A, C3-H of B), 2.88 (m, 2H, C4-CH$_2$ of B), 2.94 (m, 2H, C1-CH$_2$ of A), 3.39 (d, ^2J = 17.15 Hz, 1H, C4-H of A), 3.50 (d, ^2J = 17.10 Hz, 1H, C1-H of B), 3.72 (d, ^2J = 17.27 Hz, 1H, C4-H of A), 3.78 (d, ^2J = 17.20 Hz, 1H, C1-H of B), 6.95 (d, ^3J = 8.36 Hz, 1H, C8-H of A), 6.98 (d, ^3J = 8.50 Hz, 1H, C8-H of B), 7.11 (m, 1H, C6-H or C7-H of B), 7.13 (ddd, ^3J = 8.25 and 7.26 Hz, ^4J = 1.14 Hz, 1H, C6-H or C7-H of A), 7.21 (m, 1H, C7-H or C6-H of B), 7.23 (ddd, ^3J = 7.06 and 7.47 Hz, ^4J = 0.76 Hz, 1H, C7-H or C6-H of A), 7.58 (m, 6H, C5-H of A and B, C3'-H of A and B, C5'-H of A and B), 7.65 (dd, ^3J = 8.10 Hz, ^4J = 1.43 Hz, 2H, C2'-H and C6'-H of B), 7.67 (dd, ^3J = 7.69 Hz, ^4J = 1.38 Hz, 2H, C2'-H and C6'-H of A), 7.73 (m, 2H, C4'-H of A and B).

5h,i (DMSO-d_6): δ = 1.79 (m, 1H, C2-H), 2.35 (m, 1H, C2-H), 2.72 (m, 2H, C4-CH$_2$), 2.93 (dd, ^2J =16.77 Hz, ^3J = 5.00 Hz, 2H, C1-CH$_2$), 3.51 (m, 1H, C3-H), 6.19 (d, ^3J = 16.51 Hz, 1H, C2-vinyl-H$_{trans}$), 6.31 (d, ^3J = 9.87 Hz, 1H, C2-vinyl-H$_{cis}$), 6.92 (dd, $^3J_{trans}$ = 16.57 Hz, $^3J_{cis}$ = 9.87 Hz, 1H, C1-vinyl-H), 6.92 (d, ^3J = 8.32 Hz, 1H, C8-H), 7.09 (ddd, ^3J = 8.30 and 7.20 Hz, ^4J = 1.13 Hz, 1H, C6-H or C7-H), 7.19 (ddd, ^3J = 7.44 and 7.37 Hz, ^4J = 0.83 Hz, 1H, C7-H or C6-H), 7.49 (d, ^3J = 7.59 Hz, 1H, C5-H), 7.57 (dd, ^3J = 7.71 and 7.48 Hz, 2H, C3'-H, C5'-H), 7.66 (dd, ^3J = 7.71 Hz, ^4J = 1.37 Hz, 2H, C2'-H, C6'-H), 7.71 (m, 1H, C4'-H).

5k,l (4:1 mixture of regioisomers, DMSO-d_6): δ = 2.03 (m, 2H, C2-CH$_2$ or C3-CH$_2$ of B), 2.08 (m, 2H, C2-CH$_2$ or C3-CH$_2$ of A), 2.67 (m, 2H, C1-CH$_2$ or C4-CH$_2$ of B), 2.78 (m, 2H, C1-CH$_2$ or C4-CH$_2$ of A), 2.82 (dd, ^2J = 16.33 Hz, ^3J = 6.09 Hz, 1H, C4-H or C1-H of A), 2.93 (m, 1H, C4-H or C1-H of B), 2.96 (dd, ^2J = 16.69 Hz, ^3J = 6.02 and 5.38 Hz, 1H, C4-H or C1-H of A), 3.08 (dd, ^2J = 16.58 Hz, ^3J = 6.20 and 6.02 Hz, 1H, C4-H or C1-H of B), 3.31 (m, 2H, C2-H or C3-H of A and B), 7.04 (d, ^3J =

8.15 Hz, 2H, C8-H of A and B), 7.11 (dd, ^{3}J = 7.19 and 8.15 Hz, 1H, C6-H or C7-H of A), 7.13 (m, 1H, C6-H or C7-H of B), 7.20 (dd, ^{3}J = 7.47 and 7.32 Hz, 2H, C7-H or C6-H of A and B), 7.51 (d, ^{3}J = 7.64 Hz, 2H, C5-H of A and B), 7.58 (m, 4H, C3′-H of A and B, C5′-H of A and B), 7.66 (m, 4H, C2′-H and C6′-H of A and B), 7.71 (dd, ^{3}J = 2.40 and 7.97 Hz, 2H, C4′-H of A and B).

6 ($CDCl_3$): δ = 3.07 (m, 2H, C3a-H, C10a-H), 3.32 (dd, ^{3}J = 2.85 and 2.70 Hz, ^{2}J = 17.14 Hz, 1H, C4-H or C10-H), 3.40 (dd, ^{3}J = 3.22 and 3.10 Hz, ^{2}J = 16.50 Hz, 1H, C4-H or C10-H), 3.44 (m, 1H, C10-H or C4-H), 3.51 (m, 1H, C10-H or C4-H), 3.97 (s, 2H, Ar-CH_2-Ar′), 6.81 (s, 2H, olefinic H of maleimide), 7.04 (d, ^{3}J = 8.45 Hz, 2H, aromatic H), 7.11 (ddd, ^{3}J = 7.75 and 7.78 Hz, ^{4}J = 1.20 Hz, 1H, C7-H or C8-H), 7.21 (m, 7H, aromatic H), 7.26 (d, ^{3}J = 8.27 Hz, 1H, C6-H), 7.48 (m, 3H, C3′-H, C5′-H, C9-H), 7.62 (m, ^{3}J = 7.54 and 7.47 Hz, ^{4}J = 1.30 and 1.72 Hz, 1H, C4′-H), 7.66 (dd, ^{3}J = 7.68 Hz, ^{4}J = 1.36 Hz, 2H, C2′-H, C6′-H).

7 ($CDCl_3$): δ = 3.07 (m, 4H, 2 × C3a-H, C10a-H), 3.31 (dd, ^{3}J = 2.74 and 2.86 Hz, ^{2}J = 17.15 Hz, 2H, 2 × C4-H or C10-H), 3.39 (dd, ^{3}J = 3.28 and 3.03 Hz, ^{2}J = 16.05 Hz, 2H, 2 × C4-H or C10-H), 3.43 (m, 2H, 2 × C10-H or C4-H), 3.51 (m, 2H, 2 × C10-H or C4-H), 3.93 (s, 2H, Ar-CH_2-Ar), 7.01 (d, ^{3}J = 8.45 Hz, 4H, 2 × 2 aromatic H), 7.15 (d, ^{3}J = 8.49 Hz, 4H, 2 × 2 aromatic H), 7.19 (ddd, ^{3}J = 7.76 and 7.80 Hz, ^{4}J = 1.23 Hz, 2H, 2 × C7-H or C8-H), 7.20 (ddd, ^{3}J = 7.31 and 7.67 Hz, ^{4}J = 0.80 Hz, 2H, 2 × C8-H or C7-H), 7.25 (d, ^{3}J = 8.33 Hz, 2H, 2 × C6-H), 7.48 (m, 6H, 2 × C3′-H, C6′-H, C9-H), 7.62 (m, 2H, 2 × C4′-H), 7.66 (dd, ^{3}J = 7.27 Hz, ^{4}J = 1.13 Hz, 4H, 2 × C2′-H, C6′-H).

Received, 27th May, 1991