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STEREOSELECTIVE DIELS-ALDER REACTIONS BETWEEN 9-ALKYL-1,4-DIHYDRONAPHTHALEN-1,4-IMINES AND 2-ALKYLISOINDOLES

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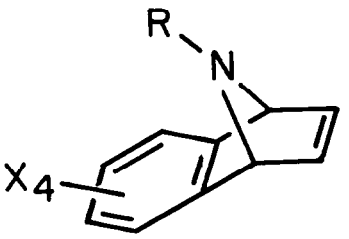
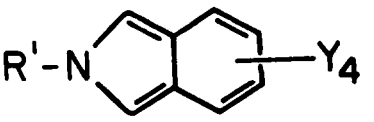
Summary: The Diels-Alder reaction between 9-alkyl-1,4-dihydronaphthalen-1,4-imines (1) and 2-alkylisoindoles (2) occurs in refluxing xylene to give exclusively the exo-endo cycloadducts 3 (D).

In continuation of our studies of the chemical[1] and physical[2] properties of arenimines, which are useful polycyclic aromatic hydrocarbon synthons,[1,3] we now describe the Diels-Alder reaction between 9-alkyl-1,4-dihydronaphthalen-1,4-imines (1) and 2-alkylisoindoles (2).

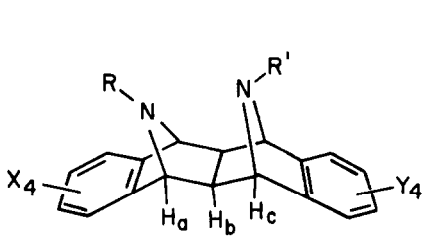


1

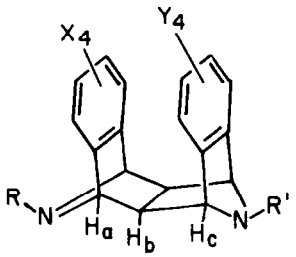


2

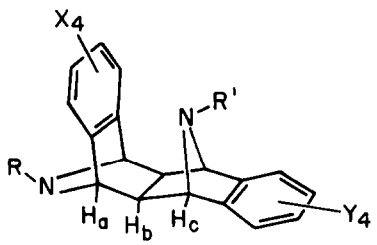
Refluxing a xylene solution of equimolar amounts of 9-methyl-5,6,7,8-tetrafluoro-1,4-naphthalen-1,4-imine (1a; R=CH_3, X=F) and 2-methylisoindole (2a; R'=CH_3, Y=H) for 48 hours affords upon workup a single, crystalline adduct 3a (mp 132-3°; $C_{20}H_{16}N_2F_4$) in 25% yield after purification. The ^{1}H-NMR spectrum of this material shows two very different N-methyl singlets (1.3 and 2.1 ppm) and three sets of two methine protons each, two sets of which are mutually coupled (confirmed by decoupling) and comprise an AA'XX' system[4] (2.5 and 4.1 ppm) and one set of which is not coupled to other protons[5] (3.8 ppm). These NMR data clearly preclude structures A and B for 3a, since these cycloadducts would each have nearly identical N-methyl signals. Furthermore, A would exhibit little or no vicinal coupling of the four bridgehead protons H_a and H_c with the two central methine protons H_b (ca. 90° dihedral angle) while cycloadduct B would exhibit equal coupling of H_b with both H_a and H_c of about 4-5 Hz (ca. 30° dihedral angle).[6] In contrast to A and B, the ^{1}H-NMR spectra of C and D would be expected to reveal one N-methyl signal at unusually high field because these methyl protons are positioned in the shielding region of the proximate benzene ring.[6d,7] One also expects to observe splitting of H_b by only one set of bridgehead protons (H_a in C and H_c in D) because of the



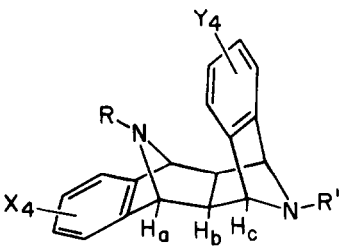
A



B



C



D(3)

dihedral angle differences noted above. Based on this analysis, the ^{1}H-NMR spectral data observed for cycloadduct 3a (vide supra) are clearly in accord with structure C or D.

Although D seems more reasonable than C on mechanistic grounds (attack on the exo side of 1 and possible secondary orbital overlap between the nitrogen lone pair in 1 and the aromatic ring in 2), they cannot be safely differentiated a priori by ^{1}H-NMR. Therefore, to decide whether C or D was the structure of 3a we prepared several adducts with different R and R' groups. Our results are summarized in the Table. Thus, 1b (R=CH_2Ph, X=F) and 2b (R'=CH_3, Y=F) gave 3b which in its ^{1}H-NMR spectrum exhibits strongly shielded N-benzyl methylene protons (2.7 ppm) but normally positioned N-methyl protons (2.0 ppm). The complementary reaction of 1a (R=CH_3, X=F) and 2c (R'=CH_2Ph, Y=F) gave 3c which in its ^{1}H-NMR spectrum exhibits normally positioned N-benzyl methylene protons (3.4 ppm) but strongly shielded N-methyl protons (1.5 ppm). These data clearly establish that the N-alkyl group in arenimine 1, and not in isoindole 2, becomes the shielded group in 3, and, hence, the structure of cycloadduct is D and not C.

The absence of exo-exo adduct A from the reaction mixture[9] is somewhat surprising because this isomer is the minor cycloadduct in the reaction of 1,4-dihydronaphthalen-1,4-oxide with 2,[6a] in the reaction of 1,4-dihydronaphthalen-1,4-oxide with isobenzofuran,[10] and in the reaction of 1 (R=CO_2Bu-t, X=H) with 2 (R'=CO_2Bu-t, Y=H).[6d] In our case the transition state leading to A may be unfavorable because of methyl-methyl (and perhaps lone-pair/lone-pair) repulsions which do not exist in the cases cited above.

The reactions shown in the Table were all run under the same conditions of time and temperature, resulting in variable yields. Lower yields obtain with the less stable isoindoles (2a) and with arenimines having bulky N-alkyl groups (i.e., 1b). Shorter or longer reaction times and higher (nitrobenzene, 1,3,5-trichlorobenzene) or lower (toluene) temperatures do not noticeably improve

yields. Control experiments demonstrate that the cycloadducts 3 are stable under the reaction conditions and do not revert to 1 and 2.[11] A competing reaction is slow decomposition of the isoindole, especially with 2a. We find also that the arenimine 1 can give rise to small amounts of the corresponding isoindole 2 (by retro Diels-Alder loss of acetylene), which then can react with 1 in the usual fashion. Thus, the reaction of 1a with 2a (toluene, reflux, 48 h) gives, in addition to 3a (31%), the octafluoro cycloadduct 3d in about 2% yield. Similarly, the reaction of 1c alone (xylene, reflux, 48 h) affords the octachloro adduct 3f (R=R'=CH_3, X=Y=Cl) (mp 240-241°) in 14% yield.

Table. Reaction of 9-Alkyl-1,4-dihydronaphthalen-1,4-imines (1) with 2-Alkylisoindoles (2)[a]

Reactants		Product[b]	Mp	Yield, %[c]
1a (R=CH_3, X=F)[d]	2a (R'=CH_3, Y=H)[e]	3a	132-133°	25
1b (R=CH_2Ph, X=F)[f]	2b (R'=CH_3, Y=F)[g]	3b	166-167°	6
1a	2c (R'=CH_2Ph, Y=F)[g]	3c	174-176°	32
1a	2b	3d	215-216°	61
1c (R=CH_3, X=Cl)[d]	2a	3e	202-203°	23

[a]Reactions were run in refluxing xylene under N_2 for 48 hours. Workup consisted of concentration in vacuo and purification of the crude product by successive column chromatography, sublimation, and crystallization from methanol / dichloromethane to give the yields and melting points listed in the Table.

[b]All products gave satisfactory elemental analyses and ^{1}H-NMR spectra: ($CDCl_3$) 3a 1.3 (s, 3H), 2.1 (s, 3H), 2.5 (m, 2H), 3.8 (bs, 2H), 4.1 (m, 2H), 7.1 (s, 4H); 3b 2.0 (s, 3H), 2.6 (m, 2H), 2.7 (s, 2H), 4.1 (bs, 2H), 4.3 (m, 2H), 6.7-7.2 (m, 5H); 3c 1.5 (s, 3H), 2.6 (m, 2H), 3.4 (s, 2H), 3.9 (bs, 2H), 4.5 (m, 2H), 7.2 (m, 5H); 3d 1.5 (s, 3H), 2.1 (s, 3H), 2.6 (m, 2H), 3.9 (bs, 2H), 4.5 (m, 2H); 3e 1.3 (s, 3H), 2.0 (s, 3H), 2.5 (m, 2H), 3.6 (s, 2H), 7.1 (s, 4H).

[c]Isolated and purified product; see footnote a.

[d]Reference 2.

[e]B. Zeeh and K. H. König, Synthesis, 45 (1972).

[f]Prepared from N-benzylpyrrole and tetrafluorobenzyne according to the general procedure in reference 2; mp 93-94°; lit.,[12] mp 93-94°.

[g]Prepared according to the method of G. M. Priestley and R. N. Warrener, Tetrahedron Lett., 4295 (1972).

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References and Notes

1. (a) G. W. Gribble, R. W. Allen, P. S. Anderson, M. E. Christy, and C. D. Colton, Tetrahedron Lett., 3673 (1976); (b) G. W. Gribble, et al., J. Org. Chem., submitted.

2. G. W. Gribble, N. R. Easton, Jr., and J. T. Eaton, Tetrahedron Lett., 1075 (1970).

3. (a) A. Sy and H. Hart, J. Org. Chem., 44, 7 (1979); (b) H. Hart and A. Teuerstein, Synthesis, 693 (1979).

4. H. Günther, Angew. Chem. internat. Edit., 11, 861 (1972).

5. These protons are coupled to the fluorines by a five-bond zig-zag pathway, J ≅ 2.5 Hz (unpublished data).

6. (a) G. Wittig and W. Reuther, Ann., 761, 21 (1972); (b) A. P. Marchand and R. W. Allen, Tetrahedron Lett., 67 (1975); (c) P. S. Anderson, Tetrahedron Lett., 1141 (1976); (d) T. Sasaki, T. Manabe, and S. Nishida, J. Org. Chem., 45, 476 (1980).

7. Dreiding models show that this methyl carbon in C (and D) is ca. 3.5 Å from the plane of the benzene ring in the invertomer shown and ca. 1.2 Å in the presumed less-stable invertomer (not shown). Since nitrogen inversion is fast at room temperature in this system,[2,8] the observed upfield N-CH_3 chemical shift in 3 reflects a weighted average of the two invertomers. By comparison, the ^{1}H-NMR spectrum of [9]paracyclophane shows four high field methylene protons centered at 0.4 ppm corresponding to two methylene carbons ca. 2.7 Å from the plane of the benzene ring: D. J. Cram and M. Goldstein, J. Am. Chem. Soc., 85, 1063 (1963).

8. W. J. Deloughry and I. O. Sutherland, Chem. Comm., 1104 (1971).

9. We carefully examined the crude reaction mixture by ^{1}H-NMR and medium pressure preparative liquid chromatography but could find no material which could be construed as cycloadduct A, B, or C. We do isolate varying amounts of 1 and 2 as well as isoindole decomposition products.

10. L. F. Fieser and M. J. Haddadin, Cand. J. Chem., 43, 1599 (1965).

11. For example, refluxing a xylene solution of 3d and 2a for 48 hours gives no crossover product 3a but only 3d (100% recovery).

12. J. Bornstein, D. E. Remy, and J. E. Shields, Tetrahedron Lett., 4247 (1974).

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