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FIRST REACTIONS OF 1,4-DIMETHYLCARBAZOLE-3-CARBALDEHYDE N,N-DIMETHYLHYDRAZONE WITH CARBO- AND AZODIENOPHILES

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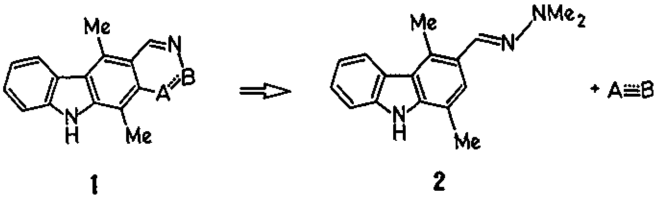
Abstract —— Reactions of 1,4-dimethylcarbazole-3-carbaldehyde N,N-dimethylhydrazone (**2**) with carbo- and azodienophiles are described. Instead of giving the primarily expected Diels-Alder adducts, attack of the electrophilic dienophiles at the hydrazone unit of **2** occurs to furnish a 3-cyanocarbazole and, in one case, a carbazolyl-urazolylhydrazone.

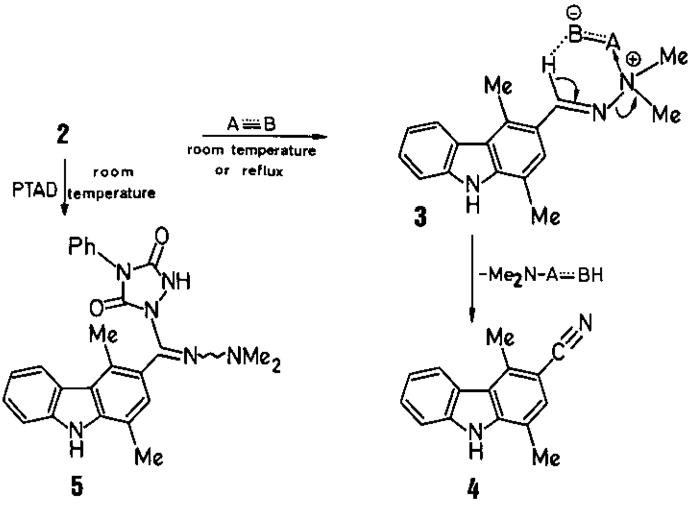
Pyrido[4,3-b]carbazole alkaloids of the ellipticine type are important since they exhibit antitumor activity.[1-3] Hence, ellipticine and its analogs (**1**) (A,B = carbon) are interesting targets for synthesis.[4] Although several routes to the ellipticines are known,[4] there is still a requirement for further short, effective, and highly convergent procedures. A potential new method involves a Diels-Alder reaction of the carbazolealdehyde hydrazone (**2**) with carbo-dienophiles and subsequent elimination of dimethylamine to furnish compounds **1** (A,B = carbon).

Scheme 1



We have now investigated this concept. The E-isomeric hydrazone (**2**) is readily and stereospecifically accessible[5] (75% yield; mp 172–175 °C; ^{1}H,^{1}H-nOe experiments) from 1,4-dimethylcarbazole-3-carbaldehyde[6] and hydrazine. In general, the azadiene moiety electronically integrated in **2** should participate in [4 + 2]cycloadditions with suitable dienophiles to form [b]annellated carbazoles of the type **1**. However, in spite of numerous variations of the reaction conditions, **2** did not undergo cycloaddition with tetracyanoethylene (TCNE), dimethyl acetylenedicarboxylate (DMAD), methyl propiolate (MP), N-phenylmaleimide (NPMI), diethyl azodicarboxylate (DEAD), or N-phenyltriazoline-3,5-dione (PTAD). In all cases studied, the reaction proceeded via a formally dienophile-catalyzed 1,2-elimination at the hydrazone function to furnish the 3-cyanocarbazole (**4**) (18–53% yield; mp 224–225 °C; Table 2), probably via intermediate (**3**) (Scheme 2).[7] It was possible to isolate the dimethylamine adduct from the reaction with DMAD whereas with PTAD under mild conditions the novel urazolyl-substituted hydrazone (**5**; mp 238–240 °C) was additionally formed exclusively as an E/Z-mixture (3:1; 47–50% yield). Hence **2** has reacted only as an ambident three-center nucleophile.[8,9]

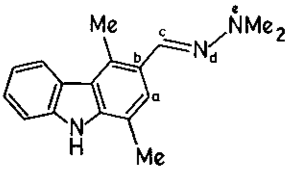
Scheme 2



A≡B = TCNE, DMAD, MP, NPMI, DEAD, PTAD

In order to rationalize these unexpected results, we performed π-SCF-MO calculations[10] on **2** and the data obtained disclosed a useful prediction for these observations (Table 1). A $HOMO_{diene}$-$LUMO_{dienophile}$ interaction of the reactants is, in principle, possible according to the FMO concept.[11] Inspection of Dreiding models demonstrates that no steric effects exist for the establishment of the Diels-Alder transition state while molecular mechanics calculations[10] reveal an energy difference for the (E)-s-cis/(E)-s-trans-conformations of 2 of only 0.70 kcal mol^{-1} (ΔE_{steric}). Thus, sufficient s-cis-conformation should be present in the reaction medium for the Diels-Alder reaction. We suggest that the resonance energy of the 14π-carbazole moiety is too high for a deblocking of the π-elec-

Table 1. π-SCF-MO calculations of 2 (fully coplanar and geometry-optimized s-cis-conformation)[10]



$E_{HOMO} = -9.1879$ eV

centers	a	b	c	d	e
HOMO coefficient	0.1061	0.2899	-0.4804	-0.3208	0.5453
π-electron density	0.9960	1.1123	1.0044	1.1669	1.8393
charge (q)	-0.04	-0.11	+0.07	-0.06	-0.01

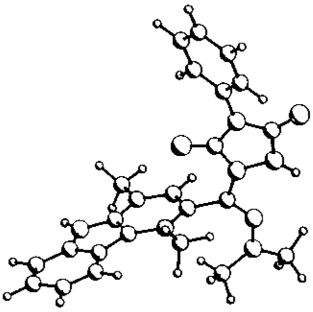


Figure 1. Energy-minimized conformation of (E)-5 by molecular mechanics calculations[10]

Table 2. Reaction conditions and yields in reactions of 2 with dienophiles

Dienophile	Reaction time at room temperature	reflux	Product	Yield
DMAD	5 d[a)]	1 d[b)]	**4**	51%
MP	15 d[a)]	-	**4**	40%
NPMI	5 d[a)]	1 d[b)]	**4**	53%
TCNE	5 d[a)]	1 d[b)]	**4**	48%
DEAD	5 d[a)]	1 d[b)]	**4**	18%
PTAD	14 h[c)]	-	**5**	50%

a) CH_2Cl_2. b) MeCN. c) Acetone.

trons on the way to the [4 + 2]transition state (Dewar resonance energy of carbazole = 171.1 kcal mol^{-1}).[12] But the π-electron densities at the hydrazone function are high enough for a one bond attack of the dienophiles as simple electrophiles (Table 1). Attack at centers c and e gives rise to the observed products (**4**) and (**5**) in accord with other results from hydrazone chemistry.[8] Thus, the primary N-attack is due to the high nucleophilicity of the hydrazone nitrogen e. On the other hand, the additional attack of the highly electrophilic PTAD at center c can be explained in terms of the significant HOMO coefficient, the sufficient π-electron density (or charge) at this reaction center, and the extremely high electrophilicity of PTAD. In the ^{13}C-nmr spectrum of **2** the imino carbon resonance is at 137 ppm, in complete agreement with the computed value obtained using the ^{13}C-nmr simulation program.[13] This shift is furthermore indicative of sufficient electron density at this carbon to explain the experimental results.

The constitutions of products (**4**) and (**5**) were unequivocally confirmed by high resolution ^{1}H- and ^{13}C-nmr spectroscopy.[9] One local minimum conformation of (E)-**5** as calculated by molecular mechanics methods[10] is depicted in Figure 1. The urazole and carbazole units are twisted from the three-center hydrazone plane ($>C=N-NMe_2$) with torsion angles of -1.75° and -78.68° for the E-isomer and of 17.11° and -93.21° for the Z-isomer. The molecular mechanics calculations also reveal that the E-isomer of **5** is thermodynamically more stable than the corresponding Z-product, in full accordance with the ratio found in the product mixture (ΔE_{steric} = 4.8 kcal mol^{-1}).

In summary, these results demonstrate new reactivity aspects of heteroarylhydrazones towards electrophilic dienophiles. Although the structural requirements for [4 + 2]cycloaddition of **2** exist in theory, experiment reveals preferred reaction at the hydrazone unit via addition/elimination, a result previously unknown in hydrazone chemistry.

ACKNOWLEDGEMENTS

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9. Products (**2**), (**4**), and (**5**) were fully characterized by spectral and analytical data. - **4**: ^{1}H-Nmr (DMSO-d_6, 400 MHz): δ = 11.80 (br, 1H, NH), 8.12 (d, *J* = 8 Hz, 1H), 7.61 (d, *J* = 8 Hz, 1H), 7.52 (s, 1H), 7.49 (t, *J* = 8 Hz, 1H), 7.28 (t, *J* = 8 Hz, 1H), 2.54 (s, 3H), 2.51 (s, 3H). - **5**: ^{1}H-Nmr (DMSO-d_6, 400 MHz): δ = 11.67 (br, 1H, NH), 8.17 (d, *J* = 8 Hz, 1H), 7.61-7.51 (m, 2H), 7.46-7.35 (m, 5H), 7.27-7.21 (m, 2H), 3.19 (s, 3H, *Z*), 2.77 (s, 3H, *Z*), 2.71 (s, 3H, *E*), 2.55 (s, 3H, *E*), 2.49 (s, 6H).
10. π-SCF-MO and molecular mechanics calculations were performed using the MMX program (Serena Software Ltd., Bloomington). MMX version by K. E. Gilbert and J. J. Gajewsky based on MM2 (Allinger QCPE 395) and MMP1 (Allinger QCPE 318) modified by K. Steliou. The π-MO calculation used was first described by N. L. Allinger, J. C. Tai, and T. W. Stuart, *Theor. Chim. Acta*, 1967, **8**, 101.
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