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INTERMOLECULAR DIELS-ALDER REACTIONS OF N-ACYL-N-ALKYL(ARYL)-1-AMINO-1,3-DIENES

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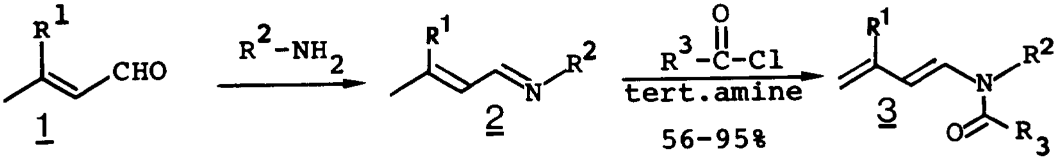
Summary. Intermolecular Diels-Alder additions of the readily available dienamides 3 to various dienophiles proceeded in a regio- and stereoselective manner, allowing the preparation of complex anilides (5), cyclohexenyl amides (6, 8) and bridged heterocycles (13).

The dienamides 3 promised to serve as useful doubly protected aminobutadiene equivalents in view of their simple preparation (1 → 2 → 3) as well as their exceptional stability.[1] We now report their reactivity in bimolecular Diels-Alder reactions.

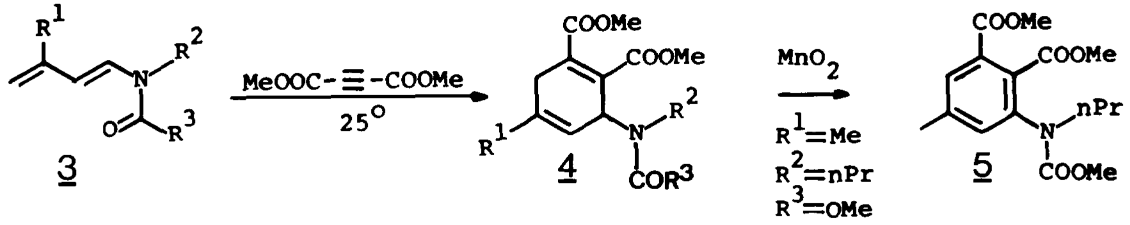


Dimethyl acetylenedicarboxylate added smoothly at room temperature to the dienes 3a, 3b and 3c giving the corresponding cyclohexadienes 4[2] in high yield (Table 1).

Table 1: Intermolecular Diels-Alder Additions of the Dienamides 3 To Dimethyl Acetylenedicarboxylate

Diene	R^1	R^2	R^3	Reaction conditions[a]	Yield of 4[2]	m.p. °C
3a	H	CH_2Ph	CH_2Ph	25°/7days	80%	95-97
3b	Me	nC_3H_7	OMe	25°/7days	79%	oil
3c	H	Ph	Ph	25°/17days	97%[b]	106-108

[a] A solution of 3 (1 mmol) and dimethyl acetylenedicarboxylate (1.2 mmol) in benzene (6 ml) was kept at 25° for several days and then evaporated. Chromatography (SiO_2, CH_2Cl_2) and crystallization of the residue (hexane) furnished pure 4. [b] Based on recovered 3c (60% conversion).



The smooth aromatization of 4, R^1=Me, R^2=nPr, R^3=OMe (excess of activated MnO_2/hexane/25°/15h) to give 5[2](m.p. 105-106°) in 77% yield, demonstrates the potential use of such cycloadditions for the preparation of polysubstituted anilides.[3]

Monosubstituted olefinic dienophiles such as acrylic esters and acrylonitrile reacted with 3d and 3e at higher temperature (80° to 110°) to furnish the stereoisomeric *"ortho"* adducts 6[2] and 7[2] in high yield (Table 2). The addition of 3d (Table 2) proceeded with over 98% regiochemical control and 76 to 86% *endo* preference according to HPLC and NMR analysis of the crude products. The regio- and stereochemical assignment of the products 6 and 7 is primarily based on the ^{1}H-NMR signals of H_A and H_B (Table 3). The predominance of *endo* versus *exo* products (7) and their NMR data parallel those of the independently studied adducts of N-butadienyl carbamates to methyl

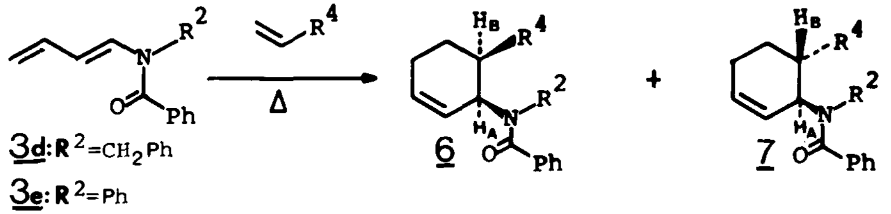


Table 2: Intermolecular Diels-Alder Additions of the Dienamides 3d and 3e to Monosubstituted Olefinic Dienophiles

Diene	Diene R^2	Dienophile R^4	Reaction conditions[a]	% yield of 6	% yield of 7
3d	CH_2Ph	COOMe	80°/3days	73[b], 53[c]	18[b]
3d	CH_2Ph	COOt-Bu	110°/10 h	71[d]	15[d]
3d	CH_2Ph	CN	80°/40 h	74[b]	24[b]
3e	Ph	CN	80°/3days	97[c]	

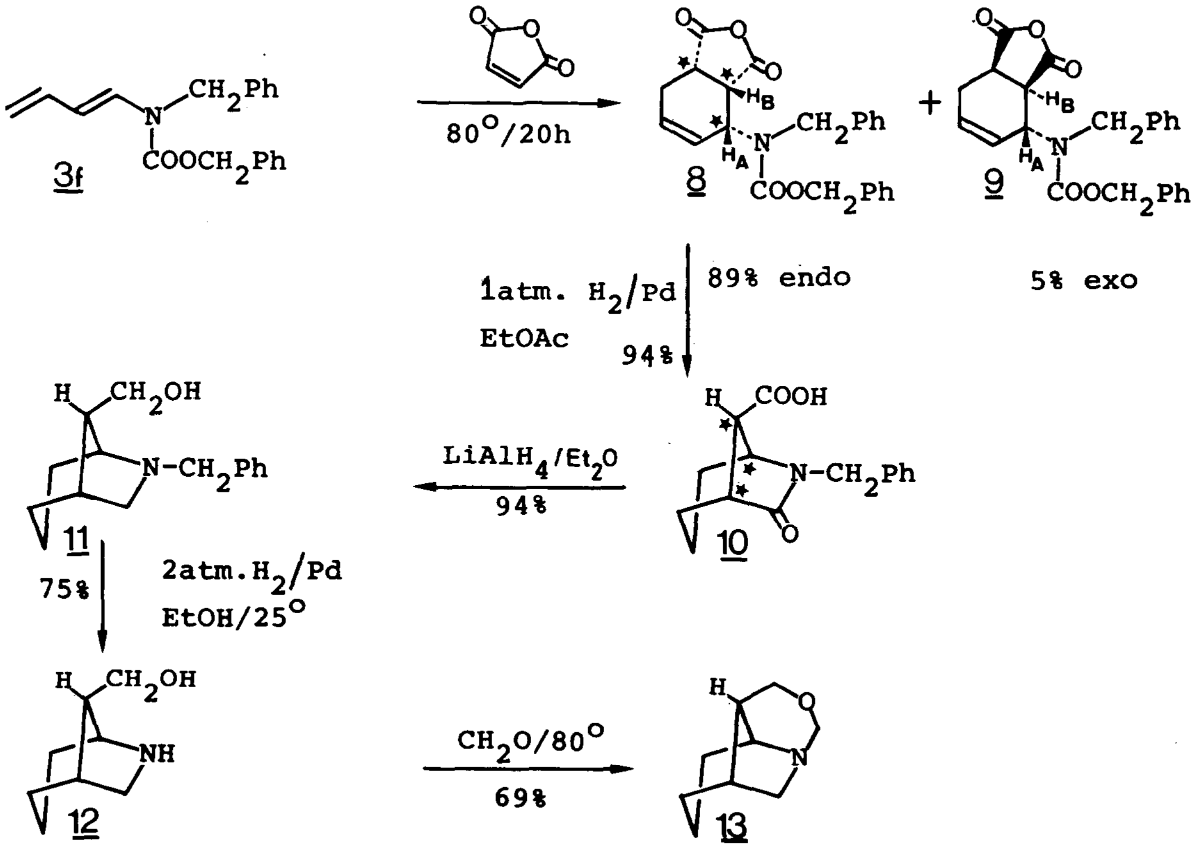
[a] Heating a 4% solution of 3 with 10 to 40 equiv. of the dienophile and a trace of hydroquinone in refluxing benzene or toluene. [b] HPLC analysis (μ-Porosil, hexane/$CHCl_3$ 3:1) of chromatographed reaction mixture. [c] Isolated by crystallization. [d] Isolated by chromatography (SiO_2, toluene/ethyl acetate).

acrylate.[4] Surprisingly, only the corresponding *endo* product $\underline{6}^2$ could be detected and isolated (97% yield) after addition of the diene $\underline{3e}$ to acrylonitrile.

Table 3: Properties of the Diels-Alder Adducts $\underline{6}^2$ and $\underline{7}^2$

Product	R^2	R^4	m.p.	^{1}H-NMR ($CDCl_3$)/90°C[a] δH_A	 δH_B	 J_{AB}
6	CH_2Ph	COOMe	116-117°	3.00	5.40	6 Hz
6	CH_2Ph	COOt-Bu	79-80°	2.95	5.40	6 Hz
7	CH_2Ph	COOt-Bu	66-68°	2.65	4.90	10 Hz
6	CH_2Ph	CN	oily mixture	3.71	5.45	6 Hz
7	CH_2Ph	CN		3.17	4.70	10 Hz
6	Ph	CN	164-165°	3.78	5.65	6 Hz

[a] The vicinal position of H_A and H_B in $\underline{6}$ and $\underline{7}$ was confirmed by double resonance experiments.



Strong *endo* preference was also observed in the addition of the diene 3f to the typical 1,2-disubstituted dienophile maleic anhydride.[5] The minor *exo* product 9[2] (m.p. 187-190°, 5% yield) precipitated from the cooled reaction mixture, whereas crystallization of the evaporated filtrate (ether/pentane) gave the major *endo* adduct 8[2] (m.p. 112.5-113.5°, 89% yield). The configuration of 8 and 9, readily assigned on the basis of NMR evidence,[6] was ultimately confirmed by the reaction sequence 8 → 10 → 11 → 12 → 13 which takes advantage of the possibility to remove the two N-protecting groups of 8 independently. Thus, catalytic hydrogenation of the olefinic bond (ethyl acetate, 1 atm. H_2, Pd/C, 25°, 8h) was accompanied by cleavage of the benzyl-urethane, followed by spontaneous cyclization of the transient benzylamine to the anhydride forming the γ-lactam carboxylic acid 10[2] (m.p. 171-172°, 94% yield). After reduction of both the acid and lactam groups of 10 with $LiAlH_4$ in refluxing ether the N-benzyl group of the resulting alcohol 11[2] (oil) was now hydrogenolyzed in ethanol (2 atm. H_2, Pd/C, 30°, 17h) to give the amino alcohol 12[2] (oil, 75% yield). The absence of an OH-band in the IR spectrum of 12 (even at high dilution) indicates a strong intramolecular hydrogen bond owing to the *cis*-relation of the amino and the alcohol groups; this configuration was finally proved by the ready cyclization 12 → 13[2] on passing a stream of gaseous formaldehyde into a refluxing solution of 12 in benzene in the presence of 4 Å molecular sieves. Further work exploiting the efficient and selective Diels-Alder reactions of the dienamides 3 is in progress.

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REFERENCES

1) W. Oppolzer, L. Bieber & E. Francotte, *Tetrahedron Letters* 1979, 981.

2) IR, ^1H-NMR and MS are in full agreement with the assigned structure. ^1H-NMR spectra in $CDCl_3$ at 100 MHz, internal standard tetramethylsilane (δ = 0 ppm), J = spin-spin coupling constant.

3) The regioselective preparation of polysubstituted anilides *via* Diels-Alder reactions of 3 has been studied first by Dr. P. Fünfschilling, Sandoz Ltd., Basel; P. Fünfschilling, *unpublished work*.

4) L.E. Overman, G.F. Taylor, K.N. Houk & L.N. Domelsmith, *J. Am. Chem. Soc.* 100, 3182 (1978).

5) 3f (5.6 g) and maleic anhydride (2 g) are heated at 85° in toluene under an argon atmosphere for 20 h.

6) 8: $\delta H_A = 3.87$, $\delta H_B = 5.20$, $J_{AB} = 6.5$ Hz. 9: $\delta H_A = 3.83$, $\delta H_B = 4.78$, $J_{AB} = 9$ Hz

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