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Cycloaddition Reactions of γ-Amino α,β-Didehydro Amino Acid Esters: A Test Case for the Principle of 1,3-Allylic Strain

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Abstract: N,N-Dibenzylamino aldehydes, readily accessible from amino acids, can be converted into γ-N,N-dibenzylamino α,β-didehydro amino acid esters without racemization; these undergo stereoselective Diels-Alder reactions and 1,3-dipolar cycloaddition with diazomethane, the sense of diastereoselectivity being opposite to that predicted by the conventional principle of 1,3-allylic strain.

The so-called α,β-didehydro amino acids not only deserve attention as biologically active compounds (e.g., as components in peptide antibiotics)[1], they are also useful as prochiral building blocks in synthetic organic chemistry (e.g., in enantioselective hydrogenation with formation of α-amino acids)[2]. We report here the synthesis and cycloaddition reactions of γ-N,N-dibenzylamino α,β-didehydro amino acid esters **3**. Using the Schöllkopf isonitrile method[3], compounds **3/4** were prepared without racemization and readily separated by chromatography or fractional crystallization[4] (Table 1).

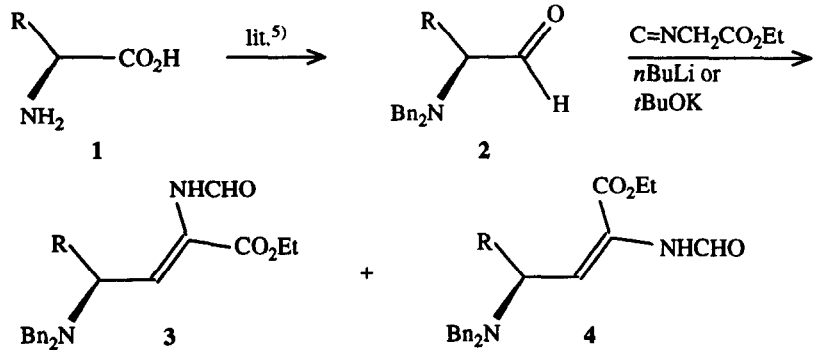


Table 1. Preparation of γ-amino α,β-didehydro amino acid ester **3/4**

Compounds	R	Yield (%)	**3**	:	**4**
3a/4a	CH_3	61	68	:	32
3b/4b	$PhCH_2$	46	54	:	46
4e/4c	$(CH_3)_2CH$	55	67	:	33
3d/4d	$(CH_3)_2CHCH_2$	85	82	:	18
3e/4e	$tBuMe_2SiOCH_2$	76	74	:	26

The Z- and E-assignments of **3** and **4**, respectively, were made on the basis of NMR data and with the help of an X-ray structure determination of **3a**[6] (Fig. 1).

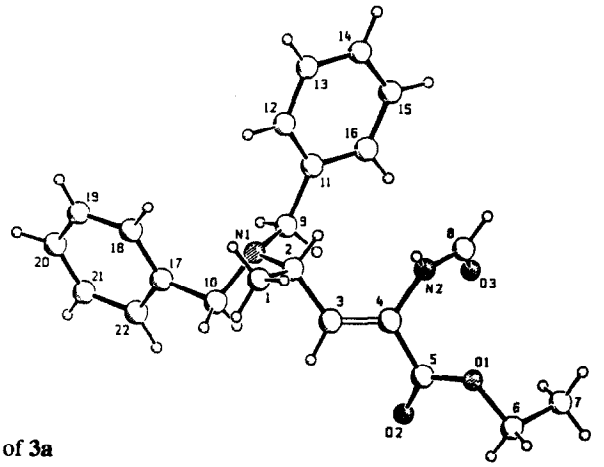
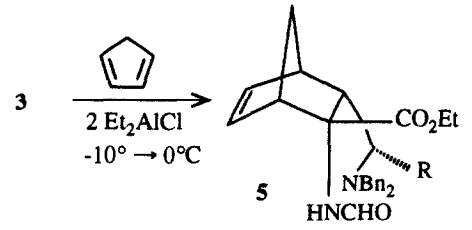


Fig. 1. Crystal structure of **3a**

Fig. 1 shows that the hydrogen at the stereogenic center occupies the "eclipsed" position in the plane of the neighboring π-system (dihedral angle C4-C3-C2-H, ϕ = 0.6°), in line with expections based on the principle of 1,3-allylic strain[7]. This makes the bottom side of the olefinic π-bond (C3-Re, C4-Si) sterically shielded, so that cycloaddition reactions should occur from the top (C3-Si, C4-Re). Upon reacting **3a** with cyclopentadiene in the presence of Et_2AlCl (2 eq./CH_2Cl_2/2d), cycloadduct **5a** was obtained essentially as a single diastereomer[8]. As proven by an X-ray structure determination of **5a**[8], the relative (and absolute) configuration is as shown in formula **5**. The result means complete endo-selectivity with respect to the formylamino group[9] as well as very high diastereofacial selectivity. Surprisingly, the sense of diastereofacial selectivity is opposite to the above expectation. Thus, cyclopentadiene adds from the bottom side (C3-Re, C4-Si) which appears to be the sterically more hindered π-face (cf. Fig. 1). Compounds **3b,d,e** react slower (9 - 12 d) and less selectively.



a R = CH_3: ds = 96%; 74% yield
b R = $PhCH_2$: ds = 82%; 60% yield
c R = $(CH_3)_2CH$: no reaction
d R = $(CH_3)_2CHCH_2$: ds = 86%; 43% yield
e R = tBuMe$_2$SiOCH$_2$: ds = 78%; 72% yield

The sense of diastereoselectivity turned out to be the same in 1,3-dipolar cycloaddition reactions using diazomethane[10] (Table 2), as shown by an X-ray structure determination of **6a**[8].

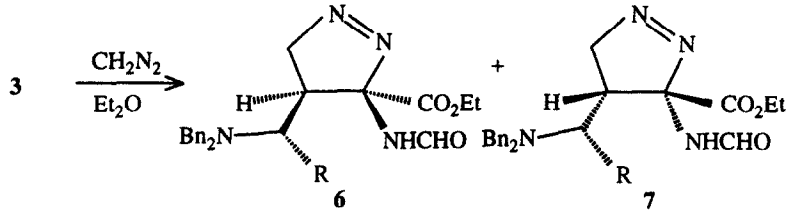
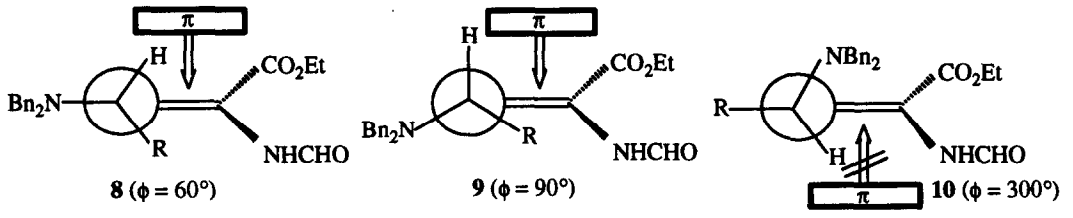


Table 2. 1,3-Dipolar Cycloaddition Reactions of **3** with Diazomethane at Room Temperature

Compound	R	Time (h)	Yield (% isolated)	**6**	:	**7**
3a	CH_3	20	71	> 95	:	< 5
3b	$PhCH_2$	18	74	86	:	14
3c	Me_2CH	120	0		——	
3d	Me_2CHCH_2	96	60	74	:	26
3e	tBuMe$_2$SiOCH$_2$	18	76	90	:	10

Clearly, conformers of the type shown in Fig. 1 cannot be involved in the transition state of cycloaddition. The geometry of the ground state in solution is difficult to determine with certainty by NMR using a modified Karplus relation[11,12] due to the presence of heteroatoms in **3**. Nevertheless, the proton coupling constants $^3J_{2,3}$ indicate that the allylic H-atom is probably not "eclipsed" with the possible exception of **3c** (**3a**: 6.6 Hz; **3b**: 6.9 Hz; **3c**: 10.1 Hz; **3d** 6.9 Hz; **3e**: 7.0 Hz). As a qualitative model for explaining the observed stereoselectivity we propose that in the transition state steric and torsional interactions within a compound **3** as well as steric repulsion between the two reactants need to be considered, and that a compromise can be achieved if the allylic H-atom points toward the incoming "flat" π-system[13] achieved by rotation of the C2-C3 bond (cf. Fig. 1), as in **8** or in **9**. This places the bulky amino group in the "outside" and the smaller R-group in the "inside" position. On this basis it becomes clear why diastereoselectivity decreases as R increases in size. Rotation of the C2-C3 bond (cf. Fig. 1) in the other direction places the bulky amino group in the "inside" position (e.g. **10**), giving rise to appreciable 1,3-allylic strain (steep rotational profile between $\phi = 270°$ and $\phi = 360°$)[8]. In the case of the bulky ester **3c** a conformer of the type shown in Fig. 1 is likely to prevail, causing effective shielding of both π-faces so that no reaction occurs. Our model seems to have some generality, since a compound related to **3a** in which the N,N-dibenzylamino moiety is replaced by a phenyl group (prepared from 2-phenylpropanal by the Schöllkopf method) reacts with CH_2N_2 to produce a 73 : 27 mixture of diastereomers, the sense of diastereoselectivity being the same (C3-Re, C4-Si attack)[8].



In summary, care must be taken in applying the principle of 1,3-allylic strain[7,12,13]. In particular, the transition state of reactions need to be considered. Our results bear some relationship to other recent reports of 1,3-allylic strain as a controlling element. For example, Barrett has coined the term "stealth stereocontrol" to explain the stereochemical reversal of certain Michael additions in which the H-atom at the chiral allylic center is believed to point toward the incoming "flat" nucleophile[14]. Meyers has also stressed the combination of 1,3-allylic strain and other factors[15].

Acknowledgement

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