Intra- and Intermolecular Hydrogen Bonding Effects in Cycloadditions between Nitrile Oxides and 4-Benzoylamino-2-cyclopenten-1-ol and Its Derivatives

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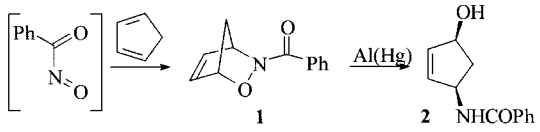
Dedicated to Prof. Paola Vita Finzi on the occasion of her 70th birthday

Keywords: Cycloadditions / Nitrile oxides / Nitroso compounds / Solvent effects / Stereoselectivity

Cycloadditions between nitrile oxides and *cis*-4-benzoylamino-2-cyclopenten-1-ol offer an example in which a strong intramolecular hydrogen bond completely offsets the *syn*-directing ability of the cyclopentene substituents. Solvents affected the conformational equilibrium of the cyclopentene dipolarophile but did not sizeably influence the cycloaddition selectivity, showing the absence of directing effects between the addends. Removal of the intramolecular hydrogen bond by OH protection or oxidation activated the *syn*-directing ability of the amido substituent and provided a convenient route to *syn* stereoselection.

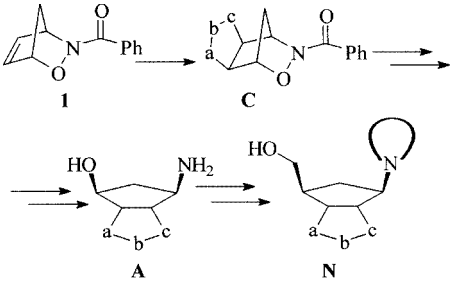
Introduction

Nitrosocarbonyl (RCONO) chemistry has wide application in organic syntheses because of the high reactivity of these intermediates in hetero-Diels−Alder (HDA) reactions and the synthetic potential of their HDA adducts.[1] HDA adducts, such as the nitrosocarbonyl benzene/cyclopentadiene HDA adduct **1**, have been widely used in many synthetic elaborations allowing for the flexible introduction of multifunctionality. While the C=C bond can be elaborated in various ways and the *N*-acyl substituent can easily be detached, the N−O bond is apt to undergo mild reductive cleavage, as shown by the ready conversion of **1** into the unsaturated *cis*-1,4-aminol derivative **2** (Scheme 1).[2]



Scheme 1

We recently reported that *N*-acyl-2-oxa-3-azanorborn-5-enes of type **1** were highly reactive dipolarophiles in 1,3-dipolar cycloadditions of nitrile oxides, affording quantitative yields of cycloadducts of type **C** (Scheme 2), which could be elaborated into other highly functionalized structures not easily accessible by direct 1,3-dipolar cycloadditions.[3]



Scheme 2

In particular, reductive cleavage of the N−O bond afforded the stereodefined *anti* aminols **A**, which served as useful precursors of modified carbocyclic nucleosides **N**. The amino group of the aminol **A** was suitable for the ready assembly of purine or pyrimidine rings, and methods for the substitution of the hydroxyl with the hydroxymethyl moiety are available.[4] Since the synthesis of modified nucleosides is a very attractive and active research area,[5] and structural diversity is appreciated in the search for new compounds with antiviral and anticancer activity, we have investigated cycloadditions between nitrile oxides and the *cis*-4-benzoylamino-2-cyclopenten-1-ol **2**, with the aim of obtaining access to the *syn* stereoisomers of the aminols **A**. The *syn*-directing effect of the allylic OH and, especially, the allylic NHCOR group is a general method for regio- and stereochemical control of many reactions[6] and has fre-

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quently been reported in the 1,3-dipolar cycloadditions of nitrile oxides.[7−9]

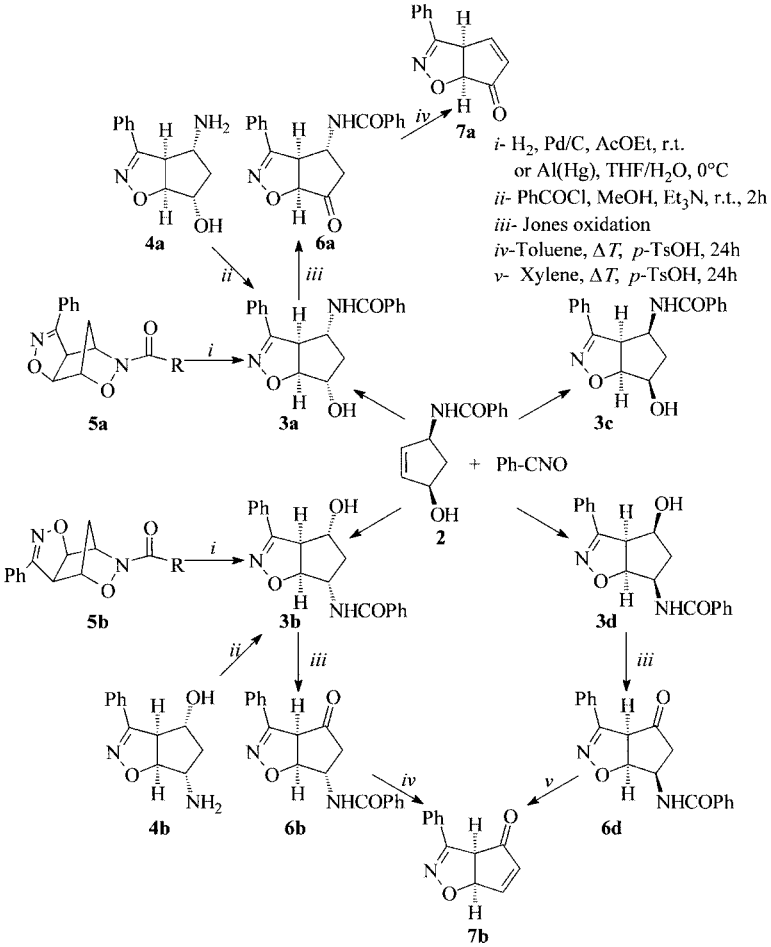
Results and Discussion

Cycloadducts

The cycloaddition between benzonitrile oxide (BNO), generated in situ from benzhydroximoyl chloride and Et_3N, and *cis*-4-benzoylamino-2-cyclopenten-1-ol (**2**) at room temp. in benzene solution gave the four regioisomeric cycloadducts **3a−d**, which were separated by column chromatography (Scheme 3). The major components were the *anti* cycloadducts **3a** and **3b**, obtained in 45% and 24% yields, respectively. The ^{1}H NMR spectra of **3a** and **3b** were consistent with the *anti* structures of the substituents, from the lack of appreciable couplings between the isoxazoline protons and the adjacent methine protons. The regiochemistry was established by NOE experiments. The methine proton coupled to the NH in cycloadduct **3a** gave an NOE (6.9%) with the *ortho* protons of the phenyl ring, while the *CH*−OH in cycloadduct **3b** gave a weaker NOE (1.9%) with the *ortho* protons of the phenyl ring. The structures of cycloadducts **3a** and **3b** were correlated with the previously described[3] aminols **4a** and **4b** by acylation and with the cycloadducts **5a** and **5b** by reductive cleavage of the N−O bond either with Al(Hg) or by catalytic hydrogenation with Pd/C in quantitative yields. Moreover, the cycloadducts **3a** and **3b** were also converted into the α,β-unsaturated ketones **7a** and **7b**[3] by Jones oxidation to the benzoylamino ketones **6a** and **6b** and subsequent benzamide elimination in refluxing toluene (24 h) in the presence of catalytic *p*TsOH.

The minor cycloadducts **3c** and **3d** were isolated in 5% and 14% yields, respectively. Their ^{1}H NMR spectra allowed stereo- and regiochemical assignment in these cases, because of the presence of sizeable couplings between the isoxazoline and the adjacent methine protons. Jones oxidation of **3d** quantitatively afforded the benzoylamino ketone **6d**, which eliminated benzamide, albeit under harsh conditions (xylene, *p*TsOH, Δ*T*, 24 h), to afford the unsaturated ketone **7b**.

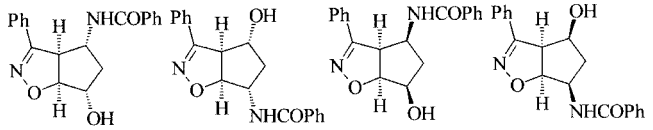
The low yields of the *syn* adducts **3c** and **3d** were rather surprising, and indicated that the *syn*-directive effects were being more than compensated by other factors opposing the *syn* attack. If steric effects alone were masking the *syn*-directive effects, we should expect a further decrease in the *syn* adducts in hydrogen bonding acceptor (HBA) solvents,[10] which compete with *syn*-directive effects and offset them.



Scheme 3

We therefore investigated solvent effects on the cycloaddition, but the selectivities changed only a little and did not show any relationship with the β parameter,[10e] a descriptor of the HBA ability of the solvents. Table 1 gives the reaction yields and the ratios of the four regio- and stereoisomeric cycloadducts in reactions performed in twelve solvents of different polarities and HBA abilities.

Table 1. Reaction yields and regioisomeric ratios of cycloadducts **3a−d**



3a **3b** **3c** **3d**

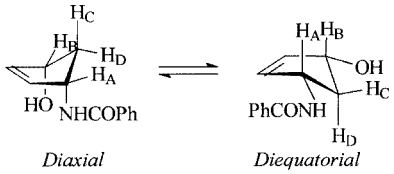
Entry	Solvents[a][b]	Yield (%)	3a	3b	3c	3d
1	Bz (0.10)	96	50	26	7	17
2	Cy (0.00)	88	44	41	2	13
3	*n*Hx (0.00)	90	40	45	3	13
4	DCM (0.00)	94	36	42	7	15
5	$CHCl_3$ (0.00)	84	39	32	9	19
6	Acetone (0.48)	84	37	47	3	13
7	EtOAc (0.45)	91	42	41	4	13
8	MeOH (0.62)	80	37	49	4	10
9	EtOH (0.77)	80	36	49	4	11
10	THF (0.55)	84	42	41	4	13
11	DIOX (0.37)	75	49	30	4	17
12	DMF (0.69)	57	44	44	1	11

[a] Bz = benzene, Cy = cyclohexane, *n*Hx = *n*-hexane, DCM = dichloromethane, DIOX = dioxane. [b] β values, see ref.[10e]

Overall, the reactions gave good yields (57−96%). The major regioisomers in all cases were the *anti* adducts **3a** and **3b**, constituting 71−88% of the reaction mixtures in ratios ranging from 2:1 to 1:1.5. The lack of any great regioselectivity in the *anti* attack can be ascribed to the comparable electron-withdrawing abilities of the hydroxy and acylamino substituents, which have similar σ_I substituent constants,[11] while the moderate scatter of the ratios was presumably related to differences in solvation of the two substituents. The *syn* adduct **3d** varied a little, from 10% in methanol (entry 9) to 19% in chloroform (entry 5), while the *syn* regioisomer **3c** was obtained in poor amounts in all the solvents examined (1−9%). Both the *syn* cycloadducts **3c** and **3d** were close to or below 20% in term of yields. The regioselectivity in the *syn* attack sizeably favoured **3d** and could be attributed to the steric effect between the bulkier ends of the dipole and the dipolarophile (i.e., the nitrile oxide carbon[8a] and the benzoylamino substituent).

Conformational Studies

The lack of any appreciable *syn*-directive effect in the cycloaddition between BNO and dipolarophile **2**, as well as the insensitivity of the product distribution to solvent effects, stood in marked contrast with expectations based on related reactions. In order to check the possible conformational origin of this unexpected behaviour, we investigated the conformational preferences of the dipolarophile. The two conceivable diaxial and diequatorial envelope conformers are shown in Figure 1, and their conformational preferences could be established[12] on the basis of the *trans* coupling constants J_{AD} and J_{BD} between the methine protons and the methylene proton H_D, which were well separated and high lying because of the deshielding of the *cis* substituents.[13]



Diaxial *Diequatorial*

Figure 1. Diaxial and diequatorial envelope conformations of dipolarophile **2**

Table 2 reports the chemical shifts and coupling constants of the labelled protons (H_A, H_B, H_C, and H_D) directly relevant to the conformational equilibrium.

Table 2. Chemical shifts (ppm) and coupling constants (Hz) of the dipolarophile **2** in different solvents

	H_A	H_B	H_C	H_D	$J_{AD} = J_{BD}$	J_{DC}	$J_{AC} = J_{BC}$
C_6D_6	5.10	4.65	2.68	1.79	3.1	14.5	7.8
$CDCl_3$	4.95	4.79	2.82	1.69	3.5	14.5	7.8
CD_3OD	4.95	4.72	2.82	1.55	5.1	13.7	7.4
[D_6]acetone	4.95	4.70	2.81	1.55	5.5	13.4	8.2
[D_8]THF	5.17	4.86	2.93	1.72	5.6	13.5	8
[D_6]DMSO	4.82	4.59	2.65	1.60	6.0	13.3	7.4

The *trans* coupling constants J_{AD} and J_{BD} varied remarkably and attained larger values (> 5 Hz) in the polar solvents, owing to the large dihedral angles between the almost antiperiplanar coupled protons in the diequatorial conformation.[13] In apolar solvents the coupling constants were small and consistent with a preference for the diaxial conformation.

While the preference for the diequatorial conformation in polar and HBA solvents is normal, owing to the bulk of the solvated substituents favouring the diequatorial disposition, the occurrence of the diaxial conformation in apolar and non-HBA solvents suggested the involvement of some stabilization due to fairly strong intramolecular hydrogen bonding between the two substituents.

Theoretical support for these results was obtained from B3LYP/6-31G* calculations[14] of the lowest-energy conformers of the acetyl analogue of dipolarophile **2**. Figure 2 shows the computed diaxial and diequatorial conformers of the acetyl analogue of **2** and their relative energies. The diaxial conformer was indeed the lower one, owing to the strong H bond (1.90 Å)[15] between the OH and the amide oxygen, while the diequatorial conformation was 2.8 kcal/mol higher in energy.

Spectroscopic results and theoretical calculations thus concurred in supporting the existence of an intramolecular

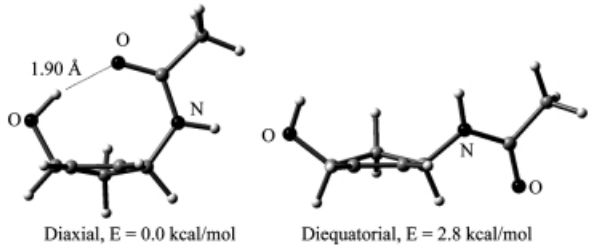


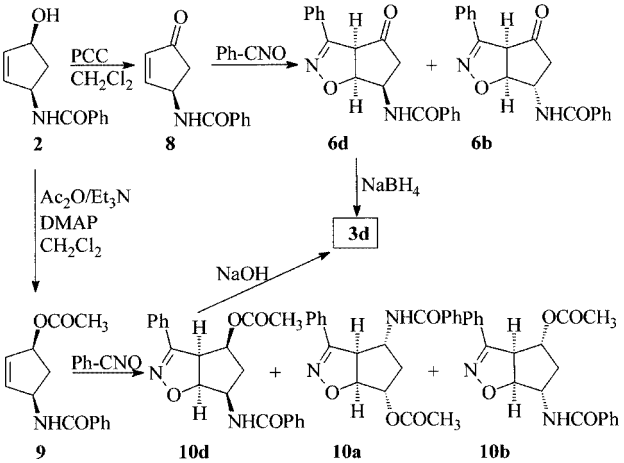
Figure 2. Geometric features and relative electronic energies of the B3LYP/6-31G*-optimized structures for the lowest-energy conformers of *cis*-4-acetylamino-2-cyclopenten-1-ol

H-bonded structure in the dipolarophile **2** in apolar solvents, nicely accounting for the predominant *anti* attack observed in the cycloaddition. In polar solvents, on the other hand, a switch to the diequatorial conformation occurred, owing to solvation of the two substituents and disruption of the intramolecular H-bond. The solvated substituents, however, lost their directing ability and predominant attack on the less hindered *anti* face was again observed.

Diversions

The strong intramolecular hydrogen bond in the dipolarophile **2** prevented the establishment of the intermolecular hydrogen bond required for efficient *syn* addition. In HBA solvents, the intramolecular hydrogen bond was relieved, but the solvated functions were no longer available for the intermolecular hydrogen bond to the 1,3-dipole. A remedy for this situation would require the removal of the intramolecular hydrogen bond with the aid of appropriate modifications of the dipolarophiles. We therefore investigated cycloadditions with the 4-benzoylamino cyclopentenone **8**, available by the mild oxidation of dipolarophile **4** by the typical PCC procedure in 80% yield,[16] as well as cycloadditions to the *O*-acetyl derivative **9**.

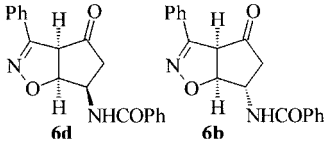
The cycloaddition between BNO and the α,β-unsaturated ketone **8** took place with high regioselectivity, as is usual with the cyclopentenone moiety,[7,17] to afford mainly a mixture of the stereoisomeric *syn* and *anti* adducts **6d** and **6b** (Scheme 4).



Scheme 4

The reactions proceeded in good yields (70−86%) in most of the solvents examined (Table 3). The *syn* stereoisomer **6d** was highly predominant in all the apolar solvents, with an average **6d/6b** ratio of 5 (entries 1−5). The **6d/6b** ratio levelled out to 1:1 with increasing solvent polarity (entries 7−12), while **6b** overtook **6d** only in the highly polar DMF (entry 13). $NaBH_4$ reduction of the ketone **6d** exclusively afforded the *syn* alcohol **3d**, thus providing a diverted practical route to the *syn* compound.

Table 3. Reaction yields and regioisomeric ratios of cycloadducts **6a−d**



Entry	Solvents[a]	Yield (%)	**6d/6b**
1	Bz	86	83:15
2	Cy	78	87:13
3	*n*Hx	79	79:21
4	DCM	82	80:19
5	$CHCl_3$	80	82:18
6	Acetone	74	43:57
7	EtOAc	82	51:49
8	MeOH	73	44:51
9	EtOH	74	48:52
10	THF	74	51:49
11	DIOX	70	57:43
12	DMF	52	20:60

[a] Bz = benzene, Cy = cyclohexane, *n*Hx = *n*-hexane, DCM = dichloromethane, DIOX = dioxane.

Cycloadditions to the *O*-acetyl derivative **9** also predominantly afforded the *syn* derivatives **10d** in acceptable yields (42% in benzene) in apolar and non-HBA solvents, along with minor amounts of the *anti* isomers **10a** (24%) and **10b** (20%). Alkaline deacetylation of **10d** readily afforded the *syn* alcohol **3d**.

Conclusions

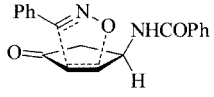
We report here an example of a strong intramolecular hydrogen bond that completely offset the *syn*-directing ability of the two substituents. In polar solvents, the intramolecular hydrogen bond was relieved and a conformational change was observed, but the solvated substituents lost their *syn*-directing power. In both cases, cycloaddition at the *anti* face of the substituted cyclopentene was directed by steric effects.

Oxidation of the OH group provided a convenient means to relieve the intramolecular hydrogen bond, allowing the amide directive effect to govern the stereoselectivity. Alternatively, *O*-acetyl protection could be used.

The rather unexpected persistence of the *syn* adduct **6d** in the cycloadditions with the 4-(benzoylamino)cyclopentenone **8** even in good HBA solvents is worth noting, and resembles the moderate diastereofacial selectivity of the re-

lated 4-oxycyclopent-2-en-1-one derivatives in the Diels−Alder cycloaddition with cyclopentadiene.[18] A delicate balance of steric and electronic (the Cieplak effect)[19] factors was suggested to account for the observed diastereoselection, and the same explanation seems to apply well in the case at hand.

In the *syn* attack shown in structure **11** the forming C···O bond is almost antiperiplanar to the C4−H bond of **8**, while in the *anti* attack shown in structure **12** the forming C···O bond is antiperiplanar to the C4−N bond. The Cieplak effect implies an electronic stabilization in the former case, because of the better electron donation of the C−H bond than the C−N bond to the electron-deficient σ* orbital of the incipient C···O bond.[20]



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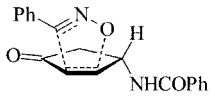

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Experimental Section

All melting points are uncorrected. Elemental analyses were performed on a C. Erba 1106 elemental analyzer. ^{1}H NMR spectra were recorded on Bruker AVANCE 300 and Bruker AC 200 spectrometers in $CDCl_3$ solutions unless otherwise stated. Chemical shifts are expressed in ppm from internal tetramethylsilane (δ). IR spectra (Nujol mulls) were recorded on an FT-IR Perkin−Elmer Paragon 1000. Quantitative HPLC analyses were performed on a Waters 510 HPLC apparatus equipped with a UV 490E detector: column RP C-18 Intersil ODS-2 (2.5 μm, ϕ = 4.6 mm, 250 mm length); eluent water/acetonitrile at 1.3 mL/min. Column chromatography and TLC: H60 and GF_{254} silica gel (Merck), respectively, eluent cyclohexane/ethyl acetate 9:1 to 5:5. The identification of samples from different experiments was confirmed by mixture melting points and superimposable IR spectra.

Materials: Benzhydroximoyl chloride, the precursor of BNO,[21] was obtained by treatment of benzaldoxime with sodium hypochlorite.[22]

cis-4-Benzoylamino-2-cyclopenten-1-ol was obtained by reductive cleavage of oxazanorbornene **1** (2.0 g, 10 mmol) with Al(Hg) (2.0 g, 74 mmol) in THF/H_2O (10:1, 100 mL) solution at 0 °C by the well established Keck procedure;[2] colourless crystals, m.p. 101−102 °C from benzene (ref.[16b] m.p. 96−97 °C).

4-Benzoylamino-2-cyclopenten-1-one (**8**) was obtained by PCC oxidation in DCM solution according to the reported synthesis by Procter;[16a] m.p. 147−148 °C (ref.[16b] m.p. 149−150 °C).

O-Acetyl-4-benzoylamino-2-cyclopentenol (**9**) was prepared by the Ac_2O/Et_3N/DMAP procedure used for related compounds.[23] Slight excesses of acetic anhydride (1.2 mL, 12 mmol) and triethylamine (1.2 mL, 12 mmol) and a catalytic amount of DMAP (10% mol) were added to a stirred solution of 4-benzoylamino-2-cyclopenten-1-ol (**2**, 2.0 g, 10 mmol) in dichloromethane (DCM) (50 mL). After having been kept for 2 h at room temp., the mixture was washed twice with water and dried with Na_2SO_4. Evaporation of the organic phase left the crude acetylated compound, which was recrystallized from benzene/ligroin: colourless crystals, 1.9 g (78%), m.p. 87−88 °C. IR: $\tilde{\nu}$ = 1727 (C=O), 3279 (NH) cm^{-1}. ^{1}H NMR: δ = 1.65 (dt, *J* = 14.7, 4.4 Hz, 1 H, CH_2), 2.01 (s, 1 H, $COCH_3$), 2.59 (dt, *J* = 14.7, 7.8 Hz, 1 H, CH_2), 5.14 (m, 1 H, CH−N), 5.56 (m, 1 H, CH−O), 6.00 (m, 1 H, CH=), 6.05 (m, 1 H, CH=), 6.58 (br. d, *J* = 8.5 Hz, 1 H, NH), 7.3−7.5 (m, 3 H, arom.), 7.78 (m, 2 H, arom.) ppm. ^{13}C NMR: δ = 21.1 (CH_3CO), 38.3 (CH_2), 53.4 (CH−N), 77.6 (CH−O), 126.9, 128.5, 131.5, 134.2 (C-arom.), 133.0 (CH=), 136.5 (CH=), 166.6 (C=O), 170.5 (C=O) ppm. $C_{14}H_{15}NO_3$ (245.3): calcd. C 68.55, H 6.16, N 5.71; found C 68.6, H 6.1, N 5.7.

Cycloaddition between Benzonitrile Oxide and *cis*-4-Benzoylamino-2-cyclopenten-1-ol (2): Triethylamine (1 mL, 7 mmol) in benzene (20 mL) was added over a 0.5 h period to a stirred solution of *cis*-4-benzoylamino-2-cyclopenten-1-ol (**2**, 1.2 g, 6 mmol) and benzhydroximoyl chloride (0.9 g, 6 mmol) in the same solvent (100 mL). After the reaction mixture had been kept for 2 days at room temp., the solvents were evaporated under reduced pressure to leave a residue that was separated by column chromatography.

The physical and analytical data and yields of the cycloadducts **3a−d** are reported in Table 4, and the NMR spectroscopic data are listed in Table 5.

Table 4. Physical and analytical data of cycloadducts **3a−d**

3	m.p. [°C] Solvent	Yield [%]	Formula (mol. mass)	C, H N found (C, H N calcd.)	$\tilde{\nu}_{OH}$, $\tilde{\nu}_{C=O}$
a	213−215 EtOH	45	$C_{19}H_{18}N_2O_3$ (322.4)	71.0, 5.6, 8.6 (70.79, 5.63, 8.69)	3304, 1632
b	181−183 EtOH	24	$C_{19}H_{18}N_2O_3$ (322.4)	70.9, 5.6, 8.6 (70.79, 5.63, 8.69)	3250, 1631
c	156−157 EtOH	5	$C_{19}H_{18}N_2O_3$ (322.4)	70.8, 5.5, 8.5 (70.79, 5.63, 8.69)	3305, 1678
d	>246 EtOH	14	$C_{19}H_{18}N_2O_3$ (322.4)	71.0, 5.5, 8.6 (70.79, 5.63, 8.69)	3319, 1637

Benzoylation of Aminols 4a/4b: An excess of benzoyl chloride (0.04 mL, 3 equiv.) was added to a stirred solution of the aminols **4a/4b**[3] (0.044 g, 0.2 mmol) and triethylamine (0.1 mL) in methanol (20 mL). After 2 h at room temp. the solvents were evaporated, and the residue was taken up with NaOH (5%) and chloroform. The organic layer was washed with water and dried, and the solvents were evaporated. Distillation of methyl benzoate under vacuum (0.1 Torr, bath up to 100 °C) in a kugelrohr apparatus left the cycloadducts **3a/3b**, identical with the previously obtained specimens.

Reduction of Cycloadducts 5a/5b: A solution of **5a/5b**[3] (0.32 g, 1 mmol) and 10% Pd/C (0.05 g) in ethyl acetate (50 mL) absorbed 1 equiv. of hydrogen within 2 hours. The catalyst was filtered off and the filtrate was concentrated under reduced pressure to give compounds **3a/3b** in quantitative yields, identical with authentic specimens.

Alternatively, Al(Hg) (7 equiv.) was added at 0 °C to a solution of **5a/5b** (0.32 g, 1 mmol) in THF/H_2O 10:1 (50 mL) by Keck's procedure.[2] Compounds **3a/3b**, identical with previously obtained specimens, were isolated in quantitative yields.

Jones Oxidation of Cycloadducts 3a/3b/3d to Benzoylamino Ketones 6a/6b/6d: An excess of Jones reagent (0.5 mL, 4 equiv.) was added at room temp to a solution of **3a/3b/3d** (0.1 g, 0.3 mmol) in acetone (20 mL). The mixtures were stirred for 1 h, 2-propanol (0.5 mL) was then added, and the mixtures were stirred for an additional

Table 5. Chemical shifts and coupling constants of cycloadducts **3a−d**

^{1}H NMR	6a-H	3a-H	4-H	6-H	CH_2	Ar	NH	OH	$J_{3a,6a}$	$J_{3a,4}$	$J_{4,CH2}$	J_{CH2}	$J_{6,CH2}$	$J_{6,6a}$	J_{NH}
3a	5.16 d	4.35 d	4.90 m	4.65 br. s	2.0 s	7.4−8.2 m	7.6 d	2.64 bs	9						8
3b	5.27 d	4.25 d	4.62 d	4.89 dd	1.96, 2.11 d, ddd	7.3−7.8 m	7.49 d	1.6 b	8.7		4.2	14	6.0		7.2
3c	5.20 dd	4.56 dd	5.24 m	4.43 q	1.95, 2.18 dt, ddd	7.1−7.7 m	6.62 d	2.35 b	10.5	8	4.5	13.5	4.5	4.2	8
3d ([D_6]acetone)	5.15 dd	4.40 t	4.24 d	4.56 m	1.88, 2.25 m, m	7.3−7.9 m	7.59 d	1.30 br. s	8.4		5.5	11.7		4.6	7.7

^{13}C NMR	C-6a	C-3a	C-4	C-6	CH_2	Ar	C=N	C=O
3a	91.4	55.5	60.6	79.1	36.3	126.8, 127.4, 128.1, 128.6, 128.8, 130.2, 131.6, 134.0	156.5	166.4
3b	91.2	57.5	77.2	61.6	37.0	126.8, 126.9, 128.4, 128.6, 128.8, 130.1, 131.7, 133.7	155.9	166.8
3c	87.5	50.2	73.1	55.1	38.3	126.2, 126.8, 127.9, 128.4, 129.8, 130.9, 133.9	157.3	166.5
3d ([D_6]acetone)	88.1	38.3	73.4	56.5	20.3	128.5, 128.6, 128.7, 129.3, 129.5, 130.3, 132.4	156.2	169.1

period (15 min). The mixtures were diluted with water, extracted with chloroform, dried with Na_2SO_4, and finally evaporated to give quantitatively the benzoylamino ketones **6a/6b/6d**.

Compound 6a: M.p. 202−203 °C from ethanol. IR: $\tilde{\nu}$ = 1640 (NC=O), 1750 (C=O), 3390 (NH) cm^{-1}. ^{1}H NMR: δ = 2.50 (d, *J* = 18.0 Hz, 1 H, CH_2), 2.73 (dd, *J* = 18, 8 Hz, 1 H, CH_2), 4.35 (dd, *J* = 8, 5 Hz, 1 H, CH−N), 4.71 (d, *J* = 9.7 Hz, 1 H, 4-isoxazoline H), 5.22 (d, *J* = 9.7 Hz, 1 H, 5-isoxazoline H), 6.70 (br. d, *J* = 5.0 Hz, 1 H, NH), 7.5−7.6 (m, 6 H, arom.), 7.80 (m, 2 H, arom.), 7.90 (m, 2 H, arom.) ppm. ^{13}C NMR: δ = 41.4 (CH_2), 50.9 (CH), 57.9 (CH−N), 84.0 (CH−O), 123.8, 126.9, 127.2, 128.8, 129.1, 130.6, 132.4, 135.4 (C-arom.), 151.3 (C=N), 167.1, 194.7 (C=O) ppm. $C_{19}H_{16}N_2O_3$ (320.3): calcd. C 71.24, H 5.03, N 8.75; found C 71.3, H 5.1, N 8.8.

Compound 6b: M.p. 191−200 °C from ethanol. IR: $\tilde{\nu}$ = 1641 (NC=O), 1752 (C=O), 3370 (NH) cm^{-1}. ^{1}H NMR: δ = 2.60 (d, *J* = 18.5 Hz, 1 H, CH_2), 2.90 (dd, *J* = 18.5, 9 Hz, 1 H, CH_2), 4.29 (dd, *J* = 9, 6.6 Hz, 1 H, CH−N), 4.78 (d, *J* = 8.9 Hz, 1 H, 4-isoxazoline H), 5.55 (d, *J* = 8.9 Hz, 1 H, 5-isoxazoline H), 6.90 (br. d, *J* = 6.6 Hz, 1 H, NH), 7.4−7.6 (m, 6 H, arom.), 7.80 (m, 2 H, arom.), 7.95 (m, 2 H, arom.) ppm. ^{13}C NMR: δ = 42.3 (CH_2), 53.9 (CH), 61.4 (CH−N), 91.7 (CH−O), 126.9, 127.6, 127.8, 128.6, 128.7, 130.3, 132.2, 132.7 (C-arom.), 153.6 (C=N), 168.1, 206.2 (C=O) ppm. $C_{19}H_{16}N_2O_3$ (320.3): calcd. C 71.24, H 5.03, N 8.75; found C 71.2, H 5.1, N 8.7.

Compound 6d: M.p. 227−229 °C from ethanol. IR: $\tilde{\nu}$ = 1631 (NC=O), 1750 (C=O), 3310 (NH) cm^{-1}. ^{1}H NMR: δ = 2.50 (dd, *J* = 17, 12 Hz, 1 H, CH_2), 2.95 (dd, *J* = 17, 7.5 Hz, 1 H, CH_2), 4.40 (d, *J* = 8.2 Hz, 1 H, 4-isoxazoline H), 5.06 (dd, *J* = 8.2, 4.8 Hz, 1 H, 5-isoxazoline H), 5.12 (m, *J* = 8.5, 7.5, 4.8 Hz, 1 H, CH−N), 6.90 (br. d, *J* = 6.6 Hz, 1 H, *NH*), 7.51 (m, 6 H, arom.), 7.90 (m, 4 H, arom.) ppm. ^{13}C NMR: δ = 41.2 (CH_2), 48.9 (CH), 62.0 (CH−N), 85.4 (CH−O), 126.9, 127.0, 127.7, 128.5, 128.6, 130.8, 132.0, 133.4, (C-arom.), 154.1 (C=N), 167.3, 205.1 (C=O) ppm. $C_{19}H_{16}N_2O_3$ (320.3): calcd. C 71.24, H 5.03, N 8.75; found C 71.3, H 5.0, N 8.7.

Benzamide Elimination to give α,β-Unsaturated Ketones 7a/7b: A solution of **6a/6b** (0.10 g, 0.3 mmol) in toluene (20 mL) and catalytic *p*TsOH was heated under reflux for 1 day. The reaction solvents were evaporated, and the residue was taken up with saturated aq. $NaHCO_3$ solution and extracted with ether. The organic phase was dried with Na_2SO_4 and concentrated at reduced pressure, leaving the unsaturated ketones **7a/7b**, identical to previously described specimens.[3]

The same procedure was followed for the benzoylamino ketone **6d**, with xylene (20 mL) as solvent. The unsaturated ketone **7b** was isolated after the workup described above.

Cycloaddition between Benzonitrile Oxide and 4-Benzoylamino-2-cyclopenten-1-one 8: The cycloaddition between BNO and **8** in benzene solution, by the general method reported for dipolarophile **2**, afforded the ketones **6d** (72%) and **6b** (10%), identical to the compounds described above, after column chromatography.

Reduction of Cycloadduct 6d with $NaBH_4$: An excess of $NaBH_4$ (0.05 g, 1.3 mmol) was added to a solution of **6d** (0.1 g, 0.3 mmol) in MeOH (20 mL). After stirring for 2 h at room temp., the reaction mixture was diluted with water and extracted with diethyl ether. After drying with Na_2SO_4, evaporation of the solvent gave the alcohol **3d** (90%), identical to the product previously obtained.

Cycloaddition between Benzonitrile Oxide and *O*-Acetyl-4-benzoylamino-2-cyclopentenol 9: The cycloaddition between BNO and **9** in benzene solution by the above general procedure afforded the regioisomeric cycloadducts **10a**, **10b** and **10d**, which were separated by column chromatography, in 24, 20, and 42% yields, respectively.

Compound 10a: M.p. 179−180 °C from ethyl acetate. IR: $\tilde{\nu}$ = 1640 (NC=O), 1738 (C=O), 3320 (NH) cm^{-1}. ^{1}H NMR: δ = 2.02 (m, 1 H, CH_2), 2.17 (m, 1 H, CH_2), 2.20 (s, 1 H, $COCH_3$), 4.40 (d, *J* =

9.0 Hz, 1 H, 3a-H), 4.89 (t, J = 6.0 Hz, 1 H, CH−N), 5.20 (dd, J = 9, 1.5 Hz, 1 H, 6a-H), 5.53 (d, J = 4.4 Hz, 1 H, CH−O), 6.91 (br. d, J = 8.4 Hz, 1 H, NH), 7.4−7.6 (m, 6 H, arom.), 7.80 (m, 2 H, arom.), 7.95 (m, 2 H, arom.) ppm. ^{13}C NMR: δ = 21.0 (CH_3CO), 34.8 (CH_2), 55.3 (3a-CH), 60.2 (CH−N), 80.7 (CH−O), 88.9 (6a-CH), 126.5, 127.4, 127.8, 128.7, 128.8, 130.3, 131.8, 133.9 (C-arom.), 156.2 (C=N), 166.4, 168.4 (C=O) ppm. $C_{21}H_{20}N_2O_4$ (364.4): calcd. C 69.21, H 5.53, N 7.69; found C 69.1, H 5.5, N 7.6.

Compound 10b: M.p. 134−135 °C from ethyl acetate. IR: ṽ = 1640 (NC=O), 1740 (C=O), 3331 (NH) cm^{-1}. ^{1}H NMR: δ = 2.05 (m, 1 H, CH_2), 2.19 (m, 1 H, CH_2), 2.20 (s, 1 H, $COCH_3$), 4.31 (dd, J = 9, 1 Hz, 1 H, 3a-H), 4.99 (dd, J = 8.4, 7.3 Hz, 1 H, CH−N), 5.26 (d, J = 9.0 Hz, 1 H, 6a-H), 5.49 (d, J = 4.5 Hz, 1 H, CH−O), 6.78 (br. d, J = 8.4 Hz, 1 H, NH), 7.4−7.6 (m, 6 H, arom.), 7.79 (m, 2 H, arom.), 7.90 (m, 2 H, arom.) ppm. ^{13}C NMR: δ = 21.1 (CH_3CO), 34.9 (CH_2), 57.2 (3a-CH), 58.9 (CH−N), 79.5 (CH−O), 90.7 (6a-CH), 126.5, 127.0, 127.9, 128.6, 128.7, 130.2, 131.6, 134.0 (C-arom.), 154.6 (C=N), 166.0, 169.0 (C=O) ppm. $C_{21}H_{20}N_2O_4$ (364.4): calcd. C 69.21, H 5.53, N 7.69; found C 69.2, H 5.5, N 7.7.

Compound 10d: M.p. 175−176 °C from ethanol. IR: ṽ = 1632 (NC=O), 1745 (C=O), 3335 (NH) cm^{-1}. ^{1}H NMR: δ = 1.34 (s, 1 H, $COCH_3$), 1.88 (m, 1 H, CH_2), 2.49 (m, 1 H, CH_2), 4.46 (t, J = 8.0 Hz, 1 H, 3a-H), 4.79 (m, 1 H, CH−N), 5.19 (dd, J = 8, 5 Hz, 1 H, 6a-H), 5.48 (m, 1 H, CH−O), 6.74 (br. d, J = 8.0 Hz, 1 H, NH), 7.4−7.7 (m, 8 H, arom.), 7.85 (m, 2 H, arom.) ppm. ^{13}C NMR: δ = 19.8 (CH_3CO), 33.4 (CH_2), 50.3 (3a-CH), 52.6 (CH−N), 72.0 (CH−O), 86.1 (6a-CH), 126.9, 127.0, 128.5, 129.7, 129.8, 131.7, 133.8, (C-arom.), 157.4 (C=N), 167.1, 170.2 (C=O) ppm. $C_{21}H_{20}N_2O_4$ (364.4): calcd. C 69.21, H 5.53, N 7.69; found C 69.1, H 5.6, N 7.7.

Acylation of cycloadducts **3a/3b/3d** by the same procedure (Ac_2O, Et_3N, DMAP, room temp. 2 h) as used for the preparation of **9** provided samples of compounds **10a/10b/10d** identical to the products described above.

A sample of **10d** was quantitatively cleaved to afford **3d** by addition of solid NaOH (0.1 g) to a solution of **10d** (0.05 g) in methanol (20 mL). After the mixture had been stirred for 2 h at room temp., the solvent was evaporated and the residue was taken up with water and chloroform. The organic phase was dried with Na_2SO_4, and the solvents were evaporated to leave **3d**, identical to the product described above.

Solvent Effect and HPLC Determinations: The dipolarophiles **2** and **8** (1.2 equiv.) were dissolved in the desired solvent (25 mL) and benzhydroximoyl chloride (1 equiv.), the precursor of BNO, was added to the solution, followed by Et_3N (1.2 equiv.). The mixtures were stirred for 2 days until complete consume of the 1,3-dipole. The reaction mixtures were evaporated to dryness, taken up with acetonitrile and submitted to HPLC analyses for quantitative determination. Yields and regioisomeric ratios were determined by suitable internal standard methods.

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