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# EFFECT OF NITROGEN SUBSTITUTION ON THE DIASTEREOSELECTION OF INTRAMOLECULAR NITRONE/ALKENE CYCLOADDITIONS

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**Abstract**: The diastereomeric ratios of several intramolecular nitrone/alkene cycloaddition reactions have been shown to be sensitive to the substituent on the nitrone nitrogen in a double diastereodifferentiation process.

As part of our continuing program aimed at developing new methodology for the synthesis of nitrogenous natural products we have been interested in controlling the stereochemical course of intramolecular cycloaddition reactions of several 5- and 6-alkenyl aldonitrones.[1] For instance, in several on-going applications we have sought assurance that cycloadditions such as that shown below could be controlled to afford the *cis/anti/cis* product in preference to the *cis/syn/cis* product. This issue was important because if the aldehyde precursor of the nitrone were derived from an optically active

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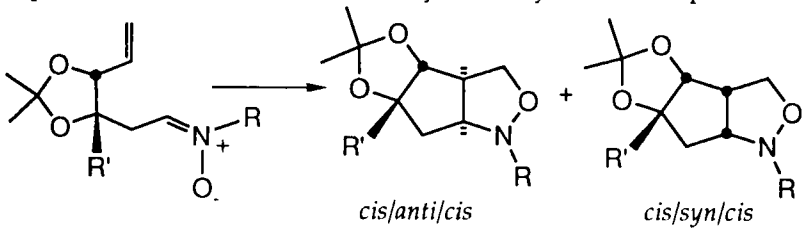
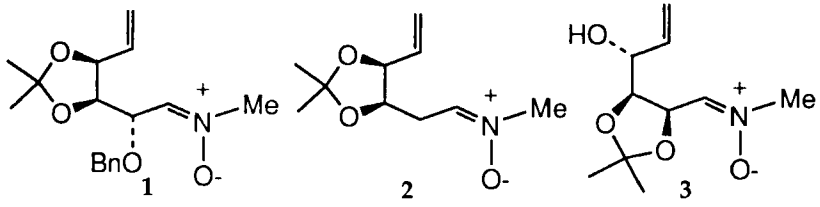
source (*e.g.*, a carbohydrate), the cycloaddition process would establish two new chiral centers whose absolute configuration would be dependent on the diastereoselectivity of the cycloaddition process.




*cis/anti/cis* *cis/syn/cis*

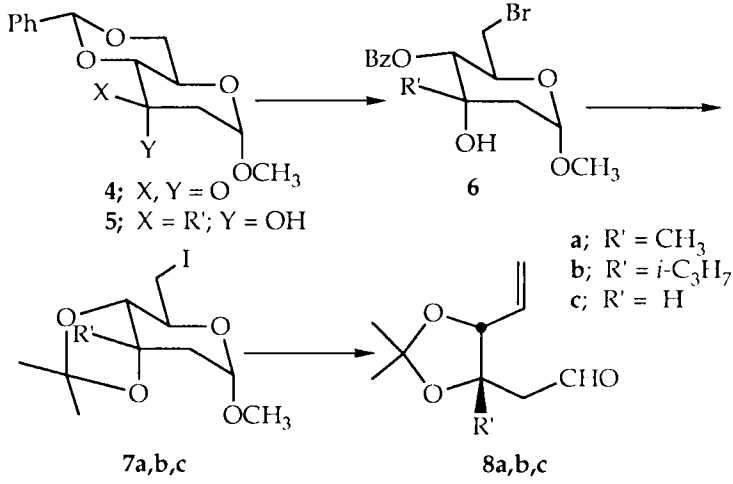
Previous workers have established that the course of similar cycloadditions is very sensitive to the nature of substituents on the carbon skeleton as well as reaction conditions. Thus, cycloaddition of the galactose-derived nitrone **1** yielded a preponderance of the *cis/syn/cis* isoxazolidine isomer while nitrones **2** and **3** gave almost exclusively *cis/anti/cis* products.[2]




Of special interest to us was the possibility that the ratio of a given cycloaddition might be sensitive to the nature of the nitrogen substituent in the starting nitrone. In particular we were interested in determining whether the diastereoselectivity of an N-methyl nitrone might be altered by replacing the methyl with a chiral substituent. Reported here are the results of experiments designed to explore this issue of double diastereoselectivity in nitrone/alkene cycloadditions.[3]

The first series of alkene-aldehyde substrates was prepared as outlined below. Exposure of ketone **4**[4] to either methyl magnesium

bromide or methyl lithium afforded known alcohol **5a** in 94% yield (>15:1 β-attack). Cleavage of the benzylidene with NBS[5] then yielded benzoate **6a** (90% yield) which was treated with LAH followed by ketalization with 2,2-dimethoxy propane to give bromoacetonide **7a** in 61% yield. Fragmentation of iodide **7a** with activated zinc as described by Ferrier[6] proceeded smoothly to yield alkene aldehyde **8a** in 85% yield. In a similar fashion, alkene aldehydes **8b** (R' = iPr) and **8c** (R' = H) were prepared from ketone **4** by initial addition of either *i*-PrMgCl or hydride (L-Selectride™) to yield **5b** or **5c**, respectively, followed by the reactions described for **5a**.




Exposure of alkene aldehyde **8a** to methyl hydroxylamine hydrochloride (benzene, $K_2CO_3$, reflux, overnight) led to a 75% yield of a 2.0/1 mixture of two products (Table, entry 1). The identities of the two isoxazolidines were established by inspection of the 300 MHz and 500 MHz proton and carbon nmr spectra of the pure isomers (separated by flash chromatography[7]) as well as by 500 MHz nuclear Overhauser experiments. Of particular value were the observed coupling constants

**Table**: Effect of Nitrogen Substituent on Diastereoselectivity of Nitrone/Alkene Cycloadditions.

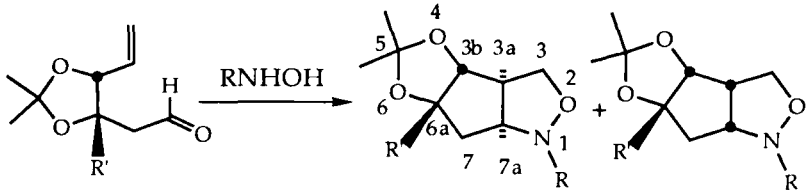
| entry | substrate | RNHOH[1] | 9/10[2] |
|---|---|---|---|
| 1 | **8a**; R' = $CH_3$ | $CH_3$ | 2.0/1 |
| 2 | **8a**; R' = $CH_3$ | R-α-MeBn | 1.9/1 |
| 3 | **8a**; R' = $CH_3$ | S-α-MeBn | 8.0/1 |
| 4 | **8b**; R' = *i*-$C_3H_7$ | $CH_3$ | 4.1/1 |
| 5 | **8b**; R' = *i*-$C_3H_7$ | R-α-MeBn | 4.6/1 |
| 6 | **8b**; R' = *i*-$C_3H_7$ | S-α-MeBn | >20/1 |
| 7 | **8c**; R' = H | $CH_3$ | 12/1 |
| 8 | **8c**; R' = H | R-α-MeBn | 5.0/1 |
| 9 | **8c**; R' = H | S-α-MeBn | >20/1 |

[1]R-α-MeBn and S-α-MeBn refer to the corresponding enantiomers of α-methylbenzyl hydroxylamine. [2] Determined by a combination of capillary gas chromatography and 300 MHz $^1H$ nmr spectroscopy.

between $H_{3a}$ and $H_{3b}$ in the two isomers. In the major isomer $H_{3b}$ occurred as a singlet at δ 4.10 (J~0 Hz) and was assigned to the *cis/anti/cis* isomer **9a** because of the expected dihedral angle of ~90° between $H_{3a}$ and $H_{3b}$. On the other hand, in the minor *cis/syn/cis* isomer **13a**, where the $H_{3a}/H_{3b}$ dihedral angle approaches 0°, $H_{3b}$ appeared as a doublet at δ 4.20 (J = 6.7 Hz). In addition the $^{13}C$ chemical shift for $C_3$ in isoxazolidines **9a** and **10a** were at 68.9 ppm and 64.2 ppm, respectively, in complete accord with trends observed by others for related compounds.[2] Similar exposure of **8b** and **8c** to methyl hydroxylamine each led to good yields of the two isoxazolidine isomers

**9 b,c** and **10b,c** in ratios of 4.1/1 and 12/1, respectively (Table, entries 4 & 7).

With the above ratios as reference, the three aldehydes **8a,b,c** were next treated with R- and S-α-methylbenzyl hydroxylamine and the resulting alkene/nitrones allowed to cyclize as before. As summarized in the Table, in each case the nitrone derived from R-α-methylbenzyl hydroxylamine led to isomer ratios which were either similar to or lower than those obtained from the reference N-methyl nitrones suggesting that the R-α-methylbenzyl group had either no effect or a negative effect on the stereochemical course of the cycloaddition process relative to the N-methyl derivative (*mismatched* set; entries 2, 5, & 8). On the other hand, the three nitrones derived from S-α-methylbenzyl hydroxylamine each cyclized to give the *cis/anti/cis* product as the nearly exclusive isomer in each case (*matched* set; entries 3, 6, & 9). In these cases the normal tendency of the starting material to give *cis/anti/cis* products was apparently reinforced by the S-α-methylbenzyl group on the nitrone nitrogen.




8 9 10

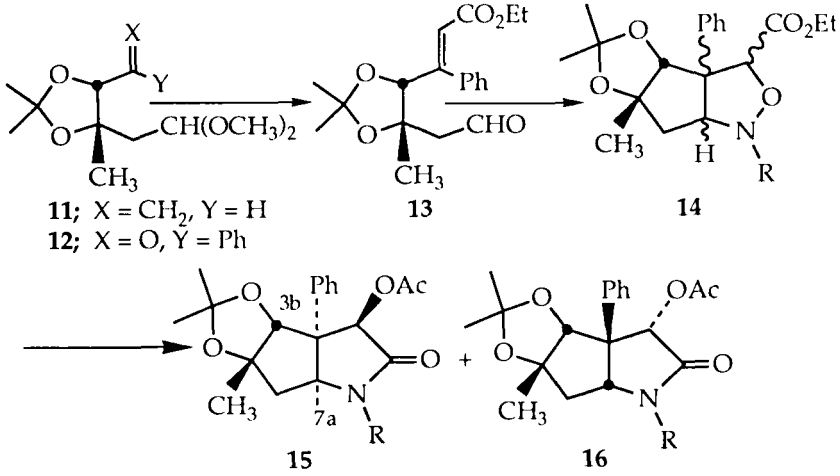
Similar results were obtained from several valine-derived hydroxylamines. Thus, when aldehyde **8a** was treated with the hydroxylamines derived from S-valine methyl ester and S-valinol methyl ether, the ratios of product isomers **9/10** were 3.7/1 and 5.0/1,

respectively, only marginally different from that obtained using N-methyl hydroxylamine. However, the R-valinol methyl ether-derived nitrone yielded the *cis/anti/cis* product **9** exclusively.[9]

Encouraged by the above results, our attention was next turned to a more complex substrate which could serve as a model for the synthesis of several optically active *Amaryllidaceae* alkaloids. Thus, aldehyde **13**, bearing a trisubstituted E-alkene, was prepared from acetal **11** in six steps in 21% yield [(1) $OsO_4$; (2) $NaIO_4$; (3) PhMgBr; (4) PDC; (5) $(EtO)_2POCHNaCO_2Et$; (6) Amberlyst 15]. The Horner-Emmons olefination[9] product of phenyl ketone **12** was a 2:1 mixture of E and Z isomers which was purified by flash chromatography to give the pure E isomer suitable for studies of the nitrone/alkene cycloaddition reaction.

Treatment of **13** with N-methyl hydroxylamine as described earlier afforded a 70% yield of a 3/1 mixture of isoxazolidine isomers **14** (capillary gc) after flash chromatography. Because of significant broadening of the proton nmr signals it was not possible to assign stereochemistry to the major and minor isoxazolidine adducts directly. However, conversion of **14** to the acetylated lactams **15** and **16** ($H_2$, 10% Pd/C; $Ac_2O$, pyridine) yielded materials whose spectra allowed the *cis/anti/cis* structure **15** to be assigned to the major isomer and the *cis/syn/cis* structure **16** to the minor isomer. Of particular value was the observation that in the 500 MHz nOe difference spectrum of **16** there was a strong through-space polarization of $H_{3b}$ ($\delta$ 5.05) on irradiation of $H_{7a}$ ($\delta$ 4.45) that was not observed for the corresponding protons in **15** ($\delta$ 5.59 & 4.48).[10]

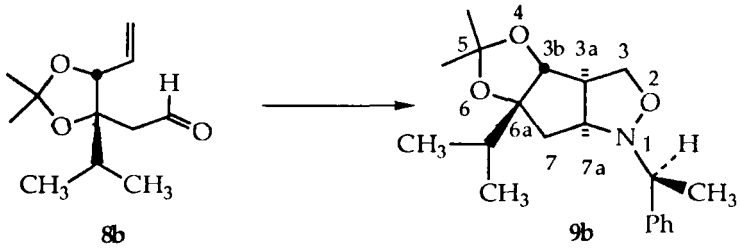
In results similar to those described earlier, exposure of **13** to R-α-methylbenzyl hydroxylamine afforded a 1.5/1 mixture of isoxazolidines **14**, the major isomer being *cis/anti/cis* **15** on analysis of the derived lactams. On the other hand, treatment of **13** with S-α-methylbenzyl hydroxylamine gave the two isoxazolidine isomers in a 16/1 ratio, the major one again being *cis/anti/cis* in accord with expectations. These results strongly suggest that the principle of double diastereodifferentiation can be extremely useful in controlling the outcome of intramolecular nitrone/alkene cycloadditions. The application of these results to several specific targets is currently in progress.




**11;** X = $CH_2$, Y = H
**12;** X = O, Y = Ph
**13** **14**

**Procedure for the "Matched" Cycloaddition of Aldehyde 8b.**

**3a(S), 3b(R), 6a(S), 7a(S) Hexahydro-N-[(S)-α-methylbenzyl]-6a-isopropyl-5,5-dimethyl-[1,3]dioxolo[3,4]cyclopent[1,2-c]isoxazole (9b).**



8b 9b

In a 50 mL round bottom flask were placed 300 mg (14.2 mmol) freshly chromatographed aldehyde **8b** and 290 mg (21.3 mmol) (S)-α-methylbenzyl hydroxylamine[11] in 30 mL reagent grade benzene. After stirring at reflux for 10h the solvent was removed at reduced pressure and chromatography of the resulting crude product ($SiO_2$, 20% ethyl acetate/petroleum ether) yielded 256 mg (55%) of colorless isoxazolidine **9b**.

Analysis of the $^1H$ NMR spectrum prior to chromatography revealed only traces (<5%) of a second isoxazolidine product.

$^1H$ NMR (300 MHz; $CDCl_3$) δ 7.37-7.34 (m, 5H, Ph), 4.37 (s, 1H, $H_{3b}$), 4.27 (t, J = 9.4, 1H, $H_{3a}$), 3.88 (m, 1H, $H_7$ & CH-$(CH_3)_2$), 1.43 (d, J = 6.3, 3H, NCH-$CH_3$), 1.33 (s, 3H, C-$(CH_3)_2$), 1.30 (s, 3H, C-$(CH_3)_2$), 0.95 (d, J = 6.6, 3H, CH-$(CH_3)_2$), 0.97 (d, J = 6.6, 3H, CH-$(CH_3)_2$).

$^{13}C$ NMR (75 MHz; $CDCl_3$) d 128.69, 127.60, 127.46, 110.22, 97.06, 87.86, 69.34, 68.46, 63.67, 60.40, 53.32, 33.45, 28.68, 21.68, 18.66, 17.75, 14.21.

Anal. Calcd for $C_{20}H_{29}NO_3$: C, 72.47; H, 8.81. Found: C, 72.35; H, 8.64.

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