Synthesis and Cycloadditions of Chiral Sugar-Derived Nitrones

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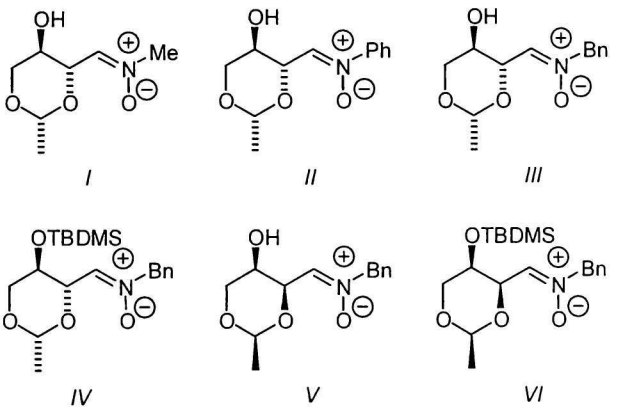
The nitrone-alkene 1,3-dipolar cycloaddition is a powerful reaction in that it can create as many as three new contiguous stereogenic centres in a single step [1]. Based on an evaluation of the nitrone cycloaddition [1, 2], it was felt that the stereochemistry of these new centres could be controlled if the reaction system was properly designed. With the goal of developing a simple route to polyhydroxylated derivatives of pyrrolizidines [3] *via* an asymmetric 1,3-dipolar cycloaddition [4, 5] we have designed chiral sugar-derived nitrones as template for a nitrone cycloaddition.

The utility of nitrones, which are known to react with organometallic reagents as well as with alkenes [6], has been extensively demonstrated. However, in spite of these such well-documented applications in organic synthesis there are only scattered reports which deal with the preparation of nitrones possessing chirality due to their carbon substituent [7—11]. Recently, *Dondoni et al.* have presented their results with regard to the preparation of chiral *N*-benzyl nitrones [11].

In connection with our current interest concerning the use of readily available chiral nitrones in asymmetric cycloadditions, we here present our preliminary results on the synthesis of chiral nitrones *I*—*VI* and the stereochemical outcome of respective 1,3-dipolar cycloadditions to styrene, bearing in mind that the N—O bond in so prepared cycloadducts can readily be cleaved [12] to obtain precursors for the synthesis of polyhydroxylated derivatives of pyrrolizidines.

The nitrones *I*—*VI*, with a "chiral" *C*-substituent, were prepared from the corresponding aldehydes by treatment with the appropriate *N*-substituted hydroxylamine in dichloromethane in the presence of anhydrous magnesium sulfate [11]. A single isomer was isolated in all cases in pure state, and the expected *Z* configuration was confirmed by nuclear Overhauser effect (NOE) difference spectroscopy. *N*-Benzyl nitrones *III*—*VI* are particularly interesting as intermediates in synthesis, since the benzyl group can readily be removed from the nitrogen atom, thus achieving the introduction of a primary amino function for further uses [12, 13].



I *II* *III* *IV* *V* *VI*

The required D-*erythro* nitrones *I*—*IV* were prepared from 2,4-*O*-ethylidene-D-erythrose [14—17] readily available from 4,6-*O*-ethylidene-D-glucose [14—16]. The typical aldehyde resonance was absent in ^{1}H and ^{13}C NMR spectra of this compound and the protected aldehyde was isolated as crystalline dimer of 2,4-*O*-ethylidene-D-erythrose, in accordance with previous papers [14—17]. Re-formation of the monomer was facilitated in our case by adding a catalytic amount of 2-pyridone [17, 18], and from this equilibrating mixture the aldehyde underwent condensation with the corresponding hydroxylamine in much better yield (50 % *vs.* 73 % for nitrone *III*). Likewise, treatment of dimer with ethyl acetate containing a catalytic amount of

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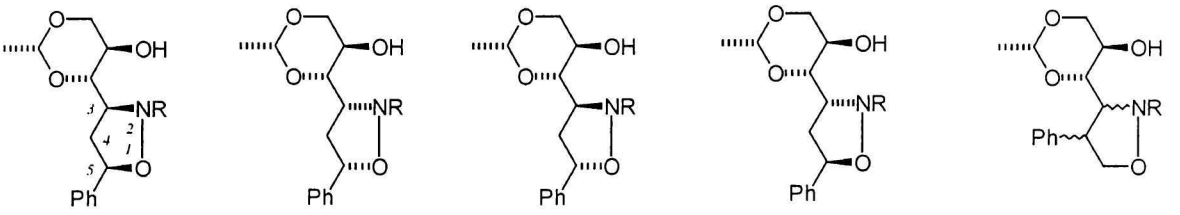

VIIa *anti-cis* | *VIIb* *syn-cis* | *VIIc* *anti-trans* | *VIId* *syn-trans* | *VIIIa—VIIIa*

R = Me, Ph, Bn

glacial acetic acid or 100 % phosphoric acid afforded the monomer [17].

The corresponding D-*threo* nitrone *V* was prepared analogously, in moderate yields from 2,4-*O*-ethylidene-D-threose, which is readily available from D-galactose [19, 20]. For cycloadditions with these nitrones blocking of the free OH group was studied also since direct *O*-silylation failed, a detour using the *N,N*-dimethylhydrazone as the protected monomeric aldehyde was used [21], to provide the *O*-TBDMS D-erythrose in excellent yield. The protected D-*erythro* nitrone *IV* and D-*threo* nitrone *VI* were prepared analogously.

The structural assignment (new compounds were characterized by their NMR spectra and their elemental compositions established by combustion analysis, only selected ^{1}H NMR data are given) to nitrones was based on the detailed ^{1}H and ^{13}C NMR analysis including 2D experiments: *III* (Yield = 73 %, m.p. = 145—146 °C, [α] (D, 23 °C, ρ = 1.95 g dm^{-3}, CH_2Cl_2) = + 87.1° ^{1}H NMR spectrum ($CDCl_3$), δ: 7.38—7.48 (m, 5H, $NCH_2\underline{Ph}$), 6.83 (d, 1H, $J_{1,2}$ = 4.1 Hz, H-1), 5.90 (br s, 1H, OH), 4.93 (s, 2H, $N\underline{CH_2}Ph$), 4.75 (dd, 1H, $J_{2,3}$ = 9.2 Hz, H-2), 4.67 (q, 1H, J = 5.1 Hz, $\underline{CH}CH_3$), 4.17 (dd, 1H, $J_{4a,4e}$ = 11.1 Hz, $J_{3,4e}$ = 5.2 Hz, H-4e), 3.82 (ddd, 1H, $J_{3,4a}$ = 10.1 Hz, H-3), 3.46 (dd, 1H, H-4a), 1.30 (d, 3H, $CH\underline{CH_3}$)), *V* (Yield = 73 %, m.p.= 181—182 °C, [α] (D, 23 °C, ρ = 1.88 g dm^{-3}, CH_2Cl_2) = −116.1° ^{1}H NMR spectrum ($CDCl_3$), δ: 7.35—7.44 (m, 5H, $NCH_2\underline{Ph}$), 6.79 (d, 1H, $J_{1,2}$ = 4.9 Hz, H-1), 4.75 (d, 1H, H-2), 4.89 (s, 2H, $N\underline{CH_2}Ph$), 4.82 (q, 1H, J = 5.1 Hz, $\underline{CH}CH_3$), 4.02 (s, 1H, H-3), 4.00 (d, 1H, $J_{4a,4e}$ = 11.1 Hz, H-4e), 3.91 (d, 1H, H-4a), 3.15 (br s, 1H, OH), 1.34 (d, 3H, $CH\underline{CH_3}$)).

The nitrones prepared were submitted to 1,3-dipolar cycloaddition with styrene. Our concern was to study the asymmetric induction of these cycloadditions stemming from the nitrone part. There are eight products possible, *exo*- and *endo*-isomers for each pair of regioisomers resulting from *anti* and *syn* face attack.

With each nitrone, the reaction proceeded smoothly in a highly regioselective manner, the cycloadditions afforded only the corresponding 5-substituted isoxazolidines *VIIa—VIId*, 4-substituted derivatives *VIIIa—VIIId* were not detected by ^{1}H NMR in the crude reaction mixture. Cycloadditions of the nitrones *I–IV* to styrene in boiling toluene for 10 h gave a mixture of four optically active adducts *VIIa—VIId* (*e.g.* for *VIIa* R = benzyl, yield = 55 %, m.p. = 162—163 °C, [α] (D, 25 °C, ρ = 1.78 g dm^{-3}, CH_2Cl_2) = −30.9° ^{1}H NMR spectrum ($CDCl_3$, 500 MHz), δ: 7.33—7.39 (m, 10H, Ph), 5.50 (br s, 1H, OH), 5.45 (dd, 1H, $J_{4b,5}$ = 8.8 Hz, $J_{4a,5}$ = 7.6 Hz, H-5), 4.57 (q, 1H, J = 5.1 Hz, $\underline{CH}CH_3$), 4.28 (d, 1H, J = 12.2 Hz, $N\underline{CH_2}Ph$), 4.06 (dd, 1H, $J_{6'a,6'e}$ = 10.0 Hz, $J_{5',6'e}$ = 3.8 Hz, H-6'e), 3.94 (d, 1H, $N\underline{CH_2}Ph$), 3.45—3.50 (m, 1H, H-3), 3.26—3.39 (m, 3H, H-4', H-5' H-6'a), 3.00 (ddd, 1H, $J_{4a,4b}$ = 13.4 Hz, $J_{3,4b}$ = 8.4 Hz, H-4b), 2.35 (ddd, 1H, $J_{3,4a}$ = 2.6 Hz, H-4a), 1.23 (d, 3H, $CH\underline{CH_3}$). ^{13}C NMR spectrum ($CDCl_3$, 125 MHz), δ: 139.41, 135.09, 129.58, 128.88, 128.66, 128.28, 128.05, and 126.42 (Ph), 99.14 ($\underline{CH}CH_3$), 80.38 (C-5'), 78.99 (C-5), 69.92 (C-6'), 68.70 (C-3), 66.25 (C-4'), 60.92 ($N\underline{CH_2}Ph$), 38.98 (C-4), 20.47 ($CH\underline{CH_3}$))in excellent yields (82—94 %). The diastereoselectivity was dependent on the steric bulk of the nitrone. The selectivity increases as the size of the nitrogen substituent of the nitrone is increased. The best diastereoselectivity was achieved by using *N*-benzyl nitrones *III* and *V* The diastereomeric ratio *w*(*VIIa*) *w*(*VIIb*) *w*(*VIIc*) *w*(*VIId*) (for nitrone *I* 69 17 10 4, for *II* 82 9 5 4, for *III* 83 10 7 and for *V* 90 5 3 2) was established by integration of the signal from C-4 of the isoxazolidine ring (^{13}C NMR spectra of crude reaction mixture). In all cases, the major product *VIIa* has a 3,5-*cis* relationship of substituents (confirmed by NOE) and *anti* relationship between existing stereocentre of the tetrose moiety and the new-formed centre at C-3 (confirmed by X-ray analysis for the adduct of styrene to nitrone *II*). The formation of the major adducts can be rationalized by *anti* attack in the *endo* mode of the more stable *Z*-nitrone.

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