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CYCLOADDITION OF NITRONES AND α,β-UNSATURATED SUGAR LACTONES

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Abstract—It was found that 1,3-cycloaddition of nitrones **1–3** to α,β-unsaturated sugar carbonyl compounds **4–8** proceeds regiospecifically to give mixtures of stereoisomers. Nitrones **1–3** entered compounds **4–8** in *trans*-relation to the existing ring substituent.

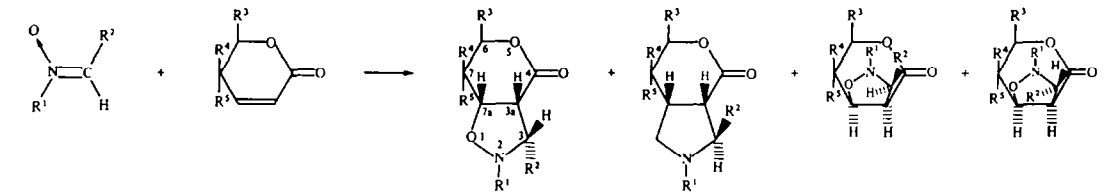
1,3-Dipolar cycloaddition involving nitrones has widely been used as a route to the important drugs,[1] alkaloids,[2] aminosugars,[3] etc.[4–6] The stereochemistry of the 5-membered ring depends mainly on configuration of a nitrone and dipolarophile since cycloadditions proceed regiospecifically and lead to the diastereoselective formation of products. The N,O bond of these adducts can be readily cleaved to produce acyclic molecules with stereocontrolled configuration at chirality centres.

The 1,2-disubstituted unsaturated esters, such as crotonates, are known to be very reactive dipolarophiles against wide representation of nitrones to give β-oxa esters.[5–8] Due to desired regiochemistry the adducts have been transformed into β-lactams via hydrogenolysis of the N,O bond followed by recyclization of the resulting β-aminoacid derivative.[5,6] Cycloaddition of nitrones and α,β-unsaturated carbonyl compounds derived from sugars opens a way for the new functionalization of the sugar molecule. It can be expected that the nitrone oxygen atom should be added to the C-3 carbon atom of the sugar lactone. This regiochemistry creates an access to enantiomerically pure β-aminoacid derivatives and subsequently to β-lactams or to branched-chain aminosugars.

The aim of the present work was the 1,3-dipolar cycloaddition of stable and ready available nitrones **1–3** with sugar lactones **4** and **5**,[9] and also with racemic model compounds **6** and **7** derived from butyl 2-methoxy-5,6-dihydro-2H-pyran-6-carboxylate[9,10] (Scheme 1). In addition we report on cycloaddition using 1-O-benzoyl-2,3-dideoxy-DL-pent-2-enopyranos-4-ulose (**8**) as the dipolarophile.

RESULTS AND DISCUSSION

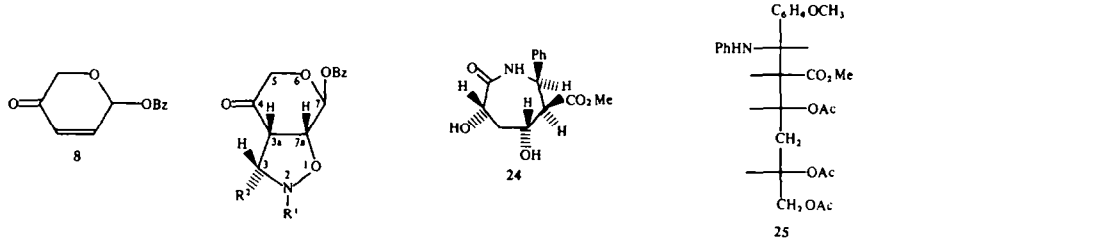
All cycloadditions were performed in boiling toluene, the diastereomeric products were separated by column chromatography or preparative TLC affording with a good yield respective adducts **9–21**. Reactions provided two diastereomeric compounds, except for lactone **6** where only one product was found, and the



1: R^1 = Ph, R^2 = p-$CH_3OC_6H_4$
2: R^1 = $PhCH_2$, R^2 = Ph
3: R^1 = Me, R^2 = p-$CH_3OC_6H_4$

4: R^3 = CH_2OAc, R^4 = H, R^5 = OAc
5: R^3 = CH_2OAc, R^4 = OAc, R^5 = H
6: R^3 = CH_2OAc, R^4 = R^5 = R^5 = H
7: R^3 = CO_2Bu, R^4 = R^5 = R^5 = H

9 | 10 | 11 | 12
7 | 18 | 19
7 | 20 | 21
13 | 14
15
16 | 17



8

22: R^1 = $PhCH_2$, R^2 = Ph
23: R^1 = Me, R^2 = p-$CH_3OC_6H_4$

24

25

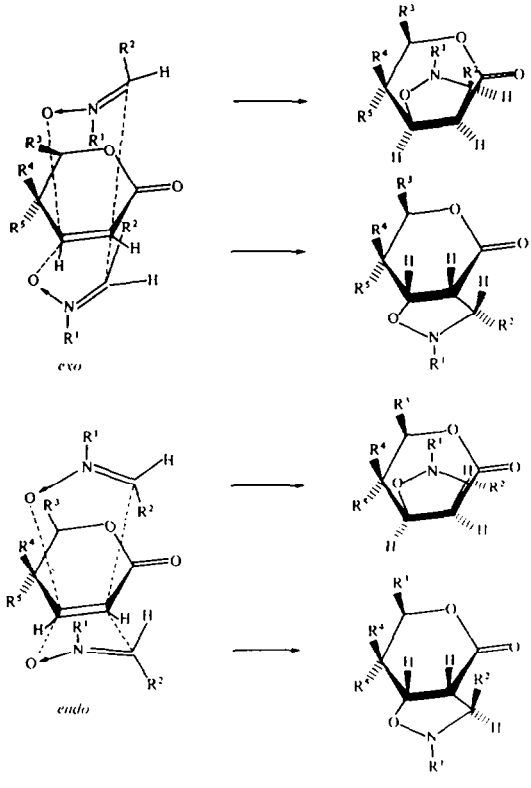
Scheme 1.

lactone **4** where four products were found. The adduct **12** was not obtained as a pure isomer. The proportion of diastereomers was assigned approximately after separation of pure components.

The structure and configuration within the pyranoid ring of adducts **9–21** are proved on the basis of their ^{1}H-NMR spectra (Table 1). All cycloadditions proceed regiospecifically and give expected β-oxalactones. The coupling constants between H-6, H-7 and/or H-7′ and H-7a of products **9–21** prove the relative configuration of the isoxazolidine ring with respect to substituents attached to the lactone ring. Except for lactone **4** nitrones **1–3** enter exclusively in *trans*-relation to the existing ring substituent. The case of addition involving nitrone **2** and lactone **7** is not clear, the proportion of isomers however exhibits the result of the isolation not the postreaction composition. In the *erythro* lactone **4** the directing influences of 4-OAc and terminal CH_2OAc groups act in opposite directions and therefore all possible stereoisomers are formed.

Nitrones **1–3** have *Z* configuration of the double bond. From our earlier observations concerning the 1,3-dipolar cycloaddition of nitrones **1–3** and simple olefins we can assume that the *exo*-transition state is energetically favoured over that of *endo*.[7] Three protons of the isoxazolidine ring in relative *cis*-orientation is the consequence of *Z* configuration of nitrones and their *exo* approach to the dipolarophile. This mutual configuration can be proved by the large values (Table 1) of vicinal coupling constants between protons H-3, H-3a and H-7a and is observed for adducts **9, 11, 13, 15, 16, 18–20**.

The smaller value of $J_{3,3a}$ found for lactones **10, 12, 14, 17** and **21** compared to the coupling found for other



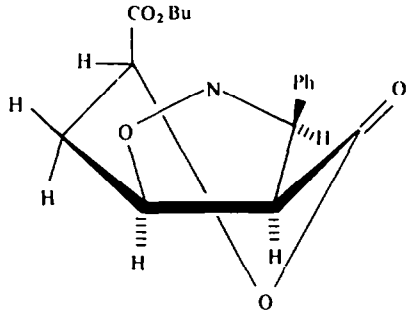
Scheme 2.

Table 1

	H-3	H-3a	H-6	H-7	H-7′	H-7a	CH_AH_BOAc	CH_AH_BOAc	$J_{3,3a}$	$J_{3a,7a}$	$J_{7a,7}$	$J_{7a,7'}$	$J_{6,7}$	$J_{6,7'}$	
9	5.29(d)	4.00(t)	4.80(m)	5.17(dd)	—	4.95(dd)	4.14(dd)	4.29(dd)	8.3	9.1	4.0	—	10.2	—	$J_{6,A}$ = 1.9, $J_{6,B}$ = 3.7, J_{AB} = 13.0Hz
10	4.63(d)	3.52(t)	5.11(m)	5.32(dd)	—	4.93(dd)	4.30(dd)	4.41(dd)	5.4	6.8	3.0	—	10.2	—	$J_{6,A}$ = 2.0, $J_{6,B}$ = 3.4, J_{AB} = 12.7Hz
11	5.22(d)	3.81(t)	4.28(m)	5.38(dd)	—	4.85(dd)	4.08(dd)	4.22(dd)	8.0	9.3	8.8	—	9.5	—	J_{6A} = 2.2, $J_{6,B}$ = 4.0, J_{AB} = 12.6Hz
12	4.88(d)	3.57(dd)	4.51(m)	5.35(dd)	—	4.83(dd)	4.26(dd)	4.41(dd)	5.1	9.1	6.1	—	10.0	—	J_{6A} = 2.4, $J_{6,B}$ = 4.9, J_{AB} = 12.7Hz
13	5.40(d)	3.92(t)	4.43(m)	—	5.27(dd)	4.59(dd)	3.93(dd)	4.16(dd)	8.8	9.3	—	3.4	—	1.0	J_{6A} = 6.8, J_{6B} = 5.6, J_{AB} = 11.7Hz
14	4.50(d)	3.64(dd)	5.10(m)	—	5.39(dd)	4.71(dd)	4.25(dd)	4.30(dd)	6.4	7.8	—	2.9	—	1.5	J_{6A} = 6.8, J_{6B} = 5.4, J_{AB} = 11.3Hz
15	5.47(d)	3.87(t)	4.22(m)	*	*	4.79(m)	3.95(dd)	4.19(dd)	9.1	9.6	3.8	1.6	10.0	*	J_{6A} = 5.4, J_{6B} = 3.4, J_{AB} = 12.1Hz
16	5.35(d)	3.80(t)	4.56(dd)	2.10(m)	2.27(m)	4.61(m)	—	—	8.6	9.4	4.7	4.1	9.6	3.2	$J_{7,7'}$ = 15.0Hz
17	4.66 (d)	3.62(dd)	4.89(m)	2.46(m)		4.89(m)	—	—	6.4	8.2	ΣJ = 12.5		ΣJ = 11.6		
18	3.95(d)	3.58(t)	5.13(m)	2.30(m)		4.66(m)	—	—	8.5	8.3	ΣJ = 10.8		ΣJ = 4.1		
19	4.31(d)	3.47(t)	4.98(m)	2.41(m)		4.66(m)	—	—	8.0	8.0	ΣJ = 7.6		ΣJ = 9.1		
20	3.75(d)	3.44(t)	5.06(dd)	2.20(m)	2.26(m)	4.55(m)	—	—	8.0	8.4	5.5	5.3	7.5	4.2	$J_{7,7'}$ = 15.1Hz
21	3.60(d)	3.60(m)	5.22(dd)	2.35(m)		4.72(m)	—	—	*		ΣJ_{7a} = 20		ΣJ = 11.5		
22	4.14(d)	3.63(t)	—	6.56(d)	—	4.73(dd)	—	—	8.2	8.5	1.7	—	*		4.41 (s, 2H, H-5, H-5′)
23	3.5(m)	3.5(m)	—	6.34(d)	—	4.00(dd)	—	—	*	8.4	1.8	—	*		4.27 (d, 1H, $J_{5,5'}$ = 18.6 Hz, H-5)
															4.31 (d, 1H, H-5′)

Chemical shifts and coupling constants of compounds **9–23**.
*Not visible or too complex for analysis.
Multiplicities of the signals are given in brackets.

adducts testify for the *trans*-configuration of coupled protons and hence for the *endo*-cycloaddition. The configuration of adduct **19** is uncertain. The $J_{3,3a}$ and $J_{3a,7a}$ are characteristic for the *exo*-addition, whereas the small values of sums $J_{7a,7}+J_{7a,7}$, should be assigned to the mutual *cis*-configuration of the isoxazolidine ring and the butoxycarbonyl group with the conformation shifted toward the form with the axial butoxycarbonyl group:



The N,O bond in adducts **9–21** can be split by hydrogenolysis over Pd catalyst in methanol solution. As the example adducts **18** and **15** were hydrogenated. In the case of **18** lactam **24** was obtained as the result of hydrogenolysis of the N,O bond followed by splitting of the benzyl group, methanolysis of the lactone ring and subsequent intramolecular cyclization. The adduct **15** provided after hydrogenolysis, methanolysis of the lactone ring, followed by acetylation, the open-chain ester **25**.

The 1,3-cycloaddition to the ketone **8** proceeds regio- and stereospecifically. The configuration of products **22** and **23** can be assigned straightforward using their ^{1}H-NMR spectra and corresponds well with the results obtained for lactones **9–21**. Adducts **22** and **23** can be used as the precursors of 3-C-substituted sugars, which are known to be an important class of natural saccharides.

The lactones **4–7** and the ketone **8** are highly functionalized compounds available in the case of **4** and **5** in pure enantiomeric forms. Adducts **9–22** derived from **4–8** can be used as convenient starting materials for syntheses of a variety of products with defined stereochemistry.

Further investigation on utilization of the 1,3-dipolar cycloaddition of nitrones to α,β-unsaturated carbonyl compounds derived from sugars are currently in progress.

EXPERIMENTAL

^{1}H-NMR spectra were recorded for solns in $CDCl_3$ on a Jeol-100, Perkin–Elmer—220, Bruker—270 and Bruker—400 spectrometers (δ scale, TMS = 0 ppm). Optical rotations were measured on a Perkin–Elmer 141 spectropolarimeter. IR spectra were recorded on a Unicam SP 200 spectrophotometer. Mass spectra were recorded with LKB G CMS 2091 mass spectrometer. TLC was performed with Merck DC Alufolien Kieselgel 60F-254, preparative TLC was carried out using 20 × 20 glass plates, coated with 0.5 mm thick layers of silica gel Merck PF-254 and column chromatography with silica gel Merck (230–400 mesh). M.ps are uncorrected.

For all new compounds satisfactory elemental analysis were obtained. For products of hydrogenolysis **23** and **24** the elemental analysis is given.

Nitrones **1–3** were prepared from the respective aldehyde and hydroxylamine according to the standard procedure. Lactones **4–7** were obtained according to the procedure described earlier.[9] Compound **8** was performed according to Ref. 11.

General method of cycloaddition. A soln (10–20%) of equimolar amounts of nitrone and α,β-unsaturated carbonyl compounds in toluene was refluxed under N_2 for 8 hr. The progress of reaction was monitored by TLC. The crude post-reaction mixture was evaporated and purified on a silica gel column. The separation of diastereomers was performed by preparative TLC.

(3R, 3aR, 6R, 7R, 7aS), (3S, 3aS, 6R, 7R, 7aS), *and* (3S, 3aS, 6R, 7R, 7aR) *and* (3R, 3aS, 6R, 7R, 7aR) - 7 - *Acetoxy* - 6 - *acetoxymethyl* - 3 - p - *methoxyphenyl* - 4 - *oxo* - 2 - *phenyl* - *tetrahydropyrano* - [3,4 -d] - *isoxazolidine* (**9, 10, 11, 12**). From **1** and **4**, yield 80%. By preparative TLC (Hex–AcOEt; 1 : 1 v/v) three following fractions in an approximate proportion 4 : 3 : 3 were obtained. Compound **11**: m.p. 192–193°; $[\alpha]_D$ −77.4° (*c* = 1, CH_2Cl_2); MS (*m/e*): 455 (M^+). Compound **10**: syrup contaminated with traces of **9**; MS (*m/e*): 455 (M^+). Compound **9**: m.p. 137–140°; $[\alpha]_D$ +55.6 (*c* = 1, CH_2Cl_2); MS (*m/e*): 455 (M^+). Compound **9** was contaminated with traces of **12**.

(3R, 3aR, 6R, 7S, 7aS) *and* (3S, 3aR, 6R, 7S, 7aS) - 7 - *Acetoxy* - 6 - *acetoxymethyl* - 3 - p - *methoxyphenyl* - 4 - *oxo* - 2 - *phenyl* - *tetrahydropyrano* - [3,4 - d] - *isoxazolidine* (**13, 14**). From **1** and **5**, yield 80%. The following two fractions in an approximate proportion 7 : 3 were isolated by preparative TLC using Hex : AcOEt (7 : 3 v/v), as eluent. Compound **12**: m.p. 135–140°; $[\alpha]_D$ +108 (*c* = 1, CH_2Cl_2); MS (*m/e*): 455 (M^+). Compound **14**: syrup; $[\alpha]_D$ −7.2 (*c* = 1, CH_2Cl_2); MS (*m/e*): 455 (M^+).

(3R*, 3aR*, 6S*, 7aR*) - 6 - *Acetoxymethyl* - 3 - p - *methoxyphenyl* - 4 - *oxo* - 2 - *phenyl* - *tetrahydropyrano* - [3,4 - d] - *isoxazolidine* (**15**). From **1** and **6**, yield 80%; m.p. 112–115°; MS (*m/e*): 397 (M^+).

(3R*, 3aR*, 6S*, 7aR*) *and* (3S*, 3aR*, 6S*, 7aR*) - 6 - *Butoxycarbonyl* - 3 - p - *methoxyphenyl* - 4 - *oxo* - 2 - *phenyl* - *tetrahydropyrano* - [3,4 - d] - *isoxazolidine* (**16, 17**). From **1** and **7**, yield 70%. Two following fractions in an approximate proportion 5 : 4 were separated by preparative TLC using Hex : EtOAc (7 : 3 v/v) as eluent. Compound **16**: m.p. 112–115°; MS (*m/e*): 425 (M^+). Compound **17**: syrup; MS (*m/e*): 425 (M^+).

(3R, 3aR*, 6S*, 7aR*) *and* (3S*, 3aS*, 6S*, 7aS*) - 2 - *Benzyl* - 6 - *butoxycarbonyl* - 4 - *oxo* - 3 - *phenyl* - *tetrahydropyrano* - [3,4 - d] - *isoxazolidine* (**18, 19**). From **2** and **7**, yield 70%. Two following fractions in a ratio of about 1 : 1 were separated by preparative TLC using Hex : EtOAc (7 : 3 v/v) as eluent. Compound **18**: m.p. 78–80°; MS (*m/e*): 409 (M^+). Compound **19**: m.p. 98–101°; MS (*m/e*): 409 (M^+).

(3R*, 3aR*, 6S*, 7aR*) *and* (3S*, 3aR*, 6S*, 7aR*) - 6 - *Butoxycarbonyl* - 3 - p - *methoxyphenyl* - 2 - *methyl* - 4 - *oxo* - *tetrahydropyrano* - [3,4 - d] - *isoxazolidine* (**20, 21**). From **3** and **7**, yield 75%. Two following fractions in a ratio of about 1 : 1 were separated by a preparative TLC using Hex : EtOAc (7 : 3 v/v) as eluent. Compound **20**: m.p. 92–93°; MS (*m/e*): 363 (M^+). Compound **21**: syrup; MS (*m/e*): 363 (M^+).

(3S*, 3aS*, 7S, 7aR*) - 7 - *Benzoyloxy* - 2 - *benzyl* - 4 - *oxo* - 3 - *phenyl* - *tetrahydropyrano* - [4,5 -d] - *isoxazolidine* (**22**). From **2** and **8**, yield 70%; m.p. 129–132°; MS (*m/e*): 429 (M^+).

(3S*, 3aS*, 7S, 7aR*) - 7 - *Benzoyloxy* - 3 - p - *methoxyphenyl* - 2 - *methyl* - 4 - *oxo* - *tetrahydropyrano* - [4,5 - d] - *isoxazolidine* (**23**). From **3** and **8**, yield 70%, m.p. 110–112°; MS (*m/e*): 383 (M^+).

3,5,6 - *Trideoxy* - 6 - *amino* - 5 - *methoxycarbonyl* - 6 - *phenyl* - DL - *manno* - 1,6 - *hexaldonolactam* (**24**). A solution of **18** (1%) in methanol was shaken at 40° in the presence of 10% Pd/C under hydrogen (7 atm) for 4 hr, subsequently MeOH was evaporated and the residue was crystallized from acetone afforded **24** (90%); m.p. 212–214°; IR (nujol): 1650, 1720 cm^{-1} (amide and ester), 3390 cm^{-1} (NH), 3500 cm^{-1} (OH); ^{1}H-NMR (pyridine-d_5; H-2 of pyridine taken as 8.60 ppm): 1.64 (dt, 1H, $J_{2,3}+J_{3,4}$ = 23.4, $J_{3,3'}$ = 13.0 Hz, H-3), 2.23 (m, 1H, $J_{2,3'}+J_{3',4}$ = 6.3 Hz, H-3'), 2.54 (s, 3H, ester OCH_3), 2.69 (t, 1H,

$J_{4,5}+J_{5,6}$ = 20.0 Hz, H-5), 3.9–4.8 (m, 3H, H-2, H-4, H-6), 6.5–6.9 (m, 5H, Ph); MS (*m/e*): 279 (M^+). (Found: C, 60.3, H, 6.2; N, 5.0. Calc for $C_{14}H_{17}NO_5$: C, 60.2; H, 6.1; N, 5.0.)

1,2,4 - *Trideoxy* - 3,5,6 - *tri* - O - *acetyl* - 2 - *methoxycarbonyl* - 1 - p - *methoxyphenyl* - 1 - N - *phenylamino* - DL - *altro* - *hexalditol* (**25**). A soln of **15** (1%) in MeOH was shaken at 50° in the presence of 10% Pd/C under hydrogen (5 atm) for 7 hr. Subsequently MeOH was evaporated and the residue was acetylated with pyridine–Ac_2O. The crude **25** was purified on a silica gel column using Hex: AcEt as an eluent afforded pure product (90%); syrup; IR (nujol): 1750 cm^{-1} (C=O), 3400 cm^{-1} (NH); ^{1}H-NMR ($CDCl_3$): 1.91, 2.03, 2.04 (3 × s, 9H, 3 × OAc), 1.9–2.1 (m, 2H, H-4, H-4'), 3.15 (dd, 1H, $J_{1,2}$ = 5.5, $J_{2,3}$ = 8.3 Hz, H-2), 3.52 (s, 3H, ester OCH_3), 3.76 (s, 3H, OCH_3), 4.03 (dd, 1H, $J_{5,6}$ = 5.7, $J_{6,6'}$ = 12.6 Hz, H-6), 4.25 (dd, 1H, $J_{5,6'}$ = 3.2 Hz, H-6'), 4.79 (d, 1H, H-1), 5.16 (m, 1H, H-5), 5.35 (m, 1H, H-3), 6.5–7.3 (m, 9H, NPh, C_6H_4); MS (*m/e*): 515 (M^+). (Found: C, 62.9; H, 6.9; N, 2.5. Calc for $C_{27}H_{23}NO_9$: C, 62.9; H, 6.4; N, 2.7.)

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