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SYNTHESIS OF AMINO SUGARS VIA ISOXAZOLINES
THE CONCEPT AND ONE APPLICATION: NITRILE OXIDE/FURAN ADDUCTS[1]

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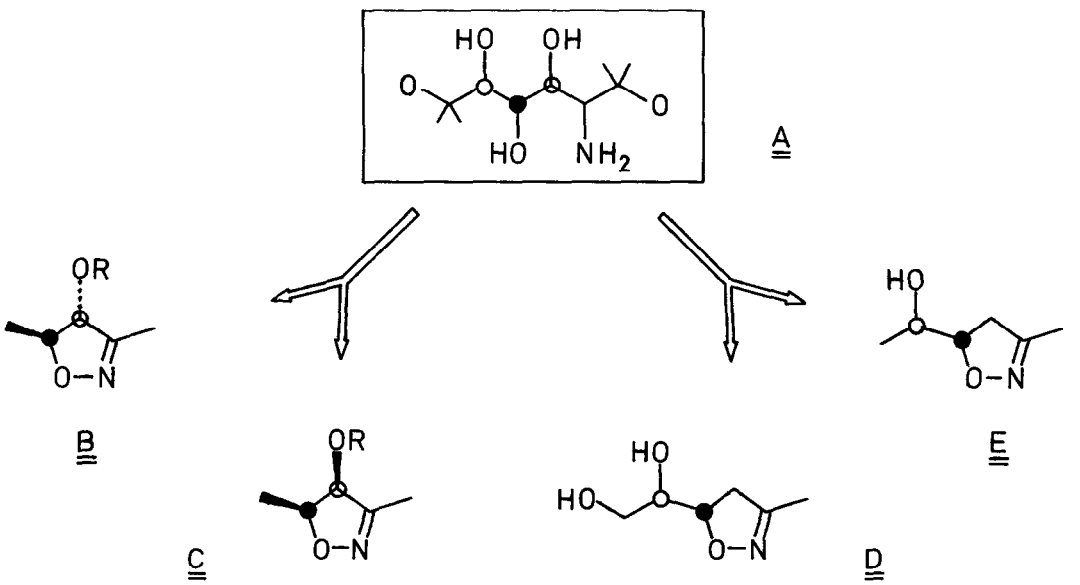
Summary: *Aliphatic nitrile oxides cycloadd to furans to afford amino sugar precursors 1. Oxidation by m-chloroperbenzoic acid and/or $LiAlH_4$ reduction give rise stereoselectively to derivatives of the* xylo *and* ido *series, 2 - 4, with 3 to 5 adjacent chiral centres.*

The concept to use isoxazolines as precursors for various classes of acyclic compounds[2] has been put to practice in several cases[2,3] and has seen an increasing number of successful applications. *Inter alia*, γ-amino alcohols are obtained by $LiAlH_4$ reduction of isoxazolines, with its stereochemical outcome now being predictable from model cases and individual substituent effects[1a,4]. This sequence has been extended to the synthesis of aminopolyols[1a,4b].

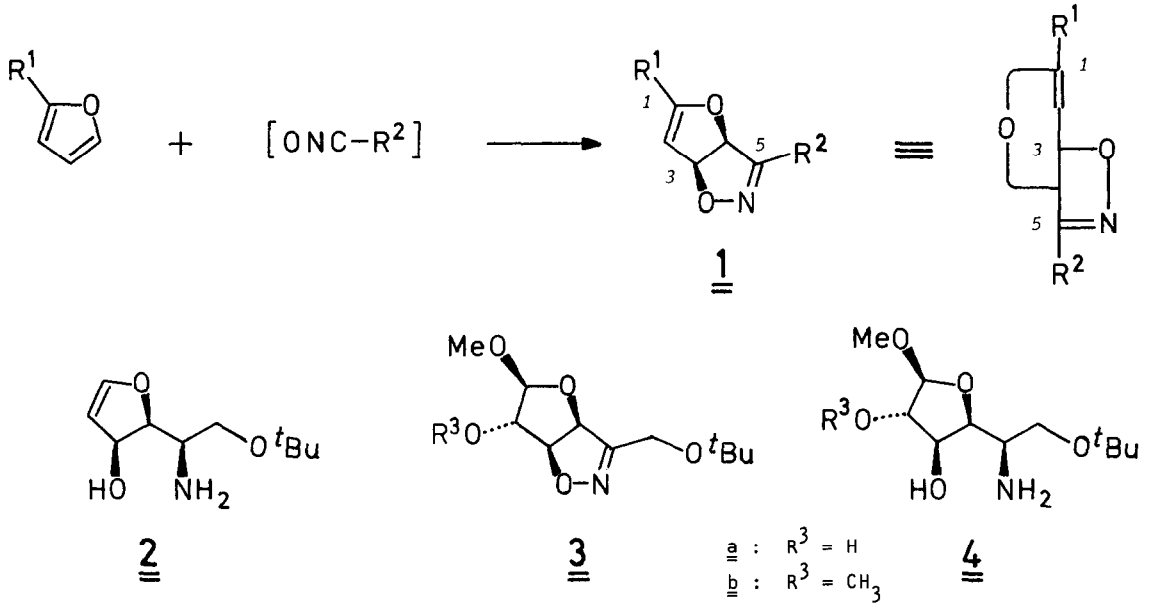
The isoxazoline route may also be suited for rational, short syntheses of many structural and stereochemical types of amino sugars as represented by formula A. Solutions to part of the inherent regio- and stereoselectivity problems may be traced back to syntheses of precursory isoxazolines B - E. Access to B – precursor to the *ribo* series – established[1a], further results in this area concerning key intermediates C/D are detailed in this letter[5].



First, the synthesis of *cis*-4-oxygenated isoxazolines C from suitable enol derivatives was studied. However, no cycloadducts with benzonitrile oxide could be obtained, and moreover, MNDO calculations on several β-substituted enols let not expect a reversal[6] of the usual regioselectivity leading to 5-OR-substituted isoxazolines. We therefore pursued our efforts

as to using furans as dipolarophiles[1b]. Furan is known to cycloadd to aromatic nitrile oxides in the desired mode, albeit very sluggishly, with low yield and numerous side products in preparative runs[7]. Optimization of this reaction with benzonitrile oxide and – more importantly – several aliphatic nitrile oxides gave the results summarized in the table[8,9].

Notably, furan or 2-methylfuran adducts 1 with nitroethanol *t*-butyl ether[4b] and nitroacetaldehyde acetal[10] are thus accessible in fair yield (30 to 50%) and ample quantity (10 to 20 g). The *in situ* liberation of the nitrile oxides (as advanced by Huisgen), carried out under high dilution conditions, proved crucial. The use of 1,4-phenylene diisocyanate, in particular, should gain broad applicability for the generation of easily dimerizing nitrile oxides from nitroalkanes (Mukaiyama's method) in the presence of (sluggish) dipolarophiles: It is almost insoluble in the reaction medium, thereby providing the very low stationary concentration of the respective nitrile oxide; work-up mainly consists in filtration from insoluble urea derivatives.



2 3 4

3 : a : R^3 = H ; b : R^3 = CH_3

The furan adducts 1 represent highly advanced, yet versatile amino sugar precursors[11]. Some further conversions are specified[9]:

a) $LiAlH_4$ reduction of 1c affords the *xylo* derivative 2 stereoselectively in 86% yield as colourless crystals, m.p. 74-75 °C.

b) m-Chloroperbenzoic acid oxidation of 1c in methanol gave the ß-*xylo* furanoside 3a as a yellow oil (b.p. 180/0.05 Torr) in 81-84% yield, containing 5-10% of the anomeric α-acetal[12]. This material on methylation (methyl iodide with KOH in DMSO for 30 min at 25°C[13]) was converted in 90% yield into colourless 3b (m.p. 77°C) after crystallization from CH_2Cl_2/petrol ether. Both 3a and 3b were reduced by $LiAlH_4$ in ether with high stereoselectivity (diastereomer ratio ≳95 : 5) in 79 and 78% yield, respectively, to produce the corresponding ß-furanosides 4a and 4b as slightly yellow oils. 4a/4b constitute protected forms of 5-amino-5-desoxy-idose (5-*epi*-nojirimycin), thus obtained in 3/4 steps and 26/23% over-all yield.

Further obvious and attractive features of this approach are, that it lends itself to a) variation of chain length, effected by choosing appropriate building blocks and/or oxidative fission of the enol ether double bond of 1, b) the option to elaborate aldehyde and/or alcohol oxidation states at either chain terminus, and c) variation of stereoselectivity in the reduction step by taking advantage of previously described substituent effects[4].

Table. Nitrile Oxide/Furan Adducts 1[9]

Compound	R^1	R^2	Yield [%][a] (Scale [mol]/Yield [g])	m.p. [°C] or b.p. [°C / Torr]	Notes
1a	H	CH_3	28 (0.05/1.26)	53 - 55/0.05[b]	c
1b	H	C_6H_5	48 (0.1/8.98)	46	d
1c	H	CH_2O^tBu	40 (0.25/19.67)	80/0.005[b]	e
1d	H	$CH(OEt)_2$	30 (0.15/9.58)	86 - 88/0.005[b]	f
1e	H_3C	CH_2O^tBu	44 (0.2/18.73)	ca. 85/0.005[b]	g
1f	H_3C	$CH(OEt)_2$	52 (0.1/12.52)	90/0.005	h

a) based on nitrile oxide precursor.

b) Spaltrohr column (Fischer) distillation.

c) dilution set-up (Normag/Vögtle); 3.6 equiv of PhNCO, 7 mol% NEt_3, 3 mol% of $BF_3 \cdot OEt_2$; nitroethane addition 8 d; work-up: filtration through basic Al_2O_3 and chromatography (silica; cyclohexane/ethyl acetate 3:1).

d) addition of HON=CClPh during 10 d; isolation of 1b by chromatography, see 1a; cp.[7b].

e) furan (1 l), nitroether, diisocyanate (0.7 mol), and NEt_3 (2 ml) kept in an autoclave 24 d at 70-80 °C; separation of 1c see note b; furan recovered 0.8 l. Improved yield (up to 64% by NMR) by adding small amounts of diisocyanate and NEt_3 every 2-3 days.

f) conditions as for 1c; 16 d at 70 °C.

g) 2-methylfuran (0.7 l), diisocyanate (0.56 mol), and NEt_3 (2 ml) at reflux for 26 d; isolation of 1d see note b; 0.5 l of methylfuran recovered.

h) 2-methylfuran (0.5 l), diisocyanate (0.3 mol), and NEt_3 (0.1 ml) at reflux for 13 d; isolation of 1f by Kugelrohr distillation; 0.3 l of methylfuran recovered.

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References and Notes

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3. Conversion to (a) α,β-enoximes, -enones (ref.[2a]); (b) β,γ-enoximes, -enones, homoallylic amines [V. Jäger, H. Grund, and W. Schwab, Angew. Chem. 91, 91 (1979); Angew. Chem., Int. Ed. Engl. 18, 78 (1979)]; (c) stereoselective synthesis of γ-amino alcohols (ref.[1a,4] and lit. cited; (d) aldols [K. Torssell *et al.*, Acta Chem. Scand. B 32, 118 (1978); B 36, 1 (1982); K. F. Burri *et al.*, J. Am. Chem. Soc. 100, 7069 (1978); M. Asoaka, T. Mukata, and H. Takei, Tetrahedron Lett. 22, 735 (1981); A. P. Kozikowski and M. Adamczyk, Tetrahedron Lett. 23, 3123 (1982); A. P. Kozikowski and P. D. Stein, J. Am. Chem. Soc., in press; D. P. Curran, J. Am. Chem. Soc., in press]; (e) β-hydroxy-nitriles [U. Stache, W. Fritsch, and H. Ruschig, Liebigs Ann. Chem. 685, 228 (1965); G. W. Moersch, E. L. Wittle, and W. A. Neuklis, J. Org. Chem. 32, 1387 (1967); R. Huisgen and M. Christl, Chem. Ber. 106, 3291 (1973); P. A. Wade and H. R. Hinney, J. Am. Chem. Soc. 101, 1320 (1979)].

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8. Numerous variations concerning reaction time, temperature, choice of isocyanate, work-up.

9. Structure and stereochemistry of compounds 1 - 4 have been established by elemental analyses, IR, ^1H, and ^{13}C NMR spectral data (Varian CFT 20, XL 100, and Bruker WH 400). The help of Dr. U. Habermalz, A. Schönke, Dr. H.-O. Kalinowski (Gießen), D. Brückner, W. v.d. Saal, and Dr. D. Scheutzow (Würzburg) is gratefully stated. Coupling constants (^1H) and chemical shifts (^1H and ^{13}C) of 2 - 4 fully agree with corresponding values of furanoses as published by B. Capon and D. Thacker, Proc. Chem. Soc. 1964, 369; J. D. Stevens and H. G. Fletcher, Jr., J. Org. Chem. 33, 1799 (1968); R. G. S. Ritchie, N. Cyr, B. Korsch, and A. S. Perlin, Can. J. Chem. 53, 1424 (1975); J. Urban, M. Marek, J. Jary, and P. Sedmera, Coll. Czech. Chem. Commun. 45, 2779 (1980).

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