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D-Xylose Derived Oxazolidin-2-ones as Chiral Auxiliaries in Stereoselective Alkylations

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Abstract : Chiral N-acylated oxazolidin-2-ones readily available from D-xylose have been demonstrated to undergo highly diastereoselective alkylation reactions via their lithium imide enolates to afford α-branched products. These are easily purified and hydrolyzed without difficulty allowing isolation of the desired ramified carboxylic acids in high enantiomeric excesses and to return the auxiliaries for reuse.

The development of chiral enolate synthons and their practical utility in bond construction has been the subject of intensive investigation and recently several enolate systems have been reported to exhibit high levels of diastereoselection in stereoselective transformations[1]. Among them chiral N-acylated oxazolidin-2-ones pioneered by D. A. Evans[2] have proved to be particularly effective for controlling a broad variety of reactions of attached acyl fragments. Due to the well established ability to functionalize oxazolidin-2-ones at nitrogen using electrophiles such as phosgene, acid chlorides, and acid anhydrides[3] and, equally important, the reported possibility to hydrolyze the N-acylated heterocycles under mild conditions[4] the employment of enantiomerically pure cyclic carbamates has become a widely used standard procedure in modern stereoselective organic chemistry[5].

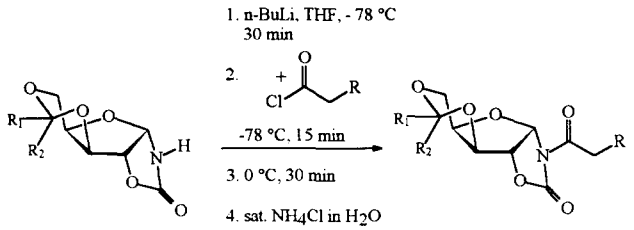
However, preparative access to chiral auxiliaries is quite difficult because enantiomerically pure amino alcohols are required or even worse, resolution of the correspondingly prepared racemic oxazolidin-2-ones is necessary. Thus several groups among them M. R. Banks[6,7] and H. Kunz[8] switched over to make use of the *chiral pool*, namely terpenes[6] and carbohydrates[7,8]. In this way M. R. Banks was able to prepare a CDA derived from (1-[*S*]-endo)-borneol[6a] . Other auxiliaries were prepared from D-galactose[7,8], D-glucose[8], and D-fructose[7].

But the irksome formation of the heterocyclic system remains a problem of all of M. R. Banks' and H. Kunz' reagents. A very simple approach to glyco-oxazolidin-2-ones was discovered in our laboratory in a joint co-operation with Hungarian colleagues by treatment of aldoses or ketoses with potassium cyanate in aqueous solutions, buffered with ammonium chloride or ammonium dihydrogenphosphate[9].

Recently we reported two new reagents, 3,5-O-isopropylidene- and 3,5-O-benzylidene-α-D-xylofurano-[1,2,d]oxazolidin-2'-one **1** and **2**, readily prepared in multigram-scale by a simple two step synthesis from inexpensive D-xylose and illustrated their practical value as CDA's for the resolution of carboxylic and sulfonic acids[10].

Herein, we want to demonstrate that these compounds can be efficiently employed as cheap chiral auxiliaries for diastereoselective C-C bond formation. Within the scope of current studies of efficiency of **1** and **2** in stereoselective synthesis we first examined α-alkylation reactions[11]. This reaction attracted interest because it enables the generation of branched carbon chains without being dependant on further functional groups.

In order to explore the limitations of **1** and **2** as auxiliaries in stereoselective transformations we varied the acyl moiety to get a number of different sterically constrained N-acyl derivatives of **1** and **2**. N-Acylations were achieved via deprotonation with n-butyl lithium followed by quenching with an appropriate acid chloride at - 78 °C to obtain the desired products **3a - 9b** in yields between 79 - 97 %.



	R_1	R_2	R		R_1	R_2	R
1	Me	Me	-	**2**	Ph	H	-
3a	Me	Me	Me	**3b**	Ph	H	Me
4a	Me	Me	Et	**4b**	Ph	H	Et
5	Me	Me	i-Pr				
6	Me	Me	t-Bu				
7	Me	Me	$CH_2C_6H_{11}$				
8a	Me	Me	Ph	**8b**	Ph	H	Ph
9a	Me	Me	Bn	**9b**	Ph	H	Bn

Figure 1 : standard N-acylation sequence[2]

During the course of our studies we came across T. Kunieda's protocol for protecting nitrogen in oxazolidin-2-ones using triethyl amine and catalytical amounts of N,N-dimethyl-4-aminopyridine (DMAP)[12]. We successfully adapted this strategy to N-acylation. With this equally well working method in hands we have got a much more efficient way to derivatize oxazolidin-2-ones at nitrogen rendering employment of cryotechniques and the use of n-butyl lithium superfluous.

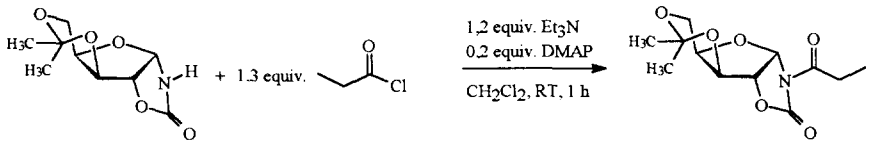


Figure 2 : exemplary N-acylation procedure converting **1** to **3a** (92 %) using catalytic amounts of DMAP

All new compounds obtained by one of these procedures are stable derivatives. Their structures were confirmed by ^{1}H- and ^{13}C-NMR and MS measurements, and microanalyses.

According to a protocol of D. A. Evans[2] the N-acyl precursors were transferred into enolates using lithium diisopropylamide (LDA) as base. In a second step a three to fivefold (methyl iodide) excess of alkyl halide was added to a solution of the enolate intermediate to get α-alkylated N-acyl compounds. To obtain alkylated products in practical yields temperatures between - 25 and -15 °C were found to be optimum to effect the desired transformation.

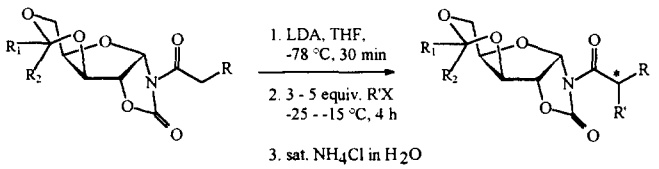


Figure 3 : α-alkyation reaction

Analyses of crude reaction mixtures by ^{1}H- and ^{13}C-NMR spectroscopy showed sufficient chemical shift differences to determine the diastereomeric ratios. The major diastereomers were readily purified on silica using petroleum ether / ethyl acetate (7 : 4 v/v) as eluent. Their structures were confirmed by microanalyses, ^{1}H- and ^{13}C-NMR, and MS measurements. As a bonus it should be noticed that the crystalline nature of these compounds also offers the opportunity to attempt purification by fractional crystallisation. The results summarised in Table 1 reflect the diastereofacial selection dictated by **1** and **2** for all alkylations.

Table 1 : α-alkylations of N-acyl derivatives **3a** - **9b**

N-acyl derivative	alkylating agent	diastereomeric ratio[a]	configuration of major product	yield of major product[b]
3a (R = methyl)	allyl bromide	8 : 1		52 %
3a (R = methyl)	benzyl bromide	8 : 1	*R*	48 %
3b (R = methyl)	allyl bromide	5 : 1	*R*	54 %
3b (R = methyl)	benzyl bromide	7 : 1	*R*	40 %
4a (R = ethyl)	methyl iodide	7 : 1	*S*	45 %
4a (R = ethyl)	allyl bromide	6 : 1	*R*	43 %
4a (R = ethyl)	benzyl bromide	5 : 1	*R*	50 %
4b (R = ethyl)	methyl iodide	5 : 1	*S*	48 %
4b (R = ethyl)	benzyl bromide	5 : 1	*R*	52 %
5 (R = iso-propyl)	methyl iodide	29 : 1	*S*	35 %
5 (R = iso-propyl)	allyl bromide	no reaction	-	-
6 (R = tert.-butyl)	methyl iodide	> 99 : 1[c]	*S*	30 %
6 (R = tert.-butyl)	allyl bromide	no reaction	-	-
7 (R = cyclohexyl methyl)	methyl iodide	12 : 1	*S*	44 %
7 (R = cyclohexyl methyl)	allyl bromide	7 : 1	*S*	40 %
8a (R = phenyl)	methyl iodide	12 : 1	*R*	63 %
8a (R = phenyl)	allyl bromide	7 : 1	*R*	60 %
8b (R = phenyl)	methyl iodide	6 : 1	*R*	67 %
8b (R = phenyl)	allyl bromide	5 : 1	*R*	56 %
8b (R = phenyl)	benzyl bromide	17 : 1	*R*	60 %
9a (R = benzyl)	methyl iodide	10 : 1	*R*	58 %
9a (R = benzyl)	allyl bromide	6 : 1	*R*	67 %
9b (R = benzyl)	methyl iodide	5 : 1	*R*	56 %
9b (R = benzyl)	allyl bromide	8 : 1	*R*	60 %

[a] determined by 300 or 500 MHz ^{1}H- and ^{13}C-NMR spectroscopy using 1D Win NMR software from *Bruker*
[b] after column chromatography; [c] within the limits of NMR spectroscopy

The absolute configurations were assigned by comparison of the specific rotations of the almost enantiopure branched carboxylic acids obtained upon cleavage of the alkylated N-acyl oxazolidin-2-ones with lithium hydroperoxide[4] with literature values. The absolute stereochemistry of the allylated product of **8a** was also proved by X-ray crystallographic analysis.

In all alkylation reactions carried out with non-arylic acyl moieties (**3** - **7**) the sense of stereochemical induction is readily interpreted by assuming a lithium chelated (*Z*)-enolate where diastereofacial *si*-face attack is dictated by the protected sugar skeleton 1-[*S*],2-[*R*] connected to the oxazolidin-2-one ring as suggested by D. A. Evans[2]. But to our initially surprise the results of arylic N-acyl precursors (**8** - **9**) cannot be interpreted in this way. As revealed by the X-ray diffraction analysis the distance between the furanoid ring oxygen atom and the arylic ring system is quite short. So we assume some stereoelectronic interaction to be responsible for a strongly preferred (*E*)-enolate. Due to this fact alkylation of the enolate proceeds from the less hindered *re*-face to produce α-alkylated products with inverse configurations compared to their non-arylic analogues.

Further examinations using other alkyl iodides as ethyl, n-propyl, and i-propyl iodide were frustrated by deacylation and undesirable by-products. These results are in accord with earlier studies dealing with the limitations of this methodology[1,6b,13]. The major restriction encountered with the use of lithium enolates (not only of oxazolidin-2-ones) is the necessity to employ alkylating agents that will react at a convenient rate at

these temperatures, namely S_N2 active reagents like methyl, allyl, and benzyl halides[14]. Primary homologues as well as secondary or tertiary alkyl halides have been reported to be not sufficiently reactive to allow alkylations with comparable systems under similar conditions[13].

Even so we have demonstrated that **1** and **2** readily available from D-xylose are effective chiral auxiliaries for selected stereoselective alkylations with the elaborated N-acyl moieties being easily removed allowing the cyclic carbamates to be recycled. Further studies are in progress using other leaving groups than halides as alkylating agents and employing other counterions to enlarge the glyco-oxazolidin-2-ones' range of application in α-alkylation reactions.

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