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D-Xylose derived oxazolidin-2-ones as chiral auxiliaries in stereoselective acylations and halogenations

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Abstract: Chiral N-acylated oxazolidin-2-ones readily available from D-xylose have been demonstrated to undergo highly diastereoselective acylation reactions via their lithium imide enolates to afford β-keto imides. These are easily purified and exhibit surprisingly high stability towards epimerization. The glyco-oxazolidin-2-ones can also be used in diastereoselective halogenation reactions via their boron enolates to get α-halogenated products.These and the branched N-acyl compounds can be hydrolyzed allowing isolation of the desired halogenated and ramified carboxylic acids and return of the auxiliaries for reuse. © 1997, Elsevier Science Ltd. All rights reserved.

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[1] and as auxiliaries in stereoselective alkylations.[2]

Herein, we demonstrate that these compounds can also be efficiently employed as cheap chiral auxiliaries for another type of diastereoselective C–C bond formation. Within the scope of current studies of efficiency of **1** and **2** in stereoselective synthesis we examined α-acylation reactions.[3] This reaction attracted interest because it enables the generation of branched carbon chains with 1,3 carbonyl functionalities. We want also like to show that the two glyco-oxazolidin-2-ones cannot only be efficiently employed as cheap chiral auxiliaries in C–C bond formation but also in diastereoselective halogen–carbon bond formation. Recently interest in this reaction increased because it provides entry into an attractive class of compounds due to their ability to be used as substrates in nucleophilic substitutions.[4]

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** (Figure 1). Several acyl chlorides were coupled with **1** and **2** using either the standard n-butyl lithium procedure[5] or N,N-dimethyl aminopyridine methodology[6] to get N-acyl oxazolidin-2-ones **3–7** in yields between 79 and 97%. All compounds obtained by this procedure are stable derivatives. Their structures were confirmed by ^{1}H- and ^{13}C-NMR and MS measurements, and microanalyses.

According to a protocol of Evans *et al.*[7] the N-acyl precursors were transformed into enolates using lithium bis(trimethylsilyl)amide (LiHMDS) as base. In a second step a 1.6-fold excess of acyl chloride was added to a solution of the enolate intermediate to get α-acylated N-acyl compounds. To obtain acylated products in practical yields a temperature of −78°C and reaction times between one and two minutes were found to be optimum to effect the desired transformation (Figure 2).

In order to afford α-halogenation we adapted a procedure of Evans *et al.*[4] N-acyl precursors were allowed to react with dibutyl boryl triflate (n-Bu_2BOTf)/tertiary amine to get boron enolates. To

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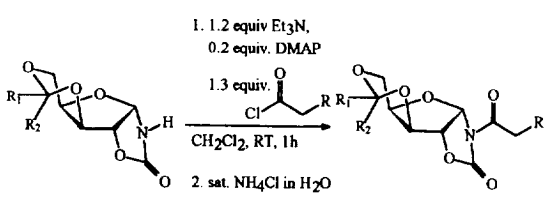

	R_1	R_2	R		R_1	R_2	R
1	Me	Me	-	2	Ph	H	-
3a	Me	Me	Me	**3b**	Ph	H	Me
4	Me	Me	Et				
5	Me	Me	i-Pr				
6a	Me	Me	Ph	**6b**	Ph	H	Ph
7	Me	Me	Bn				

Figure 1. N-acylation sequence using catalytical amounts of DMAP.

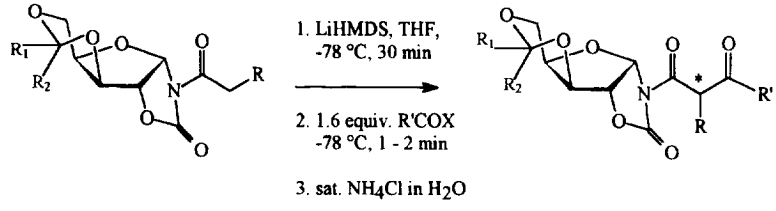

Figure 2. α-Acylation reaction.

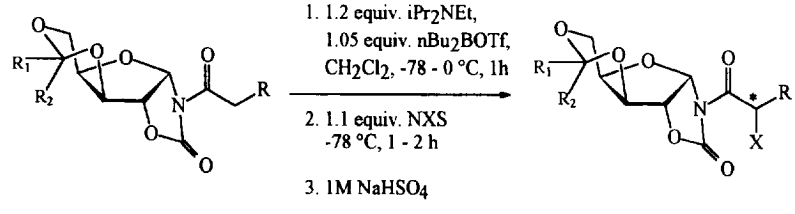

Figure 3. α-Halogenation reaction.

obtain the α-halogenated N-acyl compounds a slight excess of N-bromosuccininide (NBS) or N-chlorosuccinimide (NCS) was added to a solution of the enolate intermediate (Figure 3).

Analyses of crude reaction mixtures by ^{1}H- and ^{13}C-NMR spectroscopy showed sufficient chemical shift differences to determine the diastereomeric ratios. Most of 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.

The absolute configurations were assigned by comparison of the specific rotations of the almost enantiopure acylated or halogenated carboxylic acids obtained upon cleavage of the elaborated N-acyl oxazolidin-2-ones with lithium hydroperoxide[8] with literature values although the α-acylated acids are not very stable towards epimerization. The absolute stereochemistry of the propionylated product of **3a** was also proved by X-ray crystallographic analysis. The results summarised in Table 1 reflect the diastereofacial selection dictated by **1** and **2** for all acylations.

The most striking result of this part of our investigation is probably the initially unexpected low kinetic acidity of the β-keto imides. As already mentioned these compounds are quite stable to silica gel chromatography and even the strongly basic conditions used for preparation do not immediately effect epimerization. This might be due to allylic strain conformational effects destabilizing the conformation of the molecules wherein both carbonyl π-systems are co-planar with the methine-hydrogen which is necessary to get epimerization via enolization.[4,7] This explanation is further supported by the X-ray analysis of the propionylated product of **3a** where there is no co-planar conformation.

Table 1. α-Acylations of N-acyl derivatives **3a–7**

N-acyl derivative	acylating agent	C : O - selectivity[a]	diastereomeric ratio[a]	configuration of major product	yield of major product[b]
3a (R = methyl)	acetyl chloride	5 : 1	7 : 1	*R*	47 %
3a (R = methyl)	propionyl chloride	2 : 1	8 : 1	*R*	45 %
3a (R = methyl)	benzoyl chloride	8 : 1	12 : 1	*R*	60 %
3a (R = methyl)	pivaloyl chloride	N : O 1,5 : 1[c]	-	-	60 %[c]
3b (R = methyl)	propionyl chloride	5 : 1	7 : 1	*R*	50 %
3b (R = methyl)	benzoyl chloride	10 :1	10 : 1	*R*	65 %
3b (R = methyl)	pivaloyl chloride	N : O 1 : 1,5[c]	-	-	55 %[c]
4 (R = ethyl)	acetyl chloride	4 : 1	5 : 1	*R*	[d]
6b (R = phenyl)	acetyl chloride	1,5 : 1	2.5 : 1	*S*	25 %
6b (R = phenyl)	benzoyl chloride	6 :1	15 : 1	*S*	75 %
6b (R = phenyl)	pivaloyl chloride	no reaction	-	-	-
7 (R = benzyl)	acetyl chloride	5 :1	10 : 1	*S*	50 %
7 (R = benzyl)	propionyl chloride	2 .1	6 : 1	*S*	[d]
7 (R = benzyl)	benzoyl chloride	7 :1	5 : 1	*S*	[d]
7 (R = benzyl)	pivaloyl chloride	no reaction	-	-	-

[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] beside O-pivaloyl derivatives N-pivaloyl compounds were the only detectable products, [d] major diastereomer was still contaminated with the minor one after column chromatography

With this unforeseen observation in mind α-acylations of N-acyl derivatives provide an entry into a potentially interesting class of chiral compounds. As shown by Evans *et al.* these β-keto imides can be successfully employed as substrates in diastereoselective carbonyl addition reactions,[7] selective reductions of the β-keto-function,[7] or in aldol reactions.[9] As a highlight it should be mentioned that α-acylated N-acyl derivatives have already been used in the total syntheses of the polyether antibiotic ferensimycin B[10a] and the anti tumor antibiotic (+)-calyculin A.[10b]

In all acylation and halogenation reactions carried out with non-arylic acyl moieties (**3–4**) the sense of stereochemical induction is readily interpreted by assuming a lithium or boron 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 Evans *et al.*[4] As already found in alkylation reactions the results of arylic N-acyl precursors (**5–6**) cannot be interpreted in this way. We assume some stereoelectronic interaction between the furanoid oxygen atom and the arylic ring system in the attached acyl moiety to be responsible for a strongly preferred (*E*)-enolate. Due to this fact acylation or halogenation of the enolate proceeds from the less hindered *re*-face to produce α-substituted products with inverse configurations compared to their non-arylic analogues.

The results summarised in Table 2 reflect the diastereofacial selection dictated by **1** and **2** for all halogenations. As shown in the table NCS is the reagent of choice because NBS can lead to undesirable by-products due to the well known ability of NBS to cleave acetal protecting groups.[11]

We have demonstrated that **1** and **2**, readily available from D-xylose, are effective chiral auxiliaries for selected stereoselective acylations and halogenations with the elaborated N-acyl moieties being easily removed allowing the cyclic carbamates to be recycled. Further studies are in progress using the β-keto imides and the N-acylated compounds **3–6** in other stereoselective reactions like aldol reactions[3] to enlarge the glyco-oxazolidin-2-ones' range of application in stereoselective synthesis.

Table 2. α-Halogenations of N-acyl derivatives **3a–7**

N-acyl derivative	halogenating agent	diastereomeric ratio[a]	configuration of major product	yield of major product[b]
3a (R = methyl)	NCS	3 : 1	*S*	30 %
3a (R = methyl)	NBS	4 : 1	*S*	46 %
3b (R = methyl)	NCS	4 : 1	*S*	68 %
3b (R = methyl)	NBS	4 : 1	*S*	25 %
4 (R = ethyl)	NCS	5 : 1	*S*	44 %
5 (R = iso-propyl)	NCS	3 : 1	*S*	63 %
6a (R = phenyl)	NCS	4 : 1	*R*	[c]
6a (R = phenyl)	NBS	decomposition	-	-
7 (R = benzyl)	NCS	4 : 1	*R*	47 %

[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] major diastereomer was still contaminated with minor diastereomer after column chromatography

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