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Resolution of Racemic Carboxylic and Sulfonic Acids via D-Xylose Derived New Cyclic Carbamate Reagents (Oxazolidin-2-ones)

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Abstract : *Two new chiral oxazolidin-2-ones have been easily prepared from D-xylose and studied as chiral derivatizing agents (CDA's) for the resolution of racemic carboxylic and sulfonic acids. The resultant diastereomers are readily separated by chromatographic methods and easily hydrolyzed to isolate the resolved materials in high optical purities and to return the CDA's for reuse.*

Interest in the development of chiral derivatizing agents (CDA's) has increased enormously during the last decade. It was D. A. Evans who was the first to prepare and study enantiomerically pure oxazolidin-2-one derivatives as chiral auxiliaries[1]. Due to the well established ability to functionalize oxazolidin-2-ones at nitrogen by using electrophiles such as phosgene, acid chlorides, and acid anhydrides[2] and, equally important, the reported possibility to hydrolyze the N-acylated-oxazolidin-2-ones under mild conditions[3], the employment of optical pure cyclic carbamates became a widely used standard procedure[4] in enantioselective syntheses.

W. H. Pirkle utilized these compounds to resolve racemic amines[5]. Thus he converted chiral cyclic carbamates into its N-chloroformyl-derivatives. These derivatives were treated with racemic amines to give diastereomers that were separated on a cheap achiral column. However the synthesis of these compounds is quite difficult because enantiomerically pure aminoalcohols are required or, even worse, resolution of the correspondingly prepared racemic oxazolidin-2-ones is necessary. Thus M. R. Banks switched over to make use of compounds of the *chiral pool* namely terpenes[6] and carbohydrates[7]. In this way he was able to prepare a CDA derived from (1-[*S*]-endo)-borneol which proved to be successful in resolving racemic amines, carboxylic acids, and alcohols[6a]. Other CDA's were prepared from D-galactose and D-fructose[7].

However the irksome formation of the heterocyclic system remains a problem of all of M. R. Banks' reagents. A very simple method to synthezise 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[8].

We now want to report about two new reagents, readily prepared in multigramm-scale by a simple two step synthesis from inexpensive D-xylose. In these compounds the easily functionalized oxazolidin-2-one moiety is enriched by the powerful topological bias inherent in the acetal protected sugar skeleton The practical value of **1** and **2** as cheap auxiliaries for the normally onerous resolution of racemic carboxylic and sulfonic acids is illustrated here.

To prepare the new chiral reagents we employed the very simple reaction of D-xylose with potassium cyanate outlined in Figure 1 to get α-D-xylofurano[1,2,d]oxazolidin-2'-one as a single product[8a].

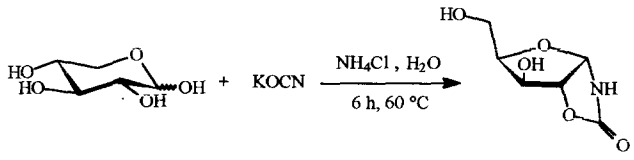
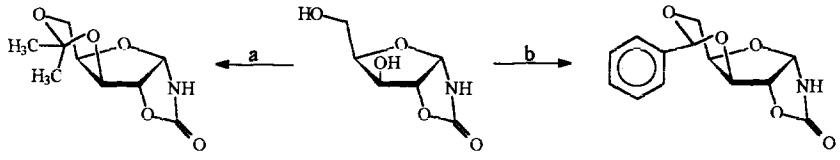


Figure 1 : Formation of α-D-xylofurano[1,2,d]oxazolidin-2'-one

The use of acetal protective groups is the method of choice because of the number and the advantageous *cis*-configuration of the remaining hydroxy functions. Moreover the conformational rigidity of these compounds increases under the influence of the acetal groups which has its positive effects on the use as CDA's. Hence isopropylidene and benzylidene groups were chosen to be suitable. As shown in Figure 2 3,5-O-isopropylidene- and 3,5-O-benzylidene-α-D-xylofurano[1,2,d]oxazolidin-2'-one **1** and **2** were obtained each as single products using standard methods[9].



1 **2**

Figure 2 : Preparation of 3,5-O-isopropylidene- and 3,5-O-benzylidene-α-D-xylofurano[1,2,d]oxazolidin-2'-one **1** and **2** : (a) acetone, conc. H_2SO_4, 1h, RT, (b) benzaldehyde, anhyd. $ZnCl_2$, 4 h, RT

Employing this procedure we obtained crystalline **1** and **2** each in overall yields of 65 %. The structures of **1** (mp 112 - 114 °C; $[\alpha]_D^{20}$ + 73, c = 1,2, acetone) and **2** (mp 216 - 218 °C; $[\alpha]_D^{20}$ + 39, c = 1, chloroform) were confirmed by microanalyses, ^{1}H- and ^{13}C-NMR and MS measurements[10].

To resolve racemic carboxylic and sulfonic acids diastereomers are prepared in the first instance.

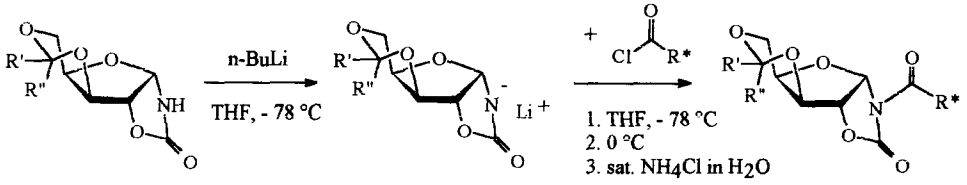


Figure 3 : Formation of diastereomeric amides

In a typical process, shown in Figure 3, 1 equiv. of an acid halide was added to a stirred solution of lithiated CDA in THF at - 78 °C. Analysis of the crude reaction mixture by ^{1}H- and ^{13}C-NMR-spectroscopy showed sufficient chemical shift differences allowing to determine the diastereomeric ratio that was in all terms nearly 1:1 as expected.

In a second step the crude mixture of diastereomers was readily separated on silica (Table I) using petroleum ether / ethyl acetate (7:4 v/v) or petroleum ether / tert.-butyl methyl ether (7:4 v/v) as eluents.

Table I : Chromatographic separation factors (α-values) of diastereomers obtained from TLC (defined as $(R_{f2}- 1) / (R_{f1} - 1)$)

racemate	1 as CDA α-value	2 as CDA α-value
D,L-O-acetyl mandelic acid	1,43[a]	1,43[a]
D,L-O-acetyl lactic acid	1,30[a]	1,34[a]
D,L-2-methyl butanoic acid	1,07[b]	1,07[b]
D,L-camphor-10-sulfonic acid	1,24[a]	1,24[a]

a petroleum ether / ethyl acetate (7:4 v/v), b petroleum ether / tert.-butyl methyl ether (7:4 v/v)

As a bonus it should be noted that the crystalline nature of these diastereomeric derivatives also offers the opportunity to attempt the separation by fractional crystallisation in individual cases. All purified diastereomers are stable compounds. Their structures were confirmed by microanalyses, ^{1}H- and ^{13}C-NMR and MS measurements.

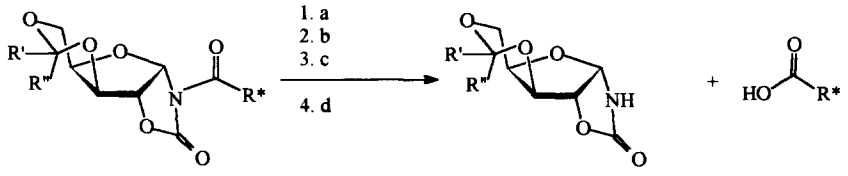


Figure 4 : Cleavage of diastereomeric amides : (a) LiOH, H_2O_2, THF/H_2O, 0 °C, (b) Na_2SO_3, $NaHCO_3$, (c) CH_2Cl_2 extraction, (d) 2 n HCl, EtOAc extraction

The cleavage of the isolated diastereomers was achieved using lithium hydroperoxide[3] allowing recovery of the CDA's in up to 98 % yield and the resolved acids in up to 91 % yield by an acid / base extraction process (Figure 4).

Table II : Nonoptimized overall yields and optical purities (defined as 100 * $[\alpha]_D^{20}{}_{exp} / [\alpha]_D^{20}{}_{lit}$) of the resolved acids

acid	1 as CDA yield	opt. pur.	2 as CDA yield	opt. pur.
[*R*]-O-acetyl mandelic acid	46 %	95 %	30 %	97 %
[*S*]-O-acetyl mandelic acid	53 %	99 %	39 %	98 %
[*R*]-O-acetyl lactic acid	61 %	98 %	40 %	96 %
[*S*]-O-acetyl lactic acid	40 %	96 %	30 %	98 %
[*R*]-2-methyl butanoic acid	66 %	90 %	49 %	90 %
[*S*]-2-methyl butanoic acid	61 %	95 %	50 %	95 %
[*S*]-camphor-10-sulfonic acid	39 %	96 %	33 %	96 %
[*R*]-camphor-10-sulfonic acid	43 %	96 %	37 %	91 %

We applied the illustrated procedure to resolution of D,L-O-acetyl mandelic acid, D,L-O-acetyl lactic acid, D,L-2-methyl butanoic acid and D,L-camphor-10-sulfonic acid. As shown in Table II all acids were

separated in satisfying yields. The reason for the higher yields using **1** as CDA is the lower sensitivity of the isopropylidene group to oxidation and hydrolysis compared with the benzylidene group. The also prepared glyco-oxazolidin-2-thione analogues[9,11] of **1** and **2** failed when used as CDA's in the above described manner due to the fact that the intermediate diastereomers are greatly affected by hydrolysis.

In conclusion the new inexpensive and easily accessible compounds **1** and **2** proved to be useful CDA's for the chromatographic resolution of carboxylic and sulfonic acids. These characteristics should ensure that **1** and **2** become powerful additions to the already available oxazolidin-2-one auxiliaries. Hence further studies of efficiency of **1** and **2** in stereoselective reactions are in progress.

Acknowledgments

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10. **1** : ^{1}H-NMR (500 MHz, $CDCl_3$) δ : 5,832 (d, H-1), 4,880 (d, $^3J_{1,2}$ = 5,1, H-2), 4,461 (d, $^3J_{2,3}$ = 0, H-3), 3,924 (m, $^3J_{3,4}$ = 2,5, H-4), 4,157 (dd, $^3J_{4,5}$ = 2,5, H-5), 4,057 (d, $^3J_{4,5'}$ = 0, $^2J_{5,5'}$ = - 13,4, H-5'), 1,471 (s, H-7), 1,392 (s, H-7'), 6,146 (s, NH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ : 85,68 (C-1), 84,57 (C-2), 70,48 (C-3), 72,44 (C-4), 59,62 (C-5), 97,99 (C-6), 28,80 (C-7), 18,66 (C-7'), 157,13 (NCOO)
    2 : ^{1}H-NMR (500 MHz, $CDCl_3$) δ : 5,899 (d, H-1), 5,020 (d, $^3J_{1,2}$ = 5,7, H-2), 4,619 (d, $^3J_{2,3}$ = 0, H-3), 4,058 (m, $^3J_{3,4}$ = 1,9, H-4), 4,464 (dd, $^3J_{4,5}$ = 1,9, H-5), 4,236 (d, $^3J_{4,5'}$ = 0, $^2J_{5,5'}$ = - 13,4, H-5'), 5,530 (s, H-6), 7,49 - 7,38 (H_{arom}), 6,030 (s, NH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ : 86,13 (C-1), 83,74 (C-2), 71,15 (C-3), 78,06 (C-4), 66,17 (C-5), 99,59 (C-6), 136,99 - 126,00 (C_{arom}), 156,86 (NCOO)
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