http://dx.doi.org/10.5012/bkcs.2013.34.2.641

Potential Pitfalls of Using Epichlorohydrin as Starting Material for Oxazolidinone Antibacterials

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Received November 13, 2012, Accepted November 14, 2012

Key Words : Epichlorohydrin, Cycloaddition, Oxazolidinone antibacterials

The importance of oxazolidinone functional group has been well documented in synthetic and medicinal chemistry.[1] In the latter area, recent interests are focused on *N*-aryl-substituted oxazolidin-2-one structures, as exemplified by linezolid and eperezolid, which represent a new class of antibacterials with activity against drug-resistant Gram-positive pathogens, including MRSA.[2]

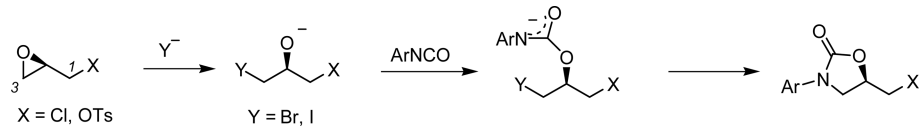
Biologically active enantiomers of the oxazolidinone antibacterials are those with the (*S*)-configuration. Synthesis of the (*S*)-enantiomers have been achieved in enantiopure form starting from various glycidol derivatives such as (*R*)-glycidyl butyrate, (*S*)- and (*R*)-epichlorohydrin, *N*-Boc-glycidylamine, and more recently, (*R*)-glycidyl tosylate.[3] Other enantiopure starting materials include 3-chloro-1,2-propanediol, mannitol, protected glyceraldehyde, and aziridine-2-carboxamide.[4] Several routes employing asymmetric reactions have also been reported.[5]

Of those enantiopure starting materials, epichlorohydrin and glycidyl tosylate are particularly useful as they are doubly activated (at both C-1 and C-3) toward nucleophilic substitutions. The tandem, three-step sequence of the epoxide ring-opening, carbamate formation and oxazolidin-2-one ring-closure (sometimes referred to as "1,3-cycloaddition") represents an atom-economic key step in the synthesis of oxazolidinone antibacterials (Scheme 1). Yu *et al.* first employed this process with epichlorohydrin as the starting material;[3f] we then followed it up with glycidyl tosylate, and showed that this crystalline and storage-stable compound was a viable starting material for oxazolidinone antibacterials.[3i]

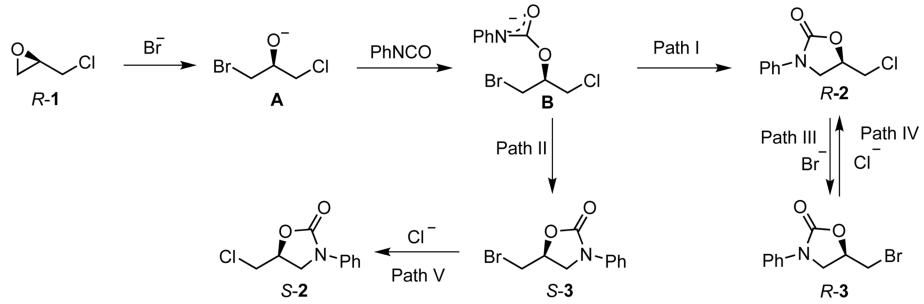
Our work with glycidyl tosylate reminded us how the issues of regio- and stereochemistry were entwined together for the doubly activated glycidol derivatives.[6] It also prompted us to wonder how these issues had played out in Yu's work with epichlorohydrin. As the details were not discussed in their original communication, we decided to re-examine the tandem, three-step sequence with epichlorohydrin as the starting material.

The 1,3-cycloaddition reaction of (*R*)-epichlorohydrin and phenyl isocyanate was performed with a catalytic amount of LiBr. In the absence of detailed experimental procedure in the original work, also to make a meaningful comparison with our findings with glycidyl tosylate, we maintained the reaction conditions as close as possible to the ones employed in the glycidyl tosylate process [in THF (0.067 M) at reflux with phenyl isocyanate (3 eq) and LiBr (0.1 eq)]. Epichlorohydrin underwent the tandem, three-step sequence more slowly with LiBr than glycidyl tosylate did with LiI. The reaction took 8 h to complete (*vs* ~30 min for glycidyl tosylate/LiI). The desired chloro oxazolidinone product was isolated in 93% yield, seemingly validating the results in the original report. A careful examination, however, revealed the presence of a by-product, suggesting concurrent side-reaction pathway(s) and potential complications in the process.

In order to gain a fuller picture of the process, we postulated possible reaction pathways for the 1,3-cycloaddition reaction of epichlorohydrin/PhNCO/LiBr and set out to assess the significance of each pathway quantitatively (Scheme 2). Model reactions revealed that the products could undergo secondary displacements, not one-way, but in both ways, hence Paths IV and V in addition to Path III. This raised an extra issue for the epichlorohydrin process. In the glycidyl tosylate process, a single reaction pathway was responsible for the formation of the desired product, whose stereochemical integrity was therefore maintained through the entire course of the reaction. In the epichlorohydrin process, on the other hand, we now needed to consider multiple pathways for the formations of the desired as well as undesired products (Paths I, IV and V for **2**; Paths II and III for **3**), each resulting in a distinct stereochemical outcome. Significance of these pathways may be assessed in a time study in which the enantiomeric purities as well as the chemical yields of both products would be determined at various reaction times.



Scheme 1. Atom-economic 1,3-cycloaddition of activated glycidol derivatives with ArNCO.



Scheme 2. Possible Reaction Pathways in the Epichlorohydrin-LiBr Process.

The 1,3-cycloaddition reaction of epichlorohydrin/PhNCO/LiBr was performed under the standard conditions and a small aliquot of the reaction mixture was quenched at regular intervals.[7] The crude products thus obtained were analyzed by NMR and HPLC. On proton NMR analysis, the Br-oxazolidinone by-product **3** was detected from the samples taken later in the reaction.[8] However, quantification of this compound was hampered by an impurity in the actual reaction samples that had a signal overlapping with the AB systems of -CH_2Br signal of product **3**.[9] Therefore, the NMR analysis provided only a limited amount of information as far as the chemical yields of the by-product **3** was concerned.

We were encountered with a similar problem with HPLC analysis. The desired Cl-oxazolidinone product **2** and the Br-by-product **3**, which were virtually indistinguishable on silica TLC, were inseparable on many chiral HPLC columns, including Chiralcel OJ-H, OD-H and Chiralpak AD-H.[10] A useful separation that we managed to obtain was on a Pirkle column (Whelk O-1), where the four compounds (two enantiomers each of the two halo-oxazolidinone products) were discernible when pure reference compounds were analyzed. In the event of the actual analysis with the crude products, two of the four products partially overlapped in some of the aliquots. Fortunately, the (*S*)-enantiomers of the Cl- and of the Br-oxazolidinones (*S*-**2** and *S*-**3**) were always cleanly separated from the other products. This allowed meaningful interpretations of the results, which are summarized in Figure 1.[11]

While the yields of the desired (*R*)-Cl-oxazolidinone *R*-**2** and of the (*R*)-Br-oxazolidinone by-product *R*-**3** could not be determined separately due to the partial overlap of the two peaks in some of the samples, the combined yields of these two products could, and they represented the Br^--displacing pathway (Path I) in the oxazolidinone ring-closing stage. From the yields of **2** (NMR) and of *S*-**2** (HPLC), the enantiomeric purities of the Cl-oxazolidinone **2** were calculated and judged to be > 98% ee (*R*) throughout the reaction. The (*S*)-enantiomer *S*-**2**, less than 1% of the major (*R*)-stereoisomer *R*-**2**, probably reflected the enantiomeric purity of the starting epichlorohydrin;[12] contribution by the secondary substitution (Path V) seemed insignificant under the reaction conditions as the enantiomeric purity remained high even at a late stage of the reaction. The presence of the (*S*)-Br-oxazolidinone *S*-**3** was a result of the "wrong" ring-closing path (Path II), while that of the (*R*)-Br-oxazolidinone *R*-**3**, clearly detected in some of the samples, was due to the secondary substitution (Path III). It was not possible to determine precisely the significance of Path III due to the overlapping peaks. At a late stage of the reaction, the Br-oxazolidinone **3** was clearly detected on NMR (> 6 h). Note that Path III would become significant at a late stage. Combining the results of the NMR and HPLC analyses, the yields of *R*-**3** were estimated to be in the range of 7-9% of those of *R*-**2** at this late stage of the reaction.

The secondary displacement (Path III) would have caused the yield of the desired (*R*)-Cl-oxazolidinone product *R*-**2** to decrease, of course. In terms of practicality, however, it may not be seriously detrimental as far as the synthesis of linezolid-type antibacterials is concerned. *R*-**3** would be as effective as *R*-**2** as a synthetic precursor and they are not even easily distinguishable chromatographically. The results of Path III -the presence of the by-product, which is hard to

Reaction Time (h)	NMR (%)		HPLC (%)		
	2	3	*R*-**2**+*R*-**3**	*S*-**2**	*S*-**3**
0.5	26	-	25.9	0.21	0.22
1	38	-	37.8	0.17	0.44
2	53	-	52.7	0.31	0.74
4	80	-	77.4	0.99	2.24
6	82	9	89.1	0.47	1.59
8	79	7	82.4	2.00	2.02
10	91	10	99.6	0.70	1.48

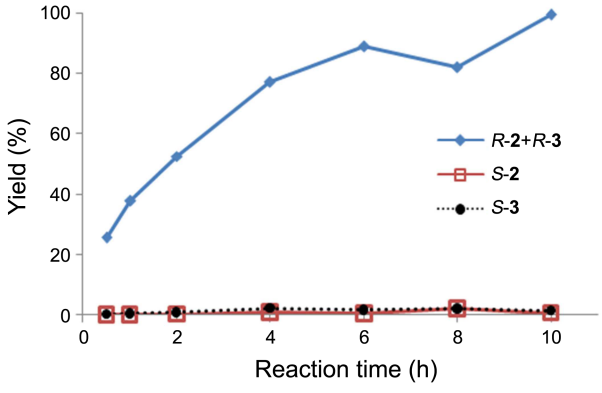


Figure 1. Time-study of the Epichlorohydrin/PhNCO/LiBr Reaction.

separate, and diminished yield of the desired product, and all- may simply be carried over to the subsequent step (azide displacement of halides), and eventually it would not matter, in terms of the chemical and optical yields of the resulting azido-oxazolidinone product, that the secondary displacement side reaction (Path III) had taken place. The secondary substitution in the opposite direction (Path IV) is also a moot point.

More serious is the regioselectivity issue in the oxazolidin-2-one ring-closing stage. The regioselectivity in the epichlorohydrin-LiBr process was estimated to be *ca*. 50:1 (Path I:Path II). While this selectivity was greater than in the glycidyl tosylate-LiI process (20:1), it may pose a more serious problem in the present process. The by-product formed in the minor pathway (Path II) is the (*S*)-Br-oxazolidinone *S*-**3**, which is not easily detected or separated from the desired (*R*)-Cl-oxazolidinone *R*-**2** (plus 7-9% *R*-**3**) unless chiral HPLC is employed. A likely outcome is that the ring-closing product, not rigorously purified, may be carried over to the subsequent step and the azido-oxazolidinone product would be obtained with diminished enantiomeric purity. About 2% of the antipodal product would be formed, which is a drop of 4% in terms of ee.

We undertook this re-examination of the epichlorohydrin/PhNCO/LiBr 1,3-cycloaddition reaction as we were interested in comparing the viability of epichlorohydrin *vs* glycidyl tosylate as starting material for the synthesis of oxazolidinone antibacterials. These two starting materials pose two issues in common, albeit to different extents: the regioselectivity in the oxazolidin-2-one ring-closing stage; and the secondary displacements. In the glycidyl tosylate process, the minor pathways led to by-products, which were easily detected and separated. The only damage was a diminished yield of the desired product. In contrast, the by-products produced via minor pathways in the epichlorohydrin process were not easily detected or separated. As much as the secondary displacements were not practically damaging, the regioselectivity issue raises a serious concern as the minor ring-closing pathway would likely contribute to a drop of 4% ee in the enantiomeric purity of the eventual *N*-aryl-oxazolidin-2-one antibacterial product.

Experimental Section

Time-study for the Epichlorohydrin/PhNCO/LiBr Cycloaddition: (*R*)-Epichlorohydrin (370 mg, 4 mmol) was dissolved in anhydrous THF (40 mL).[11] Phenyl isocyanate (1.304 mL, 12 mmol), lithium bromide (34.7 mg, 0.4 mmol), triphenylmethane (489 mg, 0.5 mmol)[7] were added in succession. The mixture was submerged in an oil bath maintained at 70 °C. At 0.5, 1, 2, 4, 6, 8 and 10 h each, about 6 mL of the reaction mixture was taken out *via* syringe and poured into a mixture of chloroform and water. The phases were separated, the aqueous phase was further extracted with portions of chloroform, and the combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated. The crude product thus obtained was analyzed by proton NMR and HPLC.

5-Chloromethyl-3-phenyloxazolidin-2-one (2): ^{1}H NMR ($CDCl_3$) δ 7.56-7.52 (m, 2H), 7.42-7.36 (m, 2H), 7.19-7.13 (m, 1H), 4.89-4.83 (m, 1H), 4.18 (t, *J* = 9.0 Hz, 1H), 3.97 (dd, *J* = 9.3, 5.7 Hz, 1H), 3.80 (1H, dd, *J* = 11.7, 4.5 Hz), 3.74 (1H, dd, *J* = 11.7, 6.6 Hz).

5-Bromomethyl-3-phenyloxazolidin-2-one (3): ^{1}H NMR ($CDCl_3$) δ 7.56-7.53 (m, 2H), 7.41-7.38 (m, 2H), 7.19-7.14 (m, 1H), 4.87-4.83 (m, 1H), 4.18 (t, *J* = 9.0 Hz, 1H), 3.92 (dd, *J* = 9.3, 5.7 Hz, 1H), 3.65 (1H, dd, *J* = 10.5, 3.9 Hz), 3.56 (1H, dd, *J* = 10.5, 7.5 Hz).

Chiral HPLC (Whelk O-1 column, hexane-*i*PrOH 95:5, 2.0 mL/min): Retention times (min) *R*-**3**: 21.16; *S*-**3**: 25.09; *R*-**2**: 22.84; *S*-**2**: 28.10.

Acknowledgments. This work was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2010-0022804).

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7. Triphenylmethane was also added to the reaction mixture as an internal standard for quantitative monitoring.
8. The desired Cl-oxazolidinone product **2** and the Br-by-product **3** had the AB systems of -CH_2X signals cleanly separated at the base-line.
9. The impurity is thought to be the 1-bromo-3-chloro-2-propyl carbamate (protonated **B**, the precursor for the ring-closing stage). The impurity had a signal that is consistent with the -CH_2Br signal of this precursor [δ 3.67 (d, J = 5.1 Hz)].
10. These chiral columns were effective in enantio-separations, *i.e*., each halo-oxazolidinone product (**2** or **3**) had the two enantiomers nicely resolved. It was Cl *vs* Br (*R*-**2** *vs R*-**3**; *S*-**2** *vs S*-**3**) that didn't get separated.
11. For practical reasons, (*S*)-epichlorohydrin was sometimes used in the time study. In order to maintain consistency and to avoid unnecessary confusion, the discussions were made as if (*R*)-epichlorohydrin had been used throughout this work.
12. Purchased from TCI.