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Glycidyl Tosylate is a Viable Starting Material for Oxazolidinone Antibacterials

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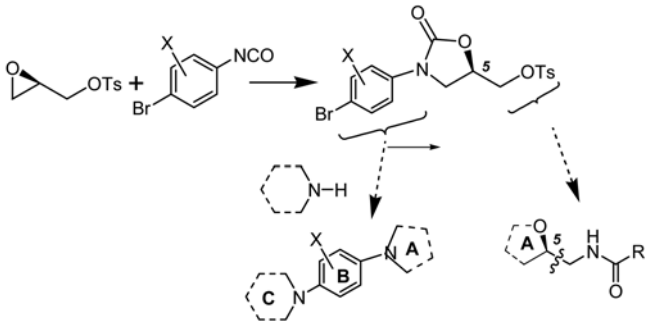
Oxazolidinones are a versatile functional group in synthetic and medicinal chemistry. Their uses as chiral auxiliaries, chiral ligands, building blocks and protecting groups appear frequently in synthetic chemistry.[1] In medicinal chemistry, the functional group has been found in numerous compounds possessing a variety of biological activities.[2] The recent attention has mostly been given to the antibacterial activity.[3] *N*-Aryl-5-substituted methyl-oxazolidin-2-one structures, as exemplified by linezolid and eperezolid, and their lead DuP-721, represent a new class of antibacterials, with activity against drug-resistant Gram-positive pathogens, including MRSA.[4] A multitude of research groups are currently engaged in the oxazolidinone anibacterials research in their efforts to identify second generation candidates with improved potency, selectivity and pharmacokinetic profiles.[5]

The biologically active (5*S*)-enantiomer of linezolid was originally prepared from (*R*)-glycidyl butyrate.[4a,6,7] Subsequently, (*S*)-3-chloro-1,2-propanediol was employed as the enantiomerically enriched starting material.[4c,8] When (*S*)-epichlorohydrin became widely available through the hydrolytic kinetic resolution (HKR), it became the starting material of choice for the synthesis of linezolid.[9,10] Other enantiomerically enriched starting materials reported in the literature include mannitol, protected glyceraldehyde, *N*-Boc-glycidylamine and aziridine-2-carboxamide.[11] Several routes employing asymmetric reactions have also been reported.[12]

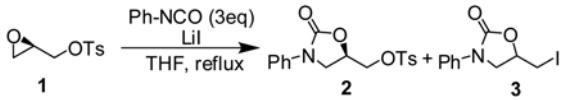
Another enantiomerically enriched glycidol derivative that has become widely available through HKR technology is glycidyl tosylate, a crystalline and storage-stable compound.[13] Like epichlorohydrin, glycidyl tosylate has both C-1 and C-3 activated toward nucleophiles, a useful feature for the introduction of the two *N*-functions at C-1 and C-3 in the synthesis of oxazolidinone antibacterials, but a double-edged one as it spawns the issue of regioselection.[14] An incompletely regioselective process results in the formation of regioisomers, each of which may lead to the product optically antipodal to each other.[14b] Described herein are the results of our investigations with (*R*)-glycidyl tosylate as a feasible starting material for the synthesis of oxazolidinone antibacterials.

The focus of out attention was on the conversion of the epoxide ring of glycidyl tosylate to oxazolidinone function in an efficient and atom-economic pathway. The halide-catalyzed reaction of epoxides with isocyanates, sometimes referred to as "1,3-cycloaddition," in fact proceeds in three steps including halide opening of the epoxide ring; resulting alkoxide reacting with the isocyanate; and the carbamate anion displacing the halide in a ring-closing reaction. The three-step sequence yields oxazolidinone product with a catalytic amount of the halide and no other products are formed.[15] The overall synthetic strategy of oxazolidinone antibacterials would then follow a modular approach consisting of three operations: the 1,3-cycloaddition of glycidyl tosylate and *p*-bromoaryl isocyanates; the replacement of the tosylate followed by subsequent transformations for the "C-5 substituent"; and the replacement of the *para*-bromine by the "C-ring" (Scheme 1).

Glycidyl tosylate is known to undergo regioselective nucleophilic displacements, with some nucleophiles reacting at C-1 (tosylate displacement) and others, including halide nucleophiles, selectively at C-3 (epoxide opening).[16] In the present task, the issue of regioselectivity is not limited to the ring-opening step, but also crucial in the cyclization step:[17] Would the carbamate anion selectively displace a halide or tosylate? We chose to use iodide catalyst in the hope to direct the cyclization step toward the displacement of the most reactive halide leaving group.[18] Model reactions were performed with (*R*)-glycidyl tosylate and phenyl isocyanate as the starting materials, and with LiI as the catalyst (eq. 1). While the original procedure employed LiBr in xylene with nBu$_3$PO as a solubilizing agent, we observed that LiI was soluble in many aprotic polar solvent without any additive. The initial results seemed promising, but also pointed to a direction for optimization.



Scheme 1



(1)

LiI (eq)	2	3
0.1	93% >98% ee *R*	7%, 36% ee *S*
0.2	79% >98% ee *R*	16%, 40% ee *R*
0.5	64% >98% ee *R*	32%, 67% ee *R*

The reaction was found to be most rapid in THF at reflux, completing in less than 30 min when phenyl isocyanate (3 equiv) was used with 20 mol % LiI (the amounts arbitrarily chosen). Isolated from this reaction was the desired (2-oxo-*N*-phenyloxazolidin-5-yl)methyl tosylate (**2**, 79%) together with the corresponding iodide (**3**, 16%). The tosylate **2** was confirmed to be the *R*-enantiomer of > 98% ee, and the iodide **3** again the *R*-enantiomer, but of *ca*. 40% ee only. With a higher loading of LiI, an increased yield of the iodide **3** was obtained at the expense of the tosylate **2** (0.5 equiv LiI: 64% **2** [> 98% ee *R*] and 32% **3** [67% ee *R*]), while with a lower loading of LiI, obtained were a higher yield of **2** (up to a point) and a lower yield of **3** of opposite configuration (0.1 equiv LiI: 93% **2** [> 98% ee *R*] and 7% **3** [36% ee *S*]). The high yields and optical purities of the tosylate product (**2**) indicated that the intended reaction did take place as the major pathway. The observed stereochemical data of the iodide (**3**) suggested multiple pathways leading to this undesired product, which needed to be suppressed.

Possible pathways for the iodide (**3**) formation were postulated, each resulting in a distinctive stereochemical outcome (Scheme 2): the "wrong" cyclization of the carbamate anion intermediate **B** to produce (*S*)-**3** (*Path b*); the secondary displacement of the desired tosylate **2** to produce (*R*)-**3** (*Path c*); other pathways involving achiral 1,3-diiodo-2-propyl phenylcarbamate intermediate to produce (*rac*)-**3** (paths in shade). The initial results indicated that *Paths b* and *c* certainly took place, the extents of which depending on the reaction conditions. *Path c* will become significant at a later stage of the reaction when there is a sufficient amount of the product **2** present in the reaction mixture, and may be suppressed to the minimum by quenching the reaction at an appropriate time. *Path b*, on the other hand, is preordained by the relative leaving group abilities of I^- *vs*. OTs^-, and there seems little to be done to suppress it. The paths leading to the *rac*-**3** were not thought to be significant, but the extents of their involvements were uncertain at this time.

A clearer picture emerged when the progress of the reaction was monitored by quenching a small aliquot of the reaction mixture at regular intervals and analyzing it by NMR and chiral HPLC. The results are summarized in Figure 1. The reaction with glycidyl tosylate (0.067 M), phenyl isocyanate (3 eq) and LiI (0.1 eq) was complete within 1 hr when performed in THF at reflux. The yield of the tosylate **2** peaked at ~40 min, then slightly decreased due to the involvement of *Path c* until all the iodide nucleophile was consumed. The enantiomeric purity of **2** was consistently > 98% ee (*R*) through the entire course of the reaction. This indicated that the tosylate **2** was formed only *via Path a*. The iodide **3** started to appear from the beginning

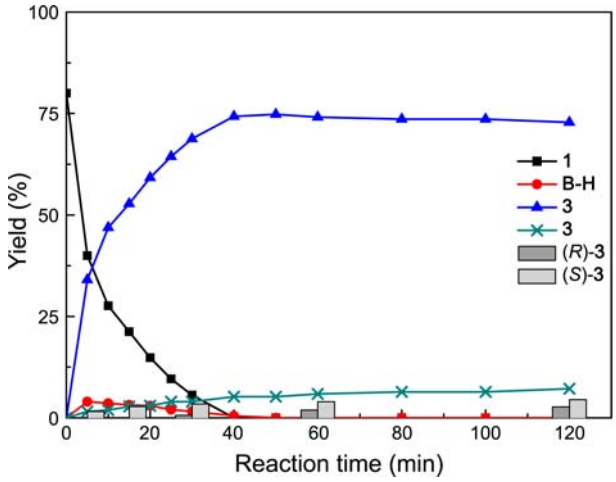
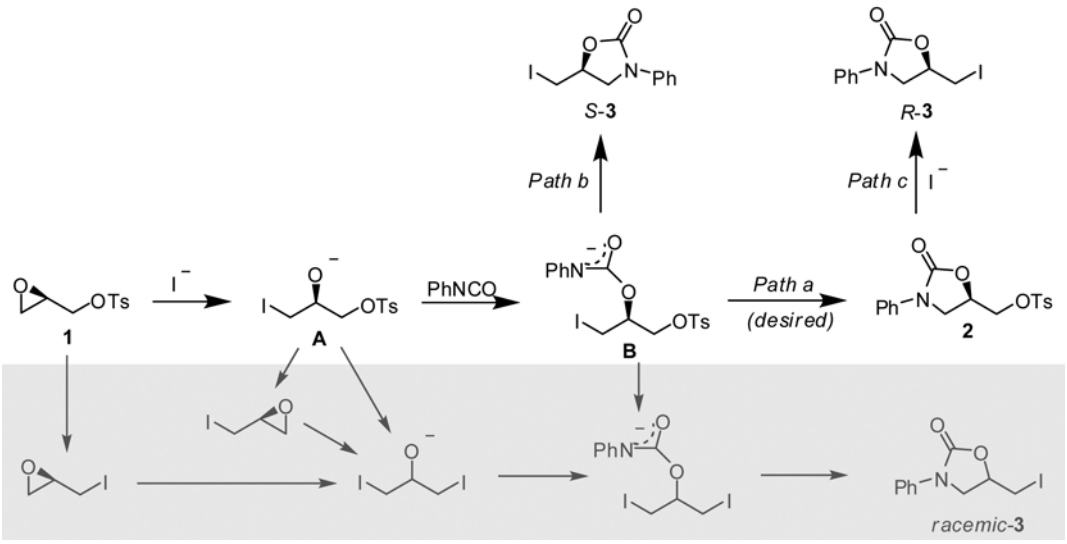


Figure 1. Time-study of the glycidyl tosylate-phenyl isocyanate reaction.



Scheme 2

of the process and the yield continued to increase until all the iodide nucleophile was consumed. The iodide **3** formed during an early stage of the process (< 15 min) was the pure (*S*)-isomer, presumably *via Path b*. After that, *Path c* started to take place to produce the (*R*)-enantiomer. The extents of the pathways leading to the (*racemic*)-**3** were negligible. The carbamate intermediate (**B**-H) was visible, but only at a low concentration, so the cyclization steps (*Paths a and b*) appeared fairly fast.

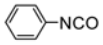
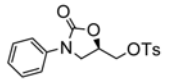
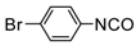
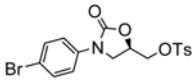
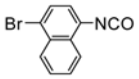
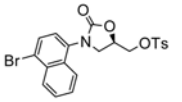
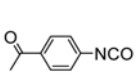
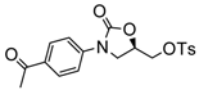
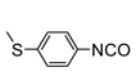
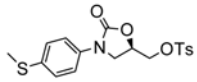
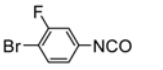
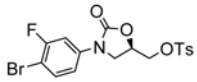
Emerging from this time-study are as follows: i) The maximum yield of the tosylate **2** would be realized when the reaction was quenched after 30-40 min. ii) The relative leaving group abilities of I^- *vs*. OTs^- (*Path a* vs. *b*) were estimated to be *ca*. 20:1 in the intermediate **B**. iii) A minimum of 7.5 mol % LiI catalyst would be necessary for a complete reaction: 5 mol % to be consumed *via Path* b; the rest *via Path c*. Indeed, when 7 or 5 mol % of LiI was employed in the reaction, the catalytic cycle was terminated prematurely when all the iodide was consumed, leaving behind unreacted starting material and a lower yield of **2**.

Having settled on the catalytic loading, other variables were investigated. A minimum 3 equiv. of phenyl isocyanate was required to ensure a complete conversion of the epoxide substrate. Li^+ was better than Cs^+ and various quaternary ammonium cations as the counter ion of the iodide nucleophile. LiI was superior to LiBr, which resulted in an incomplete reaction, presumably because the corresponding *Path a* was now slower with Br^- as the leaving group than with I^-, inducing a higher participation of the corresponding *Path b*, thereby resulting in a lower regeneration (i.e., a higher consumption) of Br^- and a premature termination of the catalytic cycle.

Thus established were the optimum reaction conditions: the reaction is run with glycidyl tosylate (0.067 M), aryl isocyanate (3 equiv.) and 10 mol % LiI in THF at reflux. Under these conditions, the reaction with phenyl isocyanate, when quenched after 30-40 min, gave the tosylate product **2** in *ca*. 90% yield after chromatographic purification. The optimum reaction conditions worked well with a number of other aryl isocyanates (Table 1). The reaction with *p*-acetylphenyl isocyanate took longer to complete (entry 4), presumably the electron-withdrawing acetyl group slowing down the ring-closing steps (those corresponding to *Paths a* and *b*); however, the yield and the enantiomeric purity of the desired oxazolidinone product were undiminished, indicating that the regioselectivity of the ring-closing steps was still very high in favor of the I^--displacement. The aryl groups listed in Table 1 represent potential precursors for some of the aryl functions (the "B-ring") found in the oxazolidinone antibacterial derivatives. For example, the reaction with 4-bromo-3-fluorophenyl isocyanate yielded the oxazolidinone product (entry 6), from which linezolid is just three steps away (the TsO^--displacement by azide, reductive acetylation and the Cu-catalyzed amination).[10a]

In conclusion, glycidyl tosylate has been converted to (2-oxo-3-aryloxazolidin-5-yl)methyl tosylates, the key intermediates for the synthesis of oxazolidinone antibacterials, *via* an atom-economic, tandem ring-openingring-closing reaction. The main reaction has closely been monitored and side pathways have been tracked to find the optimum conditions. The results show that glycidyl tosylate, a crystalline and storage-stable compound, is a viable starting material for oxazolidinone antibacterials.

Table 1. The Reactions of Aryl isocyanates with Glycidyl tosylate[a]

Entry	Aryl isocyanates	Reaction time (mins)	Product	% Yield
1		40		87
2		40		92
3		45		88
4		140		90
5		30		88
6		30		94

[a]The reactions were performed following the representative procedure.

Experimental Section

Representative Procedure for the Reaction of Glycidyl Tosylate with Aryl Isocyanate: *R*-(2-Oxo-*N*-phenyloxazolidin-5-yl)methyl Tosylate (2). (*R*)-Glycidyl tosylate (236 mg, 1 mmol) was dissolved in anhydrous THF (15 mL). Lithium iodide (14.2 mg, 0.1 mmol) and phenyl isocyanate (0.327 mL, 3.0 mmol) were added. The mixture was heated to reflux for 40 min. The reaction mixture was concentrated. The residue was partitioned between chloroform and water. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. Crystallization from chloroform and hexane produced a white solid. It was further purified by column chromatography (hexane-EtOAc 1:1), while the concentrated filtrate was purified by column chromatography (hexane-EtOAc 2:1) to yield the following products:

***R*-(2-Oxo-*N*-phenyloxazolidin-5-yl)methyl tosylate (2, 303 mg, 87%):** $[\alpha] = -94$ (*c* 1.10, $CHCl_3$); mp 152-153 °C; ^{1}H NMR ($CDCl_3$) δ 7.80-7.77 (m, 2H), 7.50-7.46 (m, 2H), 7.40-7.34 (m, 4H), 7.19-7.12 (m, 1H), 4.87-4.78 (m, 1H), 4.27 (dd, *J* = 11.0, 4.2 Hz, 1H), 4.22 (dd, *J* = 11.0, 4.7 Hz, 1H), 4.11 (t, *J* = 9.2 Hz, 1H), 3.89 (dd, *J* = 9.2, 6.0 Hz, 1H), 2.45 (3, 3H); ^{13}C NMR ($CDCl_3$) δ 153.9, 145.8, 137.9, 132.3, 130.4, 129.4, 128.2, 124.7, 118.6, 69.4, 68.5, 47.0, 21.9.

5-Iodomethyl-3-phenyloxazolidin-2-one (3, 30 mg,

10%): ^{1}H NMR ($CDCl_3$) δ 7.57-7.53 (m, 2H), 7.42-7.33 (m, 2H), 7.20-7.14 (m, 1H), 4.77-4.72 (m, 1H), 4.20 (t, J = 9.0 Hz, 1H), 3.82 (dd, J = 9.3, 6.0 Hz, 1H), 3.49 (dd, J = 10.3, 4.0 Hz, 1H), 3.36 (dd, J = 10.3, 8.5 Hz, 1H).

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