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*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

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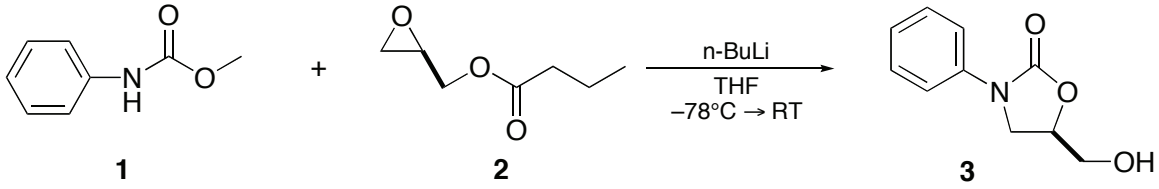
# PREPARATION OF *N*-ARYL-5*R*-HYDROXYMETHYL-2-OXAZOLIDINONES FROM *N*-ARYL CARBAMATES: *N*-PHENYL-(5*R*)-HYDROXYMETHYL-2-OXAZOLIDINONE
## [2-Oxazolidinone, 5-(hydroxymethyl)-3-phenyl-, (5R)-]




**1** **2** **3**

Submitted by Peter R. Manninen[1] and Steven J. Brickner.[2]
Checked by Ossama Darwish and Marvin J. Miller.

## 1. Procedure

*N-Phenyl-(5R)-hydroxymethyl-2-oxazolidinone*. A 2-L, three-necked, round-bottomed flask equipped with an addition funnel, rubber septum, nitrogen inlet, and a large magnetic stirbar is charged with 24.81 g (164.1 mmol) of *N*-phenylcarbamic acid methyl ester (**1**) (Notes 1, 2, 3). Freshly distilled tetrahydrofuran (THF, 750 mL) (Note 4) is added *via* syringe in 50-mL portions. The resulting solution is cooled to –78 °C in a dry ice/acetone bath while 103 mL of butyllithium solution (1.6M in hexanes, 164.8 mmol) (Note 5) is added dropwise via the addition funnel over 60 min. The addition funnel is rinsed with 10 mL of distilled THF and the rinse is added to the reaction mixture. The reaction mixture is stirred for 38 min while the flask is cooled in the dry ice/acetone bath and then 23.4 mL (164.8 mmol) of *R*-(–)-glycidyl butyrate **2** (Note 6) is added dropwise via syringe over 6 min. After 15 min, the dry ice/acetone bath is removed and the reaction mixture is allowed to warm to room temperature and stirred for 22 h. To the resulting thick slurry is then added 750 mL of saturated aqueous ammonium chloride solution and 20 mL of water (Note 7). The aqueous layer is separated and extracted with three 350-mL portions of ethyl acetate, and the combined organic layers are dried over magnesium sulfate, filtered, and concentrated

under reduced pressure. The residual solid is dried in a vacuum oven at 80 °C for 72 h to provide 29.87 g (95%) of **3** as an off-white crystalline solid (Notes 8, 9).

## 2. Notes

1. All glassware was either dried in an oven or flame-dried and cooled under nitrogen.

2. A large football-shaped stir bar is recommended because the mixture becomes a thick slurry.

3. The *N*-phenylcarbamic acid methyl ester was purchased from TCI America.

4. Tetrahydrofuran was distilled from sodium/benzophenone under nitrogen.

5. Butyllithium was purchased from Aldrich Chemical Company, Inc.

6. *R*-(–)-Glycidyl butyrate was purchased from Lonza.

7. A little water is added to dissolve the precipitate that results in the aqueous layer.

8. The submitters report obtaining the product in 99% yield. The enantiomeric excess of the Mosher ester of **3** was measured to be 98% using a Chiralcel OD column (40% 2-propanol/hexane). This optical purity measurement substantiated the optical purity assessment made by $^{1}$H NMR studies of **3** and racemic **3** prepared using a different method.[3] Addition of the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium (III) resulted in clear resolution of the respective aromatic proton signals for the two enantiomers, which was demonstrated with the racemate. Under similar conditions, NMR analysis of **3** showed that within the detectable limits of the experiment (ca. <3%), there was none of the disfavored enantiomer.

9. The product has the following physical properties: mp 139-141 °C; $^{1}$H NMR (300 MHz, $CDCl_3$) δ: 2.05 (s, broad, 1H), 3.77 (dd, $J$ = 12.6 Hz, $J'$ = 4.1 Hz, 1H), 4.02 (m, 3H), 4.76 (m, 1H), 7.15 (t, $J$ = 7.15 Hz, 1H), 7.38 (t, $J$ = 7.4 Hz, 2H), 7.54 (d, $J$ = 9.0 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ: 154.6, 138.1, 129.1, 124.2, 118.3, 72.7, 62.9, 46.3; IR (mineral oil mull):

$cm^{-1}$ 3391 (m), 1716 (s), 1424 (m), 1380 (m), 1307 (m), 1232 (m), 1146 (m); mass spectrum (EI): *m/z* (rel. abundance) 193 (100, $M^+$), 106 (42.9), 77 (38.0), (FAB): 194[100,$(MTH)^+$], 136(62.5), 106(50.1). Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.09; H, 5.80; N, 7.06. $[\alpha]_D$= –61 (*c* = 0.969, $CHCl_3$). TLC: ethyl acetate:hexane (1:1); $R_f$ = 0.13.

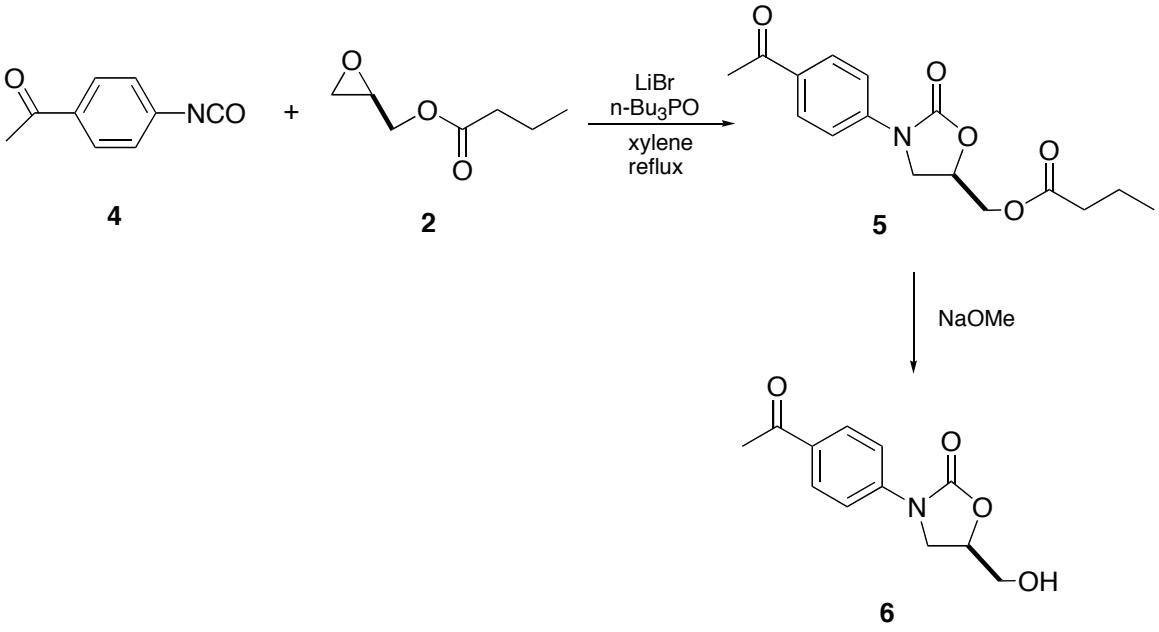
## Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory", National Academy Press; Washington, DC, 1995.

## 3. Discussion

*N*-Aryl-5-*R*-hydroxymethyl-2-oxazolidinones, represented by **3**, are important intermediates for the synthesis of oxazolidinone antibacterial agents. The procedure previously reported[3] and illustrated in Scheme 1 applied the method of Herweh–Kauffmann[4] in which an aryl isocyanate is reacted with kinetically resolved (*R*)-glycidyl butyrate in the presence of solubilized lithium bromide catalyst. While this method works well to provide the butyrate ester oxazolidinone **5** in high yield, an important limitation when utilized in a more general sense is the need to prepare non-commercially available isocyanate. This typically involves the reaction of anilines with phosgene, a reaction that generally terminates at 50% conversion, due to the formation of an equivalent of the aniline hydrochloride salt. In addition to the hazardous nature of phosgene, other limitations are the elevated temperatures required for the oxazolidinone ring formation, and the need for an additional step to cleave the butyrate ester to provide the requisite 5-(hydroxymethyl)oxazolidinone.

**Scheme 1**



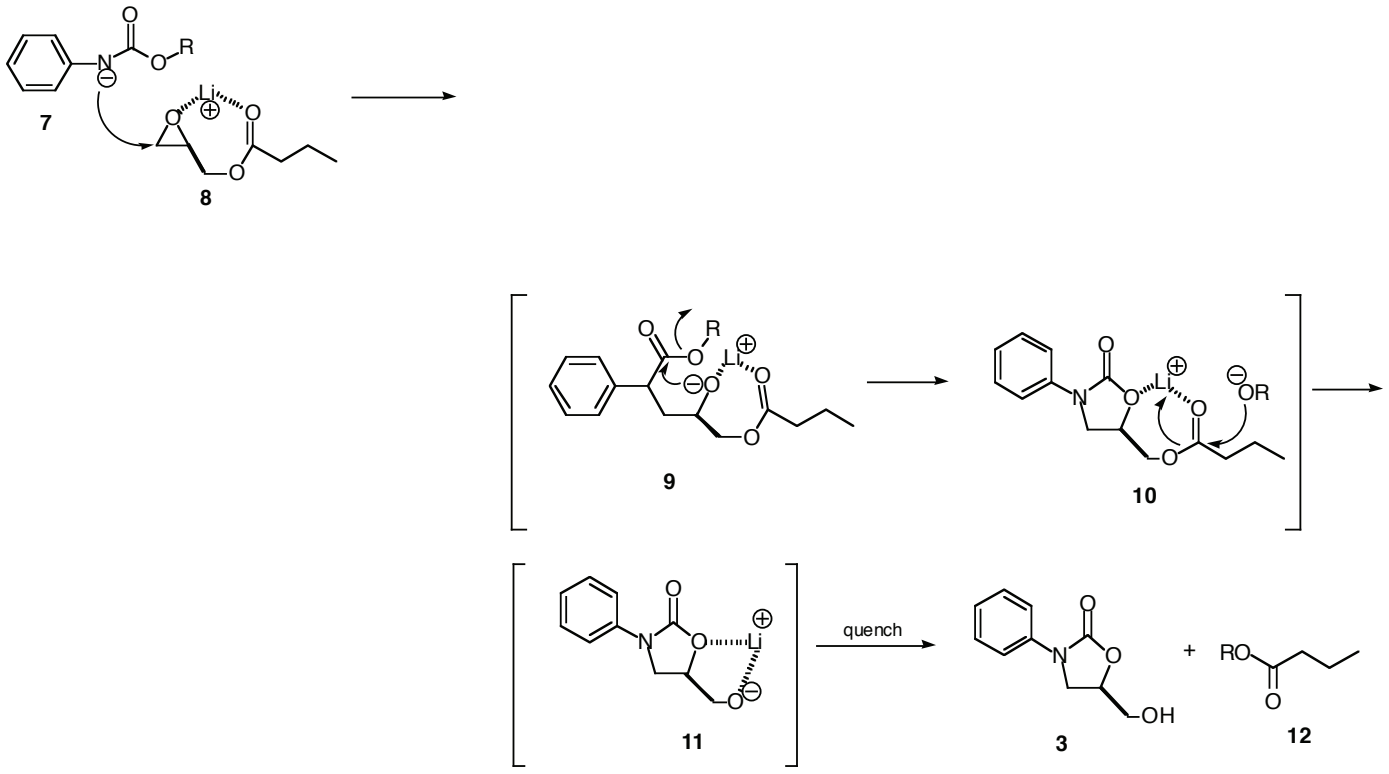

4 2 5 6

We have developed a novel and mild general approach to 5-(*R*)-hydroxymethyl-2-oxazolidinones that involves the alkylation of commercially available (*R*)-glycidyl butyrate with *N*-lithio-*N*-aryl carbamates generated by the deprotonation of aryl carbamates with *n*-butyllithium at –78 °C. The *N*-aryl-5-hydroxymethyl oxazolidinone is directly obtained from this reaction, by virtue of the *in situ* transesterification of the oxazolidinone butyrate ester with the lithium alkoxide generated in the cyclization. This transesterification equilibrium between the two esters and alkoxides is driven toward the desired pathway as a consequence of the precipitation of the lithium salt **11** of the 5-(hydroxymethyl) oxazolidinone (Scheme 2). In the case of compound **3** derived from *O*-methyl *N*-phenyl carbamate, a very clean product (with purity assessed by an acceptable combustion analysis) is obtained simply by evaporative removal of the solvent following extractive aqueous workup, which conveniently removes the by-product methyl butyrate. When the *O*-benzyl *N*-phenyl carbamate is employed, **3** is obtained in high purity by taking the crude product derived from aqueous workup and triturating with ethyl acetate–hexane (1:1), which removes the benzyl butyrate. In other

examples, it is usually necessary to chromatograph the product to attain analytical purity. Table 1 lists examples of *N*-aryl-(5*R*)-hydroxymethyl-2-oxazolidinones prepared in high yield and purity from the respective benzyl carbamate.

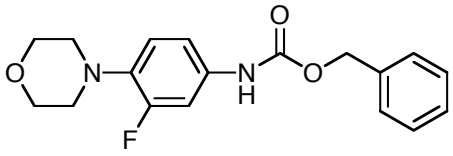
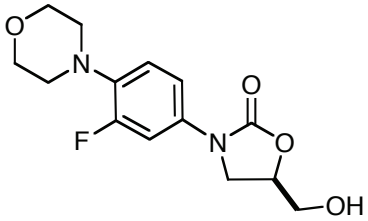
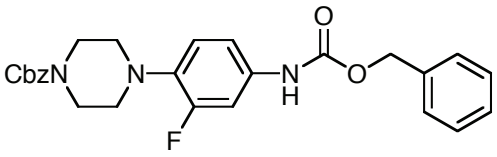
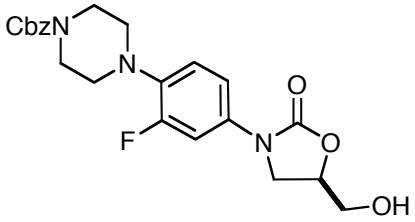
We have found in our studies that the use of the lithium counter ion in the base is essential for successful reaction with regiochemical control and allows cyclization to proceed under mild thermal conditions. In contrast, use of sodium (NaH, $NaN(SiMe_3)_2$) or potassium (KH, $KN(SiMe_3)_2$) bases require elevated temperatures, and results in poor yields of the desired product, and a mixture of several by-products, including the regioisomeric 4-hydroxymethy-2-oxazolidinone,[6] resulting from alternate processes. Thus, the lithium ion plays a very important role in the mechanism of this reaction.

**Scheme 2**



The preparation reported here represents a very general method[7] for the asymmetric synthesis of *N*-aryl-(5*R*)-hydroxymethyl-2-oxazolidinones with several distinct advantages over the previous method: (1) the oxazolidinone ring can be formed from readily available *N*-aryl carbamates, and avoids the hazards and limitations associated with the preparation and isolation of aryl isocyanates. This method significantly broadens the scope of aryl or heteroaryl substitution found in the oxazolidinone. The requisite carbamates are easily prepared from substituted anilines or heteroaryl amines and alkoxy carbonyl chlorides.[5] (2) The desired 5-(hydroxymethyl)oxazolidinone is directly obtained without need for a subsequent saponification step. (3) The reaction conditions are very mild, high-yielding, and provide the 5-(hydroxymethyl)oxazolidinone product in high enantiomeric excess, often with simple work up conditions.

Table 1.

| Carbamate | Product | Yield | Ref. |
|---|---|---|---|
|  |  | 83% | 5 |
|  |  | 85% | 5 |

1. This work was carried out in Medicinal Chemistry Research, Pharmacia, Kalamazoo MI 49001. Author's present address: Eli Lilly Corporation, Lilly Corporate Center, Drop Code 1523, Indianapolis, IN 46285.
2. Co-author's present address: Pfizer Global Research & Development, Groton, CT 06340.
3. Gregory, W. A.; Brittelli, D. R.; Wang, C. L. J.; Wounola, M. A.; McRipley, R. J.; Eustice D. C.; Eberly, V. S.; Bartholomew, P. T.; Slee, A. M.; Forbes, M. *J. Med. Chem.* **1989**, *32*, 1673.
4. Herweh, J. E.; Kauffman, W. J.; *Tetrahedron Lett*. **1971**, *12*, 809.
5. Brickner, S. J.; Hutchinson, D. K.; Barbachyn, M. R.; Manninen P. R.; Ulanowicz, D. A.; Garmon, S. A.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford. C. W.; Zurenko, G. E. *J. Med. Chem.* **1996**, *39*, 673.
6. Manninen, P. R.; Little, H. A.; Brickner, S. J.; Division of Organic Chemistry, American Chemical Society, 212th ACS National Meeting, Orlando, FL, August, 1996.
7. Citations that have used this method: Barbachyn, M. R.; Hutchinson, D. K.; Brickner, S. J.; Cynamon, M. H.; Kilburn, J. O.; Klemens, S. P.; Glickman, E. S.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford. C. W.; Zurenko, G. E. *J. Med. Chem.* **1996**, *39*, 680.; Genin, M. J.; Allwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, D. R.; Grega, K. C.; Hester, J. B.; Hutchinson, D. K.; Morris, J.; Reischer, R. J.; Ford. C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H. *J. Med. Chem.* **2000**, *43*, 953.; Tucker, J. A.; Allwine, D. A.; Grega, K. C.; Barbachyn, M. R.; Klock, J. L.; Adamski, J. L.; Brickner, S. J.; Hutchinson, D. K.; Ford. C. W.; Zurenko, G. E.; Conradi, R. A.; Burton, P. S.; Jensen, R. M. *J. Med. Chem.* **1998**, *41*, 3727.

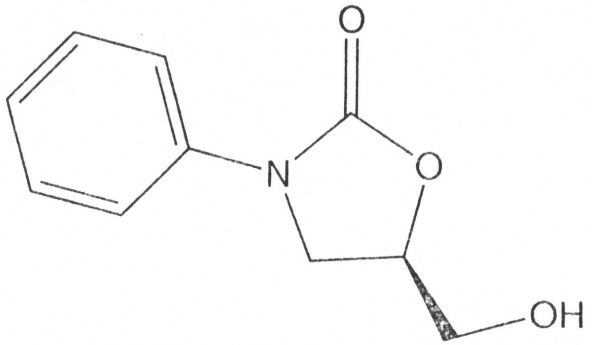
## Appendix
## Chemical Abstracts Nomenclature (Registry Number)

*N*-Phenyl-5*R*-hydroxymethyl-2-oxazolidinone: 2-Oxazolidinone; 5-(hydroxymethyl)-3-phenyl-, (5*R*)-; (87508-42-7)

*N*-Phenylcarbamic acid methyl ester: Carbamic acid, phenylmethyl ester; (2603-10-3)

n-Butyllithium: Lithium, butyl-; (109-72-8)

(*R*)-(–)-Glycidyl butyrate: Butanoic acid, (2R)-oxiranylmethyl ester; (60456-26-0).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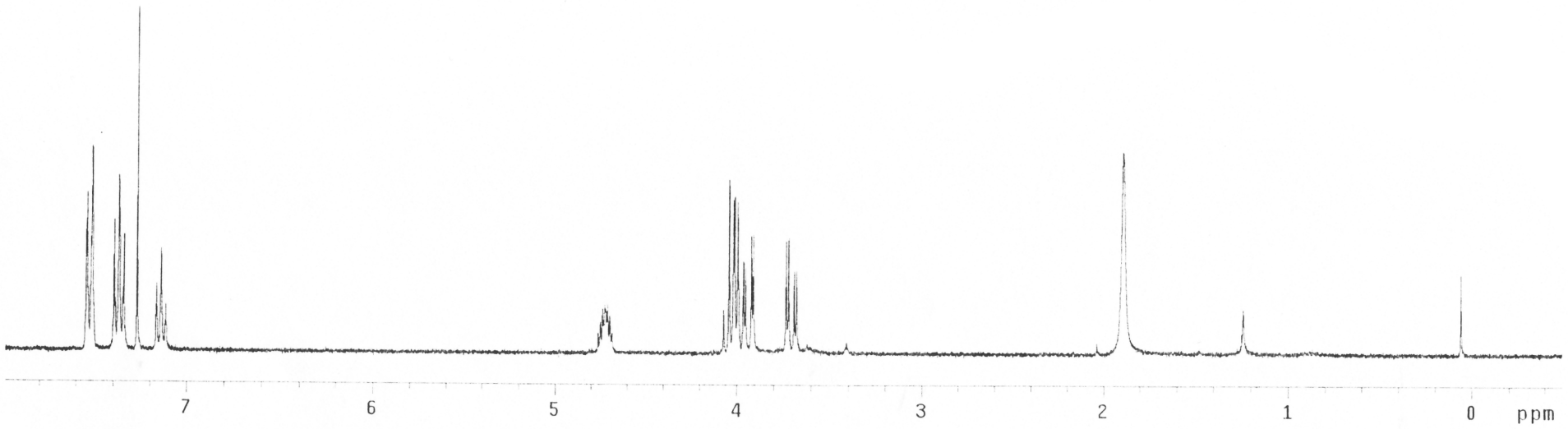
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