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Process for Developing 3β-[4-(*S*)-Arylacetylamino-4β-(2-(2-furyl)ethyl]azetidin-2-one: A Carbacephem Key Intermediate

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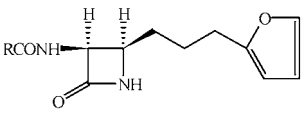
Abstract:

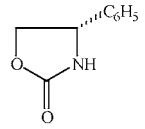
An optimized process for the stereospecific synthesis of carbacephem key intermediates 3β-[4-(*S*)-phenoxyacetylamino-4β-[2-(2-furyl)ethyl]azetidin-2-one (1) and 3β-[4-(*S*)-phenyl-acetylamino-4β-[2(2-furyl)ethyl)]azetidin-2-one] (2) is described. This report provides an efficient and cost-effective process for achieving a consistent yield and quality of intermediates 1 and 2 via Birch reduction employing a sodium/ammonia instead of lithium/ammonia system.

Introduction

The chiral auxiliary (*S*)-4-phenyl-2-oxazolidinone (**3**) has been used for the enantioselective synthesis of carbacephems employing (2 + 2) cycloaddition.[1,2] The first carbacephem antibiotic loracarbef (**4**) has been synthesized utilizing this methodology[2].



1, R = $C_6H_5OCH_2$–
2, R = $C_6H_5CH_2$–



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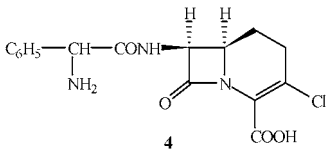

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Loracarbef

Literature survey reveals that Birch reduction using lithium/ammonia is the most efficient and commonly used method for cleavage of (*S*)-4-phenyl-2-oxazolidinone.[1] The other synthetic method reported for the above cleavage makes use of iodotrimethylsilane.[3] Use of lithium/ammonia for the synthesis of 3β-[4-(*S*)-phenoxyacetylamino-4β-[2-(2-furyl)-ethyl]azetidin-2-one (**1**) and 3β-[4-(*S*)-phenylacetylamino-4β-(2-(2-furyl)ethyl]azetidin-2-one (**2**) from benzyl-3β-[4-(*S*)-phenyl-oxazolidine-2-one-3yl]-4β-[2(2-furyl)ethenyl]-azetidine-2-one (**7**) affords inconsistent yield and quality of the desired products. In view of this, an optimized process is developed for the preparation of **1** and **2** from **7** with the use of sodium/ammonia in Birch reduction.

Results and Discussion

Intermediate **7** can be readily prepared by the cycloaddition of acid chloride of (*S*)-4-phenyl-oxazolidin-2-one-3-yl acetic acid (**5**) with 2-[3-(benzylimino)-1-propenyl]furan **6** in the presence of triethylamine[1,4] (Scheme 1). The product is crystallized from 2-propanol in >99% chromatographic purity and >99.5% diastereomeric excess. Hydrogenation of **7** with Pd/C in tetrahydrofuran gives benzyl-3β-(4-(*S*)-phenyloxazolidin-2-one-3-yl)-4β-[2-(2-furyl)ethyl]azetidin-2-one (**8**). Without isolating intermediate **8**, Birch reduction is carried out using sodium/ammonia followed by insitu acylation with phenoxyacetyl chloride giving intermediate **1** in an overall yield of 60% compared to the reported yield of 47% from intermediate **5** (Scheme 1).

Literature method for the preparation of **1** involves hydrogenation of **7** in dichloromethane and isolation of intermediate **8** using crystallization in 60% yield.[2] Birch reduction on **8** with lithium/ammonia for removal of chiral auxiliary, cleavage of the benzyl group from the β-lactam nitrogen, and acylation with phenoxy acetyl chloride gives desired amide **1** in 78% yield[2] (Scheme 1). However, our initial attempts to achieve the reported yield with lithium failed. Hence, we investigated the use of sodium for Birch reduction. It is found that reduction with sodium/ammonia drastically improves yield and quality. Further, the manufacturing cost of intermediate **1** is also reduced since lithium is much more expensive than sodium. This one pot synthesis involves hydrogenation of intermediate **7** in tetrahydrofuran without isolating intermediate **8** followed by sodium/ammonia reduction of **8** which affects the following chemical reactions. The oxazolidone auxiliary is removed to give ethyl benzene and CO_2, and the debenzylation of azetidinone nitrogen results in toluene. After the reaction, sodium or

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(1) (a) Evans, D. A.; Sjorgren, E. B. *Tetrahedron Lett*. **1985**, *26*, 3783. (b) Evans, D. A.; Sjorgren, E. B. *Tetrahedron Lett*. **1985**, *26*, 3787.

(2) Bodurow, C. C.; Boyer, B. D.; Brennan, J.; Bunnell, C. A.; Burks, J. E.; Carr, M. A.; Doecke, C. W.; Eckrich, T. M.; Fisher, J. W.; Gardner, J. P.; Graves, B. J.; Hines, P.; Hoying, R. C.; Jackson, B. G.; Kinnick, M. D.; Kochert, C. D.; Lewis, J. S.; Luke, W. D.; Moore, L. L.; Morin, J. M., Jr.; Nist, R. L.; Prather D. E.; Sparks, D. L.; Vladuchick, W. C. *Tetrahedron Lett*. **1989**, *30*, 2321.

(3) Fisher, J. W.; Dunigan, J. M.; Hatfield, L. D.; Hoying, R. C.; Ray, J. E.; Thomas, K. L. *Tetrahedron Lett*. **1993**, *34*, 4755.

(4) Evans, D. A.; Sjogren, E. A. (Harvard College) E.P. Patent 209,352, 1986.

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Scheme 1

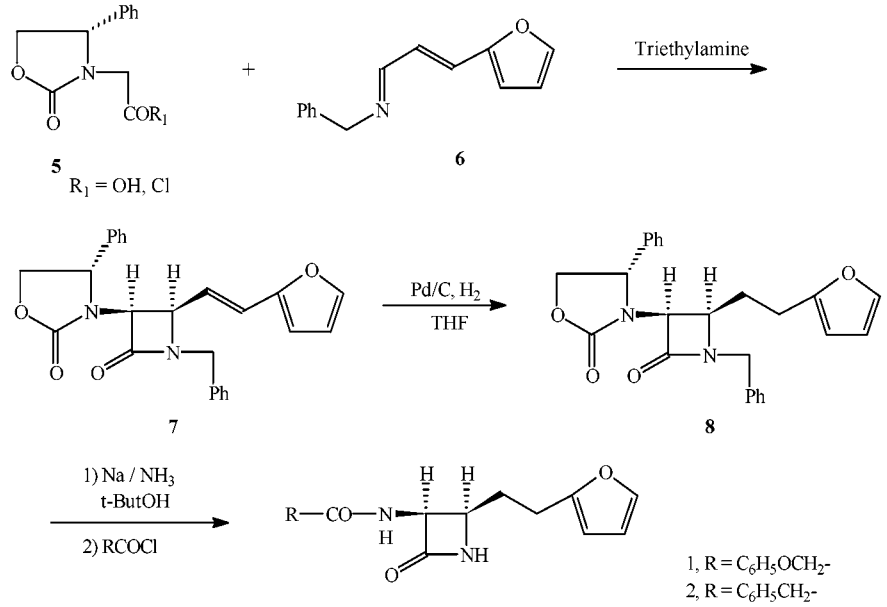

Table 1. **Synthesis of Intermediate 1 using Sodium and Lithium Metal Ammonia Reductions from 5**

reaction	yield (%)	chromatographic purity (% area by HPLC)
reduction with sodium/ammonia	~60	>98.5
reduction with lithium/ammonia	~47	95−97

sodamide is decomposed with ammonium chloride resulting in the dischargement of blue coloration of the reaction mixture.[5] Ammonia is evaporated from the reaction mixture, and the white slurry is dissolved in water followed by acidification with hydrochloric acid. In situ acylation with phenoxy acetyl chloride in the presence of $NaHCO_3$ gives the intermediate **1**.

We compared Birch reduction with lithium/ammonia and sodium/ammonia, and the following observations are made. (1) Sodium/ammonia is superior to lithium/ammonia for Birch reduction in terms of cost, yield, and quality (Table 1). (2) Experiments with lithium/ammonia results in thickening of the reaction mixture during removal of ammonia. Excess ammonia is trapped in the system due to this thickening, and excess acid is required for neutralization. This phenomenon is not observed in the case of sodium/ammonia reduction.

Thus, we found that the optimal reaction condition is the use of sodium with 12 to 15 times dilution volume of liquid ammonia of input **7**. Liquid ammonia less than 10 times by volume results in lower yield.

In conclusion, a scalable process using sodium for Birch reduction is described. This method is cost effective and affords the desired product in consistently good yield and quality.

(5) If required, add more ammonium chloride until blue colour discharges. Liquid ammonia should be in excess to dissolve sodium metal completely; add sodium metal in portions.

Experimental Section

General. Reagents are used as such without further purification. HPLC is performed with Water instrument using Kromasil C-18 (150 mm × 4.6 mm, 5μ) column.[6] ^{1}HNMR spectra are recorded using Bruker 300 MHz. The chemical shift data is reported as δ (ppm) downfield from tetramethylsilane which is used as an internal standard.

Preparation of 1-Benzyl-3β-[4-(*S*)-phenyloxazolidin-2-one-3-yl)-4β-[2-(2-furyl)ethenyl]azetidin-2-one (7).

To a solution of (*S*)-4-phenyloxazolidin-2-one-3-yl-acetic acid (100 g, 0.452 mol) in dichloromethane (800 mL) add *N*,*N*-dimethyl formamide (1.2 g) followed by thionyl chloride (80.7 g, 0.678 mol) at 20−25 °C. The reaction mixture is refluxed for 4 h and then distilled off the solvent and excess thionyl chloride under reduced pressure (150−200 mm of Hg). To the residue toluene (200 mL) is added and recovered the solvent under vacuum (~50 mm of Hg) to remove traces of thionyl chloride. The residue is dissolved in dichloromethane (1.1 L) and then cooled to −70 °C. A solution of triethylamine (100.5 g, 0.99 mol) in dichloromethane (100 mL) is added slowly by keeping the temperature at −70 to −65 °C and stirred for ~30 min at −75 to − 70 °C.

To the above reaction mixture was slowly added the Schiff base (**6**) solution [prepared from furyl acrolien (61 g, 0.50 mol) and benzylamine (53.5 g, 0.50 mol)] in dichloromethane (800 mL) at −75 to −65 °C in 15 to 20 min. The temperature of the mixture was allowed to raise to −10 °C in ~60 min, and the mixture was stirred for an additional 30 min at −10 to −5 °C. Water (1.5 L) is added, and we adjusted the pH to ~3.5 with 6 N HCl. The reaction mixture is allowed to settle and separate into layers. The organic layer is washed with 3% aqueous $NaHCO_3$ solution (600 mL) and then with

(6) HPLC analysis of intermediate **7** and **8**: mobile phase, methanol/phosphate buffer (pH 3.5) 60:40. Flow rate: 1.5 mL/min. UV detection at 210 nm. Retention time of **7** is ~9.0 min, and that of **8** is 11.30 min. HPLC analysis of intermediate **1**: mobile phase, acetonitrile/phosphate buffer (pH 2.5, KH_2PO_4 1.36 g/L; adjust pH with orthophosphoric acid). Flow rate: 2 mL/min (gradient acetonitrile: buffer 5:95 to 50:50 in 30 min and 75:25 in 45 min). UV detection at 210 nm. Retention time: 14.5 min.

5% aqueous sodium chloride solution (500 mL). The resulting organic solution is concentrated under vacuum to recover the solvent and added 2-propanol (1.0 L). The reaction mixture is cooled to 10 °C and stirred for 60 min at 5−10 °C. The solid is filtered, washed with cold 2-propanol (300 mL), and dried to yield 141 g (75.4%) of **7**. Chromatographic purity (by HPLC) > 99%. ^{1}H NMR ($CDCl_3$) δ 7.45−7.07 (m, 11, ArH), 6.36 (dd, 1H, J = 1.8, 3.3 Hz, OCH═C*H*), 6.25 (d, 1H, J = 16 Hz, N−CH−CH═C*H*), 6.20 (d, 1H, J = 3.3 Hz, O−C═C*H*), 5.75 (dd, 1H, J = 16, 8.9 Hz, N−CH−C*H*═CH), 4.90 (dd, 1H, J = 8.8, 7.4 Hz, OCH_2CH), 4.65 (t, 1H, J = 8.9 Hz, 1 × OCH_2CH), 4.60 (d, 1H, J = 15 Hz, 1H × $ArCH_2$), 4.50 (d, 1H, J = 4.8 Hz, C-3H), 4.20 (dd, 1H, J = 7.4, 8.8 Hz, 1 × OCH_2CH), 4.11 (dd, 1H, J = 4.8, 8.9 Hz, C−4H), 4.00 (d, 1H, J = 15 Hz, 1H × $ArCH_2$).

Preparation of 3*β*-(4-(*S*)-Phenoxyacetylamino-4*β*-[2-(2-furyl)ethyl]acetidin-2-one (1). To a solution of **7** (100 g, 0.24 mol) in tetrahydrofuran (800 mL), 2.5% Pd/carbon (50% wet, 30 g) is added under nitrogen at 20−25 °C and H_2 gas is bubbled for ∼3 h. The reaction is monitored by HPLC. After completion of reaction, the catalyst is filtered and washed with THF (200 mL) and the combined THF solution containing **8** is used as such after adding *tert*-butyl alcohol (100 mL).

Small pieces of sodium (45.5 g, 1.98 mol) are slowly added in ∼30 min to liquid ammonia (∼1.5 L) at −70 to −75 °C and allowed to stir for 30 min at the same temperature until the metal pieces dissolve. To this blue coloured solution, the above-mentioned THF solution of **8** is added in 30−40 min at −75 to −60 °C, and stirring is continued for additional 30 min at −65 to −60 °C. Ammonium chloride (100 g, 1.88 mol) is added in portions in 10−15 min. (Blue colour discharged.) The temperature was slowly raised from 30 to 35 °C to remove ammonia completely from the reaction mixture. To the resulting white slurry water (1.0 L) is added, and we adjusted the pH with concentrated HCl (∼100 mL) to ∼4.0 at 10−20 °C. Sodium bicarbonate (71 g, 0.84 mol) is added and stirred for 10−15 min. The reaction mixture is diluted with THF (400 mL), and we added a solution of phenoxy acetyl chloride (41 g, 0.24 mol) in THF (100 mL) in 30−40 min at 15−20 °C. Stirring is continued for 5−6 h at 25−30 °C and monitored by HPLC for reaction completion. The reaction mixture is allowed to settle and separate into layers. The organic layer is collected and evaporated under reduced pressure (60−100 mmHg). To the resulting white slurry isopropyl alcohol is added, and we recovered ∼100 mL solvent under vacuum (60−100 mmHg). The mixture was stirred for 30 min at room temperature and then cooled to 5 °C. After stirring for 3 h at 5−8 °C, the mixture was filtered and washed with cold IPA (200 mL). We air dried the wet material at 40−45 °C for 6 h to yield the titled compound **1** in 80% (60.3 g) yield.

Chromatographic purity (By HPLC): >98.5%; ^{1}H NMR (DMSO-d_6) 1.70 (m, 2H, N−CH−CH_2−CH_2), 2.57 (m, 2H, CH_2−CH_2−O−CH), 3.62 (m, 1H, *H*-4), 4.57 (s, 2H, O−CH_2), 5.10 (m, 1H, H-3), 6.05 (dd, 1H, O−C═C*H*), 6.35 (dd, 1H, O−CH═C*H*−), 6.94 (m, 3H, Ar*H*), 7.24 (m, 2H, Ar*H*), 7.50 (d, 1H, J = 3.1 Hz, O−C*H*═CH−), 8.43 (br, 1H, NH), 8.93 (d, 1H, CO−N*H*).

Preparation of 3*β*-[4-(*S*)-Phenylacetylamino-4*β*-(2-(2-furyl)ethyl]azetidin-2-one (2). The titled compound is prepared following the above method using phenyl acetyl chloride (37.4 g, 0.24 mol) instead of phenoxy acetyl chloride in 62% yield. Chromatographic purity (HPLC) >98.5%; ^{1}H NMR (DMSO-d_6) 1.64 (m, 2H, NH−CH−CH_2−CH_2), 2.50 (m, 2H, −CH−CH_2−CH_2−C−O), 3.48 (s, 2H, CH_2−Ph), 3.60 (m, H, *H*-4), 5.04 (m, 1H, H-3), 6.00 (dd, 1H, −O−C═C*H*), 6.35 (dd, 1H, O−CH═*CH*), 7.22 (m, 5H, Ar*H*), 7.50 (d, 1H, O−C*H*═CH), 8.41 (br 1H, N*H*), 8.87 (m, 1H, CO−N*H*).

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