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An Improved Method of Oxazolidinone Hydrolysis in the Asymmetric Synthesis of α-Alkylprolines

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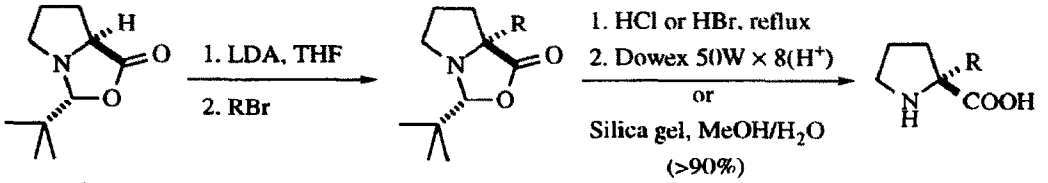
Abstract: An improvement in Seebach's method for the synthesis of α-alkylprolines is reported wherein the hydrolysis of the chiral oxazolidinone **2** is performed on a suspension of silica gel in MeOH/H_2O. Following hydrolysis, the pure α-alkylproline can be obtained by filtration thereby avoiding a tedious ion exchange purification.

The elegant method for the synthesis of α-substituted prolines developed by Seebach and coworkers[1,2] has been widely employed for the asymmetric synthesis of novel amino acids[3] and peptidomimetics.[4-9] This method involves the alkylation of the chiral lithium enolate of the oxazolidinone **1** to give the alkylated derivative **2** in high yields with essentially complete retention of stereochemistry (Scheme 1). Although the subsequent conversion of **2** to the desired α-alkylproline **3** is generally high yielding, the method described by Seebach, et. al.[1-3] uses a rigorous hydrolysis in concentrated acid followed by a very tedious ion exchange purification procedure.



1 **2** **3**

a: R = CH_3; **b**: R = $CH_2CH{=}CH_2$; **c**: R = $CH_2C_6H_5$; **d**: R = $CH_2CO_2CH_3$

Scheme 1.

We report here an alternative method of converting **2** to the corresponding α-alkylproline **3** that not only avoids the use of an ion exchange chromatographic step but also allows the desired product to be more easily purified. Our method involves a simple hydrolysis of **2** with a suspension of silica gel in MeOH/H_2O (Scheme 1).[10] Filtration of the reaction mixture followed by evaporation of the solvent gives a residue which is purified via a simple filtration process to afford pure α-alkylated prolines.[11] Alternatively, crystallization[12] of the residue can be done to provide analytically pure material. This

preparatory technique was found to be general for alkylated oxazolidinones (**2**) regardless of the conditions required to hydrolyze these compounds in acid.

The ease of hydrolysis of **2** by concentrated acid is dependent on the bulkiness of the α-alkyl substituent. Whereas **2a** can be hydrolyzed in 15% HBr at room temperature, **2c** requires refluxing 48% HBr to give complete hydrolysis.[2] When we applied our method to **2c** the solid material initially obtained appeared to be a stable hemiaminal of trimethylacetaldehyde and (*R*)-α-benzylproline.[13] Steam distillation of a solution containing this material effectively removed the aldehyde and provided pure **3c**.[14] In addition, the application of this method to **2d** gave a product in which the methyl ester functionality[15] was retained thereby illustrating the usefulness of this method in the preparation of an analog of aspartic acid in which the α and β carboxyl functions are chemically differentiated. In summary, application of this hydrolysis procedure should prove useful in the preparation of other α-alkylated proline derivatives prepared via Seebach's alkylation method.

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10. **General procedure:** Alkylated oxazolidinone **2** (13.4 mmol) was dissolved in MeOH/H_2O (6:1, 35 mL). Silica gel 200-400 mesh, 60Å (3.0 g, Aldrich) was added and the mixture was stirred overnight. The silica gel was filtered off and washed with MeOH. Removal of the solvent in vacuo gave a yellow residue which was dissolved in $CHCl_3$/MeOH (20:1). This solution was filtered through a 0.45 μ filter disc (Acrodisk® CR PTFE) to remove suspended silica gel. Solvent was evaporated in vacuo and the residue obtained was triturated in Et_2O. The α-alkylated proline product was isolated by filtration as a white solid in high yield.
11. Optical rotations of the α-alkylated prolines: **3a**: $[\alpha]_D$ -74.4° (*c* 1.2, MeOH) [Lit.[8] $[\alpha]_D$ -75° (*c* 2.0, MeOH)]; **3b**:$[\alpha]_D$ -50.0° (*c* 0.65, H_2O) [Lit.[8] $[\alpha]_D$ -47.1° (*c* 1.60, H_2O)]; **3c**: $[\alpha]_D$ -18.1° (*c* 0.27, H_2O) [Lit.[8] $[\alpha]_D$ -19.3° (*c* 2.7, H_2O)]; **3d**:$[\alpha]_D$ -106° (*c* 1.35, MeOH).
12. Crystallization of the deprotected product can be done by slow evaporation of the $CHCl_3$/MeOH solution at room temperature. Alternatively, the product can be crystallized from MeOH/Et_2O. The first crop of crystals generally contains 50-70% of the total material. The mother liquor from this crystallization contains the remaining product and usually yellow impurities. Vapor diffusion of the supernate against Et_2O in a closed environment often results in additional product crystallization.
13. The solid had the following properties: mp 321-325°C (d); $[\alpha]_D$ -9.92 (*c* 0.32, H_2O). ^1H NMR (300 MHz, D_2O) δ 7.21-7.45 (m, 5 H, Ph), 3.69,4.37 (s, 1 H), 3.43 (d, J = 14.7 Hz, 1 H), 3.01 (d, J = 14.7 Hz, 1 H), 3.32 (t, J = 7.5 Hz, 2 H), 2.41-2.47 (m, 1 H), 1.86-2.16 (m, 3H), 1.01-1.10 (m, 9 H).
14. Final conversion of the solid from **2c** into **3c** was accomplished by dissolving the material in hot water and removing up to half of the solution by steam distillation. The material obtained from drying this solution is pure **3c** as indicated by optical rotation and ^1H NMR.
15. ^1H NMR spectra of **3d** (300 MHz, CD_3OD) δ 3.68 (s, 3 H), 3.46-3.53 (m, 1 H), 3.22-3.32 (m, 1 H), 3.27 (d, J = 17.1 Hz, 1 H), 2.82 (d, J = 17.1 Hz, 1 H), 2.27-2.31 (m, 1 H), 1.89-2.01 (m, 3H).

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