Efficacious Preparation of Oppolzer’s Glycylsultam via the Delépine Reaction

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Abstract: A new preparative route to Oppolzer’s glycylsultam, the ‘NC’ component in the asymmetric [C+NC+CC] coupling reaction leading to functionalized pyrrolidines, is described. The synthesis features a novel application of the Delépine reaction, providing a safe, efficient, and environmentally benign route to this useful chiral reagent for pyrrolidine synthesis.

Key words: asymmetric synthesis, chiral auxiliaries, chiral pool, Delépine reaction, Oppolzer’s camphorsultam

We recently described a set of stereocomplementary multicomponent [C+NC+CC] coupling reactions that provide direct access to functionalized pyrrolidines (Scheme 1, ‘C’ can be a complex aldehyde). Since the pyrroline ring is an important structural motif found in many bioactive molecules, the asymmetric [C+NC+CC] coupling reaction is expected to find widespread application in synthesis. During the course of these studies, we required a supply of both the L- and D-versions of Oppolzer’s glycylsultam, which serves as the ‘NC’ component in the asymmetric [C+NC+CC] coupling reaction. Prior syntheses of this sultam, which features a novel application of the Delépine reaction, providing a safe, efficient, and environmentally benign process was clearly desirable.

It was in this context that we began investigating a new route to the glycylsultam based on the Delépine reaction. Though often overlooked, this classical transformation can provide an excellent route to primary amines on a preparative scale. The mechanism of this two-step process involves (a) nucleophilic displacement of an activated halide by the inexpensive and relatively nontoxic hexamethylenetetramine (HMTA), followed by (b) decomposition of the intermediate quaternary hexamethylenetetramine salt with ethanolic hydrogen chloride. This reaction sequence results in a mixture of ammonium salts and diethoxymethane, from which the desired primary amine can be obtained after neutralization. The first step of the process is usually performed in a chlorinated hydrocarbon solvent, from which the quaternary hexamethylenetetramine salt precipitates. A simplified one-pot Delépine procedure using ethanol as the solvent for both steps has also been reported.

We began by developing a more convenient and scalable synthesis of the known chloroacetylcamphorsultam (Scheme 2). Acid-catalyzed acylation of the parent L-camphorsultam with chloroacetic anhydride gave in high yield. This compound had previously been made via N-metalation of 1 with sodium hydride followed by low-temperature acylation with chloroacetyl chloride. Although there was a precedent for the Delépine displacement of activated chlorides, compound 2 did not react

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significantly with hexamethylenetetramine under a variety of reaction conditions. Conversion of chloride 2 into the more reactive bromoacetylsultam 3 by use of lithium bromide in tetrahydrofuran (Scheme 2) solved this reactivity dilemma. Bromide 3 could also be formed directly from 1 — albeit in lower yield18 — by acylation in the presence of a mixture of bromoacetyl bromide and catalytic bromoacetic acid (Scheme 2). Both of these routes to 3 were found to be more practical than the previously reported synthesis.

In conclusion, the Delépine reaction forms the basis for a convenient synthesis of Oppolzer’s glycylsultam 6. This short sequence proceeds in good overall yield (52% over 3 steps) on a multigram scale and does not require any chromatographic separations. The ready availability of 6 (as well as its enantiopure ent-6), made possible by this new procedure, will encourage use of the asymmetric [C+NC+CC] coupling technology.

Oven-dried glassware under Drierite drying tubes were used for nonaqueous reactions. Anhyd THF was distilled from Na/benzophenone ketyl under argon. Hexamethylenetetramine (HMTA) was recrystallized from 95% EtOH prior to use. All other commercial reagents were used as received. The progress of reactions was monitored by analytical TLC. Plates were visualized by charring with 5% anisaldehyde in EtOH–AcOH–H2SO4 (95:5:1). Melting points were uncorrected. Optical rotations were measured at ±0.1° using a Perkin-Elmer 241 polarimeter calibrated with a sucrose standard. 1H NMR spectra of samples in CDCl3 were recorded at 300 MHz and are referenced to TMS. 13C NMR spectra were recorded at 75 MHz and are referenced to CDCl3 (δ = 77.00). Data from COSY, NOESY, and HMQC 2D experiments were used for making the 1H and 13C NMR assignments for compounds 2, 3, and 6. MALDI-HRMS was carried out with an α-cyano-4-hydroxycinnamic acid matrix.

(3aS,6R,7aR)-1-(Chloroacetyl)-8,8-dimethylhexahydro-3a,6-methano-2,1-benzothiazole 2,2-Dioxide (2)

Sultam 1 (20.5 g, 95.0 mmol) was added in five portions over 5 min to a stirred soln of chloroacetic anhydride (technical grade, 19.9 g, 0.105 mol) and concd H2SO4 (0.254 mL, 4.57 mmol) at 80 °C. The temperature was then increased to 140 °C, and the mixture was stirred until TLC analysis showed the reaction to be completed (ca. 2.5 h). The mixture was cooled to r.t. and then transferred to an Erlenmeyer flask containing a mixture of CH3Cl (200 mL) and H2O (100 mL); it was then carefully neutralized with 0.712 M NaOH (200 mL, 0.142 mol) to pH 7.5. The aqueous layer was extracted further with CH2Cl2 (200 mL). The combined organic layers were dried (MgSO4), filtered through a pad of charcoal and Celite, and concentrated under reduced pressure; this yielded crude 2 as a tan solid, which was used for the next step without further purification. Yield: 25.8 g (93%); mp 115–120 °C (Lit.15 120–122 °C); [α]D23 0.44 (hexanes–EtOAc, 3:1).

A sample was recrystallized from i-Pr2O–CH2Cl2 for optical rotation and combustion analysis; mp 131–134 °C; [α]D23 –118.2, [α]D25 –140.7 (c 2.16, CHCl3).

1H NMR (300 MHz, CDCl3): δ = 4.50 (s, 2 H), 3.92 (dd, J = 7.5, 5.1 Hz, 1 H), 3.54 (d, J = 13.8 Hz, 1 H), 3.47 (d, J = 13.8 Hz, 1 H), 2.23–2.07 (m, 2 H), 1.99–1.84 (m, 3 H), 1.48–1.33 (m, 2 H), 1.15 (s, 3 H), 0.98 (s, 3 H).

13C NMR (75 MHz, CDCl3): δ = 164.6, 65.5, 52.6, 49.1, 47.9, 44.5, 42.3, 38.0, 32.7, 26.4, 20.7, 19.8.

Anal. Calcd for C12H18ClNO3S: C, 49.39; H, 6.22; N, 4.80. Found: C, 49.60; H, 6.19; N, 4.64.

(3aS,6R,7aR)-1-(Bromoacetyl)-8,8-dimethylhexahydro-3a,6-methano-2,1-benzothiazole 2,2-Dioxide (3) by Procedure A (from 2)

A soln of crude (chloroacetyl)sultam 2 (12.9 g, 44.1 mmol) in anhyd THF (20 mL) was added to a stirred soln of LiBr (38.1 g, 0.441 mol) in anhyd THF (67 mL) kept in a bath at 90–95 °C. The mixture was stirred at this temperature for 20 h, after which it was allowed to cool to r.t. and partitioned between H2O (125 mL) and CH3Cl (250 mL).
The aqueous layer was extracted further with CH₂Cl₂ (2 × 7.5 mL). The aqueous layer was extracted with CH₂Cl₂ (2 × 400 mL) to remove any neutral materials. The combined CH₂Cl₂ layers were washed with H₂O (2 × 400 mL), dried (MgSO₄), filtered, and concentrated, to give a slightly yellowish oil, which solidified upon standing overnight (22.1 g). ¹H NMR analysis of this crude mixture showed a 3:1 ratio of 3:1. Recrystallization from CH₂Cl₂–absolute EtOH gave pure 3 as a colorless solid; yield: 11.52 g (49%); mp 114–115 °C. The filtrate was concentrated to give a yellow oil, which consisted of a 3:1 mixture in a 2:3 ratio.

(3aS,6R,7aR)-1-(Aminoacyl)-8,8-dimethylhexahydro-3a,6-methano-2,1-benzothiazole 2,2-Dioxide (6)
A mixture of (bromoacetyl)sultam 3 (10.0 g, 29.8 mmol) and HMTA (4.61 g, 32.8 mmol) in CHCl₃ (reagent grade, 50 mL) was stirred at r.t. for 20 h, and was then concentrated by rotary evaporation to give the crude Delépine adduct 4. EtOH (95%, 25 mL) was added to this white solid. After stirring at r.t. for 6 h, the heterogeneous reaction mixture was cooled in an ice bath and filtered to remove NH₄Cl; the filter cake was washed with EtOH (95%, 200 mL). The filtrate and washings were concentrated, to give a slightly yellow-residue material that contained 5 mol% camphorsultam 1.³² Yield: 6.09 g (75%); mp 112–117 °C; [α]D₂₀ +115.0, [α]d₂⁰ +135.2 (c 2.00, abs EtOH); Rf = 0.51 (CH₂Cl₂–MeOH, 9:1).

¹H NMR (300 MHz, CDCl₃): δ = 3.90 (d, J = 18.9 Hz, 1 H), 3.88 (dd, J = 7.5, 5.1 Hz, 1 H), 3.76 (d, J = 18.0 Hz, 1 H), 3.50 (d, J = 13.8 Hz, 1 H), 3.43 (d, J = 13.8 Hz, 1 H), 2.20–2.04 (m, 2 H), 1.95–1.83 (m, 3 H), 1.52 (br s, 2 H), 1.46–1.33 (m, 2 H), 1.15 (s, 3 H), 0.98 (s, 3 H).

¹C NMR (75 MHz, CDCl₃): δ = 172.9, 165.1, 152.7, 49.1, 47.8, 45.4, 44.6, 38.2, 32.8, 26.4, 20.7, 19.8.


Supporting Information
This article is available online at http://www.thieme-connect.com/ejourнал/soc/synthesis.

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References
(3) The value of our [C+NC+CC] coupling reaction in a complex synthetic scenario (synthesis of the natural products cyanocycline A and bioxalomycin b) has already been demonstrated. See: Kaniskan, H. Ü.; Garner, P. J. Am. Chem. Soc. 2007, 129, 15460.
(5) Although Oppolzer did not actually report a synthesis of the parent glycytlsultam, we feel that it is appropriate to refer to it as ‘Oppolzer’s glycytlsultam’ for descriptive reasons.

The modest yield of this reaction was due to competitive addition of HBr to 1 that resulted in an unstable compound tentatively identified as 7 on the basis of diagnostic peaks in its ¹H NMR spectrum: ¹H NMR (300 MHz, CDCl₃): δ = 8.15 (br s, NH₄⁺), 5.28 (d, J = 14.2 Hz, 1 H), 3.94 (d, J = 14.2 Hz, 1 H). Attempts to suppress this side reaction were unsuccessful. In a separate control experiment, compound 7 was produced quantitatively by the action of HBr gas on 1.
dissolved in CDCl₃ (Scheme 3). Byproduct 7 reverts back to camphorsultam 1 upon exposure to water.

Scheme 3

(19) Monoalkylation of HMTA with the chiral bromide 3 breaks its $T_d$ molecular symmetry, resulting in AB quartets for both sets of diastereotopic HMTA methylene protons in 4. This Delépine salt was unstable, but these key HMTA signals could be observed in the $^1$H NMR spectrum: $^1$H NMR (300 MHz, CDCl₃): $\delta = 5.90$ (d, $J = 11.1$ Hz, 3 H), 5.82 (d, $J = 11.1$ Hz, 3 H), 4.76 (d, $J = 13.0$ Hz, 3 H), 4.54 (d, $J = 13.0$ Hz, 3 H).

(20) The proposed structure of 8 (Figure 1) was supported by its exact mass (HRMS: $m/z$ [M – H]$^+$ calcd for C₃₉H₅₉N₆O₉S₃: 851.3500; found: 851.2368) and the presence of an aminal carbon signal in its $^{13}$C NMR spectrum: $^{13}$C NMR (75 MHz, CDCl₃): $\delta = 73.1$.

Figure 1

(21) Solutions of the free glycylsultam 6 were found to be susceptible to nucleophile-induced deacylation to give back starting camphorsultam 1. The level of contamination ranged from 3 mol% on a 0.5-g scale to 5 mol% on a 10-g scale of bromosultam 3. However, a solid sample of 6 that had been kept at room temperature for more than one month showed minimal decomposition.