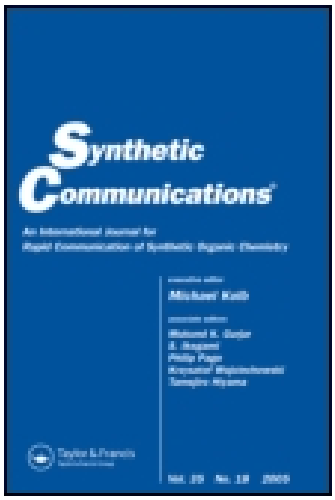

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A Practical Process for the Preparation of Azetidine-3-carboxylic Acid

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ABSTRACT

A practical and convenient synthesis of azetidine-3-carboxylic acid (**1**) that proceeded in 55% overall yield from commercially available diethylbis(hydroxymethyl)malonate (**3**) is reported. Azetidine ring-formation was achieved in high yield by cyclization of bistrifiate of the diol (**3**) and benzylamine. Decarboxylation under carefully pH-controlled conditions gave the mono acid azetidine that was hydrogenated to give the title compound.

Key Words: Amino acid; Azetidine.

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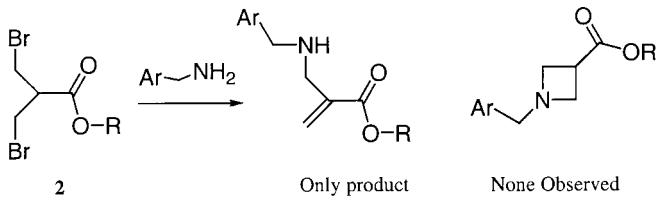
β-Amino acids are found in peptidic natural products possessing pharmacological properties and are commonly substituted for α-amino acids in peptidomimetics by medicinal chemists. Hydrolytic stability to peptidases over the α-amino acid derivatives gives these unnatural derivatives an advantage over the natural ones. As such, new and better syntheses of challenging β-amino acids are important to the synthetic chemistry community.[1] Azetidine-3-carboxylic acid (**1**), a β-amino acid used for the preparation of a variety of pharmaceutically active compounds, including CCR5 receptor modulators, procollagen C-proteinase inhibitors, tryptase inhibitors, IL-5 inhibitors, growth hormone secretagogues, and others.[2] However, only one literature report has appeared on the preparation of this compound.[3a] This approach was based on the condensation of epichlorohydrin with benzhydrylamine followed by a cyanide displacement. The productivity of this lone literature synthesis was not high and relied on the use of highly toxic starting materials and reagents that are not readily available. We therefore investigated alternate syntheses that would be practical for large scale preparation. Herein we report the results of our studies.

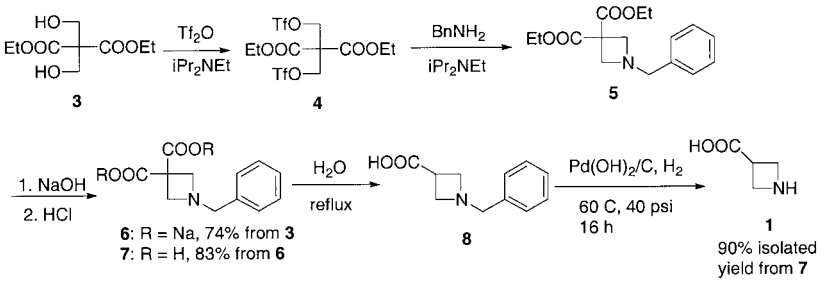
Different routes to give azetidine acid has been tried previously (Sch. 1). As reported by Anderson and Lok,[3a] double displacement of dibromide (**2**) with benzhydrylamine gave only monodisplacement and elimination products (Sch. 1); therefore, this approach was not a viable alternative route.

To prevent this elimination problem, we used a malonate ester during the azetidine ring-forming step. Simple hydrolysis/zthermal malonate decarboxylation would then generate the desired mono-acid. The required starting material, diethyl *bis*(hydroxymethyl)malonate (**3**), is commercially available or easily made from diethylmalonate.[4] Conversion to the crystalline *bis*-mesylate proceeded in high yield using Hunig's base and mesyl chloride (Sch. 2). Attempted azetidine formation using benzylamine or ammonia gave either starting material or complex mixtures. The *bis*-mesylate was stable under a variety of conditions



2 Only product None Observed

Scheme 1.



Scheme 2.

tested, so a more reactive leaving group was sought. Conversion of (**3**) to the *bis*-triflate (**4**) proceeded in high yield using triflic anhydride under acidic conditions (<5% oxetane detected).[5] Addition of Hunig's base, benzylamine, and heating to reflux induced cyclization to the azetidine ring.

Initially, the *bis*-triflate formation and cyclization were carried out as two separate steps using 1.1 equiv. of benzylamine. Simply doing the two steps in one-pot gave the desired product **5** but in about 20% lower yield compared to the stepwise approach. The intermediate *bis*-triflate was found to slowly decompose at room temperature, which makes the one-pot process much advantageous. Further investigation confirmed that polymerization was not a major competitive pathway to the desired intra-molecular cyclization in the reaction between *bis*-triflate and benzylamine. The one-pot process to the azetidine malonate was achieved in comparable yield to the two-step sequence by simply increasing the amount of benzylamine from 1.1 to 1.5 equiv. The logic in this change was that 4 equiv. of triflic acid released during the one-step process would be neutralized by 5 equiv. of Hunig's base; however, benzylamine can be competitively protonated by triflic acid thereby slowing down the desired alkylation reaction. Under the reaction temperature (70°C), the *bis*-triflate will decompose faster than the reaction takes place, resulting in the 20% lower yield. The azetidine malonate was not sufficiently crystalline to isolate; therefore, the malonate was hydrolyzed directly to the solid *bis*-sodium salt (**6**) using methanolic sodium hydroxide in 74% overall yield from (**3**). Subsequent methanol wash of the solid removed most organic impurities. Acidification with HCl gave the crystalline diacid **7** in 83% isolated yield from disodium salt **6**. The inorganic impurities and sodium chloride generated from this step remained in the aqueous mother liquor. The diacid **7** thus obtained is essentially inorganic free and showed a 98 wt% purity by our assay.

Initial studies on the decarboxylation of **7** showed that elimination to form an acrylate (Sch. 1, **2b**) would be a competing pathway. Acrylate formation was minimal when the benzyl group of **7** was still in place compared to the decarboxylation of the corresponding N-H compound. Also, the high water solubility of azetidine-3-carboxylic acid **1** could be more easily managed when a hydrogenation was the last step. Decarboxylation was carried out by heating a slurry of the isolated diacid **7** in water at reflux. After about 6 h, the reaction was completed and the solution was used directly in the subsequent debenzylation step. Debenzylation was best carried out using palladium hydroxide on carbon under 40 psi hydrogen pressure at 60°C overnight.[6] Isolation of the water-soluble azetidine-3-carboxylic acid was easily achieved by azeotropic distillation of the ethanol–water slurry until the water content was less than 2% and then simple filtration to isolate the crystalline **1**. HPLC assay of the isolated solid indicated high purity by weight (>96.8%).

In conclusion, an improved synthesis of the β-amino acid azetidine-3-carboxylic acid was reported. The synthesis was streamlined into a three isolation-procedure and was successfully demonstrated on large scale.

EXPERIMENTAL

General

All solvents and reagents were purchased from commercial sources and used without purification.

Preparation of 1-(phenylmethyl)-3,3-azetidinedicarboxylic acid diethyl ester (5). Into a 100 L flask under a nitrogen atmosphere was charged diethyl *bis*(hydroxymethyl)malonate **3** (3.5 kg, 15.89 mol), 52 L of anhydrous acetonitrile and the solution was cooled to −20°C. Triflic anhydride (5.61 L, 33.37 mol, 2.1 equiv.) was charged via addition funnel over 50 min while keeping temperature below −10°C. *N*,*N*-Diisopropylethylamine (5.14 kg, 39.72 mol, 2.5 equiv.) was then added slowly over 1.5 h to the reaction mixture via addition funnel while maintaining temperature of reaction mixture below −10°C. *Bis*-triflate **4** formed cleanly as checked by NMR. ^{1}H NMR ($CDCl_3$): δ 1.28 (6H, t, $J = 7.1$ Hz), 4.29 (4H, q, $J = 7.1$ Hz), 4.95 (4H, s). While the reaction mixture was still at −10°C, more *N*,*N*-diisopropylethylamine (5.14 kg, 39.72 mol, 2.5 equiv.) was added via an addition funnel over 10 min. Benzylamine (2.60 L, 23.84 mol, 1.5 equiv.) was then charged over 5 min, and the resulting mixture was heated to 70°C (reflux) and aged for 2 h. Completion of the cyclization reaction was confirmed by HPLC

(<2 A% *bis*-triflate **4**). The batch was cooled to room temperature, transferred to a workup vessel containing 52 L of toluene, and washed with 2×60 L of water. Quantitative assay of the toluene layer gave a yield of 86%. The pH of aqueous layer was 9–10 and yield loss in aqueous layers was less than 2%. The batch was concentrated and solvent switched to of methanol (total vol. 40 L) under reduced pressure. Amount of toluene at the end of solvent switch was determined to be 6 v% by GC. The methanol solution of diester **5** was directly used in the subsequent step. **5**, ^{1}H NMR ($CDCl_3$): δ 1.26 (6H, t, $J = 7.2$ Hz), 3.65 (2H, s), 3.66 (4H, s), 4.22 (2H, q, $J = 7.2$ Hz), 7.22–7.32 (5H, m). ^{13}C NMR ($CDCl_3$): δ 13.9, 49.4, 59.5, 61.7, 62.7, 127.1, 128.2, 128.4, 137.2, 169.7.

Preparation of disodium 1-(phenylmethyl)-3,3-azetidinedicarboxylate (6). To the methanol solution of diester **5** from above (quantitative assay showed 3.98 kg of **5**) at room temperature, was added 4.0 L 10 N NaOH in one portion, and the resulting mixture was heated to 50°C and aged over 45 min. The resultant slurry was cooled to room temperature and sampled for assay, which showed the hydrolysis was incomplete, so an additional 400 mL 10 N NaOH was added. The slurry was aged at 50°C for an additional 30 min, cooled to room temperature and filtered. The solid was then washed with 16 L of MeOH. The wet solid was transferred to a flask with 28 L methanol and stirred overnight at room temperature. The slurry was filtered and the wet cake washed with 2×12 L methanol. The product was dried in a vacuum oven at room temperature overnight giving 3.61 kg (approximately 90 wt% pure, 3.25 kg pure basis) disodium salt **6** as an off-white solid **6**, ^{1}H NMR (D_2O): δ 3.54 (4H, s), 3.62 (2H, s), 7.24–7.37 (5H, m). ^{13}C NMR (D_2O): δ 53.4, 60.8, 61.8, 127.5, 128.5, 128.8, 136.8, 178.9.

Preparation of 1-(phenylmethyl)-3,3-azetidinedicarboxylic acid (7). Solid disodium salt (**6**) (3.33 kg) and 12 L of water were stirred approximately 10 min until homogeneity was achieved. Five normal HCl (4.77 L) was then added via an addition funnel over 45 min without cooling, temperature rose +7°C to 30°C during the addition. The mixture became a slurry at the end of addition. The batch was then cooled with an ice/water bath, aged for 1 h and filtered. The solid was washed with 14 L of MeOH and left to dry under a nitrogen atmosphere overnight. A total of 2.12 kg solid (**7**) was obtained in 98 wt% and 83% yield (corrected for purity). **7**, ^{1}H NMR (D_2O): δ 4.37 (2H, s), 4.38 (4H, m), 7.38–7.48 (5H, m). ^{13}C NMR (D_2O): δ 49.0, 58.2, 58.7, 128.9, 129.3, 130.0, 130.1, 173.0, 173.1. HRMS calcd. for $C_{12}H_{14}NO_4$ (M+H): 236.0923. Found: 236.0917.

Preparation of 1-(phenylmethyl)-3-azetidinecarboxylic acid (8). To 2.12 kg (9.01 mol) of diacid (**7**) was charged 20 L of distilled water and

the suspension was heated to reflux (internal temperature 96°C). After 6 h, the reaction was complete as indicated by HPLC analysis (diacid <1A%). The reaction mixture was then cooled to room temperature and filtered via in-line filter to remove inorganic insolubles. The solution was used directly in the next step. **8**, ^{1}H NMR (D_2O): δ 3.42 (1H, m), 4.03–4.22 (4H, m), 4.28 (2H, s), 7.34–7.46 (5H, m). HRMS calcd. for $C_{11}H_{14}NO_2$ (M + H): 192.1018. Found: 192.1019.

Preparation of azetidine-3-carboxylic acid (1). To the monoacid **8** solution in water from the previous step was added ethanol (4.8 L and $Pd(OH)_2$/C (20 wt%, 212 g). The reaction mixture was hydrogenated at 60°C and 40 psi hydrogen for 16 h. After completion of the reaction, the mixture was filtered through Solka Floc, washing with 20 L of water. The combined filtrates and washes were concentrated under reduced pressure to a minimum volume of approximately 5 L and then ethanol was added slowly over 30 min, during which time a slurry resulted. The distillation was then continued until less than 2 wt% water remained, as determined by Karl Fisher titration. The slurry was then cooled to room temperature, filtered, and washed with 12 L of ethanol. Total filtrate losses were less than 2%. After drying overnight under nitrogen, 806.2 g of white solid was obtained in 96.8 wt% purity. **1**, ^{1}H NMR (D_2O): δ 3.63 (1H, m), 4.18–4.26 (4H, m). ^{13}C NMR (D_2O): δ 36.8, 49.2, 178.2.

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