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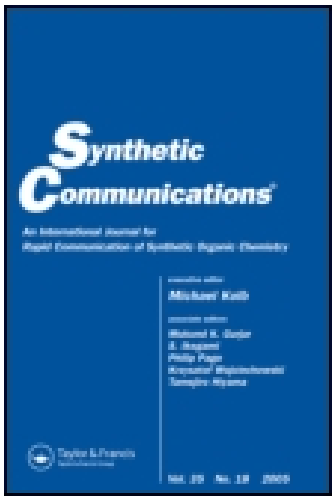

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An Efficient Procedure for Preparation of C- and N-Protected 1-Aminocyclobutane Carboxylic Acid

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An Efficient Procedure for Preparation of *C*- and *N*-Protected 1-Aminocyclobutane Carboxylic Acid

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ABSTRACT

An efficient method for the synthesis of differentially protected 1-aminocyclobutane carboxylic acid is described. Synthetically useful intermediates **7** and **8** were prepared from ethyl 1-bromocyclobutane-carboxylate in excellent yields (95% and 69%, respectively).

Key Words: 1-Aminocyclobutane carboxylic acid; Ethyl 1-bromocyclobutane carboxylate; Tertiary α-bromo esters.

1-Aminocyclobutane carboxylic acid is an amino acid that is attracting increasing interest due to its inherent biological activity and utility as a

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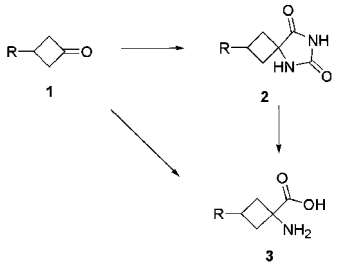
substitute for natural amino acids. As a monomer, this α-amino acid and several of its derivatives are known antagonists at excitatory amino acid receptors, particularly NMDA receptors in the central nervous system.[1–4] Incorporated into peptides, 1-aminocyclobutane carboxylic acid can induce unique conformational restrictions, thereby modulating their physical properties, biological activities, and bioavailabilities. For example, this α-amino acid has been used in studies examining the role of 1-aminocycloalkane carboxylic acids in a series of *L*-aspartyl dipeptide sweeteners,[5] as well as in studies of conformational properties of peptides.[6]

In support of a medicinal chemistry program, we required ready access to the 1-aminocycloalkane amino acid series: *c*-propane, *c*-butane, *c*-pentane, and *c*-hexane. While the 3-, 5-, and 6-membered ring amino acids are reliably obtained at reasonable cost from commercial sources, 1-aminocyclobutane carboxylic acid **4** and its protected derivatives **7** and **8** are not only expensive ($1700–$4200/g), but are also difficult to obtain. Due to these limitations, we found it necessary to prepare both the *C*- and *N*-protected forms of 1-aminocyclobutane carboxylic acid (**7** and **8**).

Several methods to prepare the 1-aminocyclobutane carboxylic acid scaffold have been reported.[1,3,7–10] The most common approaches to **3** include the Strecker synthesis, starting from cyclobutanone **1**, and the Bucherer-Bergs reaction of **1** via hydantoin **2** (Sch. 1).[1,7] However, these methods suffer from low overall yields or involve time-consuming steps. Woodard reported the synthesis of amino acid **4** beginning with *N*-formylglycine ethyl ester (Sch. 2),[8] but again in low overall yield (<30%). Hence, an alternative methodology for the preparation of these useful intermediates was explored. Herein we report an operationally simple and highly efficient procedure for the synthesis of 1-aminocyclobutane carboxylic acid in conveniently protected forms.

Ethyl 1-bromocyclobutane carboxylate **5** serves as the commercially available starting material (Sch. 3). Addition of this bromide to a suspension



Scheme 1.

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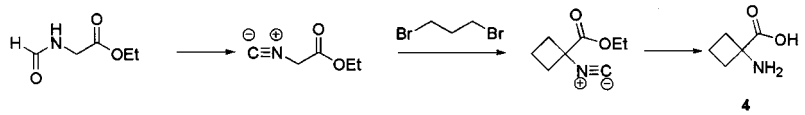
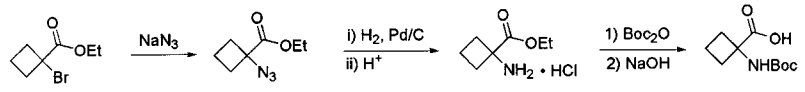


4

Scheme 2.

of sodium azide in DMSO, followed by warming to 40°C for 7 hours, afforded the desired azide adduct **6** in nearly quantitative yield. Although this reaction can be performed at ambient temperature, the reaction typically stalls at ~75% conversion after 24 hours. The presence of unreacted bromide **5**, however, does not affect subsequent steps (vida infra). Concern over the potential volatility of **6** dictated that a low-boiling solvent (diethyl ether) be used to extract the desired azide from an aqueous/DMSO mixture during work-up. Hydrogenation of the crude azide **6** in methanol with 10% Pd/C gave the corresponding amine, which was converted to the HCl salt **7** to facilitate isolation and handling of this low molecular weight compound. In this manner, the ethyl ester of 1-aminocyclobutane carboxylic acid (**7**) was obtained in two simple steps without purification in 95% overall yield. In practice, even if the initial azide displacement reaction does not proceed to completion, residual **5** is reduced to ethyl cyclobutane carboxylate upon hydrogenation, which evaporates during solvent removal. The Boc-protected amino acid **8** was obtained by reacting **7** with di-*tert*-butyl dicarbonate followed by conventional saponification.

Secondary α-bromo esters have been converted to the corresponding azides en route to preparing α-amino acids.[11–13] Although tertiary α-bromo esters have been reported in mechanistic studies to react through S_N2 displacement when treated with metal azides,[14,15] the product azides were never elaborated to quaternary α-amino acids. To our knowledge, this is the first reported conversion of a quaternary α-bromo ester into the corresponding amino acid via the azide. Since tertiary α-bromo esters can be accessed by bromination of the corresponding esters by known methods,[16,17] the methodology reported in this paper should be applicable to the synthesis of a wide range of quaternary α-amino acids.



5 **6** **7** **8**

Scheme 3.

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In conclusion, we have described a highly efficient procedure for the synthesis of both protected forms of 1-aminocyclobutane carboxylic acid. The operational simplicity, excellent yields, and cost effectiveness of this synthesis make this procedure very attractive.

EXPERIMENTAL

^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Varian VXR 400 spectrometer. The chemical shifts are reported in δ (ppm) using the δ 0.00 signal of Me_4Si (^{1}H) and the δ 49.15 signal of MeOH-d_4 (^{13}C) as internal standards. High-resolution MS data were obtained on a Bruker Daltonics FTICR/MS. HPLC data were obtained on a Waters 2695 LC using a 3 mm × 5 cm YMCPRO C-18 column and a 14–100% CH_3CN/H_2O gradient eluted over 4 minutes to record retention times.

Ethyl 1-azidocyclobutanecarboxylate (6). To a suspension of sodium azide (3.14 g, 48.3 mmol) in anhydrous DMSO (50 mL) was added ethyl 1-bromocyclobutanecarboxylate **5** (5.00 g, 24.2 mmol) dropwise under nitrogen. A modest temperature rise was observed. The reaction vessel was sealed and heated at 40°C for 7 hours. Upon cooling to room temperature, the reaction solution was partitioned between water (700 mL) and diethyl ether (200 mL). The organic layer was washed with half brine three times and then with saturated brine. The solution was dried over sodium sulfate, filtered, and carefully concentrated in vacuo to obtain an oil (4.00 g, 98% yield). ^{1}H NMR ($CDCl_3$): δ 1.34 (t, $J = 7.2$ Hz, 3H), 2.11–1.94 (m, 2H), 2.27 (m, 2H), 2.61 (m, 2H), 4.27 (q, $J = 7.2$ Hz, 2H). HPLC: t = 2.34 min.

Ethyl 1-aminocyclobutanecarboxylate hydrochloride (7). A solution of **6** (4.00 g, 23.6 mmol) in MeOH (150 mL) was purged with nitrogen prior to the addition of 10% Pd/C catalyst (840 mg). The mixture was again purged with nitrogen and then purged with hydrogen from a balloon. The mixture was stirred under hydrogen for 3 hours. Upon completion, the reaction mixture was filtered through a pad of celite. The filtrate was acidified by addition of HCl in ether (4M) and then concentrated in vacuo to provide an oil (4.14 g, 97% yield) that crystallized over time.[a] ^{1}H NMR ($CDCl_3$): δ 1.36 (t, $J = 7.2$ Hz, 3H), 2.18 (m, 1H), 2.34 (m, 1H), 2.81–2.64 (m, 4H), 4.32 (q, $J = 7.2$ Hz, 2H), 9.21 (bs, 3H). ^{13}C NMR (CD_3OD): δ 14.5, 15.5, 30.9, 58.6, 63.9, 172.0.

[a]Although methanol is the preferred solvent, some trans-esterification to the methyl ester can occur at this stage (~5–10%). However, performing the hydrogenation in ethanol provides **7** free of methyl ester.

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HRMS (ES): calc'd for $C_7H_{14}NO_2$: 144.1019, found: 144.1025. HPLC: t = 0.52 min.

Ethyl 1-[(*tert*-butoxycarbonyl)amino]cyclobutanecarboxylate. To a solution of **7** (1.53 g, 8.52 mmol) and di-*tert*-butyl dicarbonate (1.86 g, 8.52 mmol) in DMF (16 mL) was added triethylamine (1.03 g, 10.2 mmol) dropwise. After 2 hours, the reaction mixture was partitioned between water (160 mL) and diethyl ether (160 mL). The organic layer was washed with saturated copper sulfate, half brine, and saturated brine. The organic layer was then dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography to give the title compound (1.67 g, 81% yield) as a clear oil. ^{1}H NMR (CD_3OD): δ 1.26 (t, J = 6.8 Hz, 3H), 1.42 (s, 9H), 1.99 (m, 2H), 2.17 (m, 2H), 2.56 (m, 2H), 4.17 (q, J = 6.8 Hz, 2H). ^{13}C NMR (CD_3OD): δ 14.7, 16.3, 28.9, 32.2, 59.6, 62.2, 80.3, 157.3, 175.7. HRMS (ES): calc'd for $C_{12}H_{21}NO_4Na$: 266.1363, found: 266.1377. HPLC: t = 2.21 min.

1-[(*tert*-Butoxycarbonyl)amino]cyclobutanecarboxylic acid (8). Into a solution of ethyl 1-[(*tert*-butoxycarbonyl)amino]cyclobutanecarboxylate (1.67 g, 6.85 mmol) in THF (50 mL) was added 1N NaOH (10.3 mL). The reaction vessel was sealed and heated at 40°C overnight. Solvent was removed in vacuo. The residual aqueous layer was diluted with water and extracted three times with diethyl ether. The aqueous layer was then neutralized by addition of 1N HCl (10.3 mL) and saturated with sodium chloride. The product in the aqueous phase was extracted with ethyl acetate three times. The combined ethyl acetate extracts were dried over sodium sulfate, filtered, and concentrated to provide **8** (1.35 g, 91% yield) as a white solid. ^{1}H NMR (CD_3OD): δ 1.42 (s, 9H), 2.00 (m, 2H), 2.20 (m, 2H), 2.57 (m, 2H). ^{13}C NMR (CD_3OD): δ 16.3, 28.9, 32.3, 59.4, 80.4, 157.4, 177.7. HRMS (ES): calc'd for $C_{10}H_{18}NO_4$: 216.1230, found: 216.1245. HPLC: t = 1.54 min.

REFERENCES

1. Allan, R.D.; Hanrahan, J.R.; Hambley, T.W.; Johnston, G.A.R.; Mewett, K.N.; Mitrovic, A.D. Synthesis and activity of a potent *N*-methyl-D-aspartic acid agonist, *trans*-1-aminocyclobutane-1,3-dicarboxylic acid, and related phosphonic and carboxylic acids. J. Med. Chem. **1990**, *33*, 2905.
2. Gaoni, Y.; Chapman, A.G.; Parvez, N.; Pook, P.C.-K.; Jane, D.E.; Watkins, J.C. Synthesis, NMDA receptor antagonist activity, and anticonvulsant action of 1-aminocyclobutanecarboxylic acid derivatives. J. Med. Chem. **1994**, *37*, 4288.

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3. Hanrahan, J.R.; Taylor, P.C.; Errington, W. The synthesis of 3-phosphonocyclobutyl amino acid analogues of glutamic acid *via* diethyl 3-oxycyclobutylphosphonate, a versatile synthetic intermediate. J. Chem. Soc. Perkin Trans. 1. **1997**, 493.
4. Gershonov, E.; Granoth, R.; Tzehoval, E.; Gaoni, Y.; Fridkin, M. 1-Aminocyclobutanecarboxylic acid derivatives as novel structural elements in bioactive peptides: application to tuftsin analogs. J. Med. Chem. **1996**, *39*, 4833.
5. Tsang, J.W.; Schmied, B.; Nyfeler, R.; Goodman, M. Peptide sweeteners. 6. Structural studies on the C-terminal amino acid of L-aspartyl dipeptide sweeteners. J. Med. Chem. **1984**, *27*, 1663.
6. Gatos, M.; Formaggio, F.; Crisma, M.; Toniolo, C.; Bonora, G.M.; Benedetti, Z.; Di Blasio, B.; Iacovino, R.; Santini, A.; Saviano, M.; Kamphuis, J. Conformational characterization of the 1-aminocyclobutane-1-carboxylic acid residue in model peptides. J. Pept. Sci. **1997**, *3*, 110.
7. Srivastava, R.R.; Singhaus, R.R.; Kabalka, G.W. 1-Amino-3-[2-(1,7-dicarba-*closo*-dodecaboran(12)-1-yl)ethyl]cyclobutanecarboxylic acid: a potential BNCT agent. J. Org. Chem. **1997**, *62*, 4476.
8. Kalvin, D.; Ramalingam, K.; Woodard, R. A facile procedure for the preparation of alicyclic α-amino acids. Synth. Commun. **1985**, *15*, 267.
9. Park, K.-H.; Kurth, M.J. Diastereoselective synthesis of hydantoin- and isoxazoline-substituted dispirocyclobutanoids. J. Org. Chem. **2000**, *65*, 3520.
10. Gaoni, Y. Synthesis of aminocyclobutane mono- and dicarboxylic acids and derivatives thereof from (phenylsulfonyl)bicyclobutanes. Org. Prep. Proced. Int. **1995**, *27*, 185.
11. Corey, E.J.; Lee, D.-H.; Choi, S. An enantioselective synthesis of (*2S*,*3S*)- and (*2R*,*3S*)-3-hydroxyleucine. Tetrahedron Lett. **1992**, *33*, 6735.
12. Righi, G.; Rumboldt, G.; Bonini, C. A simple route to *syn* α-amino-β-hydroxy esters by C-2 regioselective opening of α,β-epoxy esters with metal halides. Tetrahedron **1995**, *51*, 13401.
13. Saito, S.; Yokoyama, H.; Ishikawa, T.; Niwa, N.; Moriwake, T. Hydrogen azide-amine systems as an azide nucleophile for substitutions of sulfonates, halides, and vicinal disulfonates. Tetrahedron Lett. **1991**, *32*, 663.
14. Edwards, O.E.; Grieco, C. S_N2 displacement at tertiary carbon. Can. J. Chem. **1974**, *52*, 3561.
15. Watanabe, M.; Okada, H.; Teshima, T.; Noguchi, M.; Kakehi, A. A facile and regio- and stereoselective preparation of bicyclic guanidines by iodocyclization of 3-(alk-2-enyl)-2-(substituted amino)-1-imidazolin-4-ones. Tetrahedron **1996**, *52*, 2827.

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16. Chavan, S.P.; Zubaidha, P.K.; Dhondge, V.D. A short and efficient synthesis of (−) mintlactone and (+) *iso*-mintlactone. Tetrahedron **1993**, *49*, 6429.
17. Greene, A.E.; Edgar, M.T. Synthesis of oxoisodehydroleucodin: a novel guaianolide from *Montanoa imbricata*. J. Org. Chem. **1989**, *54*, 1468.

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