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Efficient synthesis of *N*-benzyl-3-aminopyrrolidine-2,5-dione and *N*-benzyl-3-aminopyrrolidin-2-one

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Abstract—Reaction of *N-tert*-butyloxycarbonylasparagine (Boc-Asn) with 2 equiv of benzyl bromide in presence of cesium carbonate led to *N*-benzyl-3-Boc-amino-pyrrolidin-2,5-dione **1a** (*N*-benzyl-3-Boc-aminosuccinimide). Borane dimethylsulfide reduced 3-Boc-aminopyrrolidine-2,5-dione **1a** into 3-Boc-aminopyrrolidin-2-one **2a**. The same procedure could also be used to prepare derivatives **1** and **2** substituted on the aromatic ring.

Succinimides are an important class of heterocyclic compounds with numerous pharmacological applications in different fields such as inhibition of human leukocyte elastase, cathepsin G, and proteinase 3.[1] Furthermore, aminosuccinimides are useful synthetic intermediates. They can be reduced with lithium aluminum hydride or borane dimethylsulfide[2] or by catalytic hydrosilylation[3] to aminopyrrolidines, which have been incorporated into numerous biologically active compounds.[4] Sodium borohydride reduced 3-aminosuccinimide to 3-amino-5-hydroxypyrrolidine-2-one.[5] *N*-Benzyl-3-benzyloxycarbonyl-aminosuccinimide was prepared from *N*-benzyloxycarbonyl-asparagine (Z-Asn) in a three step procedure.[6]

The 3-aminopyrrolidin-2-one motive is present in compounds of biological interest such as antithrombotics[7] and farnesyltransferase inhibitors.[8] *N*-Benzyl-3-Boc-aminopyrrolidin-2-one derivatives are obtained by cyclization of 2-Boc-amino-4-amino-butanoic acid followed by N-alkylation of the lactam.[9] Another classical approach relies on the cyclization of *S*-dimethylsulfonium derivative of methionine amides.[10]

All syntheses of these two series of compounds imply multistep procedures and/or expensive reagents and in most cases these methods are not appropriate on a larger scale. We wish to present a fast and cheap access to these compounds. The approach relies on a one step efficient synthesis of *N*-benzyl-3-Boc-aminopyrrolidin-2,5-dione **1a**, which only differs from the previously described product by the protecting group,[6] from Boc-Asn and further its reduction to *N*-benzyl-3-aminopyrrolidin-2-one **2a**. We have previously described several syntheses of cyclic imides.[11] These procedures are based on reaction of primary amines with diacids in presence of *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCCl) and of *N*-hydroxybenzotriazole (HOBt). EDCCl is a rather expensive coupling agent.

As Boc-Asn benzyl ester is routinely prepared by alkylation of Boc-Asn cesium salt with benzyl bromide,[12] we observed the formation of noticeable amounts (5–10%) of **1a** as side product. The conditions were optimized in order to drive the reaction toward this compound **1a**. When the reaction was conducted with 1.5 equiv of Cs_2CO_3 and 2 equiv of benzyl bromide compound **1a** was the only formed product (Scheme 1).[13] This cyclization performed at room temperature worked also with substituted benzyl bromides (Table 1) and with Z-Asn. Alternative basic conditions were tried without success.[14]

With regard to the mechanism of formation of **1a**, although N-alkylation of the nitrogen imide by electrophiles is well documented,[6] we observed under the same

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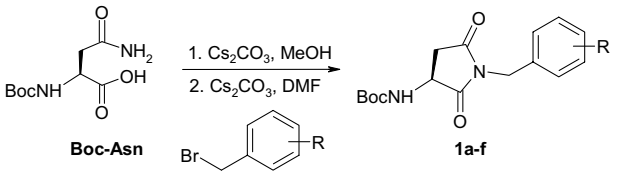


Scheme 1.

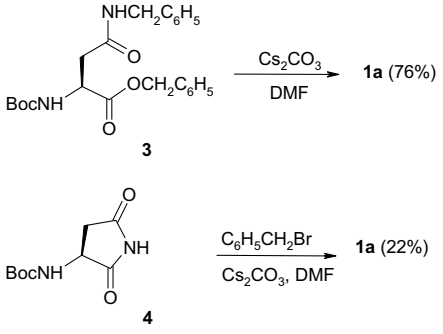
Table 1. Aminosuccinimide derivatives **1a**–**f** produced via Scheme 1

Entry	Derivative	R	Yield (%)
1	**1a**	H	70
2	**1b**	3-Chloro	71
3	**1c**	4-Fluoro	38
4	**1d**	4-Cyano	55
5	**1e**	4-Methoxycarbonyl	67
6	**1f**	4-Nitro	13

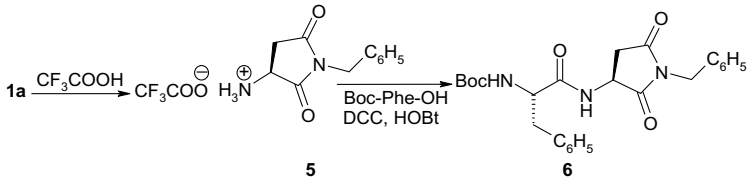
reaction conditions, that cyclization of **3** took place with better outputs than alkylation of **4** (Scheme 2). This is an argument in favor of the amide N-alkylation of Boc-Asn benzyl ester prior to cyclization.

In order to establish its enantiomeric purity, **1a** was coupled with *N*-Boc-phenylalanine (Boc-Phe) and the purity of the dipeptide **6** was determined by ^{1}H NMR and HPLC (Scheme 3).[15] The formation of a single diastereoisomer was observed (d.r.>98:2).

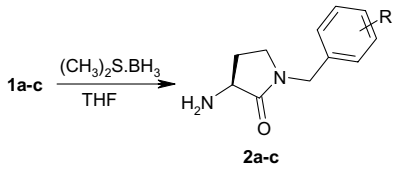
In contrast to a previous report,[2] the reduction of **1a**–**c** with borane hydride–dimethylsulfide complex selectively afforded the 3-aminopyrrolidin-2-one **2a**–**c** (Scheme 4).[16] The less hindered carbonyl group is the only one to be reduced in these conditions. Such a selectivity may be



Scheme 2.



Scheme 3.



Scheme 4.

Table 2. Aminopyrrolidinone derivatives **2a**–**c** produced via Scheme 4

Entry	Derivative	R	Yield (%)
1	**2a**	H	40
2	**2b**	3-Chloro	54
3	**2c**	4-Fluoro	58

explained by the presence of the Boc-amino group (Table 2).

As expected, formation of aminopyrrolidinone **2** from pyrrolidinedione **1** is limited to derivatives insensitive to the reducing agent. Thus, reduction of **1d** led to a complex mixture.

The procedure presented in this paper offers a short and efficient route to several chiral heterocycles useful for drug synthesis. For example, the presented approach provides a shorter route to **2c** as part of farnesyltransferase inhibitors.[8a] Purification by recrystallization from isopropanol of the aminosuccinimide **1** makes this approach suitable for a large scale synthesis.

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13. To 300 mL of a 1:2 hydromethanolic solution of Boc-Asn (13.92 g, 60 mmol), was added cesium carbonate (34.2 g, 105 mmol) and the mixture was evaporated to dryness. Anhydrous dimethylformamide (DMF 150 mL) was added and the solid was brought in suspension by stirring. DMF was removed under vacuum. Anhydrous DMF (150 mL) was added once more, the suspension was cooled at 15 °C and benzyl bromide (14.27 mL, 120 mmol) was added dropwise. The mixture was further stirred for 6 h at room temperature after completion of the addition. After evaporation of DMF under vacuum, the residue was taken up in ethyl acetate (100 mL) and washed in water (2×75 mL). The organic layer was dried and evaporated. The product was purified by crystallization from isopropanol (12 g, 70%). Compound **1a**: colorless crystals: mp 144 °C. ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.36 (s, 9H), 2.88 (dd, 1H, $J_1 = 17.0$ Hz, $J_2 = 4.5$ Hz), 3.94 (dd, 1H, $J_1 = 17.0$ Hz, $J_2 = 8.2$ Hz), 4.25 (m, 1H), 4.62 (d, 1H, $J = 14.5$ Hz), 4.69 (d, 1H, $J = 14.5$ Hz), 5.12 (s, 1H), 7.28 (m, 5H). ^{13}C NMR (270 MHz, $CDCl_3$) δ (ppm): 28.5 (3C, CH_3), 36.3 (CH_2), 43.7 (CH), 48.3 (NCH_2), 81.1 (C quat.), 128.1–129.3 (C Ar), 155.5, 174.1, 175.9 (C=O). Compound **1b**: colorless crystals: mp 122–123 °C. ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.50 (s, 9H), 2.94 (dd, 1H, $J_1 = 17.8$ Hz, $J_2 = 4.7$ Hz), 3.12 (dd, 1H, $J_1 = 17.8$ Hz, $J_2 = 9.1$ Hz), 4.20 (m, 1H), 4.65 (d, 1H, $J = 14.4$ Hz), 4.70 (d, 1H, $J = 14.4$ Hz), 5.30 (s, 1H), 7.25 (m, 3H), 7.40 (m, 1H). ^{13}C NMR (270 MHz, $CDCl_3$) δ (ppm): 27.9 (3C, CH_3), 35.4 (CH_2), 41.6 (CH), 49.8 (NCH_2), 80.7 (C quat.), 128.2–129.8 (4C Ar), 134.1, 136.8 (quat. Ar), 154.7, 173.6, 175.3 (C=O). Compound **1c**: colorless crystals: mp 130 °C. ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.42 (s, 9H), 2.95 (dd, 1H, $J_1 = 17.5$ Hz, $J_2 = 4.7$ Hz), 3.14 (dd, 1H, $J_1 = 17.5$ Hz, $J_2 = 9.1$ Hz), 4.12 (m, 1H), 4.71 (s, 2H), 5.14 (s, 1H), 7.33 (d, 2H, $J = 8.0$ Hz), 8.11 (d, 2H, $J = 8.0$ Hz). Compound **1d**: colorless crystals: mp 188–192 °C. ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.50 (s, 9H), 2.93 (dd, 1H, $J_1 = 17.8$ Hz, $J_2 = 4.7$ Hz), 3.15 (dd, 1H, $J_1 = 17.8$ Hz, $J_2 = 9.2$ Hz), 4.15 (dd, 1H, $J_1 = 14.9$ Hz, $J_2 = 6.1$ Hz), 4.70 (d, 1H, $J = 15.7$ Hz), 4.77 (d, 1H, $J = 15.7$ Hz), 5.25 (s, 1H), 7.53 (d, 2H, $J = 8.0$ Hz), 7.62 (d, 2H, $J = 8.0$ Hz). Compound **1e**: colorless crystals: mp 157–159 °C. ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.48 (s, 9H), 2.95 (dd, 1H, $J_1 = 17.8$ Hz, $J_2 = 4.3$ Hz), 3.11 (dd, 1H, $J_1 = 17.8$ Hz, $J_2 = 9.1$ Hz), 4.14 (m, 1H), 4.71 (d, 1H, $J = 14.5$ Hz), 4.77 (d, 1H, $J = 14.5$ Hz), 5.12 (br s, 1H), 7.20 (d, 2H, $J = 7.9$ Hz), 7.95 (d, 2H, $J = 7.9$ Hz). Compound **1f**: colorless crystals: mp 180–183 °C. ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.33 (s, 9H), 2.95 (dd, 1H, $J_1 = 17.5$ Hz, $J_2 = 4.5$ Hz), 3.14 (dd, 1H, $J_1 = 17.5$ Hz), 4.16 (m, 1H), 4.62 (s, 2H), 5.11 (s, 1H), 6.93 (d, 2H, $J = 8.0$ Hz), 7.32 (d, 2H, $J = 8.0$ Hz). To avoid the preparation of cesium carbonate salt in hydromethanolic solution, we developed an alternative procedure: cesium carbonate (0.853 g, 2.63 mmol) was added to Boc-Asn (0.205 g, 0.88 mmol) in 5 mL of DMF. The mixture was stirred for 2 days at room temperature to complete the salt formation. Then benzyl bromide (42 μL, 2.2 mmol) was added. After stirring for 6 h at room temperature, the same treatment was applied. 1-Benzyl-3-Bocaminosuccinimide **1a**, was isolated in a similar yield.
14. Other unsuccessful experimented basic conditions: triethylamine, *N*,*N*-dimethyl-4-aminopyridine, calcium carbonate in DMF or CH_3CN.
15. After elimination of the Boc group in **1a**, the acylation of 1-benzyl-3-aminosuccinimide with BocPhe was achieved with dicyclohexylcarbodiimide (DCC) and hydroxybenzotriazole (HOBt) as coupling reagents in AcOEt. HPLC was performed on a Chiracel OJ (25 cm×4.6 mm) column using a photodiode array detector (Waters 994) and a polarimetric detector (Jasco OR 990). MeOH (100%) was used as mobile phase and the flow rate 1 mL min^{-1}.
16. To a cold (0 °C) solution of **1a** (5.7 g, 18.75 mmol) in 70 mL THF was added 28 mL borane dimethylsulfide 2 M in THF (56 mmol). After 1 h stirring at room temperature the mixture is refluxed for 6 h. After cooling to 0 °C, NaF (9.58 g, 228 mmol) in water (75 mL) and concentrated HCl was carefully added. The mixture was refluxed for 2 h. After cooling, the solution was neutralized with 4 N NaOH. The mixture was then extracted with CH_2Cl_2 (3×75 mL). The crude 3-aminopyrrolidinone was purified by column chromatography (CH_2Cl_2/MeOH 100:5 +NEt_3 0.1%). Thick oil, ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.62 (m, 1H), 2.33 (m, 1H), 3.11 (dd, 2H, $J_1 = 9$ Hz, $J_2 = 4.5$ Hz), 3.55 (dd, 1H, $J_1 = 9.0$ Hz, $J_2 = 9.4$ Hz), 4.37 (s, 2H), 7.15–7.37 (m, 5H). The trifluoroacetate of **2a** was prepared: mp 95–97 °C. ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 2.12 (m, 1H), 2.40 (m, 1H), 3.25 (m, 2H), 4.05 (t, 1H, $J = 9$ Hz), 4.31 (d, 1H $J = 15$ Hz), 4.38 (d, 1H $J = 15$ Hz), 7.20–7.35 (m, 5H), 8.4 (br s, 3H).