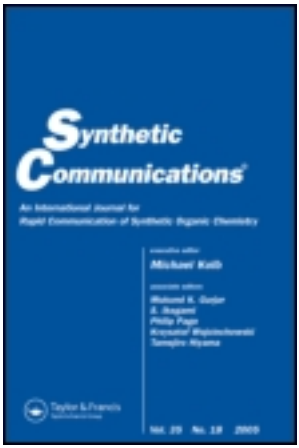

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A Convenient Synthesis of N-Boc-Protected α-Aminonitriles from α-Amidosulfones

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A Convenient Synthesis of *N*-Boc-Protected α-Aminonitriles from α-Amidosulfones

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ABSTRACT

Synthesis of *N*-Boc-protected α-aminonitriles starting from *N*-Boc-protected α-aminosulfones is described. Treatment of the sulfone with two equivalents of potassium cyanide in 2-propanol or dichloromethane-H_2O under phase transfer condition affords crystalline *N*-Boc-protected α-aminonitriles in good yield. Hydrolysis of the aminonitriles provides a convenient access to racemic α-amino acids.

Key Words: Amino acids; Imines; Nucleophilic additions; Phase-transfer catalysis; Strecker.

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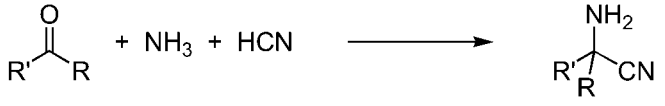
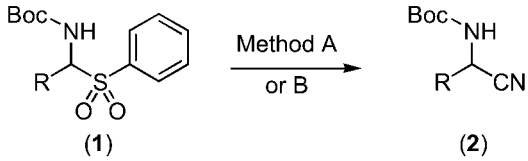
Alpha-amino acid, an important building block for peptides, can be obtained from hydrolysis of α-aminonitriles prepared from the Strecker reaction. Classical Strecker reaction via treatment of an aldehyde or ketone, NH_3, and a CN^- source (Sch. 1) suffers drawbacks from its reversible nature.[1] Many variants of the Strecker reaction exist, e.g., use of amines or $(NH_4)_2CO_3$ for NH_3 or bisulfite adduct for free aldehydes.[2] However, these methods are not yet sufficient in terms of efficiency or generality. Furthermore, when amines other than NH_3 are used, a suitable deprotection must follow that may not be straightforward. We propose that addition of CN^- to *N*-acylimines should provide an efficient entry to *N*-acyl-protected α-aminonitriles. Subsequent hydrolysis should give a direct synthesis of α-amino acids. *N*-protected α-aminonitriles are also starting materials for many heterocyclic and biologically active compounds.[3,4] They are generally obtained from α-amino acids via α-aminoamides by dehydration with reagents such as TsCl[3a] or MsCl,[4b] TFAA,[5] cyanuric chloride,[3b,6] oxalyl chloride,[4c,4d,7] or dialkyltin oxide.[8] In 1990, Katritzky reported an *N*-acyl α-aminonitriles synthesis from α-amidobenzotriazoles and had extended this method to peptide synthesis.[9] More recently, α-amidosulfones **1** have attracted attention as a versatile acylimine equivalent. These stable solids are easily prepared from aldehydes, amides or carbamates, and sodium benzenesulfinate or sodium *p*-toluenesulfinate.[10,11] They react with nucleophiles such as lithium enolates,[12,13] RMgX,[14] and ZnR_2,[15–17] among others.[18–21] There has been a report on the synthesis of *N*-protected α-amino acids via $KMnO_4$-oxidation of the sodium nitronate-**1** adduct.[22] We reasoned that CN^- should be a sufficiently strong base to cause elimination of the sulfinate ion from **1** to provide acylimines, which can then undergo irreversible cyanide addition to provide *N*-acyl α-aminonitriles. To our knowledge, there is no other literature report on the synthesis of α-aminonitriles by this approach.

Initially, the *N*-Boc-α-amidosulfone **1a** (R = Ph) derived from benzaldehyde was treated with potassium cyanide under a variety of conditions (Sch. 2). In lower alcohols such as methanol and ethanol, although the reaction was fast, a significant amount of by-product derived from alkoxide substitution was observed. The reaction was significantly slower in dipolar aprotic solvents including *N*,*N*-dimethylformamide (DMF) and MeCN. The



Scheme 1.



(1) (2)

Method A: 2 eq KCN/^{i}PrOH, rt, 3h
Method B: 2 eq KCN/10 % mol $Bu_4N^+HSO_4^-$ in CH_2Cl_2:H_2O, rt, 3 h

Scheme 2.

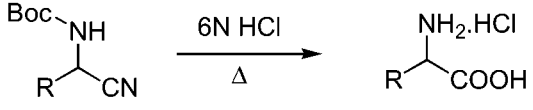
best yield (66%) was obtained when 2-propanol was used as a solvent (method A). At least two equivalents of KCN were required to obtain good yields. This suggested that one equivalent of KCN may act as a base to eliminate the phenylsulfinate ion to form the *N*-Boc imine in situ, which was then further attacked by the second equivalent of the cyanide. Attempts to reduce the amounts of KCN to one equivalent by addition of another external base were marginally successful. K_2CO_3 was found to be an acceptable external base, while organic bases like triethylamine were ineffective. However, the use of two equivalents of KCN provided a better yield, hence is the preferred method. The reaction could also be conveniently carried out under phase transfer condition in a dichloromethane-water mixture (method B) to give the same product in slightly better yield (73%). Both tetrabutylammonium hydrogensulfate and benzyltriethylammonium chloride were effective phase transfer catalysts. In both methods, the reaction rates were considerably faster (requires less than 3 hr) than cyanide addition to Katritzky's amidobenzotriazole (requires more than 10 hr to several days),[9] presumably due to the better leaving ability of the sulfinate compared to that of benzotriazolate ions. The opportunity of using a chiral phase transfer catalyst to induce asymmetric cyanation was also explored. Unfortunately, the aminonitrile **2a** (R = Ph) obtained from the reaction of **1** (R = Ph) and potassium cyanide in the presence of *N*-benzylcinchonidinium chloride (10 mol %) as catalyst was found to be racemic.

Both reaction conditions were tested with *N*-Boc-α-aminosulfones **1** derived from a variety of aromatic and aliphatic aldehydes. We were pleased to find that the reaction is compatible with a wide variety of functional groups. In most cases the stable crystalline *N*-Boc-α-aminonitriles **2** were obtained after simple aqueous work-up followed by column chromatography. All products revealed a characteristic infrared (IR) absorption around 2200 cm^{-1}, a pair of ^{1}H resonance between 4 and 6 ppm (C_αH and NH), and a ^{13}C resonance of C≡N between 116 and 118 ppm in addition to all

expected resonances. Both aromatic and aliphatic substrates are well tolerated. The electronic nature and position of substituents on the aromatic ring appeared to have little effect on the yield (ranging from 36% to 86%) and reaction rate, except for those containing strong electron-withdrawing groups such as cyano (**1h**) and nitro (**1e–g**), where the yields were only modest. In these cases, the reaction under phase-transfer condition provided somewhat cleaner reaction, hence better yields (ranging from 36% to 55%). Heteroaromatic substrates such as 2-furyl (**1q**) and 2-thienyl (**1r**) also gave satisfactory yields (>80%). However, only complex mixtures were obtained with 2- and 4-pyridyl substrates under both conditions. It was reasoned that nucleophilic addition may also take place on the pyridyl ring. For aliphatic substrates, the degree of branching is well tolerated (R = ^{i}Pr, ^{t}Bu, ^{i}Bu, and cyclohexyl). Equally good results were obtained with those easily tautomerizable substrates bearing α-unbranched alkyl groups, especially when R = $PhCH_2$ (**1z**).

The *N*-Boc-α-aminonitriles **2** may be readily converted to the corresponding amino acids by refluxing with aqueous HCl according to known procedures.[23] The amino acid hydrochlorides were obtained simply by evaporation of the solvent and washing or recrystallizing the residue with water. Some representative examples are summarized in Sch. 3.

In conclusion, a very simple yet effective method for the synthesis of *N*-Boc-α-aminonitriles based on Strecker-type reaction of *N*-Boc-α-aminosulfones with potassium cyanide is developed. Acid hydrolysis of the *N*-Boc-α-aminonitriles provides a convenient preparation of racemic α-amino acids. The procedure compares very well in terms of yield and efficiency to other existing methods of α-amino acid synthesis, with an added advantage of being extremely simple. It also provides access to phenylglycine derivatives, which are not accessible by the alternative synthetic route involving alkylation of glycine equivalents. Since aldehydes are widely available, this method should provide a very convenient route to unnatural amino acids.



R	=		
		Ph	74 %
		4-MeC_6H_4	78 %
		4-ClC_6H_4	78 %
		n-C_9H_{19}	73 %

Scheme 3.

EXPERIMENTAL

General

Melting points were recorded on an Electrothermal 9100 melting point apparatus and are quoted uncorrected. Elemental analyses were performed on a Perkin-Elmer Elemental Analyzer 2400 CHNS/O at the Research Equipment Centre, Chulalongkorn University. Routine ^{1}H nuclear megnetic resonance (NMR) spectra were obtained on a Varian Mercury Plus operating at 400 MHz (^{1}H) and 100 MHz (^{13}C) or Bruker AMX200 operating at 200 MHz (^{1}H) and 50 MHz (^{13}C). Chemical shifts are reported in parts per million (ppm, δ) downfield relative to the internal standard tetramethylsilane. Unless otherwise noted, all reagent-grade chemicals and solvents were obtained from commercial suppliers (Aldrich, Fluka, and Merck) and were used as received. Reactions were performed under ambient conditions without the need for anhydrous solvents or inert atmosphere.

Typical Procedure for the Synthesis of *N*-Boc-α-aminonitriles (2)

Method A

The sulfone **1** (0.30 mmol) and potassium cyanide (39 mg, 0.60 mmol) were stirred in 2-propanol (4 mL) at room temperature for 3 hr. The solvent was removed under reduced pressure and the residue dissolved in ethyl acetate. The ethyl acetate solution was washed with brine, dried ($MgSO_4$), and evaporated. The crude product was purified by chromatography on silica gel.

Method B

The sulfone **1** (0.30 mmol), potassium cyanide (39 mg, 0.60 mmol), and tetrabutylammonium hydrogensulfate (10.2 mg, 0.03 mmol) were stirred vigorously in a mixture of dichloromethane (4 mL) and water (0.2 mL) at room temperature. After usual aqueous work-up, the crude product was purified by flash silica gel column chromatography to afford the pure product.

Spectroscopic and Analytical Data of *N*-Boc-α-aminonitriles

N-Boc-amino-phenylacetonitrile (**2a**) (R = Ph)

White solid. Isolated yield: 66% (method A), 73% (method B). m.p. 179°C–181°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.47–7.24 (m, 5H), 5.72

(br d, $J = 8.7$ Hz, 1H), 5.37 (d, $J = 8.7$ Hz, 1H), 1.40 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.3, 133.5, 129.4, 129.3, 126.9, 117.8, 81.5, 46.1, 28.2; m/z (EI) 232 [M^+]; Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.01; H, 6.78; N, 12.14.

N-Boc-amino-(4′-methylphenyl)acetonitrile (**2b**) (R = 4-$CH_3C_6H_4$)

White solid. Isolated yield: 76% (method A), 82% (method B). m.p. 163°C–165°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34 (d, $J = 8.0$ Hz, 2H), 7.16 (d, $J = 8.0$ Hz, 2H), 5.66 (d, $J = 8.0$ Hz, 1H), 5.40 (d, $J = 8.0$ Hz, 1H), 2.32 (s, 3H) 1.44 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.3, 139.4, 130.6, 129.8, 126.8, 117.9, 81.4, 45.8, 28.2, 21.1; m/z (EI) 246 [M^+]; Anal. Calcd. for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.36; H, 7.35; N, 11.35.

N-Boc-amino-(4′-isopropylphenyl)acetonitrile (**2c**) (R = 4-^{i}PrC$_6$H$_4$)

White solid. Isolated yield: 74% (method A), 79% (method B). m.p. 140°C–141°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38 (d, $J = 8.0$ Hz, 2H), 7.25 (d, $J = 8.0$ Hz, 2H), 5.70 (d, $J = 8.5$ Hz, 1H), 5.44 (d, $J = 8.5$ Hz, 1H), 2.92 (m, 1H) 1.44 (s, 9H), 1.27 (d, $J = 7.0$ Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.3, 150.3, 130.9, 127.3, 126.9, 117.9, 81.3, 45.8, 33.8, 28.2, 23.8; m/z (EI) 274 [M^+]; Anal. Calcd. for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.19; H, 8.08; N, 10.36.

N-Boc-amino-(4′-*tert*-butylphenyl)acetonitrile (**2d**) (R = 4-^{t}BuC$_6$H$_4$)

White solid. Isolated yield: 74% (method A), 78% (method B). m.p. 131°C–132°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40 (m, 4H), 5.72 (d, $J = 8.0$ Hz, 1H), 5.31 (d, $J = 8.0$ Hz, 1H), 1.45 (s, 9H), 1.29 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.2, 152.7, 130.5, 126.7, 126.2, 117.9, 81.4, 45.8, 34.7, 31.2, 28.2; m/z (EI) 288 [M^+]; Anal. Calcd. for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.91; H, 8.59; N, 9.71.

N-Boc-amino-(4′-nitrophenyl)acetonitrile (**2e**) (R = 4-$O_2NC_6H_4$)

Light yellow solid. Isolated yield: 50% (method A), 55% (method B). m.p. 157°C–159°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.30 (d, $J = 8.0$ Hz, 2H), 7.67 (d, $J = 8.0$ Hz, 2H), 5.91 (br d, $J = 8.7$ Hz, 1H), 5.31 (d, $J = 8.7$ Hz, 1H), 1.46 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.0, 148.5, 140.3, 127.9, 124.5, 116.6, 82.5, 45.4, 28.2; m/z (EI) 277 [M^+];

Anal. Calcd. for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.15. Found: C, 56.37; H, 5.54; N, 15.20.

N-Boc-amino-(3′-nitrophenyl)acetonitrile (**2f**) (R = 3-$O_2NC_6H_4$)

Light yellow solid. Isolated yield: 36% (method A), 36% (method B). m.p. 144°C–146°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.33 (d, $J = 8.0$ Hz, 1H), 7.83 (d, $J = 7.5$ Hz, 1H), 7.62 (apparent t, 1H), 5.96 (br m, 1H), 5.42 (br m, 1H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 148.5, 136.0, 133.2, 130.1, 124.3, 122.0, 116.6, 82.2, 45.7, 28.2; m/z (EI) 277 [M^+]; Anal. Calcd. for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.15. Found: C, 56.31; H, 5.44; N, 15.17.

N-Boc-amino-(2′-nitrophenyl)acetonitrile (**2g**) (R = 2-$O_2NC_6H_4$)

Light yellow solid. Isolated yield: 36% (method A), 47% (method B). m.p. 98°C–99°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, $J = 8.0$ Hz, 1H), 7.73–7.78 (m, 2H), 7.62 (apparent t, 1H), 6.29 (d, $J = 8.8$ Hz, 1H), 5.83 (br m, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 148.5, 134.8, 131.7, 131.5, 126.0, 122.0, 116.3, 82.3, 44.4, 28.1; m/z (EI) 277 [M^+]; Anal. Calcd. for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.15. Found: C, 56.35; H, 5.28; N, 15.12.

N-Boc-amino-(4′-cyanophenyl)acetonitrile (**2h**) (R = 4-NCC_6H_4)

White solid. Isolated yield: 42% (method B). m.p. 106°C–107°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.74–7.59 (2 × d, 4H), 5.87 (br d, $J = 8.9$ Hz, 1H), 5.26 (d, $J = 8.9$ Hz, 1H), 1.46 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.0, 138.6, 133.0, 127.6, 117.8, 116.7, 113.6, 82.3, 45.6, 28.2 (3C); m/z (EI) 257 [M^+]; Anal. Calcd. for $C_{14}H_{15}N_3O_2$: C, 65.36; H, 5.88; N, 16.33. Found: C, 55.59; H, 5.50; N, 16.33.

N-Boc-amino-(4′-fluorophenyl)acetonitrile (**2i**) (R = 4-FC_6H_4)

White solid. Isolated yield: 64% (method A), 83% (method B). m.p. 119°C–121°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.45 (m, 2H), 6.97 (m, 2H), 5.70 (br, 1H), 5.54 (d, $J = 8.0$ Hz, 1H), 1.41 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 163.1 (d, $^1J_{13C\text{-}19F} = 248$ Hz), 154.3, 129.5, 128.8 (d, $^3J_{13C\text{-}19F} = 8.5$ Hz), 117.7, 116.2 (d, $^2J_{13C\text{-}19F} = 22.0$ Hz), 81.6, 45.4, 28.2; m/z (EI) 250 [M^+]; Anal. Calcd. for $C_{13}H_{15}N_2O_2F$: C, 62.39; H, 6.04; N, 11.19. Found: C, 62.48; H, 6.03; N, 11.08.

N-Boc-amino-(4′-chlorophenyl)acetonitrile (**2j**) (R = 4-ClC_6H_4)

White solid. Isolated yield: 60% (method A), 84% (method B). m.p. 155°C–157°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38 (m, 4H), 5.74 (br d, $J = 8.5$ Hz, 1H), 5.43 (d, $J = 8.5$ Hz, 1H), 1.42 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.2, 135.5, 132.1, 129.4, 128.2, 117.4, 81.7, 45.4, 28.2; m/z (EI) 266 [M^+]; Anal. Calcd. for $C_{13}H_{15}N_2O_2Cl$: C, 58.54; H, 5.67; N, 10.50. Found: C, 58.52; H, 5.63; N, 10.64.

N-Boc-amino-(4′-bromophenyl)acetonitrile (**2k**) (R = 4-BrC_6H_4)

White solid. Isolated yield: 63% (method A), 83% (method B). m.p. 168°C–169°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.50 (d, $J = 8.0$ Hz, 2H), 7.28 (d, $J = 8.0$ Hz, 2H), 5.73 (br d, $J = 8.1$ Hz, 1H), 5.32 (d, $J = 8.5$ Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.1, 132.4, 128.5, 123.7, 117.3, 81.9, 45.5, 28.2 (3C); m/z (EI) 310 and 312 [M^+]; Anal. Calcd. for $C_{13}H_{15}N_2O_2Br$: C, 50.18; H, 4.86; N, 9.00. Found: C, 50.19; H, 4.83; N, 9.02. m.p. 168°C–169°C.

N-Boc-amino-(3′-hydroxyphenyl)acetonitrile (**2l**) (R = 3-HOC_6H_4)

White solid. Isolated yield: 74% (method A), 81% (method B). m.p. 142°C–143°C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.68 (s, 1H), 8.33 (br d, 1H), 7.20 (apparent t, 1H), 6.85–6.73 (m, 3H), 5.70–5.90 (m, 2H), 1.40 (s, 9H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 157.6, 154.6, 136.0, 129.9, 118.8, 117.2, 115.6, 113.6, 79.5, 44.9, 28.0; m/z (EI) 248 [M^+]; Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.85; H, 6.54; N, 11.35.

N-Boc-amino-(4′-methoxyphenyl)acetonitrile (**2m**) (R = 4-$CH_3OC_6H_4$)

White solid. Isolated yield: 76% (method A), 79% (method B). m.p. 134°C–135°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38 (d, $J = 8.0$ Hz, 2H), 6.95 (d, $J = 8.0$ Hz, 2H), 5.66 (br d, $J = 7.4$ Hz, 1H), 5.19 (br m, 1H), 3.80 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 160.4, 154.2, 128.3, 125.5, 118.0, 114.6, 81.5, 55.4, 45.6, 28.2; m/z (EI) 262 [M^+]; Anal. Calcd. for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.03; H, 6.77; N, 10.69.

N-Boc-amino-(3′-methoxyphenyl)acetonitrile (**2n**) (R = 3-$CH_3OC_6H_4$)

White solid. Isolated yield: 80% (method A), 82% (method B). m.p. 102°C–103°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.27 (apparent t, 1H),

7.02–6.83 (m, 3H), 5.69 (d, $J = 8.1$ Hz, 1H), 5.51 (d, $J = 8.3$ Hz, 1H), 3.75 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 160.0, 154.4, 134.9, 130.3, 118.9, 117.8, 114.9, 112.5, 81.5, 55.4, 45.9, 28.2; m/z (EI) 262 [M^+]; Anal. Calcd. for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.19; H, 6.77; N, 10.69.

N-Boc-amino-(2′-methoxyphenyl)acetonitrile (**2o**) (R = 2-$CH_3OC_6H_4$)

White solid. Isolated yield: 62% (method A), 74% (method B). m.p. 94°C–96°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30–7.35 (m, 2H), 6.90–7.05 (m, 2H), 5.77 (d, $J = 8.5$ Hz, 1H), 5.57 (br, 1H), 3.90 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.0, 154.1, 131.2, 129.0, 121.9, 121.0, 118.1, 111.4, 81.1, 55.8, 42.9, 28.2; m/z (EI) 262 [M^+]; Anal. Calcd. for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.11; H, 6.92; N, 10.68.

N-Boc-amino-(1-naphthyl)acetonitrile (**2p**) (R = 1-naphthyl)

White solid. Isolated yield: 73% (method A), 80% (method B). m.p. 190°C–192°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.94–7.41 (m, 7H), 5.40 (d, $J = 8.5$ Hz, 1H), 5.26 (br, 1H), 1.46 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.1, 134.0, 130.7, 129.8, 129.1, 128.7, 127.6, 126.6, 126.1, 125.1, 122.5, 118.0, 81.6, 44.4, 28.2; m/z (EI) 282 [M^+]; Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.38; H, 6.52; N, 10.00.

N-Boc-amino-(2-furyl)acetonitrile (**2q**) (R = 2-furyl)

White solid. Isolated yield: 81% (method A), 84% (method B). m.p. 76°C–78°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 1H), 6.58 (m, 1H), 6.42 (m, 1H), 5.82 (br, 1H), 5.26 (br, 1H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 145.8, 144.0, 116.1, 111.1, 109.8, 82.2, 40.1, 28.2; m/z (EI) 222 [M^+]; Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.61. Found: C, 59.15; H, 6.36; N, 12.62.

N-Boc-amino-(2-thienyl)acetonitrile (**2r**) (R = 2-thienyl)

White solid. Isolated yield: 80% (method A), 84% (method B). m.p. 115°C–116°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, 1H), 7.26 (d, 1H), 7.10 (m, 1H), 5.82 (br, 1H), 5.37 (br, 1H), 1.46 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.3, 146.2, 127.8, 127.7, 127.4, 116.5, 82.2, 42.1, 28.2; m/z (EI) 238 [M^+]; Anal. Calcd. for $C_{11}H_{14}N_2O_2S$: C, 55.44; H, 5.92; N, 11.76. Found: C, 55.46; H, 6.02; N, 11.75.

N-Boc-2-amino-butyronitrile (**2s**) (R = Et)

White solid. Isolated yield: 72% (method A), 78% (method B). m.p. 95°C–96°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.02 (br m, 1H), 4.48 (br m, 1H), 1.79 (m, 2H), 1.46 (s, 9H), 1.05 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.4, 118.8, 81.1, 43.6, 28.2, 26.8, 9.8; m/z (EI) 184 [M^+]; Anal. Calcd. for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.21. Found: C, 58.59; H, 8.72; N, 15.37.

N-Boc-2-amino-valeronitrile (**2t**) (R = ^{n}Pr)

White solid. Isolated yield: 76% (method A), 81% (method B). m.p. 65°C–66°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.18 (br m, 1H), 4.50 (br m, 1H), 1.73 (m, 2H), 1.46 (s, 9H), 1.36 (m, 2H), 1.00 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.4, 119.0, 80.9, 42.0, 35.17, 28.2, 18.6, 13.2; m/z (EI) 198 [M^+]; Anal. Calcd. for $C_{10}H_{18}N_2O_2$: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.57; H, 9.24; N, 14.21.

N-Boc-2-amino-3-methyl-butyronitrile (**2u**) (R = ^{i}Pr)

White solid. Isolated yield: 72% (method A), 81% (method B). m.p. 91°C–92°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.16 (br m, 1H), 4.39 (br m, 1H), 1.96 (m, 1H), 1.37 (s, 9H), 1.04 (2 × d, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.5, 118.0, 81.0, 48.4, 31.7, 28.2, 18.5, 17.9; m/z (EI) 198 [M^+]; Anal. Calcd. for $C_{10}H_{18}N_2O_2$: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.59; H, 9.09; N, 14.39.

N-Boc-2-amino-hexanenitrile (**2v**) (R = ^{n}Bu)

Colorless oil. Isolated yield: 73% (method A), 79% (method B). ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.96 (br m, 1H), 4.50 (br m, 1H), 1.78 (m, 2H), 1.47 (s, 9H), 1.29–1.33 (m, 4H), 0.96 (t, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.3, 119.0, 81.1, 42.3, 33.0, 28.2, 27.3, 21.9, 13.7; m/z (EI) 212 [M^+]; Anal. Calcd. for $C_{11}H_{20}N_2O_2$: C, 62.24; H, 9.50; N, 13.20. Found: C, 62.24; H, 9.64; N, 13.21.

N-Boc-2-amino-undecanenitrile (**2w**) (R = $^nC_9H_{19}$)

White solid. Isolated yield: 86% (method A), 88% (method B). m.p. 44°C–45°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.17 (br m, 1H), 4.47 (br m, 1H), 1.75 (m, 2H), 1.45 (s, 9H), 1.36–1.20 (m, 14H), 0.82 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.4, 119.0, 80.9, 42.2, 33.3, 31.8,

29.3, 29.2, 29.1, 28.7, 28.2, 25.3, 22.6, 14.0; *m/z* (EI) 282 [M^+]; Anal. Calcd. for $C_{16}H_{30}N_2O_2$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.12; H, 10.79; N, 9.96.

N-Boc-2-amino-3,3-dimethyl-butyronitrile (**2x**) (R = ^{t}Bu)

White solid. Isolated yield: 78% (method A), 82% (method B). m.p. 124°C–125°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.87 (br d, $J = 8.3$ Hz, 1H), 4.3 (d, $J = 8.1$ Hz, 1H), 1.47 (s, 9H), 1.16 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.6, 118.0, 81.1, 52.2, 34.9, 28.2, 25.6; *m/z* (EI) 212 [M^+]; Anal. Calcd. for $C_{11}H_{20}N_2O_2$: C, 62.24; H, 9.50; N, 13.20. Found: C, 62.31; H, 9.55; N, 13.21.

N-Boc-2-amino-4-methyl-valeronitrile (**2y**) (R = ^{i}Bu)

White solid. Isolated yield: 74% (method A), 80% (method B). m.p. 179°C–181°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 (d, $J = 8.4$ Hz, 1H), 4.58 (m, 1H), 1.84 (m, 1H), 1.65 (m, 2H), 1.47 (s, 9H), 0.98 (d, $J = 7.0$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 119.0, 81.7, 42.3, 40.8, 28.2, 24.3, 21.9, 21.7; *m/z* (EI) 212 [M^+]; Anal. Calcd. for $C_{11}H_{20}N_2O_2$: C, 62.24; H, 9.50; N, 13.20. Found: C, 62.19; H, 9.53; N, 13.18.

N-Boc-2-amino-3-phenyl-propionitrile (**2z**) (R = $PhCH_2$)

White solid. Isolated yield: 75% (method A), 81% (method B). m.p. 118°C–119°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.22 (m, 5H), 4.97 (br, 1H), 4.83 (br, 1H), 3.22 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 134.0, 129.8, 129.1, 128.0, 118.2, 81.8, 43.8, 38.7, 28.2; *m/z* (EI) 246 [M^+]; Anal. Calcd. for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.38; H, 7.22; N, 11.50.

N-Boc-2-amino-4-phenyl-butyronitrile (**2aa**) (R = $PhCH_2CH_2$)

White solid. Isolated yield: 75% (method A), 82% (method B). m.p. 114°C–115°C; ^{1}H NMR (400 Mz, $CDCl_3$) δ 7.38–7.18 (m, 5H), 5.12 (br, 1H), 4.57 (br, 1H), 2.81 (m, 2H), 2.15 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 139.4, 129.1, 128.8, 126.2, 119.1, 81.6, 42.2, 35.1, 31.7, 28.2; *m/z* (EI) 260 [M^+]; Anal. Calcd. for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.24; H, 7.35; N, 10.79.

N-Boc-2-amino-cyclohexylacetonitrile (**2bb**) (R = ^{c}Hex)

White solid. Isolated yield: 82% (method A), 85% (method B). m.p. 110°C–111°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.96 (br m, 1H), 4.44 (br m, 1H), 1.90–1.00 (m, 11H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 119.0, 81.6, 47.9, 41.3, 29.2, 28.5, 28.2, 25.9, 25.1; m/z (EI) 238 [M^+]; Anal. Calcd. for $C_{13}H_{22}N_2O_2$: C, 65.51; H, 9.30; N, 11.75. Found: C, 65.53; H, 9.39; N, 11.80.

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