High regioselectivity in electrochemical α-methoxylation of N-protected cyclic amines

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This paper is dedicated to the loving memories of Professor Yoshihiro Matsumura

Abstract

N-Protecting groups of α-substituted cyclic amines strongly affected the regioselectivity in electrochemical methoxylation of these compounds. Namely, N-acyl derivatives were transformed into α'-methoxylated compounds, while N-cyano derivatives changed into α-methoxylated derivatives. Furthermore, Lewis acid catalyzed nucleophilic substitution of the α-methoxylated compounds protected with cyano group afforded α,α-disubstituted cyclic amines.
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1. Introduction

Selective methods for preparation of cyclic amine derivatives having quaternary carbon center at the α position are important in organic synthesis.[1] Xiao and co-workers reported that 2-phenyl substituted pyrrolidine and piperidine are lithiated at the C-2 or C-5 in the case of pyrrolidine and the C-2 or C-6 for piperidine depending on diamine ligand used.[2] However, alkyl substituents are exclusively lithiated at the C-5 for pyrrolidine and the C-6 for piperidine.[3] A uniform method to achieve regioselective activation of the C-2 of both pyrrolidine and piperidine is highly desirable,[2] so far, no method is available to this end.

Electrochemical methoxylation of N-protected cyclic amines **1** selectively functionalizes readily available amines as starting materials for building biologically active molecules that contain nitrogen atoms.[4] Alkoxycarbonylated or acylated amines which direct methoxylation to less substituted site (Path a in Scheme 1) have been extensively studied,[5,6]

although a mechanism for high regioselectivity has not been investigated.
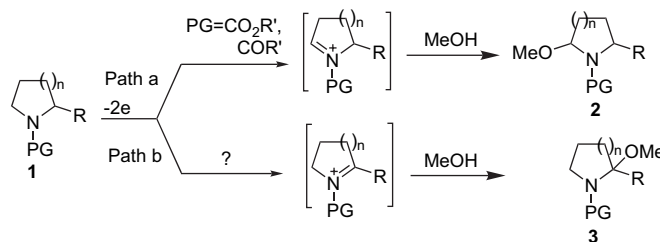
Scheme 1. Electrochemical methoxylation of N-protected cyclic amines **1**.

On the other hand, electrochemically selective activation of the more substituted site has not been achieved to date (Path b in Scheme 1).[7] Finding a method to achieve it is both synthetically and mechanistically worthwhile.

2. Result and discussion

We envisioned that since the product formed is determined by the most stable iminium ion, and that the stability of this iminium ion must depend on the protecting group on the

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Table 1

Screening of N-protecting group of 2-methylpiperidines **1a**–**g** and 2-methylpyrrolidines **1h**, **i**

| Entry | Substrate | n | PG | Ratio of product | | Yield of |
				2a–i (%)	**3a–i** (%)	**2a–i+3a–i** (%)
1	**1a**	2	CO_2Me	**2a** (100)	**3a** (0)	78
2	**1b**	2	Ts	**2b** (100)	**3b** (0)	91
3	**1c**	2	CHO	**2c** (100)	**3c** (0)	98
4	**1d**	2	$CONH_2$	**2d** (100)	**3d** (0)	92
5	**1e**	2	Cbz	**2e** (100)	**3e** (0)	82
6	**1f**	2	Boc	**2f** (100)[a]	**3f** (0)	95
7	**1g**	2	CN	**2g** (18)	**3g** (82)	85
8	**1h**	1	CN	**2h** (48)	**3h** (52)	85
9	**1i**	1	CO_2Me	**2i** (100)	**3i** (0)	78

[a] Since **2f** was somewhat unstable, it was transformed into the corresponding 1,2,3,4-tetrahydropyridine on silica gel.

nitrogen. Therefore, the protecting group must play a role on the regioselectivity of the final product. We began thus by surveying different N-protecting groups (PG) as a chemical device (Eq. 1). Into an undivided electrochemical cell containing Et_4NBF_4 (0.5 mmol), MeOH (5 mL), and N-protected 2-methyl cyclic amines **1a**–**i** (1 mmol) were placed Pt electrodes and 3 F/mol of electricity was passed through at a constant current of 0.1 A (terminal voltage; ca. 10 V) at room temperature. The results are summarized in Table 1.

$$(1)$$
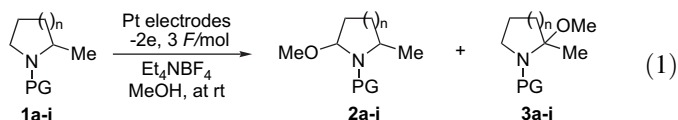
All protecting groups screened directed methoxyl group to the least substituted site (Table 1, entries 1–6 and 9) except cyano group, which gave an almost 2:8 mixture of regio-isomers **2g** and **3g** from **1g** (entry 7) and an almost 1:1 mixture of regio-isomers **2h** and **3h** from **1h** (entry 8). Impressed by the findings we sort a way to improve this regioselectivity.

We tried different anode materials with platinum giving the lowest selectivity to oxidize **1h** (Table 2, entry 1), while glassy carbon had the lowest yield due to lower current efficiency (entry 3). Graphite gave the best result both in yield and selectivity because the reaction takes place on its surface thus regiocontrol is possible (entry 4). To improve these results further, we examined temperature effect on regioselectivity. When the reaction was carried out at −20 °C, there was a marked improvement on the regioselectivity of **3h** (entry 5). At −50 °C the best regioselectivity was achieved (entry

Table 2

Effect of electrodes and temperature on the electrochemical oxidation of **1h**

| Entry | Electrodes | Temp (°C) | F/mol | Ratio | | Yield of |
				2h (%)	**3h** (%)	**2h+3h** (%)
1	Pt	rt	3.0	48	52	85
2	Carbon fiber	rt	2.5	28	72	95
3	Glassy carbon	rt	5.0	26	74	40
4	Graphite	rt	2.5	22	78	96
5	Graphite	−20	2.5	16	84	96
6	Graphite	−50	2.5	13	87	98

Table 3

Electrochemical methoxylation of various 2-substituted N-cyanocyclic amines **1g, j**–**r**[a]

| Entry | Substrate | R | n | Ratio of product | | Yield of |
				2g,j–r (%)	**3g,j–r** (%)	**2g, j–r+ 3g, j–r** (%)
1	**1j**	Et	1	**2j** (13)	**3j** (87)	99
2	**1k**	n-Pr	1	**2k** (18)	**3k** (82)	96
3	**1l**	Allyl	1	**2l** (17)	**3l** (83)	73
4	**1g**	Me	2	**2g** (13)	**3g** (87)	93
5	**1m**	Et	2	**2m** (7)	**3m** (93)	96
6	**1n**	n-Pr	2	**2n** (3)	**3n** (97)	97
7	**1o**	Allyl	2	**2o** (30)	**3o** (70)	50
8	**1p**	Ph	2	**2p** (0)	**3p** (100)	98
9[b]	**1q**	⌇⟨C₆H₃⟩—OMe, Br	2	**2q** (9)	**3q** (91)	96
10	**1r**	⌇⟨C₆H₄⟩—Me	2	**2r** (0)	**3r** (100)	75

[a] Graphite electrodes were used. 2.5 F/mol of electricity was passed at −50 °C.
[b] Reaction was carried out at room temperature.

6), further lowering of reaction temperature led to supporting electrolyte precipitate out of the solution.[8]

The optimized reaction condition was then applied to various substrates **1g**, **j**–**r** (Eq. 2). The results are summarized in Table 3.

$$(2)$$
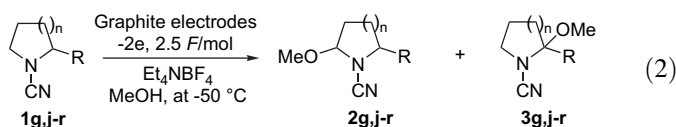
Increase in size of the R substituent at the C-2 for pyrrolidine had little effect on regioselectivity (entries 1 and 2), while in the case of piperidine ring it led to better selectivity (entries 4–6). To our delight, phenyl substituents, which are found in many biologically interesting compounds gave excellent regioselectivity (entries 8 and 10).[9] Introduction of methoxyl and bromo groups on the phenyl substituent was well tolerated and gave 9:91 regioselectivity at room temperature (entry 9), however, on lowering the temperature the reaction did not proceed. Allyl substituent on the pyrrolidine ring gave good selectivity 17:83 (entry 3), while that on piperidine gave moderate selectivity (entry 7).

To understand the mechanism behind the regiocontrol in N-protected cyclic amines we considered the intermediary iminium ions **A** and **B** for cyanopiperidine while **C** and **D** for methoxycarbonyl protecting group representing the least substituted position directing groups (Fig. 1).

Since stabilities of iminium ions might determine the regioselectivities, we calculated the LUMO for iminium ions **A**–**D** using DFT/6-31G* method of Gaussian 03 software. Iminium ion **A** is much more stable than iminium ion **B** thus leading to methoxylation on the more substituted side (Table 4, entries 1 and 2). In contrast, for methoxycarbonyl protected iminium ions, iminium ion **D** is somewhat stable compared with iminium ion **C**, thereby leading to methoxylation on the less substituted side (entries 3 and 4).
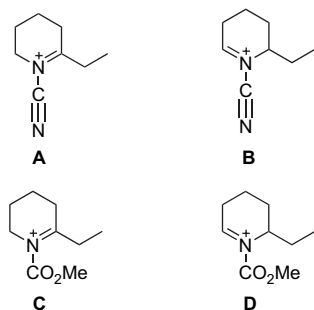
Figure 1. Plausible intermediary iminium ions for the oxidation of *N*-cyano-2-ethylpiperidine and *N*-methoxycarbonyl-2-ethylpiperidine.

Table 4
LUMO values for **A**, **B**, **C**, and **D**[a]

| Entry	Iminium ions	LUMO[b]
1	**A**	0.09412
2	**B**	0.00824
3	**C**	−0.07393
4	**D**	−0.08117

[a] Calculated with DFT/6-31G* method of Gaussian 03 software.
[b] Relatively stable species have bigger absolute value than that of relatively unstable species.

We could apply our product **3g** to Lewis acid catalyzed cyanation and allylation for preparation of 2,2-disubstituted piperidines **4** and **5**, respectively (Eqs. 3 and 4).

(3)

(4)
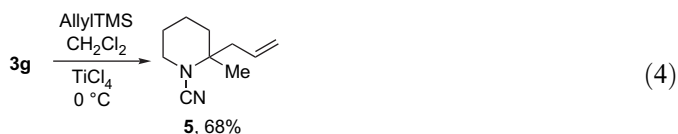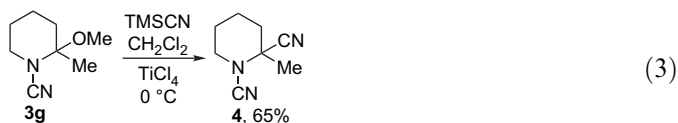
Similarly the allylation of **3l** afforded 2,2-diallylated pyrrolidine **6**, which might easily be transformed to pharmaceutically important spiro compounds, which are challenging to synthesize (Eq. 5).[7,10]

(5)
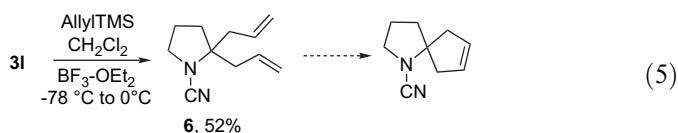
3. Conclusion

We have for the first time demonstrated a method for high regioselectivity in electrochemical oxidation of *N*-protected cyclic amines and also proposed a mechanism for least and most substituted methoxylation. We have also shown the application for the methoxylated intermediates.[11]

4. Experimental section

4.1. General

Electrochemical reactions were carried out using DC Power Supply (GP 050-2) of Takasago Seisakusho, Inc. ^{1}H NMR spectra were measured on a Varian Gemini 300 and 400 spectrometer with TMS as an internal standard. ^{13}C NMR spectra were measured on a Varian Gemini 400 spectrometer with TMS as an internal standard. IR spectra were obtained on a Shimadzu FTIR-8100A. Elemental analyses were carried in Center for Instrumental Analysis, Nagasaki University. Mass spectra were obtained on a JEOL JMS-DX 303 instrument.

All solvents were used as supplied without further purification.

4.2. Starting N-protected (except for N-cyano) cyclic amines

N-Protected cyclic amines **1a**,[4a] **1b**,[12] **1c**,[5d] **1d**,[13] **1e**,[14] **1f**,[3b] and **1i**[15] are known compounds with their spectroscopic data available in literature.

4.2.1. N-Cyanation of cyclic amines

A 50 mL flask containing 5 mmol of cyclic amine, K_2CO_3 (829 mg, 6 mmol), and BrCN (530 mg, 5 mmol) in MeCN (10 mL) was stirred for 6 h at room temperature monitored by TLC. After completion of reaction, the reaction mixture was filtered and then the filtrate was concentrated in vacuo. The residue was run through a silica gel column to obtain a quantitative yield of protected amines **1j** and **1m**.

N-Cyanoamines **1g**[13] and **1h**[16] are known compounds.

4.2.2. 2-Ethylpyrrolidine-1-carbonitrile (1j)

^{1}H NMR (400 MHz, CDCl$_3$) δ 3.52–3.37 (m, 3H), 2.08–1.97 (m, 1H), 1.96–1.76 (m, 3H), 1.59–1.43 (m, 2H), 0.97 (t, *J*=7.8 Hz, 3H); IR ν cm^{-1} (neat): 2961, 2210, 1460, 1356; High Resolution Mass Spectrum [FAB(+)]: *m/z* calcd for C$_7$H$_{13}$N$_2$ [M+H]$^+$ 125.1079, found 125.1072.

4.2.3. 2-Ethylpiperidine-1-carbonitrile (1m)

^{1}H NMR (300 MHz, CDCl$_3$) δ 3.50–3.38 (m, 1H), 3.06–2.95 (m, 1H), 2.77 (t, *J*=6.3 Hz, 1H), 1.82–1.52 (m, 6H), 1.49–1.21 (m, 2H), 0.99 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 Hz, CDCl$_3$) δ 117.32 (1C), 60.58 (1C), 51.16 (1C), 29.90 (1C), 26.49 (1C), 24.68 (1C), 23.51 (1C), 10.39 (1C); IR ν cm^{-1} (neat): 2966, 2214, 1446, 1383, 1223; High Resolution Mass Spectrum [EI(+)]: *m/z* calcd for C$_8$H$_{14}$N$_2$ [M]$^+$ 138.1157, found 138.1162.

4.2.4. 2-Propylpyrrolidine-1-carbonitrile (1k)

2-Methoxypyrrolidine-1-carboxylic acid benzyl ester (1176 mg, 5 mmol) prepared according to literature[17] was transferred into a 50 mL flask containing allyltrimethylsilane (1714 mg, 15 mmol) and CH$_2$Cl$_2$ (20 mL). The mixture was stirred at 0 °C as BF$_3$·OEt$_2$ (1.28 mL, 10 mmol) was added dropwise and left to stir for 8 h. After confirmation of

completion of reaction by TLC, 10 mL of H_2O was added and the organic layer separated. The aqueous layer was extracted by AcOEt (3×10 mL) and the combined organic layer dried by $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The crude product was then transferred to a 20 mL flask containing 5% Pd on activated carbon and MeOH (5 mL). The mixture was then stirred under 1 atm of H_2 for 8 h. Upon completion of reaction the mixture was then filtered through Celite and solvent removed in vacuo to obtain 2-propylpyrrolidine, which was protected according to the procedure above without further purification to afford **1k** as an oil (415 mg, 3 mmol) (60%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 3.58–3.50 (m, 1H), 3.48–3.36 (m, 2H), 2.05–1.74 (m, 4H), 1.57–1.48 (m, 1H), 1.46–1.35 (m, 3H), 0.96 (t, J=7.3 Hz, 3H); IR ν cm^{-1} (neat): 2961, 2210, 1460, 1356; High Resolution Mass Spectrum [FAB(+)]: m/z calcd for C$_8$H$_{15}$N$_2$ [M+H]$^+$ 139.1236, found 139.1244.

4.2.5. 2-Allylpyrrolidine-1-carbonitrile (1l) [from 7]

A 50 mL flask containing 2-methoxypyrrolidine-1-carbonitrile (**7**) (631 mg, 5 mmol) and allyltrimethylsilane (857 mg, 7.5 mmol) in CH$_2$Cl$_2$ (10 mL) under nitrogen was stirred at 0 °C as BF$_3$·OEt$_2$ (1.28 mL, 10 mmol) was added dropwise. The mixture was then stirred at 0 °C as reaction was monitored by TLC. On completion of the reaction, H$_2$O (6 mL) was slowly added and then the mixture extracted by AcOEt (3×10 mL). The combined organic layer was dried using MgSO$_4$ and solvent removed in vacuo. Crude product was purified using silica gel column (n-hexane/AcOEt 10:1) to afford a pure product (136 mg, 20%) (**1l**).

^{1}H NMR (400 MHz, CDCl$_3$) δ 5.82–5.70 (m, 1H), 5.21–5.10 (m, 2H), 3.68–3.61 (m, 1H), 3.48–3.38 (m, 2H), 2.57–2.46 (m, 1H), 2.31–2.20 (m, 1H), 2.05–1.83 (m, 3H), 1.67–1.58 (m, 1H); IR ν cm^{-1} (neat): 2978, 2210, 1641, 1458, 1439; High Resolution Mass Spectrum [FAB(+)]: m/z calcd for C$_8$H$_{13}$N$_2$ [M+H]$^+$ 137.1078, found 137.1099.

4.2.6. 2-Propylpiperidine-1-carbonitrile (1n)

2-Methoxypiperidine-1-carboxylic acid benzyl ester (1247 mg, 5 mmol) prepared according to literature[18] was transferred into a 50 mL flask containing allyltrimethylsilane (1714 mg, 15 mmol) and CH$_2$Cl$_2$ (20 mL). The mixture was stirred at 0 °C as BF$_3$·OEt$_2$ (1.28 mL, 10 mmol) was added dropwise and left to stir for 8 h. After confirmation of completion of reaction by TLC, 10 mL of H$_2$O was added and the organic layer separated. The aqueous layer was extracted by AcOEt (3×10 mL) and the combined organic layer dried by MgSO$_4$ and filtered. The solvent was removed under reduced pressure. The crude product was then transferred to a 20 mL flask containing 5% Pd on activated carbon and MeOH (5 mL). The mixture was then stirred under 1 atm of H$_2$ for 8 h. Upon completion of reaction the mixture was then filtered through Celite and solvent removed in vacuo to obtain 2-propylpiperidine, which was protected according to the procedure above without further purification to afford **1n**[19] as an oil (639 mg, 4.2 mmol) (60%).

4.2.7. 2-Allylpiperidine-1-carbonitrile (1o) [from 8]

A 50 mL flask containing 2-methoxypiperidine-1-carbonitrile (**8**) (701 mg, 5 mmol) and allyltrimethylsilane (857 mg, 7.5 mmol) in CH$_2$Cl$_2$ (10 mL) under nitrogen was stirred at 0 °C as TiCl$_4$ (0.35 mL, 2.5 mmol) was added dropwise. The mixture was then stirred at 0 °C as reaction was monitored by TLC. On completion of the reaction, H$_2$O (6 mL) was slowly added and then the mixture extracted by AcOEt (3×10 mL). The combined organic layer was dried using MgSO$_4$ and solvent removed in vacuo.

Crude product was purified using silica gel column (n-hexane/AcOEt=10:1) to afford a pure product **1o** (526 mg, 70%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 5.83–5.73 (m, 1H), 5.18 (d, J=19.0 Hz, 1H), 5.13 (d, J=10.5 Hz, 1H), 3.45 (d, J=4.2 Hz, 1H), 3.06–2.93 (m, 2H), 2.58–2.51 (m, 1H), 2.35–2.27 (m, 1H), 1.85–1.58 (m, 4H), 1.47–1.34 (m, 2H); ^{13}C NMR (100 Hz, CDCl$_3$) δ 133.17 (1C), 118.34 (1C), 116.86 (1C), 58.30 (1C), 50.88 (1C), 37.57 (1C), 29.54 (1C), 24.21 (1C), 23.01 (1C); IR ν cm^{-1} (neat): 2942, 2859, 2209, 1644, 1445; High Resolution Mass Spectrum [EI(+)]: m/z calcd for C$_9$H$_{14}$N$_2$ [M]$^+$ 150.1157, found 150.1127.

4.2.8. 2-Phenylpiperidine-1-carbonitrile (1p) [from 8]

A 50 mL flask containing **8** (701 mg, 5 mmol) in benzene (15 mL) was stirred at room temperature as AlCl$_3$ (1333 mg, 10 mmol), was added slowly. The mixture was left to stir at the same condition for 8 h monitored by TLC. The reaction was then quenched by adding H$_2$O (6 mL) slowly, then extracted with AcOEt (3×10 mL). The combined organic layer was then dried with MgSO$_4$, solvent removed in vacuo and the crude product purified on silica gel (n-hexane/AcOEt=10:1) to give **1p** (466 mg, 50%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.36 (s, 5H), 3.97 (dd, J=10.7 and 2.9 Hz, 1H), 3.56 (dt, J=12.2 and 3.2 Hz, 1H), 3.21 (td, J=11.7 and 3.9 Hz, 1H), 1.94–1.52 (m, 5H), 1.54–1.48 (m, 1H); ^{13}C NMR (100 Hz, CDCl$_3$) δ 138.78 (1C), 128.74 (2C), 128.66 (1C), 127.57 (2C), 117.41 (1C), 63.80 (1C), 51.44 (1C), 32.48 (1C), 24.35 (1C), 23.48 (1C); IR ν cm^{-1} (neat): 2943, 2858, 2210, 1495, 1454, 1377, 1267; High Resolution Mass Spectrum [EI(+)]: m/z calcd for C$_{12}$H$_{14}$N$_2$ [M]$^+$ 186.1157, found 186.1132.

4.2.9. 2-(3-Bromo-4-methoxyphenyl)piperidine-1-carbonitrile (1q) [from 8]

A 50 mL flask containing **8** (701 mg, 5 mmol) in CH$_2$Cl$_2$ (10 mL) and 2-bromoanisole (1870 mg, 10 mmol) was stirred at room temperature as AlCl$_3$ (1333 mg, 10 mmol) was added slowly. The reaction was left to stir for 12 h and then H$_2$O (5 mL) was slowly added. The mixture was extracted by AcOEt (3×10 mL), then the combined organic layer was dried by MgSO$_4$, solvent removed in vacuo, and the crude product purified on silica gel column (n-hexane/AcOEt=10:1) to afford **1q** as white solid (1328 mg, 90%).

Solid, mp=104 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.55 (s, 1H), 7.30 (d, J=6.8 Hz, 1H), 6.90 (d, J=8.8 Hz, 1H), 3.89 (s, 4H), 3.56 (dd, J=12.2 and 3.4 Hz, 1H), 3.19 (td, J=12.0 and 3.7 Hz, 1H), 1.94–1.84 (m, 2H), 1.79–1.47 (m, 4H);

^{13}C NMR (100 Hz, CDCl$_3$) δ 156.11, 132.60, 132.35, 127.92, 117.24, 111.95, 62.75, 56.22, 51.51, 32.41, 24.27, 23.54; IR ν cm^{-1} (neat): 2926, 2855, 2361, 2209, 1605, 1501, 1458; High Resolution Mass Spectrum [FAB(+)]: m/z calcd for C$_{13}$H$_{16}$BrN$_2$O [M+H]$^+$ 295.0446, found 295.0431.

4.2.10. 2-(4-Methylphenyl)piperidine-1-carbonitrile (1r) [from 8]

A 50 mL flask containing **8** (701 mg, 5 mmol) in toluene (15 mL) was stirred at room temperature as AlCl$_3$ (1333 mg, 10 mmol), was added slowly. The mixture was left to stir at the same condition for 8 h monitored by TLC. The reaction was then quenched by adding H$_2$O (6 mL) slowly, then extracted with AcOEt (3×10 mL). The combined organic layer was then dried with MgSO$_4$, solvent removed in vacuo, and the crude product purified on silica gel (n-hexane/AcOEt=10:1) to give **1r** (400 mg, 40%).

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.30–7.14 (m, 4H), 3.94 (dd, J=10.2, 3.6 Hz, 1H), 3.60–3.47 (m, 1H), 3.19 (t, J=11.7 Hz, 1H), 2.34 (s, 3H), 2.04–1.41 (m, 6H); IR ν cm^{-1} (neat): 2943, 2858, 2210, 1516, 1444, 1375, 1267, 1228; High Resolution Mass Spectrum [FAB(+)]: m/z calcd for C$_{13}$H$_{17}$N$_2$ [M+H]$^+$ 201.1392, found 201.1412.

4.3. General procedure for electrochemical methoxylation of N-protected amines

The substrate (1 mmol) was measured into an electrochemical cell containing Et$_4$NBF$_4$ (109 mg, 0.5 mmol), graphite anode and cathode electrodes and a stirring bar. MeOH (6 mL) was added and the mixture stirred for 1 min to dissolve the reactants. The cell was then placed at −60 °C and allowed to attain this temperature, 2.5 F/mol of electricity was then passed through, then the reaction mixture was transferred to a 50 mL flask and the solvent removed in vacuo. The crude mixture was re-dissolved in AcOEt (1 mL) and filtered. The filtrate was concentrated and then flash chromatography was done on the residue to afford methoxylated product as oil.

Compounds **2a**,[4a] **2b**,[12] and **2c**[5d] are known compounds with their spectroscopic data available in literature.

4.3.1. 1-Carbamoyl-2-methoxy-6-methylpiperidine (2d) [from 1d]

^{1}H NMR (300 MHz, CDCl$_3$) δ 5.46 (br s, 1H), 4.80 (br s, 2H), 3.95 (br s, 1H), 3.29 (s, 3H), 1.97–1.49 (m, 6H), 1.34 (d, J=7.2 Hz, 3H); IR ν cm^{-1} (neat): 3360, 2944, 1655, 1591, 1426; High Resolution Mass Spectrum [EI(+)]: m/z calcd for C$_8$H$_{16}$N$_2$O$_2$ [M]$^+$ 172.1211, found 172.1202.

4.3.2. 2-Methoxy-6-methylpiperidine-1-carboxylic acid benzyl ester (2e) [from 1e]

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.36 (s, 5H), 5.52–5.32 (m, 1H), 5.20–5.10 (m, 2H), 4.52–4.30 (m, 1H), 3.22 (br s, 3H), 2.00–1.27 (m, 6H), 1.29 and 1.25 (2d, J=7.2 Hz, 3H); IR ν cm^{-1} (neat): 2957, 2930, 1709, 1655, 1415, 1392; High Resolution Mass Spectrum [FAB(+)]: m/z calcd for C$_{15}$H$_{22}$NO$_3$ [M+H]$^+$ 264.1600, found 264.1578.

4.3.3. 1,2,3,4-Tetrahydro-2-methylpyridine-1-carboxylic acid tert-butyl ester (2f) [from 1f]

Electrochemical methoxylation of **1f** gave 6-methoxylated compound **2f**, which was somewhat unstable to be changed to 1,2,3,4-tetrahydropyridine on silica gel.

^{1}H NMR (300 MHz, CDCl$_3$) δ 6.82–6.60 (m, 1H), 4.90–4.72 (m, 1H), 4.42–4.22 (m, 1H), 2.14–1.55 (m, 4H), 1.49 (s, 9H), 1.10 (d, J=6.6 Hz, 3H); IR ν cm^{-1} (neat): 2978, 1713, 1697, 1651, 1410, 1180, 1105; High Resolution Mass Spectrum [FAB(+)]: m/z calcd for C$_{11}$H$_{20}$NO$_2$ [M+H]$^+$ 198.1494, found 198.1494.

4.3.4. 5-Methoxy-2-methylpyrrolidine-1-carboxylic acid methyl ester (2i) [from 1i]

^{1}H NMR (300 MHz, CDCl$_3$) δ 5.29–5.12 (m, 1H), 4.00–3.81 (m, 1H), 3.73 (s, 3H), 3.34 (br s, 3H), 2.18–1.68 (m, 4H), 1.36–1.30 (m, 3H); IR ν cm^{-1} (neat): 2988, 2876, 1724, 1697, 1456, 1388, 1368, 1319; High Resolution Mass Spectrum [FAB(+)]: m/z calcd for C$_8$H$_{16}$NO$_3$ [M+H]$^+$ 174.1130, found 174.1120.

4.3.5. 2-Methoxypyrrolidine-1-carbonitrile (7) [from pyrrolidine-1-carbonitrile]

^{1}H NMR (300 MHz, CDCl$_3$) δ 4.91 (d,, J=3.9 Hz, 1H), 3.63–3.57 (m, 1H), 3.44 (s, 3H), 3.39–3.48 (m, 1H), 2.03–1.90 (m, 4H); IR ν cm^{-1} (neat): 2986, 2218, 1458, 1356, 1252, 1205; High Resolution Mass Spectrum [EI(+)]: m/z calcd for C$_6$H$_{10}$N$_2$O [M]$^+$ 126.0793, found 126.0799.

4.3.6. 2-Methoxypiperidine-1-carbonitrile (8) [from piperidine-1-carbonitrile]

Piperidine-1-carbonitrile (2.20 g, 20 mmol) was measured into a 100 mL beaker containing Et$_4$NBF$_4$ (1.10 g, 5 mmol), a stirring bar and fitted with platinum electrodes and then 60 mL of MeOH was added and the beaker placed at 0 °C, then 3 F/mol of current was passed through it.

The mixture was then transferred to a 200 mL flask and the solvent removed in vacuo. The crude mixture was re-dissolved in AcOEt (10 mL) and filtered. The filtrate was concentrated and then flash chromatography was done on the residue to afford **8** as oil (2.75 g, 98% yield).

^{1}H NMR (300 MHz, CDCl$_3$) δ 4.50 (s, 1H), 3.47 (s, 3H), 3.40–3.26 (m, 1H), 3.18 (d, J=12.6 Hz, 1H), 1.81–1.64 (m, 6H); IR ν cm^{-1} (neat): 2972, 2218; High Resolution Mass Spectrum [EI(+)]: m/z calcd for C$_7$H$_{12}$N$_2$O [M]$^+$ 140.0949, found: 140.0939.

4.3.7. 2-Ethyl-2-methoxypyrrolidine-1-carbonitrile (3j) [from 1j]

^{1}H NMR (300 MHz, CDCl$_3$) δ 3.62 (m, 2H), 3.26 (s, 3H), 2.19–1.66 (m, 6H), 0.99 (t, J=7.5 Hz, 3H); IR ν cm^{-1} (neat): 2883, 2220, 1466, 1354; High Resolution Mass Spectrum [FAB(+)]: m/z calcd for C$_8$H$_{15}$N$_2$O [M+H]$^+$ 155.1185, found 155.1188.

The ratio of **2j/3j** was determined by gas chromatography [(Shinwa Chemical Industries, Ltd. HR-1, 0.25 mmφ×25 m,

160 °C): **2j/3j**=13:87 (retention time: 11.58 and 11.73 min, respectively)].

4.3.8. 2-Methoxy-2-propylpyrrolidine-1-carbonitrile (3k) [from 1k]

^{1}H NMR (300 MHz, CDCl$_3$) δ 3.63–3.47 (m, 2H), 3.26 (s, 3H), 2.18–1.50 (m, 6H), 1.45–1.32 (m, 2H), 0.99 (t, J=7.2 Hz, 3H); IR ν cm^{-1} (neat): 2964, 2218, 1713, 1460, 1367; High Resolution Mass Spectrum [FAB(+)]: m/z calcd for C$_9$H$_{17}$N$_2$O [M+H]$^+$ 169.1341, found 169.1347.

The ratio of **2k/3k** was determined by gas chromatography [(Shinwa Chemical Industries, Ltd. HR-1, 0.25 mmϕ×25 m, 80 °C): **2k/3k**=18:82 (retention time: 12.71 and 13.25 min, respectively)].

4.3.9. 2-Allyl-2-methoxypyrrolidine-1-carbonitrile (3l) [from 1l]

^{1}H NMR (400 MHz, CDCl$_3$) δ 5.85–5.72 (m, 1H), 5.25–5.12 (m, 2H), 3.72–3.51 (m, 2H), 3.30 (s, 3H), 2.84 (dd, J=14.4 and 7.1 Hz, 1H), 2.51 (dd, J=14.4 and 7.1 Hz, 1H), 2.13–1.81 (m, 4H); IR ν cm^{-1} (neat): 2982, 2216, 1643, 1462, 1441; High Resolution Mass Spectrum [FAB(+)]: m/z calcd for C$_9$H$_{15}$N$_2$O [M+H]$^+$ 167.1184, found 167.1199.

The ratio of **2l/3l** was determined by gas chromatography [(Shinwa Chemical Industries, Ltd. HR-1, 0.25 mmϕ×25 m, 80 °C): **2l/3l**=17:83 (retention time: 12.45 and 12.91 min, respectively)].

4.3.10. 2-Methoxy-2-methylpyrrolidine-1-carbonitrile (3h) [from 1h]

^{1}H NMR (400 MHz, CDCl$_3$) δ 3.54–3.46 (m, 2H), 3.29 (s, 3H), 2.27–1.91 (m, 3H), 1.78–1.74 (m, 1H), 1.62 (s, 3H); ^{13}C NMR (100 Hz, CDCl$_3$) δ 115.13 (1C), 94.66 (1C), 50.49 (1C), 50.05 (1C), 37.58 (1C), 22.80 (1C), 21.44 (1C); IR ν cm^{-1} (neat): 2986, 2890, 2220, 1713, 1487, 1383; High Resolution Mass Spectrum [EI(+)]: m/z calcd for C$_7$H$_{12}$N$_2$O [M]$^+$ 140.0949, found: 140.0967.

The ratio of **2h/3h** was determined by gas chromatography [(Shinwa Chemical Industries, Ltd. HR-1, 0.25 mmϕ×25 m, 80 °C): **2h/3h**=13:87 (retention time: 18.05 and 16.86 min, respectively)].

4.3.11. 2-Methoxy-2-methylpiperidine-1-carbonitrile (3g) [from 1g]

^{1}H NMR (300 MHz, CDCl$_3$) δ 3.28 (s, 3H), 3.28–3.20 (m, 2H), 1.90–1.56 (m, 6H), 1.54 (s, 3H); ^{13}C NMR (100 Hz, CDCl$_3$) δ 118.15 (1C), 86.03 (1C), 50.91 (1C), 46.34 (1C), 36.54 (1C), 23.96 (1C), 22.44 (1C), 18.92 (1C); IR ν cm^{-1} (neat): 2948, 2215, 1715, 1449, 1385; High Resolution Mass Spectrum [EI(+)]: m/z calcd for C$_8$H$_{14}$N$_2$O [M]$^+$ 154.1107, found: 154.1084.

The ratio of **2g/3g** was determined by gas chromatography [(Shinwa Chemical Industries, Ltd. HR-1, 0.25 mmϕ×25 m, 80 °C): **2g/3g**=13:87 (retention time: 21.59 and 19.82 min, respectively)].

4.3.12. 2-Ethyl-2-methoxypiperidine-1-carbonitrile (3m) [from 1m]

^{1}H NMR (400 MHz, CDCl$_3$) δ 3.40–3.15 (m, 2H), 3.23 (s, 3H), 2.20–2.03 (m, 1H), 1.88–1.30 (m, 7H), 0.95 (t, J=7.5 Hz, 3H); ^{13}C NMR (100 Hz, CDCl$_3$) δ 116.47 (1C), 88.02 (1C), 48.52 (1C), 46.69 (1C), 32.82 (1C), 27.13 (1C), 24.22 (1C), 18.70 (1C), 7.13 (1C); IR ν cm^{-1} (neat): 2946, 2211, 1676, 1447, 1375; High Resolution Mass Spectrum [EI(+)]: m/z calcd for C$_9$H$_{16}$N$_2$O [M]$^+$ 168.1262, found 168.1249.

The ratio of **2m/3m** was determined by gas chromatography [(Shinwa Chemical Industries, Ltd. HR-1, 0.25 mmϕ×25 m, 190 °C): **2m/3m**=7:93 (retention time: 11.92 and 11.34 min, respectively)].

4.3.13. 2-Methoxy-2-propylpiperidine-1-carbonitrile (3n) [from 1n]

^{1}H NMR (400 MHz, CDCl$_3$) δ 3.41–3.25 (m, 2H), 3.23 (s, 3H), 2.05–1.70 (m, 6H), 1.63–1.30 (m, 4H), 0.98 (t, J=6.8 Hz, 3H); IR ν cm^{-1} (neat): 2969, 2876, 2222, 1221; High Resolution Mass Spectrum [EI(+)]: m/z calcd for C$_{10}$H$_{18}$N$_2$O [M]$^+$ 182.1419, found 182.1409.

The ratio of **2n/3n** was determined by gas chromatography [(Shinwa Chemical Industries, Ltd. HR-1, 0.25 mmϕ×25 m, 200 °C): **2n/3n**=3:97 (retention time: 13.20 and 12.69 min, respectively)].

4.3.14. A mixture of 2-allyl-2-methoxypiperidine-1-carbonitrile (3o) and 2-allyl-6-methoxypiperidine-1-carbonitrile (2o) [from 1o]

^{1}H NMR (400 MHz, CDCl$_3$) δ 5.88–5.69 (m, 1H), 5.23–5.11 (m, 2H), 4.59 (s, 0.3H), 3.44 (s, 0.9H) and 3.30 (s, 2.1H), 3.29–2.28 (m, 3.7H), 1.86–1.60 (m, 4H), 1.58–1.24 (m, 2H); IR ν cm^{-1} (neat): 2946, 2215, 1738, 1644, 1445, 1377; High Resolution Mass Spectrum [FAB(+)]: m/z calcd for C$_{10}$H$_{17}$N$_2$O [M+H]$^+$ 181.1341, found 181.1334.

The ratio of **2o/3o** was determined by gas chromatography [(Shinwa Chemical Industries, Ltd. HR-1, 0.25 mmϕ×25 m, 200 °C): **2o/3o**=30:70 (retention time: 12.89 and 12.47 min, respectively)].

4.3.15. 2-Methoxy-2-phenylpiperidine-1-carbonitrile (3p) [from 1p]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.52–7.36 (m, 5H), 3.52–3.46 (m, 2H), 3.39 (s, 3H), 1.90–1.59 (m, 6H); ^{13}C NMR (100 Hz, CDCl$_3$) δ 138.98 (1C), 128.75 (2C), 128.69 (1C), 126.49 (2C), 116.93 (1C), 91.28 (1C), 51.07 (1C), 47.72 (1C), 40.09 (1C), 24.04 (1C), 19.54 (1C); IR ν cm^{-1} (neat): 3061, 2948, 2211, 1448, 1244, 1132; High Resolution Mass Spectrum [EI(+)]: m/z calcd for C$_{13}$H$_{16}$N$_2$O [M]$^+$ 216.1263, found 216.1237.

Obtained **3p** was deduced to be the single regio-isomer by use of GC (Shinwa Chemical Industries, Ltd. HR-1, 0.25 mmϕ×25 m) and NMR.

4.3.16. 2-(3-Bromo-4-methoxyphenyl)-2-methoxypiperidine-1-carbonitrile (3q) [from 1q]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.65 (s, 1H), 7.42 (d, J=6.8 Hz, 1H), 6.94 (d, J=8.8 Hz, 1H), 3.91 (s, 3H), 3.57–3.49 (m, 2H), 3.37 (s, 3H), 1.90–1.61 (m, 6H); ^{13}C NMR (100 Hz, CDCl$_3$) δ 156.10, 132.55, 131.53, 127.09, 116.65, 111.94, 90.50, 56.27, 51.05, 47.75, 39.79, 23.92, 19.52; IR ν cm^{-1} (neat): 2944, 2215, 1734, 1601, 1499, 1458; High Resolution Mass Spectrum [FAB(+)]: m/z calcd for C$_{14}$H$_{18}$BrN$_2$O$_2$ [M+H]$^+$ 325.0552, found 325.0557.

4.3.17. 2-(4-Methylphenyl)-2-methoxypiperidine-1-carbonitrile (3r) [from 1r]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.38 (d, J=8.3 Hz, 2H), 7.25 (d, J=7.8 Hz, 2H), 3.60–3.41 (m, 2H), 3.38 (s, 3H), 2.36 (s, 3H), 1.90–1.55 (m, 6H); IR ν cm^{-1} (neat): 2941, 2872, 2214, 1653, 1512, 1448, 1375, 1352, 1319; High Resolution Mass Spectrum [FAB(+)]: m/z calcd for C$_{14}$H$_{19}$N$_2$O [M+H]$^+$ 231.1497, found 231.1506.

4.4. 2-Methylpiperidine-1,2-dicarbonitrile (4) [from 3g]

A 50 mL flask containing 3g (154 mg, 1 mmol) and trimethylsilyl cyanide (198 mg, 2 mmol) in CH$_2$Cl$_2$ (3 mL) was stirred at 0 °C and TiCl$_4$ (0.07 mL, 0.5 mmol) was added dropwise. The mixture was then left to stir at this temperature while being monitored by TLC. Upon completion of the reaction, it was quenched by addition of 10 mL of H$_2$O and then extracted with CH$_2$Cl$_2$ (3×10 mL). The combined organic layer was then dried by anhydrous MgSO$_4$ and solvent removed in vacuo. The crude product was then subjected to silica gel column (n-hexane/AcOEt=10:1) to obtain 4 as an oil (97 mg, 65%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.58–3.44 (m, 1H), 3.38 (t, J=12.3 Hz, 1H), 2.08–1.79 (m, 3H), 1.78 (s, 3H), 1.72–1.55 (m, 3H); IR ν cm^{-1} (neat): 2992, 2224; High Resolution Mass Spectrum [EI(+)]: m/z calcd for C$_8$H$_{11}$N$_3$ [M]$^+$ 149.0953, found 149.0944.

4.5. 2-Allyl-2-methylpiperidine-1-carbonitrile (5) [from 3g]

A 50 mL flask containing 3g (154 mg, 1 mmol) and allyltrimethylsilane (228 mg, 2 mmol) in CH$_2$Cl$_2$ (3 mL) was stirred at 0 °C and TiCl$_4$ (95 mg, 0.5 mmol) was added dropwise. The mixture was then left to stir at this temperature while being monitored by TLC. Upon completion of the reaction, it was quenched by addition of 10 mL of H$_2$O and then extracted with CH$_2$Cl$_2$ (3×10 mL). The combined organic layer was then dried by anhydrous MgSO$_4$ and solvent removed in vacuo. The crude product was then subjected to silica gel column (n-hexane/AcOEt=10:1) to obtain 5 as an oil (112 mg, 68%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.84–5.72 (m, 1H), 5.19–5.11 (m, 2H), 3.42–3.20 (m, 2H), 2.61–2.36 (m, 2H), 1.78–1.40 (m, 6H), 1.30 (s, 3H); IR ν cm^{-1} (neat): 2970, 2945, 2868, 2212, 1641, 1456, 1383, 1311. Anal. Calcd for C$_{10}$H$_{16}$N$_2$: C, 73.13; H, 9.82; N, 17.06. Found: C, 72.82; H, 9.94; N, 17.24.

4.6. 2,2-Diallylpiperidine-1-carbonitrile (6) [from 3l]

A 50 mL flask containing 3l (176 mg, 1 mmol) and allyltrimethylsilane (228 mg, 2 mmol) in CH$_2$Cl$_2$ (3 mL) was stirred at −78 °C and BF$_3$·Et$_2$O (0.13 mL, 1 mmol) was added dropwise. The mixture was then left to stir as temperature increased to 0 °C while being monitored by TLC. Upon completion of the reaction, it was quenched by addition of 10 mL of H$_2$O and then extracted with CH$_2$Cl$_2$ (3×10 mL). The combined organic layer was then dried by anhydrous MgSO$_4$ and solvent removed in vacuo. The crude product was then subjected to silica gel column (n-hexane/AcOEt=10:1) to obtain 6 as an oil (91 mg, 52%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.82–5.65 (m, 2H), 5.22–5.10 (m, 4H), 3.76–3.60 (m, 2H), 2.59–2.45 (m, 2H), 2.40–2.20 (m, 2H), 2.19–1.85 (m, 2H), 1.80–1.50 (m, 2H).; IR ν cm^{-1} (neat): 2978, 2928, 2204, 1641, 1591, 1525, 1483, 1475; High Resolution Mass Spectrum [FAB(+)]: m/z calcd for C$_{11}$H$_{17}$N$_2$ [M+H]$^+$ 177.1392, found 177.1415.

Acknowledgements

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