Tetrahedron
journal homepage: www.elsevier.com

A formal method for the de-*N*,*N*-dialkylation of Sommelet–Hauser rearrangement products

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Amino acid
Ammonium ylide
De-alkylation
Rearrangement
Substitution

ABSTRACT

Selective amine de-alkylation enables the conversion of Sommelet–Hauser rearrangement products into 2-aryl-2-bromoacetic acid derivatives. These compounds are valuable synthetic intermediates in the synthesis of α-aryl-α-amino or α-aryl-β-amino acid derivatives. The method presented herein is a formal de-*N*,*N*-dialkylation of Sommelet–Hauser rearrangement products.

1. Introduction

The base-induced Sommelet–Hauser (S–H) rearrangement of *N*-benzylic glycine-derived tetraalkylammonium ylides is an interesting transformation in organic synthesis that can provide easy access to α-aryl-α-amino acid derivatives.[1,2] However, the synthetic utility of this rearrangement has been limited because the rearrangement affords an *N*,*N*-dialkyl-α-aryl-α-amino acid derivative as the product. No successful methods for removal of the *N*,*N*-dialkyl substituents to yield the corresponding *N*-free α-aryl-α-amino acid derivatives have been reported. *N*,*N*-Diallylic and *N*,*N*-dibenzylic substituents are known to be removable *N*,*N*-dialkyl substituents;[3,4] however, these substituents also function as reactive migrating groups and produce the corresponding [1,2] or [2,3] Stevens rearrangement products; this migration severely restricts the scope of substrates that can be used in the S–H rearrangement. Recently, we reported the amine de-alkylation[5,6] of α-amino acid analogs **1** with ethyl chloroformate to obtain the ring-opening product **2** (Scheme 1, path A).[7] The reaction of phenylalanine derivative **1a** afforded the ring-opening product **2a** as the sole product in an 88% yield; however, when the reaction of phenylglycine derivative **1b** was carried out under the same conditions, α-chloro-substituted (de-dialkylaminated) product **3b** (path B) was obtained as the major product (**2b**: 30%, **3b**: 34%). The phenyl substituent at the α-position, as in **1b**, would improve the reactivity for α-substitution to afford **3b**. Through further studies of the amine de-alkylation of **1b**, we found that the product ratio of **2**/**3** can be dramatically reversed by changing the structure of the *N*,*N*-substituents, and the α-halo-substituted product **3** is obtained with high selectivity. Herein, we report a selective amine de-alkylation, which enables the conversion of S–H rearrangement products (*N*,*N*-dialkyl-α-aryl-α-amino acid derivatives) into 2-aryl-2-haloacetic acid derivatives. The products act as valuable synthetic intermediates to afford α-aryl-α-amino- or β-amino acid analogs. Our method is a formal de-*N*,*N*-dialkylation method for Sommelet–Hauser rearrangement products.

2. Results and discussion

To investigate the substitution effects on the amine de-alkylation of *N*,*N*-dialkyl-α-aryl-α-amino acid derivatives, we prepared methyl 2-(dialkylamino)-2-phenylacetates **1** as a model S–H rearrangement product and examined their reactions (Table 1). First, we attempted the reaction of methyl 2-(dimethylamino)-2-phenylacetate (**1c**) with ethyl chloroformate (1.2 equiv) under reflux temperature in dichloromethane (entry 1). The corresponding de-methylated *N*-ethoxycarbonyl derivative **2c** (51%) and α-chloro-substituted product **3b** (41%) were obtained. When using cyanogen bromide (3 equiv) instead of ethyl chloroformate, the reaction proceeded smoothly at room temperature. The corresponding *N*-cyano derivative **2c'** (46%) and α-bromo-substituted product **3b'** (34%) were obtained (entry 2). Interestingly, the product ratios of the **2** to **3** were dramatically reversed by changing the structure of the *N*,*N*-substituents. For example, when the reactions of pyrrolidine derivatives **1d** were carried out with ethyl chloroformate or cyanogen bromide, the ring-opening products **2** were obtained in

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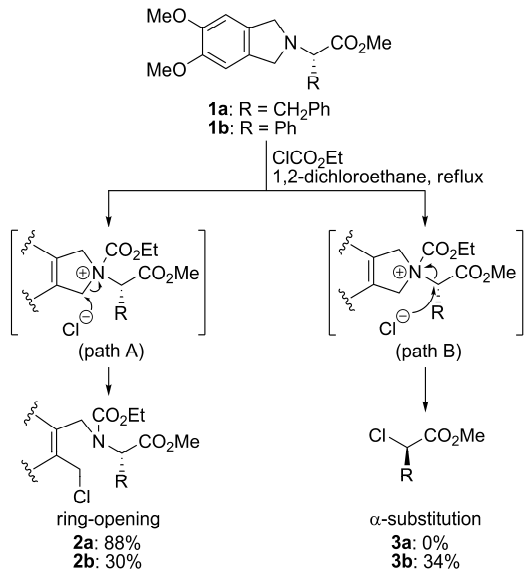
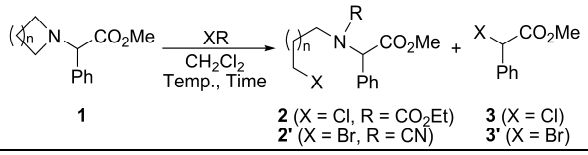
excellent yields (entry 3, **2d**: 93%; entry 4, **2d'**: 94%). In contrast, the reaction of piperidine derivative **1e** afforded **3** as the sole product without the formation of **2**. Although the reaction of **1e** with ethyl chloroformate resulted in a lower yield of **3b** (entry 5, 10%), the use of cyanogen bromide with a longer reaction time gave **3b'** in a good yield (entry 6, 89%).



Scheme 1 Pathways in the amine de-alkylation of **1** (ref. 7)

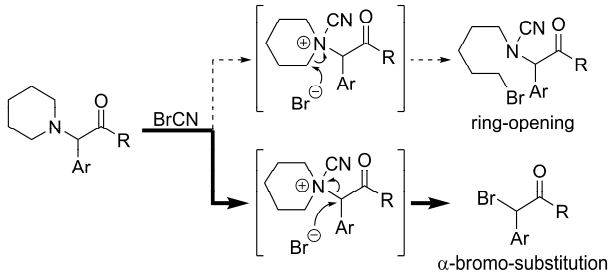
Table 1 The effects of *N*,*N*-substituents on the amine de-alkylation of **1**



Entry	n	XR[a]	Temp.	Time (h)	**2** (%)	**3** (%)
1	0 (**1c**)	$ClCO_2Et$	reflux	12	51[b] (**2c**)	41[c] (**3b**)
2	0 (**1c**)	BrCN	rt	1	46[c] (**2c'**)	34[b] (**3b'**)
3	2 (**1d**)	$ClCO_2Et$	reflux	12	93[b] (**2d**)	5[c] (**3b**)
4	2 (**1d**)	BrCN	rt	1	94[b] (**2d'**)	2[c] (**3b'**)
5	3 (**1e**)	$ClCO_2Et$	reflux	12	0 (**2e**)	10[c] (**3b**)
6	3 (**1e**)	BrCN	rt	12	trace[c] (**2e'**)	89[b] (**3b'**)

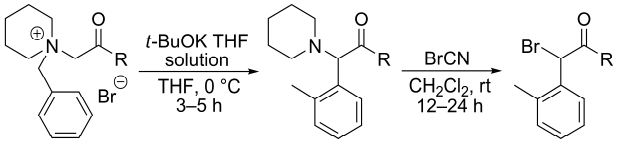
[a] $ClCO_2Et$: 1.2 equiv, BrCN: 3.0 equiv. [b] Isolated yield. [c] Determined by ^1H NMR assay of the crude product using mesitylene as an internal standard.

Prompted by this observation, we decided to investigate the scope and limitations of this type of α-bromo-substitution[8] (Scheme 2), which enables the conversion of S–H rearrangement products into α-aryl-α-bromoacetic acid derivatives **6** (Table 2). First, we examined the S–H rearrangement of ester- and amide-derived piperidinium salts **4a**–**4h** with potassium *tert*-butoxide THF solution.[2a] The corresponding rearrangement products **5a**–**5f** were obtained in good yields (entries 1–6, 78–99%). The rearrangement of Weinreb amide derivative **4g** resulted in a lower yield of **5g** (entry 7, 15%); however, the rearrangement of morpholine amide **4h**, the alternative derivative of Weinreb amide,[9] afforded the desired product **5h** in a good yield (entry 8, 82%). Next, the products **5**, thus obtained, were subjected to α-bromo-substitution by treatment with cyanogen bromide. Unfortunately, the reaction of ester derivatives **5a**–**5c** resulted in lower yields of **6** (entries 1–3, 20–56%) with the recovery of the starting material. The use of secondary amide derivative **5d** did not improve the yield of **6** (entry 4, **6d**: 21%); however, reactions of tertiary amides, such as *N*,*N*-dimethyl (**5e**), *N*,*N*-diethyl (**5f**), and morpholine (**5h**) amide derivatives proceeded to give the corresponding α-bromoacetamides **6** in acceptable yields (entry 5, **6e**: 68%; entry 6, **6f**: 70%; entry 8, **6h**: 76%) except for the reaction of Weinreb amide derivative **5g** (entry 7, **6g**: 53%).



Scheme 2 The α-substitution of piperidine derivative with cyanogen bromide

Table 2 Preparation of α-bromo-(*o*-tolyl)acetic acid derivatives **6** via S–H rearrangement and α-substitution with cyanogen bromide



Entry	R		**5** (%)[a]	**6** (%)[a]
1	OMe	**a**	78	20[b]
2	OEt	**b**	79	23[b]
3	OBu^t	**c**	96	56[b]
4	$NHBu^t$	**d**	83	21[b]
5	NMe_2	**e**	80	68
6	NEt_2	**f**	99	70
7	N(OMe)Me	**g**	15	53
8	morpholin-4-yl	**h**	82	76[b]

[a] Isolated yield. [b] The starting materials **5** were recovered (**5a**: 78%, **5b**: 55%, **5c**: 22%, **5d**: 76%, **5h**: 16%).

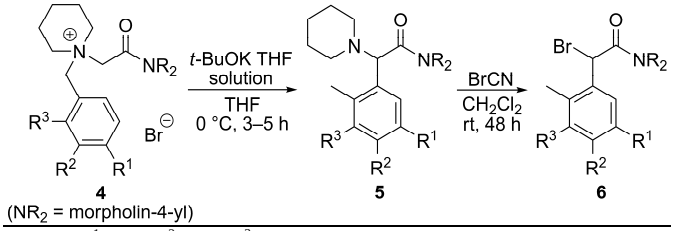
To further expand the scope of the present synthetic method, we prepared *ortho*-, *meta*-, and *para*-methyl- or chloro-substituted *N*-benzylic morpholine amide-derived piperidinium salts **4i**–**4n** and performed reactions with these compounds (Table 3). Because the morpholine amide serves as a useful precursor for further synthetic manipulation.[9] The desired products **6i**–**6n** were obtained in similar yields (entries 1–6).

The α-aryl-α-bromoacetamides **6**, thus obtained, can be converted into the corresponding amino acid precursors by re-substitution with nitrogen-containing nucleophiles (Table 4). The direct preparation of α-amino acid amide **7h** by treatment with aqueous ammonia failed (entries 1, 2). Thus, we prepared α-azide amide **8h** as a precursor of **7h** in a quantitative yield by treatment with sodium azide (entry 3). A reaction with sodium cyanide in acetonitrile did not proceed at all (entry 4); however, when the reaction was carried out in methanol, the corresponding α-cyano derivative **9h** was obtained in a quantitative yield (entry 5).

These results in hand, we prepared *N*-Boc-α-aryl-α-amino aldehydes **11** from **4** via S–H rearrangement and α-bromo substitution (Scheme 3). The substitution of **6** with sodium azide and hydrogenation of **8** afforded α-aryl-α-amino acid amides **7** in 81–94% yields (2 steps from **6**). A formal method for de-*N*,*N*-dialkylation of the S–H rearrangement product was successfully

developed. Furthermore, the Boc-protection of **7** and the reduction of the morpholine amide, as in **10**, with DIBAH afforded *N*-Boc-α-aryl amino aldehydes **11** in 66–70% yields (2 steps from **7**).

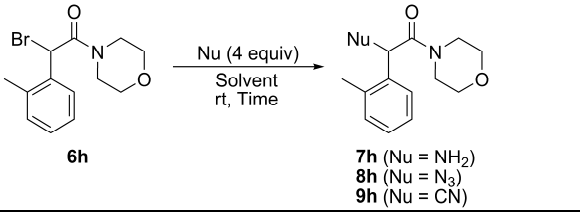
Table 3 Preparation of various types of α-aryl-α-bromoacetamides **6**



Entry	R^1	R^2	R^3		**5** (%)[a]	**6** (%)[a]
1	Me	H	H	**i**	93	76
2	H	Me	H	**j**	57[b]	81
3	H	H	Me	**k**	83	77
4	Cl	H	H	**l**	86	72
5	H	Cl	H	**m**	56[c]	68
6	H	H	Cl	**n**	82	69

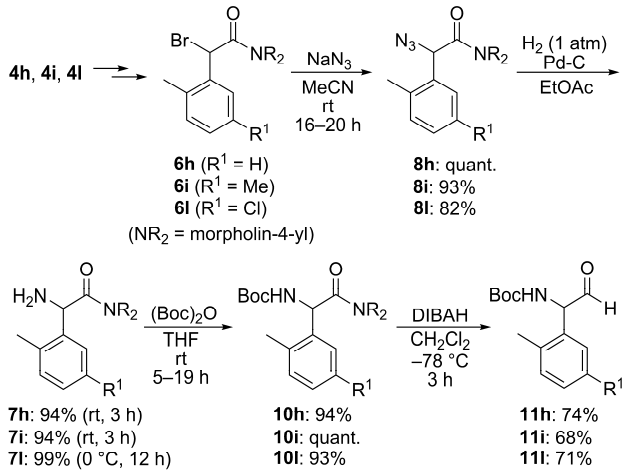
[a] Isolated yield. [b] The 2,6-dimethyl isomer was obtained in a 20% yield. [c] The 2-chloro-6-methyl isomer was obtained in a 24% yield.

Table 4 Preparation of amino acid precursors **7h**–**9h** by re-substitution of **6h** with nitrogen-containing nucleophiles



Entry	Nu	Solvent	Time (h)	Yield (%)[a]
1	aq. NH_3	MeCN	6	0 (**7h**)
2	aq. NH_3	MeOH	6	0 (**7h**)
3	NaN_3	MeCN	13	quant. (**8h**)
4	NaCN	MeCN	18	0[b] (**9h**)
5	NaCN	MeOH	24	quant. (**9h**)

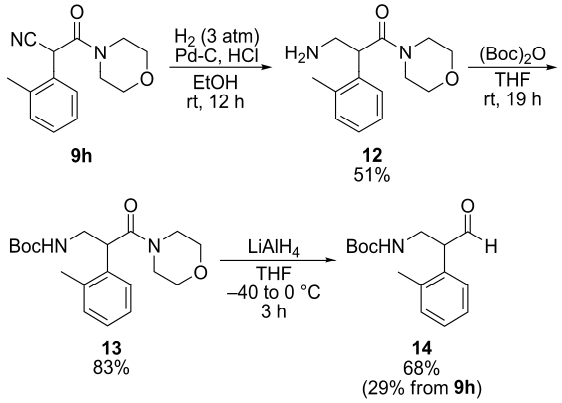
[a] Isolated yield. [b] The starting material **6h** was recovered quantitatively.



Scheme 3 Preparation of *N*-Boc-α-aryl-α-amino aldehydes **11**

Finally, our method was applied to preparation of α-aryl-β-amino aldehyde **14** from α-aryl-α-cyano amide **9h** by procedures similar to those shown in Scheme 3 (Scheme 4). The reduction of the cyano group by hydrogenation under a medium pressure (3 atm) in the presence of hydrogen chloride, the Boc-protection of the resulting primary amine **12**, and the reduction of morpholine amide **13** with lithium aluminum hydride[10] afforded **14** in a 29% overall yield.

In conclusion, we report the successful amine de-dialkylation of 2-(piperidin-1-yl)acetic acid derivatives **5** with cyanogen bromide. The products, 2-aryl-2-bromoacetic acid derivatives **6**, thus obtained are valuable synthetic intermediates and provide α-aryl-α-amino or β-amino acid derivatives. This method is a formal de-*N*,*N*-dialkylation of Sommelet–Hauser rearrangement products.



Scheme 4 Preparation of *N*-Boc-α-aryl-β-amino aldehydes **14**

3. Experimental

3.1. General

Infrared spectra were recorded on a Perkin Elmer Spectrum GX FT-IR spectrometer or a HITACHI Infrared 270–30 spectrometer. ^{1}H and ^{13}C NMR spectra were measured on a Varian 400 MHz spectrometer (^{1}H: 400 MHz, ^{13}C: 100 MHz), a 500 MHz spectrometer (^{1}H: 500 MHz, ^{13}C: 125 MHz), and a 700 MHz spectrometer (^{1}H: 700 MHz, ^{13}C: 175 MHz). The splitting patterns are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad peak. High-resolution mass spectra were measured on a Thermo Fisher Scientific LC/FT-MS spectrometer. Elemental analyses were performed on a Yanaco CHN Corder JM10. Reactions involving air- or moisture-sensitive compounds were conducted in appropriate round-bottomed flasks with a magnetic stirring bars under an argon atmosphere. Tetrahydrofuran (THF) was purchased from KANTO Chemical Co., Inc., Japan as an anhydrous solvent. Cyanogen bromide was purchased from KANTO Chemical Co., Inc., Japan. A 1.0 M THF solution of potassium *tert*-butoxide was purchased from Tokyo Chemical Industry Co., Ltd (TCI). For thin layer chromatography (TLC) analysis throughout this work, Merck TLC plates (silica gel 60 F_{254}) were used. The products were purified by preparative column chromatography on silica gel (silica gel 60N, spherical neutral, KANTO Chemical Co., Inc., Japan).

*3.2. Representative procedure for the amine de-alkylation of **1d** with ethyl chloroformate*

A solution of **1d** (133 mg, 0.607 mmol) in dichloromethane (3.0 mL) was treated with ethyl chloroformate (95%, 73 μL, 0.73 mmol) and refluxed for 12 h under an argon atmosphere. The resulting mixture was cooled at room temperature, and the volatiles were removed by evaporation. Purification of the residue by chromatography on silica gel (hexane/ethyl acetate = 5/1 to 3/1 as the eluent) gave **2d** (185 mg, 93% yield) as a colorless oil.

*3.2.1. Methyl 2-((ethoxycarbonyl)methylamino)-2-phenylacetate (**2c**)*

Colorless oil. IR (film) 3064, 3032, 2982, 2954, 1748, 1698, 1442, 1399, 1382, 1315, 1252, 1212, 1146, 1097, 1060, 1020, 902, 852, 776, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.31 (3H, m, Ph), 7.28-7.20 (2H, br, Ph), 6.18-5.82 (1H, br, CHCO), 4.21 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 3.79 (3H, s, OCH_3), 2.73 (3H, s, NCH_3), 1.29 (3H, t, *J* = 7.0 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 157.1, 134.5, 128.8, 128.7, 128.3, 62.1, 61.8, 52.1, 30.6, 14.5; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{13}H_{17}NO_4Na$: 274.1050. Found: 274.1042.

*3.2.2. Methyl 2-((4-chlorobutyl)(ethoxycarbonyl) amino)-2-phenylacetate (**2d**)*

Colorless oil. IR (film) 3064, 3031, 2981, 2955, 2872, 1749, 1697, 1454, 1435, 1413, 1383, 1299, 1263, 1210, 1158, 1112, 1075, 1023, 902, 854, 778, 742, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.25 (5H, m, Ph), 6.00-5.56 (1H, br, CHCO), 4.20 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 3.75 (3H, s, OCH_3), 3.40-3.22 (3H, br, CH_2Cl and NCH_2), 3.16-3.00 (1H, br, NCH_2), 1.62-1.40 (3H, br, CH_2), 1.37-1.04 (4H, br, CH_2 and OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 156.7, 134.3, 129.0, 128.5, 128.4, 62.6, 61.6, 52.0, 44.8, 44.2, 29.5, 26.2, 14.3; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{16}H_{22}ClNO_4Na$: 350.1130. Found: 350.1119.

*3.2.3. Methyl 2-chloro-2-phenylacetate (**3b**)*[11]

Colorless oil. IR (film) 3066, 3034, 3007, 2955, 2847, 1757, 1496, 1454, 1436, 1344, 1285, 1231, 1196, 1164, 1076, 1005, 924, 899, 855, 773, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51-7.46 (2H, m, Ph), 7.41-7.32 (3H, m, Ph), 5.36 (1H, s, CHCO), 3.76 (3H, s, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 135.7, 129.3, 128.8, 127.9, 58.9, 53.3.

*3.3. Representative procedure for the amine de-alkylation of **1e** with cyanogen bromide*

A solution of cyanogen bromide (95%, 0.16 g, 1.4 mmol) in dichloromethane (1.0 mL) was added to a solution of **1e** (112 mg, 0.480 mmol) in dichloromethane (1.4 mL) at room temperature under an argon atmosphere, and the solution was stirred for 12 h. The resulting solution was treated with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The combined extracts were washed with saturated aqueous sodium bromide, dried over sodium sulfate, and concentrated by evaporation. Purification of the residue by chromatography on silica gel (hexane/ethyl acetate = 15/1 to 10/1 as the eluent) afforded **3b'** (98 mg, 89% yield) as a colorless oil.

*3.3.1. Methyl 2-(N-methylcyanamido)-2-phenylacetate (**2c'**)*

White solid. IR (KBr) 2217, 1742, 1454, 1438, 1368, 1343, 1311, 1256, 1217, 1179, 1146, 1127, 1059, 986, 928, 876, 840, 770, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.33 (5H, m, Ph), 4.77 (1H, s, CHCO), 3.82 (3H, s, OCH_3), 2.91 (3H, s, NCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 132.2, 129.8, 129.1, 128.7, 116.7, 67.3, 52.8, 38.1; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{11}H_{12}N_2O_2Na$: 227.0791. Found: 227.0786.

*3.3.2. Methyl 2-(N-(4-bromobutyl)cyanamido)-2-phenylacetate (**2d'**)*

Colorless oil. IR (film) 3034, 2953, 2886, 2212, 1746, 1495, 1454, 1436, 1391, 1345, 1258, 1212, 1176, 1116, 1078, 1032, 1005, 992, 925, 868, 836, 773, 735, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48-7.41 (3H, m, Ph), 7.39-7.34 (2H, m, Ph), 4.80 (1H, s, CHCO), 3.82 (3H, s, OCH_3), 3.45-3.35 (2H, m, CH_2Br or NCH_2), 3.18-3.06 (2H, m, CH_2Br or NCH_2), 1.97-1.81 (4H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 132.3, 129.7, 129.1, 128.6, 115.2, 66.5, 52.8, 49.9, 32.6, 29.2, 26.0; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{14}H_{17}BrN_2O_2Na$: 347.0366. Found: 347.0358.

*3.3.3. Methyl 2-bromo-2-phenylacetate (**3b'**)*[12]

Colorless oil. IR (film) 3065, 3032, 3006, 2954, 1749, 1496, 1454, 1435, 1349, 1306, 1279, 1218, 1145, 1075, 1006, 924, 897, 843, 782 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57-7.50 (2H, m, Ph), 7.39-7.30 (3H, m, Ph), 5.36 (1H, s, CHCO), 3.77 (3H, s, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 135.7, 129.2, 128.8, 128.6, 53.3, 46.5.

*3.4. Representative procedure for the Sommelet–Hauser rearrangement of **4h***

A 1.0 M THF solution of potassium *tert*-butoxide (0.64 mL, 0.64 mmol) was added to a solution of **4h** (206 mg, 0.537 mmol) in THF (5.8 mL) at 0 °C. The mixture was stirred for 4 h at the same temperature under an argon atmosphere. The resulting mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined extracts were washed with saturated aqueous sodium hydrogen carbonate and brine. The solution was dried over sodium sulfate and concentrated. Purification of the residue by chromatography on silica gel (hexane/ethyl acetate = 1/6 to 1/8 as the eluent) gave **5h** (133 mg, 82% yield) as a pale yellow oil.

*3.4.1. Methyl 2-(2-methylphenyl)-2-(piperidin-1-yl)acetate (**5a**)*

Colorless oil. IR (film) 2916, 2848, 2790, 2745, 1722, 1430, 1255, 1150, 1120, 1010, 860, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57-7.51 (1H, m, ArH), 7.22-7.12 (3H, m, ArH), 4.26 (1H, s, CHCO), 3.66 (3H, s, OCH_3), 2.48-2.36 (4H, m, NCH_2), 2.42 (3H, s, $ArCH_3$), 1.62-1.52 (4H, m, CH_2), 1.48-1.40 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 137.3, 134.7, 130.5, 128.3, 127.6, 126.1, 70.4, 52.0, 51.7, 25.9, 24.4, 19.7; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{15}H_{22}NO_2$: 248.1645. Found: 248.1643.

*3.4.2. Ethyl 2-(2-methylphenyl)-2-(piperidin-1-yl)acetate (**5b**)*

Colorless oil. IR (film) 3064, 2934, 2853, 2802, 2757, 2709, 1744, 1486, 1444, 1389, 1368, 1336, 1307, 1258, 1186, 1154, 1123, 1067, 1030, 999, 940, 883, 860, 811, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58-7.52 (1H, m, ArH), 7.21-7.12 (3H, m, ArH), 4.23 (1H, s, CHCO), 4.16 (1H, dq, *J* = 10.7, 7.2 Hz, CH_2CH_3), 4.10 (1H, dq, *J* = 10.7, 7.2 Hz, CH_2CH_3), 2.48-2.37 (4H, m, NCH_2), 2.42 (3H, s, $ArCH_3$), 1.61-1.51 (4H, m, piperidinyl-CH_2), 1.48-1.40 (2H, m, piperidinyl-CH_2), 1.19 (3H, t, *J* = 7.2 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 137.2, 134.8, 130.4, 128.3, 127.5, 126.0, 70.4, 60.5, 51.9, 25.9, 24.5, 19.6, 14.1; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{24}NO_2$: 262.1802. Found: 262.1797.

*3.4.3. tert-Butyl 2-(2-methylphenyl)-2-(piperidin-1-yl)acetate (**5c**)*

Colorless oil. IR (film) 3059, 2975, 2933, 2854, 2801, 2757, 2709, 1740, 1455, 1392, 1367, 1340, 1275, 1257, 1230, 1205, 1145, 1038, 1003, 945, 883, 856, 815, 778, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57-7.51 (1H, m, ArH), 7.20-7.10 (3H, m, ArH), 4.12 (1H, s, CHCO), 2.51-2.36 (4H, m, NCH_2), 2.41 (3H, s, $ArCH_3$), 1.62-1.50 (4H, m, CH_2), 1.47-1.39 (2H, m, CH_2), 1.37 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 137.2, 135.4, 130.3, 128.2, 127.3, 125.9, 80.8, 70.9, 51.9, 27.9, 26.0, 24.6, 19.6; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{28}NO_2$: 290.2115. Found: 290.2110.

*3.4.4. N-tert-Butyl-2-(2-methylphenyl)-2-(piperidin-1-yl)acetamide (**5d**)*

White solid. IR (film) 3335, 3054, 3023, 2933, 2857, 2806, 2758, 1681, 1508, 1454, 1391, 1363, 1275, 1254, 1228, 1177, 1154, 1108, 1093, 1037, 992, 961, 874, 817, 788, 757, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.25 (1H, m, ArH), 7.20 (1H, br, NH), 7.18-7.10 (3H, m, ArH), 4.01 (1H, s, CHCO), 2.44 (3H, s, $ArCH_3$), 2.43-2.32 (4H, m, NCH_2), 1.63-1.41 (6H, m, CH_2), 1.35 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 137.5, 135.5, 130.7, 127.3, 127.2, 125.9, 71.7, 52.7, 50.4, 28.6, 26.4, 24.4, 20.5; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{29}N_2O$: 289.2274. Found: 289.2271.

*3.4.5. N,N-Dimethyl-2-(2-methylphenyl)-2-(piperidin-1-yl)acetamide (**5e**)*

Pale yellow oil. IR (film) 3020, 2930, 2850, 2752, 1645, 1487, 1454, 1396, 1335, 1306, 1260, 1217, 1136, 1117, 1103, 1055, 1036, 1001, 957, 878, 853, 795, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.34 (1H, m, ArH), 7.20-7.12 (3H, m, ArH), 4.57 (1H, s, CHCO), 2.93 (3H, s, NCH_3), 2.83 (3H, s, NCH_3), 2.73-2.65 (2H, m, NCH_2), 2.58-2.50 (2H, m, NCH_2), 2.45 (3H, s, $ArCH_3$), 1.57-1.39 (6H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 137.4, 134.6, 130.5, 128.8, 127.4, 125.7, 67.6, 51.0, 36.7, 35.7, 26.5, 24.7, 19.4; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{25}N_2O$: 261.1961. Found: 261.1956.

*3.4.6. N,N-Diethyl-2-(2-methylphenyl)-2-(piperidin-1-yl)acetamide (**5f**)*

Pale yellow oil. IR (film) 2968, 2931, 2850, 1648, 1454, 1427, 1378, 1305, 1250, 1218, 1135, 1118, 1104, 1035, 997, 949, 872, 860, 840, 778, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (1H, d, *J* = 7.2 Hz, ArH), 7.20-7.11 (3H, m, ArH), 4.53 (1H, s, CHCO), 3.54 (1H, dq, *J* = 14.3, 7.0 Hz, C*H*$_2$CH$_3$), 3.24-3.10 (2H, m, C*H*$_2$CH$_3$), 2.96 (1H, dq, *J* = 14.3, 7.0 Hz, C*H*$_2$CH$_3$), 2.78-2.69 (2H, m, piperidinyl-NCH_2), 2.60-2.51 (2H, m, piperidinyl-NCH_2), 2.44 (3H, s, $ArCH_3$), 1.57-1.38 (6H, m, piperidinyl-CH_2), 1.09 (3H, t, *J* = 7.0 Hz, CH$_2$C*H*$_3$), 0.96 (3H, t, *J* = 7.0 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 137.5, 134.9, 130.5, 128.9, 127.4, 125.6, 67.2, 50.8, 41.0, 40.0, 26.7, 24.7, 19.3, 14.0, 12.7; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{29}N_2O$: 289.2274. Found: 289.2270.

*3.4.7. N-Methoxy-N-methyl-2-(2-methylphenyl)-2-(piperidin-1-yl)acetamide (**5g**)*

Pale yellow oil. IR (film) 3059, 3018, 2933, 2851, 2749, 1671, 1460, 1411, 1377, 1305, 1287, 1271, 1212, 1172, 1114, 1086, 1036, 1008, 986, 878, 840, 810, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48-7.43 (1H, m, ArH), 7.21-7.12 (3H, m, ArH), 4.75 (1H, s, CHCO), 3.37 (3H, s, OCH_3), 3.13 (3H, s, NCH_3), 2.62-2.48 (4H, m, NCH_2), 2.44 (3H, s, $ArCH_3$), 1.60-1.47 (4H, m, CH_2), 1.47-1.37 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 137.6, 134.5, 130.3, 129.0, 127.5, 125.8, 65.9, 60.7, 51.6, 32.2, 26.2, 24.6, 19.5; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{25}N_2O_2$: 277.1911. Found: 277.1908.

*3.4.8. 2-(2-Methylphenyl)-1-morpholino-2-(piperidin-1-yl)ethanone (**5h**)*

Pale yellow gum. IR (film) 3063, 2927, 2852, 2756, 1650, 1486, 1452, 1429, 1360, 1300, 1271, 1228, 1173, 1115, 1068, 1034, 999, 961, 910, 856, 789, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.32 (1H, m, ArH), 7.20-7.14 (3H, m, ArH), 4.54 (1H, s, CHCO), 3.81-3.13 (8H, m, morpholinyl-CH_2), 2.76-2.65 (2H, m, piperidinyl-NCH_2), 2.59-2.50 (2H, m, piperidinyl-NCH_2), 2.43 (3H, s, $ArCH_3$), 1.59-1.40 (6H, m, piperidinyl-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 137.4, 134.5, 130.9, 128.8, 127.7, 125.7, 68.2, 66.9, 66.2, 51.2, 45.7, 42.0, 26.5, 24.7, 19.5; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{27}N_2O_2$: 303.2067. Found: 303.2060.

*3.4.9. 2-(2,5-Dimethylphenyl)-1-morpholino-2-(piperidin-1-yl)ethanone (**5i**)*

Pale yellow gum. IR (film) 2912, 2836, 1612, 1412, 1292, 1260, 1206, 1160, 1104, 1065, 1026, 990, 908, 846, 808, 786 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.16 (1H, d, *J* = 1.4 Hz, ArH), 7.06 (1H, d, *J* = 7.6 Hz, ArH), 7.00 (1H, dd, *J* = 7.6, 1.4 Hz, ArH), 4.48 (1H, s, CHCO), 3.85-3.07 (8H, m, morpholinyl-CH_2), 2.72-2.64 (2H, m, piperidinyl-NCH_2), 2.61-2.52 (2H, m, piperidinyl-NCH_2), 2.38 (3H, s, $ArCH_3$), 2.30 (3H, s, $ArCH_3$), 1.59-1.39 (6H, m, piperidinyl-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 135.1, 134.1, 133.9, 130.6, 129.3, 128.3, 67.8, 66.8, 66.1, 51.2, 45.6, 42.0, 26.4, 24.6, 20.9, 19.0; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{19}H_{29}N_2O_2$: 317.2224. Found: 317.2219.

*3.4.10. 2-(2,4-Dimethylphenyl)-1-morpholino-2-(piperidin-1-yl)ethanone (**5j**)*

Pale yellow oil. IR (film) 3030, 2916, 2844, 1626, 1418, 1256, 1224, 1165, 1104, 1030, 994, 848 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (1H, d, *J* = 8.0 Hz, ArH), 7.02-6.96 (2H, m, ArH), 4.49 (1H, s, CHCO), 3.82-3.14 (8H, m, morpholinyl-CH_2), 2.75-2.65 (2H, m, piperidinyl-NCH_2), 2.60-2.49 (2H, m, piperidinyl-NCH_2), 2.39 (3H, s, $ArCH_3$), 2.30 (3H, s, $ArCH_3$), 1.59-1.39 (6H, m, piperidinyl-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 137.2, 137.0, 131.6, 131.3, 128.7, 126.4, 67.9, 66.8, 66.2, 51.1, 45.6, 42.0, 26.5, 24.6, 20.9, 19.3; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{19}H_{29}N_2O_2$: 317.2224. Found: 317.2221.

*3.4.11. 2-(2,3-Dimethylphenyl)-1-morpholino-2-(piperidin-1-yl)ethanone (**5k**)*

Colorless gum. IR (film) 2908, 2844, 1626, 1418, 1255, 1216, 1168, 1106, 1026, 996, 854 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.16 (1H, d, *J* = 7.7 Hz, ArH), 7.10 (1H, d, *J* = 7.7 Hz, ArH), 7.06 (1H, dd, *J* = 7.7, 7.7 Hz, ArH), 4.59 (1H, s, CHCO), 3.81-3.30 (6H, m, morpholinyl-CH_2), 3.27-3.08 (2H, m, morpholinyl-CH_2), 2.77-2.71 (2H, m, piperidinyl-NCH_2), 2.60-2.53 (2H, m, piperidinyl-NCH_2), 2.32 (3H, s, $ArCH_3$), 2.30 (3H, s, $ArCH_3$), 1.55-1.41 (6H, m, piperidinyl-CH_2); ^{13}C NMR (175 MHz, $CDCl_3$) δ 170.8, 137.4, 136.0, 134.3, 129.4, 126.6, 125.0, 68.3, 66.8, 66.1, 50.9, 45.6, 41.9, 26.6, 24.7, 20.9, 15.0; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{19}H_{29}N_2O_2$: 317.2224. Found: 317.2217.

*3.4.12. 2-(5-Chloro-2-methylphenyl)-1-morpholino-2-(piperidin-1-yl)ethanone (**5l**)*

Pale yellow gum. IR (film) 2916, 2848, 1624, 1420, 1395, 1258, 1220, 1104, 1030, 880, 855, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (1H, d, *J* = 2.2 Hz, ArH), 7.17 (1H, dd, *J* = 8.3, 2.2 Hz, ArH), 7.11 (1H, d, *J* = 8.3 Hz, ArH), 4.51 (1H, s, CHCO), 3.80-3.25 (8H, m, morpholinyl-CH_2), 2.73-2.63 (2H, m, piperidinyl-NCH_2), 2.59-2.48 (2H, m, piperidinyl-NCH_2), 2.39 (3H, s, $ArCH_3$), 1.62-1.40 (6H, m, piperidinyl-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 136.5, 135.7, 132.1, 131.6, 128.6, 127.7, 68.1, 66.9, 66.3, 51.3, 45.7, 42.2, 26.4, 24.5, 19.0; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{26}ClN_2O_2$: 337.1677. Found: 337.1671.

*3.4.13. 2-(4-Chloro-2-methylphenyl)-1-morpholino-2-(piperidin-1-yl)ethanone (**5m**)*

Pale yellow gum. IR (film) 2920, 2848, 1622, 1418, 1260, 1210, 1166, 1100, 1028, 996, 844 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.32 (1H, d, *J* = 8.4 Hz, ArH), 7.18 (1H, d, *J* = 2.1 Hz, ArH), 7.16 (1H, dd, *J* = 8.4, 2.1 Hz, ArH), 4.50 (1H, s, CHCO), 3.79-3.19 (8H, m, morpholinyl-CH_2), 2.71-2.65 (2H, m, piperidinyl-NCH_2), 2.56-2.49 (2H, m, piperidinyl-NCH_2), 2.41 (3H, s, $ArCH_3$), 1.59-1.41 (6H, m, piperidinyl-CH_2); ^{13}C NMR (175 MHz, $CDCl_3$) δ 169.8, 139.2, 133.15, 133.13, 130.6, 130.1, 125.7, 67.4, 66.8, 66.2, 51.1, 45.6, 42.0, 26.4, 24.5, 19.3; HRMS–ESI

(*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{26}ClN_2O_2$: 337.1677. Found: 337.1670.

*3.4.14. 2-(3-Chloro-2-methylphenyl)-1-morpholino-2-(piperidin-1-yl)ethanone (**5n**)*

Colorless oil. IR (film) 2892, 2844, 1624, 1565, 1414, 1294, 1206, 1166, 1104, 1065, 994, 850, 760, 730, 712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (1H, dd, *J* = 8.0, 1.2 Hz, ArH), 7.26 (1H, dd, *J* = 8.0, 1.2 Hz, ArH), 7.11 (1H, dd, *J* = 8.0, 8.0 Hz, ArH), 4.60 (1H, s, CHCO), 3.82-3.12 (8H, m, morpholinyl-CH_2), 2.80-2.69 (2H, m, piperidinyl-NCH_2), 2.61-2.51 (2H, m, piperidinyl-NCH_2), 2.48 (3H, s, $ArCH_3$), 1.58-1.40 (6H, m, piperidinyl-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 136.6, 135.6, 135.5, 128.8, 127.4, 126.3, 68.2, 66.8, 66.2, 50.9, 45.7, 42.0, 26.6, 24.6, 15.9; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{26}ClN_2O_2$: 337.1677. Found: 337.1672.

*3.5. Representative procedure for the substitution of **5h** with cyanogen bromide*

A solution of cyanogen bromide (120 mg, 1.08 mmol) in dichloromethane (0.55 mL) was added to a solution of **5h** (110 mg, 0.364 mmol) in dichloromethane (1.3 mL) at room temperature, and the solution was stirred for 24 h under an argon atmosphere. The reactant was quenched with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The combined extracts were washed with saturated aqueous sodium bromide, dried over sodium sulfate, and concentrated. Purification of the residue by chromatography on silica gel (hexane/ethyl acetate = 2/1 to 1/1 as the eluent) gave **6h** (82 mg, 76% yield) as a white solid.

*3.5.1. Methyl 2-bromo-2-(2-methylphenyl)acetate (**6a**)*

Colorless oil. IR (film) 2944, 1720, 1428, 1315, 1200, 1138, 996, 902, 850, 722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63-7.57 (1H, m, ArH), 7.27-7.15 (3H, m, ArH), 5.65 (1H, s, CHCO), 3.79 (3H, s, OCH_3), 2.41 (3H, s, $ArCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 136.0, 134.3, 130.8, 129.2, 128.7, 126.9, 53.4, 44.4, 19.2. Anal. Calcd for $C_{10}H_{11}BrO_2$: C, 49.41; H, 4.56. Found: C, 49.59; H, 4.62.

*3.5.2. Ethyl 2-bromo-2-(2-methylphenyl)acetate (**6b**)*

Colorless oil. IR (film) 3066, 2981, 2935, 2868, 1750, 1489, 1463, 1388, 1368, 1323, 1276, 1207, 1143, 1097, 1025, 956, 940, 866, 768, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64-7.59 (1H, m, ArH), 7.26-7.21 (2H, m, ArH), 7.20-7.15 (1H, m, ArH), 5.62 (1H, s, CHCO), 4.28 (1H, dq, *J* = 10.8, 7.2 Hz, CH_2CH$_3$), 4.23 (1H, dq, *J* = 10.8, 7.2 Hz, CH_2CH$_3$), 2.41 (3H, s, $ArCH_3$), 1.28 (3H, t, *J* = 7.2 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 136.0, 134.4, 130.8, 129.2, 128.7, 126.8, 62.6, 44.7, 19.3, 14.0. Anal. Calcd for $C_{11}H_{13}BrO_2$: C, 51.38; H, 5.10. Found: C, 51.52; H, 5.11.

*3.5.3. tert-Butyl 2-bromo-2-(2-methylphenyl)acetate (**6c**)*

Colorless oil. IR (film) 3067, 2979, 2931, 1745, 1484, 1460, 1393, 1369, 1323, 1284, 1256, 1225, 1135, 1054, 1034, 961, 846, 811, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63-7.58 (1H, m, ArH), 7.24-7.19 (2H, m, ArH), 7.18-7.13 (1H, m, ArH), 5.54 (1H, s, CHCO), 2.40 (3H, s, $ArCH_3$), 1.46 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 136.0, 134.8, 130.7, 128.9, 128.6, 126.7, 83.2, 46.2, 27.8, 19.3. Anal. Calcd for $C_{13}H_{17}BrO_2$: C, 54.75; H, 6.01. Found: C, 54.91; H, 6.01.

*3.5.4. 2-Bromo-N-tert-butyl-2-(2-methylphenyl)acetamide (**6d**)*

White solid. IR (KBr) 3292, 3072, 2976, 2925, 1656, 1551, 1482, 1456, 1393, 1364, 1348, 1290, 1253, 1223, 1183, 933, 852, 793, 773, 744, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.34 (1H, m, ArH), 7.23-7.13 (3H, m, ArH), 6.68 (1H, br, NH), 5.56 (1H, s, CHCO), 2.41 (3H, s, $ArCH_3$), 1.42 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 136.8, 136.5, 131.0, 129.1, 128.0, 126.7, 52.2, 50.2, 28.4, 19.2; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{13}H_{18}BrNONa$: 306.0464. Found: 306.0458.

*3.5.5. 2-Bromo-N,N-dimethyl-2-(2-methylphenyl)acetamide (**6e**)*

White solid. IR (KBr) 3004, 2924, 2857, 1650, 1602, 1487, 1458, 1396, 1311, 1288, 1264, 1204, 1174, 1136, 1056, 983, 851, 784, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59-7.53 (1H, m, ArH), 7.25-7.16 (3H, m, ArH), 5.95 (1H, s, CHCO), 3.04 (3H, s, NCH_3), 2.88 (3H, s, NCH_3), 2.42 (3H, s, $ArCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 135.2, 134.7, 130.7, 129.0, 128.5, 127.0, 46.6, 37.2, 36.8, 19.1; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{11}H_{14}BrNONa$: 278.0151. Found: 278.0148.

*3.5.6. 2-Bromo-N,N-diethyl-2-(2-methylphenyl)acetamide (**6f**)*

Pale yellow oil. IR (film) 3064, 2975, 2935, 2874, 1651, 1484, 1459, 1429, 1381, 1362, 1320, 1278, 1245, 1217, 1192, 1131, 1097, 1033, 952, 847, 822, 769, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63-7.56 (1H, m, ArH), 7.26-7.15 (3H, m, ArH), 5.91 (1H, s, CHCO), 3.52 (1H, dq, *J* = 13.4, 7.0 Hz, NCH_2CH$_3$), 3.34 (1H, dq, *J* = 13.4, 7.0 Hz, NCH_2CH$_3$), 3.16 (1H, dq, *J* = 14.9, 7.2 Hz, NCH_2CH$_3$), 3.12 (1H, dq, *J* = 14.9, 7.2 Hz, NCH_2CH$_3$), 2.42 (3H, s, $ArCH_3$), 1.14 (3H, t, *J* = 7.0 Hz, NCH_2CH_3), 1.04 (3H, t, *J* = 7.2 Hz, NCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 135.3, 135.1, 130.8, 129.0, 128.6, 127.1, 46.7, 42.3, 41.4, 19.1, 13.9, 12.5; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{13}H_{18}BrNONa$: 306.0464. Found: 306.0460.

*3.5.7. 2-Bromo-N-methoxy-N-methyl-2-(2-methylphenyl)acetamide (**6g**)*

Pale yellow oil. IR (film) 3064, 3023, 2973, 2938, 1679, 1488, 1461, 1413, 1381, 1313, 1290, 1256, 1168, 1117, 1088, 1053, 1033, 996, 939, 847, 818, 774, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61-7.55 (1H, m, ArH), 7.25-7.14 (3H, m, ArH), 6.22 (1H, s, CHCO), 3.34 (3H, s, OCH_3), 3.22 (3H, s, NCH_3), 2.43 (3H, s, $ArCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 135.5, 135.3, 130.6, 128.9, 128.5, 126.9, 61.0, 45.3, 32.9, 19.0; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{11}H_{14}BrNO_2Na$: 294.0100. Found: 294.0095.

*3.5.8. 2-Bromo-2-(2-methylphenyl)-1-morpholinoethanone (**6h**)*

White solid. IR (KBr) 2989, 2961, 2926, 2865, 1648, 1491, 1434, 1364, 1305, 1279, 1229, 1201, 1188, 1115, 1069, 1039, 970, 921, 858, 819, 779, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54-7.49 (1H, m, ArH), 7.28-7.17 (3H, m, ArH), 5.90 (1H, s, CHCO), 3.85-3.51 (5H, m, CH_2), 3.43-3.32 (1H, m, CH_2), 3.31-3.21 (1H, m, CH_2), 3.20-3.09 (1H, m, CH_2), 2.41 (3H, s, $ArCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 135.0, 134.6, 131.0, 129.2, 128.5, 127.1, 66.6, 66.0, 46.7, 46.4, 43.2, 19.2; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{13}H_{16}BrNO_2Na$: 320.0257. Found: 320.0252.

*3.5.9. 2-Bromo-2-(2,5-dimethylphenyl)-1-morpholinoethanone (**6i**)*

White solid. IR (film) 2960, 2916, 2848, 1642, 1418, 1258, 1230, 1206, 1108, 1028, 960 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (1H, s, ArH), 7.08 (1H, d, *J* = 8.1 Hz, ArH), 7.05 (1H, dd, *J* = 8.1, 1.4 Hz, ArH), 5.89 (1H, s, CHCO), 3.85-3.50 (5H, m, CH_2), 3.42-3.30 (1H, m, CH_2), 3.30-3.19 (1H, m, CH_2), 3.19-3.08 (1H, m, CH_2), 2.36 (3H, s, $ArCH_3$), 2.31 (3H, s, $ArCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 136.7, 134.3, 131.8, 130.9, 130.1,

128.8, 66.6, 66.0, 47.0, 46.4, 43.2, 20.9, 18.7; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{14}H_{19}BrNO_2$: 312.0594. Found: 312.0590.

*3.5.10. 2-Bromo-2-(2,4-dimethylphenyl)-1-morpholinoethanone (**6j**)*

White solid. IR (film) 2950, 2900, 2848, 1638, 1418, 1262, 1216, 1185, 1106, 1065, 1028, 962, 806, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (1H, d, *J* = 8.0 Hz, ArH), 7.04 (1H, d, *J* = 8.0 Hz, ArH), 7.01 (1H, s, ArH), 5.90 (1H, s, CHCO), 3.84-3.51 (5H, m, CH_2), 3.40-3.30 (1H, m, CH_2), 3.29-3.20 (1H, m, CH_2), 3.18-3.08 (1H, m, CH_2), 2.37 (3H, s, $ArCH_3$), 2.31 (3H, s, $ArCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 139.3, 134.8, 131.7, 131.6, 128.3, 127.8, 66.6, 66.0, 47.1, 46.4, 43.2, 21.0, 19.1; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{14}H_{19}BrNO_2$: 312.0594. Found: 312.0587.

*3.5.11. 2-Bromo-2-(2,3-dimethylphenyl)-1-morpholinoethanone (**6k**)*

White solid. IR (film) 3045, 2970, 2908, 2852, 1640, 1418, 1260, 1245, 1216, 1185, 1108, 1026, 960, 888, 850 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (1H, dd, *J* = 7.0, 2.2 Hz, ArH), 7.17-7.09 (2H, m, ArH), 5.97 (1H, s, CHCO), 3.85-3.49 (5H, m, CH_2), 3.39-3.19 (2H, m, CH_2), 3.17-3.06 (1H, m, CH_2), 2.31 (3H, s, $ArCH_3$), 2.30 (3H, s, $ArCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 137.7, 134.5, 133.6, 130.9, 126.4, 126.0, 66.6, 65.9, 48.2, 46.4, 43.2, 20.8, 14.9; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{14}H_{18}BrNO_2Na$: 334.0413. Found: 334.0408.

*3.5.12. 2-Bromo-2-(5-chloro-2-methylphenyl)-1-morpholinoethanone (**6l**)*

White solid. IR (film) 3045, 2920, 2852, 1642, 1414, 1258, 1215, 1110, 1030, 960, 886, 810, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (1H, d, *J* = 2.0 Hz, ArH), 7.21 (1H, dd, *J* = 8.1, 2.0 Hz, ArH), 7.12 (1H, d, *J* = 8.1 Hz, ArH), 5.79 (1H, s, CHCO), 3.79-3.58 (5H, m, CH_2), 3.49-3.34 (2H, m, CH_2), 3.30-3.18 (1H, m, CH_2), 2.35 (3H, s, $ArCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 136.3, 133.4, 132.6, 132.1, 129.2, 129.0, 66.7, 66.1, 46.5, 44.7, 43.3, 18.8; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{13}H_{15}BrClNO_2Na$: 353.9867. Found: 353.9863.

*3.5.13. 2-Bromo-2-(4-chloro-2-methylphenyl)-1-morpholinoethanone (**6m**)*

White solid. IR (film) 3035, 2956, 2908, 2848, 1626, 1594, 1416, 1258, 1212, 1104, 1065, 1030, 960, 875, 854, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (1H, d, *J* = 8.4 Hz, ArH), 7.23 (1H, dd, *J* = 8.4, 2.4 Hz, ArH), 7.19 (1H, d, *J* = 2.4 Hz, ArH), 5.81 (1H, s, CHCO), 3.79-3.58 (5H, m, CH_2), 3.47-3.32 (2H, m, CH_2), 3.26-3.14 (1H, m, CH_2), 2.38 (3H, s, $ArCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 136.8, 134.8, 133.1, 130.7, 130.3, 127.1, 66.6, 66.0, 46.4, 44.9, 43.2, 19.1; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{13}H_{15}BrClNO_2Na$: 353.9867. Found: 353.9861.

*3.5.14. 2-Bromo-2-(3-chloro-2-methylphenyl)-1-morpholinoethanone (**6n**)*

White solid. IR (film) 3030, 2960, 2892, 2848, 1636, 1570, 1416, 1260, 1216, 1108, 1012, 965, 846 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (1H, dd, *J* = 8.0, 0.8 Hz, ArH), 7.37 (1H, dd, *J* = 8.0, 0.8 Hz, ArH), 7.18 (1H, dd, *J* = 8.0, 8.0 Hz, ArH), 5.91 (1H, s, CHCO), 3.80-3.55 (5H, m, CH_2), 3.45-3.28 (2H, m, CH_2), 3.22-3.11 (1H, m, CH_2), 2.45 (3H, s, $ArCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 136.5, 135.4, 133.2, 130.0, 127.4, 127.3, 66.6, 66.0, 46.49, 46.46, 43.2, 15.8; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{13}H_{16}BrClNO_2$: 332.0047. Found: 332.0042.

*3.6. Representative procedure for the preparation of **8h** by the substitution of **6h** with sodium azide*

Sodium azide (0.47 g, 7.2 mmol) was added to a solution of **6h** (519 mg, 1.74 mmol) in acetonitrile (9 mL) at room temperature, and the mixture was stirred for 13 h. The resulting mixture was diluted with water and extracted with hexane. The combined extracts were washed with brine, dried over sodium sulfate, and concentrated to give **8h** (450 mg, quant.) as a white solid. The crude product was pure without further purification.

*3.6.1. 2-Azido-2-(2-methylphenyl)-1-morpholinoethanone (**8h**)*

White solid. IR (film) 3040, 2960, 2900, 2852, 2088, 1636, 1424, 1212, 1106, 1060, 1034, 966, 866 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.22 (4H, m, ArH), 4.97 (1H, s, CHCO), 3.93-3.83 (1H, m, CH_2), 3.77-3.68 (1H, m, CH_2), 3.64-3.43 (3H, m, CH_2), 3.22-3.07 (2H, m, CH_2), 2.96-2.86 (1H, m, CH_2), 2.44 (3H, s, $ArCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 136.3, 131.6, 131.5, 129.5, 127.1, 126.7, 66.6, 65.8, 60.7, 45.4, 42.5, 19.1; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{13}H_{16}N_4O_2Na$: 283.1165. Found: 283.1159.

*3.6.2. 2-Azido-2-(2,5-dimethylphenyl)-1-morpholinoethanone (**8i**)*

White solid. IR (film) 2904, 2848, 2076, 1634, 1424, 1210, 1102, 1060, 1032, 966, 925, 865, 810 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (1H, d, *J* = 7.8 Hz, ArH), 7.12 (1H, dd, *J* = 7.8, 1.2 Hz, ArH), 7.04 (1H, s, ArH), 4.95 (1H, s, CHCO), 3.93-3.83 (1H, m, CH_2), 3.78-3.67 (1H, m, CH_2), 3.65-3.43 (3H, m, CH_2), 3.22-3.06 (2H, m, CH_2), 2.97-2.87 (1H, m, CH_2), 2.38 (3H, s, $ArCH_3$), 2.32 (3H, s, $ArCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 136.3, 133.0, 131.4, 131.3, 130.2, 127.6, 66.6, 65.8, 60.7, 45.4, 42.5, 21.0, 18.6; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{14}H_{18}N_4O_2Na$: 297.1322. Found: 297.1319.

*3.6.3. 2-Azido-2-(5-chloro-2-methylphenyl)-1-morpholinoethanone (**8l**)*

White solid. IR (film) 3040, 2960, 2912, 2852, 2088, 1642, 1426, 1216, 1108, 1034, 968, 864, 816 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (1H, dd, *J* = 8.1, 2.0 Hz, ArH), 7.26 (1H, d, *J* = 2.0 Hz, ArH), 7.23 (1H, d, *J* = 8.1 Hz, ArH), 4.94 (1H, s, CHCO), 3.93-3.82 (1H, m, CH_2), 3.80-3.69 (1H, m, CH_2), 3.68-3.47 (3H, m, CH_2), 3.26-3.13 (2H, m, CH_2), 3.00-2.89 (1H, m, CH_2), 2.40 (3H, s, $ArCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 134.9, 133.5, 132.7, 132.5, 129.6, 127.1, 66.6, 65.9, 60.3, 45.5, 42.6, 18.7; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{13}H_{15}ClN_4O_2Na$: 317.0776. Found: 317.0772.

*3.7. Representative procedure for the preparation of **7h** by the hydrogenation of **8h***

A mixture of **8h** (165 mg, 0.634 mmol) and palladium on activated carbon (loading: 10 wt.%, 16 mg) in ethyl acetate (6.4 mL) was stirred for 3 h at room temperature under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite, and the filtrate was concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 1/1 to dichloromethane/methanol = 10/1 as the eluent) to obtain **7h** (140 mg, 94% yield) as a colorless oil.

*3.7.1. 2-Amino-2-(2-methylphenyl)-1-morpholinoethanone (**7h**)*

Colorless oil. IR (film) 3536, 3365, 3298, 2962, 2921, 2857, 1735, 1645, 1491, 1435, 1361, 1300, 1271, 1237, 1174, 1115, 1069, 1033, 967, 922, 891, 849, 819, 764, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25-7.14 (3H, m, ArH), 7.12-7.08 (1H, m, ArH), 4.77 (1H, s, CHCO), 3.91-3.79 (1H, m, CH_2), 3.75-3.64 (1H, m, CH_2), 3.62-3.49 (2H, m, CH_2), 3.49-3.39 (1H, m, CH_2), 3.23-3.13 (1H, m, CH_2), 3.10-3.00 (1H, m, CH_2), 3.00-2.90 (1H, m, CH_2), 2.47 (3H, s, $ArCH_3$), 2.25 (2H, br, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 138.7, 135.2, 131.0, 128.0, 126.8, 126.0,

66.6, 65.8, 53.9, 45.1, 42.6, 18.9; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{13}H_{19}N_2O_2$: 235.1441. Found: 235.1438.

*3.7.2. 2-Amino-2-(2,5-dimethylphenyl)-1-morpholinoethanone (**7i**)*

Colorless oil. IR (film) 3348, 3280, 2892, 2844, 1628, 1495, 1424, 1216, 1106, 1065, 1026, 955, 910, 880, 835, 808 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.09 (1H, d, *J* = 7.7 Hz, ArH), 7.01 (1H, dd, *J* = 7.7, 1.0 Hz, ArH), 6.92 (1H, s, ArH), 4.74 (1H, s, CHCO), 3.92-3.80 (1H, m, CH_2), 3.77-3.65 (1H, m, CH_2), 3.62-3.49 (2H, m, CH_2), 3.49-3.38 (1H, m, CH_2), 3.24-3.13 (1H, m, CH_2), 3.10-3.01 (1H, m, CH_2), 3.01-2.91 (1H, m, CH_2), 2.41 (3H, s, $ArCH_3$), 2.28 (3H, s, $ArCH_3$), 2.06 (2H, s, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 138.5, 136.4, 131.9, 131.0, 128.7, 126.6, 66.7, 65.9, 53.9, 45.1, 42.6, 20.9, 18.5; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{14}H_{21}N_2O_2$: 249.1598. Found: 249.1594.

*3.7.3. 2-Amino-2-(5-chloro-2-methylphenyl)-1-morpholinoethanone (**7l**)*

Colorless oil. IR (film) 3348, 2896, 2850, 1596, 1430, 1226, 1100, 1015, 968, 875, 814 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.18 (1H, dd, *J* = 8.1, 2.1 Hz, ArH), 7.15 (1H, d, *J* = 8.1 Hz, ArH), 7.12 (1H, d, *J* = 2.1 Hz, ArH), 4.74 (1H, s, CHCO), 3.89-3.82 (1H, m, CH_2), 3.75-3.68 (1H, m, CH_2), 3.63-3.53 (2H, m, CH_2), 3.52-3.46 (1H, m, CH_2), 3.24-3.17 (1H, m, CH_2), 3.16-3.10 (1H, m, CH_2), 3.01-2.93 (1H, m, CH_2), 2.43 (3H, s, $ArCH_3$), 2.03 (2H, s, NH_2); ^{13}C NMR (175 MHz, $CDCl_3$) δ 171.7, 140.5, 133.7, 132.4, 132.3, 128.0, 126.1, 66.6, 65.8, 53.6, 45.1, 42.6, 18.5; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{13}H_{18}ClN_2O_2$: 269.1051. Found: 269.1048.

*3.8. Representative procedure for the preparation of **10h** by the Boc-protection of **7h***

A mixture of **7h** (225 mg, 0.960 mmol) and di-*tert*-butyl dicarbonate (0.25 mL, 1.1 mmol) in THF (4.6 mL) was stirred for 5 h at room temperature. The solution was concentrated, and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 2/1 to 1/1 as the eluent) to obtain **10h** (301 mg, 94% yield) as a white solid.

*3.8.1. 2-(tert-Butoxycarbonylamino)-2-(2-methylphenyl)-1-morpholinoethanone (**10h**)*

White solid. IR (film) 3400, 3320, 3040, 2956, 2920, 2850, 1632, 1428, 1360, 1230, 1154, 1110, 1016, 885, 828 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26-7.15 (4H, m, ArH), 5.66 (1H, d, *J* = 8.8 Hz, CHCO or NH), 5.55 (1H, d, *J* = 8.8 Hz, CHCO or NH), 3.87-3.64 (2H, m, CH_2), 3.60-3.43 (3H, m, CH_2), 3.35-3.23 (1H, m, CH_2), 3.11-2.96 (2H, m, CH_2), 2.47 (3H, s, $ArCH_3$), 1.43 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 155.3, 136.3, 135.3, 131.2, 128.5, 127.1, 126.7, 79.8, 66.6, 65.9, 52.7, 45.4, 42.6, 28.3, 19.3; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{18}H_{26}N_2O_4Na$: 357.1785. Found: 357.1779.

*3.8.2. 2-(tert-Butoxycarbonylamino)-2-(2,5-dimethylphenyl)-1-morpholinoethanone (**10i**)*

White solid. IR (film) 3308, 2908, 2860, 1690, 1638, 1432, 1360, 1232, 1154, 1110, 1014, 810 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.09 (1H, d, *J* = 7.8 Hz, ArH), 7.03 (1H, dd, *J* = 7.8, 1.2 Hz, ArH), 6.98 (1H, s, ArH), 5.63 (1H, d, *J* = 9.0 Hz, CHCO or NH), 5.53 (1H, d, *J* = 9.0 Hz, CHCO or NH), 3.88-3.76 (1H, m, CH_2), 3.76-3.64 (1H, m, CH_2), 3.62-3.43 (3H, m, CH_2), 3.35-3.23 (1H, m, CH_2), 3.13-2.96 (2H, m, CH_2), 2.42 (3H, s, $ArCH_3$), 2.27 (3H, s, $ArCH_3$), 1.43 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 155.2, 136.2, 135.1, 132.9, 131.1, 129.2, 127.6, 79.7, 66.6, 65.9, 52.5, 45.3, 42.7, 28.3, 20.9, 18.8; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{19}H_{28}N_2O_4Na$: 371.1941. Found: 371.1938.

*3.8.3. 2-(tert-Butoxycarbonylamino)-2-(5-chloro-2-methylphenyl)-1-morpholinoethanone (**10l**)*

White solid. IR (film) 3300, 2950, 2916, 2852, 1685, 1638, 1430, 1362, 1232, 1154, 1110, 1018, 910, 890, 850, 812 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.20 (1H, dd, *J* = 8.1, 2.1 Hz, ArH), 7.19 (1H, s, ArH), 7.14 (1H, d, *J* = 8.1 Hz, ArH), 5.68 (1H, d, *J* = 8.8 Hz, CHCO or NH), 5.63 (1H, d, *J* = 8.8 Hz, CHCO or NH), 3.83-3.76 (1H, m, CH_2), 3.74-3.68 (1H, m, CH_2), 3.61-3.51 (3H, m, CH_2), 3.35-3.28 (1H, m, CH_2), 3.16-3.09 (1H, m, CH_2), 3.09-3.02 (1H, m, CH_2), 2.45 (3H, s, $ArCH_3$), 1.43 (9H, s, *t*-Bu); ^{13}C NMR (175 MHz, $CDCl_3$) δ 168.8, 155.1, 137.3, 134.6, 132.5, 132.2, 128.5, 127.1, 80.0, 66.6, 65.9, 52.1, 45.4, 42.7, 28.2, 18.8; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{18}H_{25}ClN_2O_4Na$: 391.1395. Found: 391.1392.

*3.9. Representative procedure for the preparation of **11h** by the reduction of **10h** with diisobutylaluminum hydride (DIBAH)*

A 1 M DIBAH solution in hexane (0.39 mL, 0.39 mmol) was added to a solution of **10h** (65 mg, 0.19 mmol) in dichloromethane (2 mL) at –78 °C under an argon atmosphere. The solution was stirred for 3 h at the same temperature and poured into ice-cold saturated aqueous potassium sodium tartrate. The mixture was extracted with dichloromethane, and the combined extracts were washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 2/1 as the eluent) to obtain **11h** (35 mg, 74% yield) as a colorless oil.

*3.9.1. 2-(tert-Butoxycarbonylamino)-2-(2-methylphenyl)acetaldehyde (**11h**)*

Colorless oil. IR (film) 3421, 3345, 3064, 2978, 2931, 2722, 1714, 1488, 1391, 1367, 1289, 1250, 1167, 1097, 1059, 1026, 944, 867, 823, 757, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.53 (1H, s, CHO), 7.29-7.18 (3H, m, ArH), 7.10 (1H, d, *J* = 6.8 Hz, ArH), 5.67-5.35 (2H, br, CHCO and NH), 2.48 (3H, s, $ArCH_3$), 1.43 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 155.1, 136.9, 132.0, 131.3, 128.7, 127.7, 126.8, 80.2, 61.7, 28.2, 19.5; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{14}H_{19}NO_3Na$: 272.1257. Found: 272.1257.

*3.9.2. 2-(tert-Butoxycarbonylamino)-2-(2,5-dimethylphenyl)acetaldehyde (**11i**)*

Pale yellow solid. IR (film) 3423, 3343, 3049, 2978, 2929, 2871, 2728, 1713, 1616, 1502, 1391, 1367, 1248, 1166, 1097, 1058, 1026, 951, 854, 814, 781, 738, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.52 (1H, s, CHO), 7.13 (1H, d, *J* = 7.8 Hz, ArH), 7.05 (1H, dd, *J* = 7.8, 1.2 Hz, ArH), 6.89 (1H, s, ArH), 5.64-5.49 (2H, m, CHCO and NH), 2.43 (3H, s, $ArCH_3$), 2.29 (3H, s, $ArCH_3$), 1.44 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.3, 155.0, 136.4, 133.8, 131.6, 131.2, 129.5, 128.3, 80.1, 61.7, 28.3, 20.9, 19.0; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{15}H_{21}NO_3Na$: 286.1414. Found: 286.1411.

*3.9.3. 2-(tert-Butoxycarbonylamino)-2-(5-chloro-2-methylphenyl)acetaldehyde (**11l**)*

Colorless oil. IR (film) 3419, 3338, 3054, 2977, 2925, 2868, 2725, 1702, 1598, 1491, 1390, 1367, 1276, 1250, 1165, 1120, 1088, 1056, 922, 876, 842, 814, 782, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.49 (1H, s, CHO), 7.22 (1H, dd, *J* = 8.1, 2.2 Hz, ArH), 7.17 (1H, d, *J* = 8.1 Hz, ArH), 7.11 (1H, s, ArH), 5.72 (1H, br, CHCO or NH), 5.55 (1H, d, *J* = 5.6 Hz, CHCO or NH), 2.46 (3H, s, $ArCH_3$), 1.44 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 154.9, 135.2, 133.9, 132.5, 128.7, 127.5, 80.5, 61.5, 28.2, 19.0; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{14}H_{18}ClNO_3Na$: 306.0867. Found: 306.0866.

*3.10. Preparation of **9h** by substitution of **6h** with sodium cyanide*

Sodium cyanide (150 mg, 3.1 mmol) was added to a solution of **6h** (218 mg, 0.731 mmol) in methanol (8 mL) at room temperature, and the mixture was stirred for 24 h. The resulting mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 1/1 to 1/2 as the eluent) to give 2-(2-methylphenyl)-3-morpholino-3-oxopropanenitrile (**9h**) (178 mg, quant.) as a white solid. IR (film) 2900, 2848, 2236, 1636, 1424, 1355, 1238, 1210, 1106, 1065, 1030, 992, 854, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (1H, dd, *J* = 7.4, 1.8 Hz, ArH), 7.34-7.22 (3H, m, ArH), 5.04 (1H, s, CHCO), 3.82-3.50 (5H, m, CH_2), 3.42-3.25 (2H, m, CH_2), 3.22-3.10 (1H, m, CH_2), 2.38 (3H, s, $ArCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 135.7, 131.3, 129.3, 128.8, 127.9, 127.2, 115.8, 66.4, 65.8, 46.3, 43.0, 40.3, 19.3; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{14}H_{16}N_2O_2Na$: 267.1104. Found: 267.1103.

*3.11. Preparation of **12** by the hydrogenation of **9h***

A mixture of **9h** (48 mg, 0.20 mmol) in ethanol (2 mL) was treated with a 4 M hydrogen chloride 1,4-dioxane solution (50 μL, 0.20 mmol) at 0 °C. Palladium on activated carbon (loading: 10 wt.%, 12 mg) was added to the solution, and the mixture was stirred for 12 h at room temperature under a medium pressure of hydrogen (3 atm). The resulting mixture was filtered through a pad of Celite, and the filtrate was concentrated. The residue was treated with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by chromatography on silica gel (dichloromethane/methanol = 10/1 to 5/1 as the eluent) to obtain 3-amino-2-(2-methylphenyl)-1-morpholinopropan-1-one (**12**) (25 mg, 51% yield) as a white gum. IR (film) 3376, 3297, 3062, 2962, 2923, 2858, 1638, 1490, 1459, 1435, 1385, 1361, 1300, 1270, 1235, 1173, 1115, 1068, 1034, 987, 964, 922, 841, 759, 728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22-7.08 (4H, m, ArH), 3.92 (1H, dd, *J* = 9.2, 3.6 Hz, CHCO), 3.89-3.82 (1H, m, morpholinyl-CH_2), 3.73-3.64 (1H, m, morpholinyl-CH_2), 3.57-3.40 (3H, m, morpholinyl-CH_2), 3.28 (1H, dd, *J* = 12.6, 9.2 Hz, C*H*$_2$CHCO), 3.26-3.17 (1H, m, morpholinyl-CH_2), 3.04-2.92 (2H, m, morpholinyl-CH_2), 2.79 (1H, dd, *J* = 12.6, 3.6 Hz, C*H*$_2$CHCO), 2.40 (3H, s, $ArCH_3$), 2.07 (2H, br, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 135.7, 134.5, 130.8, 127.2, 127.0, 126.6, 66.5, 65.9, 48.9, 45.3, 44.8, 42.0, 19.3; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{14}H_{21}N_2O_2$: 249.1598. Found: 249.1594.

*3.12. Preparation of **13** by Boc-protection of **12***

A mixture of **12** (72 mg, 0.29 mmol) and di-*tert*-butyl dicarbonate (75 μL, 0.33 mmol) in THF (3 mL) was stirred for 19 h at room temperature. The solution was concentrated, and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 1/1 as the eluent) to obtain 3-(*tert*-butoxycarbonylamino)-2-(2-methylphenyl)-1-morpholinopropan-1-one (**13**) (84 mg, 83% yield) as a white solid. IR (film) 3449, 3350, 3055, 2978, 2927, 2859, 1707, 1640, 1497, 1458, 1435, 1391, 1366, 1329, 1267, 1233, 1171, 1116, 1069, 1033, 937, 908, 862, 846, 738, 704 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.22-7.13 (3H, m, ArH), 7.08 (1H, dd, *J* = 7.4, 1.1 Hz, ArH), 5.33 (1H, br, NH), 4.06 (1H, dd, *J* = 9.1, 2.8 Hz, CHCO), 3.89-3.83 (1H, m, morpholinyl-CH_2), 3.72-3.66 (1H, m, morpholinyl-CH_2), 3.52 (1H, ddd, *J* = 11.2, 8.1, 2.8 Hz, C*H*$_2$CHCO), 3.49-3.38 (4H, m, C*H*$_2$CHCO and morpholinyl-CH_2), 3.23-3.15 (1H, m, morpholinyl-CH_2), 3.01-2.93 (2H, m, morpholinyl-CH_2), 2.48 (3H, s, $ArCH_3$), 1.42 (9H, s, *t*-Bu); ^{13}C NMR (175 MHz, $CDCl_3$) δ 171.3, 155.8, 135.2, 135.0, 130.9, 127.5, 126.8, 126.5, 78.9, 66.5, 65.8, 46.3, 45.4, 42.9, 42.1, 28.3, 19.2; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{19}H_{28}N_2O_4Na$: 371.1941. Found: 371.1935.

*3.13. Preparation of **14** by the reduction of **13** with lithium aluminum hydride*

A solution of **13** (52 mg, 0.15 mmol) in THF (1 mL) was added to a suspension of lithium aluminum hydride (15 mg, 0.32 mmol) in THF (0.5 mL) at –40 °C under an argon atmosphere. The mixture was stirred for 3 h at 0 °C and quenched with a small amount of 1 M aqueous potassium hydrogen sulfate. The mixture was filtered through a pad of Celite, and the filtrate was concentrated. The filtrate was diluted with ethyl acetate and washed with ice-cold 1 M hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine. The organic solution was dried over sodium sulfate and concentrated. Purification of the residue by chromatography on silica gel (hexane/ethyl acetate = 3/1 as the eluent) gave 3-(*tert*-butoxycarbonylamino)-2-(2-methylphenyl)propanal (**14**) (27 mg, 68% yield) as a colorless gum. IR (film) 3450, 3055, 2980, 2929, 2855, 2726, 1716, 1503, 1458, 1392, 1367, 1334, 1266, 1169, 1046, 980, 931, 892, 855, 739, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.70 (1H, s, CHO), 7.30-7.16 (3H, m, ArH), 6.91 (1H, dd, *J* = 7.4, 1.4 Hz, ArH), 4.96 (1H, br, NH), 4.13 (1H, dd, *J* = 8.2, 5.2 Hz, CHCO), 3.59 (1H, ddd, *J* = 14.2, 8.2, 6.0 Hz, C*H*$_2$CHCO), 3.44 (1H, dddd, *J* = 14.2, 7.2, 5.2, 0.8 Hz, C*H*$_2$CHCO), 2.45 (3H, s, $ArCH_3$), 1.41 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4, 155.7, 137.6, 132.0, 131.3, 128.0, 126.5, 79.4, 55.4, 40.4, 28.3, 19.7; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{15}H_{21}NO_3Na$: 286.1414. Found: 286.1411.

Acknowledgments

This work was supported by KAKENHI (Grant-in-Aid for Young Scientists (B), 23750037).

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at XXX.