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Radical Aminomethylation of Imines

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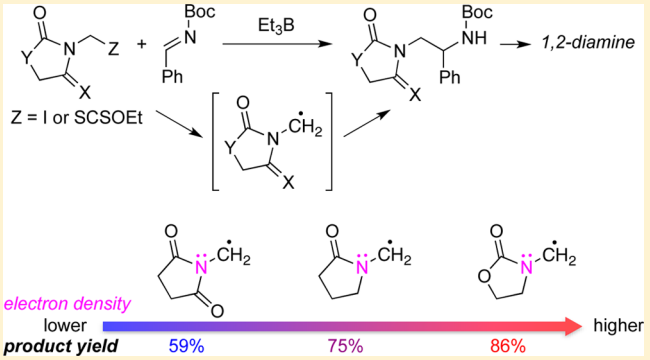
Supporting Information

ABSTRACT: Taking advantage of the high level of performance of *N*-alkoxycarbonyl-imines, we achieved the first example of addition of the aminomethyl radical to imine. The reaction efficiency depended on the structure of the radical precursor, whether it is an iodide or a xanthate, and an electron-withdrawing group on the nitrogen atom of the radical. This reaction allows direct introduction of an N-substituted aminomethyl group onto imine to provide 1,2-diamine as well as the short-step synthesis of ICI-199,441.



INTRODUCTION

1,2-Diamine is an abundant structural motif often found in natural products,[1] medicinal agents,[2] and ligands in metal catalysts,[3] and many efforts have been made to synthesize this functionality.[4] Addition of 1-aminoalkyl equivalents to imines is an attractive approach because vicinal arrangement of two amino functionalities and C−C bond formation are realized in one reaction. For example, the nitro-Mannich[5] and Strecker reactions[6] utilized nitronate and cyanide as 1-aminoalkyl and aminomethyl anion[7] equivalents, respectively. Compared with these anionic reactions, few were reported for a radical variant.[8]

Advantages of radical reactions in synthetic chemistry are their unique reactivity and functional group tolerance that is often complementary to ionic reactions. Alkyl radicals bearing an α-amino functionality are of great utility for the synthesis of amino acids, alkaloids, and other nitrogen-containing products.[9−15] A reduction process, which is required to obtain an amino functionality in nitro-Mannich and Strecker approaches, is avoidable. To date, addition reactions of 1-aminoalkyl, 1-amidoalkyl, or 1-imidoalkyl radicals to internal alkene,[9] aldehyde,[10] isocyanate,[11] external alkene or alkyne,[12] alkylidenemalonate,[13] fumarate,[14] and aromatic rings[15] have been developed; however, the reaction with imine has never been reported.[16] The difficulty in developing this reaction is likely due to (1) the instability of 1-amido- and 1-aminoalkyl radical precursors compared with their oxo analogues,[17] (2) the decreased nucleophilicity of 1-imidoalkyl radicals, and (3) the moderate electrophilicity of C═N bonds.[18]

We have been involved in the development of radical reactions[19] and recently reported that *N*-alkoxycarbonyl-imine as a radical acceptor was superior to the corresponding *N*-tosyl and *N*-*p*-methoxyphenyl analogues in the triethylborane-mediated addition reaction of alkyl radicals.[20] We expected that factors (2) and (3) mentioned above could be overcome by the use of *N*-alkoxycarbonyl-imine as a radical acceptor. Herein, we report addition of α-aminomethyl radicals to *N*-alkoxycarbonyl-imines to give 1,2-diamines and also the correlation between the reaction efficiency and the electron density on the nitrogen atoms of the radicals. To the best of our knowledge, this is the first example of an addition reaction of alkyl radicals bearing an α-amino functionality onto imine.

RESULTS AND DISCUSSION

To a solution of phthalimide **1a**[21] (3.0 equiv) and *N*-Boc-imine **2a** (1.0 mmol) in dichloromethane (1 mL) was added a 1.0 M solution of triethylborane (3.0 equiv) in hexane at −20 °C. The mixture was stirred at the same temperature while additional triethylborane (1.0 equiv each) was added every 2 h. After a total of 6 h, the expected adduct **5** was obtained in 48% yield (Table 1, entry 1). The use of succinimide **1b**, in place of **1a**, improved the reaction efficiency to give **6a** in 59% yield after 8 h (entry 2), probably because of the better solubility. Xanthate **1c**[12a] was not an efficient radical precursor in this reaction, and adduct **6a** was produced in only 11% yield (entry 3). The low efficiency of **1c** can be attributed to the low concentration of succinimidomethyl radical **B** due to the favorable reverse reaction to form a stable intermediate **A** (Scheme 1).[22]

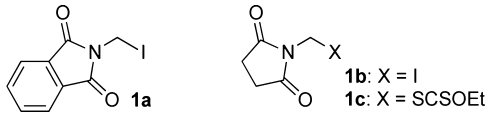


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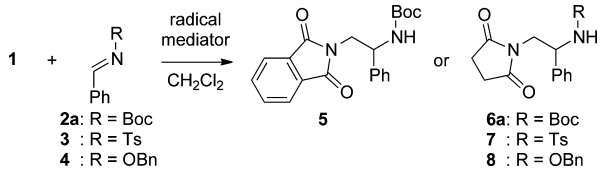
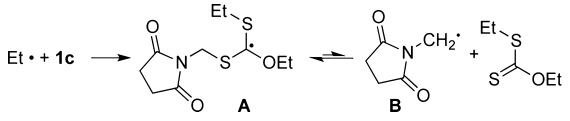
Table 1. Optimization of Conditions



entry	1	imine	mediator (equiv)	temp	time (h)	adduct	yield (%)
1	**1a**	**2a**	Et_3B (5)	−20 °C	6	**5**	48
2	**1b**	**2a**	Et_3B (6)	−20 °C	8	**6a**	59
3	**1c**	**2a**	Et_3B (7)	−20 °C	10	**6a**	11
4	**1b**	**2a**	Et_3B (5)	0 °C	6	**6a**	46
5	**1b**	**2a**	Et_3B (7)	−78 °C	10	**6a**	58
6	**1b**	**2a**	Me_2Zn (4)	−78 °C	4	**6a**	0
7	**1b**	**3**	Et_3B (6)	rt	8	**7**	16[a]
8[b]	**1b**	**4**	Et_3B (8)	rt	12	**8**	0

[a]*N*-(1-Phenylpropyl)-*p*-tosylamide was obtained in 61% yield. [b]In the presence of $BF_3{\cdot}OEt_2$ (2 equiv).

Scheme 1. Formation of Succinimidomethyl Radical B from 1c via A

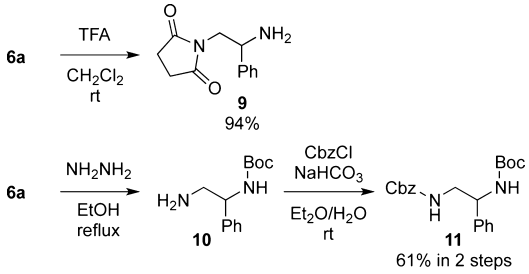


When the reaction with **1b** was conducted at 0 °C, the yield of **6a** was decreased to 46%, likely because of isocyanate formation (entry 4).[23] The reaction proceeded at −78 °C with the same level of efficiency, without any improvement in the yield (entry 5). The use of dimethylzinc in place of triethylborane led to the production of a complex mixture even at −78 °C (entry 6). As expected, the use of *N*-alkoxycarbonyl-imine is important for the reaction to proceed smoothly; the reaction of *N*-tosyl-imine **3**, instead of **2a**, was much slower even at rt, and **7** was produced in only 16% yield along with the ethyl adduct, *N*-(1-phenylpropyl)-*p*-tosylamide in 61% yield after 8 h (entry 7). Oxime ether **4**[24] failed to give the corresponding product in the absence or presence of $BF_3{\cdot}OEt_2$ (entry 8).

The established conditions (Table 1, entry 2) were applied to imidomethylation of other imines (Table 2). *N*-Cbz-imine **2b** was also a good acceptor for giving the corresponding adduct **6b** in good yield (entry 2). The reaction proceeded smoothly with *o*-tolualdimine **2c** bearing a sterically hindering methyl substituent. Electron-rich *p*-tolualdimine **2d** and *p*-anisaldimine **2e** as well as imines **2f** and **2g** having an electron-withdrawing group provided the corresponding products **6c**−**g** at similar yields (entries 3−7, respectively). The yields that were lower than those of the reactions with acyloxymethyl radical[20] likely indicate the decreased nucleophilicity of imidomethyl radical, due to the existence of the second carbonyl group. It is an advantage of this reaction that bromo and cyano substituents, labile functionalities under anionic conditions, were tolerated. The reaction with aliphatic imines, such as hydrocinnamaldimine, failed to proceed.

The two protecting groups of **6a** were selectively removable (Scheme 2). The treatment of **6a** with TFA removed the Boc

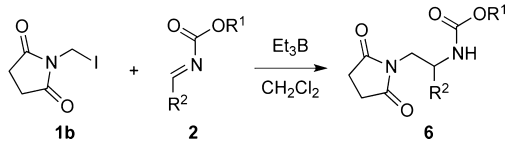
Scheme 2. Selective Deprotection



group to furnish **9** in 94% yield. The succinoyl group was removed using hydrazine, and after *N*-Cbz protection, the resulting amine **10** was isolated as dicarbamate **11** in 61% yield.

This methodology has the potential to directly introduce not only protected aminoalkyl groups but also those bearing desired N-substituents onto imines; thus, the reaction of *N*-alkylaminomethyl radical was next investigated (Scheme 3). It has been reported that the radical derived from xanthate **1e**, bearing a pyrrolidone moiety, underwent addition to alkene in poor yield because of its low stability.[12a] To our delight, the reaction of **1e** proceeded more smoothly than that with **1b**, and the desired product **12** was produced in 75% yield (eq 1). This observed difference seems reasonable because an alkene is nucleophilic while an imine is electrophilic. On the basis of the electron donating ability of an acylamino group being better than that of an acyloxy group, a higher nucleophilicity was expected for amidomethyl radicals. The yield, however, was not

Table 2. Substrate Scope



entry	2	R^1	R^2	Et_3B (equiv)	temp (°C)	time (h)	6	yield (%)
1[a]	**2a**	*t*-Bu	Ph	6	−20	8	**6a**	59
2	**2b**	Bn	Ph	8	−78	12	**6b**	58
3	**2c**	*t*-Bu	2-MeC_6H_4	7	−20	10	**6c**	62
4	**2d**	*t*-Bu	4-MeC_6H_4	7	−20	10	**6d**	59
5	**2e**	*t*-Bu	4-$MeOC_6H_4$	7	0	10	**6e**	58
6	**2f**	*t*-Bu	4-BrC_6H_4	7	−20	10	**6f**	64
7	**2g**	*t*-Bu	4-CNC_6H_4	8	−20	12	**6g**	59

[a]From entry 2 of Table 1 for comparison.

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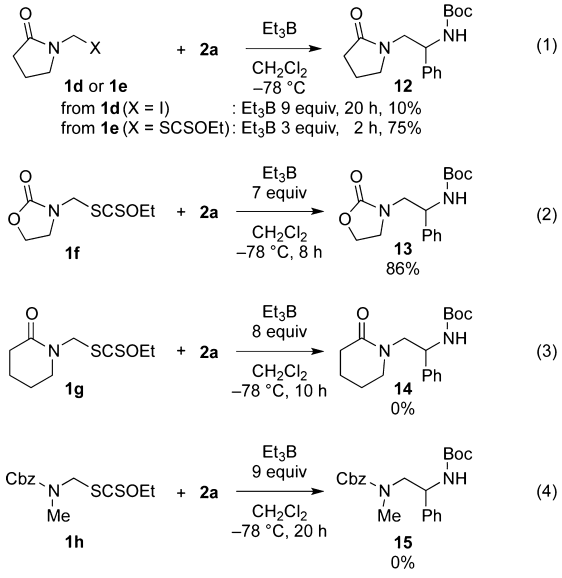
Scheme 3. Reactions with *N*-Alkylaminomethyl Radical Precursors 1d–h (3 equiv)

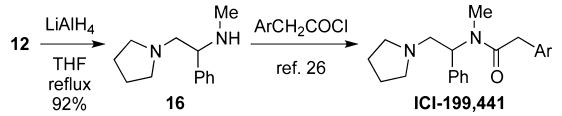


as high as those of the reaction with acyloxymethyl radicals (86–96%).[20] This could be explained by the low concentration of the amidomethyl radical generated from xanthate **1e**, due to the reversibility of its formation as shown in Scheme 1. Iodide **1d** was an unstable compound and used without purification. The reaction using crude **1d** gave **12** in only 10% yield along with a complex mixture, due to decomposition of the precursor.

Xanthate **1f**, bearing an oxazolidinone moiety, was a much better radical precursor, giving adduct **13** in 86% yield (eq 2). The results with **1b**, **1e**, and **1f** indicate that the performance of the radicals in this reaction should be correlated to the electron density on the nitrogen atom; the more rich in electrons the nitrogen, the higher the yield of the adduct. Interestingly, the reactions with six-membered and acyclic analogues **1g** and **1h** failed to proceed, resulting in hydrolysis of **2a**. Although the reason is so far unclear, the strain of the five-membered rings might result in enhancement of the electron donating character of the nitrogen atoms in the radicals derived from **1a–f**.

Adduct **12** was readily converted into a selective κ-opioid agonist ICI-199,441 (Scheme 4).[25] Reduction of **12** with

Scheme 4. Concise Synthesis of ICI-199,441 (Ar = 3,4-$Cl_2C_6H_3$)



lithium aluminum hydride converted the pyrrolidone into pyrrolidine and the carbamate into *N*-methylamine to give known intermediate **16**[26] in 92% yield. Unfortunately, an attempt to directly obtain the pyrrolidinylmethylated product using pyrrolidin-1-ylmethyl xanthate was unsuccessful, giving a complex mixture containing no detectable amount of the desired product. This was due to the instability of the xanthate, which was used as a crude material to prevent its decomposition during purification.

CONCLUSION

The first example of an addition reaction of alkyl radicals having an α-nitrogen functionality with imines was developed. In this reaction, N-substituted aminomethyl groups were introduced onto imines. The use of *N*-alkoxycarbonyl-imine was the key to overcoming the inferior nucleophilicity and/or low concentration of the radicals. In contrast to the addition reaction to alkenes, more electron-rich radicals showed better performance. The concentration of N-substituted aminomethyl radicals was likely another important factor. Therefore, to form the radicals at higher concentrations, iodides, rather than xanthates, should be the choice of radical precursors in this reaction unless they decompose under the reaction conditions. The difficulty of this reaction is in the trade-off between nucleophilicity and stability; the higher the nucleophilicity of the radical, the lower the stability of its precursor.

EXPERIMENTAL SECTION

General. All melting points are uncorrected. Silica gel was used for column chromatography. NMR (500 and 125 MHz for ^1H and ^{13}C, respectively) was measured in $CDCl_3$ unless otherwise mentioned. Chemical shifts (δ) and coupling constants (J) are presented in parts per million relative to tetramethylsilane and hertz, respectively. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C peak multiplicity assignments were made on the basis of DEPT data. The wave numbers of maximal absorption peaks of IR spectroscopy are presented in inverse centimeters. Quadrupole, double-focusing magnetic sector, and TOF mass spectrometers were used for EI-, FAB-, and ESI-MS, respectively. Solvents, including anhydrous dichloromethane and THF, hexane solutions of dimethylzinc and triethylborane, and oxazolidin-2-one, were purchased and used as received.

Starting Materials. Imines **2a**,[27] **2b**,[28] **2c–f**,[27] **2g**,[29] **3**,[30] and **4**;[31] iodides **1a**;[14] and xanthates **1c** and **1e**[12a] were prepared according to literature procedures.

*N-Iodomethylsuccinimide (**1b**).* A solution of *N*-chloromethylsuccinimide[32] (6.86 g, 46.0 mmol) and NaI (13.7 g, 103 mmol) in acetone (46 mL) was stirred at rt in the dark for 4 h and concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (46 mL) and filtered through an Al_2O_3 column (150 g). The filtrate was concentrated *in vacuo* and purified by recrystallization from EtOAc (2.5 mL) to afford the title compound (4.35 g, 40%) as white solids: mp 98.0–98.5 °C (EtOAc); ^1H NMR δ 2.75 (s, 4H), 5.20 (s, 2H); ^{13}C NMR δ 28.2 (CH_2), 174.5 (C); IR (KBr) 1750, 1141; EIMS m/z 239 (M^+), 112 (M − I). Anal. Calcd for $C_5H_6NO_2I$: C, 25.13; H, 2.53; N, 5.86. Found: C, 25.17; H, 2.65; N, 5.83. ^1H NMR data were identical to those reported previously.[33]

*O-Ethyl S-[(2-Oxooxazolidin-3-yl)methyl]dithiocarbonate (**1f**).* **1f** was prepared according to the reported procedure[12b] as follows. A stirred solution of oxazolidin-2-one (4.35 g, 50.0 mmol), paraformaldehyde (1.65 g, 55.0 mmol), and freshly distillated TMSCl (2.7 g, 0.25 mol) in acetonitrile (50 mL) was heated under reflux. After 16 h, volatile materials were removed by evaporation, and the residue was dissolved in acetone (50 mL). To the solution cooled in an ice–water bath was added potassium *O*-ethyl dithiocarbonate (8.80 g, 55.0 mmol) in one portion, and after 10 min, the cooling bath was removed. After 30 min, volatile materials were removed by evaporation, and the resulting solids were partitioned between water and CH_2Cl_2. The organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by column chromatography ($CHCl_3$) afforded the title compound (9.50 g, 86%) as a yellow oil: ^1H NMR δ 1.45 (t, J = 7.0, 3H), 3.67 (t, J = 8.0, 2H), 4.34 (t, J = 8.0, 2H), 4.69 (q, J = 7.0, 2H), 5.17 (s, 2H); ^{13}C NMR δ 13.7 (CH_3), 43.8 (CH_2), 50.4 (CH), 62.2 (CH_2), 70.8 (CH_2), 157.6 (C), 213.3 (C); IR (neat) 2985, 2901, 2885, 1759; ESIMS m/z 244 (M + Na), 192 (M − Et); HRMS-

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ESI (m/z) [M + Na]$^+$ calcd for $C_7H_{11}NNaO_3S_2$ 244.0073, found 244.0069.

*O-Ethyl S-[(2-Oxopiperidin-1-yl)methyl]dithiocarbonate (**1g**).* The same procedure as that for **1f** with piperidin-2-one (4.23 g, 50.0 mmol) in place of oxazolidin-2-one gave the title compound (9.09 g, 78%) as a yellow oil: ^{1}H NMR δ 1.44 (t, J = 7.0, 3H), 1.77−1.86 (m, 4H), 2.40 (t, J = 6.5, 2H), 3.46 (t, J = 6.0, 2H), 4.68 (q, J = 7.0, 2H), 5.24 (s, 2H); ^{13}C NMR δ 13.7 (CH_3), 21.1 (CH_2), 23.0 (CH_2), 32.3 (CH_2), 48.2 (CH_2), 52.7 (CH_2), 70.4 (CH_2), 170.5 (C), 214.7 (C); IR (neat) 2986, 1639, 1489; ESIMS m/z 256 (M + Na), 244 (M + H); HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_9H_{15}NNaO_2S_2$ 256.0436, found 256.0438.

*O-Ethyl S-[(N-Benzyloxycarbonyl-N-methylamino)methyl]-dithiocarbonate (**1h**).* The same procedure as that for **1f** with benzyl *N*-methylcarbamate[34] (8.26 g, 50.0 mmol) in place of oxazolidin-2-one gave the title compound (9.28 g, 62%) as a yellow oil: ^{1}H NMR δ 1.43 (t, J = 7.0, 3H), 3.02 (s, 3H), 4.63−4.69 (m, 2H), 5.12−5.23 (m, 4H), 7.25−7.37 (m, 5H); ^{13}C NMR δ 13.7 (CH_3), 34.2 and 34.8 (CH_3, rotamers), 55.5 and 55.9 (CH_2, rotamers), 67.7 (CH_2), 70.3 (CH_2), 127.9 (CH), 128.2 (CH), 128.5 (CH), 136.1 and 136.2 (C, rotamers), 155.4 and 156.0 (C, rotamers), 213.4 and 214.0 (C, rotamers); IR (neat) 3012, 1705, 1454, 1396; ESIMS m/z 322 (M + Na); HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{13}H_{17}NNaO_3S_2$ 322.0542, found 322.0540.

Radical Aminomethylation. *Typical Procedure (Table 2, entry 1). tert-Butyl N-(1-Phenyl-2-succinimidoethyl)carbamate (**6a**).* Imine **2a** (102 mg, 0.500 mmol) and iodide **1b** (365 mg, 1.50 mmol) in a dried 50 mL round-bottom flask capped with an argon balloon were dissolved in CH_2Cl_2 (2.5 mL). To the stirred solution cooled at −20 °C was added a 1.0 M hexane solution of Et_3B (1.5 mL, 1.5 mmol), and the argon balloon was replaced with a NaOH drying tube. The solution of Et_3B (0.5 mL, 0.5 mmol each) was added every 2 h. After the addition of 3 mmol of triethylborane in total, the mixture was stirred for an additional 2 h (total of 8 h) and concentrated. The resulting residue was purified by column chromatography (from 9/1 to 1/1 toluene/EtOAc) to give the title compound (94 mg, 59%) as a white solid: mp 161.0−161.5 °C (EtOAc); ^{1}H NMR δ 1.46 (s, 9H), 2.62−2.77 (m, 4H), 3.69 (dd, J = 3.5, 13.5, 1H), 3.85 (dd, J = 13.5, 13.5, 1H), 5.00 (m, 1H), 5.15 (d, J = 9.0, 1H), 7.28−7.38 (m, 5H); ^{13}C NMR δ 28.0 (CH_3), 28.2 (CH_2), 44.0 (CH), 53.3 (CH_2), 79.4 (C), 126.2 (CH), 127.7 (CH), 128.6 (CH), 139.2 (C), 155.3 (C), 177.1 (C); IR (KBr) 3317, 2970, 1767, 1697, 1535, 1435, 1404, 1319, 1250, 1173, 1080; FABMS m/z 319 (M + H), 202 (M − BocNH); HRMS-FAB (m/z) [M + H]$^+$ calcd for $C_{17}H_{23}N_2O_4$ 319.1658, found 319.1654.

*tert-Butyl N-(1-Phenyl-2-phthalimidoethyl)carbamate (**5**).* The typical procedure using **1a** (431 mg, 1.50 mmol) in place of **1b** under the conditions indicated in Table 1 and purification by column chromatography (from 19/1 to 1/1 toluene/EtOAc) gave the title compound (88 mg, 48%) as a white solid: mp 148.0−148.5 °C (EtOAc); ^{1}H NMR δ 1.25 (s, 9H), 3.85−4.05 (m, 2H), 5.10 (m, 1H), 5.32 (d, J = 8.0, 1H), 7.27−7.42 (m, 5H), 7.70−7.76 (m, 2H), 7.86 (dd, J = 3.0, 5.3, 2H); ^{13}C NMR δ 28.1 (CH_3), 43.2 (CH), 54.0 (CH_2), 79.5 (C), 123.4 (CH), 126.3 (CH), 127.9 (C), 128.8 (CH), 131.9 (C), 134.0 (CH), 139.2 (C), 155.3 (C), 168.4 (C); IR (neat) 3371, 3062, 1775, 1708, 1681, 1519, 1400, 1366, 1250, 1169; ESIMS m/z 389 (M + Na), 333 (M + Na − isobutene); HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{21}H_{22}N_2NaO_4$ 389.1472, found 389.1466.

*Benzyl N-(1-Phenyl-2-succinimidoethyl)carbamate (**6b**).* The typical procedure using **2b** (120 mg, 0.50 mmol) in place of **2a** under the conditions indicated in Table 2 gave the title compound (102 mg, 58%) as a white solid: mp 123.0−123.5 °C (EtOAc); ^{1}H NMR δ 2.48−2.65 (m, 4H), 3.71 (dd, J = 3.0, 14.0, 1H), 3.85 (dd, J = 10.5, 14.0, 1H), 4.98 (d, J = 12.5, 1H), 5.05 (m, 1H), 5.09 (d, J = 12.5, 1H), 5.58 (br s, 1H), 7.29−7.38 (m, 10H); ^{13}C NMR δ 27.9 (CH_3), 43.7 (CH), 54.0 (CH_2), 66.7 (CH_2), 126.3 (CH), 128.1 (CH), 128.4 (CH), 128.8 (CH), 136.4 (C), 138.6 (C), 155.9 (C), 177.5 (C); IR (neat) 3341, 3017, 2974, 2943, 1775, 1697, 1516, 1400, 1327, 1234, 1215, 1169, 1042; ESIMS m/z 375 (M + Na), 202 (M − CbzNH), 236 (M − succinimidomethyl), 235 (M − NHBoc); HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{20}H_{20}N_2NaO_4$ 375.1315, found 375.1299.

*tert-Butyl N-(2-Succinimido-1-o-tolylethyl)carbamate (**6c**).* The typical procedure using **2c** (110 mg, 0.50 mmol) in place of **2a** under the conditions indicated in Table 2 gave the title compound (103 mg, 62%) as a white solid: mp 164.0−164.5 °C (EtOAc); ^{1}H NMR δ 1.39 (s, 9H), 2.47 (s, 3H), 2.63−2.77 (m, 4H), 3.61 (d, J = 13.0, 1H), 3.86 (m, 1H), 5.16−5.28 (br s, 2H), 7.18−7.24 (m, 4H); ^{13}C NMR δ 19.1 (CH_3), 28.1 (CH_3), 28.2 (CH_2), 43.3 (CH), 49.7 (CH_2), 79.6 (C), 124.6 (CH), 126.3 (CH), 127.9 (CH), 131.0 (CH), 136.1 (C), 137.2 (C), 155.5 (C), 177.6 (C); IR (neat) 3394, 2978, 2935, 1705, 1504, 1400, 1366, 1250, 1173; ESIMS m/z 355 (M + Na), 234 (M − succinimido), 216 (M − NHBoc); HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{18}H_{24}N_2NaO_4$ 355.1628, found 355.1619.

*tert-Butyl N-(2-Succinimido-1-p-tolylethyl)carbamate (**6d**).* The typical procedure using **2d** (110 mg, 0.50 mmol) in place of **2a** under the conditions indicated in Table 2 gave the title compound (98 mg, 59%) as a white solid: mp 167.0−167.5 °C (EtOAc); ^{1}H NMR δ 1.39 (s, 9H), 2.34 (s, 3H), 2.62−2.76 (m, 4H), 3.67 (dd, J = 3.0, 12.5, 1H), 3.84 (dd, J = 12.0, 12.5, 1H), 4.97 (m, 1H), 5.15 (br d, J = 7.5, 1H), 7.17 (d, J = 8.0, 2H), 7.22 (d, J = 8.0, 2H); ^{13}C NMR δ 21.0 (CH_3), 28.1 (CH_3), 28.2 (CH_2), 44.2 (CH), 52.9 (CH_2), 79.5 (C), 126.2 (CH), 129.5 (CH), 135.9 (C), 137.7(C), 155.4 (C), 177.4 (C); IR (neat) 3363, 2978, 2947, 1775, 1701, 1508, 1400, 1172; ESIMS m/z 355 (M + Na), 234 (M − succinimido), 216 (M − NHBoc); HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{18}H_{24}N_2NaO_4$ 355.1628, found 355.1628.

*tert-Butyl N-[1-(4-Methoxyphenyl)-2-succinimidoethyl]-carbamate (**6e**).* The typical procedure using **2e** (118 mg, 0.50 mmol) in place of **2a** under the conditions indicated in Table 2 gave the title compound (101 mg, 58%) as a white solid: mp 150.0−150.5 °C (EtOAc); ^{1}H NMR δ 1.39 (s, 9H), 2.62−2.76 (m, 4H), 3.66 (dd, J = 3.0, 13.5, 1H), 3.80 (s, 3H), 3.84 (dd, J = 10.5, 13.5, 1H), 4.96 (m, 1H), 5.13 (br d, J = 7.0, 1H), 6.89 (d, J = 8.5, 2H), 7.25 (d, J = 8.5, 2H); ^{13}C NMR δ 28.1 (CH_3), 28.2 (CH_2), 44.2 (CH), 52.6 (CH_2), 55.3 (CH_3), 79.5 (C), 114.2 (CH), 127.5 (CH), 131.0 (C), 155.5 (C), 159.2 (C), 177.5 (C); IR (neat) 3371, 2974, 2897, 1701, 1400, 1049; ESIMS m/z 371 (M + Na), 250 (M − succinimido), 232 (M − NHBoc); HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{18}H_{24}N_2NaO_5$ 371.1577, found 371.1570.

*tert-Butyl N-[1-(4-Bromophenyl)-2-succinimidoethyl]carbamate (**6f**).* The typical procedure using **2f** (142 mg, 0.50 mmol) in place of **2a** under the conditions indicated in Table 2 gave the title compound (127 mg, 64%) as a white solid: mp 201.0−201.5 °C (EtOAc); ^{1}H NMR δ 1.39 (s, 9H), 2.64−2.77 (m, 4H), 3.67 (d, J = 11.5, 1H), 3.81 (dd, J = 11.5, 12.5, 1H), 4.95 (dd, J = 6.5, 12.5, 1H), 5.31 (d, J = 6.5, 1H), 7.22 (d, J = 8.5, 2H), 7.49 (d, J = 8.5, 2H); ^{13}C NMR δ 28.1 (CH_3), 28.2 (CH_2), 43.7 (CH), 53.1 (CH_2), 79.9 (C), 121.9 (C), 128.0 (CH), 131.9 (CH), 138.1 (C), 155.3 (C), 177.4 (C); IR (neat) 3345, 2974, 1775, 1697, 1512, 1400, 1169, 1072, 1045; ESIMS m/z 419 (M + Na), 299 (M − succinimido), 280 (M − NHBoc); HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{17}H_{21}BrN_2NaO_4$ 419.0577, found 419.0575.

*tert-Butyl N-[1-(4-Cyanophenyl)-2-succinimidoethyl]carbamate (**6g**).* The typical procedure using **2g** (115 mg, 0.50 mmol) in place of **2a** under the conditions indicated in Table 2 gave the title compound (101 mg, 59%) as a white solid: mp 198.0−198.5 °C (EtOAc); ^{1}H NMR δ 1.39 (s, 9H), 2.68−2.77 (m, 4H), 3.70 (d, J = 13.5, 1H), 3.81 (dd, J = 10.5, 13.5, 1H), 5.00 (m, 1H), 5.51 (d, J = 7.0, 1H), 7.46 (d, J = 8.0, 2H), 7.66 (d, J = 8.0, 2H); ^{13}C NMR δ 28.1 (CH_3), 28.2 (CH_2), 43.4 (CH), 53.9 (CH_2), 80.2 (C), 111.9 (C), 118.5 (C), 127.0 (CH), 132.6 (CH), 144.6 (C), 155.2 (C), 177.3 (C); IR (neat) 3391, 2974, 2230, 1701, 1508, 1404, 1215, 1169, 1049; ESIMS m/z 366 (M + Na), 227 (M − NHBoc); HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{18}H_{21}N_3NaO_4$ 366.1424, found 366.1415.

*N-(1-Phenyl-2-succinimidoethyl)-p-toluenesulfonamide (**7**).* The typical procedure using **3** (130 mg, 0.50 mmol) in place of **2a** under the conditions indicated in Table 1 and purification by column chromatography (from 19/1 to 1/1 toluene/EtOAc) gave the title compound (30 mg, 16%) as a white solid: mp 190.0−190.5 °C

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(EtOAc); ^{1}H NMR δ 2.37 (s, 3H), 2.63 (s, 4H), 3.59 (dd, J = 4.0, 14.0, 1H), 3.88 (dd, J = 11.0, 14.0, 1H), 4.63 (ddd, J = 4.0, 8.5, 11.0, 1H), 5.57 (d, J = 8.5, 1H), 7.13−7.25 (m, 7H), 7.58 (d, J = 8.0, 2H); ^{13}C NMR δ 21.4 (CH_3), 28.1 (CH_2), 43.6 (CH), 55.9 (CH_2), 126.3 (CH), 127.0 (CH), 128.1 (CH), 128.7 (CH), 129.4 (CH), 137.4 (C), 137.7 (C), 143.2 (C), 177.8 (C); IR (KBr) 3209, 1689, 1404, 1335, 1157, 1096; FABMS m/z 373 (M + H), 202 (M − TsNH); HRMS-FAB (m/z) [M + H]$^+$ calcd for $C_{19}H_{21}N_2O_4S$ 373.1217. found 373.1244. *N*-(1-Phenylpropyl)-*p*-tosylamide (87 mg, 61%) was also obtained[35] as a white solid and identified by ^{1}H NMR.[36]

*tert-Butyl N-[2-(2-Oxopyrrolidin-1-yl)-1-phenylethyl]carbamate (**12**).* 1-(Iodomethyl)pyrrolidin-2-one (**1d**) was prepared as follows. 1-(Chloromethyl)pyrrolidin-2-one[37] (268 mg, 2.01 mmol) and NaI (630 mg, 4.20 mmol) were dissolved in acetone (2 mL). The mixture was stirred at rt in the dark for 4 h and concentrated *in vacuo*. The residue was suspended in CH_2Cl_2 (1.3 mL), and the supernatant (1.0 mL) was used as a solution of 1.5 mmol of **1d** in the following reaction without purification. ^{1}H NMR indicated the supernatant mainly contained **1d**: ^{1}H NMR δ 2.11 (tt, J = 7.0, 8.0, 2H), 2.29 (t, J = 8.0, 2H), 3.34 (t, J = 7.0, 2H), 5.26 (s, 2H).

The typical procedure using **1d** (the solution described above) and **1e** (329 mg, 1.50 mmol) in place of **1b** under the conditions indicated in Scheme 3 and purification by column chromatography (9/1 hexane/EtOAc) gave the title compound (15 mg, 10%; 114 mg, 75%) as a white solid: mp 168.0−168.5 °C (EtOAc); ^{1}H NMR δ 1.40 (s, 9H), 1.93−2.02 (m, 2H), 2.38 (t, J = 8.0, 2H), 3.10 (m, 1H), 3.28 (dd, J = 4.0, 14.0, 1H), 3.53 (m, 1H), 3.78 (dd, J = 10.0, 14.0, 1H), 4.90 (m, 1H), 5.64 (d, J = 7.0, 1H), 7.27−7.36 (m, 5H); ^{13}C NMR δ 18.1 (CH_2), 28.3 (CH_3), 30.8 (CH_2), 47.9 (CH_2), 48.3 (CH_2), 53.6 (CH), 79.5 (C), 126.2 (CH), 127.6 (CH), 128.7 (CH), 140.0 (C), 155.5 (C), 176.4 (C); IR (neat) 3302, 2974, 2908, 2839, 1701, 1674, 1546, 1362, 1273, 1173, 1045; ESIMS m/z 327 (M + Na), 271 (M + Na − isobutene); HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{17}H_{24}N_2NaO_3$ 327.1679, found 327.1673.

*tert-Butyl N-[2-(2-Oxooxazolidin-3-yl)-1-phenylethyl]carbamate (**13**).* The typical procedure using **1f** (332 mg, 1.50 mmol) in place of **1b** under the conditions indicated in Scheme 3 and purification by column chromatography (9/1 hexane/EtOAc) gave the title compound (132 mg, 86%) as a white solid: mp 202.0−202.5 °C (EtOAc); ^{1}H NMR 1.42 (s, 9H), 3.33−3.39 (m, 2H), 3.70−3.79 (m, 2H), 4.27−4.31 (m, 2H), 4.94 (br m, 1H), 5.29 (br d, J = 7.0, 1H), 7.28−7.38 (m, 5H); ^{13}C NMR δ 28.2 (CH_3), 44.7 (CH), 49.5 (CH_2), 52.9 (CH), 62.1 (CH_2), 79.8 (C), 126.3 (CH), 127.9 (CH), 128.9 (CH), 139.3 (C), 155.6 (C), 159.2 (C); IR (neat) 3323, 2978, 1735, 1701, 1520, 1489, 1442, 1366, 1265, 1250, 1165, 1049; ESIMS m/z 307 (M + H), 251 (M + H − isobutene); HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{16}H_{23}N_2O_4$ 307.1652, found 307.1649.

Deprotection of 6a. *N-(2-Amino-2-phenylethyl)succinimide (**9**).* To a solution of **6a** (64 mg, 0.20 mmol) in CH_2Cl_2 (0.8 mL) was added TFA (0.4 mL) at rt. The mixture was stirred for 30 min and concentrated *in vacuo*. The remaining TFA was removed by three-time azeotropic distillation with toluene. The residue, containing a TFA salt of the title compound, was dissolved in Et_2O (2 mL) and poured into stirred aqueous 10% NaOH cooled in an ice−water bath. The whole was extracted three times with Et_2O. The combined organic layers were washed with brine, dried over K_2CO_3, and concentrated *in vacuo* to give the title compound (40 mg, 94%) as a colorless oil: ^{1}H NMR δ 2.68 (s, 4H), 3.02 (br s, 2H), 3.67 (dd, J = 4.5, 14.0, 1H), 3.82 (dd, J = 10.0, 14.0, 1H), 4.38 (br m, 1H), 7.30−7.42 (m, 5H); ^{13}C NMR 28.1 (CH_2), 45.9 (CH), 54.1 (CH_2), 126.2 (CH), 127.8 (CH), 128.7 (CH), 142.9 (C), 177.4 (C); IR (neat) 3352, 2360, 2337, 1697, 1651; ESIMS m/z 219 (M + H); HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{12}H_{15}N_2O_2$ 219.1128, found 219.1109.

*Benzyl N-(2-(tert-Butoxycarbonylamino)-2-phenylethyl)-carbamate (**11**).* To a solution of **6a** (64 mg, 0.20 mmol) in EtOH (1 mL) was added hydrazine monohydrate (58 μL, 1.2 mmol) at rt. The solution was heated under reflux for 48 h and cooled to rt. After the addition of water (1 mL), the whole was extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in Et_2O (1 mL), and saturated aqueous $NaHCO_3$ and $ClCO_2Bn$ (43 μL, 0.30 mmol) were added. The mixture was stirred for 30 min and extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting crude material was purified by column chromatography to afford the title compound (45 mg, 61%) as a colorless oil: ^{1}H NMR δ 1.40 (s, 9H), 3.51 (br s, 2H), 4.78 (br s, 1H), 5.07 (br s, 1H), 5.10 (d, J = 12.5, 1H), 5.11 (d, J = 12.5, 1H), 5.30 (br s, 1H), 7.22−7.40 (m, 10H); ^{13}C NMR δ 28.3 (CH_3), 46.4 (CH), 55.3 (CH_2), 66.9 (CH_2), 79.8 (C), 126.3 (CH), 127.7 (CH), 128.0 (CH), 128.1 (CH), 128.5 (CH), 128.8 (CH), 136.3 (C), 139.8 (C), 155.7 (C), 157.0 (C); IR (neat) 3365, 2978, 2886, 1775, 1709, 1519, 1219, 1138; ESIMS m/z 393 (M + Na), 313 (M − t-Bu); HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{21}H_{26}N_2NaO_4$ 393.1785, found 393.1785.

Formal Synthesis of ICI-199,441. *N-Methyl-1-phenyl-2-(pyrrolidin-1-yl)ethan-1-amine (**16**).* To a stirred solution of **12** (244 mg, 0.80 mmol) in anhydrous THF (1 mL) was added lithium aluminum hydride (128 mg, 3.20 mmol) portion-wise. The mixture was heated under reflux for 36 h and cooled to rt. After the addition of water (0.13 mL), 15% aqueous NaOH (0.13 mL), and then water (0.38 mL), the mixture was filtered through a Celite pad, which was washed successively with Et_2O. The combined filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography (EtOAc) to afford the title compound (150 mg, 92%) as a colorless oil: ^{1}H NMR δ 1.75−1.78 (m, 4H), 2.27 (m, 1H), 2.29 (s, 3H), 2.42−2.48 (m, 3H), 2.60−2.64 (m, 2H), 2.83 (dd, J = 11.0, 12.0, 1H), 3.58 (dd, J = 3.5, 11.0, 1H), 7.22−7.36 (m, 5H); ^{13}C NMR 23.5 (CH_2), 34.8 (CH_3), 54.1 (CH_2), 63.8 (CH), 64.3 (CH_2), 127.0 (CH), 127.3 (CH), 128.3 (CH), 142.7 (C); IR (neat) 3325, 2966, 2785, 1492, 1439, 1350, 1219, 1142, 1119, 1049; ESIMS m/z 227 (M + Na), 205 (M + H); HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{13}H_{20}N_2Na$ 227.1519, found 227.1521. ^{1}H and ^{13}C NMR data were identical to those reported previously.[38]

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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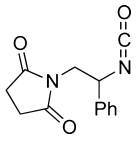

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