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Selective Ring-Opening of *N*-Alkyl Pyrrolidines with Chloroformates to 4-Chlorobutyl Carbamates

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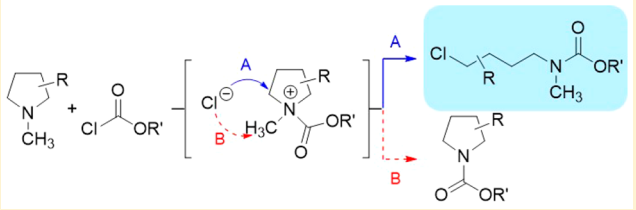
Supporting Information

ABSTRACT: Our study shows that among aza-heterocycles of various ring sizes, including aziridines, azetidines, pyrrolidines, and piperidines, only *N*-alkyl pyrrolidines undergo competitive reaction pathways with chloroformates to yield N-dealkylated pyrrolidines and 4-chlorobutyl carbamates. The pathway taken depends on the substituent on the nitrogen, i.e., ring-opening with methyl and ethyl substituents and dealkylation with a benzyl substituent. Computational calculations support the substituent-dependent product formation by showing the energy difference between the transition states of both reaction pathways. Selective ring-opening reactions of *N*-methyl and *N*-ethyl pyrrolidine derivatives with chloroformates were utilized to prepare various 4-chlorobutyl carbamate derivatives as valuable 1,4-bifunctional compounds.



1. INTRODUCTION

Reaction of *N*-alkyl-substituted cyclic amines with chloroformates can adopt two different pathways: N-dealkylation and ring-opening. Both pathways involve the formation of a common ammonium ion intermediate arising from a nucleophilic acyl substitution and differ at the subsequent reaction of the chloride ion at two different sites of the intermediate (Scheme 1).[1] Interestingly, it has been shown that the preference to either N-dealkylation or ring-opening processes varies with the size of the aza-ring. In general, reactions of *N*-alkyl aziridines and azetidines (three- and four-membered rings, respectively) generate 2-chloroethyl and 3-chloropropyl carbamates, respectively, through a ring-opening pathway with the release of ring strain [pathway (i), Scheme 1a].[2,3] Instead, *N*-alkyl piperidines (six-membered rings) give the corresponding *N*-cyclic carbamates via the dominant dealkylation pathway [pathway (ii), Scheme 1b].[4] In contrast, *N*-alkyl pyrrolidines (five-membered rings) may take both dealkylation and ring-opening pathways.[5] Since the scopes of the earlier studies on *N*-alkyl pyrrolidines are limited to a few reaction examples, systematic studies of a selective transformation of *N*-alkyl pyrrolidines are needed. This report describes the selective ring-opening reactions of *N*-methyl and *N*-ethyl pyrrolidines with chloroformates to generate various 4-chlorobutyl carbamate derivatives as valuable 1,4-bifunctional butane compounds [Scheme 1c]. Corroborated evidence for the selective transformation was found in the energy difference between the transition states of both reaction pathways obtained from computational calculations based on density functional theory (DFT).

Synthesis of 1,4-bifunctional chloroalkyl carbamates is challenging due to the presence of both nucleophilic and electrophilic moieties in the molecule. 4-Chlorobutyl carbamates are valuable compounds and can be utilized in many synthetic transformations, such as coupling reactions. They can also be easily converted to isocyanates and amine derivatives.

2. RESULTS AND DISCUSSION

To understand the dependence of selectivity on the *N*-alkyl substituent, we initiated our studies by investigating the reaction of several *N*-alkyl pyrrolidines (**1**) with isopropyl chloroformate (**2a**) (Scheme 2). The reaction of *N*-1-cyclohexenyl pyrrolidine (**1a**) with **2a** in CH_2Cl_2 was unselective and generated a mixture of dealkylated and ring-opened products [Scheme 2(1)], and the reaction of *N*-benzyl pyrrolidine (**1b**) with **2a** in CH_2Cl_2 gave mainly the debenzylated product [Scheme 2(2)].[3a] On the contrary, the reactions of *N*-ethyl (**1c**) and *N*-methyl pyrrolidines (**1d**) with **2a** selectively provided the corresponding 4-chlorobutyl carbamates (**4**) via the ring-opening pathway [Scheme 2(3) and (4)]. These results suggest that the preference to either the N-dealkylation or ring-opening pathway is highly dependent on the *N*-alkyl substituent.

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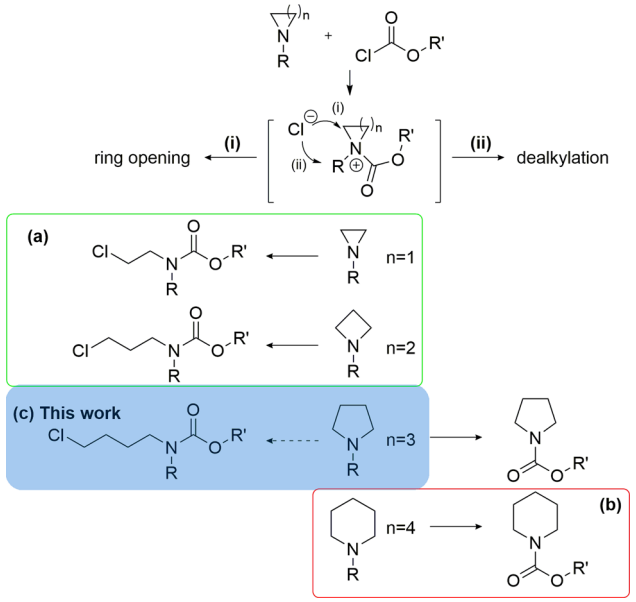
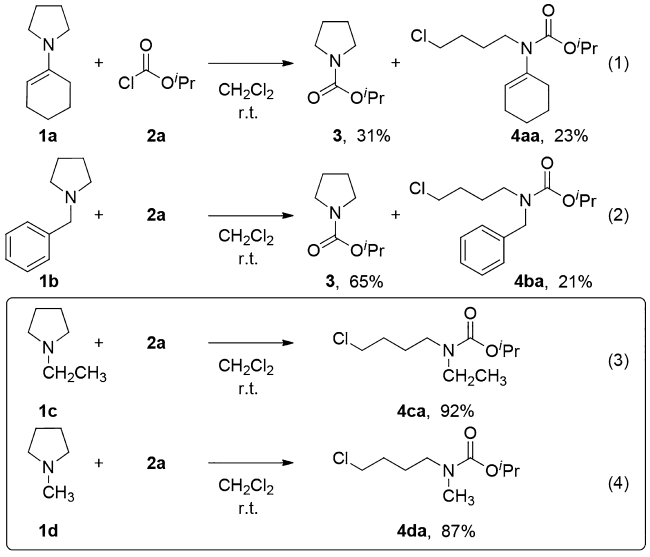
Scheme 1. (a) Ring-Opening Reactions of *N*-Alkyl Aziridines and Azetidines via Pathway (i), (b) N-Dealkylation of *N*-Alkyl Piperidines via Pathway (ii), and (c) Our Strategy for the Selective Ring-Opening Reaction of *N*-Alkyl Pyrrolidines



Scheme 2. Reactions of *N*-Alkyl Pyrrolidines (1) with Isopropyl Chloroformate (2a)[a]



[a]Yields of isolated products.

We assumed that the different reaction pathways taken by the *N*-alkyl pyrrolidines are strongly influenced by the conformation of the ammonium intermediates with chloride ion, which is determined by the *N*-alkyl substituent. This idea was supported by a computational approach through DFT calculations,[6] showing that the energies of the transition states of two reaction pathways significantly depend on the *N*-alkyl substituent. DFT calculations were performed using Gaussian 09 program[7] with the hybrid B3LYP[8] exchange−correlation functional and the 6-31++G(d,p)[9] basis set. The solvation effect by CH_2Cl_2 was taken into account by the polarization continuum model using IEFPCM.[10] Figure 1(1) shows the possible reaction pathways between *N*-methyl pyrrolidine (**1d**)

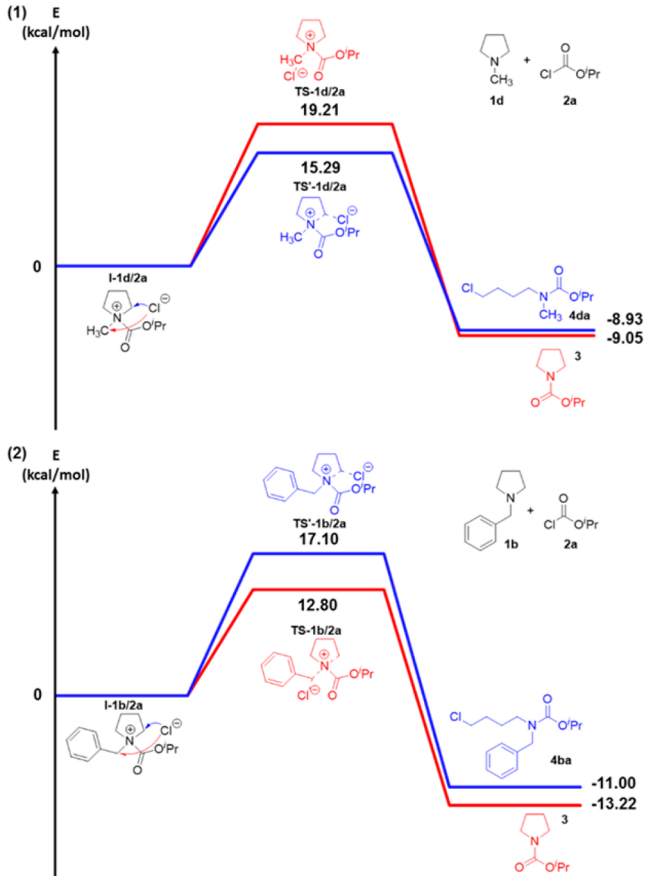


Figure 1. Energy profiles for the stationary points corresponding to the reaction of **2a** with **1d** (1) and **1b** (2).

and isopropyl chloroformate (**2a**). Starting from the intermediate complex (**I-1d/2a**) of the ammonium intermediate and the chloride ion, two reaction pathways can be hypothesized: one leading to the ring-opened product and the other to the demethylated product. The relative energies of the transition states and products in both pathways were calculated. Demethylated product **3** was obtained through transition state **TS-1d/2a**, and ring-opened product **4da** was obtained through transition state **TS′-1d/2a**. The difference in energy between the two transition states is 3.92 kcal/mol, corresponding to a 100/0 ratio of products **4da**/**3**. Thus, the ring-opening pathway yielding product **4da** is kinetically more favorable than the demethylation pathway yielding **3**. This result is in good agreement with the observed exclusive formation of **4da** shown in Scheme 2(4).[11] The same trend was observed in the DFT calculation results for the reaction between *N*-ethyl pyrrolidine (**1c**) and isopropyl chloroformate (**2a**) (Figure S1 in Supporting Information).

Figure 1(2) shows the preference of the dealkylation pathway in the reaction of *N*-benzyl pyrrolidine (**1b**) with isopropyl chloroformate (**2a**). The debenzylated product (**3**) is both kinetically and thermodynamically more favorable than the ring-opened product (**4ba**); this result also fits with the experimental results shown in Scheme 2(2). This favorable N-debenzylation was previously reported in the work of Couty, Evano, and co-workers by experiments and DFT calculations for the reaction of *N*-benzyl pyrrolidine with methyl chloroformate.[3a]

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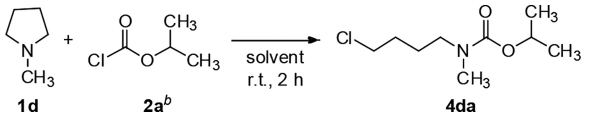
Having recognized the dependence of reactivity with the *N*-alkyl substituent of the pyrrolidines, the ring-opening process was utilized for the selective formation of valuable 4-chlorobutyl carbamate derivatives using *N*-methyl or *N*-ethyl-substituted pyrrolidines.

First, we studied the solvent and concentration effect on the selective ring-opening reaction of *N*-methyl pyrrolidine (**1d**) and isopropyl chloroformate (**2a**) as model substrates (Table 1). While chlorinated solvents including CH_2Cl_2, $CHCl_3$ (chloroform), and $C_2H_4Cl_2$ (dichloroethane) worked well (Table 1, entries 1−3), CH_3CN (acetonitrile) showed a relatively low reactivity (Table 1, entry 4) despite the same regioselectivity for the ring-opening process.[12] The reaction concentration did not show a significant effect on the reactivity (Table 1, entries 1, 5, and 6). It is noted that the selective transformation proceeds under extremely mild conditions of room temperature and in the absence of any additional additives.

Table 1. Optimization Studies with 1d[a]



1d **2a**[b] **4da**

entry	solvent	concentration (M)	yield (%)[c]
1	**CH_2Cl_2**	**0.2**	**86**
2	$CHCl_3$	0.2	83
3	$C_2H_4Cl_2$	0.2	81
4	CH_3CN	0.2	31
5	CH_2Cl_2	0.5	79
6	CH_2Cl_2	0.05	70

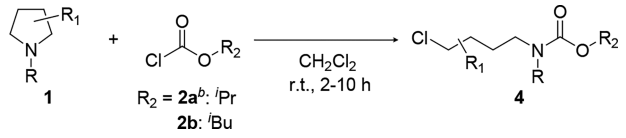
[a]Reaction conditions: **1d** (0.1 mmol), **2a** (0.14 mmol). [b]**2a** (1.0 M in toluene). [c]The yields were determined by gas chromatography with dodecane as an internal standard.

Next, we explored the reaction scope of the ring-opening process under the optimized conditions (0.2 M concentration in CH_2Cl_2) (Table 2). Several *N*-methyl and *N*-ethyl pyrrolidine derivatives (**1**) reacted efficiently with isopropyl chloroformate (**2a**) or isobutyl chloroformate (**2b**) to give the corresponding (4-chlorobutyl) (alkyl) carbamate derivatives in moderate to good yields. Notably, the abundant and well-known small natural product nicotine (**1e**) was utilized as a substrate toward the selective ring-opening process, providing highly functionalized chiral compounds (Table 2, entries 5 and 6). *N*-methyl indoline (**1f**) and *N*-ethyl indoline (**1g**) were also suitable substrates for the transformation (Table 2, entries 7−10). The reaction of *N*-ethyl ethyl prolinate (**1h**) provided a mixture of regioisomeric ring-opened products (Table 2, entries 11 and 12).

Interestingly, the reaction of the substrate containing a hydroxyl group, *N*-methyl-2-pyrrolidine ethanol (**1i**), generated ring-expanded oxepane-product **4ia′** by a further consecutive intramolecular nucleophilic substitution between the chloride and hydroxyl group of the ring-opened product (**4ia**) (Scheme 3).

The generality of the ring-opening process was further investigated using **1d** with various acid chloride derivatives, including benzyl chloroformate (**5**), allyl chloroformate (**7**), 4-chlorobenzoyl chloride (**9**), and *p*-toluenesulfonyl chloride (**11**) (Scheme 4). Despite the high regioselectivity of the ring-opening process, the reactions provided low yields of products with large amounts of acid chloride substrates remaining unreacted. Nevertheless, increasing the reaction temperature to 80 °C did not improve the reactivity, and similar yields were obtained.

Table 2. Substrate Scope for Ring-Opening Pathway of *N*-Methyl and *N*-Ethyl Pyrrolidine Derivatives[a]

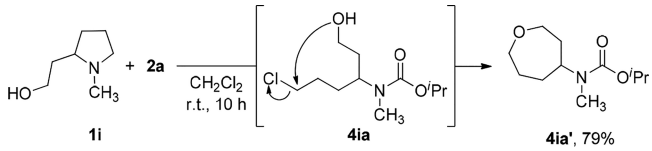


1 R_2 = **2a**[b]: ^{i}Pr, **2b**: ^{i}Bu **4**

entry	substrates	products	yield(%)[c]
1	**1c**	R_2 = ^{i}Pr, **4ca**	91
2	**1c**	R_2 = ^{i}Bu, **4cb**	93
3	**1d**	R_2 = ^{i}Pr, **4da**	85
4	**1d**	R_2 = ^{i}Bu, **4db**	91
5	**1e**	R_2 = ^{i}Pr, **4ea**	59
6	**1e**	R_2 = ^{i}Bu, **4eb**	67
7	**1f**	R_2 = ^{i}Pr, **4fa**	45[d]
8	**1f**	R_2 = ^{i}Bu, **4fb**	40[e]
9	**1g**	R_2 = ^{i}Pr, **4ga**	68[d]
10	**1g**	R_2 = ^{i}Bu, **4gb**	77[e]
11[f,g]	**1h**	R_2 = ^{i}Pr, **4ha**	86 (2:1)
12[f,g]	**1h**	R_2 = ^{i}Bu, **4hb**	90 (2:1)

[a]Reaction conditions: **1a** (1 mmol), **2a** (1.4 mmol). [b]**2a** (1.0 M in toluene). [c]Isolated yield. [d]48 h reaction time. [e]30 h reaction time. [f]0.5 mmol scale. [g]The minor regioisomeric position is labeled with "*".

Scheme 3. Reaction of 1i with 2a



1i **4ia** **4ia′**, 79%

Given the selectivity dependence of ring-opening and dealkylation pathways on the size of the aza-rings, the reaction

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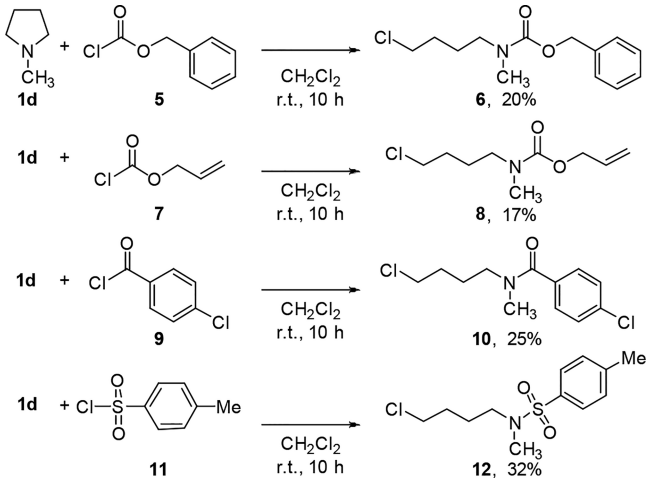
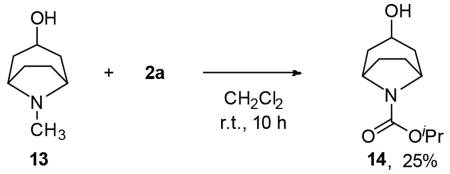
Scheme 4. Reaction of 1d with Various Acid Chloride Derivatives



of the natural product tropine (**13**) is of particular interest because the amine in **13** is part of a five- and a seven-membered ring at the same time. As an *N*-methyl-substituted five-membered ring amine, it would be expected to undergo a ring-opening process. Instead, a selective demethylation occurs, and **14** is exclusively obtained, together with unreacted **13**; the ring-opened product is not observed (Scheme 5). The energy profiles of both reaction pathways are shown in Figure S2 (Supporting Information).

Scheme 5. Reaction of Tropine (13) with 2a



3. CONCLUSIONS

In summary, we have described the selective ring-opening reactions of *N*-methyl and *N*-ethyl pyrrolidine derivatives with chloroformates to generate 4-chlorobutyl carbamate derivatives. The selectivity of the pathway is highly dependent on the *N*-alkyl substituent on the pyrrolidine ring, and the results are supported by DFT calculations. Readily available substituted *N*-alkyl pyrrolidines including nicotine and indoline could be utilized to generate highly 1,4-bifunctionalized 4-chlorobutyl carbamate derivatives via the ring-opening process. We believe that this method will provide a wide range of applications in organic synthesis and medicinal chemistry.

4. EXPERIMENTAL SECTION

General Information. CH_2Cl_2, $CHCl_3$, $C_2H_4Cl_2$, and CH_3CN were purchased from Sigma-Aldrich chemical company in Sure-Seal bottles. All other reagents were purchased from Sigma-Aldrich, Alfa Aesar, or TCI companies. Flash column chromatography was performed using Merck silica gel 60 (70−230 mesh).

General Analytical Information. The (4-chlorobutyl) (alkyl) carbamate products were characterized by ^{1}H, ^{13}C NMR, and FT-IR spectroscopy. NMR spectra were recorded on a Varian 600 MHz instrument (600 MHz for ^{1}H NMR and 151 MHz for ^{13}C NMR). Copies of ^{1}H and ^{13}C NMR spectra can be found at the end of the Supporting Information. ^{1}H NMR experiments are reported in units, parts per million (ppm), and were measured relative to residual chloroform (7.26 ppm) and dimethyl sulfoxide (2.50 ppm) in the deuterated solvent. ^{13}C NMR spectra are reported in ppm relative to deuterochloroform (77.23 ppm), and all were obtained with ^{1}H decoupling. Coupling constants were reported in Hz. FT-IR spectra were recorded on a Nicolet iS 10 ThermoFisher FT-IR spectrometer. Reactions were monitored by thin-layer chromatography (TLC) and GC-MS using the Agilent GC 7890*B*/5977A inert MSD with Triple-Axis Detector. Mass spectral data of all unknown compounds were obtained from the Korea Basic Science Institute (Daegu) on a Jeol JMS 700 high-resolution mass spectrometer. The mass analyzer type used for HRMS measurements is quadrupole. The chiralities of **4ea** and **4eb** were determined by polarimeter using the Rudolph Research Analytical Autopol IV.

Method for DFT Calculation. DFT was used with hybrid B3LYP exchange−correlation functional and 6-31++G(d,p) basis set. Using the Gaussian 09 program, all the molecules were optimized within the polarizable continuum model. The absence of vibrational normal modes with imaginary frequencies was checked to verify the quality of minimization procedure except for the transition state (TS) calculations. The TS geometries were verified by confirming the presence of vibrational normal modes with an imaginary frequency.

General Experimental Procedure for the Synthesis of 4-Chlorobutyl Carbamate (4). A tube equipped with a magnetic stirring bar was charged with *N*-alkyl pyrrolidine **1** (1 mmol). Then, CH_2Cl_2 (5 mL, 0.20 M) and isopropyl chloroformate **2a** (1.0 M in toluene, 1.4 mmol) were added, and the mixture was allowed to stir at room temperature for 2−10 h. The reaction was monitored by TLC. Upon completion, the reaction mixture was concentrated using a rotary evaporator and purified by silica gel column chromatography to give the corresponding 4-chlorobutyl carbamate **4**.

3:[3a] 102 mg, 65%, colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.90 (hept, J = 6.2 Hz, 1H), 3.39−3.34 (m, 2H), 3.32−3.27 (m, 2H), 1.88−1.78 (m, 4H), 1.23 (d, J = 6.2 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.2, 68.1, [46.2 and 45.9 (rotamers)], [25.9 and 25.2 (rotamers)], 22.6; MS m/z (EI) calcd for $C_8H_{15}NO_2$ [M+] 157.1103, found 157.0; R_f 0.66 (hex/EtOAc, 4/1).

4ba:[3a] 59 mg, 21%, colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (dd, J = 7.5, 7.3 Hz, 2H), 7.29−7.18 (m, 3H), 4.98 (hept, J = 6.2 Hz, 1H), 4.47 (s, 2H, rotamers), 3.56−3.46 (m, 2H), 3.32−3.14 (m, 2H), 1.80−1.55 (m, 4H), 1.26 (d, J = 6.2 Hz, 6H, rotamers); ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.6, 138.3, 128.7, 128.0, 127.5, 69.0, [50.4 and 50.2 (rotamers)], [46.0 and 45.3 (rotamers)], [44.9 and 44.8 (rotamers)], 29.9, [25.6 and 25.3 (rotamers)], 22.4; MS m/z (EI) calcd for $C_{15}H_{22}ClNO_2$ [M+] 283.1339, found 283.1; R_f 0.47 (hex/EtOAc, 4/1).

4ca: 201 mg, 91%, colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.88 (hept, J = 6.2 Hz 1H), 3.52 (t, J = 6.6 Hz, 2H), 3.28−3.16 (m, 4H), 1.74 (tt, J = 6.8, 6.6 Hz, 2H), 1.64 (tt, J = 7.0, 6.8 Hz, 2H), 1.20 (d, J = 6.2 Hz, 6H), 1.07 (t, J = 6.7 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ [156.1 and 155.8 (rotamers)], 68.3, [46.1 and 45.5 (rotamers)], 44.8, [42.0 and 41.7 (rotamers)], 29.9, [26.1 and 25.9 (rotamers)], 22.4, [14.0 and 13.5 (rotamers)]; IR (neat): ν_{max} = 2977, 2934, 1684, 1421, 1265, 1176, 1111, 910, 728 cm^{-1}; HRMS m/z (EI) calcd for $C_{10}H_{20}ClNO_2$ [M+] 221.1183, found 221.1180; R_f 0.52 (hex/EtOAc, 4/1).

4cb: 219 mg, 93%, colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.83 (d, J = 6.5 Hz, 2H), 3.53 (t, J = 6.4 Hz, 2H), 3.32−3.12 (m, 4H), 1.90 (hept of t, J = 6.8, 6.5 Hz, 1H), 1.75 (tt, J = 6.8, 6.4 Hz, 2H), 1.66 (tt, J = 7.1, 6.8 Hz, 2H), 1.10 (t, J = 7.1 Hz, 3H), 0.91 (d, J = 6.8 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ [156.6 and 156.3 (rotamers)], 71.5, [46.2 and 45.9 (rotamers)], 44.8, [42.2 and 41.8 (rotamers)], 29.9, 28.2, [26.3 and 25.8 (rotamers)], 19.3, [14.0 and 13.5 (rotamers)]; IR (neat): ν_{max} = 2960, 1693, 1423, 1265, 1177, 1074, 1005, 770 cm^{-1}; HRMS m/z (EI) calcd for $C_{11}H_{22}ClNO_2$ [M+] 235.1339, found 235.1336; R_f 0.51 (hex/EtOAc, 4/1).

4da: 176 mg, 85%, colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.83 (hept, J = 6.3 Hz 1H), 3.50 (t, J = 6.0 Hz, 2H), 3.27−3.17 (m, 2H), 2.81 (s, 3H), 1.70 (tt, J = 6.5, 6.0 Hz, 2H), 1.61 (tt, J = 6.5, 6.5

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Hz, 2H), 1.17 (d, J = 6.3 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.2, 68.4, [47.8 and 47.6 (rotamers)], [44.7 and 44.6 (rotamers)], [34.3 and 33.7 (rotamers)], 29.6, [25.2 and 24.9 (rotamers)], 22.3; IR (neat): ν_{max} = 2978, 2934, 1687, 1177, 1111, 923, 729 cm^{-1}; HRMS m/z (EI) calcd for $C_9H_{18}ClNO_2$ [M+] 207.1026, found 207.1026; R_f 0.51 (hex/EtOAc, 4/1).

4db: 201 mg, 91%, colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.83 (d, J = 6.3 Hz, 2H), 3.57−3.52 (m, 2H), 3.32−3.24 (m, 2H), 2.88 (s, 3H), 1.91 (hept of t, J = 6.7, 6.3 Hz, 1H), 1.75 (tt, J = 6.7, 6.4 Hz, 2H), 1.67 (tt, J = 7.1, 6.7 Hz, 2H), 0.92 (d, J = 6.7, Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.8, 71.7, 48.1, [44.9 and 44.7 (rotamers)], [34.6 and 33.9 (rotamers)], 29.8, 28.2, [25.5 and 25.0 (rotamers)], 19.3; IR (neat): ν_{max} = 2958, 1694, 1465, 1186, 1127, 770 cm^{-1}; HRMS m/z (EI) calcd for $C_{10}H_{20}ClNO_2$ [M+] 221.1183, found 221.1184; R_f 0.43 (hex/EtOAc, 4/1).

4ea: 168 mg, 59%, light yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.35 (d, J = 4.9 Hz, 1H), 7.55 (d, J = 7.9 Hz, 1H), 7.11 (dd, J = 7.9, 4.9 Hz, 1H), 4.82 (hept, J = 5.9 Hz, 1H), 4.76−4.64 (m, 1H), 3.26−3.15 (m, 1H), 3.11−3.02 (m, 1H), 2.64 (s, 3H), 1.96−1.86 (m, 1H), 1.85−1.75 (m, 1H), 1.60−1.49 (m, 1H), 1.47−1.32 (m, 1H), 1.01 (d, J = 5.9 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ [156.0 and 155.7 (rotamers)], 149.3, 148.1, [137.2 and 137.0 (rotamers)], 134.2, 123.4, 68.2, 60.0, [47.3 and 47.2 (rotamers)], 36.5, [34.0 and 33.3 (rotamers)], [25.0 and 24.5 (rotamers)], 22.0; IR (neat): ν_{max} = 2979, 1683, 1401, 1199, 1111, 908, 726 cm^{-1}; HRMS m/z (EI) calcd for $C_{14}H_{21}ClN_2O_2$ [M+] 284.1292, found 284.1289; $[\alpha]^{25}$ = +4.55 (c 1.0, $CHCl_3$); R_f 0.46 (hex/EtOAc, 2/1).

4eb: 200 mg, 67%, light yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.52 (d, J = 4.7 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.28 (dd, J = 7.8, 4.7 Hz, 1H), 4.99−4.80 (m, 1H), 3.81 (d, J = 6.6 Hz, 2H), 3.42−3.21 (m, 2H), 2.83 (s, 3H), 2.12−2.02 (m, 1H), 2.02−1.92 (m, 1H), 1.92−1.82(m, 1H), 1.74 (t of hept, J = 6.6, 5.9 Hz, 1H), 1.64−1.51 (m, 1H), 0.88(d, J = 5.9 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ [156.8 and 156.6 (rotamers)], 149.7, 148.5, [137.5 and 137.3 (rotamers)], 134.5, 123.7, 71.7, 60.4, [47.9 and 47.8 (rotamers)], [37.1 and 36.9 (rotamers)], [34.6 and 33.8 (rotamers)], 28.2, [25.5 and 25.0 (rotamers)], 19.2; IR (neat): ν_{max} = 2959, 1694, 1427, 1195, 1137, 713 cm^{-1}; HRMS m/z (EI) calcd for $C_{15}H_{23}ClN_2O_2$ [M+] 298.1448, found 298.1450; $[\alpha]^{25}$ = +22.50 (c 1.0, $CHCl_3$); R_f 0.44 (hex/EtOAc, 1/1).

4fa: 115 mg, 45%, light yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$, rotamers major:minor = 2:1) δ 7.31−7.24 (m, 3H), 7.20−7.06 (m, 1H), 5.00−4.87 (m, 1H), 3.81−3.62 (m, 2H), 3.19 (s, 3H), 3.04−2.95 (m, 2H), 1.36−1.02 (m, 6H); ^{1}H NMR (600 MHz, DMSO-d_6, rotamers major:minor = 2:1) δ 7.42−7.37 (m, 1H), 7.31−7.26 (m, 2H), 7.25−7.18 (m, 1H), 4.86−4.74 (m, 1H), 3.82 (t, J = 7.4 Hz, 2H), 3.34 (s, 3H), 2.96−2.90 (m, 2H), 1.34−0.94 (m, 6H); ^{1}H NMR (600 MHz, DMSO-d_6, 358 K) δ 7.37 (dd, J = 6.2, 3.3 Hz, 1H), 7.32−7.24 (m, 2H), 7.18 (dd, J = 6.4, 2.8 Hz, 1H), 4.82 (hept, J = 6.2 Hz, 1H), 3.81 (t, J = 7.3 Hz, 2H), 3.13 (s, 3H), 2.97 (t, J = 7.3 Hz, 2H), 1.25−1.01 (m, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.8, [142.7 and 142.2 (rotamers)], [136.0 and 135.6 (rotamers)], 130.2, [128.3 and 128.2 (rotamers)] 128.0, 127.8, 69.2, 43.7, 38.1, [34.9 and 34.5 (rotamers)], 22.1; IR (neat): ν_{max} = 2978, 1694, 1373, 1300, 1163, 1107, 981, 913, 768, 713 cm^{-1}; HRMS m/z (EI) calcd for $C_{13}H_{18}ClNO_2$ [M+] 255.1026, found 255.1023; R_f 0.46 (hex/EtOAc, 4/1).

4fb: 108 mg, 40%, light yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$, rotamers major:minor = 2:1) δ 7.32−7.24 (m, 3H), 7.20−7.10 (m, 1H), 4.02−3.62 (m, 4H), 3.21 (s, 3H), 3.01 (t, J = 7.5 Hz, 2H), 1.72 (m, 1H), 1.05−0.65 (m, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.3, [142.7 and 142.1 (rotamers)], [136.0 and 135.7 (rotamers)], 130.3, [128.4 and 128.2 (rotamers)], 128.0, 127.9, 72.0, 43.8, 38.2, [34.8 and 34.5 (rotamers)], [28.2 and 28.0 (rotamers)], [19.3 and 19.0 (rotamers)]; IR (neat): ν_{max} = 2960, 1698, 1352, 1155, 1003, 907, 729, 648 cm^{-1}; HRMS m/z (EI) calcd for $C_{14}H_{20}ClNO_2$ [M+] 269.1183, found 269.1183; R_f 0.49 (hex/EtOAc, 4/1).

4ga: 183 mg, 68%, light yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32−7.22 (m, 3H), 7.20−7.02 (m, 1H), 5.02−4.87 (m, 1H), 3.91−3.68 (m, 2H), 3.69−3.63 (m, 1H), 3.43−3.33 (m, 1H), 3.09−3.02 (m, 1H), 2.99−2.92 (m, 1H), 1.40−1.00 (m, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.4, 140.5, 136.1, 130.1, 129.4, 128.1, 127.8, 69.0, 45.4, 43.6, [34.8 and 34.4 (rotamers)], 29.8, 22.2, [14.2 and 13.5-(rotamers)]; MS m/z (EI) calcd for $C_{14}H_{20}ClNO_2$ [M+] 269.1183, found 269.1; R_f 0.45 (hex/EtOAc, 3/1).

4gb: 218 mg, 77%, light yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35−7.22 (m, 3H), 7.20−7.06 (m, 1H), 4.03−3.60 (m, 5H), 3.47−3.28 (m, 1H), 3.09−3.03 (m, 1H), 3.03−2.96 (m, 1H), 1.80−1.65 (m, 1H), 1.40−0.50 (m, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.8, 140.3, [136.2 and 136.0 (rotamers)], 130.0, 129.3, 127.8, 127.7, 71.6, 45.2, 43.5, [34.4 and 34.2 (rotamers)], 28.0, [19.1 and 19.0 (rotamers)], 14.1, 13.4; MS m/z (EI) calcd for $C_{15}H_{22}ClNO_2$ [M+] 283.1339, found 283.1; R_f 0.49 (hex/EtOAc, 3/1).

4ha: 126 mg, 86%, light yellow oil; Regioisomer major:minor = 2:1; Major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.91 (hept, J = 6.4 Hz, 1H), 4.38−4.18 (m, 1H), 4.23 (q, J = 7.1 Hz, 2H), 3.37−3.15 (m, 4H), 2.06−1.96 (m, 1H), 1.96−1.87 (m, 1H), 1.76−1.69 (m, 1H), 1.69−1.60 (m, 1H), 1.32−1.07 (m, 12H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.6, [156.5 and 156.1 (rotamers)], 68.4, 62.1, 59.2, [45.9 and 45.4 (rotamers)], [42.6 and 42.0 (rotamers)], 32.1, 29.6, [25.3 and 25.0 (rotamers)], 22.3, 14.1; minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.94 (hept, J = 6.4 Hz, 1H), 4.54−4.47 (m, 1H), 4.21−4.08 (m, 2H), 3.62−3.52 (m, 2H), 3.52−3.31 (m, 1H), 3.19−3.03 (m, 1H), 2.18−2.10 (m, 1H), 2.03−1.87 (m, 1H), 1.87−1.80 (m, 2H), 1.32−1.08 (m, 12H); ^{13}C NMR (151 MHz, $CDCl_3$) δ [171.5 and 171.4 (rotamers)], [155.8 and 155.4 (rotamers)], 69.0, 61.2, [59.3 and 59.0 (rotamers)], 44.6, [41.7 and 40.9 (rotamers)], [30.0 and 29.8 (rotamers)], [25.3 and 25.0 (rotamers)], 22.2, 14.2, [13.9 and 13.4 (rotamers)]; MS m/z (EI) calcd for $C_{13}H_{24}ClNO_4$ [M+] 293.1394, found 293.1; R_f 0.47 (hex/EtOAc, 4/1).

4hb: 138 mg, 90%, light yellow oil; Regioisomer major:minor = 2:1; major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.40−4.20 (m, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.83 (d, J = 6.5 Hz, 2H), 3.56−2.91 (m, 4H), 2.10−1.81 (m, 3H), 1.80−1.55 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H), 1.10 (t, J = 7.1 Hz, 3H), 0.92 (d, J = 6.7 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.7, [156.6 and 156.3 (rotamers)], 71.6, 62.2, 57.3, [46.1 and 45.8 (rotamers)], [42.3 and 41.8 (rotamers)], 32.3, 28.2, [25.5 and 25.0 (rotamers)], 19.4, 14.2, [14.0 and 13.5 (rotamers)]; minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.30−4.08 (m, 3H), 3.91 (d, J = 6.6 Hz, 2H), 3.52 (t, J = 6.4 Hz, 2H), 3.54−3.34 (m, 1H), 3.23−3.03 (m, 1H), 2.26−2.09 (m, 1H), 2.03−1.82 (m, 4H), 1.26 (t, J = 7.1 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H), 0.99−0.85 (m, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ [171.6 and 171.4 (rotamers)], 157.1, 72.0, 61.4, [59.4 and 59.2 (rotamers)], 44.6, 41.0, 29.6, 28.3, [27.7 and 27.1 (rotamers)], 19.31, 19.29, [14.0 and 13.5 (rotamers)]; MS m/z (EI) calcd for $C_{14}H_{26}ClNO_4$ [M+] 307.1550, found 307.1; R_f 0.52 (hex/EtOAc, 4/1).

4ia′: 170 mg, 79%, light yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.51 (hept, J = 6.2 Hz, 1H), 4.02−3.93 (m, 1H), 3.87−3.81 (m, 1H), 3.45−3.36 (m, 1H), 3.10−3.02 (m, 1H), 2.85−2.78 (m, 1H), 2.58 (s, 3H), 2.11−2.00 (m, 2H), 2.00−1.87 (m, 1H), 1.87−1.75 (m, 2H), 1.65−1.55 (m, 1H), 0.96 (d, J = 6.2 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.70, 71.8, 65.4, 63.5, [55.3 and 55.2 (rotamers)], 38.4, 29.1, 28.8, 21.2, 21.0; IR (neat): ν_{max} = 2983, 1736, 1261, 1093, 907, 723 cm^{-1}; HRMS m/z (EI) calcd for $C_{11}H_{21}NO_3$ [M+] 215.1521, found 215.1522; R_f 0.44. (hex/EtOAc, 1/1).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00681.

Additional DFT calculation results, ^{1}H and ^{13}C NMR spectra of products (PDF)

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Notes

The authors declare no competing financial interest.

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