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Ring-Chain Tautomerism in Organic Synthesis: Synthesis of Heterocyclic Enamines from a Novel and Practical Formal Ring Transformation Reaction of Lactones

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A novel approach to heterocyclic enamines has been developed from the formal ring transformation reaction of lactones. The synthesis comprises consecutive Reformatsky reaction of lactones and mesylation of the resulting mixture of ring-chain tautomers in a one-pot reaction, followed by cyclocondensation reaction with primary amines. The synthetic application of this method was demonstrated by a straightforward preparation of indolizidine compounds via *N*-(3-bromopropyl)-substituted enamine intermediates. The use of cheap and readily available materials and reagents under very mild conditions renders this formal ring transformation method practical and applicable in the preparation of various heterocyclic enamines that are the precursors for (poly)hydroxylated alkaloid derivatives.

Introduction

Heterocyclic enamines, also known as *exo*-cyclic enamino esters, are powerful and versatile intermediates in the preparation of natural products[1,2] and fused heterocyclic compounds.[1,3] The syntheses of heterocyclic enamines have been extensively studied mainly utilizing *N*-heterocyclic compounds as starting materials.[1] The Eshenmoser synthesis,[4] a widely used method, for example, employed the reaction of a thiolactam with a bromomethyl ketone or ester, followed by sulfur extrusion in the presence of triphenylphosphine. The condensation reaction between active methylene or methyl compounds and lactim ethers,[5] pioneered by Eshenmoser and co-workers[6] during the synthetic study of corrin, and lactam-derived iminium salts[7,8] or acetals[7] has been developed into another popular approach to heterocyclic enamines. Other methods reported comprise coupling reactions of organometallic reagents with lactams[9] and thiolactames[10] and their derivates.[11] In contrast, the synthesis of heterocyclic enamines by constructing the *N*-heterocyclic ring moiety has only been reported in a few cases. The reaction of ω-mesylated alkylnitriles with methyl bromoacetate, developed by Kishi,[12] provided an efficient route to pyrroline-containing heterocyclic enamines. Carrie and co-workers[13] reported a more general approach utilizing the intramolecular aza-Wittig reaction of ω-azido β-dicarbonyl intermediates that were prepared through

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the γ-alkylation of β-dicarbonyl dianions with α,ω-dihaloalkane compounds followed by a nucleophilic substitution by sodium azide. The reaction was extended by Michael and co-workers[14] to synthesize alkyl (*E*)-(1-aryl-2-pyrrolidinylidene)acetates by reacting anilines bearing electron-donating substituent(s) with 6-chloro-3-oxohexanoate.

In the course of synthetic study of (poly)hydroxylated pyrrolizidine, indolizidine, and quinolizidine alkaloids including swainsonine and castanospermine,[3] we require a general and practical method to produce (poly)hydroxylated chiral heterocyclic enamines starting from cheap and readily available materials. Considering the easy accessibility to sugar lactones[15] that are derived easily from the naturally abundant sugar compounds, it appears desirable to explore the transformation of lactones into heterocyclic enamines. As a prelude to studying the synthesis of hydroxylated chiral heterocyclic enamines, we have systematically undertaken the current study and here we report a formal ring transformation of lactones into the corresponding heterocyclic enamines utilizing ring-chain tautomerism as the key step.

Results and Discussion

Ring-chain tautomerism has been known for a long time. The tautomerism between hydroxyketones and hemiketals, the simplest ring-chain tautomerism, for example, has been fully studied. Surprisingly, however, most of the tautomerim has been used only for the construction of heterocycles, and its application in the synthesis of chain compounds has been rarely reported.[16] Our synthesis was devised on the basis that the hemiketals **2** resulting from the Reformatsky reaction of lactones could co-exit in tautomeric equilibrium with their chain isomers **2′** and **2″**. Subsequent mesylation of the ω-hydroxy group of the chain tautomers would drive the equilibrium into the side of methylsulfonate compounds **3** and **3′**, which are the key precursors of heterocyclic enamines (Scheme 1).

In the presence of activated zinc dust and a catalytic amount of copper dust, the Reformatsky reaction of lactones **1** with *tert*-butyl bromoacatate proceeded effectively in warm tetrahydrofuran (THF) under argon atmosphere. The ^{1}H NMR spectra of the isolated products **2a**−**c** appeared to be chaos. However, a careful inspection revealed that the products were indeed an equilibrium mixture of ring and chain tautomers, which was evidenced by the observation of two or three singlet peaks around 1.48 ppm corresponding to tertiary butyl protons and a vinyl proton signal around 4.9 ppm corresponding to the enol structure. Mesylation of the Reformatsky products with methylsulfonyl chloride using pyridine as an acid scavenger afforded methylsulfonate derivatives **3a**−**c** in moderate to good yield. The tidy ^{1}H NMR spectra indicated that the products were also a mixture of ketone and enol tautomers, but with the former being a dominant isomer. To improve the overall chemical yield of methylsulfonates from lactones and to avoid somewhat tedious chromatographic isolation of the Reformatsky adducts **2**, the Reformatsky reaction and mesylation were conducted consecutively in a one-pot manner, without isolation and purification of intermediates **2**. Gratifyingly, this simple and convenient experimental operation led to a much higher overall yield of **3** (Table 1).

SCHEME 1. Preparation of Heterocyclic Enamines via the Ring Transformation of Lactones

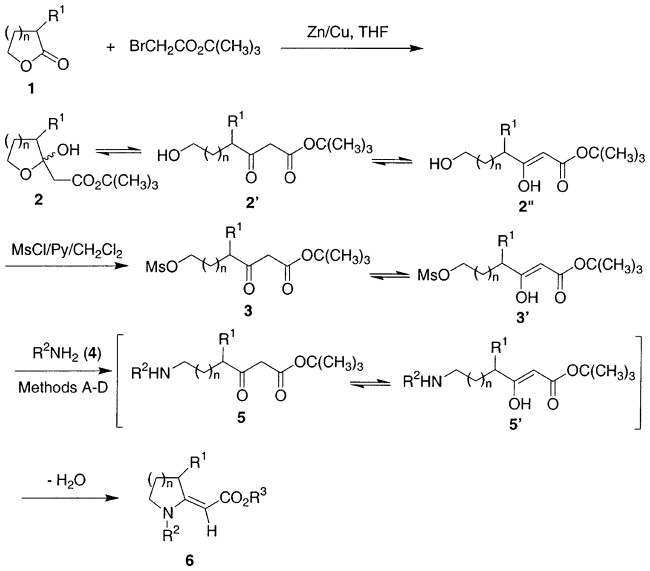

TABLE 1. Synthesis of Methylsulfonate Compounds 3 from Lactones 1

entry	**1**	*n*	R^1	**2** (%)[a]	**3** (%)[a]	**3** (overall yield by two-step synthesis, %)[a]	**3** (yield by one-pot synthesis, %)[a]
1	**1a**	1	H	70	56	39	58
2	**1b**	1	MeO	72	61	44	66
3	**1c**	1	AllO	81	85	69	
4	**1d**	1	BzO				53
5	**1e**	2	H				49

[a] Isolated yield.

Being reactive toward almost all types of primary amines, methylsulfonates **3** appeared as excellent intermediates for the preparation of heterocyclic enamines (Scheme 1). As illustrated in Table 2, **3** reacted with aliphatic amines including glycine ethyl ester smoothly at ambient temperature in dichloromethane to afford *N*-alkyl heterocyclic enamines **6** (Method A). The presence of molecular sieves (4 Å) was found to facilitate cyclocondensation (Method B). Efficient synthesis of *N*-aryl heterocyclic enamines **6** was achieved from the reaction of methylsulfonates with anilines when a polar solvent such as ethanol was used (Methods C and D), albeit the ester interchange was observed in some cases. It was also noticeable that the synthesis was not limited to anilines bearing an electron-donating substituent.[14] In other words, all anilines that bear either an electron-donating or electron-withdrawing group readily reacted with methylsulfonates to furnish heterocyclic enamine products. It should be noted that, during the course of reaction between *o*-bromoaniline and methylsulfonates, a trace amount of unstable ω-(*o*-bromoanilino)-β-oxoalkanoate intermediates **5** and **5′** was observed from mass

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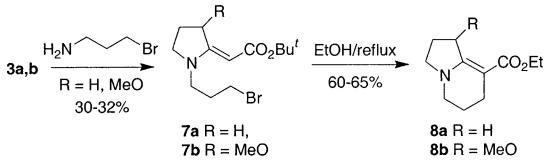
TABLE 2. Compounds 6 Prepared from the Reaction between Methylsulfonates 3 and Amines 4

entry	6	*n*	R^1	R^2	R^3	reaction conditions[a]	yield (%)[b]
1	**6a**	1	H	$PhCH_2$	Bu^t	Method A	57
2	**6b**	1	H	$CH_2{=}CHCH_2$	Bu^t	Method B	44
3	**6c**	1	H	EtO_2CCH_2	Bu^t	Method B	42
4	**6d**	1	H	Ph	Et	Method C	80
5	**6e**	1	H	*o*-$MeOC_6H_4$	Bu^t	Method C	69
6	**6f**	1	H	*m*-$MeOC_6H_4$	Bu^t	Method C	75
7	**6g**	1	H	*p*-$MeOC_6H_4$	Bu^t	Method C	75
8	**6h**	1	H	*o*-MeC_6H_4	Bu^t	Method C	71
9	**6i**	1	H	*m*-BrC_6H_4	Bu^t	Method C	42
10	**6j**	1	H	*p*-BrC_6H_4	Et	Method C	62
11	**6k**	1	H	*p*-ClC_6H_4	Et	Method C	63
12	**6l**	1	H	*p*-$NO_2C_6H_4$	Et	Method D	40
13	**6m**	1	H	Naph	Bu^t	Method C	66
14	**6n**	1	MeO	Me	Bu^t	Method A	66
15	**6o**	1	MeO	$PhCH_2$	Bu^t	Method A	57
16	**6p**	1	MeO	Ph	Bu^t	Method C	85
17	**6q**	1	$CH_2{=}CHCH_2O$	$PhCH_2$	Bu^t	Method B	44
18	**6r**	1	$CH_2{=}CHCH_2O$	EtO_2CCH_2	Bu^t	Method B	41
19	**6s**	1	$PhCH_2O$	Me	Bu^t	Method A	61
20	**6t**	1	$PhCH_2O$	$PhCH_2$	Bu^t	Method B	68
21	**6u**	1	$PhCH_2O$	$CH_2{=}CHCH_2$	Bu^t	Method B	75
22	**6v**	1	$PhCH_2O$	EtO_2CCH_2	Bu^t	Method B	78
23	**6w**	1	$PhCH_2O$	Ph	Bu^t	Method C	75
24	**6x**	2	H	$PhCH_2$	Bu^t	Method C	61
25	**6y**	2	H	$CH_2{=}CHCH_2$	Bu^t	Method C	53

[a] Reactions, which were not optimized, were terminated in about 24 h. Method A: Dichloromethane was used as the solvent and reaction was carried out at room temperature. Method B: Same as Method A but with molecular sieves (4 Å). Method C: Ethanol was used as the solvent. Method D: Reaction was carried out in warm ethanol (35−45 °C) solution. [b] Isolated yield.

SCHEME 2. Preparation of Indolizidine Derivatives



spectra. This suggests that the substitution reaction of methylsulfonate by an amine proceeded prior to condensation with the ketone moiety, a reaction pathway different from the reaction of anilines with 6-chloro-3-oxohexanoate,[14] which also explains high reactivity of methylsulfonates **3** toward anilines including *p*-nitroaniline of low nucleophilicity.

Since the formation of heterocyclic enamines via the ring transformation of lactones was general, being not limited to amine structures, we attempted the preparation of *N*-bromoalkyl-substituted enamine intermediates for indolizidine synthesis. Both methylsulfonates **3a** and **3b** reacted effectively with 3-bromopropylamine hydrobromide to afford the desired enamines **7a** and **7b** in moderate yield. Reflux of **7** in ethanol led to the formation of indolizidine product **8** in a yield of 60−65% (Scheme 2). To our knowledge, this is the shortest route to the indolizidine structure.

Conclusion

In summary, we have provided a novel approach to heterocyclic enamines from the formal ring transformation of lactones, which comprised consecutively the Reformatsky reaction of lactones, mesylation of the resulting mixture of ring and chain tautomers, followed by cyclocondensation reaction with primary amines. Since only the readily available and cheap starting materials and reagents were required, the reaction conditions were mild and experimental operations were very simple and convenient, the synthesis appeared practical and applicable in the preparation of various heterocyclic enamines. The synthetic potential of this new transformation was demonstrated by a facile and straightforward preparation of indolizidine compounds, using 3-bromopropylamine as the amine reactant. The method would open a new venue to synthetically versatile heterocyclic enamines from sugar lactones. Application of this method in the total synthesis of (poly)hydroxylated indolizidine alkaloids is under investigation in this laboratory.

Experimental Section

Melting points are uncorrected. Elemental analyses were performed at the Analytical Laboratory of the Institute. All chemicals were dried or purified according to standard procedures prior to use, and molecular sieves (4 Å) were ground into fine powder.

General Procedure for the Reformatsky Reaction of Lactones. A mixture of lactone (20 mmol), *tert*-butyl bromoacetate (30−36 mmol), activated zinc dust (20−30 mmol), and copper dust (2 mmol) in dry THF was refluxed gently under argon. After the starting lactone was consumed, which was monitored by TLC, the mixture was cooled and the solvent was removed under vacuum. The residue was stirred vigorously with a mixture of ethyl acetate (50 mL) and water (2 mL) for 5 min and then was filtrated through a Celite pad. The filtrate was washed with brine and dried with anhydrous Na_2SO_4. After removal of solvent and column chromatography, product **2** was obtained as colorless liquid. ^1H NMR spectra showed that it was a mixture of ring and chain tautomers (see Supporting Information). Without column chromatography, the crude product can be used directly for mesylation reaction.

General Procedure for the Preparation of Methylsulfonate Compounds 3. To a mixture of isolated Reformatsky adducts **2** (5 mmol) or the crude **2** (obtained from 5.5 mmol of lactone) without purification by column chromatography and

pyridine (3 equiv) in dichloromethane (12 mL) under argon was added methanesulfonyl chloride (3 equiv) dropwise with continued stirring and cooling at 0 C°. After 3 h, the reaction mixture was warmed gradually to room temperature and stirred for another day. A saturated $NaHCO_3$ aqueous dichloromethane (15 mL) solution was added and the organic mixture was washed with brine and then dried with anhydrous Na_2SO_4. After removal of solvent, the residue was purified by flash chromatography with use of a silica gel column and a mixture of petroleum ether and ethyl acetate (2:1) as an eluent to give methylsulfonate derivatives **3**. All methylsulfonates **3** were not very stable and were used immediately after isolation.

General Procedure for the Preparation of Heterocyclic Enamines 6 from the Annulation Reaction of Methylsulfonates 3 with Primary Amines. A mixture of a methylsulfonate with 1 equiv of an amine or ammonium was stirred for a period of time at room temperature in dichloromethane (Method A) with 4 Å molecular sieves (Method B), or in ethanol (Method C) or in warm ethanol (35−45 °C) (Method D). After completion of the reaction, the precipitated was filtrated and the filtrate was concentrated and chromarographied to give heterocyclic enamines **6**.

1-Benzyl-2-[(*tert*-butoxycarbonyl)methylidene]pyrrolidine (6a). White solid, mp 116 °C; ^{1}H NMR ($CDCl_3$) δ 7.35−7.25 (m, 3H), 7.17 (d, J = 7.3 Hz, 2H), 4.63 (s, 1H), 4.34 (s, 2H), 3.29 (t, J = 7.1 Hz, 2H), 3.20 (t, J = 7.7 Hz, 2H), 1.94 (quin, J = 7.4 Hz, 2H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 169.2, 164.3, 136.1, 128.5, 127.2, 127.0, 80.0, 77.4, 52.0, 49.7, 32.3, 28.5, 21.0; IR (KBr) 1680 (C═O), 1602 cm^{-1} (C═C); MS (FAB) m/z 274 (M + H). Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.52; H, 8.57; N, 4.82.

1-Allyl-2-[(*tert*-butoxycarbonyl)methylidene]pyrrolidine (6b). White solid, mp 42−43 °C; ^{1}H NMR ($CDCl_3$) δ 5.82−5.66 (m, 1H), 5.17 (d, J = 8.4 Hz, 1H), 5.13 (d, J = 15.7 Hz, 1H), 4.48 (s, 1H), 3.74 (d, J = 5.4 Hz, 2H), 3.32 (t, J = 7.0 Hz, 2H), 3.13 (t, J = 7.7 Hz, 2H), 1.92 (quin, J = 7.4 Hz, 2H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 169.3, 164.0, 131.1, 117.2, 79.9, 77.4, 52.0, 48.7, 32.4, 28.7, 21.1; IR (KBr) 1676 (C═O), 1600 cm^{-1} (C═C); MS (EI) m/z 223 (M$^+$, 12%), 167 (16), 166 (12), 150 (20), 122 (100). Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 70.10; H, 9.77; N, 6.17.

1-(Ethoxycarbonylmethyl)-2-[(*tert*-butoxycarbonyl)-methylidene]pyrrolidine (6c). ^{1}H NMR ($CDCl_3$) δ 4.43 (s, 1H), 4.38 (q, J = 7.1 Hz, 2H), 3.92 (s, 2H), 3.47 (t, J = 7.1 Hz, 2H), 3.19 (t, J = 7.7 Hz, 2H), 2.00 (quin, J = 7.4 Hz, 2H), 1.49 (s, 9H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 168.8, 168.5, 164.1, 81.1, 77.6, 61.3, 53.1, 47.6, 32.0, 28.6, 21.3, 14.1; IR (KBr) 1748 (C═O), 1683 (C═O), 1600 cm^{-1} (C═C); MS (EI) m/z 269 (M$^+$, 35%), 213 (43), 196 (54), 140 (100). HRMS calcd for $C_{14}H_{23}NO_4$ (M + 1) 270.1704. Found 270.1700.

1-Phenyl-2-[(ethoxycarbonyl)methylidene]pyrrolidine (6d). White solid, mp 62 °C; ^{1}H NMR ($CDCl_3$) δ 7.42−7.19 (m, 5H), 4.91 (s, 1H), 4.07 (q, J = 7.1 Hz, 2H), 3.74 (t, J = 7.0 Hz, 2H), 3.32 (t, J = 7.7 Hz, 2H), 2.10 (quin, J = 7.4 Hz, 2H), 1.22 (t, J = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 169.2, 163.7, 141.2, 129.2, 125.7, 124.3, 80.8, 58.2, 54.3, 32.4, 21.3, 14.4; IR (KBr) 1686 (C═O), 1608 cm^{-1} (C═C); MS (EI) m/z 231 (M$^+$, 43%), 186 (70), 158 (100). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.74; H, 7.25; N, 6.11.

1-(2-Methoxyphenyl)-2-[(*tert*-butoxycarbonyl)methylidene]pyrrolidine (6e). White solid, mp 113−114 °C; ^{1}H NMR ($CDCl_3$) δ 7.29−6.94 (m, 4H), 4.34 (s, 1H), 3.80 (s, 3H), 3.70 (br, 2H), 3.25 (t, J = 7.7 Hz, 2H), 2.08 (quin, J = 7.3 Hz, 2H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 169.4, 165.0, 155.3, 129.4, 129.1, 128.6, 121.1, 112.4, 81.8, 77.2, 55.6, 53.4, 32.0, 28.6, 22.0; IR (KBr) 1680 (C═O), 1610 cm^{-1} (C═C); MS (EI) m/z 289 (M$^+$, 9%), 216 (13), 174 (100). Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.78; H, 8.09; N, 4.76.

1-(3-Methoxyphenyl)-2-[(*tert*-butoxycarbonyl)methylidene]pyrrolidine (6f). White solid, mp 94−95 °C; ^{1}H NMR ($CDCl_3$) δ 7.29 (t, J = 8.0 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.78 (s, 1H), 6.74 (d, J = 8.3 Hz, 1H), 4.91 (s, 1H), 3.80 (s, 3H), 3.68 (t, J = 6.9 Hz, 2H), 3.27 (t, J = 7.7 Hz, 2H), 2.05 (quin, J = 7.3 Hz, 2H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 169.3, 162.6, 160.3, 142.8, 130.0, 116.8, 111.0, 110.4, 83.5, 77.7, 55.3, 54.3, 32.4, 28.6, 21.5; IR (KBr) 1675 (C═O), 1618 cm^{-1} (C═C); MS (EI) m/z 289 (M$^+$, 12%), 233 (18), 216 (17), 188 (100). Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.73; H, 8.13; N, 4.65.

1-(4-Methoxyphenyl)-2-[(*tert*-butoxycarbonyl)methylidene]pyrrolidine (6g). White solid, mp 101 °C; ^{1}H NMR ($CDCl_3$) δ 7.16 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 4.66 (s, 1H), 3.82 (s, 3H), 3.66 (t, J = 7.0 Hz, 2H), 3.28 (t, J = 7.7 Hz, 2H), 2.07 (quin, J = 7.3 Hz, 2H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 168.9, 163.4, 157.1, 133.8, 125.9, 114.1, 81.8, 54.9, 54.3, 31.8, 28.1, 21.1; IR (KBr) 1677 (C═O), 1599 cm^{-1} (C═C); MS (EI) m/z 289 (M$^+$, 42%), 233 (100), 216 (53), 189 (48), 188 (51), 174 (36). Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.60; H, 8.08; N, 4.67.

1-(2-Methylphenyl)-2-[(*tert*-butoxycarbonyl)methylidene]pyrrolidine (6h). White solid, mp 130 °C; ^{1}H NMR ($CDCl_3$) δ 7.40−7.10 (m, 4H), 4.20 (s, 1H), 3.56 (t, J = 7.0 Hz, 2H), 3.70−3.25 (m, 2H), 2.15 (s, 1H), 2.14−2.00 (m, 2H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 169.4, 164.1, 139.6, 135.9, 131.3, 127.8, 127.4, 82.0, 77.5, 54.2, 31.9, 28.6, 22.1, 17.5; IR (KBr) 1675 (C═O), 1608 cm^{-1} (C═C); MS (EI) m/z 273 (M$^+$, 6%), 200 (17), 172 (13), 158 (100). Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.67; H, 8.53; N, 4.86.

1-(3-Bromophenyl)-2-[(*tert*-butoxycarbonyl)methylidene]pyrrolidine (6i). White solid, mp 100−101 °C; ^{1}H NMR ($CDCl_3$) δ 7.34 (s, 1H), 7.29−7.15 (m, 4H), 4.88 (s, 1H), 3.63 (t, J = 6.9 Hz, 2H), 3.23 (t, J = 7.6 Hz, 2H), 2.02 (quin, J = 7.3 Hz, 2H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 169.0, 162.1, 143.1, 130.6, 128.5, 127.3, 123.1, 122.8, 84.4, 78.0, 54.1, 32.3, 28.6, 21.6; IR (KBr) 1670 (C═O), 1610 cm^{-1} (C═C); MS (EI) m/z 339 (M + 2, 15), 337 (M$^+$, 18%), 283 (48), 281 (51), 266 (36), 264 (17), 238 (41), 237 (43), 236 (54), 157 (100). Anal. Calcd for $C_{16}H_{20}BrNO_3$: C, 56.82; H, 5.96; N, 4.14. Found: C, 56.92; H, 5.85; N, 3.84.

1-(4-Bromophenyl)-2-[(ethoxycarbonyl)methylidene]-pyrrolidine (6j). White solid, mp 111−112 °C; ^{1}H NMR ($CDCl_3$) δ 7.46 (d, J = 8.6 Hz, 2H), 7.10 (d, J = 8.6 Hz, 2H), 4.89 (s, 1H), 4.04 (q, J = 7.1 Hz, 2H), 3.66 (t, J = 7.1 Hz, 2H), 3.27 (t, J = 7.0 Hz, 2H), 2.05 (quin, J = 7.3 Hz, 2H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 169.2, 163.2, 140.5, 132.5, 126.0, 118.8, 82.0, 58.5, 54.3, 32.4, 21.5, 14.6; IR (KBr) 1687 (C═O), 1604 cm^{-1} (C═O); MS (EI) m/z 311 (M + 2, 56), 309 (M$^+$, 58%), 266 (52), 264 (52), 239 (64), 238 (72), 237 (74), 236 (65), 185 (65), 157 (100). Anal. Calcd for $C_{14}H_{16}BrNO_3$: C, 54.21; H, 5.20; N, 4.52. Found: C, 54.55; H, 5.26; N, 4.06.

1-(4-Chlorophenyl)-2-[(ethoxycarbonyl)methylidene]-pyrrolidine (6k). White solid, mp 79 °C; ^{1}H NMR ($CDCl_3$) δ 7.38 (d, J = 6.9 Hz, 2H), 7.22 (d, J = 6.9 Hz, 2H), 4.92 (s, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.72 (t, J = 7.0 Hz, 2H), 3.33 (t, J = 7.7 Hz, 2H), 2.12 (quin, J = 7.4 Hz, 2H), 1.25 (t, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 169.1, 163.3, 139.8, 130.9, 129.4, 125.6, 81.6, 58.4, 54.2, 32.3, 21.3, 14.4; IR (KBr) 1688 (C═O), 1608 cm^{-1} (C═C); MS (EI) m/z 267 (M + 2, 16), 265 (M$^+$, 51%), 222 (29), 220 (89), 195 (21), 194 (41), 193 (70), 192 (100). Anal. Calcd for $C_{14}H_{26}NO_2Cl$: C, 63.28; H, 6.07; N, 5.27. Found: C, 63.14; H, 5.90; N, 5.19.

1-(4-Nitrophenyl)-2-[(ethoxycarbonyl)methylidene]pyrrolidine (6l). White solid, mp 90−92 °C; ^{1}H NMR ($CDCl_3$) δ 8.25 (d, J = 9.1 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H), 5.40 (s, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.80 (t, J = 6.9 Hz, 2H), 3.34 (t, J = 7.6 Hz, 2H), 2.12 (quin, J = 7.3 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 169.2, 161.2, 148.0, 143.7, 125.4, 122.6, 86.7, 59.5, 54.0, 32.8, 21.6, 15.0; IR (KBr) 1684 (C═O), 1615 (C═C), 1578, 1325 cm^{-1}; MS (EI) m/z 276 (M$^+$, 68%), 247 (15), 231 (59), 204 (74), 203 (100), 185 (61). HRMS Calcd for $C_{14}H_{17}N_2O_4$ (M + 1) 277.1183. Found 277.1183.

1-(2-Naphthyl)-2-[(*tert*-butoxycarbonyl)methylidene]-pyrrolidine (6m). White solid, mp 185−186 °C; ^{1}H NMR ($CDCl_3$) δ 7.88−7.31 (m, 7H), 4.20 (s, 1H), 3.75−3.48 (m, 3H),

3.37−3.28 (m, 1H), 2.20 (quin, J = 7.3 Hz, 2H), 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 169.3, 165.4, 137.9, 134.8, 129.7, 128.6, 128.2, 126.8, 126.5, 126.1, 125.2, 122.9, 83.2, 77.5, 55.4, 32.2, 28.6, 22.4; IR (KBr) 1677 (C=O), 1602 cm^{-1}; MS (EI) m/z 309 (M^+, 31%), 253 (60), 252 (52), 236 (36), 209 (52), 208 (100), 207 (88). Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.58; H, 7.42; N, 4.39.

3-Methoxy-1-methyl-2-[(*tert*-butoxycarbonyl)methylidene]pyrrolidine (6n). Colorless oil: ^{1}H NMR ($CDCl_3$) δ 5.30 (d, J = 5.3 Hz, 1H), 4.48 (s, 1H), 3.60 (dt, J = 6.1, 9.5 Hz, 1H), 3.47 (s, 3H), 3.20 (t, J = 9.0 Hz, 1H), 2.80 (s, 3H), 2.09−2.02 (m, 1H), 1.98−1.69 (m, 1H), 1.49 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 168.1, 161.3, 81.5, 79.0, 77.6, 57.2, 52.1, 33.0, 28.6, 28.4. IR (KBr) 1685 (C=O), 1614 cm^{-1} (C=C); MS (EI) m/z 227 (M^+, 5%), 197 (8), 154 (16), 141 (53), 41 (100). HRMS calcd for $C_{12}H_{21}NO_3$ (M + 1) 228.1597. Found 228.1594.

1-Benzyl-3-methoxy-2-[(*tert*-butoxycarbonyl)methylidene]pyrrolidine (6o). Solid, mp 84−85 °C; ^{1}H NMR ($CDCl_3$) δ 7.38−7.25 (m, 3H), 7.19 (d, J = 7.3 Hz, 2H), 5.42 (d, J = 5.1 Hz, 1H), 4.66 (s, 1H), 4.35 (s, 2H), 3.62−3.52 (m, 1H), 3.49 (s, 3H), 3.20 (t, J = 9.0 Hz, 1H), 2.13−2.07 (m, 1H), 2.01−1.93 (m, 1H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 168.3, 160.9, 135.8, 128.6, 127.2, 126.8, 82.3, 78.9, 77.7, 57.1, 50.1, 49.5, 28.5; IR (KBr) 1677 (C=O), 1610 cm^{-1} (C=C); MS (EI) m/z 303 (M^+, 12%), 273 (26), 261 (38), 230 (73), 217 (84), 216 (75), 215 (63), 170 (99), 91 (100). Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.32; H, 8.43; N, 4.49.

3-Methoxy-1-phenyl-2-[(*tert*-butoxycarbonyl)methylidene]pyrrolidine (6p). White solid, mp 75−76 °C; ^{1}H NMR ($CDCl_3$) δ 7.42−7.14 (m, 5H), 5.49 (d, J = 5.0 Hz, 1H), 5.00 (s, 1H), 3.97−3.89 (m, 1H), 3.62 (t, J = 9.0 Hz, 1H), 3.54 (s, 3H), 2.22−2.00 (m, 2H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 168.3, 159.2, 141.5, 129.4, 125.6, 124.3, 86.0, 78.7, 78.1, 57.3, 52.1, 28.7, 28.5; IR (KBr) 1682 (C=O), 1616 cm^{-1} (C=C); MS (EI) m/z 289 (M^+, 9%), 259 (22), 216 (21), 203 (100). Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.54; H, 8.05; N, 4.98.

3-Allyloxy-1-benzyl-2-[(*tert*-butoxycarbonyl)methylidene]pyrrolidine (6q). Oil; ^{1}H NMR ($CDCl_3$) δ 7.37−7.25 (m, 3H), 7.18 (d, J = 7.5 Hz, 2H), 6.06−5.94 (m, 1H), 6.01 (d, J = 5.0 Hz, 1H), 5.31 (d, J = 17.2 Hz, 1H), 5.17 (d, J = 10.4 Hz, 1H), 4.67 (s, 1H), 4.38 (s, 2H), 4.25 (s, br, 2H), 3.62 (dt, J = 6.1, 9.7 Hz, 1H), 3.20 (t, J = 8.9 Hz, 1H), 2.13−1.97 (m, 2H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 168.4, 161.3, 136.0, 135.5, 128.7, 127.3, 126.9, 116.5, 82.2, 77.8, 77.6, 70.7, 50.3, 49.5, 29.5, 28.6; IR (KBr) 1684 (C=O), 1611 cm^{-1} (C=C); MS (EI) m/z 329 (M^+, 3%), 273 (12), 256 (8), 232 (6), 217 (42), 91 (100). HRMS calcd for $C_{20}H_{27}NO_3$ (M + 1) 330.2062. Found 330.2064.

3-Allyloxy-1-(ethoxycarbonylmethyl)-2-[(*tert*-butoxycarbonyl)methylidene]pyrrolidine (6r). ^{1}H NMR ($CDCl_3$) δ 6.00−5.85 (m, 1H), 5.46 (d, J = 4.6 Hz, 1H), 5.24 (d, J = 17.2 Hz, 1H), 5.09 (d, J = 10.4 Hz, 1H), 4.42 (s, 1H), 4.20−4.14 (m, 4H), 3.89 (d, J = 15.0 Hz, 1H), 3.80 (d, J = 15.0 Hz, 1H), 3.69−3.61 (m, 1H), 3.28 (t, J = 8.3 Hz, 2H), 2.07−1.96 (m, 2H), 1.42 (s, 9H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 168.4, 167.7, 160.8, 135.4, 116.4, 83.2, 77.9, 77.1, 70.6, 61.3, 51.0, 47.5, 29.6, 28.5, 14.1; IR (KBr) 1748 (C=O), 1688 (C=O), 1614 cm^{-1} (C=C); MS (EI) m/z 325 (M^+, 3%), 269 (11), 252 (11), 228 (5), 213 (23), 196 (19), 140 (100). HRMS calcd for $C_{17}H_{27}NO_5$ (M + 1) 326.1964. Found 326.1962.

3-Benzyloxy-1-methyl-2-[(*tert*-butoxycarbonyl)methylidene]pyrrolidine (6s). Oil; ^{1}H NMR ($CDCl_3$) δ 7.41−7.24 (m, 5H), 5.62 (d, J = 5.3 Hz, 1H), 4.80 (d, J = 10.9 Hz, 1H), 4.68 (d, J = 10.9 Hz, 1H), 4.50 (s, 1H), 3.64 (dd, J = 15.8, 9.4 Hz, 1H), 3.21 (t, J = 8.9 Hz, 1H), 2.80 (s, 3H), 2.12−1.74 (m, 2H), 1.54 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 168.3, 161.8, 139.0, 128.2, 128.1, 127.5, 81.3, 78.6, 77.6, 72.3, 52.3, 33.1, 29.1, 28.7; IR (KBr) 1682 (C=O), 1613 cm^{-1} (C=C); MS (EI) m/z 230 (M − 73, 8%), 197 (26), 141 (100), 140 (33), 91 (37). HRMS calcd for $C_{18}H_{25}NO_3$ (M + 1) 304.1906. Found 304.1907.

1-Benzyl-3-benzyloxy-2-[(*tert*-butoxycarbonyl)methylidene]pyrrolidine (6t). White solid, mp 66−67 °C; ^{1}H NMR ($CDCl_3$) δ 7.38−7.17 (m, 10H), 5.72 (d, J = 5.1 Hz, 1H), 4.80 (d, J = 11.1 Hz, 1H), 4.69 (d, J = 10.7 Hz, 1H), 4.68 (s, 1H), 4.37 (s, 2H), 3.62 (dt, J = 6.3, 9.2 Hz, 1H), 3.20 (t, J = 8.3 Hz, 1H), 2.13−1.97 (m, 2H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 168.4, 161.2, 138.9, 135.8, 128.5, 128.0, 127.8, 127.3, 127.2, 126.8, 82.1, 78.1, 77.7, 71.7, 50.2, 49.4, 29.2, 28.5; IR (KBr) 1682 (C=O), 1608 cm^{-1} (C=C); MS (EI) m/z 306 (M − 73, 4%), 273 (14), 217 (46), 170 (9), 91 (100). HRMS calcd for $C_{24}H_{29}NO_3$ (M + 1) 380.2222. Found 380.2220.

1-Allyl-3-benzyloxy-2-[(*tert*-butoxycarbonyl)methylidene]pyrrolidine (6u). Oil; ^{1}H NMR ($CDCl_3$) δ 7.36−7.20 (m, 5H), 5.77−5.64 (m, 1H), 5.63 (d, J = 5.3 Hz, 1H), 5.18−5.11 (m, 2H), 4.75 (d, J = 11.1 Hz, 1H), 4.66 (d, J = 11.1 Hz, 1H), 4.54 (s, 1H), 3.76 (s, 2H), 3.60 (dt, J = 15.4, 8.8 Hz, 1H), 3.22 (s, br, 1H), 2.10−1.93 (m, 2H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 168.5, 161.0, 139.1, 130.8, 128.2, 128.0, 127.4, 117.0, 81.9, 78.4, 77.7, 72.0, 50.2, 48.5, 29.3, 28.7; IR (KBr) 1683 (C=O), 1609 cm^{-1} (C=C); MS (EI) m/z 329 (M^+, 4%), 256 (11), 223 (23), 167 (100), 91 (72). HRMS calcd for $C_{20}H_{29}NO_3$ (M + 1) 330.2065. Found 330.2064.

3-Benzyloxy-1-(ethoxycarbonylmethyl)-2-[(*tert*-butoxycarbonyl)methylidene]pyrrolidine (6v). White solid, mp 68−69 °C; ^{1}H NMR ($CDCl_3$) δ 7.38−7.21 (m, 5H), 5.63 (d, J = 4.6 Hz, 1H), 4.75 (d, J = 11.0 Hz, 1H), 4.66 (d, J = 11.1 Hz, 1H), 4.48 (s, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.93 (d, J = 17.8 Hz, 1H), 3.76 (d, J = 17.8 Hz, 1H), 3.68 (dt, J = 15.8, 9.0 Hz, 1H), 3.33 (t, J = 8.2 Hz, 2H), 2.14−2.01 (m, 2H), 1.48 (s, 9H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 168.5, 167.9, 160.9, 139.0, 128.2, 128.0, 127.4, 83.3, 78.0, 77.8, 71.9, 61.4, 51.2, 47.6, 29.6, 28.6, 14.2; IR (KBr) 1754 (C=O), 1687 (C=O), 1607 cm^{-1} (C=C); MS (EI) m/z 302 (M − 73, 8%), 269 (23), 213 (36), 140 (100). HRMS calcd for $C_{21}H_{29}NO_5$ (M + 1) 376.2120. Found 376.2118.

3-Benzyloxy-1-phenyl-2-[(*tert*-butoxycarbonyl)methylidene]pyrrolidine (6w). White solid, mp 110−111 °C; ^{1}H NMR ($CDCl_3$) δ 7.41−7.14 (m, 10H), 5.77 (d, J = 5.0 Hz, 1H), 5.04 (s, 1H), 4.83 (d, J = 11.0 Hz, 1H), 4.72 (d, J = 11.0 Hz, 1H), 3.98 (dt, J = 6.1, 9.5 Hz, 1H), 3.31 (t, J = 8.6 Hz, 1H), 2.23−2.07 (m, 2H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 168.5, 159.5, 141.5, 139.0, 129.4, 128.2, 128.0, 127.5, 125.5, 124.2, 86.0, 78.1, 72.2, 52.2, 29.4, 28.6; IR (KBr) 1685 (C=O), 1612 cm^{-1} (C=C); MS (EI) m/z 292 (M − 73, 6%), 259 (31), 203 (100). Anal. Calcd for $C_{22}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83. Found: C, 75.73; H, 7.36; N, 3.83.

1-Benzyl-2-[(*tert*-butoxycarbonyl)methylidene]piperidine (6x). White solid, mp 110−111 °C; ^{1}H NMR ($CDCl_3$) δ 7.34−7.13 (m, 5H), 4.62 (s, 1H), 4.36 (s, 2H), 3.20−3.13 (m, 4H), 1.75−1.67 (m, 4H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 169.2, 162.0, 136.4, 128.7, 127.1, 126.8, 84.5, 77.4, 55.0, 49.6, 28.7, 26.8, 23.4, 19.9; IR (KBr) 1673 (C=O), 1566 cm^{-1}; MS (EI) m/z 287 (M^+, 12%), 231 (32), 230 (22), 214 (17), 186 (37), 91 (100). Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.26; H, 8.86; N, 4.71.

1-Allyl-2-[(*tert*-butoxycarbonyl)methylidene]piperidine (6y). Oil; ^{1}H NMR ($CDCl_3$) δ 5.74−5.66 (m, 1H), 5.12 (d, J = 11.5 Hz, 1H), 5.06 (d, J = 18.6 Hz, 1H), 4.47 (s, 1H), 3.69 (s, 2H), 3.11 (t, J = 5.3 Hz, 2H), 3.00 (t, J = 5.4 Hz, 2H), 1.69 (quin, J = 4.9 Hz, 2H), 1.57 (quin, J = 5.1 Hz, 2H), 1.37 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 168.9, 161.1, 131.1, 116.8, 84.0, 54.2, 49.1, 28.6, 26.6, 23.3, 19.7; IR (KBr) 1679 (C=O), 1569 cm^{-1}; MS (EI) m/z 237 (M^+, 11%), 181 (20), 164 (21), 149 (7), 136 (100), 122 (30). HRMS calcd for $C_{14}H_{23}NO_2$ (M + 1) 238.1804. Found 238.1801.

Preparation of Ethyl 1,2,3,5,6,7-Hexahydroindolizine-8-carboxylate (8a). The reaction of **3a** with 3-bromopropylamine hydrobromide following the procedure described above (Method B) gave 1-(3-bromopropyl)-2-[(*tert*-butoxycarbonyl)-methylidene]pyrrolidine (**7a**): 30%; oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.48 (s, 1H), 3.42−3.34 (m, 6H), 3.13 (t, J = 7.6 Hz, 2H), 2.14 (quin, J = 6.5 Hz, 2H), 1.95 (quin, J = 7.3 Hz, 2H), 1.57 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 169.1, 163.9, 80.0, 77.6, 53.0, 44.6, 32.4, 30.8, 29.1, 28.7, 21.2. Compound **7a** was then

refluxed in ethanol for 5 h. After removal of the solvent, dichloromethane was added, and the mixture was washed with saturated sodium carbonate aqueous solution and brine successively. Column chromatography gave ethyl 1,2,3,5,6,7-hexahydroindolizine-8-carboxylate (**8a**): 65%; oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.14 (t, J = 7.1 Hz, 2H), 3.31 (t, J = 7.0 Hz, 2H), 3.18 (t, J = 5.7 Hz, 2H), 3.09 (t, J = 7.7 Hz, 2H), 2.39 (t, J = 6.3 Hz, 2H), 1.95 (quin, J = 7.4 Hz, 2H), 1.87 (quin, J = 6.0 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 169.3, 159.6, 87.9, 58.8, 53.4, 45.4, 33.1, 22.0, 21.4, 15.2; IR (KBr) 1675, 1594 cm^{-1}; MS (EI) *m*/*z* 195 (M^+, 54%), 166 (61), 150 (90), 122 (100). HRMS calcd for $C_{11}H_{18}NO_2$ (M + 1) 196.1334. Found 196.1332.

Preparation of Ethyl 3-Methoxy-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate (8b). The reaction of **3b** with 3-bromopropylamine hydrobromide following the procedure described above (Method B) gave 1-(3-bromopropyl)-3-methoxy-2-[(*tert*-butoxycarbonyl)methylidene]pyrrolidine (**7b**): 32%; oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.28 (d, J = 5.1 Hz, 1H), 4.49 (s, 1H), 3.59−3.52 (m, 1H), 3.41 (s, 3H), 3.36 (t, J = 6.4 Hz, 2H), 3.29 (q, J = 6.4 Hz, 1H), 3.21 (t, J = 9.0 Hz, 1H), 2.14−1.98 (m, 1H), 1.91−1.80 (m, 1H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 168.0, 160.4, 82.2, 78.9, 77.8, 57.2, 51.2, 44.3, 30.7, 28.9, 28.6, 28.5. Following the procedure for the preparation of **8a**, compound **7b** was transformed into ethyl 3-methoxy-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate (**8b**): 60%; oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.05 (d, J = 5.5 Hz, 1H), 4.05 (t, J = 7.1 Hz, 2H), 3.47−3.30 (m, 1H), 3.36 (s, 1H), 3.12−3.06 (m, 3H), 2.41−2.21 (m, 2H), 2.00−1.68 (m, 4H), 1.18 (t, J = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 168.3, 156.5, 89.9, 80.7, 59.1, 57.7, 51.2, 45.3, 28.2, 22.1, 21.4, 15.2; IR (KBr) 1677, 1606 cm^{-1}; MS (EI) *m*/*z* 225 (M^+, 61%), 210 (15), 195 (100), 180 (74), 152 (28). HRMS calcd for $C_{12}H_{20}NO_2$ (M + 1) 226.1439. Found 226.1438.

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Supporting Information Available: ^{1}H NMR spectra of compounds **2** and **3**, and ^{1}H NMR and ^{13}C NMR spectra of compounds **6a**, **6d**, **6g**, **6j**, **6m**, **6o**, **6s**, **6x**, and **6y**. This material is available free of charge via the Internet at http://pubs.acs.org.

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