Chichibabin Indolizine Synthesis Revisited: Synthesis of Indolizinones by Solvolysis of 4-Alkoxycarbonyl-3-oxotetrahydroquinolizinium Ylides†

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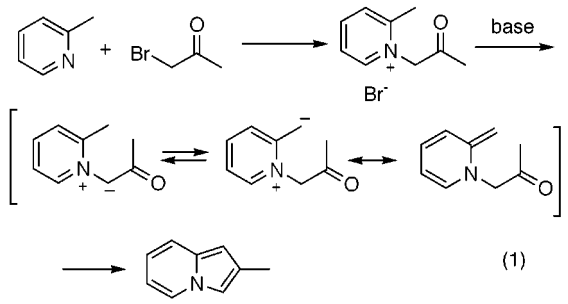
Solvolysis of 4-alkoxycarbonyl-(or 4-acyl)-3-oxo-1,2,3,4-tetrahydroquinolizinium ylides (**1**−**4**) was studied and three types of reactions were found to proceed competitively. Thus, alcoholysis afforded the Chichibabin rearrangement products, 2,3-dihydro-2-indolizinones (**5**−**8**), solvolysis in trifluoroethanol or in aqueous methanol caused ring opening (and subsequent ester cleavage) to 2-alkoxycarbonylethylpyridinium-1-acetates **10**, **15**, and **16**, and hydrolysis resulted in ring opening to 1-alkoxycarbonylmethylpyridinium-2-propionates **11** or **13** (and subsequently to **12** or **14**). Characteristically, all the types of reactions proceeded significantly faster with *t*-butoxycarbonyl substituted ylides than with smaller alkoxycarbonyl substituted ones. The general mechanism for the solvolysis, involving a ketene intermediate, is proposed based on kinetic measurements.

Introduction

Chichibabin indolizine synthesis, a base-mediated cyclization reaction of 1-(2-oxoalkyl)-2-methylpyridinium salts, is very useful for the synthesis of a variety of indolizines.[1−4] For example, 2-substituted indolizines were produced from the reaction of a picoline derivative with bromoacetone followed by base treatment (eq 1).[2] Later, the reaction was successfully expanded to the 1-(alkoxycarbonyl)methyl-2-methylpyridinium system leading to 2,3-dihydro-2-indolizinones.[5] A mechanism proposed for the reaction was that by the base-treatment of the pyridinium salts, the corresponding ylide was formed as an reactive intermediate and indolizines were produced via an intramolecular nucleophilic attack of the active methylene to the carbonyl group followed by elimination of water (or alcohol).[5]

Recently, we described syntheses of a new type of stable cyclic iminium ylides, 4-alkoxycarbonyl- and 4-acyl-substituted 3-oxo-1,2,3,4-tetrahydroquinolizinium ylides (**1**−**4**) and their chemical reactivities for the 1,3-dipolar cycloaddition reactions.[6] These uniquely stable ylides can also be regarded as reactive intermediates of the Chichibabin indolizine synthesis, and we are interested in exploring the synthesis of indolizinones from **1** to **4**. In this article, we would like to report the solvolysis of 4-alkoxycarbonyl- and 4-acyl-substituted 3-oxo-1,2,3,4-tetrahydroquinolizinium ylides to give indolizines and, in addition, a mechanistic study on the Chichibabin indolizine formation reaction leading to 2,3-dihydro-2-indolizinones.



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Results and Discussion

Chichibabin indolizine synthesis was typically carried out by stepwise treatment of a 2-methylpyridine with a halocarbonyl compound followed by base treatment without isolation of the intermediate. Because cyclic iminium ylides **1**−**4** are regarded to have similar structural features to the intermediate of the Chichibabin indolizine formation reaction, their solvolytic transformation was examined in detail. After extensive survey of the reaction conditions, we found that the rearrangement of the ylides to indolizines proceeded smoothly in an alcoholic solvent without additional bases. Thus, in methanol, alkoxycarbonyl ylides **1a**−**d** afforded the ring contraction products, 2,3-dihydroindolizinones **5** (R^2 = Me), nearly quantitatively (eq 2; Table 1, entries 1−4). In ethanol and benzyl alcohol the rearrangement of **1a** proceeded rather slowly to afford indolizinones **6** and **7**, respectively (eq 2; Table 1, entries 5 and 6). Similarly, in methanol, 2-methyl-substituted ylide **2** was converted into **8** (eq 3; Table 1, entry 7), whereas acyl-substituted ylide **3** afforded **9** beside the recovered starting material after prolonged

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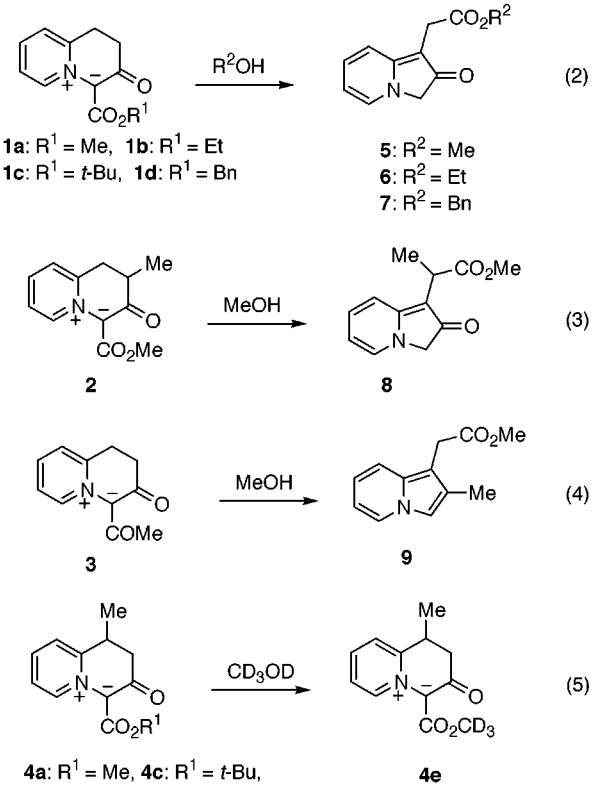
Table 1. Solvolysis of Ylides 1−4 at 60 °C

entry	ylide	R^1	R^2OH	product	time (m)[a]	yield (%)[d]
1	**1a**	Me	MeOH	**5**	90	95
2	**1b**	Et	MeOH	**5**	80	96
3	**1c**	*t*-Bu	MeOH	**5**	25	95
4	**1d**	Bn	MeOH	**5**	95	95
5	**1a**	Me	EtOH	**6**	420	90
6	**1a**	Me	BnOH	**7**	410	95
7	**2**		MeOH	**8**	120	93
8	**3**		MeOH	**9**	360	22[e] (**3**, 40%)[e]
9	**4a**	Me	CD_3OD	**4e**	270	55
10	**4c**	*t*-Bu	CD_3OD	**4e**	60	53
11	**1c**	*t*-Bu	CF_3CH_2OH	**10c, 10c′** (1:4)	120	86[f]
12	**1a**	Me	D_2O	**11a**	85 (41 h)[b]	97[g]
13	**1b**	Et	D_2O	**11b**	87	98
14	**1c**	*t*-Bu	D_2O	**11c, 12**	28 (100)[b]	87[h]
15	**4a**	Me	D_2O	**13a**	240 (48 h)[c]	94[i]
16	**1a**	Me	CD_3OD/D_2O, 11:1	**5, 15**	90	98
17	**4a**	Me	CD_3OD/D_2O, 10:1	**16**	380	88

[a] Time of full conversion of the substrate. [b] Time of conversion of **11a** or **c** into **12**. [c] Time of conversion of **13** into **14**. [d] NMR yields. [e] Isolated yield. [f] Isolated yield of **10c′**. [g] NMR yield of **11a**. [h] NMR yield of **12** after conversion to **12**. [i] NMR yield of **13a**.

heating under reflux (eq 4; Table 1, entry 8). Contrary to these results, 1-methyl-substituted ylides **4a** and **4c** did not form indolizinones in methanol, but only transesterification was observed in CD_3OD (eq 5; Table 1, entries 9 and 10). It should be noted that such a transesterification was not observed in the solvolysis of **1a**−**c** in CD_3OD. Structures of the rearrangement products **5**−**9** were determined on the basis of spectroscopic characterization. The results are summarized in Table 1.



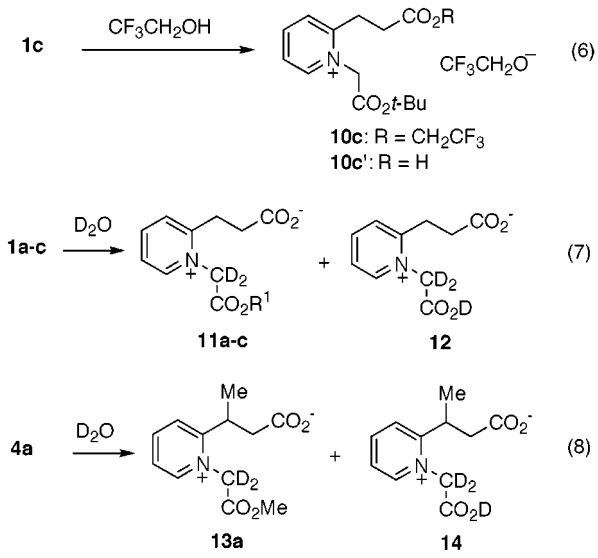
On the basis of these results, it seems conceivable that the ylides **1**−**3** were the actual precursors of the Chichibabin indolizine formation reaction. To know more about the reaction, solvolysis in other solvents including water was investigated. Thus, in trifluoroethanol, no indolizinone was formed from **1c**, whereas ring opening products **10** were obtained (eq 6; Table 1, entry 11). Hydrolysis of

Table 2. Product Ratios 5/15 in the Reaction of Ylide 1a with Deuteromethanol−Water Mixtures[a]

entry	solvent	**5**/**15**
1	CD_3OD/D_2O, 11:1	60:40
2	CD_3OD/D_2O, 5:1	40:60
3	CD_3OD/H_2O, 10:1	55:45
4	CH_3OD/H_2O, 10:1	40:60

[a] Reactions were carried out at 60 °C.

1a−**c** in D_2O also caused ring opening to form pyridinium betaines **11a**−**c**, and further hydrolysis afforded 1-(carboxymethyl)pyridinium-2-propionate (**12**) (eq 7; Table 1, entries 12−14). The same type of hydrolysis was observed for 1-methyl-substituted ylide **4a** in D_2O (eq 8; Table 1, entry 15).



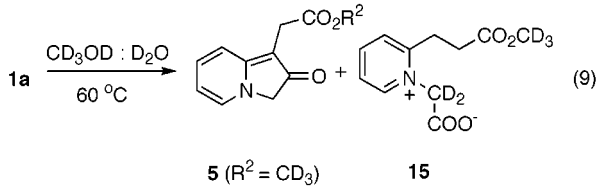
The observed difference in the reaction course of the solvolysis of ylides **1**−**4** in methanol and water led us to examine the solvolysis of **1a** in methanol−water mixtures (Table 1, entry 16, and Table 2). NMR analysis of **1a** in the mixed solvent showed the formation of betaine **15** (not **11**) and rearrangement product **5** (eq 9), the ratio of **5** to **15** being dependent on the solvent composition. Surprisingly, even with higher water contents (CD_3OD/D_2O = 5:1) the hydrolysis product **11** was not found in the reaction products, but more betaine **15** was formed.

Table 3. Reaction Orders and Rate Constants for the Reaction of 1 with Deuterated Methanols[a]

entry	ylide	R^1	solvent	*n*, reaction order	k_{obs} (sec^{-1})[b]	$k_2 \times 10^4$ ($M^{-1} \times sec^{-1}$)[b,c]
1	**1a**	Me	CD_3OD	1	0.016 ±	7.2 ±
2	**1a**	Me	CD_3OH	0.98	0.028 ±	12.1 ±
3	**1a**	Me	CH_3OD	0.85	0.017 ±	7.6 ±
4	**1c**	*t*-Bu	CD_3OD	0.71	0.11 ±	48 ±
5	**1c**	*t*-Bu	CD_3OH	0.95	0.14 ± 0.003	62 ± 1
6	**1d**	Bn	CD_3OD	0.8	0.016 ±	7.0 ±
7	**1a**	Me	CD_3OD/D_2O, 11:1	0.99	0.015 ±	6.3 ±
8	**1a**	Me	CD_3OD/D_2O, 5:1	0.86	0.013 ±	5.9 ±

[a] Reaction was carried out in 0.04 mol/l solution at 52.0 °C. The temperature is accurate to ± 0.2 °C and precise to ± 0.01 °C. [b] The error limits are standard deviations. [c] $k_2 = k_{obs}$[ROH].

The structures of **15** and **11** were unequivocally distinguished by HMBC. It should be added that the ratio of **5** to **15** was somewhat changed in the CH_3OD/D_2O = 10:1 mixture that favored the formation of **15** (Table 2). This exemplifies that in CH_3OD the relative rate of formation of **15** increases. More to be added is that 1-methyl-substituted ylide **4a** was converted into betaine **16** in CD_3OD/D_2O (10:1) (eq 10; Table 1, entry 17).



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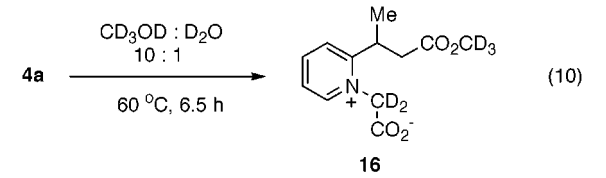

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Thus, it was found that three types of reaction took place competitively in methanol and water, i.e., ring contraction to **5**−**7**, solvolytic ring opening and subsequent ester cleavage to **10**, **15**, and **16**, and hydrolytic ring opening to **11** or **13** (and subsequently to **12** or **14**). It should be noted that all the reactions described here proceeded significantly faster with *tert*-butyl esters (**1c**, **4c**) than with smaller esters (**1a,d** and **4a**) (compare entries 1, 2, and 4−6 with 3; 9 with 10; 12, 13, and 15 with 14 in Table 1) and significantly slower with 1-methyl-substituted ylides than with 1-unsubstituted ones (compare entries 1 with 9; 3 with 10 in Table 1).

To clarify the mechanism of these transformations, we performed a kinetics study on the solvolysis of **1a,d** and found remarkably high reactivity of *tert*-butyl ester **1c** compared to methyl ester **1a** (compare entries 1 with 4; 2 with 5 in Table 3). The higher reactivity of *tert*-butyl esters (**1c** and **4c**) excluded a mechanistic possibility for the solvolytic nucleophilic substitution. Almost the same rate constants observed in both CD_3OD and mixed solvent CD_3OD/D_2O (Table 3, entries 1, 7, and 8) indicate that water was not involved in the rate-determining step in the mixed solvent to form **5** and **15**. This also suggests that the products were formed from the same intermediate after the rate-determining step. The solvent isotope effect (1.68 for **1a** and 1.29 for **1c**) was observed for the reactions in CD_3OD and CD_3OH (Table 3, entries 1 and 2 and 4 and 5), but not for those in CD_3OD and CH_3OD (entries 1 and 3).

Scheme 1 demonstrates a plausible mechanism of the solvolysis of ylides **A**. Because the protons at C-1 of unsubstituted ylides **A** (R^3 = H) are readily exchanged with deuterium in CD_3OD in its ^1H NMR, unsubstituted ylides **A** are in a rapid equilibrium with **A′** and **A″**. Solvolysis takes place through protonation on the most basic enamine moiety of **A″** (see **B**). The lower reactivities of 1-methyl-substituted ylides **4** (R^3 = Me, Scheme 4) (Table 1, entries 9, 10, 15 and 17) and acyl-substituted ylide **3** (Table 1, entry 8) than that of unsubstituted quinolizinium ylides **1** can be ascribed to both a less favorable equilibrium between **A**, **A′**, and **A″** due to the presence of a methyl group at C-1 and the stabilization of anionic charge more by the acyl group than the alkoxycarbonyl group. Although no difference in rates was observed between the reactions in CH_3OD and CH_3OD, significantly slower reaction in EtOH or BnOH than that in MeOH suggests that the rate-determining step should involve the nucleophilic attack of solvent (alcohol or water) at the ring carbonyl. The higher rates of solvolysis of *tert*-butyl esters, including ethanolysis, should be attributed to the release of steric congestion during the ring opening accompanied by the nucleophilic attack.[7] The pyridinium betaine **C**, thus formed by the ring opening, must be a reactive intermediate of the solvolysis as was suggested for the Chichibabin indolizine synthesis (see eq 1).[5] However, a more detailed mechanistic profile, which follows thereafter, must be involved to explain the observed substituent effects.

For alcoholysis (R ≠ H), cyclization to indolizinone **F** proceeds through ketene intermediate **E**, which is formed from **C** by the elimination of R^1 presumably via the E1cB mechanism. From the common intermediate **E**, two competing reactions proceed: addition of alcohol or water, and cyclization to indolizinones **F**. With unsubstitutd ylides, the cyclization overrides the addition process to afford indolizinone preferentially. In the case of alcoholysis of 1-methyl-substituted ylides **4a** and **4c**, cyclization of **E** is retarded because of steric hindrance of the disubstituted enamine, so that the following process goes entirely to the ester exchange product **C** (R^3 = Me, R^1 = OR) and eventually goes back to the starting ylide **A** (R^1 = OR) (Table 1, entries 9 and 10). In CF_3CH_2OH, the resulting ring opening product **C** is protonated to form a pyridinium salt of $CF_3CH_2O^-$ and, therefore, ketene formation is retarded.

For hydrolysis (R = H), after the ring cleavage of **B** to **C** by water, the resulting ylidic betaine is converted to amino acid betaine **H** by proton transfer. Because the ketene formation from **H** is impossible, cyclization to indolizine cannot take place. Instead, hydrolysis to diacid **I** proceeds slowly.

In the mixed solvent of methanol and water, the ring cleavage of **B** proceeds preferentially via methanolysis to produce **C** (R = Me). Betaine **C** (R = Me) is converted to ketene **E**, which cyclizes to **F** in competition with the addition of water to **E** leading to **G** depending on the reaction media. It is interesting to note that the rate of addition to the ketene was in the order of $CD_3OD > D_2O > CH_3OD$ because the distribution of products **5** and **15** changed accordingly (Table 2).

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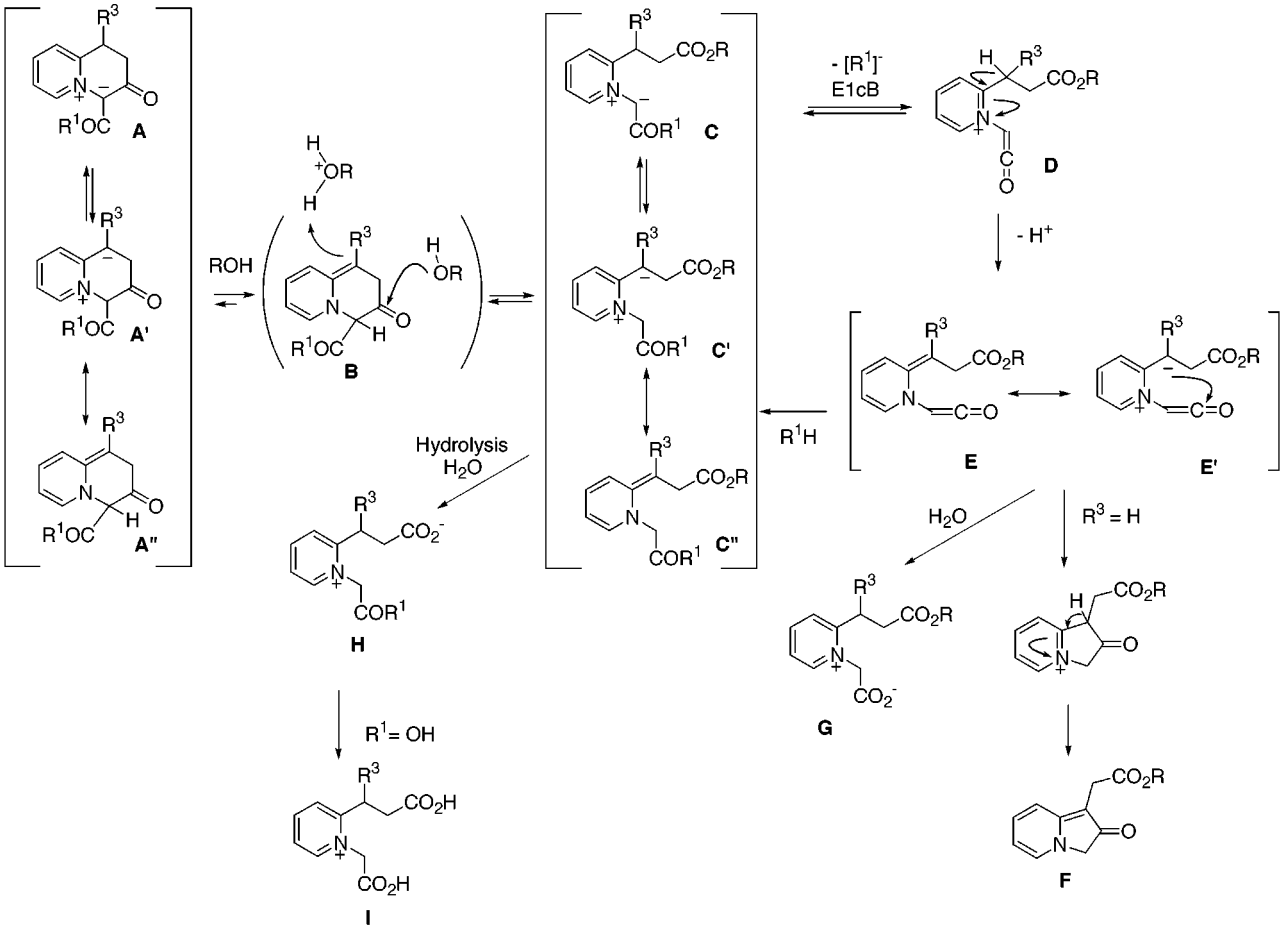
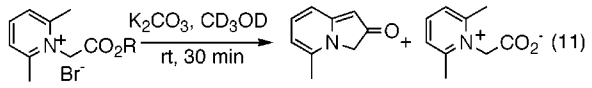
Scheme 1[a]



[a] Structures **A** (**A′**, **A″**) refer to ylides **1**−**4**, where R^1 is either Me (**3**) or alkoxy (**1**, **2**, **4**) and R^3 is either Me or H.

The possible formation of ketene intermediate **E** via **D** was supported again by the facile Chichibabin cyclization of lutidinium salts **17**, where both ethyl and *tert*-butyl esters afforded the indolizinone **18** with comparable rates (eq 11).[8] Furthermore, the formation of hydrolyzed betaine **19** in both reactions, though in low yield, was only explained by the ketene intermediate via the E1cB mechanism because no hydrolysis was observed with *tert*-butyl ester **17c** in water.



17		**18**		**19**
17b: R = Et	77%	91	:	9
17c: R = *t*-Bu	85%	88	:	12

In conclusion, we found that the Chichibabin-type indolizinone formation proceeds from tetrahydroquinolizinium ylides **1**−**4** under solvolytic conditions without bases. Also clarified are the following: (1) the reaction involves solvolysis on the six-membered ring of **1** in the rate determining step, and (2) a ketene species is involved and playing a role as a common intermediate for the Chichibabin indolizine synthesis.

(8) Similar transformations were reported. See ref 5.

Experimental Section

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. ^{1}H NMR spectra (500 MHz) and ^{13}C NMR spectra (126 MHz) were measured in $CDCl_3$ unless otherwise noted, and assignment was done on the basis of CH−COSY, HMBC, and NOE procedures. UV spectra were measured in EtOH. All reactions were performed in oven-dried glassware under a nitrogen atmosphere, unless otherwise noted.

General Procedure for the Solvolysis of Ylides (1−4). A solution of 1 mmol of ylide **1**−**4** in 20 mL of an alcohol was warmed at 60 °C for a specified period (Table 1), and the solvent was removed under reduced pressure. The crude product was purified by a flash column chromatography with a 15% methanol−methylene chloride mixture. Indolizinones **5**−**8**, as oils, were rather unstable and gradually decomposed when exposed to air. Thus, they were mainly characterized by NMR analysis.

Methyl 2,3-Dihydro-2-oxoindolizin-1-acetate (5). Yellow oil; IR (KBr) 1736, 1637(shl), 1593, 1545, 1495 cm^{-1}; ^{1}H NMR δ 3.30 (2H, s; CH_2CO$_2$Me), 3.68 (3H, s; MeO), 4.27 (2H, s; H3), 6.28 (1H, t, J = 8 Hz; H6), 6.81 (1H, d, J = 8.3 Hz; H8), 7.26 (1H, t, J = 8 Hz; H7), 7.47 (1H, d, J = 7.8 Hz; H5); ^{13}C NMR δ 26.6 (*C*H$_2$CO$_2$Me), 51.8 (MeO), 57.9 (C3), 94.6 (C1), 108.8 (C6), 114.9 (C8), 136.0 (C5), 138.2 (C7), 164.4 (C8a), 172.1 (*C*O$_2$Me), 186.6 (C2); MS *m*/*z* (relative intensity) 205 (M$^+$, 80), 185 (10), 155 (12), 146 (100), 129 (11), 117 (26), 106 (16), 69 (33), 57 (20); HRMS calcd for $C_{11}H_{11}NO_3$ 205.0739, found 205.0743; UV λ_{max} (log ϵ), 300 (4.60), 425 (3.96) nm.

Ethyl 2,3-Dihydro-2-oxoindolizin-1-acetate (6). Yellow oil; IR (KBr) 1726, 1637, 1617, 1603, 1538, 1514 cm^{-1}; ^{1}H NMR δ 1.25 (3H, t, J = 7.1 Hz; CH_3CH$_2$O), 3.28 (2H, s; CH_2CO$_2$Et),

4.13 (2H, q, J = 7.1 Hz; OCH_2CH$_3$), 4.27 (2H, s; H3), 6.28 (1H, t, J = 8 Hz; H6), 6.81 (1H, d, J = 8.2 Hz; H8), 7.26 (1H, t, J = 8 Hz; H7), 7.49 (1H, d, J = 7.5 Hz; H5); ^{13}C NMR δ 14.1 (OCH$_2$*C*H$_3$), 26.7 (*C*H$_2$CO$_2$Et), 57.9 (C3), 60.6 (O*C*H$_2$CH$_3$), 94.7 (C1), 108.8 (C6), 115.0 (C8), 136.0 (C5), 138.1 (C7), 164.4 (C8a), 171.6 (*C*O$_2$Et), 186.6 (C2); UV λ_{max} (log ϵ), 301 (4.52), 424 (3.90) nm.

Benzyl 2,3-Dihydro-2-oxoindolizin-1-acetate (7). Orange needles (*i*-PrOH); mp 134.5−135 °C (dec); IR (KBr) 1726, 1638(shl), 1622(shl), 1601, 1543, 1508, 1470 cm^{-1}; ^{1}H NMR δ 3.24 (2H, s; C*H*$_2$CO$_2$Bn), 4.11 (2H, s; H3), 5.01 (2H, s; C*H*$_2$-Ph), 6.16 (1H, t, J = 8 Hz; H6), 6.64 (1H, d, J = 8.3 Hz; H8), 7.12 (1H, t, J = 8 Hz; H7), 7.20 (5H, m; Ph), 7.35 (1H, d, J = 7.8 Hz; H5); ^{13}C NMR δ 26.6 (*C*H$_2$CO$_2$Bn), 57.7 (C3), 66.2 (*C*H$_2$-Ph), 94.2 (C1), 108.8 (C6), 114.6 (C8), 126.7, 127.9, 128.2, 135.7 (Ph), 136.0 (C5), 138.0 (C7), 164.1 (C8a), 171.3 (*C*O$_2$Bn), 186.3 (C2).

Methyl 2,3-Dihydro-2-oxoindolizin-1-(2-propionate) (8). Yellow oil; IR (KBr) 1728, 1637(shl), 1591, 1543, 1493 cm^{-1}; ^{1}H NMR δ 1.37 (3H, d, J = 7.4 Hz; Me), 3.66 (3H, s; MeO), 3.84 (1H, q, J = 7.4 Hz; C*H*CO$_2$Me), 4.25 (2H, s; H3), 6.26 (1H, t, J = 8 Hz; H6), 6.94 (1H, d, J = 8.3 Hz; H8), 7.24 (1H, t, J = 8.0 Hz; H7), 7.46 (1H, d, J = 7.5 Hz; H5); ^{13}C NMR δ 15.2 (Me), 32.6 (*C*HCO$_2$Me), 51.8 (MeO), 57.7 (C3), 101.1 (C1), 108.6 (C6), 115.5 (C8), 136.2 (C5), 138.1 (C7), 163.5 (C8a), 175.3 (*C*O$_2$Me), 186.0 (C2); UV λmax (log ϵ), 302 (4.05), 428 (3.42) nm.

Methyl 2-Methyl-indolizine-1-acetate (9). Colorless oil; IR (KBr) 1736 cm^{-1}; ^{1}H NMR δ 2.18 (3H, s; Me), 3.57 (3H, s; MeO), 3.62 (2H, s; C*H*$_2$CO$_2$Me), 6.27 (1H, t, J = 8 Hz; H6), 6.51 (1H, dd, J = 8.9 and 6.8 Hz; H7), 7.00 (1H, s; H3), 7.19 (1H, d, J = 8.9 Hz; H8), 7.66 (1H, d, J = 6.8 Hz; H5); ^{13}C NMR δ 10.5 (Me), 29.9 (*C*H$_2$CO$_2$Me), 51.8 (MeO), 103.4, 109.4 (C6), 110.8 (C3), 116.4 (C8), 116.4 (C7), 123.9, 124.6 (C5), 130.9, 172.5 (*C*O$_2$Me). (Three quaternary carbons at C1, C2, and C8a were not assigned.)

Reaction of 1c with 2,2,2-Trifluoroethanol. A solution of 0.2 mmol of ylide **1c** in 2 mL of 2,2,2-trifluoroethanol was warmed at 60 °C for 2 h. After the solvent was removed under reduced pressure, 65 mg of an oily residue was obtained, which was identified as a 1:4 mixture of **10c** and **10c′** by ^{1}H NMR. Treatment of the mixture with water (2 mL) at room temperature and removal of the solvent under reduced pressure gave **10c′** as a sole product.

1-(*tert*-Butoxycarbonylmethyl)-2-(2,2,2-trifluoroethoxycarbonylethyl)pyridinium 2,2,2-Trifluoroethoxide (10c, taken from the mixture with 10c′). ^{1}H NMR (CD$_3$OD) δ 1.52 (9H, s; *t*-BuO), 3.09 (2H, t, J = 7.0 Hz; CH$_2$C*H*$_2$CO$_2$), 3.25 (2H, t, J = 7.0 Hz; C*H*$_2$CH$_2$CO$_2$), 3.86 (2H, q, J = 9.1 Hz; CF$_3$C*H*$_2$O$^-$), 4.63 (2H, q, J = 8.5 Hz; C*H*$_2$CF$_3$), 5.27 (2H, s; N$^+$C*H*$_2$CO$_2$), 7.84 (1H, t, J = 7 Hz; H5), 8.00 (1H, d, J = 7.3 Hz; H3), 8.41 (1H, t, J = 7 Hz; H4), 8.73 (1H, d, J = 6.8 Hz; H6).

1-(*tert*-Butoxycarbonylmethyl)-2-(carboxyethyl)pyridinium 2,2,2-Trifluoroethoxide (10c′). Oil; ^{1}H NMR (CD$_3$OD) δ 1.52 (9H, s; *t*-BuO), 2.70 (2H, t, J = 7.0 Hz; CH$_2$C*H*$_2$-CO$_2$), 3.21 (2H, t, J = 7.0 Hz; C*H*$_2$CH$_2$CO$_2$), 3.86 (2H, q, J = 9.1 Hz; CF$_3$C*H*$_2$O$^-$), 5.67 (2H, s; N$^+$C*H*$_2$CO$_2$), 7.92 (1H, t, J = 7 Hz; H5), 8.10 (1H, d, J = 7.5 Hz; H3), 8.52 (1H, t, J = 7 Hz; H4), 8.81 (1H, d, J = 6.8 Hz; H6); ^{13}C NMR (CD$_3$OD) δ 28.2 (C(*Me*)$_3$), 30.3 (CH$_2$*C*H$_2$CO$_2$), 36.3 (*C*H$_2$CH$_2$CO$_2$), 61.5, 61.3, 61.1, 60.9 (*C*H$_2$CF$_3$), 86.2 (*C*(Me)$_3$ and N$^+$*C*H$_2$CO$_2$*t*-Bu), 126.5 (CH$_2$*C*F$_3$), 127.3, 130.0, 147.5, 147.8, 162.2 (Py), 166.3 (N$^+$-CH$_2$*C*O$_2$*t*-Bu), 178.2 (CH$_2$CH$_2$*C*O$_2$).

Reaction of Ylides 1a−c and 4a with D$_2$O. A solution of 0.8 mmol of ylide **1a−c** (or **4a**) in 10 mL of D$_2$O was warmed at 60 °C (Table 1). Concentration of the reaction mixture under reduced pressure gave betaines **11a−c** (**13a**) as oils. Further heating of the betaine solution as indicated in Table 1 afforded **12** (**14**) after removal of the solvent under reduced pressure.

1-(Methoxycarbonyl-*d*$_2$-methyl)pyridinium-2-propionate (11a). Oil; ^{1}H NMR (D$_2$O) δ 2.63 (2H, t, J = 7.0 Hz; CH$_2$C*H*$_2$CO$_2$), 3.17 (2H, t, J = 7.0 Hz; C*H*$_2$CH$_2$CO$_2$), 3.78 (3H, s; CO$_2$C*H*$_3$), 7.85 (1H, t, J = 7 Hz; H5), 7.94 (1H, d, J = 7.0 Hz; H3), 8.45 (1H, t, J = 7 Hz; H4), 8.64 (1H, d, J = 6.8 Hz; H6); ^{13}C NMR (D$_2$O) δ 28.2 (CH$_2$*C*H$_2$CO$_2$), 33.6 (*C*H$_2$CH$_2$CO$_2$), 54.0 (MeO), 57.8 (N$^+$*C*H$_2$CO$_2$Me), 125.7, 128.4, 145.6, 146.7, 158.8 (py), 167.4 (N$^+$CH$_2$*C*O$_2$Me), 177.8 (CH$_2$CH$_2$*C*O$_2$).

The structure of **11a** was determined by the HMBC cross-peaks of the sample compound **11a′** obtained from the reaction in H$_2$O. **11a′** (**11a**−1-CH$_2$CO$_2$Me): ^{1}H NMR (CD$_3$OD) δ 2.73 (2H, t, J = 7.0 Hz; CH$_2$C*H*$_2$CO$_2$), 3.25 (2H, t, J = 7.0 Hz; C*H*$_2$-CH$_2$CO$_2$), 3.87 (3H, s; CO$_2$C*H*$_3$), 5.79 (br, CDH), 5.80 (s), 7.95 (1H, t, J = 7 Hz; H5), 8.12 (1H, d, J = 7.1 Hz; H3), 8.55 (1H, t, J = 7 Hz; H4), 8.87 (1H, d, J = 6.8 Hz; H6); ^{13}C NMR (CD$_3$-OD) δ 30.0 (CH$_2$*C*H$_2$CO$_2$), 36.3 (*C*H$_2$CH$_2$CO$_2$), 54.2 (MeO), 59.0 (N$^+$*C*H$_2$CO$_2$Me), 126.7, 129.9, 147.6, 147.7, 162.0 (py), 167.9 (N$^+$CH$_2$*C*O$_2$Me), 177.8 (CH$_2$CH$_2$*C*O$_2$); HMBC cross-peaks (CD$_3$-OD) (proton-carbon) 2.73−177.8, 5.80−167.9, 3.87−167.9 ppm.

1-(Ethoxycarbonyl-*d*$_2$-methyl)pyridinium-2-propionate (11b). Oil; ^{1}H NMR (D$_2$O) δ 1.19 (3H, t, J = 6.8 Hz), 2.68 (2H, t, J = 7.0 Hz), 3.17 (2H, t, J = 7.0 Hz), 4.22 (2H, q, J = 6.8 Hz), 7.84 (1H, t, J = 7 Hz), 7.94 (1H, d, J = 7.5 Hz), 8.44 (1H, t, J = 7 Hz), 8.64 (1H, d, J = 6.8 Hz).

1-(*tert*-Butoxycarbonyl-*d*$_2$-methyl)pyridinium-2-propionate (11c). Oil; ^{1}H NMR (D$_2$O) δ 1.39 (9H, s), 2.61 (2H, t, J = 7.0 Hz), 3.15 (2H, t, J = 7.0 Hz), 7.85 (1H, t, J = 7 Hz), 7.94 (1H, d, J = 7.2 Hz), 8.45 (1H, t, J = 7 Hz), 8.63 (1H, d, J = 6.8 Hz).

1-(Carboxy-*d*$_2$-methyl)pyridinium-2-propionate (12). Colorless prisms (water−methanol). The analytical sample caused D−H exchange during recrystallization. Mp 147−148.5 °C (decomp); IR (KBr) 1691, 1628 cm^{-1}; ^{1}H NMR (D$_2$O) δ 2.84 (2H, t, J = 7.0 Hz), 3.22 (2H, t, J = 6.9 Hz), 5.17 (2H, s), 7.82 (1H, t, J = 7 Hz), 7.90 (1H, d, J = 7.4 Hz), 8.38 (1H, t, J = 7 Hz), 8.59 (1H, d, J = 6.8 Hz); ^{13}C NMR (D$_2$O) δ 27.9, 33.3, 60.5, 125.5, 128.0, 146.0, 146.4, 157.7, 170.4, 177.6; MS (FAB) *m*/*z* (relative intensity) 210 (M$^+$, 100), 166 (8), 154 (15), 137 (17), 136 (10), 75 (11), 57 (4); HRMS calcd for C$_{10}$H$_{12}$NO$_4$ 210.0759, found 210.0767. Anal. Calcd for C$_{10}$H$_{11}$NO$_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.11; H, 5.15; N, 6.56.

1-(Methoxycarbonyl-*d*$_2$-methyl)pyridinium-2-(*β*-methylpropionate) (13a). Oil; ^{1}H NMR (D$_2$O) δ 1.28 (3H, d, J = 6.6 Hz), 2.61 (1H, A of ABX, J_{AB} = 17.5, J_{AX}= 6.5 Hz), 2.65 (1H, B of ABX, J_{AB} = 17.5, J_{BX}= 8.5 Hz), 3.51 (1H, m), 3.78 (3H, s), 7.82 (1H, t, J = 7 Hz), 8.06 (1H, d, J = 7.4 Hz), 8.47 (1H, t, J = 7 Hz), 8.61 (1H, d, J = 7.0 Hz); ^{13}C NMR (D$_2$O) δ 19.6, 33.4, 53.9, 123.6, 125.4, 126.7, 146.2, 147.1, 164.4, 167.7.

1-(*d*$_1$-Carboxy-*d*$_2$-methyl)pyridinium-2-(*β*-methylpropionate) (14). ^{1}H NMR (D$_2$O) δ 1.28 (3H, d, J = 6.9 Hz), 2.79 (2H, m), 3.55 (1H, m), 7.77 (1H, t, J = 7 Hz), 7.98 (1H, d, J = 7.4 Hz), 8.39 (1H, t, J = 7 Hz), 8.55 (1H, d, J = 6.8 Hz); ^{13}C NMR (D$_2$O) δ 19.3, 32.8, 44.1, 58.2, 125.2, 125.5, 126.4, 145.8, 146.1, 163.1, 167.7.

1-(Carboxymethyl)pyridinium-2-(*β*-methylpropionate) (14−1-CH$_2$CO$_2$H). This sample was obtained by the reaction in H$_2$O. Colorless needles (water−MeOH); mp 146−147 °C (dec); IR (KBr) 1701, 1628 cm^{-1}; ^{1}H NMR (D$_2$O) δ 1.28 (3H, d, J = 6.6 Hz), 2.68 (2H, m), 3.53 (1H, secst, J = 6.6 Hz), 5.11 (1H, A of ABq, J_{AB} = 17.0 Hz), 5.46 (1H, B of ABq, J_{AB} = 17.0 Hz), 7.76 (1H, t, J = 7 Hz), 7.97 (1H, d, J = 7.5 Hz), 8.38 (1H, t, J = 7 Hz), 8.54 (1H, d, J = 6.8 Hz); Anal. Calcd for C$_{11}$H$_{13}$NO$_4$: C, 59.19; H, 5.87; N, 6.28. Found: C, 59.24; H, 5.85; N, 6.09.

Solvolysis of Ylides 1a and 4a in Methanol−Water Mixtures. Reactions were carried out as described above for the hydrolysis. The ratios of **15** and **5** were determined by NMR. Compounds **15** (as a mixture of **5**) and **16** were characterized with those obtained from the reaction in CH$_3$-OH−H$_2$O mixtures.

2-(Methoxycarbonylethyl)pyridinium-1-acetate (15). ^{1}H NMR (CD$_3$OD) δ 2.94 (2H, t, J = 7.3 Hz; CH$_2$C*H*$_2$CO$_2$Me), 3.34 (2H, t, J = 7.3 Hz; C*H*$_2$CH$_2$CO$_2$Me), 3.68 (3H, s; CO$_2$C*H*$_3$), 5.23 (2H, s; N$^+$C*H*$_2$COO), 7.89 (1H, dt, J = 1.0, 7 and 7 Hz), 8.02 (1H, d, J = 7.4 Hz), 8.45 (1H, dt, J = 1.0, 7 and 7 Hz), 8.79 (1H, d, J = 6.9 Hz); ^{13}C NMR (CD$_3$OD) δ 28.5 (CH$_2$*C*H$_2$-CO$_2$Me), 32.4 (*C*H$_2$CH$_2$CO$_2$Me), 52.6 (N$^+$*C*H$_2$CO$_2^-$), 62.5 (CO$_2$*C*H$_3$), 126.7, 129.6, 146.4, 147.9, 159.1 (py), 169.7 (CH$_2$*C*O$_2^-$), 173.4 (*C*OOMe); HMBC cross-peaks (proton-carbon) 5.23−169.7, 5.23−159.1 ppm.

2-(2-Methoxycarbonyl-1-methylethyl)pyridinium-1-acetate (16). Oil; ^{1}H NMR (CD_3OD) δ 1.44 (3H, d, J = 7.0 Hz; CH_3CH), 2.90 (1H, A of ABX, J_{AB} = 17.5 Hz, J_{AX} = 6.1 Hz; CHCH_2CO$_2$Me), 2.96 (1H, B of ABX, J_{AB} = 17.5 Hz, J_{BX} = 8.8 Hz; CHCH_2CO$_2$Me), 3.60 (3H, s; OCH_3), 3.73 (1H, ddq, J = 8.8, 6.1 and 7.0 Hz; CH$_3$CHCH$_2$), 5.22 (1H, A of ABq, J_{AB} = 15.8 Hz; NCH_2CO$_2^-$), 5.56 (1H, B of ABq, J_{AB} = 15.8 Hz; NCH_2CO$_2^-$), 7.88 (1H, t, J = 7 Hz), 8.15 (1H, d, J = 7.3 Hz), 8.48 (1H, t, J = 7 Hz), 8.80 (1H, d, J = 7.0 Hz); ^{13}C NMR (CD_3-OD) δ 20.6 (*C*H$_3$CH), 33.6 (CH$_3$*C*H), 41.5 (CH*C*H$_2$CO$_2$Me), 52.5 (CH$_2$CO$_2$*C*H$_3$), 63.2 (N$^+$*C*H$_2$CO$_2^-$), 126.5, 127.6, 146.6, 147.6, 164.6 (C2), 169.9 (N$^+$CH$_2$*C*O$_2^-$), 173.4 (CH$_2$*C*O$_2$Me); HMBC cross-peaks (proton−carbon) 2.90, 2.96−173.4, 3.60−173.4, 3.73−173.4, 5.22, 5.56−169.9, 5.22, 5.56−164.6 ppm.

Methanolysis of Lutidinium Bromides (17). To a solution of 0.274 g (1 mmol) of 1-ethoxycarbonylmethyl-2,6-dimethylpyridinium bromide (**17b**) in 8 mL of methanol 0.138 g (1.1 mmol) of anhydrous potassium carbonate was added, and the mixture was stirred at room temperature for 1 h. Removal of the solvent followed by silica gel column chromatography with 11% methanol in methylene chloride gave 0.135 g (92%) of **18**.

2,3-Dihydro-5-methylindolizin-2-one (18).[5] Orange oil; ^{1}H NMR (CD_3OD) δ 2.42 (3H, s), 5.14 (2H, s), 5.49 (1H, s), 6.57 (1H, d, J = 7.8 Hz), 6.94 (1H, d, J = 8.2 Hz), 7.51 (1H, t, J = 8.0 Hz); ^{13}C NMR (CD_3OD) δ 18.8, 91.5, 113.0, 114.6, 128.6, 141.4, 149.7, 167.1, 189.3.

To a solution of 0.274 g (1 mmol) of 1-ethoxycarbonylmethyl-2,6-dimethylpyridinium bromide (**17b**) in 8 mL of water 0.138 g (1.1 mmol) of anhydrous potassium carbonate was added, and the mixture was stirred at room temperature for 2 h. Removal of the solvent followed by silica gel column chromatography with 10% water in methanol gave 0.13 g of oily residue, which was identified as 2,6-dimethylpyridinium-1-acetate (**19**).

19 (partially deuterated at N$^+$C*H*$_2$CO$_2$). Oil; ^{1}H NMR (CD_3OD) δ 2.76 (6H, s; Me), 5.04 (br; 1-C*H*DCO$_2^-$), 5.06 (s; 1-CH_2CO$_2^-$), 7.83 (2H, d, J = 8.0 Hz), 8.27 (1H, t, J = 8.0 Hz); ^{13}C NMR (CD_3OD) δ 21.7 (br), 57.8 (br), 128.6, 145.6, 157.2, 169.3.

NMR Experiment of Methanolysis of Lutidinium Bromides (17). A mixture of **17** (27 mg of **17b** or 30 mg of **17c**; 0.1 mmol) and anhydrous potassium carbonate (14 mg, 0.11 mmol) in CD_3OD (0.8 mL) was shaken well in a NMR tube. After 30 min, ^{1}H NMR was recorded and the ratio of **17**, **18**, and **19** was determined.

Kinetics. The kinetics of the methanolysis were determined by NMR using DRX-500 Bruker spectrometer. Temperature was controlled by using a thermostat-controlled cell holder. Reactions were carried out in 0.04 M solutions of ylides in methanol. An ylide and an internal standard (mesitylene) were weighed in an NMR sample tube, which was stoppered with septum cup and flashed with nitrogen. Deuterated methanol (Aldrich) was added by a microsyringe shortly before the measurement. The measurement was started immediately after the tube was loaded into the cell. The obtained exponential trace was found to correspond to a first-order rate law. The reaction orders (Table 3) were calculated using the van't Hoff method. The observed first-order rate constants were calculated from the integrated first-order rate law. The first-order rate constants thus obtained were treated as a function of methanol concentration (assumed as constant) to yield second-order rate constants.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **5**, **6**, **7**, **8**, **9**, **11a**, and **15**, HCCO spectra of **5** and **9**, and HMBC spectra of **11a** and **15** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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