Ring Contractions of 4-Oxoquinolizine-3-diazonium Tetrafluoroborates, by an Aza Wolff Rearrangement, to Alkyl Indolizine-3-carboxylates

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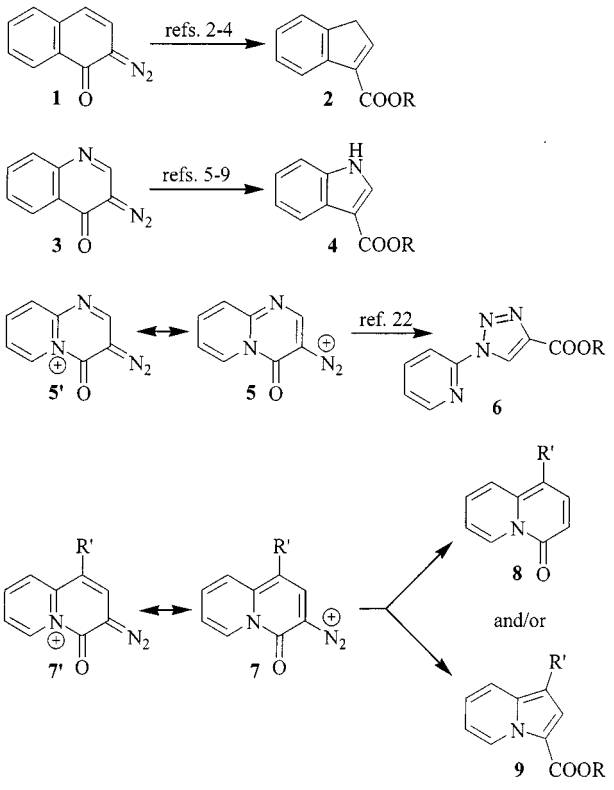
The 1-substituted 3-amino-4*H*-quinolizin-4-ones **13**, available in two steps from **10** and methyl (*Z*)-2-benzyloxycarbonylamino-3-(dimethylamino)propenoate (**11**), were diazotized to give the stable diazonium tetrafluoroborates **7a** and **7b**. Heating of these diazonium salts in alcohols gave mixtures of 3-unsubstituted quinolizine derivatives **8a** and **8b** and the alkyl indolizine-3-carboxylates **9a**–**h**. The ratio of the two types of products **8** and **9** was dependent on the type of alcohol employed. Thus, treatment of **7a** or **7b** with 2-propanol predominantly resulted in the 3-unsubstituted quinolizinones **8**, while treatment of **7a** or **7b** with primary alcohols gave the indolizine-3-carboxylates **9** as the major products in most cases. The transformation of the 4-oxoquinolizine-3-diazonium tetrafluoroborates **7a** and **7b** into the alkyl indolizine-3-carboxylates **9a**–**h** represents the first example of a Wolff rearrangement in the fused cyclic α-diazoamide series.

Introduction

α-Diazocarbonyl compounds are an important class of organic compounds, with wide and versatile use in organic synthesis. An example of their synthetic utility is the Wolff rearrangement, which is applied in Arndt−Eistert homologation of carbocyclic acids and in ring contractions of cyclic α-diazocarbonyl compounds.[1] In this context, the ring contractions of 2-diazonaphthoquinones (**1**) into indene-3-carboxylic acid derivatives (**2**)[2−4] and related rearrangements of 3-diazoquinolin-4-ones (**3**) into alkyl indole-3-carboxylates (**4**)[5−9] have been extensively studied. However, only a few examples of similar rearrangements in the α-diazoamide series are known.[10−12] Such rare examples include the photochemical ring contraction of 4-diazopyrazolidine-3,5-diones into aza-β-lactams[13,14] and sporadic instances of Wolff rearrangements in the acyclic α-diazoamide series.[15−17] Recently, 1-benzyloxycarbonyl-3-diazopyrrolidin-2-one has been prepared as a potential precursor for the synthesis of important azetidine derivatives,[18] while 3-amino-4*H*-pyridino[1,2-*a*]pyrimidin-4-ones and 3-amino-4*H*-quinolizin-4-ones[19,20] are easily available from alkyl 2-(substituted amino)-3-(dimethylamino)prop-2-enoates.[21] In this context, we have recently shown that 4-oxo-4*H*-pyridino[1,2-*a*]pyrimidine-3-diazonium tetrafluoroborates (**5**) undergo a "ring-switching" transformation with primary alcohols to give the alkyl 1-(pyridin-2-yl)-1*H*-1,2,3-triazole-4-carboxylates **6**.[22] In continuation of our research, we now report the preparation of the stable 1-substituted 4-oxo-4*H*-quinolizine-3-diazonium tetrafluoroborates **7** and their transformations into the 1-substituted 4*H*-quinolizin-4-ones **8** and alkyl 1-substituted indolizine-3-carboxylates **9**. The transformation of the diazonium salts **7** into the indolizine-3-carboxylates **9** represents the first example of a Wolff rearrangement of diazonium salts derived from fused azinones with a bridgehead nitrogen atom (Scheme 1).



Scheme 1

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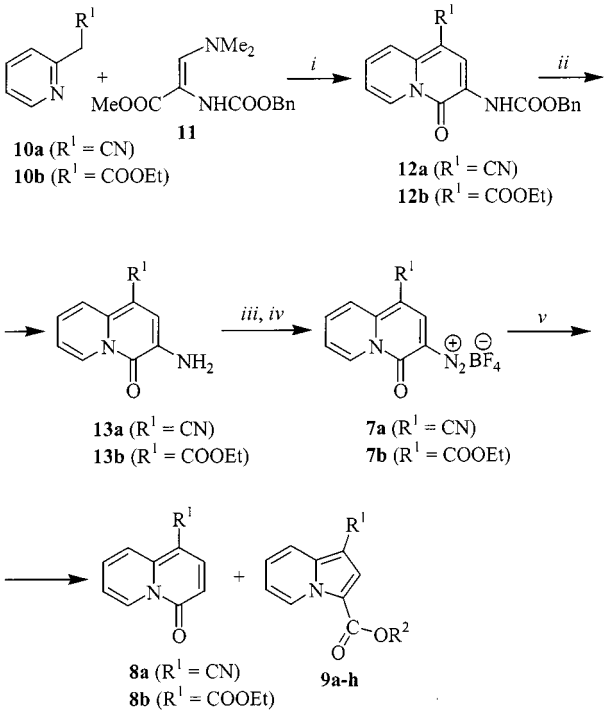
Results and Discussion

The starting materials 3-amino-1-cyano-4*H*-quinolizin-4-one (**13a**) and ethyl 3-amino-4-oxo-4*H*-quinolizine-1-carboxylate (**13b**), were prepared in two steps from methyl (*Z*)-2-benzyloxycarbonylamino-3-(dimethylamino)prop-2-enoate (**11**), according to the procedures described previously.[23] Nitrosation of the 3-aminoquinolizines **13a** and **13b** gave the stable 4-oxo-4*H*-quinolizine-3-diazonium tetrafluoroborates **7a** and **7b** in 84% and 86% yields, respectively. Treatment of **7a** and **7b** with anhydrous alcohols such as methanol, ethanol, 1-propanol, and 2-propanol, at 50−80 °C, gave mixtures of the 3-unsubstituted 4*H*-quinolizin-4-ones **8a** and **8b** and the alkyl indolizine-3-carboxylates **9a**−**h**. In most cases the selectivity of these transformations was dependent upon the type of alcohol employed. Thus, heating **7a** or **7b** in methanol or 1-propanol afforded the corresponding methyl and *n*-propyl indolizine-3-carboxylates **9a**, **9c**, **9e**, and **9g**, while treatment of **7a** and **7b** with 2-propanol under reflux gave the corresponding dediazonized 4*H*-quinolizin-4-ones **8a** and **8b** as the major products. When the reaction was performed in ethanol, both sets of products, the 4*H*-quinolizin-4-ones **8a** and **8b** and the ethyl indolizine-3-carboxylates **9b** and **9f**, respectively, were obtained in similar yields (Scheme 2, Table 1).



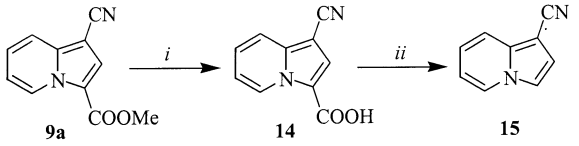
Scheme 2. Reagents and conditions: *i*) AcOH, reflux; *ii*) cyclohexene, EtOH, 10% Pd−C, reflux; *iii*) $NaNO_2$, HCl, H_2O, −5 to 0 °C; *iv*) 50% HBF_4 (aq.); *v*) R^2OH, 50−80 °C

The structures of all novel compounds **7**−**9** were determined by spectroscopic methods (NMR, IR, MS or HRMS) and by elemental analysis (C, H, and N). The spectral and analytical data for 1-cyano-4*H*-quinolizin-4-one (**8a**), ethyl 4-oxo-4*H*-quinolizine-1-carboxylate (**8b**),[24] ethyl 1-cyanoindolizine-3-carboxylate (**9b**),[25] and diethyl indolizine-1,3-dicarboxylate (**9f**),[26] were in accordance with the data reported previously. ^1H and ^{13}C NMR spectroscopic data for the indolizines **9a**−**g** were in agreement with those reported for other indolizine derivatives.[27,28] The structures of methyl 1-cyanoindolizine-3-carboxylate (**9a**) and 1-ethyl 3-methyl indolizine-1,3-dicarboxylate (**9e**) were also confirmed by HMQC and HMBC NMR techniques. The carbon atoms at positions 2, 5, 6, 7, and 8 were assigned on the basis of the HMQC spectrum, while the carbon atoms at positions 1, 3, and 9 were assigned on the basis of the HMBC spectrum. Because of the small difference between the ^{13}C chemical shifts for the CN group and C(3) (δ = 115.5, 115.7) in indolizine **9a**, we have so far been unable to distinguish between these two carbon atoms; in the related compound **9e**, the signal for C(3) appears at δ = 115.1 (see Figures 1−4 in the Supporting Information).

Table 1. Experimental data for treatment of diazonium salts **7a** and **7b** with alcohols

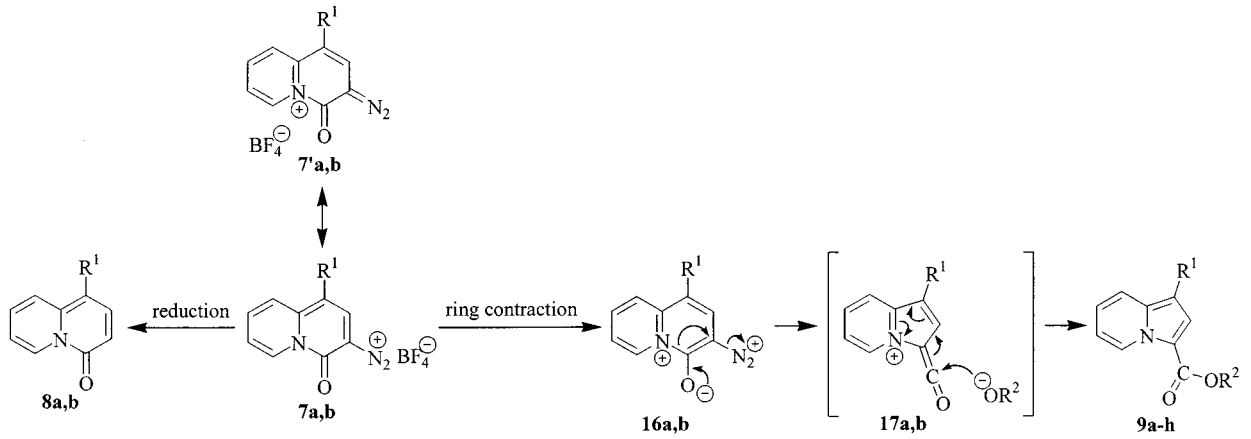
Reaction	Solvent	R^1	R^2	T [°C]	Time [h]	Yield [%] **8**	**9**
7a → **8a** + **9a**	MeOH	CN	Me	60	5	25	53
7a → **8a** + **9b**	EtOH	CN	Et	60	6	35	44
7a → **8a** + **9c**	*n*-PrOH	CN	*n*Pr	70	8	23	50
7a → **8a** + **9d**	*i*PrOH	CN	*i*Pr	70	7	69	25
7a → **8a** + **9d**	*i*PrOH	CN	*i*Pr	reflux	12	73	7.5
7b → **8b** + **9e**	MeOH	COOEt	Me	60	15	8	57
7b → **8b** + **9f**	EtOH	COOEt	Et	50	7	49	38
7b → **8b** + **9g**	*n*PrOH	COOEt	*n*Pr	60	7	11	42
7b → **8b** + **9h**	*i*PrOH	COOEt	*i*Pr	reflux	8	85	-

The structures of the alkyl indolizine-3-carboxylates **9** were also proven by the transformation of **9a** into the carboxylic acid **14**, followed by thermal decarboxylation to furnish the known 1-cyanoindolizine (**15**) (Scheme 3).[29]



Scheme 3. Reagents and conditions: *i*) NaOH, H_2O, MeOH, 50 °C; *ii*) anisole, reflux

Apparently, two competitive reactions take place when heteroaryldiazonium salts **7** are heated in alcohols: a) dediazoniation (reduction) to give the 3-unsubstituted quinolizinones **8**, and b) ring-contraction (rearrangement) to give the indolizines **9**. The reduction of the diazonium salts **7** with alcohols at elevated temperatures was not surprising, since closely related reductions in the aryldiazonium series are well documented in the literature, with ethanol as the reducing agent in most cases.[30,31] On the other hand, formation of the indolizine derivatives **9** can formally be regarded as an aza Wolff rearrangement.[32] Recent calculations on 6,6-fused heterocycles with a bridgehead nitrogen atom support the existence of the α-diazocarbonyl mesomeric structures **7′**,[33] thus making the carbenoid rearrangement mechanism feasible (Scheme 4).



Scheme 4

Conclusion

The ring contraction of the 4-oxo-4*H*-quinolizine-3-diazonium tetrafluoroborates **7** into the alkyl indolizine-3-carboxylates **9** is the first example of an aza Wolff rearrangement of quinolizin-4-one-3-diazonium salts into indolizine derivatives. Since the diazonium salts **7** are easily available in high yields from **11**, these transformations might also represent a novel alternative synthetic route for the preparation of indolizine-3-carboxylates **9** under mild conditions.

Experimental Section

General: Melting points were taken with a Kofler micro hot-stage apparatus. The ^{1}H NMR, ^{13}C NMR, 2D HMQC, and 2D HMBC spectra were obtained with a Bruker Avance DPX 300 (300 MHz) spectrometer with [D$_6$]DMSO and $CDCl_3$ as solvents and Me_4Si as internal standard. IR: Perkin−Elmer Spectrum BX FT-IR (Model 1600) spectrophotometer. Elemental analyses: Perkin−Elmer CHN Analyser 2400. TLC: Merck, Alufolien 60 F 254 Kieselgel, 0.2mm. Column chromatography was performed on silica gel (Fluka, Kieselgel 60, 0.04−0.063 mm). 3-Amino-1-cyano-4*H*-quinolizin-4-one (**13a**) and 3-amino-1-ethoxycarbonyl-4*H*-quinolizin-4-one (**13b**) were prepared according to the procedures described in the literature.[23]

General Procedure for the Preparation of 1-Substituted 4-Oxo-4*H*-quinolizine-3-diazonium Tetrafluoroborates (7a and 7b): The amine **13** (10 mmol) was dissolved in a mixture of water (12 mL) and concentrated hydrochloric acid (12 mL) and the solution was cooled in an ice bath for about 20 min. The temperature was maintained at 0−5 °C and an aqueous solution of sodium nitrite (4 mL, 11 mmol) was added portionwise to the vigorously stirred solution. After approximately 5 min., the completion of the reaction was checked using moist potassium iodide-starch paper as an external indicator. The solution was then stirred at 0−5 °C for another 10 min. A cold solution of tetrafluoroboric acid (50% aqueous solution; 6 mL) was then added. The precipitate was collected by suction filtration and carefully washed with small portions of cold water, methanol, and diethyl ether. After each washing, the precipitate was carefully dried. The following compounds were prepared in this manner:

1-Cyano-4-oxo-4*H*-quinolizine-3-diazonium Tetrafluoroborate (7a): From **13a**, yield: 2.443 g (86%), green-yellow crystals, m.p. 196−198 °C. − IR: $\tilde{\nu}$ = 3490, 3080, 2220 (CN, N_2^+), 1720 (C=O), 1290, 1040 cm^{-1} (BF_4^-). − MS (FAB): *m*/*z* = 197 [$M^+ - BF_4^-$]. − ^{1}H NMR (300 MHz, [D$_6$] DMSO): δ = 8.21 (ddd, *J* = 1.3, 6.8, 7.3 Hz, 1 H, H$_7$), 8.45 (ddd, *J* = 0.7, 1.3, 8.4 Hz, 1 H, H$_9$), 8.83 (ddd, *J* = 1.4, 7.3, 8.4 Hz, 1 H, H$_8$), 9.12 (s, 1 H, H$_2$), 9.66 (ddd, *J* = 0.7, 1.4, 6.8 Hz, 1 H, H$_6$). − ^{13}C NMR (75.5 MHz, [D$_6$] DMSO): δ = 86.3, 114.7, 125.7, 126.2, 135.1, 142.2, 147.1, 148.9, 155.2, 159.3. − $C_{10}H_5BF_4N_4O$ (284.0): C 42.30, H 1.77, N 19.73; found C 42.53, H 1.54, N 19.43.

1-Ethoxycarbonyl-4-oxo-4*H*-quinolizine-3-diazonium Tetrafluoroborate (7b): From **13b**, yield: 2.781 g (84%), yellow crystals, m.p. 187−188 °C. − IR: $\tilde{\nu}$ = 2990, 2160 (N_2^+), 1720 and 1690 (C=O), 1490, 1280, 1020 cm^{-1} (BF_4^-). − MS (FAB): *m*/*z* = 244 [$M^+ - BF_4$]. − ^{1}H NMR (300 MHz, [D$_6$] DMSO): δ = 1.38 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 4.39 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 8.13 (ddd, *J* = 1.4, 6.9, 7.2 Hz, 1 H, H$_7$), 8.77 (ddd, *J* = 1.5, 6.9, 8.7 Hz, 1 H, H$_8$), 9.20 (s, 1 H, H$_2$), 9.30 (ddd, *J* = 0.7, 1.4, 8.7 Hz, 1 H, H$_9$), 9.63 (ddd, *J* = 0.7, 1.5, 6.9 Hz, 1 H, H$_6$). − ^{13}C NMR (75.5 MHz, [D$_6$] DMSO): δ = 14.9, 62.9, 85.4, 109.7, 124.8, 126.5, 134.7, 139.6, 147.4, 147.6, 156.1, 162.9. − $C_{12}H_{10}BF_4N_3O_3$ (331.0): C 43.54, H 3.04, N 12.69; found C 43.83, H 2.72, N 12.66.

General Procedure for the Preparation of the 1-Substituted 4*H*-Quinolizin-4-ones (8a, 8b) and the 1-Substituted Alkyl Indolizine-3-carboxylates (9a−g): A mixture of 1-substituted 4-oxo-4*H*-quinolizine-3-diazonium tetrafluoroborate **7** (0.100 g) and an anhydrous alcohol (15−25 mL) was heated at 50−80 °C for 5−15 h. The volatile components were evaporated in vacuo and the solid residue was purified by column chromatography (eluent: ethyl acetate/hexane, 1:1). Indolizine-3-carboxylate **9** was eluted first, followed by 4*H*-quinolizin-4-one **8**. Fractions containing the corresponding products **8** and **9** were combined and volatile components evaporated in vacuo to give the quinolizinone derivative **8** and the indolizine derivative **9**. The following compounds were prepared in this manner:

1-Cyano-4*H*-quinolizin-4-one (8a): This compound was prepared from **7a** (0.100 g, 0.35 mmol) and 2-propanol (20 mL), reflux for 12 h, yield: 0.044 g (73%), yellow crystals, m.p. 211−212 °C (ref.:[24] 213 °C). − IR: $\tilde{\nu}$ = 3030, 2200 (CN), 1670 (C=O), 1460, 780 cm^{-1}. − MS (EI): *m*/*z* = 170 [M^+]. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.57 (d, *J* = 9.4 Hz, 1 H, H$_3$), 7.25 (ddd, *J* = 1.1, 6.8, 7.2 Hz, 1 H, H$_7$), 7.74 (ddd, *J* = 1.1, 6.8, 9.0 Hz, 1 H, H$_8$), 7.84 (d, *J* = 9.4 Hz,

1 H, H_2), 8.00 (dd, J = 1.1, 9.0 Hz, 1 H, H_9), 9.24 (dd, J = 1.1, 7.2 Hz, 1 H, H_6). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 85.3, 109.1, 117.1, 117.5, 123.7, 129.2, 134.9, 140.9, 146.4, 157.8. − HRMS calcd. for $C_{10}H_6N_2O$: 170.048013; found 170.048398. The minor product **9d** was isolated in 7.5% yield (0.006 g).

Ethyl 4-Oxo-4*H*-quinolizine-1-carboxylate (8b): This compound was prepared from **7b** (0.100 g, 0.30 mmol) and 2-propanol (20 mL), reflux for 8 h, yield: 0.056 g (85%), pale yellow crystals, m.p. 112−114 °C (ref.:[24] 115 °C). − IR: $\tilde{\nu}$ = 2960, 1715 (C=O), 1670 (C=O), 1465, 1215, 780 cm^{-1}. − MS (EI): m/z = 217 [M$^+$]. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (t, J = 7.2 Hz, 3 H, $COOCH_2CH_3$), 4.38 (q, J = 7.2 Hz, 2 H, $COOCH_2CH_3$), 6.54 (d, J = 9.4 Hz, 1 H, H_3), 7.19 (ddd, J = 1.1, 6.9, 7.1 Hz, 1 H, H_7), 7.66 (ddd, J = 1.5, 6.8, 9.1 Hz, 1 H, H_8), 8.42 (d, J = 9.4 Hz, 1 H, H_2), 9.29 (dd, J = 1.1, 9.1 Hz, 1 H, H_9), 9.31 (dd, J = 1.5, 7.1 Hz, 1 H, H_6). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.8, 61.1, 102.7, 107.4, 116.5, 124.5, 128.9, 133.9, 141.4, 145.6, 158.9, 165.6. − HRMS calcd. for $C_{12}H_{11}NO_3$: 217.073893; found 217.074210. The minor product **9h** was formed only in traces and could not be isolated.

Methyl 1-Cyanoindolizine-3-carboxylate (9a): This compound was prepared from **7a** (0.100 g, 0.35 mmol) and methanol (15 mL), 60 °C, 5 h. Yield: 0.037 g (53%), white crystals, m.p. 129 °C. − IR: $\tilde{\nu}$ = 3120, 2210 (CN), 1680 (C=O), 1230, 1210, 750 cm^{-1}. − MS (FAB): m/z = 201 [MH$^+$]; (EI): m/z = 200 [M$^+$]. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.93 (s, 3 H, $COOCH_3$), 7.05 (ddd, J = 1.3, 7.1, 7.2 Hz, 1 H, H_6), 7.35 (ddd, J = 1.1, 7.1, 9.0 Hz, 1 H, H_7), 7.75 (s, 1 H, H_2), 7.77 (dd, J = 1.3, 9.0 Hz, 1 H, H_8), 9.53 (dd, J = 1.1, 7.2 Hz, 1 H, H_5). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 52.1, 84.3, 115.4, 115.5, 115.7, 118.0, 125.1, 126.3, 128.6, 141.0, 161.1. − $C_{11}H_8N_2O_2$ (200.2): C 65.99, H 4.03, N 13.99; found C 66.05, H 4.34, N 13.65. − HRMS calcd. for $C_{11}H_8N_2O_2$: 200.058578; found 200.059300. The minor product **8a** was isolated in 25% yield (0.015 g).

Ethyl 1-Cyanoindolizine-3-carboxylate (9b): This compound was prepared from **7a** (0.100 g, 0.35 mmol) and ethanol (15 mL), 60 °C, 6 h. Yield: 0.033 g (44%), white crystals, m.p. 72−73 °C (ref.:[25] 75 °C). − IR: $\tilde{\nu}$ = 3120, 2215 (CN), 1696 (C=O), 1220, 756 cm^{-1}. − MS (EI): m/z = 214 [M$^+$]. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (t, J = 7.2 Hz, 3 H, $COOCH_2CH_3$), 4.40 (q, J = 7.2 Hz, 2 H, $COOCH_2CH_3$), 7.03 (ddd, J = 1.2, 6.9, 7.1 Hz, 1 H, H_6), 7.34 (ddd, J = 1.1, 6.9, 8.9 Hz, 1 H, H_7), 7.76 (dd, J = 1.2, 8.9 Hz, 1 H, H_8), 7.77 (s, 1 H, H_2), 9.53 (dd, J = 1.1, 7.1 Hz, 1 H, H_5). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.8, 61.1, 84.2, 115.3, 115.8, 115.9, 118.0, 125.0, 126.2, 128.7, 140.9, 160.7. − HRMS calcd. for $C_{12}H_{10}N_2O_2$: 214.074228; found 214.075350. The minor product **8a** was isolated in 35% yield (0.021 g).

Propyl 1-Cyanoindolizine-3-carboxylate (9c): This compound was prepared from **7a** (0.100 g, 0.35 mmol) and 1-propanol (25 mL), 70 °C, 8 h. Yield: 0.040 g (50%), pale yellow crystals, m.p. 65−67 °C. − IR: $\tilde{\nu}$ = 3120, 2975, 2218 (CN), 1690 (C=O), 1350, 1215, 1070, 750 cm^{-1}. − MS (FAB): m/z = 229 [MH$^+$]; (EI): m/z = 228 [M$^+$]. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 (t, J = 7.5 Hz, 3 H, $COOCH_2CH_2CH_3$), 1.80 (tq, J = 6.8, 7.5 Hz, 2 H, $COOCH_2CH_2CH_3$), 4.38 (t, J = 6.8 Hz, 2 H, $COOCH_2CH_2CH_3$), 7.03 (ddd, J = 1.1, 6.9, 7.1 Hz, 1 H, H_6), 7.34 (ddd, J = 1.1, 6.9, 9.0 Hz, 1 H, H_7), 7.76 (dd, J = 1.2, 9.0 Hz, 1 H, H_8), 7.77 (s, 1 H, H_2), 9.53 (dd, J = 1.1, 7.1 Hz, 1 H, H_5). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 10.8, 22.5, 66.6, 84.1, 115.3, 115.7, 115.8, 118.0, 125.0, 126.2, 128.6, 140.9, 160.8. − $C_{13}H_{12}N_2O_2$ (228.3): C 68.41, H 5.30, N 12.27; found C 68.58, H 5.20, N 11.99. − HRMS calcd. for $C_{13}H_{12}N_2O_2$: 228.089878; found 228.090580. The minor product **8a** was isolated in 23% yield (0.014 g).

Isopropyl 1-Cyanoindolizine-3-carboxylate (9d): This compound was prepared from **7a** (0.100 g, 0.35 mmol) and 2-propanol (25 mL), 70 °C, 7 h. Yield: 0.020 g (25%), white crystals, m.p. 73−76 °C. − IR: $\tilde{\nu}$ = 2960, 2210 (CN), 1680 (C=O), 1200, 750 cm^{-1}. − MS (FAB): m/z = 229 [MH$^+$]; (EI): m/z = 228 [M$^+$]. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (d, J = 6.1 Hz, 6 H, 2×CH_3), 5.23−5.33 (m, J = 6.1 Hz, $COOCH(CH_3)_2$], 7.03 (ddd, J = 1.2, 6.8, 7.1 Hz, 1 H, H_6), 7.33 (ddd, J = 1.1, 6.8, 9.0 Hz, 1 H, H_7), 7.75 (dd, J = 1.2, 9.0 Hz, 1 H, H_8), 7.76 (s, 1 H, H_2), 9.54 (dd, J = 1.1, 7.1 Hz, 1 H, H_5). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 22.4, 68.8, 84.1, 115.2, 115.8, 115.9, 118.0, 125.0, 126.1, 128.7, 140.9, 160.4. − $C_{13}H_{12}N_2O_2$ (228.3): C 68.41, H 5.30, N 12.27; found C 68.18, H 5.40, N 12.16. − HRMS calcd. for $C_{13}H_{12}N_2O_2$: 228.089878; found 228.090570. The major product **8a** was isolated in 69% yield (0.041 g).

1-Ethyl 3-Methylindolizine-1,3-dicarboxylate (9e): This compound was prepared from **7b** (0.100 g, 0.30 mmol) and methanol (25 mL), 60 °C, 15 h. Yield: 0.042 g (57%), white crystals, m.p. 92−93 °C. − IR: $\tilde{\nu}$ = 2980, 1690 (C=O), 1215, 760 cm^{-1}. − MS (FAB): m/z = 248 [MH$^+$]; (EI): m/z = 247 [M$^+$]. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (t, J = 7.1 Hz, 3 H, $COOCH_2CH_3$), 3.92 (s, 3 H, $COOCH_3$), 4.38 (q, J = 7.1 Hz, 2 H, $COOCH_2CH_3$), 6.98 (ddd, J = 1.2, 6.9, 7.1 Hz, 1 H, H_6), 7.31 (ddd, J = 1.2, 6.9, 9.0 Hz, 1 H, H_7), 7.99 (s, 1 H, H_2), 8.34 (dd, J = 1.2, 9.0 Hz, 1 H, H_8), 9.52 (dd, J = 1.2, 7.1 Hz, 1 H, H_5). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.9, 51.7, 60.3, 105.7, 114.8, 115.1, 120.0, 124.7, 126.0, 128.2, 139.4, 161.9, 164.5. − $C_{13}H_{13}NO_4$ (247.3): C 63.15, H 5.30, N 5.67; found C 63.44, H 5.40, N 5.59. − HRMS calcd. for $C_{13}H_{13}NO_4$: 247.084458; found 247.084980. The minor product **8b** was isolated in 8% yield (0.005 g).

Diethyl Indolizine-1,3-dicarboxylate (9f): This compound was prepared from **7b** (0.100 g, 0.30 mmol) and ethanol (25 mL), 50 °C, 7 h. Yield: 0.030 g (38%), white crystals, m.p. 128−130 °C (ref.:[26] 130−131 °C). − IR: $\tilde{\nu}$ = 2960, 1675 (C=O), 1190, 1030, 750 cm^{-1}. − MS (FAB): m/z = 262 [MH$^+$]; (EI): m/z = 261 [M$^+$]. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (2 × t, J = 7.2 Hz, 6 H, 2 × $COOCH_2CH_3$), 4.38 (2 × q, J = 7.2 Hz, 4 H, 2 × $COOCH_2CH_3$), 6.97 (ddd, J = 1.3, 6.8, 7.2 Hz, 1 H, H_6), 7.31 (ddd, J = 1.1, 6.8, 9.1 Hz, 1 H, H_7), 8.00 (s, 1 H, H_2), 8.34 (dd, J = 1.3, 9.1 Hz, 1 H, H_8), 9.53 (dd, J = 1.1, 7.2 Hz, 1 H, H_5). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.8, 14.9, 60.3, 60.6, 105.6, 114.7, 115.1, 120.0, 124.6, 125.9, 128.3, 139.4, 161.6, 164.6. − $C_{14}H_{15}NO_4$ (261.3): C 64.36, H 5.79, N 5.36; found C 64.42, H 5.82, N 5.21. − HRMS calcd. for $C_{14}H_{15}NO_4$: 261.100108; found 261.101080. The major product **8b** was isolated in 49% yield (0.032 g).

1-Ethyl 3-(1-Propylindolizine)-1,3-dicarboxylate (9g): This compound was prepared from **7b** (0.100 g, 0.30 mmol) and 1-propanol (30 mL), 60 °C, 7 h. Yield: 0.035 g (42%), white crystals, m.p. 52−53 °C. − IR: $\tilde{\nu}$ = 2960, 1680 (C=O), 1200, 1040, 750 cm^{-1}. − MS (FAB): m/z = 276 [MH$^+$]; (EI): m/z = 275 [M$^+$]. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (t, J = 7.2 Hz, 3 H, $COOCH_2CH_2CH_3$), 1.42 (t, J = 7.2 Hz, 3 H, $COOCH_2CH_3$), 1.75−1.87 (m, J = 6.4, 7.2 Hz, 2 H, $COOCH_2CH_2CH_3$), 4.29 (t, J = 6.4 Hz, 2 H, $COOCH_2CH_2CH_3$), 4.38 (q, J = 7.2 Hz, 2 H, $COOCH_2CH_3$), 6.97 (ddd, J = 1.2, 6.8, 7.1 Hz, 1 H, H_6), 7.30 (ddd, J = 1.1, 6.8, 9.0 Hz, 1 H, H_7), 7.99 (s, 1 H, H_2), 8.33 (dd, J = 1.2, 9.0 Hz, 1 H, H_8), 9.52 (dd, J = 1.1, 7.1 Hz, 1 H, H_5). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 10.9, 15.0, 22.6, 60.3, 66.3, 105.6, 114.7, 115.1, 120.0, 124.6, 125.9, 128.3, 139.4, 161.7, 164.6. − $C_{15}H_{17}NO_4$

(275.3): C 65.44, H 6.22, N 5.09; found C 65.75, H 6.34, N 5.10. − HRMS calcd. for $C_{15}H_{17}NO_4$: 275.115758; found 275.116250. The minor product **8b** was isolated in 11% yield (0.007 g).

1-Cyanoindolizine-3-carboxylic Acid (14): Methyl 1-cyanoindolizine-3-carboxylate (**9a**; 0.100 g, 0.5 mmol) was dissolved in methanol (10 mL). Aqueous sodium hydroxide (2 N, 2 mL) was then added and the solution was heated at 50 °C for 1 h. The solution was then cooled and acidified with hydrochloric acid (2 N, 3 mL) to pH 1−2. The precipitate was collected by filtration and washed with methanol to give **8**. Yield: 0.087 g (94%), white crystals, m.p. 245−246 °C. − IR: $\tilde{\nu}$ = 3122 (broad signal), 2229 (CN), 1665 (C=O), 1223 cm^{-1}. − MS (EI): *m/z* = 186 [M^+]. − ^{1}H NMR (300 MHz, [D_6] DMSO): δ = 7.24 (ddd, *J* = 1.1, 6.8, 7.2 Hz, 1 H, H_6), 7.51 (ddd, *J* = 1.1, 6.8, 9.1 Hz, 1 H, H_7), 7.85 (dd, *J* = 1.1, 9.1 Hz, 1 H, H_8), 7.94 (s, 1 H, H_2), 9.51 (dd, *J* = 1.1, 7.2 Hz, 1 H, H_5), 13.04 (br s, 1 H, COO*H*). − ^{13}C NMR (75.5 MHz, [D_6] DMSO): δ = 83.1, 116.3, 116.3, 116.7, 118.1, 125.5, 127.5, 129.0, 140.8, 162.1. − $C_{10}H_6N_2O_2$ (186.2): C 64.52, H 3.25, N 15.05; found C 64.54, H 3.22, N 14.73. − HRMS calcd. for $C_{10}H_6N_2O_2$: 186.042928; found 186.043500.

1-Cyanoindolizine (15): 1-Cyanoindolizine-3-carboxylic acid (**14**; 0.093 g, 0.5 mmol) was dissolved in anisole (10 mL) and the solution was heated under reflux for 24 h. The volatile components were evaporated in vacuo and the solid residue was purified by flash chromatography (eluent: ethyl acetate) to give **9**. Yield: 0.063 g (89%), colorless crystals, m.p. 49−51 °C (ref.:[29] 52−53 °C). − IR: $\tilde{\nu}$ = 2209 (CN), 1514, 738 cm^{-1}. − MS (EI): *m/z* = 142 [M^+]. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.74 (ddd, *J* = 1.0, 6.7, 6.9 Hz, 1 H, H_6), 7.03 (d, *J* = 2.8 Hz, 1 H, H_2), 7.05 (ddd, *J* = 0.9, 6.7, 9.0 Hz, 1 H, H_7), 7.24 (dd, *J* = 0.7, 2.8 Hz, 1 H, H_3), 7.64 (ddd, *J* = 0.7, 1.0, 9.0 Hz, 1 H, H_8), 8.01 (dd, *J* = 0.9, 6.9 Hz, 1 H, H_5). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 81.8, 113.0, 114.0, 117.0, 118.0, 122.5, 122.5, 126.5, 137.9. − HRMS calcd. for $C_9H_6N_2$: 142.053098; found 142.053650.

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