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# A Modular Synthesis of Polysubstituted Indolizines

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The N-alkylation of pyridines with cyanohydrin triflates or  $\alpha$ -halonitriles furnishes 1-(1-cyanoalkyl)pyridinium salts that can react with nitroolefins under basic conditions to furnish polysubstituted indolizines. Overall, the indolizine core can be constructed from a pyridine, two aldehydes, and a nitroalkane, and no undesired functional groups remain in the products. When bromoacetonitrile was used for the N-alkylation, indolizine-3-carbonitriles were obtained instead. The pyridine component may be replaced by other azines, giving rise to related heterocyclic systems.

## Introduction

Indolizines are an important class of N-heterocycles due to their wide range of biological activities. For example, they can function as potential calcium entry blockers,<sup>[1]</sup> central nervous system depressants,<sup>[2]</sup> cardiovascular agents,<sup>[3]</sup> and anti-tuberculosis agents.<sup>[4]</sup> Numerous synthetic approaches to the indolizine skeleton have been devised<sup>[5]</sup> involving, for example, the Scholtz reaction of acetic acid<sup>[6]</sup> or the 1,5-cyclization of unsaturated pyridinium ylides.<sup>[7]</sup> A frequently employed synthetic approach to the indolizine skeleton is the 1,3-dipolar cycloaddition of pyridinium ylides derived from α-halocarbonyl compounds with electron-deficient olefins or alkynes. In this case, however, at least one acceptor group remains in the products.<sup>[8]</sup>

Compared to the aforementioned procedures, a smaller number of methods permit the construction of the azabicyclic system without electron-withdrawing substituents.<sup>[9]</sup> A prominent example for the latter class of processes is the Tschitschibabin reaction of 2-alkylpyridines with  $\alpha$ haloketones which, under intermediate formation of the Nalkylpyridinium salt, forms the C1-C2 bond of the indolizine in a cyclocondensation step.<sup>[10]</sup> However, the versatility of the method is limited by the availability of various substituted 2-alkylpyridines. Another important method for the preparation of electronically unbiased indolizines is the transition-metal-catalyzed cycloisomerization of 2-alkynyl or 2-propargyl-substituted N-heterocycles with formation of the C3-N4 bond.<sup>[11]</sup> Indolizines devoid of acceptor groups have been employed, for example, as histamine H3 receptor antagonists,<sup>[12]</sup> as inhibitors of phosphodiesterase 5A or phospholipase A2,<sup>[13]</sup> or as starting materials for the preparation of indolizidines by catalytic hydrogenation.[9d,11c,14]

Here, we present a short, convergent synthesis that allows the modular assembly of tri- and tetrasubstituted indolizines from a pyridine, two aldehydes, and a primary nitroalkane as readily available starting materials, and leaves no undesired functionalities in the products. Its key step is the formal [3+2] cycloaddition of a 1-(1-cyanoalkyl)pyridinium vlide<sup>[15]</sup> to an  $\alpha$ , $\beta$ -disubstituted nitroolefin.

## **Results and Discussion**

The synthesis of 1-(1-cyanoalkyl)pyridinium salts 2 can start either from  $\alpha$ -halonitriles or from cyanohydrin triflates 1, which, in turn, can be obtained from aldehyde cyanohydrins and Tf<sub>2</sub>O.<sup>[16]</sup> Whereas the preparation of  $\alpha$ -halonitriles does not require the use of HCN,<sup>[17]</sup> the cyanohydrin route<sup>[18]</sup> only uses a slight excess of this reagent. Pyridinium salts 2 were obtained in moderate to very high yield and could be purified by recrystallization from polar aprotic solvents (Table 1).

Table 1. Preparation of 1-(1-cyanoalkyl)pyridinium salts 2.

	R <sup>1</sup>	> R <sup>2</sup> 1 	$ \begin{array}{c}     CN \\     \hline     CN \\     \hline     \hline     20 \\     t. \\   \end{array} $ $ \begin{array}{c}     R^{2} \\     \hline     R^{2} \end{array} $	N⊕ X <sup>⊖</sup> 2 2 2	
Entry	Product	$\mathbb{R}^1$	$\mathbb{R}^2$	Х	Yield [%]
1	2a	Н	Me	OTf	95
2	2b	Н	<i>i</i> Pr	OTf	98
3	2c	Η	$4-ClC_6H_4$	Cl	96
4	2d	4-Ph	Me	OTf	79
5	2e	4- <i>t</i> Bu	Me	OTf	64
6	2f	2-Me	Me	OTf	71
7	2g	Н	$CH_2CH_2Ph$	OTf	74

For the optimization of the cycloaddition/elimination sequence to indolizines 4, pyridinium triflate 2a and 1-chloro-

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## 4-[(1*E*)-2-nitroprop-1-en-1-yl]benzene<sup>[19]</sup> (**3a**) were used as test compounds. Various bases, solvents, and temperature ranges were screened (Table 2) and it turned out that the best yields were obtained by using KO*t*Bu as the base in *N*,*N*-dimethylformamide (DMF) or tetrahydrofuran (THF) at 0 °C (Table 2, entries 13 and 14); the use of Cs<sub>2</sub>CO<sub>3</sub> in hot DMF also proved effective (Table 2, entries 7 and 8).

Table 2. Optimization of the cycloaddition to indolizines 4.

H <sub>3</sub> C	OTf <sup>©</sup> + CI	CH <sub>3</sub> base (3 equiv.) solvent 3a	CH <sub>3</sub> N CH <sub>3</sub>	
Entry	Base	Solvent	<i>Т</i> [°С]	Yield [%]
1	K <sub>2</sub> CO <sub>3</sub>	MeOH	reflux	40
2	Al <sub>2</sub> O <sub>3</sub>	none	250 <sup>[a]</sup>	n.d.
3	Et <sub>3</sub> N	DMF	90	57
4	$Cs_2CO_3$	DMF <sup>[b]</sup>	90	59
5	$Cs_2CO_3[c]$	DMF	90	45
6	$Cs_2CO_3$	DMF	75	49
7	$Cs_2CO_3$	DMF	90	60
8	$Cs_2CO_3$	DMF	reflux	65
9	$Li_2CO_3$	THF	reflux	n.d.
10	pyridine	pyridine	90	12
11	KOtBu	THF	reflux	20
12	KOtBu	THF	25	31
13	KOtBu <sup>[d]</sup>	THF	0	72
14	KOtBu <sup>[d]</sup>	DMF	0	77
15	KO <i>t</i> Bu	DMF/tBuOH	0	42
16	NaOMe <sup>[d]</sup>	DMF/MeOH	0→25	61
17	NaOMe <sup>[e]</sup>	MeOH	0→25	51

<sup>[</sup>a] Microwave heating. [b] Molecular sieves (3 Å) were added. [c] Ag<sub>2</sub>O (1.0 mmol) was added. [d] 4.0 equiv. of base was used. [e] 8.0 equiv. of base was used.

The optimized conditions were then applied to the reaction of pyridinium salts 2a-d with various nitroolefins (Table 3). Whereas a 2-substituent in the parent pyridinium salt (2f) led to diminished yield (product 4k), 4-substituents did not affect the efficiency of indolizine formation.

On the other hand, attempts to obtain 2,3-disubstituted indolizines from  $\alpha$ -unsubstituted nitroolefins such as  $\beta$ -ni-trostyrene were unsuccessful. In contrast to the Barton–Zard synthesis, in which ethyl isocyanoacetate reacts with nitroolefins with formation of pyrroles, neither 9-nitrophen-anthrene nor 5-nitro[1,10]phenanthroline gave indolizines when reacted with **3a**.<sup>[20]</sup> Presumably, the reactivity of the intermediate pyridinium ylide in these cases is insufficient to compensate for the loss of aromaticity in the addition step.

The presence of an  $\alpha$ -substituent in the pyridinium salt appears to be required for the elimination of cyanide after ring closure because 1-(cyanomethyl)pyridinium bromide exclusively yielded indolizine-3-carbonitriles **6** instead of 3unsubstituted indolizines under all tested conditions.<sup>[21]</sup> Because this process involves an oxidative step, several oxidants were tested for their ability to improve the efficiency of formation of **6**; silver(I) carbonate in THF at reflux

R <sup>1</sup>	$R^1$ $R^4$	
L'	KOtBu	
	$\mathbb{N}O_2 \longrightarrow \mathbb{N}O_2 \longrightarrow \mathbb{R}^3$	
N OTf ⊂		
- 2	R <sup>4</sup> 0 °C →2	

Table 3. Indolizines 4 prepared under the optimized conditions.

		R⁴	0 °C	$\dot{R}^2$	
2		3		4	
Product	$\mathbb{R}^1$	$\mathbb{R}^2$	R <sup>3</sup>	$\mathbb{R}^4$	Yield [%]
4a	Н	Me	$4-ClC_6H_4$	Me	77
4b	Н	Me	2-naphth	Et	54
4c	Н	Me	4- CNC <sub>6</sub> H <sub>4</sub>	Et	62
4d	Η	Me	$4-FC_6H_4$	Me	65
<b>4</b> e	Н	Me	-(CH <sub>2</sub>	$_{2})_{4}-$	39
<b>4</b> f	Н	CH <sub>2</sub> CH <sub>2</sub> Pl	n Ph	Me	32
4g	7-tBu	Me	$4-ClC_6H_4$	Me	71
4h	7-Ph	Me	$4-ClC_6H_4$	Me	72
<b>4</b> i	Н	<i>i</i> Pr	$4-ClC_6H_4$	Me	55
4j	Н	$4-ClC_6H_4$	$4-ClC_6H_4$	Me	39
<b>4</b> k	5-Me	Me	$4-ClC_6H_4$	Me	21
41	7-Ph	Me	<i>i</i> Pr	Me	37
	$ \begin{array}{c}       \mathbb{R}^2 \\       \mathbb{CN} \\       \mathbb{2} \\       \mathbb{P} roduct \\       4a \\       4b \\       4c \\       4d \\       4c \\       4d \\       4e \\       4f \\       4g \\       4h \\       4i \\       4j \\       4k \\       4l   \end{array} $	$R^2$ CN           Product $R^1$ 4a         H           4b         H           4c         H           4d         H           4e         H           4f         H           4g         7-tBu           4h         7-Ph           4i         H           4j         H           4k         5-Me           4l         7-Ph	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$

turned out to give the highest yields. The results of the reaction of various nitroolefins **3** with 1-(cyanomethyl)pyridinium bromide (**5**) under these conditions are shown in Table 4.

Table 4. Indolizine-3-carbonitriles 6 prepared under the optimized conditions.

	NC 5 Br <sup>⊖</sup> +	R <sup>3</sup> NO <sub>2</sub> -	Ag <sub>2</sub> CO <sub>3</sub> THF reflux	$R^4$ $R^3$ CN 6
Entry	Product	<b>R</b> <sup>3</sup>	$\mathbb{R}^4$	Yield [%]
1	6a	$4-ClC_6H_4$	Me	81
2	6b	2-naphth	Et	82
3	6c	$4-CNC_6H_4$	Et	70
4	6d	$4-FC_6H_4$	Me	81

A possible explanation for the different behavior of  $\alpha$ substituted and  $\alpha$ -unsubstituted 1-(cyanomethyl)pyridinium salts may be the CH-acidity of intermediate **9** formed after concerted or stepwise addition of pyridinium ylide **7** to nitroolefin **3** and base-induced elimination of nitrite (Scheme 1). In the presence of an  $\alpha$ -substituent (R<sup>2</sup>), dehydrocyanation is the only option to produce an aromatic system, whereas in the unsubstituted series, deprotonation followed by oxidation becomes the dominant process.

Whereas indolizines devoid of electron-withdrawing groups (EWGs) such as compounds 4a-1 can be sensitive towards aerial oxidation, indolizine-3-carbonitriles 6a-d are much more stable and can be purified and stored without special precautions.<sup>[9f,21,22]</sup>

To determine the applicability of the indolizine synthesis to parent systems other than pyridine, different N-heterocycles were treated with a cyanohydrin triflate or bromoacetonitrile. The azinium ylides generated from the salts with KOtBu were treated with 1-chloro-4-[(1E)-2-nitroprop-1A Modular Synthesis of Polysubstituted Indolizines



Scheme 1. Proposed mechanism for the syntheses of indolizines.

en-1-yl]benzene (**3a**) (method A) or diethyl azodicarboxylate (DEAD) (method B) as an even more reactive electrophile (Table 5).

In the case of isoquinoline and benzothiazole, the respective annulated products without an EWG could be obtained in pure form and acceptable yield (Table 5, entries 1 and 4). Whereas phthalazinium salt **12b** reacted with both **3a** and DEAD (Table 5, entries 2 and 6), 1-methylimidazol-3-ium salt **12c** only reacted with the alkyne to yield pyrrolo[1,2-*a*]imidazole **13c** in appreciable yield (Table 5, entry 3). As in the case of pyridine, pyrrolo[2,1-*a*]isoquinoline-3-carbonitrile (**13e**) was obtained in high yield (Table 5, entry 5) from **12e** using Ag<sub>2</sub>CO<sub>3</sub>. In contrast, the application of method A to phenanthridine and 1-phenylpyrazole failed, and the use of pyridazine only yielded an impure product. Thus, the procedure works in both the six- and the fivemembered series but is not generally applicable.

## Conclusions

A short and modular synthesis of highly substituted indolizines and N-fused pyrrole-containing heterocycles such as pyrroloisoquinoline, pyrrolophthalazine, pyrroloimidazole, and pyrrolobenzothiazole has been developed that generates the additional C1–C3 fragment from two aldehydes and a nitroalkane. In addition to this method, indolizine-3-carbonitriles have been synthesized in high yield via  $\alpha$ -unsubstituted ylides with silver(I) carbonate. The reaction conditions were also applied to different azinium salts to compare the reactivity of ylides.

## **Experimental Section**

General: All reactions were carried out in dried glassware under an inert atmosphere (argon) in anhydrous solvents using standard



[a] Reaction conditions: KOtBu (4 equiv.), DMF, 0 °C. [b] Isolated yield of azinium salt formation from the corresponding heterocycle. [c] Isolated yield of the pyrrolo-fused compounds. [d]  $Ag_2CO_3$  (2 equiv.) was used as base.

syringe and septa techniques. Anhydrous THF was distilled from potassium/benzophenone under argon. Anhydrous dichlorometh-

Table 5. Synthesis of pyrrolo-fused N-heterocycles.[a]

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ane was distilled from CaH<sub>2</sub> under argon. The solvents used for flash chromatography were distilled prior to use. Solvents were degassed using an ultrasonic bath under an argon atmosphere. All other solvents and reagents were purchased from commercial suppliers and were used without further purification. TLC experiments were carried out on aluminum sheets (Merck) coated with silica gel 60 F<sub>254</sub> and spots were visualized with UV-light (254 nm, 366 nm) and developed with phosphomolybdic acid reagent or ninhydrin. Flash chromatography was carried out on silica gel (32-63 µm, 60 Å, 230–400 mesh, Acros). Melting points were determined with a Dr. Tottoli apparatus and are uncorrected. NMR spectra were recorded with a 300, 400, or 600 MHz spectrometer. The spectra were measured in CDCl<sub>3</sub>, [D<sub>6</sub>]DMSO, CD<sub>3</sub>OD, or [D<sub>6</sub>]acetone and the chemical shifts were referenced to the residual solvent signal (CDCl<sub>3</sub>:  $\delta_{\rm H}$  = 7.26 ppm,  $\delta_{\rm C}$  = 77.16 ppm; [D<sub>6</sub>]DMSO:  $\delta_{\rm H}$  = 2.50 ppm,  $\delta_{\rm C}$  = 39.52 ppm, CD<sub>3</sub>OD:  $\delta_{\rm H}$  = 3.31 ppm,  $\delta_{\rm C}$  = 49.00 ppm, [D<sub>6</sub>]acetone:  $\delta_{\rm H}$  = 2.05 ppm,  $\delta_{\rm C}$  = 29.84 ppm).<sup>[23]</sup> IR spectra were recorded on routine FTIR spectrometers using a diamond ATR unit. MS spectra were recorded with double-focusing spectrometers (FD-MS, FAB-MS, EI-MS) or with a linear ion trap LC/MSD detector (ESI-MS). ESI-HRMS spectra were recorded with a high-resolution Q-TOF spectrometer with a dual source and a suitable external calibrant.

2-Hydroxypropanenitrile,<sup>[18a,24]</sup> 2-hydroxy-3-methylbutanenitrile,<sup>[25]</sup> and 2-hydroxy-4-phenylbutanenitrile,<sup>[18b]</sup> were prepared from the corresponding aldehydes using a slight excess of cyanide source as described in the literature. 2-Chloro-2-(4-chlorophenyl)-acetonitrile (1c)<sup>[26]</sup> and the nitroolefins **3a–d**, **3f** and **3g**<sup>[19,21]</sup> were synthesized from the corresponding aldehydes according to literature procedures. Nitroolefin **3e** was obtained from commercial sources, 1-(cyanomethyl)pyridinium bromide (**5**)<sup>[15b,27]</sup> and 2-(cyanomethyl)isoquinolinium bromide (**12e**) were prepared according to literature procedures.

**Preparation of Cyanohydrin Triflates:**<sup>[8b]</sup> 1-Cyanoethyl trifluoromethanesulfonate and 1-cyano-2-methylpropyl trifluoromethanesulfonate were prepared from the corresponding cyanohydrin and trifluoromethanesulfonic anhydride. To a solution of cyanohydrin (1.0 equiv.) and distilled pyridine (1.2 equiv.) in anhydrous  $CH_2Cl_2$ was slowly added trifluoromethanesulfonic anhydride (1.2 equiv.) at 0 °C. After stirring for 15 min, the solvent was evaporated in vacuo. The residue was dissolved in ether and filtered to remove pyridinium triflate and the filtrate was evaporated to obtain the crude cyanohydrin triflate.

**1-Cyanoethyl Trifluoromethanesulfonate (1a):** The title compound was synthesized from acetaldehyde cyanohydrin (3.00 g, 42.2 mmol), Tf<sub>2</sub>O (14.11 g, 50.0 mmol) and pyridine (3.95 g, 50.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (200 mL). The crude product was further purified by filtering through neutral Al<sub>2</sub>O<sub>3</sub> to yield the triflate of acetaldehyde cyanohydrin as a slightly pink oil (7.00 g, 82%). IR (neat):  $\tilde{v} = 2981$ , 1423, 1213, 1141 (s), 926 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 5.44$  (q, J = 6.9 Hz, 1 H, CH), 1.83 (d, J = 6.9 Hz, 3 H, CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta = 118.3$  (q, <sup>1</sup> $J_{C,F} = 320$  Hz, CF<sub>3</sub>), 114.6 (C=N), 68.8 (CH), 20.1 (CH<sub>3</sub>) ppm. C<sub>4</sub>H<sub>4</sub>F<sub>3</sub>NO<sub>3</sub>S (203.13): calcd. C 23.65, H 1.98, N 6.90, S 15.76; found C 23.96, H 1.94, N 6.88. The compound decomposed during the ESI-MS measurement.

**1-Cyano-2-methylpropyl Trifluoromethanesulfonate (1b):**<sup>[8b]</sup> The title compound was synthesized from 2-hydroxy-3-methylbutanenitrile (1.98 g, 20.0 mmol), Tf<sub>2</sub>O (6.77 g, 24.0 mmol) and pyridine (1.90 g, 24.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The crude product was further purified by filtering through neutral Al<sub>2</sub>O<sub>3</sub> to yield 1-cyano-2-methylpropyl trifluoromethanesulfonate as an oil (3.4 g, 74%). <sup>1</sup>H

NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 5.16 (d, J = 5.6 Hz, 1 H, CHCN), 2.35 (m, 1 H, CH), 1.19 (overlapping doublets, 6 H, 2 CH<sub>3</sub>) ppm.

#### **General Procedure A**

Synthesis of Ylide Precursors 2a–g: Cyanohydrin triflate or 2chloro-2-(4-chlorophenyl)acetonitrile (1.0 equiv.) and the corresponding heterocyclic compound (1.0 equiv.) were dissolved in anhydrous diethyl ether (1 mL/1 mmol) and the reaction mixture was stirred at room temperature for 2 h. The product was collected by filtration and the salt was washed with diethyl ether. In some cases for which the removal of the excess N-heterocycle was not complicated, an excess amount of the azine was used.

**1-(1-Cyanoethyl)pyridinium Triflate (2a):** The title compound was prepared according to general procedure A from pyridine (2.69 g, 34.0 mmol) and **1a** (6.90 g, 34.0 mmol). The crude product was further purified by recrystallization from EtOAc to yield **2a** as a crystalline solid (9.11 g, 32.0 mmol, 95%); m.p. 65–67 °C. IR (neat):  $\bar{v}$  = 3136, 2970, 1255, 1149, 756 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, [D<sub>6</sub>]-DMSO):  $\delta$  = 9.30 (m<sub>c</sub>, 2 H, H2,6), 8.74 (tt, *J* = 7.8, 1.3 Hz, 1 H, H4), 8.28 (m<sub>c</sub>, 2 H, H3,5), 6.31 (q, *J* = 7.1 Hz, 1 H, CHCN), 2.03 (d, *J* = 7.1 Hz, 3 H, CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (75 MHz, [D<sub>6</sub>]DMSO):  $\delta$  = 147.8 (C4), 144.1 (C2,6), 128.8 (C3,5), 120.7 (q, <sup>1</sup>*J*<sub>C,F</sub> = 322 Hz, CF<sub>3</sub>), 116.5 (C≡N), 56.3 (CH), 20.3 (CH<sub>3</sub>) ppm. C<sub>9</sub>H<sub>9</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub>S (282.24): calcd. C 38.30, H 3.21, N 9.93, S 11.36; found C 38.09, H 3.24, N 9.87, S 11.45. MS (ESI): *m/z* (%) = 133.1 (100) [M]<sup>+</sup>.

**1-(1-Cyano-2-methylpropyl)pyridinium Triflate (2b):** The title compound was prepared according to general procedure A from excess pyridine (1.98 g, 25 mmol) and **1b** (1.20 g, 5.19 mmol). The crude product was recrystallized from EtOAc/diethyl ether to yield **2b** (1.54 g, 5.07 mmol, 98%) as a solid; m.p. 99–102 °C. IR (neat):  $\tilde{v} = 2968$ , 1259, 1028, 741 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, [D<sub>6</sub>]DMSO):  $\delta$  = 9.24 (m<sub>c</sub>, 2 H, H2,6), 8.79 (t, *J* = 7.4 Hz, 1 H, H4), 8.31 (m<sub>c</sub>, 2 H, H3,5), 6.19 (d, *J* = 8.0 Hz, 1 H, H1'), 2.65 (m, 1 H, H2'), 1.10 (d, *J* = 6.5 Hz, 3 H, CH<sub>3</sub>), 0.89 (d, *J* = 6.6 Hz, 3 H, CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (75 MHz, [D<sub>6</sub>]DMSO):  $\delta$  = 148.1 (C4), 144.2 (C2,6), 129.0 (C3,5), 120.7 (q, <sup>1</sup>*J*<sub>C,F</sub> = 322 Hz, CF<sub>3</sub>), 114.7 (C≡N), 65.8 (CHCN), 33.5 [CH(CH<sub>3</sub>)<sub>2</sub>], 17.7 (CH<sub>3</sub>), 17.6 (CH<sub>3</sub>) ppm. C<sub>11</sub>H<sub>13</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub>S (310.29): calcd. C 42.54, H 4.22, N 9.03, S 10.33; found C 42.39, H 3.98, N 9.07, S 11.40. MS (ESI): *m/z* (%) = 161.1 (100) [M]<sup>+</sup>.

1-[(4-Chlorophenyl)(cvano)methyl]pyridinium Chloride (2c): The title compound was synthesized from 2-chloro-2-(4-chlorophenyl)acetonitrile and pyridine. 2-Chloro-2-(4-chlorophenyl)acetonitrile (1c) (1.24 g, 6.67 mmol) was added into freshly distilled pyridine (4.91 g, 62.1 mmol) and the reaction mixture was stirred at r.t. for 2 d. Diethyl ether (20 mL) was added to the reaction vessel and crude product was collected through filtration after washing several times with diethyl ether, and then dried to yield 2c (1.70 g, 6.41 mmol, 96%) as a highly hygroscopic yellow solid. The melting point range could not be determined due to the highly hygroscopic nature of the material. IR (neat):  $\tilde{v} = 2952$ , 1487, 1094, 799 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, [D<sub>6</sub>]DMSO):  $\delta$  = 9.61 (m<sub>c</sub>, 2 H, H2,6), 8.77 (br. t, J = 7.8 Hz, 1 H, H4), 8.59 (s, 1 H, CH), 8.35–8.24 (m, 2 H, H3, H5), 7.89 (AA' part of AA'-BB' system, 2 H, H3'',5''), 7.70-7.64 (m, BB' part of AA'-BB' system, 2 H, H2'',6'') ppm. <sup>13</sup>C NMR (75 MHz,  $[D_6]DMSO$ ):  $\delta = 148.3$  (C4), 144.2 (C2,6), 136.3 (C-Cl), 130.4 (2 CH<sub>Ar</sub>), 129.9 (2 CH<sub>Ar</sub>), 129.3 (2 CH<sub>Ar</sub>), 126.8 (C<sub>a</sub>), 114.6 (C=N), 60.9 (CH) ppm. MS (ESI): m/z (%) = 229 (100) [M]<sup>+</sup>. HRMS (ESI): calcd. for [C<sub>13</sub>H<sub>10</sub>ClN<sub>2</sub>]<sup>+</sup> 229.0533; found 229.0530.

**1-(1-Cyanoethyl)-4-phenylpyridinium Triflate (2d):** The title compound was prepared according to general procedure A from 4-phenylpyridine (1.15 g, 7.40 mmol) and **1a** (1.50 g, 7.40 mmol). The

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crude product was recrystallized from CH<sub>2</sub>Cl<sub>2</sub> to yield **2d** (2.08 g, 5.85 mmol, 79%) as a solid; m.p. 135–137 °C. IR (neat):  $\tilde{v} = 3051$ , 1258, 1152, 994, 854 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, [D<sub>6</sub>]DMSO):  $\delta = 9.31$  (AA' part of AA'–BB' system, 2 H, H2,6), 8.64 (BB' part of AA'–BB' system, 2 H, H3,5), 8.16–8.11 (m, 2 H), 7.75–7.62 (m, 3 H), 6.28 (q, J = 7.1 Hz, 1 H, CH), 2.05 (d, J = 7.1 Hz, 3 H, CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (75 MHz, [D<sub>6</sub>]DMSO):  $\delta = 156.7$  (C4), 144.0 (C2,6), 133.2 (C1'),132.7 (C4'), 129.8 (2 CH<sub>Ar</sub>), 125.0 (2 CH<sub>Ar</sub>), 120.7 (2 CH<sub>Ar</sub>), 116.6 (C≡N), 55.4 (CH), 20.0 (CH<sub>3</sub>) ppm. C<sub>15</sub>H<sub>13</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub>S (358.33): calcd. C 50.28, H 3.66, N 7.82, S 8.95; found C 50.34, H 3.73, N 7.78, S 8.95. MS (ESI): m/z (%) = 209.1 (100) [M]<sup>+</sup>.

**4-***tert***-Butyl-1-(1-cyanoethyl)pyridinium Triflate (2e):** The title compound was prepared according to general procedure A from 4-*tert*-butylpyridine (676 mg, 5.00 mmol) and **1a** (1.02 g, 5.00 mmol). The crude product was recrystallized from EtOAc to yield **2e** (1.08 g, 3.2 mmol, 64%) as a solid; m.p. 137–140 °C. IR (neat):  $\tilde{v} = 3081$ , 3056, 2968, 1463, 1253, 1029 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, [D<sub>6</sub>]-DMSO):  $\delta = 9.19$  (AA' part of AA' -BB' system, 2 H, H2,6), 8.30 (BB' part of AA' -BB' system, 2 H, H3,5), 6.26 (q, *J* = 7.1 Hz, 1 H, CH), 2.01 (d, *J* = 7.1 Hz, 3 H, CH<sub>3</sub>), 1.38 [s, 9 H, C(CH<sub>3</sub>) 3] ppm. <sup>13</sup>C NMR (100.6 MHz, [D<sub>6</sub>]DMSO):  $\delta = 172.4$  (C4), 143.4 (C2,6), 125.8 (C3,5), 120.7 (q, <sup>1</sup>*J*<sub>C,F</sub> = 322 Hz, CF<sub>3</sub>), 116.6 (C=N), 55.4 (CH), 36.6 [*C*(CH<sub>3</sub>)<sub>3</sub>], 29.4 [*C*(*C*H<sub>3</sub>)<sub>3</sub>], 20.1 (CH<sub>3</sub>) ppm. C<sub>13</sub>H<sub>17</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub>S (338.34): calcd. C 46.15, H 5.06, N 8.28, S 9.48; found C 46.00, H 4.97, N 8.27, S 9.46. MS (ESI): *m*/*z* (%) = 189.1 (100) [M]<sup>+</sup>.

**1-(1-Cyanoethyl)-2-methylpyridinium Triflate (2f):** The title compound was prepared according to general procedure A from α-picoline (466 mg, 5.00 mmol) and **1a** (1.02 g, 5.00 mmol). The solid was recrystallized from chloroform to yield crystalline **2f** (1.05 g, 3.55 mmol, 71%); m.p. 150–151 °C. IR (neat):  $\tilde{v} = 2957$ , 2925, 1261, 1150, 994 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, [D<sub>6</sub>]DMSO):  $\delta = 9.31$  (dd, J = 6.4, 1.4 Hz, 1 H, H6), 8.59 (td, J = 7.9, 1.4 Hz, 1 H, H4), 8.16–8.07 (m, 2 H, H3,5), 6.37 (q, J = 7.0 Hz, 1 H, CH), 2.90 (s, 3 H, 2-CH<sub>3</sub>), 1.97 (d, J = 7.0 Hz, 3 H, CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (75 MHz, [D<sub>6</sub>]DMSO):  $\delta = 156.1$  (C2), 147.0 (C4), 142.9 (C6),130.6 (C3), 126.6 (C5), 120.7 (q, <sup>1</sup>J<sub>C,F</sub> = 322 Hz, CF<sub>3</sub>), 116.7 (C≡N), 52.2 (CH), 20.2 (CH<sub>3</sub>), 19.7 (CH<sub>3</sub>) ppm. C<sub>10</sub>H<sub>11</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub>S (296.26): calcd. C 40.54, H 3.74, N 9.46, S 11.32; found C 40.45, H 3.40, N 9.49, S 10.64. MS (ESI): m/z (%) = 147.1 (100) [M]<sup>+</sup>.

**1-(1-Cyano-3-phenylpropyl)pyridinium Triflate (2g):** The title compound was prepared according to general procedure A from pyridine (79 mg, 1.00 mmol) and 2-hydroxy-4-phenylbutanenitrile (**1d**; 293 mg, 1.00 mmol). The crude product was recrystallized from CH<sub>2</sub>Cl<sub>2</sub>/diethyl ether mixture to yield **2g** (276 g, 0.74 mmol, 74%) as a solid; m.p. 82–84 °C. IR (neat):  $\tilde{v} = 3062$ , 2950, 1255, 1157, 1029 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, [D<sub>6</sub>]DMSO):  $\delta = 9.30$  (m<sub>c</sub>, 2 H, H2,6), 8.74 (tt, J = 7.8, 1.2 Hz, 1 H, H4), 8.28 (m<sub>c</sub>, 2 H, H3,5), 7.33–7.27 (m, 2 H, H-Ph), 7.25–7.18 (m, 3 H, H-Ph), 6.32 (t, J = 7.1 Hz, 1 H, H1'), 2.87–2.61 (m, 4 H, H2', H3') ppm. <sup>13</sup>C NMR (75 MHz, [D<sub>6</sub>]DMSO):  $\delta = 147.9$ , 144.3, 138.7, 128.9, 128.6, 128.3, 126.6, 115.5 (CN), 60.2 (CH), 34.9 (CH<sub>2</sub>), 30.6 (CH<sub>2</sub>) ppm. C<sub>16</sub>H<sub>15</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub>S (372.36): calcd. C 51.61, H 4.06, N 7.52, S 8.61; found C 51.77, H 3.83, N 7.38, S 8.72. MS (ESI): *m/z* (%) = 223.1 (100) [M]<sup>+</sup>.

### **General Procedure B**

Synthesis of Indolizines 4a–1: A solution of KOtBu (4 mmol) in anhydrous DMF (5.0 mL) was slowly added to a stirred solution of pyridinium salt (1 mmol) and nitroolefin (1 mmol) in anhydrous DMF (10 mL) at 0 °C under argon. The mixture was stirred at 0 °C, and the reaction was monitored by TLC. When the conversion was complete, the solvent was evaporated in vacuo. The residue was dissolved in ethyl acetate and washed with water. The aqueous phase was extracted twice with ethyl acetate and the combined organic layers were washed with brine, dried with MgSO<sub>4</sub>, and the solvent was removed in vacuo.

2-(4-Chlorophenyl)-1,3-dimethylindolizine (4a): The title compound was prepared according to general procedure B from 2a (282 mg, 1.00 mmol) and (E)-1-chloro-4-(2-nitroprop-1-enyl)benzene (3a; 198 mg, 1.00 mmol). The crude product was purified by filtration through silica (ethyl acetate/cyclohexane, 1:10) to obtain 4a (196 mg, 0.77 mmol, 77%) as a yellow solid; m.p. 138–140 °C;  $R_{\rm f}$ = 0.74 (ethyl acetate/cyclohexane, 1:10). IR (neat):  $\tilde{v}$  = 3076 (s), 3041, 2924, 2856, 1454, 1317, 842, 721 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, COSY, HSQC, HMBC): *δ* = 7.66 (dt, *J* = 7.1, 1.2 Hz, 1 H, H5), 7.45-7.41 (AA' part of AA'-BB' system, 2 H, H3',5'), 7.36 (dt, J = 9.0, 1.3 Hz, 1 H, H8), 7.32-7.27 (BB' part of AA'-BB' system, 2 H, H2',6'), 6.63 (ddd, J = 9.0, 6.4, 1.1 Hz, 1 H, H7), 6.53 (ddd, J = 7.1, 6.4, 1.3 Hz, 1 H, H6), 2.42 (s, 3 H, 3-CH<sub>3</sub>), 2.32 (s, 3 H,3 H, 1-CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 134.6 (C4'), 132.3 (C1'), 131.8 (2 C, C2',6'), 129.3 (C8a), 128.5 (2 C, C3',5'), 126.3 (C2), 121.6 (C5), 117.5 (C8), 116.3 (C3), 114.6 (C7), 110.2 (C6), 105.6 (C1), 10.2 (3-CH<sub>3</sub>), 9.4 (1-CH<sub>3</sub>) ppm. MS (ESI): m/z (%) = 288.0 (9)  $[M + 2O + H]^+$ , 271.9 (22)  $[M + OH]^+$ , 256.0 (100)  $[M + H]^+$ . HRMS (ESI): calcd. for  $[C_{16}H_{14}CIN]^+$  255.0815; found 255.0819.

1-Ethyl-3-methyl-2-(2-naphthyl)indolizine (4b): The title compound was prepared according to general procedure B from 2a (282 mg, 1.00 mmol) and (E)-2-(2-nitrobut-1-enyl)naphthalene (3b; 227 mg, 1.00 mmol). The crude product was purified by filtration through silica (ethyl acetate/cyclohexane, 1:10) to obtain 4b (154 mg, 0.54 mmol, 54%) as a yellow oil.  $R_{\rm f} = 0.67$  (ethyl acetate/cyclohexane, 1:10). IR (neat):  $\tilde{v} = 3053$ , 2965, 1460, 1016, 947, 860, 820, 736 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.96–7.88 (m, 3 H, H<sub>naphth</sub>), 7.83 (d, *J* = 1.6 Hz, 1 H, H<sub>naphth</sub>), 7.70 (dt, *J* = 7.0, 1.0 Hz, 1 H, H5), 7.58–7.50 (m, 3 H,  $H_{naphth}$ ), 7.45 (dt, J = 9.0, 1.2 Hz, 1 H, H8), 6.66 (ddd, J = 8.9, 6.4, 1.4 Hz, 1 H, H7), 6.56 (ddd, J = 6.9, 6.4, 1.4 Hz, 1 H, H6), 2.87 (q, J = 7.5 Hz, 2 H, CH<sub>2</sub>), 2.45 (s, 3 H, 3-CH<sub>3</sub>), 1.16 (t, J = 7.5 Hz, 3 H, CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 133.9 (C<sub>q,naphth</sub>), 133.6 (C<sub>q,naphth</sub>), 132.2 (Cq,naphth), 129.1 (CHnaphth), 129.0 (CHnaphth), 128.7 (C8a), 128.0 (CH<sub>naphth</sub>), 127.8 (CH<sub>naphth</sub>), 127.7 (CH<sub>naphth</sub>), 127.0 (C2), 126.1 (CH<sub>naphth</sub>), 125.7 (CH<sub>naphth</sub>), 121.7 (C5), 117.6 (C8), 116.6 (C3), 114.5 (C7), 113.4 (C1), 110.2 (C6), 17.6 (CH<sub>2</sub>), 16.6 (CH<sub>3</sub>), 10.2 (CH<sub>3</sub>) ppm. MS (ESI): m/z (%) = 318.1 (30) [M + 2O + H]<sup>+</sup>, 302.1 (47) [M + OH]<sup>+</sup>, 286.1 (100) [M + H]<sup>+</sup>, 285.0 (33) [M]<sup>+</sup>. HRMS (ESI): calcd. for  $[C_{21}H_{19}N]^+$  285.1517; found 285.1515.

2-(4-Cyanophenyl)-1-ethyl-3-methylindolizine (4c): The title compound was prepared according to general procedure B from 2a (282 mg, 1.00 mmol) and (E)-4-(2-nitrobut-1-enyl)benzonitrile (3c; 202 mg, 1.00 mmol). The crude product was purified by filtration through silica (ethyl acetate/cyclohexane, 1:10) to obtain 4c (161 mg, 0.62 mmol, 62%) as a yellow solid; m.p. 98–100 °C;  $R_{\rm f}$  = 0.65 (ethyl acetate/cyclohexane, 1:10). IR (neat):  $\tilde{v} = 3067, 2970,$ 2931, 2227, 1360, 855, 795 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.76-7.70 (AA' part of AA'-BB' system, 2 H, H3',5'), 7.67 (dt, J = 7.0, 1.3 Hz, 1 H, H5), 7.49-7.43 (BB' part of AA'-BB' system, 2 H, H2',6'), 7.40 (dt, J = 9.0, 1.3 Hz, 1 H, H8), 6.65 (ddd, J = 9.0, 6.4, 1.2 Hz, 1 H, H7), 6.56 (td, J = 6.7, 1.3 Hz, 1 H, H6), 2.78 (q, J = 7.5 Hz, 3 H, CH<sub>2</sub>), 2.39 (s, 3 H, 3-CH<sub>3</sub>), 1.11 (t, J = 7.5 Hz, 3 H, CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 141.7, 132.1, 131.0, 129.0, 125.3, 121.7, 119.4, 117.7, 116.4, 115.1, 112.9, 110.7, 110.0, 29.8, 27.0, 17.4, 16.5, 10.1 ppm. MS (ESI): m/z (%) = 293.1

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(36)  $[M + 2O + H]^+$ , 277.0 (100)  $[M + OH]^+$ , 261.0 (87)  $[M + H]^+$ , 260.1 (95)  $[M]^+$ . HRMS (ESI): calcd. for  $[C_{18}H_{16}N_2]^+$  260.1313; found 260.1303.

2-(4-Fluorophenyl)-1,3-dimethylindolizine (4d): The title compound was prepared according to general procedure B from 2a (282 mg, 1.00 mmol) and (E)-1-fluoro-4-(2-nitroprop-1-enyl)benzene (3d; 181 mg, 1.00 mmol). The crude product was purified by filtration through silica (ethyl acetate/cyclohexane, 1:10) to obtain 4d (165 mg, 0.65 mmol, 65%) as a yellow solid; m.p. 118–119 °C;  $R_{\rm f}$ = 0.76 (ethyl acetate/cyclohexane, 1:10). IR (neat):  $\tilde{v}$  = 3067, 2992, 1505, 1470, 843, 784 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.65 (br. d, J = 7.0 Hz, 1 H, H5), 7.36–7.27 (m, 3 H, H3',5', H8), 7.18– 7.07 (m<sub>c</sub>, 2 H, H2',6'), 6.61 (br. dd, J = 8.9, 6.4 Hz, 1 H, H7), 6.51 (ddd, J = 7.2, 6.4, 1.4 Hz, 1 H, H6), 2.39 (s, 3 H, 3-CH<sub>3</sub>), 2.29(s, 3 H, 1-CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz, [D<sub>6</sub>]DMSO, HSQC, HMBC):  $\delta = 161.0$  (d,  ${}^{1}J_{C,F} = 243.1$  Hz, C4'), 131.8 (d,  ${}^{3}J_{C,F} =$ 8.0 Hz, 2 C, C2',6'), 131.7 (d,  ${}^{4}J_{C,F}$  = 3.1 Hz, C1'), 128.5 (C8a), 125.5 (C2), 122.2 (C5), 117.1 (C8), 116.0 (C3), 115.2 (d,  ${}^{2}J_{CF}$  = 21.1 Hz, 2 C, C3',5'), 114.5 (C7), 109.9 (C6), 104.6 (C1), 9.8 (3-CH<sub>3</sub>), 9.2 (1-CH<sub>3</sub>) ppm. MS (ESI): m/z (%) = 272.1 (52) [M + 20 + H]<sup>+</sup>, 256.1 (63) [M + OH]<sup>+</sup>, 240.1 (100) [M + H]<sup>+</sup>, 239.2 (73) [M] <sup>+</sup>. HRMS (ESI): calcd. for [C<sub>16</sub>H<sub>14</sub>FN]<sup>+</sup> 239.1110; found 239.1119.

6-Methyl-7,8,9,10-tetrahydropyrido[2,1-a]isoindole (4e): The title compound was prepared according to general procedure B from 2a (282 mg, 1.00 mmol) and 1-nitrocyclohex-1-ene (3e; 127 mg, 113 µL, 1.00 mmol). The crude product was purified by filtration through silica (ethyl acetate/cyclohexane, 1:10) to obtain 4e (72 mg, 0.39 mmol, 39%) as a slightly vellowish oil.  $R_{\rm f} = 0.72$  (ethyl acetate/ cyclohexane, 1:10). IR (neat):  $\tilde{v} = 2923$ , 1590, 1465 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.59 (d, J = 7.0 Hz, 1 H, H5), 7.24 (dd, J = 8.7, 1.2 Hz, 1 H, H1), 6.56–6.50 (m, 1 H, H2), 6.45 (td, J = 6.7,1.2 Hz, 1 H, H3), 2.86-2.77 (m, 2 H, CH<sub>2</sub>), 2.77-2.68 (m, 2 H, CH<sub>2</sub>), 2.35 (s, 3 H, CH<sub>3</sub>), 1.90–1.84 (m, 4 H, H8, H9) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 127.6 (C10b), 122.7 (C6a), 121.0 (C4), 116.6 (C1), 114.4 (C10a), 113.3 (C2), 109.5 (C3), 108.4 (C6), 24.2 (CH<sub>2</sub>), 24.0 (CH<sub>2</sub>), 22.1 (CH<sub>2</sub>), 21.2 (CH<sub>2</sub>), 9.2 (CH<sub>3</sub>) ppm. MS (ESI): m/z (%) = 218.1 (14) [M + 2O + H]<sup>+</sup>, 202.1 (100) [M +  $OH^{+}_{1}$ , 186.1 (2)  $[M + H^{+}_{1}]$ . HRMS (ESI): calcd. for  $[C_{13}H_{15}N^{+}_{1}]$ 185.1214; found 185.1204.

1-Methyl-2-phenyl-3-(2-phenylethyl)indolizine (4f): The title compound was prepared according to general procedure B from 2g (186 mg, 0.50 mmol) and (E)-(2-nitroprop-1-enyl)benzene (3f; 82 mg, 0.50 mmol). The crude product was purified by filtration through silica (ethyl acetate/cyclohexane, 1:10) to obtain 4f (50 mg, 0.16 mmol, 32%) as a yellow oil.  $R_{\rm f} = 0.78$  (ethyl acetate/cyclohexane, 1:10). IR (neat):  $\tilde{v} = 3063$ , 2923, 1453, 762, 731, 700 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz,  $[D_6]$ acetone):  $\delta = 8.04$  (d, J = 7.0 Hz, 1 H, H5), 7.47-7.09 (m, 11 H, PhH, H8), 6.64 (ddd, J = 8.8, 6.3, 0.8 Hz, 1 H, H7), 6.57-6.51 (m, 1 H, H6), 3.20-3.12 (m, 2 H CH<sub>2</sub>), 2.94-2.87 (m, 2 H, CH<sub>2</sub>), 2.23 (s, 3 H, CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (75 MHz,  $[D_6]$ acetone):  $\delta = 142.2, 137.6, 136.8, 130.9, 129.6, 129.1, 129.0,$ 128.8, 127.0, 126.7, 122.7, 120.6, 118.1, 115.2, 110.6, 106.2, 34.6, 27.2, 9.2 ppm. MS (ESI): m/z (%) = 384.2 (77) [M + 2O + H]<sup>+</sup>, 328.3 (100) [M + O + H]<sup>+</sup>, 312.2 (12) [M + H]<sup>+</sup>. HRMS (ESI): calcd. for  $[C_{23}H_{21}N + H]^+$  312.1752; found 312.1762.

7-*tert*-Butyl-2-(4-chlorophenyl)-1,3-dimethylindolizine (4g): The title compound was prepared according to general procedure B from 2e (338 mg, 1.00 mmol) and (*E*)-1-chloro-4-(2-nitroprop-1-enyl)benzene (3a; 198 mg, 1.00 mmol). The crude product was purified by filtration through silica (ethyl acetate/cyclohexane, 1:10) to obtain 4g (221 mg, 0.71 mmol, 71%) as a yellow solid; m.p. 136–138 °C;  $R_{\rm f} = 0.84$  (ethyl acetate/cyclohexane, 1:10). IR (neat):  $\tilde{v} = 2964$ , 2869, 1592, 1488, 1090, 811, 740 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.62 (br d, J = 7.4 Hz, 1 H, H5), 7.45–7.39 (AA' part of AA'–BB' system, 2 H, H3',5'), 7.32–7.26 (BB' part of AA'–BB' system, 2 H, H2',6'), 7.21 (d, J = 1.0 Hz, 1 H, H8), 6.61 (dd, J = 7.4, 2.0 Hz, 1 H, H6), 2.40 (s, 3 H, 3-CH<sub>3</sub>), 2.31 (s, 3 H, 1-CH<sub>3</sub>), 1.35 [s, 9 H, C(CH<sub>3</sub>)<sub>3</sub>] ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 138.0 (C7), 134.9 (C4'), 132.2 (C1'), 131.8 (C2',6'), 130.6 (C8a), 128.4 (C3',5'), 126.3 (C2), 121.3 (C5), 115.3 (C3), 111.2 (C8), 109.7 (C6), 104.7 (C1), 34.4 [C(CH<sub>3</sub>)<sub>3</sub>], 30.7 [(CH<sub>3</sub>)<sub>3</sub>C], 10.1 (3-CH<sub>3</sub>), 9.4 (1-CH<sub>3</sub>) ppm. MS (ESI): m/z (%) = 344.2 (28) [M + 2O + H]<sup>+</sup>, 328.3 (100) [M + OH]<sup>+</sup>, 312.3 (28) [M + H]<sup>+</sup>, 311.3 (32) [M]<sup>+</sup>. HRMS (ESI): calcd. for [C<sub>20</sub>H<sub>22</sub>NCl]<sup>+</sup> 311.1441; found 311.1452.

7-Phenyl-2-(4-chlorophenyl)-1,3-dimethylindolizine (4h): The title compound was prepared according to general procedure B from 2d(358 mg, 1.00 mmol) and (E)-1-chloro-4-(2-nitroprop-1-enyl)benzene (3a; 198 mg, 1.00 mmol). The crude product was purified by filtration through silica (ethyl acetate/cyclohexane, 1:10) to obtain **4h** (240 mg, 0.72 mmol, 72%) as a green solid; m.p. 194–195 °C; *R*<sub>f</sub> = 0.74 (ethyl acetate/cyclohexane, 1:10). IR (neat):  $\tilde{v}$  = 3025, 2924, 1489, 1091, 832, 796, 728 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, COSY, HSQC, HMBC):  $\delta$  = 7.72 (dd, J = 7.4, 1.0 Hz, 1 H, H5), 7.69–7.65 (m, 2 H, H2'', 6''), 7.59 (dd, J = 1.9, 1.0 Hz, 1 H, H8), 7.48-7.41 (m, 4 H, H3",5", H3',5"), 7.35-7.27 (m, 3 H, H2',6', H4''), 6.86 (dd, J = 7.3, 1.9 Hz, 1 H, H6), 2.44 (s, 3 H, 3-CH<sub>3</sub>), 2.35 (s, 3 H, 1-CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (75 MHz, [D<sub>6</sub>]DMSO):  $\delta$  = 138.9 (C1''), 134.2 (C4'), 131.7 (C2',6'), 131.2 (C1'), 128.9 (3 C, C8a,3'',5''), 128.4 (C3',5'), 126.8 (C4''), 126.1 (C2), 126.0 (C7), 125.6 (C2'',6''), 122.6 (C5), 116.6 (C3), 113.7 (C8), 109.1 (C6), 106.3 (C1), 9.9 (C3-CH<sub>3</sub>), 9.3 (C1-CH<sub>3</sub>) ppm. MS (ESI): m/z (%)  $= 364.0 (33) [M + 2O + H]^{+}, 348.1 (100) [M + OH]^{+}, 332.1 (17)$  $[M + H]^+$ , 331.1 (31)  $[M]^+$ . HRMS (ESI): calcd. for  $[C_{22}H_{18}NC1]^+$ 331.1128; found 311.1118.

2-(4-Chlorophenyl)-1-isopropyl-3-methylindolizine (4i): The title compound was prepared according to general procedure B from 2b (310 mg, 1.00 mmol) and (E)-1-chloro-4-(2-nitroprop-1-enyl)benzene (3a; 198 mg, 1.00 mmol). The crude product was purified by filtration through silica (ethyl acetate/cyclohexane, 1:10) to obtain 4i (157 mg, 0.55 mmol, 55%) as a yellow solid; m.p. 140-142 °C;  $R_{\rm f} = 0.78$  (ethyl acetate/cyclohexane, 1:10). IR (neat):  $\tilde{v} = 3073$ , 2965, 1480, 1092, 843, 731, 703 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.88 (dt, J = 7.2, 1.0 Hz, 1 H, H5), 7.42–7.36 (AA' part of AA'-BB' system, 2 H, H3',5'), 7.33 (dt, J = 9.0, 1.2 Hz, 1 H, H8), 7.26-7.20 (BB' part of AA'-BB' system, 2 H, H2',6'), 6.59 (ddd, *J* = 9.0, 6.4, 1.0 Hz, 1 H, H7), 6.46 (ddd, *J* = 7.2, 6.4, 1.2 Hz, 1 H, H6), 3.38 (sept, J = 7.2 Hz, 1 H, 1-CH), 2.17 (s, 3 H, 1-CH<sub>3</sub>), 1.31 [d, J = 7.3 Hz, 6 H, (CH<sub>3</sub>)<sub>2</sub>CH] ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta = 135.5 \text{ (C4')}, 132.6 \text{ (C1')}, 132.1 \text{ (C2',6')}, 129.2 \text{ (C8a)}, 128.2$ (C3',5'), 125.9 (C2), 125.6 (C3), 122.8 (C5), 117.9 (C8), 114.5 (C7), 109.9 (C6), 106.5 (C1), 25.8 (1-CH), 20.4 [(CH<sub>3</sub>)<sub>2</sub>CH], 9.13 (1-CH<sub>3</sub>) ppm. MS (ESI): m/z (%) = 316 (10) [M + 2O + H]<sup>+</sup>, 300.0 (6)  $[M + OH]^+$ , 284.0 (100)  $[M + H]^+$ . HRMS (ESI): calcd. for  $[C_{18}H_{18}NC1 + H]^+$  284.1206; found 284.1219.

**2,3-Bis(4-chlorophenyl)-1-methylindolizine (4j):** The title compound was prepared according to general procedure B from **2c** (265 mg, 1.00 mmol) and (*E*)-1-chloro-4-(2-nitroprop-1-enyl)benzene (**3a**; 198 mg, 1.00 mmol). The crude product was purified by filtration through silica (ethyl acetate/cyclohexane, 1:10) to obtain **4j** (110 mg, 0.39 mmol, 39%) as a yellow solid; m.p. 169–171 °C;  $R_{\rm f}$  = 0.68 (ethyl acetate/cyclohexane, 1:10). IR (neat):  $\tilde{v}$  = 3070, 3051, 2922, 1396, 1091, 833, 826, 737 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.99 (br d, J = 7.1 Hz, 1 H, H5), 7.39 (dt, J = 9.0, 1.2 Hz, 1 H, H8), 7.36–7.30 (m, 2 H, CH<sub>Ar</sub>), 7.29–7.17 (m, 2 H, CH<sub>Ar</sub>), 7.14–

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7.08 (m, 2 H, CH<sub>Ar</sub>), 6.74–6.64 (m, 1 H, H7), 6.45 (t, J = 7.0 Hz, 1 H, H6), 2.33 (s, 3 H, CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$ = 133.9 (C<sub>q</sub>), 133.2 (C<sub>q</sub>), 132.4 (C<sub>q</sub>), 132.0 (CH<sub>Ar</sub>), 131.7 (CH<sub>Ar</sub>), 130.8 (C<sub>q</sub>), 129.9 (C<sub>q</sub>), 129.3 (CH<sub>Ar</sub>), 128.5 (CH<sub>Ar</sub>), 127.1 (C<sub>q</sub>), 121.9 (C5), 120.3 (C3), 117.8 (C8), 116.6 (C7), 111.0 (C6), 107.3 (C1), 9.4 (CH<sub>3</sub>) ppm. MS (ESI): m/z (%) = 384.1 (46) [M + 20 + H]<sup>+</sup>, 368.2 (67) [M + OH]<sup>+</sup>, 352.2 (36) [M + H]<sup>+</sup>, 351.2 (100) [M]<sup>+</sup>. HRMS (ESI): calcd. for [C<sub>21</sub>H<sub>15</sub>NCl<sub>2</sub>]<sup>+</sup> 351.0582; found 351.0582.

2-(4-Chlorophenyl)-1,3,5-trimethylindolizine (4k): The title compound was prepared according to general procedure B from 2f (296 mg, 1.00 mmol) and (E)-1-chloro-4-(2-nitroprop-1-enyl)benzene (3a; 198 mg, 1.00 mmol). The crude product was purified by filtration through silica (ethyl acetate/cyclohexane, 1:10) to obtain 4k (56 mg, 0.21 mmol, 21%) as a yellow solid; m.p. 105–107 °C;  $R_{\rm f}$ = 0.75 (ethyl acetate/cyclohexane, 1:10). IR (neat):  $\tilde{v}$  = 2923, 1488, 1376, 1090, 830, 795, 725 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.42-7.37 (AA' part of AA'-BB' system, 2 H, H3',5'), 7.24-7.19 (BB' part of AA'-BB' system, 2 H, H2',6'), 7.15 (ddd, J = 9.0, 1.3, 0.6 Hz, 1 H, H8), 6.44 (dd, J = 9.0, 6.4 Hz, 1 H, H7), 6.13– 6.10 (m, 1 H, H6), 2.83 (s, 3 H, 5-CH<sub>3</sub>), 2.73 (s, 3 H, 3-CH<sub>3</sub>), 2.18 (s, 3 H, 1-CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz,  $[D_6]DMSO$ ):  $\delta = 134.7$ (C4'), 134.4 (C5), 132.2 (2 C, C2',6'), 131.2 (C1'), 130.6 (C8a), 128.2 (2 C, C3',5'), 127.2 (C2), 118.2 (C3), 115.6 (C8), 115.1 (C7), 111.4 (C6), 105.1 (C1), 21.3 (5-CH<sub>3</sub>), 14.1 (3-CH<sub>3</sub>), 9.2 (1-CH<sub>3</sub>) ppm. MS (ESI): m/z (%) = 286.0 (60) [M + OH]<sup>+</sup>, 270.0 (100)  $[M + H]^+$ . HRMS (ESI): calcd. for  $[C_{17}H_{16}NCI + H]^+$  270.1050; found 270.1037.

2-Isopropyl-1,3-dimethyl-7-phenylindolizine (41): The title compound was prepared according to general procedure B from 2d (358 mg, 1.00 mmol) and (*E*)-4-methyl-2-nitropent-2-ene (3g; 129 mg, 1.00 mmol). The crude product was purified by filtration through silica (ethyl acetate/cyclohexane, 1:10) to obtain 4l (97 mg, 0.37 mmol, 37%) as a yellow solid; m.p. 84–85 °C;  $R_{\rm f} = 0.79$  (ethyl acetate/cyclohexane, 1:10). IR (neat):  $\tilde{v} = 2959, 2925, 1390, 1362,$ 1259, 750 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD, COSY, HSQC, HMBC):  $\delta$  = 7.75 (d, J = 7.3 Hz, 1 H, H5), 7.64 (m<sub>c</sub>, 2 H, H2', 6'), 7.51 (br s 1 H, H8), 7.42–7.37 (m<sub>c</sub>, 2 H, H3',5'), 7.25 (t, *J* = 7.4 Hz, 1 H, H4'), 6.79 (dd, J = 7.3, 1.7 Hz, 1 H, H6), 3.18 (sept, J =7.1 Hz, 1 H, CH), 2.42 (s, 3 H, 3-CH<sub>3</sub>), 2.37 (s, 3 H, 1-CH<sub>3</sub>), 1.36 [d, J = 7.1 Hz, 6 H, (CH<sub>3</sub>)<sub>2</sub>CH] ppm. <sup>13</sup>C NMR (100.6 MHz, CD<sub>3</sub>OD):  $\delta = 141.6$  (C1'), 132.5 (C2), 130.7 (C8a), 129.8 (C3',5'), 127.4 (C4'), 127.2 (C7), 126.8 (C2',6'), 122.4 (C5), 116.1 (C3), 114.1 (C8), 109.5 (C6), 107.1 (C1), 27.3 (CH), 23.3 [(CH<sub>3</sub>)<sub>2</sub>CH], 10.0 (CH<sub>3</sub>), 9.9 (CH<sub>3</sub>) ppm. MS (ESI): m/z (%) = 296.1 (17) [M +  $2O + H]^+$ , 280.1 (16)  $[M + OH]^+$ , 264.1 (100)  $[M + H]^+$ , 263.1 (21)  $[M]^+$ . HRMS (ESI): calcd. for  $[C_{19}H_{21}N + H]^+$  264.1752; found 264.1750.

#### General Procedure C

Synthesis of 3-Cyanoindolizines: 1-(Cyanomethyl)pyridinium bromide (5; 1.0 equiv.) and the nitroolefin 3a-d (1.0 equiv.) were dissolved in freshly distilled THF (20 mL/mmol nitroolefin) at room temperature. Ag<sub>2</sub>CO<sub>3</sub> (2.0 equiv.) was added in one portion and the reaction mixture was heated to reflux under an argon atmosphere for 2 h. The solvent was removed in vacuo and the remaining solid was extracted with ethyl acetate. The solution was decanted and washed with water. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried with MgSO<sub>4</sub> and the solvent was removed in vacuo.

**2-(4-Chlorophenyl)-1-methylindolizine-3-carbonitrile (6a):** The title compound was prepared according to general procedure C from **5** (1.00 mmol) and (*E*)-1-chloro-4-(2-nitroprop-1-enyl)benzene (**3a**; 1.00 mmol). The crude product was purified by column chromatog-

raphy (ethyl acetate/cyclohexane, 1:5) to obtain **6a** (216 mg, 81%) as a solid; m.p. 156–159 °C;  $R_{\rm f}$  = 0.44 (ethyl acetate/cyclohexane, 1:5). IR (neat):  $\tilde{v}$  = 3094, 2922, 2195, 1382, 1096, 828, 740, 725 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, COSY, HSQC, HMBC):  $\delta$  = 8.22 (dt, J = 6.8, 0.9 Hz, 1 H, H5), 7.50–7.44 (m, 5 H, H8, 4× CH<sub>Ar</sub>), 7.01 (ddd, J = 9.0, 6.8, 0.9 Hz, 1 H, H7), 6.80 (td, J = 6.8, 1.2 Hz, 1 H, H6), 2.33 (s, 3 H, CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 135.3 (C2), 135.2 (C8a), 134.2 (Cq), 131.0 (Cq), 130.8 (CH<sub>Ar</sub>), 129.1 (CH<sub>Ar</sub>), 125.3 (C5), 121.6 (C7), 118.0 (C8), 114.7 (CN), 113.3 (C6), 108.4 (C1), 93.1 (C3), 9.3 (CH<sub>3</sub>) ppm. C<sub>16</sub>H<sub>11</sub>CIN<sub>2</sub> (266.73): calcd. C 72.05, H 4.16, N 10.50; found C 71.94, H 4.26, N 10.51. MS (ESI): *m/z* (%) = 288.9 (34) [M + Na]<sup>+</sup>, 266.9 (100) [M + H]<sup>+</sup>. HRMS (ESI): calcd. for [C<sub>16</sub>H<sub>11</sub>NCl]<sup>+</sup> 266.0611; found 266.0621.

1-Ethyl-2-(naphthalen-2-yl)indolizine-3-carbonitrile (6b): The title compound was prepared according to general procedure C from 5 (100 mg, 0.50 mmol) and (*E*)-2-(2-nitrobut-1-enyl)naphthalene (**3b**; 114 mg, 0.50 mmol). The crude product was purified by column chromatography (ethyl acetate/cyclohexane, 1:5) to obtain 6b (121 mg, 0.41 mmol, 82%) as a yellow solid; m.p. 113–116 °C;  $R_{\rm f}$ = 0.50 (ethyl acetate/cyclohexane, 1:5). IR (neat):  $\tilde{v}$  = 3054, 2964, 2928, 2194, 1427, 1216, 1130, 859, 814, 751, 728 cm<sup>-1</sup>. <sup>1</sup>H NMR  $(300 \text{ MHz}, \text{ CDCl}_3)$ :  $\delta = 8.28 \text{ (dt, } J = 6.9, 1.0 \text{ Hz}, 1 \text{ H}, \text{ H5}), 8.00$ (br. s, 1 H, H1'), 7.99–7.88 (m, 3 H,  $3CH_{naphth}$ ), 7.66 (dt, J = 8.4, 1.7 Hz, 1 H, H8), 7.59–7.48 (m, 3 H,  $3 \times$  CH<sub>naphth</sub>), 7.01 (ddd, J = 9.0, 6.7, 1.0 Hz, 1 H, H7), 6.81 (td, J = 6.9, 1.2 Hz, 1 H, H6),2.88 (q, J = 7.5 Hz, 2 H, CH<sub>2</sub>), 1.21 (q, J = 7.5 Hz, 3 H, CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 136.3 (C<sub>q</sub>), 134.7 (C<sub>q</sub>), 133.5 (C<sub>q</sub>), 133.0 (Cq), 130.1 (Cq), 128.7 (CH<sub>naphth</sub>), 128.5 (CH<sub>naphth</sub>), 128.4 (CH<sub>naphth</sub>), 127.9 (CH<sub>naphth</sub>), 127.2 (CH<sub>naphth</sub>), 126.5 (CH<sub>naphth</sub>), 126.5 (CH<sub>naphth</sub>), 125.4 (C5), 121.5 (C7), 118.0 (C8), 115.7 (C<sub>q</sub>), 114.8 (C<sub>q</sub>), 113.1 (C6), 93.7 (C3), 17.3 (CH<sub>2</sub>), 15.9 (CH<sub>3</sub>) ppm. MS (ESI): m/z (%) = 319.2 (21) [M + Na]<sup>+</sup>, 297.2 (100) [M + H]<sup>+</sup>. HRMS (ESI): calcd. for  $[C_{21}H_{16}N_2 + Na]^+$  319.1211; found 319.1211.

2-(4-Cyanophenyl)-1-ethylindolizine-3-carbonitrile (6c): The title compound was prepared according to general procedure C from 5 (100 mg, 0.50 mmol) and (E)-4-(2-nitrobut-1-enyl)benzonitrile (3c; 101 mg, 0.50 mmol). The crude product was purified by column chromatography (ethyl acetate/cyclohexane, 1:5) to obtain 6c (95 mg, 0.35 mmol, 70%) as a solid; m.p. 147–149 °C;  $R_{\rm f} = 0.32$ (ethyl acetate/cyclohexane, 1:5). IR (neat):  $\tilde{v} = 2965, 2926, 2227,$ 2196, 1534, 1453, 1356, 1224, 859, 754, 732 cm<sup>-1</sup>. <sup>1</sup>H NMR  $(300 \text{ MHz}, \text{CDCl}_3)$ :  $\delta = 8.27 \text{ (dt, } J = 6.9, 1.0 \text{ Hz}, 1 \text{ H}, \text{H5}), 7.82 \text{--}$ 7.76 (AA' part of AA'-BB' system, 2 H, H3',5'), 7.67-7.61 (BB' part of AA'-BB' system, 2 H, H2',6'), 7.54 (dt, J = 9.0, 1.1 Hz, 1 H, H8), 7.06 (ddd, J = 9.0, 6.7, 1.0 Hz, 1 H, H7), 6.87 (td, J = 6.8, 1.2 Hz, 1 H, H6), 2.80 (q, J = 7.6 Hz, 2 H, CH<sub>2</sub>), 1.18 (q, J =7.6 Hz, 3 H, CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 137.6 (C4'), 134.7 (C2), 134.0 (C8a), 132.7 (C2',6'), 130.1 (C3',5'), 125.5 (C5), 122.0 (C7), 118.8 (C<sub>a</sub>), 118.2 (C8), 115.7 (C<sub>a</sub>), 114.2 (CN), 113.9 (C6), 111.9 (C1), 93.3 (C3), 17.2 (CH<sub>2</sub>), 15.9 (CH<sub>3</sub>) ppm. C<sub>18</sub>H<sub>13</sub>N<sub>3</sub> (271.32): calcd. C 79.68, H 4.83, N 15.49; found C 79.28, H 4.77, N 15.75. MS (ESI): m/z (%) = 294.0 (94) [M + Na]<sup>+</sup>, 288.0 (37) [M + OH]<sup>+</sup>, 272.0 (100) [M + H]<sup>+</sup>. HRMS (ESI): calcd. for [C<sub>18</sub>H<sub>13</sub>N<sub>3</sub>]<sup>+</sup> 271.1109; found 271.1109.

**2-(4-Fluorophenyl)-1-methylindolizine-3-carbonitrile (6d):** The title compound was prepared according to general procedure C from **5** (100 mg, 0.50 mmol) and (*E*)-1-fluoro-4-(2-nitroprop-1-enyl)benzene (**3d**; 91 mg, 0.50 mmol). The crude product was purified by column chromatography (ethyl acetate/cyclohexane, 1:5) to obtain **6d** (102 mg, 0.41 mmol, 81%) as a solid; m.p. 162–164 °C;  $R_{\rm f}$  =

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0.44 (ethyl acetate/cyclohexane, 1:5). IR (neat):  $\hat{v} = 3070$ , 2914, 2191, 1536, 1384, 1156, 859, 736, 726 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 8.24$  (dt, J = 6.8, 1.1 Hz, 1 H, H5), 7.55–7.49 (m<sub>c</sub>, 2 H, H3',5'), 7.47 (dt, J = 9.0, 6.7, 1.1 Hz, 1 H, H8), 7.24–7.14 (m<sub>c</sub>, 2 H, H2',6'), 7.01 (ddd, J = 9.0, 6.7, 1.1 Hz, 1 H, H7), 6.81 (td, J = 6.8, 1.2 Hz, 1 H, H6), 2.34 (s, 3 H, CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta = 162.2$  (d, <sup>1</sup> $J_{C,F} = 247.8$  Hz, C-F), 135.6 (C2), 135.1 (C8a), 131.2 (d, <sup>3</sup> $J_{C,F} = 8.1$  Hz, C2',6'), 128.5 (d, <sup>4</sup> $J_{C,F} = 3.6$  Hz, C1'), 125.3 (C5), 121.5 (C7), 117.9 (C8), 116.0 (d, <sup>2</sup> $J_{C,F} = 21.6$  Hz, C3',5'), 114.8 (CN), 113.2 (C6), 108.3 (C1), 93.2 (C3), 9.3 (CH<sub>3</sub>) ppm. MS (ESI): m/z (%) = 273.1 (3) [M + Na]<sup>+</sup>, 251.1 (100) [M + H]<sup>+</sup>. HRMS (ESI): calcd. for [C<sub>16</sub>H<sub>11</sub>N<sub>2</sub>F + H]<sup>+</sup> 251.0985; found 251.0993.

**2-(1-Cyanoethyl)isoquinolinium Triflate (12a):** The title compound was prepared according to general procedure A from isoquinoline (646 mg, 5.00 mmol) and 1-cyanoethyl trifluoromethanesulfonate (1.22 g, 6.00 mmol). The white solid was filtered, washed with cold diethyl ether and recrystallized from diethyl ether to yield compound **12a** (1.55 g, 4.66 mmol, 93%) as a solid; m.p. 155–156 °C. IR (neat):  $\tilde{v} = 3066$ , 1644, 1403, 1264, 1167 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, [D<sub>6</sub>]-

DMSO):  $\delta = 10.26$  (s, 1 H, H1), 9.03 (d, J = 6.8 Hz, 1 H, H3), 8.72 (d, J = 6.9 Hz, 1 H, H4), 8.60 (d, J = 8.0 Hz, 1 H, H8), 8.38 (m, 2 H, H6, H7), 8.15 (d, J = 8.0 Hz, 1 H, H5), 6.41 (q, J = 7.0 Hz, 1 H, CH), 2.11 (d, J = 7.0 Hz, 3 H, CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (75 MHz, [D<sub>6</sub>]DMSO):  $\delta = 150.5$  (C1), 138.1 (C6), 137.7 (C4a), 133.0 (C3), 131.7 (C7), 131.2 (C8), 127.4 (C5), 127.2 (C8a), 126.7 (C4), 120.7 (q,  ${}^{1}J_{C,F} = 322$  Hz, CF<sub>3</sub>), 116.6 (C=N), 56.1 (CH), 20.1 (CH<sub>3</sub>) ppm. C<sub>13</sub>H<sub>11</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub>S (332.30): calcd. C 46.99, H 3.34, N 8.43, S 9.65; found C 46.84, H 3.18, N 8.10, S 9.73. MS (ESI): m/z (%) = 183.1 (100) [M]<sup>+</sup>, 158.1 (22).

2-(1-Cyano-2-methylpropyl)phthalazin-2-ium Triflate (12b): The title compound was prepared according to general procedure A from phthalazine (1.30 g, 10.0 mmol) and **1b** (2.31 g, 10.0 mmol). The white solid was filtered, washed with diethyl ether and recrystallized from EtOAc to yield 12b (2.79 g, 7.7 mmol, 77%); m.p. 122–123 °C. IR (neat):  $\tilde{v} = 3010, 2976, 1484, 1225, 1153, 1027 \text{ cm}^{-1}$ . <sup>1</sup>H NMR (300 MHz, [D<sub>6</sub>]DMSO):  $\delta$  = 10.72 (s, 1 H, H1), 10.21 (s, 1 H, H4), 8.75 (d, J = 8.0 Hz, 1 H, H8), 8.68-8.59 (m, 2 H, H5, H7), 8.49 (ddd, J = 8.3, 6.4, 2.1 Hz, H6), 6.41 (d, J = 7.1 Hz, 1 H, H1'), 2.83–2.65 (m, 1 H, H2'), 1.18 (d, J = 6.7 Hz, 3 H, CH<sub>3</sub>), 1.04  $(d, J = 6.7 \text{ Hz}, 3 \text{ H}, \text{CH}_3) \text{ ppm.}$  <sup>13</sup>C NMR (75 MHz,  $[D_6]\text{DMSO}$ ):  $\delta = 155.4$  (CH), 153.3 (CH), 140.4 (CH), 136.7 (CH), 131.4 (CH), 128.7 (CH), 128.1 (Cq), 127.6 (C<sub>q</sub>), 120.6 (q,  ${}^{1}J_{C,F}$  = 322 Hz, CF<sub>3</sub>), 114.4 (CN), 68.2 (C1'), 33.3 (C2'), 18.2 (CH<sub>3</sub>), 17.7 (CH<sub>3</sub>) ppm. C<sub>14</sub>H<sub>14</sub>F<sub>3</sub>N<sub>3</sub>O<sub>3</sub>S (361.34): calcd. C 46.54, H 3.91, N 11.63, S 8.87; found C 46.60, H 3.90, N 11.81, S 8.92. MS (ESI): m/z (%) = 212.1  $(100) [M + H]^+$ .

**3-(1-Cyanoethyl)-1-methyl-1***H***-imidazol-3-ium Triflate (12c):** Prepared according to general procedure A from 1-methyl-imidazole (328 mg, 4.00 mmol) and **1a** (813 mg, 4.00 mmol). The white solid was filtered, washed with diethyl ether and recrystallized from CH<sub>2</sub>Cl<sub>2</sub> to yield **12c** (938 mg, 3.29 mmol, 82%); m.p. 52–54 °C. IR (neat):  $\tilde{v} = 3155$ , 3110, 2962, 1583, 1557, 1250, 1157, 1028, 733 cm<sup>-1.</sup> <sup>1</sup>H NMR (300 MHz, [D<sub>6</sub>]DMSO):  $\delta = 9.35$  (s,1 H, H2), 8.07 (d, J = 1.4 Hz, 1 H, H4), 7.82 (d, J = 1.4 Hz, 1 H, H5), 5.98 (q, J = 7.1 Hz, 1 H, H1'), 3.88 (s, 3 H, NCH<sub>3</sub>), 1.88 (d, J = 7.1 Hz, 3 H, H2') ppm. <sup>13</sup>C NMR (75 MHz, [D<sub>6</sub>]DMSO):  $\delta = 137.0$  (C2), 124.6 (C5), 120.9 (C4), 117.1 (CN), 45.3 (CH), 36.2 (NCH<sub>3</sub>), 19.0 (CH<sub>3</sub>) ppm. C<sub>8</sub>H<sub>10</sub>F<sub>3</sub>N<sub>3</sub>O<sub>3</sub>S (285.24): calcd. C 33.69, H 3.53, N 14.73, S 11.24; found C 33.50, H 3.56, N 14.85, S 11.31. MS (ESI): m/z (%) = 136.2 (100) [M + H]<sup>+</sup>.

3-(1-Cyanoethyl)-1,3-benzothiazol-3-ium Triflate (12d): The title compound was prepared according to general procedure A from benzothiazole (541 mg, 4.00 mmol) and 1a (1.22 g, 6.00 mmol). The white solid was filtered, washed with diethyl ether and recrystallized from CH<sub>2</sub>Cl<sub>2</sub> to yield **12d** (1.12 g, 3.31 mmol, 83%); m.p. 94–96 °C. IR (neat):  $\tilde{v} = 3081$ , 1582, 1504, 1255, 1160, 1125 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, [D<sub>6</sub>]DMSO):  $\delta$  = 10.75 (s, 1 H, H2), 8.58 (d, J = 8.2 Hz, 1 H), 8.48 (d, J = 8.4 Hz, 1 H), 8.03 (pseudo t, J =7.9 Hz, 1 H), 7.92 (pseudo t, J = 7.7 Hz, 1 H), 6.72 (q, J = 7.0 Hz, 1 H, CH), 2.14 (d, J = 7.1 Hz, 3 H, CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (75 MHz,  $[D_6]DMSO$ :  $\delta = 168.4$  (C2), 164.4 (CH), 140.4 (C3a), 131.0 (C7a), 130.0 (CH), 128.8 (CH), 125.6 (CH), 120.7 (g,  ${}^{1}J_{CF} = 322$  Hz, CF<sub>3</sub>), 116.6 (C=N), 60.7 (CH), 17.2 (CH<sub>3</sub>) ppm.  $C_{11}H_9F_3N_2O_3S_2$ (338.32): calcd. C 39.05, H 2.68, N 8.28, S 18.96; found C 39.17, H 2.72, N 8.27, S 19.07. MS (ESI): m/z (%) = 207.0 (100) [M + H<sub>2</sub>O]<sup>+</sup>, 189.0 (64) [M]<sup>+</sup>, 164.1 (39).

### Synthesis of N-Fused-Pyrrole-Containing Heterocycles

Method A: To a solution of azinium salt (1 equiv.) and nitroolefin (1 equiv.) in anhydrous DMF (10 mL/mmol azine) was slowly added a solution of KOtBu (4 equiv.) in anhydrous DMF (5.0 mL/mmol azine) at 0 °C. The mixture was stirred at this temperature and monitored by TLC. When the reaction was complete, the solvent was evaporated in vacuo. The residue was dissolved in ethyl acetate, washed with water and the aqueous phase was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried with MgSO<sub>4</sub> and the solvent was removed in vacuo. In one case (Table 5, entry 5),  $Ag_2CO_3$  (2 equiv.) was used instead of KOtBu.

**Method B:** A solution of KOtBu (4 equiv.) in anhydrous DMF (5.0 mL/mmol azine) was slowly added to a stirred solution of azinium salt (1 equiv.) and DEAD (1 equiv.) in anhydrous DMF (10 mL/mmol azine) at 0 °C. The mixture was stirred at 0 °C, and the reaction was monitored by TLC. When the conversion was complete, the solvent was evaporated in vacuo. The residue was dissolved in ethyl acetate and washed with water. The aqueous phase was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried with MgSO<sub>4</sub>, and the solvent was removed in vacuo.

2-(4-Chlorophenyl)-1,3-dimethylpyrrolo[2,1-a]isoquinoline (13a): The title compound was prepared according to method A from 12a (332 mg, 1.00 mmol) and (E)-1-chloro-4-(2-nitroprop-1-enyl)benzene (3a; 198 mg, 1.00 mmol). The crude product was purified by column chromatography over silica (ethyl acetate/cyclohexane, 1:10) to obtain 13a (150 mg, 0.49 mmol, 49%) as a yellow solid; m.p. 148–149 °C;  $R_{\rm f} = 0.54$  (ethyl acetate/cyclohexane, 1:10). IR (neat):  $\tilde{v} = 2960, 2923, 1547, 1480, 1359, 1087, 848, 779, 757 \text{ cm}^{-1}$ . <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.23 (d, J = 8.1 Hz, 1 H, H5), 7.59 (pseudo t, J = 8.1 Hz, 2 H, H9, H10), 7.52–7.42 [m, 3 H, H8(7), H3',5'], 7.37–7.26 [m, 3 H, H7(8), H2',6'], 6.75 (d, J =7.4 Hz, 1 H, H6), 2.57 (s, 3 H, CH<sub>3</sub>), 2.42 (s, 3 H, CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 134.3, 132.4, 132.3, 131.7, 128.5, 128.0, 127.24, 127.20, 126.9, 125.9, 124.5, 122.5, 121.5, 118.5, 110.7, 110.4, 13.1, 10.3 ppm. MS (ESI): m/z (%) = 338.2 (92) [M +  $2O + H^{+}$ , 322.2 (100) [M + OH]<sup>+</sup>, 306.2 (56) [M + H]<sup>+</sup>, 305.2 (65)  $[M]^+$ . HRMS (ESI): calcd. for  $[C_{20}H_{16}NCl]^+$  305.0971; found 305.0980.

**2-(4-Chlorophenyl)-1-methyl-3-(propan-2-yl)pyrrolo[2,1-***a***]<b>phthalazine (13b):** The title compound was prepared according to method B from **12b** (361 mg, 1.00 mmol) and **3a** (198 mg, 1.00 mmol). The crude product was purified by filtration through silica (ethyl acetate/cyclohexane, 1:10) to obtain **13b** (114 mg, 0.34 mmol, 34%) as a yellow solid; m.p. 136–138 °C;  $R_f = 0.50$  (ethyl acetate/cyclohex-

#### A Modular Synthesis of Polysubstituted Indolizines

ane, 1:5). IR (neat):  $\tilde{v} = 2962, 2932, 1357, 1202, 1016, 840,$ 752 cm<sup>-1</sup>. <sup>1</sup>H NMR (600 MHz, [D<sub>6</sub>]acetone, COSY, HSQC, HMBC):  $\delta = 8.47$  (s, 1 H, H6), 8.15 (dd, J = 8.2, 1.1 Hz, 1 H, H10), 7.87 (dd, *J* = 7.9, 1.4 Hz, 1 H, H7), 7.75 (ddd, *J* = 8.1, 7.3, 1.0 Hz, 1 H, H9), 7.52-7.50 (AA' part of AA'-BB' system, 2 H, H3',5'), 7.46 (ddd, J = 7.9, 7.5, 0.7 Hz, 1 H, H8), 7.37–7.34 (BB' part of AA'-BB' system, 2 H, H2',6'), 3.48 (sept, J = 7.2 Hz, 1 H,  $CH_{iPr}$ ), 2.41 (s, 3 H, 1-CH<sub>3</sub>), 1.38 [d, J = 7.1 Hz, 6 H,  $(CH_3)_2$ -CH] ppm. <sup>13</sup>C NMR (151 MHz, [D<sub>6</sub>]acetone):  $\delta$  = 143.2 (C6), 135.6 (C4'), 133.5 (2 C, C2',6'), 133.1 (C1'), 133.0 (C9), 131.8 (C3), 130.2 (C6a), 129.0 (2 C, C3',5'), 128.8 (C7), 125.8 (C8), 123.7 (C2), 122.2 (C10), 120.5 (C10a), 118.5 (C10b), 109.9 (C1), 26.8 (CH<sub>iPr</sub>), 20.9  $[2 C, (CH_3)_2CH], 12.3 (1-CH_3) ppm. MS (ESI): m/z (\%) = 367.3$ (39) [M + 2O + H]<sup>+</sup>, 351.4(100) [M + O + H]<sup>+</sup>, 335.5 (34) [M + H]<sup>+</sup>. HRMS (ESI): calcd. for [C<sub>21</sub>H<sub>19</sub>N<sub>2</sub>C 1 + H]<sup>+</sup> 335.1315; found 335.1312.

Diethyl 1,5-Dimethyl-1H-pyrrolo[1,2-a]imidazole-6,7-dicarboxylate (13c): The title compound was prepared according to method B from 12c (157 mg, 0.55 mmol) and DEAD (94 mg, 0.55 mmol). The crude product was purified by flash chromatography over silica (ethyl acetate/cyclohexane, 1:3) to obtain **13c** (89 mg, 0.32 mmol, 58%) as a yellow solid; m.p. 118–120 °C;  $R_f = 0.22$  (ethyl acetate/ cyclohexane, 1:3). IR (neat):  $\tilde{v} = 2980, 1670, 1589, 1454, 1189,$ 1083, 1048 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, COSY, HSQC, HMBC):  $\delta$  = 6.80 (d, J = 2.2 Hz, 1 H, H3), 6.67 (d, J = 2.2 Hz, 1 H, H2), 4.31 (q, J = 7.1 Hz, 2 H, C2'), 4.21 (q, J = 7.1 Hz, 2 H, C2''), 3.96 (s, 3 H, NCH<sub>3</sub>), 2.33 (s, 3 H, 5-CH<sub>3</sub>), 1.35 (t, *J* = 7.1 Hz, 3 H, H3'), 1.29 (t, J = 7.1 Hz, 3 H, H3'') ppm. <sup>13</sup>C NMR  $(101 \text{ MHz}, \text{CDCl}_3): \delta = 166.7 \text{ (C1')}, 163.8 \text{ (C1'')}, 139.0 \text{ (C7a)},$ 123.8 (C2), 117.9 (C6), 115.5 (C5), 104.1 (C3), 85.1 (C7), 60.7 (C2'), 59.3 (C2''), 35.8 (NCH<sub>3</sub>), 14.6 (C3''), 14.4 (C3'), 10.3 (5-CH<sub>3</sub>) ppm. MS (ESI): m/z (%) = 301.3 (100) [M + Na]<sup>+</sup>, 279.3 (51)  $[M + H]^+$ , 233.2 (49)  $[M - OC_2H_5]^+$ . HRMS (ESI): calcd. for  $[C_{14}H_{18}N_2O_4 + H]^+$  279.1345; found 279.1346.

2-(4-Chlorophenyl)-1,3-dimethylpyrrolo[2,1-b][1,3]benzothiazole (13d): The title compound was prepared according to method A from 12d (338 mg, 1.00 mmol) and 3a (198 mg, 1.00 mmol). The crude product was purified by chromatography over silica (ethyl acetate/cyclohexane, 1:10) to obtain 13d (80 mg, 0.26 mmol, 26%) as slightly brown solid; m.p. 134–137 °C;  $R_f = 0.60$  (ethyl acetate/ cyclohexane, 1:10). IR (neat):  $\tilde{v} = 3058, 3033, 2920, 1476, 1028,$ 763, 742 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, COSY, HSQC, HMBC):  $\delta = 7.75$  (dd, J = 8.2, 0.6 Hz, 1 H, H5), 7.61 (dd, J = 7.9, 1.0 Hz, 1 H, H8), 7.44-7.39 (AA' part of AA'-BB' system, 2 H, H3',5'), 7.31 (td, J = 7.9, 1.2 Hz, 1 H, H6), 7.28–7.24 (BB' part of AA'-BB' system, 2 H, H2',6'), 7.19 (ddd overlapped, J = 7.8, 7.6,1.0 Hz, 1 H, H7), 2.67 (s, 3 H, C1-CH<sub>3</sub>), 2.12 (s, 3 H, C3-*C*H<sub>3</sub>) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 136.4 (C8a), 134.2 (C4'), 132.2 (C1'), 131.7 (C4a), 131.6 (C2',6'), 128.5 (C3',5'), 127.2 (C2), 125.3 (C6), 124.0 (C8), 123.4 (C3a), 123.0 (C7), 120.1 (C1), 112.8 (C5), 106.3 (C3), 12.7 (C1-CH<sub>3</sub>), 10.8 (C3-CH<sub>3</sub>) ppm. MS (ESI): m/z (%) = 344.2 (23) [M + 2O + H]<sup>+</sup>, 328.2 (100) [M + OH]<sup>+</sup>, 312.2 (28) [M + H]<sup>+</sup>, 311.2 (46) [M]<sup>+</sup>. HRMS (ESI): calcd. for [C<sub>18</sub>H<sub>14</sub>NClS]<sup>+</sup> 311.0535; found 311.0545.

**2-(4-Chlorophenyl)-1-methylpyrrolo[2,1-***a***]isoquinoline-3-carbonitrile (13e): The title compound was prepared according to method A from 2-(cyanomethyl)isoquinolinium bromide (12e; 249 mg, 1.00 mmol) and 3a (198 mg, 1.00 mmol). The crude product was purified by chromatography over silica (ethyl acetate/cyclohexane, 1:10) to obtain 13e (150 mg, 0.49 mmol, 49%) as a yellow solid; m.p. 198–200 °C; R\_{\rm f} = 0.48 (ethyl acetate/cyclohexane, 1:10). IR (neat): \tilde{v} = 3090, 2917, 2196, 1516, 1366, 1224, 1095, 820 cm<sup>-1</sup>. <sup>1</sup>H** 

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NMR (400 MHz, [D<sub>6</sub>]DMSO):  $\delta = 8.39$  (d, J = 8.1 Hz, 1 H, H10), 8.24 (d, J = 7.3 Hz, 1 H, H5), 7.89 (dd, J = 7.7, 0.9 Hz, 1 H, H7), 7.71–7.67 (m, 1 H, H9), 7.67–7.64 (AA' part of AA'-BB' system, 2 H, H3',5'), 7.64–7.59 (m, 1 H, H8), 7.59–7.53 (BB' part of AA'-BB' system, 2 H, H2',6'), 7.30 (d, J = 7.3 Hz, 1 H, H6), 2.58 (s, 3 H, CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz, [D<sub>6</sub>]DMSO):  $\delta = 135.1$  (C2), 133.2 (C1'), 131.5 (2 C, C2',6'), 130.5 (C4'), 129.8 (C10b), 129.0 (2 C, C3',5'), 128.5 (C9), 128.4 (C10a), 127.7 (C7), 127.6 (C8), 125.6 (C6a), 123.5 (C10), 123.1 (C5), 113.9 (C6), 113.6 (CN), 112.1 (C1), 94.7 (C3), 12.5 (CH<sub>3</sub>) ppm. MS (ESI): m/z (%) = 339.4 (100) [M + Na]<sup>+</sup>, 317.5 (22) [M + H]<sup>+</sup>. C<sub>20</sub>H<sub>13</sub>ClN<sub>2</sub> (316.79): calcd. C 75.83, H 4.14, N 8.84; found C 75.46, H 3.87, N 8.74.

Diethyl 3-(Propan-2-yl)pyrrolo[2,1-a]phthalazine-1,2-dicarboxylate (13f): The title compound was prepared according to method B from 12b (361 mg, 1.00 mmol) and DEAD (170 mg, 1.00 mmol). The crude product was purified by flash chromatography over silica (ethyl acetate/cyclohexane, 1:5) to obtain 13f (180 mg, 0.508 mmol, 51%) as a solid; m.p. 68–69 °C;  $R_{\rm f} = 0.31$  (ethyl acetate/cyclohexane, 1:5). IR (neat):  $\tilde{v} = 2979$ , 2937, 1704, 1621, 1456, 1173, 757 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, COSY, HSQC, HMBC):  $\delta$ = 8.88 (br. d, J = 8.7 Hz, 1 H, H10), 8.44 (s, 1 H, H6), 7.75–7.68 (m, 2 H, H7, H9), 7.54 (td, J = 7.5, 1.0 Hz, 1 H, H8), 4.42 (q, J =7.2 Hz, 2 H, H2'), 4.37 (q, J = 7.2 Hz, 2 H, H2''), 4.01 (sept, J =7.1 Hz, 1 H, H1'''), 1.46 {d, J = 7.1 Hz, 6 H, [(CH<sub>3</sub>)<sub>2</sub>CH]}, 1.40 (t, J = 7.2 Hz, 3 H, H3'), 1.39 (t, J = 7.2 Hz, 3 H, H3'') ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 166.3 (C1<sup>''</sup>), 166.1 (C1<sup>'</sup>), 145.1 (C6), 137.3 (C3), 132.7 (C7), 127.9 (C8), 127.8 (C9), 127.5 (C10a), 124.5 (C10), 122.9 (C10b), 120.8 (C6a), 114.9 (C2), 106.6 (C1), 61.2 (C2'), 61.1 (C2''), 25.6 (C1'''), 20.1 [(CH<sub>3</sub>)<sub>2</sub>CH], 14.4 (C3''), 14.3 (C3') ppm. MS (ESI): m/z (%) = 377.2 (100) [M + Na]<sup>+</sup>, 355.3(30)  $[M + H]^+$ , 309.3 (71)  $[M - OC_2H_5]^+$ . HRMS (ESI): calcd. for  $[C_{20}H_{22}N_2O_4 + Na]^+$  377.1477; found 377.1477.

Diethyl 3-Methylindolizine-1,2-dicarboxylate (13g): The title compound was prepared according to method B from 2a (282 mg, 1.00 mmol) and DEAD (170 mg, 1.00 mmol). The crude product was purified by flash chromatography over silica (ethyl acetate/cyclohexane, 1:10) to obtain 13g (210 mg, 0.76 mmol, 76%) as a yellow waxy oil.  $R_{\rm f} = 0.18$  (ethyl acetate/cyclohexane, 1:4). IR (neat):  $\tilde{v} = 2982, 1734, 1689, 1527, 1236, 1200, 1088, 1041, 782, 739 \text{ cm}^{-1}$ . <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.15 (dd, J = 9.2, 0.9 Hz, 1 H, H5), 7.78 (dd, J = 7.1, 0.9 Hz, 1 H, H8), 7.06 (ddd, J = 9.0, 6.6, 1.0 Hz, 1 H), 6.79 (td, J = 6.8, 1.3 Hz), 4.40 (q, J = 7.2 Hz, 2 H, OCH<sub>2</sub>), 4.34 (q, J = 7.2 Hz, 2 H, OCH<sub>2</sub>), 2.50 (s, 3 H, 3-CH<sub>3</sub>), 1.40 (t, J = 7.2 Hz, 3 H, CH<sub>3</sub>), 1.35 (t, J = 7.2 Hz, 3 H, CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 166.7 (CO<sub>2</sub>Et), 164.1 (CO<sub>2</sub>Et), 135.1 (Cq), 122.8, 122.5, 122.1 (Cq), 120.6 (Cq), 120.4, 113.4 (CN), 101.7 (C<sub>q</sub>), 61.3 (OCH<sub>2</sub>), 59.9 (OCH<sub>2</sub>), 14.6 (CH<sub>3</sub>), 14.4 (CH<sub>3</sub>), 10.1 (CH<sub>3</sub>) ppm. MS (ESI): m/z (%) = 298.2 (100) [M + Na]<sup>+</sup>, 276.2 (29)  $[M + H]^+$ , 230.1 (28)  $[M - OC_2H_5]^+$ . HRMS (ESI): calcd. for  $[C_{15}H_{17}NO_4 + Na]^+$  298.1055; found 298.1056.

**Supporting Information** (see footnote on the first page of this article): Copies of the <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra for all new compounds.

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## **FULL PAPER**

- J. Gubin, H. de Vogelaer, H. Inion, C. Houben, J. Lucchetti, J. Mahaux, G. Rosseels, M. Peiren, M. Clinet, P. Polster, P. Chatelain, J. Med. Chem. 1993, 36, 1425–1433.
- [2] W. B. Harrell, R. F. Doerge, J. Pharm. Sci. 1967, 56, 225-228.
- [3] J. Gubin, M. Descamps, P. Chatelain, D. Nisato, *Eur. Pat. Appl.* 1987, EP 235 111.
- [4] L. L. Gundersen, C. Charnock, A. H. Negussie, F. Rise, S. Teklu, *Eur. J. Pharm. Sci.* 2007, 30, 26–35.
- [5] a) D. R. Bragg, D. G. Wibberley, J. Chem. Soc. 1963, 3277–3281; b) W. Flitsch, E. Gerstmann, Chem. Ber. 1969, 102, 1309–1311; c) D. H. Wadsworth, S. L. Bender, D. L. Smith, H. R. Luss, C. H. Weidner, J. Org. Chem. 1986, 51, 4639–4644; d) M. L. Bode, P. T. Kaye, J. Chem. Soc. Perkin Trans. 1 1993, 1809–1813; e) A. R. Katritzky, G. Qiu, B. Yang, H.-Y. He, J. Org. Chem. 1999, 64, 7618–7621; f) X.-C. Zhang, W.-Y. Huang, Synthesis 1999, 51–54; g) D. Basavaiah, A. Jaganmohan Rao, Chem. Commun. 2003, 604–605; h) T. Uchida, K. Matsumoto, Synthesis 1976, 209–236; i) J. Jacobs, E. V. Hende, S. Claessens, N. De Kimpe, Curr. Org. Chem. 2011, 15, 1340–1362; j) G. S. Singh, E. E. Mmatli, Eur. J. Med. Chem. 2011, 46, 5237–5257.
- [6] M. Scholtz, Ber. Dtsch. Chem. Ges. 1912, 45, 734-746.
- [7] Y. Tamura, N. Tsujimoto, Y. Sumida, M. Ikeda, *Tetrahedron* 1972, 28, 21–27.
- [8] a) O. Diels, R. Meyer, Justus Liebigs Ann. Chem. 1934, 513, 129-145; b) K. Shiosaki, G. Fels, H. Rapoport, J. Org. Chem. 1981, 46, 3230-3234; c) E. T. Borrows, D. O. Holland, J. Chem. Soc. 1947, 670-672; d) R. M. Acheson, P. J. Ansell, J. Chem. Soc. Perkin Trans. 1 1987, 1275-1281; e) Y. Tominaga, Y. Ichihara, A. Hosomi, Heterocycles 1988, 27, 2345-2348; f) Y. Tominaga, Y. Ichihara, T. Mori, C. Kamio, A. Hosomi, J. Heterocycl. Chem. 1990, 27, 263-268; g) X. Wei, Y. Hu, T. Li, H. Hu, J. Chem. Soc. Perkin Trans. 1 1993, 2487-2489; h) G. Poissonnet, M.-H. Théret-Bettiol, R. H. Dodd, J. Org. Chem. 1996, 61, 2273-2282; i) X.-C. Zhang, W.-Y. Huang, J. Fluorine Chem. 1998, 92, 13-16; j) B. Wang, X. Zhang, Y. Li, X. Jiang, Y. Hu, H. Hu, J. Chem. Soc. Perkin Trans. 1 1999, 1571-1576; k) S.-Z. Zhu, C.-Y. Qin, Y.-L. Wang, Q.-l. Chu, J. Fluorine Chem. 1999, 99, 183-188; 1) Y. Shen, Y. Zhang, G.-F. Jiang, Synthesis 2002, 714-716; m) X. Fang, Y.-M. Wu, J. Deng, S.-W. Wang, Tetrahedron 2004, 60, 5487-5493; n) A. Hazra, S. Mondal, A. Maity, S. Naskar, P. Saha, R. Paira, K. B. Sahu, P. Paira, S. Ghosh, C. Sinha, A. Samanta, S. Banerjee, N. B. Mondal, Eur. J. Med. Chem. 2011, 46, 2132-2140; o) Y. Yang, C. Kuang, H. Jin, Q. Yang, Synthesis 2011, 3447-3452.
- [9] a) O. B. Østby, B. Dalhus, L.-L. Gundersen, F. Rise, A. Bast, G. R. M. M. Haenen, Eur. J. Org. Chem. 2000, 3763-3770; b) K. Matsumoto, T. Uchida, Synthesis 1978, 207-208; c) J. Heer, K. Hoffmann, Helv. Chim. Acta 1956, 39, 1820-1825; d) W. Chai, A. Kwok, V. Wong, N. I. Carruthers, J. Wu, Synlett 2003, 2086-2088; e) L.-L. Gundersen, A. H. Negussie, F. Rise, O. B. Østby, Arch. Pharm. 2003, 336, 191-195; f) J. Kaloko, A. Hayford, Org. Lett. 2005, 7, 4305-4308; g) Y. Bai, J. Zeng, J. Ma, B. K. Gorityala, X.-W. Liu, J. Comb. Chem. 2010, 12, 696-699; h) B. Yan, Y. Liu, Org. Lett. 2007, 9, 4323-4326; i) B. Yan, Y. Zhou, H. Zhang, J. Chen, Y. Liu, J. Org. Chem. 2007, 72, 7783-7786; j) L. Zhu, M. Vimolratana, S. P. Brown, J. C. Medina, Tetrahedron Lett. 2008, 49, 1768-1770; k) Y. Liu, Z. Song, B. Yan, Org. Lett. 2007, 9, 409-412; 1) L.-L. Gundersen, K. E. Malterud, A. H. Negussie, F. Rise, S. Teklu, O. B. Østby, Bioorg. Med. Chem. 2003, 11, 5409-5415.
- [10] a) A. E. Tschitschibabin, Ber. Dtsch. Chem. Ges. 1927, 60, 1607–1617; b) D. O. Holland, J. H. C. Nayler, J. Chem. Soc.

**1955**, 1657–1662; c) Z. Xia, T. Przewloka, K. Koya, M. Ono, S. Chen, L. Sun, *Tetrahedron Lett.* **2006**, *47*, 8817–8820.

- [11] a) D. Chernyak, S. B. Gadamsetty, V. Gevorgyan, Org. Lett.
  2008, 10, 2307–2310; b) I. V. Seregin, V. Gevorgyan, J. Am. Chem. Soc. 2006, 128, 12050–12051; c) A. V. Kel'in, A. W. Sromek, V. Gevorgyan, J. Am. Chem. Soc. 2001, 123, 2074–2075; d) I. V. Seregin, A. W. Schammel, V. Gevorgyan, Tetrahedron 2008, 64, 6876–6883; e) D. Chernyak, C. Skontos, V. Gevorgyan, Org. Lett. 2010, 12, 3242–3245; f) A. R. Hardin, R. Sarpong, Org. Lett. 2007, 9, 4547–4550; g) T. Schwier, A. W. Sromek, D. M. L. Yap, D. Chernyak, V. Gevorgyan, J. Am. Chem. Soc. 2007, 129, 9868–9878.
- [12] W. Chai, J. G. Breitenbucher, A. Kwok, X. Li, V. Wong, N. I. Carruthers, T. W. Lovenberg, C. Mazur, S. J. Wilson, F. U. Axe, T. K. Jones, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1767–1770.
- [13] S. Hagishita, M. Yamada, K. Shirahase, T. Okada, Y. Murakami, Y. Ito, T. Matsuura, M. Wada, T. Kato, M. Ueno, Y. Chikazawa, K. Yamada, T. Ono, I. Teshirogi, M. Ohtani, *J. Med. Chem.* **1996**, *39*, 3636–3658.
- [14] a) J. E. Saxton, J. Chem. Soc. 1951, 3239–3241; b) C. Jiang,
   A. J. Frontier, Org. Lett. 2007, 9, 4939–4942.
- [15] a) F. Kröhnke, *Ber. Dtsch. Chem. Ges. A/B* 1939, 72, 83–89; b)
  O. Tsuge, S. Kanemasa, S. Takenaka, *Bull. Chem. Soc. Jpn.* 1985, 58, 3137–3157; c) K. Matsumoto, N. Tanaka, T. Uchida, Y. Ikemi, N. Hayashi, K. Aoyama, A. Kakehi, *Heterocycles* 2001, 54, 611–614; d) E. Boultadakis, B. Chung, M. R. J. Elsegood, G. W. Weaver, *Synlett* 2002, 1547–1549; e) A. H. Cook, J. Downer, B. Hornung, *J. Chem. Soc.* 1941, 502–506; f) S. Muthusaravanan, S. Perumal, P. Yogeeswari, D. Sriram, *Tetrahedron Lett.* 2010, 51, 6439–6443.
- [16] a) S. Nazabadioko, R. J. Pérez, R. Brieva, V. Gotor, *Tetrahe-dron: Asymmetry* **1998**, *9*, 1597–1604; b) P. Karrer, A. Epprecht, *Helv. Chim. Acta* **1941**, *24*, 1039–1045.
- [17] a) W. Eberbach, J. Roser, *Tetrahedron* 1986, 42, 2221–2234; b) G. Broggini, L. Garanti, G. Molteni, G. Zecchi, *Synthesis* 1995, 1483–1484; c) P. Molina, C. López-Leonardo, J. Llamas-Botía, C. Foces-Foces, C. Fernández-Castaño, *Tetrahedron* 1996, 52, 9629–9642.
- [18] a) S. D. Young, C. T. Buse, C. H. Heathcock, *Organic Syntheses*, Wiley, New York, **1990**, Collect. Vol. 7, p. 381; b) T. Watahiki, S. Ohba, T. Oriyama, *Org. Lett.* **2003**, *5*, 2679–2681.
- [19] Y. Kawai, Y. Inaba, N. Tokitoh, *Tetrahedron: Asymmetry* 2001, 12, 309–318.
- [20] D. H. R. Barton, J. Kervagoret, S. Z. Zard, *Tetrahedron* 1990, 46, 7587–7598.
- [21] I. Bergner, T. Opatz, J. Org. Chem. 2007, 72, 7083-7090.
- [22] J.-Z. Tian, Z.-G. Zhang, X.-L. Yang, H.-K. Fun, J.-H. Xu, J. Org. Chem. 2001, 66, 8230–8235.
- [23] H. E. Gottlieb, V. Kotlyar, A. Nudelman, J. Org. Chem. 1997, 62, 7512–7515.
- [24] F. Toda, R. Toyotaka, H. Fukuda, *Tetrahedron: Asymmetry* 1990, 1, 303–306.
- [25] a) L. Meerpoel, G. Hoornaert, *Synthesis* 1990, 905–908; b) J. Robertson, M. J. Hall, S. P. Green, *Tetrahedron* 2009, 65, 5541–5551.
- [26] a) S. Kiyooka, R. Fujiyama, K. Kawaguchi, *Chem. Lett.* **1984**, 1979–1980; b) M. Sandberg, L. K. Sydnes, *Org. Lett.* **2000**, *2*, 687–689.
- [27] X. Ding, K. Taniguchi, Y. Hamamoto, K. Sada, S. Fujinami, Y. Ukaji, K. Inomata, *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1069– 1083.

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### Heterocyclic Chemistry

Polysubstituted indolizines were synthesized through [3+2] cycloaddition of nitroalkenes with pyridinium ylides. In contrast to previous reports of 1,3-dipolar cycloadditions, in this work no electron-deficient groups remain in the products.



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A Modular Synthesis of Polysubstituted Indolizines

**Keywords:** Cycloaddition / Nitrogen heterocycles / Sulfur heterocycles / Ylides