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Synthesis of indolizidines from dialkylated isocyanides: a novel radical cyclisation/N-alkylation/ring closing metathesis approach

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ABSTRACT

Two dialkylated isocyanides were first synthesised from simple starting materials and then used as building blocks for the synthesis of indolizidines via a novel radical cyclisation/N-alkylation/ring closing metathesis strategy. Several functionalised indolizidines were accessed in good to excellent yields.

Indolizidine alkaloids (Fig. 1), isolated from the skin secretions of Central and South American frogs, fungi and plants, represent a class of pharmacologically important compounds.[1–5] These alkaloids are very important targets in organic synthesis due to their scarcity in natural sources and important physiological effects. Polyhydroxylated derivatives such as castanospermine, lentiginosine and swainsonine have been known to inhibit glycosidase and cardiotonic activity with potential antibacterial, antitumoural, antiviral, antidiabetic activity and also act as anti-HIV agents.[6–8]

Coniceine, containing the simplest indolizidine skeleton, has attracted great attention from synthetic chemists to establish a general route for the preparation of more complex derivatives and this has resulted in several successful approaches to the compound both in racemic and in optically active form.[9–13] We envisaged that indolizidine analogues could be accessed starting from bis-alkenyl isocyanides, easily accessible with already established methodology,[14] using a radical cyclisation/N-alkylation/ring closing metathesis[15–19] strategy for the formation of the 1-azabiciclo-[4.3.0]-nonane skeleton (Scheme 1).

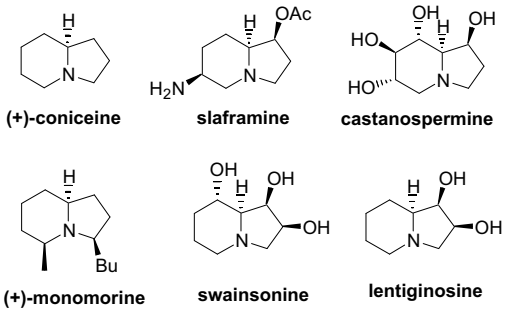
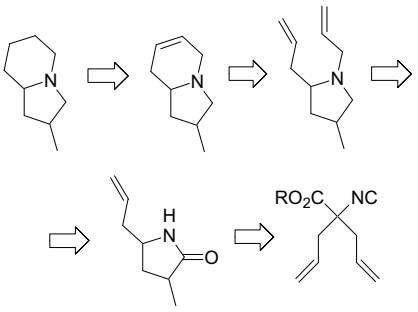
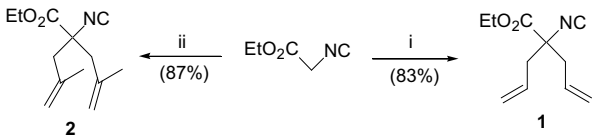


Figure. 1. Some examples of indolizidine alkaloids.



Scheme 1. Retrosynthetic strategy to access indolizidines.



Scheme 2. Synthesis of bis-alkenyl isocyanides. Reagents and conditions: (i) allyl bromide (2.5 equiv), K_2CO_3, TBAB, MeCN, reflux 20 h; (ii) methallyl bromide (2.5 equiv), K_2CO_3, TBAB, MeCN, reflux 20 h.

Two alkenyl isocyanides were synthesised using phase transfer conditions (K_2CO_3/TBAB), according to Scheme 2.

Ethylisocyanoacetate was alkylated with allyl bromide and methallyl bromide to give the corresponding dialkylated isocyanides **1** and **2** in high yields. 2-Mercaptoethanol mediated radical cyclisation of these two substrates, under microwave irradiation, gave the expected pyroglutamates **3**[14] (as a 1.6:1 cis/trans diastereomeric mixture), and 4, in good yields (Scheme 3).

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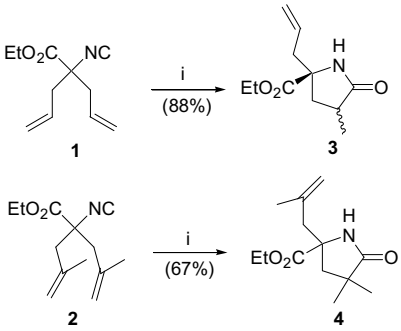
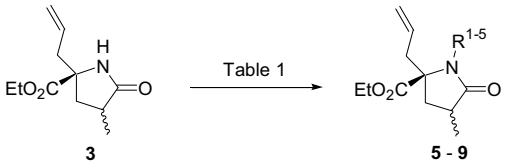
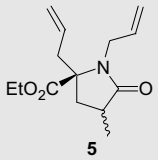
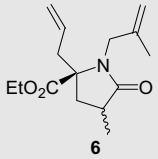
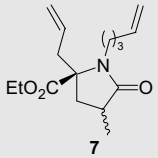
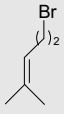
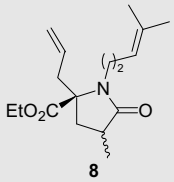
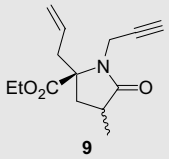


Scheme 3. Microwave assisted radical cyclisation of dialkylated isocyanides **1** and **2**. Reagents and conditions: (i) 2-mercaptoethanol (3.0 equiv), AIBN (0.2 equiv) in toluene, μω 130 °C 2 × 5 min.

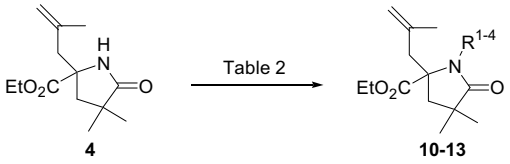


Scheme 4. N-alkylation of pyroglutamate **3**.

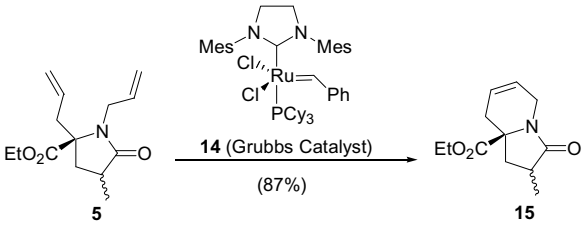
Table 1
Reagents and conditions for N-alkylation of alkenyl pyroglutamate **3**

Entry	R–X	Conditions[a]	Product	Yield[b] (%)	Cis/trans[c]
1a		A	 **5**	67	2:1
1b		B		19	2:1
2		A	 **6**	95	2:1
3		A	 **7**	38	1.3:1
4		A	 **8**	15	1.8:1
5a		A	 **9**	82	1.6:1
5b		C		100	1.7:1

[a] Conditions: method A: R–X (1.5 equiv), BEMP (1.5 equiv), MeCN, 12 h at 80 °C; method B: R–X (1.5 equiv), BEMP (2.0 equiv), MeCN, μω10 min at 110 °C; method C: R–X (1.5 equiv), BTPP (1.5 equiv), MeCN, 12 h at 80 °C.
[b] Isolated yield after column chromatography.
[c] Calculated by ^{1}H and ^{13}C NMR.



Scheme 5. N-alkylation of pyroglutamate **4**.



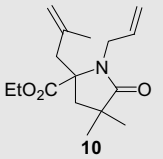
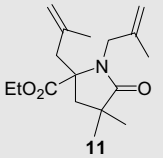
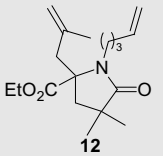
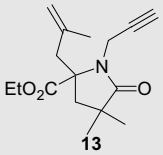
Scheme 6. Reagents and conditions: **14** (10 mol %), DCM, 2 h at rt.

Pyroglutamate **3** was then N-alkylated with various alkenyl bromides and propargyl bromide to give the corresponding N-alkylated pyroglutamates **5**–**9** (Scheme 4 and Table 1).

Although NaH or NaOH, under phase transfer conditions, are the bases employed for N-alkylation of either proline or pyroglutamates in the literature,[20] our previous experience in the use of iminophosphorane bases prompted an investigation into their use. Alkylation of pyroglutamate **3** was successfully achieved using BEMP[21] (Table 1, entries 1a–5a). N-alkylated pyroglutamates were obtained in good yields, except in one case (Table 1, entry 4) where competing elimination was a problem.

Microwave irradiation was also used, in an attempt to reduce reaction times and to increase yields, but it proved to be ineffective

Table 2
N-Alkylation of alkenyl pyroglutamate **4**

Entry	R–X	Conditions[a]	Product	Yield[b] (%)
1		A	 **10**	85
2		A	 **11**	79
3		A	 **12**	76
4		A	 **13**	99

[a] Conditions: method A: R–X (1.5 equiv), BTPP (1.5 equiv), MeCN, 12 h at 80 °C.
[b] Isolated yield after column chromatography.

(Table 1, entry 1b). Use of a stronger iminophosphorane base (BTPP)[21] gave instead better results (Table 1, entry 5b), in terms of better yields, and was used for the next alkylations.

Pyroglutamate **4** was then N-alkylated, under BTPP conditions (Scheme 5 and Table 2). The expected N-alkylated products **10–13** were obtained in good yields.

The N-alkylated pyroglutamates **5–13** were then used to test the ring closing metathesis to access indolizidines.[20]

Pyroglutamate **5** was reacted with 10 mol % of second generation Grubbs catalyst (**14**) in DCM at room temperature (Scheme 6). The reaction was complete in 2 h and the expected indolizidine **15** was obtained in good 87% yield (cis/trans ratio 1.6:1).[22]

It was also possible to separate the two diastereoisomers by column chromatography. The ring closing metathesis of pyroglutamates **6–9** was then performed using a catalytic amount of **14** (Table 3).

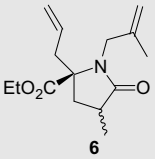
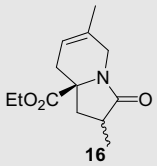
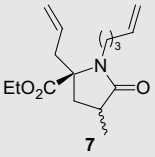
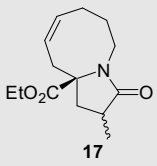
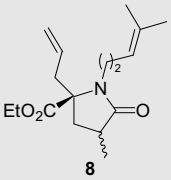
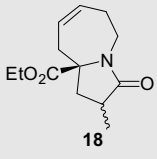
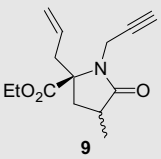
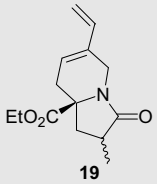
Excellent results were obtained, the expected bicyclic lactams **16–18** were isolated in 99%, 89% and 81% yields respectively. The reactions were completed in 2 h, using 10 mol % of catalyst **14**. Ring closing enyne metathesis of **9** afforded indolizidine **19** in good 72% yield, even though slightly contaminated by the styrene addition byproduct (2% by NMR). In order to avoid this problem the amount of catalyst used was reduced (5 mol %) but it was still not possible to obtain completely pure products.

Ring closing metathesis of more hindered substrates (**10–12**) was also studied, the results obtained are shown in Table 4.

Pyroglutamates **12** and **14** gave the corresponding cyclised products in excellent yields (Table 4, entries 1 and 3), but long reaction times had to be employed. Cyclisation of **13** was unsuccessful, even after 4 days and use of 20 mol % of Grubbs catalyst only starting material could be recovered (Table 4, entry 2a). However. when the substrate was reacted with 10 mol % catalyst under microwave irradiation (Table 4, entry 2b), the expected indolizidine **21** was obtained in excellent 97% yield.

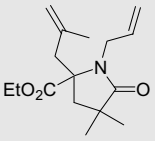
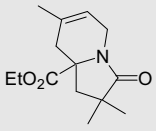
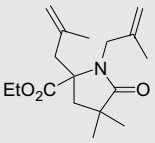
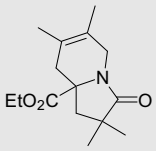
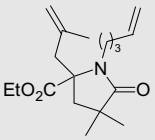
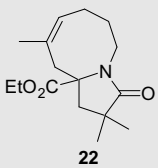
In conclusion, we have demonstrated that simple isocyanides could be used as starting building blocks for the synthesis of functionalised indolizidines, via a radical cyclisation/N-alkylation/ring closing metathesis strategy, in good overall yields.

Table 3
Ring closing metathesis of pyroglutamates **6–9**

Entry	Substrate	Cond.[a]	Product	Yield[b] (%)	Cis/trans[c]
1	 **6**	A	 **16**	99	2.5:1
2	 **7**	A	 **17**	89	1.1:1
3	 **8**	A	 **18**	81	1.8:1
4	 **9**	B	 **19**	72	1:1

[a] Method A: **14** (10 mol %), DCM, 2 h at rt; method B: **14** (14 mol %), DCM, 48 h at rt or μω 30 min at 100 °C; method C: **14** (8–14 mol %), DCM, 12–48 h at rt.
[b] Isolated yield after column chromatography.
[c] Calculated by ^{1}H and ^{13}C NMR.

Table 4
RCM of pyroglutamates **10–12**

Entry	Substrate	Cond.[a]	Product	Yield[b] (%)
1	 **12**	A	 **20**	98
2a	 **13**	B	 **21**	0
2b		C		97
3	 **14**	D	 **22**	86

[a] Method A: **14** (10 mol %), DCM, 6 h at rt; method B: **14** (20 mol %), DCM, 4d at rt; method C: **14** (10 mol %), DCM, μω 30 min at 100 °C; method D: **14** (10 mol %), DCM, 20 h at rt.
[b] Isolated yield after column chromatography.

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21. Schwesinger, R.; Willaredt, J.; Schlemper, H.; Keller, M.; Schmitt, D.; Fritz, H. *Chem. Ber.* **1994**, *127*, 2435.
22. *Selected data for compound* **1** δ_H (300 MHz; $CDCl_3$): 1.3 (3H, t, J = 7.0 Hz, CH_3CH_2O), 2.5–2.7 (4H, m, 2 × CCH_2), 4.23 (2H, q, J = 7.0 Hz, CH_2O), 5.2–5.3 (4H, m, 2 × CH=CH_2), 5.7–5.9 (2H, m, 2 × CH=CH_2); δ_C (75 MHz; $CDCl_3$): 14.3, 42.7, 56.3, 62.8, 121.2, 130.0, 159.6, 167.9; GC/MS (C.I.). m/z, relative intensity and ion. 211 (12%), $[M+NH_4]^+$; 194 (100%), $[M+H]^+$; 168 (38%), $[(M-NC)+H]^+$; 152 (8%), $[(M-allyl)+H]^+$; HRMS (EI): m/z calculated for $C_{11}H_{16}NO_2$ $[M+H]^+$ 194.11810, found 194.11811; *I.R.* (neat) ν_{max} = 2138, 1746 (cm^{-1}). Compound **3**

(1.6:1 inseparable mixture of diastereoisomers).[18] Cis diastereoisomer: δ_H (300 MHz; $CDCl_3$): 1.13 (3H, d, J = 7.0 Hz, CH_3CH), 1.23 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.68 (1H, dd, J = 13.0, 10.5 Hz, NCC*H*H), 2.32–2.42 (1H, m, C*H*HCH=CH_2), 2.47–2.54 (2H, m, CH*H*CH=CH_2 and CH_3CH), 2.71 (1H, dd, J = 13.0, 8.0 Hz, NCCH*H*), 4.1 (2H, q, J = 7.0 Hz, CH_2O), 5.07–5.15 (2H, m, CH=CH_2), 5.5–5.72 (1H, m, CH=CH_2), 6.59 (1H, br s, NH); δ_C (75 MHz; $CDCl_3$): 14.5, 16.1, 35.8, 38.8, 43.8, 62.0, 63.4, 120.6, 131.4, 173.5, 179.2; Trans diastereoisomer: δ_H (300 MHz; $CDCl_3$): 1.13 (3H, d, J = 7.0 Hz, CH_3CH), 1.24 (3H, t, J = 7.0 Hz, CH_3CH_2O), 2.05 (1H, dd, J = 13.5, 8.5 Hz, NCC*H*H), 2.32–2.42 (1H, m, C*H*HCH=CH_2), 2.38 (1H, dd, J = 13.0, 9.0 Hz, NCCH*H*), 2.47–2.54 (1H, m, CH*H*CH=CH_2), 2.60 (1H, m, CH_3CH); 4.17 (2H, q, J = 7.0 Hz, CH_2O), 5.07–5.15 (2H, m, CH=CH_2), 5.5–5.72 (1H, m, CH=CH_2), 6.64 (1H, br s, NH); δ_C (75 MHz; $CDCl_3$): 14.5, 16.5, 35.9, 39.7, 43.8, 62.1, 63.6, 120.8, 131.6, 173.6, 179.8; ES^+/MS: m/z 212 (100%), $[M+H]^+$; m/z 234 (43%), $[M+Na]^+$; m/z 1.423 (55%), $[2M+H]^+$; m/z 445 (65%), $[2M+Na]^+$; HRMS (ES^+): m/z calculated for $C_{11}H_{17}NO_3$ $[M+H]^+$ 212.1281, found 212.1279. *I.R.* (neat) ν_{max} = 1700, 1460 (cm^{-1}); mp = 45–47 °C. Elemental analysis: found C, 62.26; H, 8.15; N, 6.58: $C_{11}H_{17}NO_3$ requires C, 62.54; H, 8.11; N, 6.63. Compound **5** cis diastereoisomer: δ_H (400 MHz; $CDCl_3$): 1.18 (3H, d, J = 7.0 Hz, CH_3CH), 1.25 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.62 (1H, dd, J = 13.0, 10.5 Hz, CH_3CHCHH), 2.38 (1H, dd, J = 13.0, 9.0 Hz, CH_3CHCHH), 2.48–2.65 (2H, m, CCH_2CH=CH_2), 2.72 (1H, m, CH_3CH), 3.79–4.0 (2H, m, NCH_2CH=CH_2), 4.14 (2H, q, J = 7.0 Hz, CH_2O), 5.08–5.21 (4H, m, NCH_2CH=CH_2 and CCH_2CH=CH_2), 5.58–5.69 (2H, m, CCH_2CH=CH_2), 5.72–5.86 (1H, m, NCH_2CH=CH_2); δ_c (100 MHz; $CDCl_3$): 14.4, 16.6, 35.2, 36.4, 39.3, 44.3, 61.9, 66.7, 117.6, 120.6, 131.8, 133.8, 173.4, 178.2; *C.I.* GC/MS. m/z, relative intensity and ion. 252 (100%), $[M+H]^+$; retention time: 11.71 min; trans diastereoisomer: δ_H (300 MHz; $CDCl_3$): 1.21 (3H, d, J = 7.0 Hz, CH_3CH), 1.27 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.92 (1H, dd, J = 7.5, 13.5 Hz, CH_3CHCHH), 2.31 (1H, dd, J = 13.5, 10.0 Hz, CH_3CHCHH), 2.5–2.65 (3H, m, CCH_2CH=CH_2 and CH_3CH), 3.79–4.0 (2H, m, NCH_2CH=CH_2), 4.13 (2H, q, J = 7.0 Hz, CH_2O), 5.08–5.21 (4H, m, NCH_2CH=CH_2 and CCH_2CH=CH_2), 5.58–5.69 (2H, m, CCH_2CH=CH_2), 5.72–5.86 (1H, m, NCH_2CH=CH_2); δ_c (100 MHz; $CDCl_3$): 14.4, 17.5, 35.3, 37.5, 39.6, 44.7, 62.0, 67.5, 117.8, 120.7, 131.8, 133.9, 173.5, 178.5; C.I. GC/MS. m/z, relative intensity and ion. 252 (100%), $[M+H]^+$; retention time: 11.58 min; HRMS (ES^+): m/z calculated for $C_{14}H_{21}NO_3Na$ $[M+Na]^+$ 274.1413, found 274.1413; *I.R.* (neat) ν_{max} = 1731, 1693, 1451, 1391, 1254, 1192, 1144 (cm^{-1}). Compound **15** cis diastereoisomer: δ_H (400 MHz; $CDCl_3$): 1.19 (3H, d, J = 7.0 Hz, CH_3CH), 1.21 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.61 (1H, dd, J = 13.0, 10.0 Hz, CH_3CHCHH), 2.09–2.16 (1H, m, NCH_2CH=$CHCHH$), 2.45–2.55 (1H, m, CH_3CH), 2.62 (1H, dd, J = 13.0, 8.5 Hz, CH_3CHCHH), 2.97–3.03 (1H, m, NCH_2CH=$CHCHH$), 3.64–3.70 (1H, m, NCH*H*C=$CHCH_2$), 4.08–4.19 (1H, m, NC*H*HCH=$CHCH_2$), 4.15 (2H, q, J = 7.0 Hz, CH_2O), 5.67–5.74 (2H, m, NCH_2CH=CH); δ_c (100 MHz; $CDCl_3$): 14.5, 16.5, 35.4, 35.7, 40.4, 41.3, 62.0, 62.8, 123.0, 123.7, 173.6, 177.3; C.I. GC/MS. m/z, relative intensity and ion. 224 (100%), $[M+H]^+$; retention time: 11.91 min; HRMS (EI): m/z calculated for $C_{12}H_{17}NO_3$ $(M)^+$ 223.12084, found 223.12073. I.R. (neat) ν_{max} = 1729, 1690, 1596, 1453, 1416, 1305, 1269, 1201 (cm^{-1}). Trans diastereoisomer: δ_H (400 MHz; $CDCl_3$): 1.22 (3H, d, J = 7.0 Hz, CH_3CH), 1.24 (3H, t, J = 7.0 Hz, CH_3CH_2O), 1.89 (1H, dd, J = 13.5, 6.5 Hz, CH_3CHCHH), 2.14–2.21 (1H, m, NCH_2CH=$CHCHH$), 2.29 (1H, dd, J = 13.0, 9.5 Hz, CH_3CHCHH), 2.51 (1H, m, CH_3CH), 2.83–2.89 (1H, m, NCH_2CH=$CHCHH$), 3.68–3.74 (1H, m, NCH*H*CH=$CHCH_2$), 4.18 (2H, q, J = 7.0 Hz, CH_2O), 4.27–4.33 (1H, m, NC*H*HCH=$CHCH_2$), 5.65–5.74 (2H, m, NCH_2CH=$CHCH_2$); δ_c (100 MHz; $CDCl_3$): 14.4, 17.3, 34.2, 35.6, 39.0, 40.4, 62.0, 63.1, 123.4, 124.5, 173.9, 176.8; C.I. GC/MS. m/z, relative intensity and ion. 224 (100%), $[M+H]^+$; retention time: 12.07 min; HRMS (ES^+): m/z calculated for $C_{12}H_{17}NO_3Na$ $[M+Na]^+$ 246.1100, found 246.1099; I.R. (neat) ν_{max} = 1731, 1690, 1409, 1304, 1267, 1194,1141, 1026 (cm^{-1}).