The Intramolecular Heck Reaction and the Synthesis of Indolizidinone, Quinolizidinone and Benzoazepinone Derivatives

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Received 26 January 2001; revised 15 June 2001

Abstract: The intramolecular Heck cyclization of N-allyl-, -aryl- or -benzyl-5-allyl-2-pyrrolidinones and N-allyl-, -aryl- or -benzyl-6-allyl-2-piperidinones (1a–f), prepared through allyltrimethylsilane addition to the corresponding cyclic N-acyliminium ions, afforded indolizidinones (3a, 5a, 5b), quinolizidinones (3b, 4b) and benzoazepinones (7a, 8a, 7b, 8b) in moderate to good yields (56–90%). Exclusive exo-trig over endo-trig mode of cyclization was observed in all examples investigated, and it was accompanied by double bond migration, which precluded our attempts of a one-pot tandem Diels–Alder cycloaddition with dienophiles such as maleic anhydride, methyl vinyl ketone and diethyl azodicarboxylate. Catalytic hydrogenation of a 2:1 mixture of regioisomeric indolizidinones 5a–5b afforded the stereoisomerically enriched cis indolizidinone 6a (20:1 mixture) in quantitative yield. A similar behavior was observed in the catalytic hydrogenation of regioisomeric benzoazepinones 7b–8b.

Key words: Heck reaction, intramolecular cyclization, hydrogenation

Over the last decade palladium-catalyzed reactions have emerged as extremely versatile methods for the synthesis of highly complex carbo- and heterocyclic systems.1 The coupling of vinyl or aryl halides, triflates or similar intermediates with alkenes under palladium(0) catalysis is known as the Heck reaction and both its inter- and intramolecular versions are powerful tools in organic synthesis due to their chemo- and regioselectivity, mild reaction conditions and efficiency.2 In particular, the Heck reaction has proved its synthetic value when incorporated in a tandem process, which allows the regio- and stereocontrolled formation of several bonds and/or ring systems in a single synthetic operation.3 An interesting sequence for the construction of bicyclic systems containing at least one six membered ring arises when an intramolecular Heck reaction or palladium-catalyzed enyne cyclomonomerization, which gives a vicinal exo-bis substituted cycloalkane is immediately followed by a Diels–Alder reaction.4

The intramolecular Heck coupling of bromodialkenyl amines, lactams and ethers has been reported5 and recently de Meijere6 and coworkers described the formation of substituted tetrahydroisoindolines, tetrahydroisoindolin-1-ones and hexahydrobenzo[c]furans through the intramolecular 5-exo cyclization of 2-bromo-4-aza- and 2-bromo-4-oxa-1,6-dienes, followed by in situ [4+2] cycloaddition.

As part of our current interest in the synthesis of pyrrolizidine and indolizidine alkaloids,7 we were attracted to study the regiochemistry of the intramolecular Heck reaction when applied to 2-allyl lactams derived from 2-pyrrolidinone and 2-piperidinone. These compounds feature a 2-bromo-4-aza-1,7-diene moiety amenable to undergo either a 6-exo-trig or a 7-endo-trig cyclization. Additionally, the intramolecular 7-exo-trig vs. 8-endo-trig Heck reaction of N-(o-halobenzyl)-2-allyllactams was envisioned as a short approach to benzoazepine derivatives. Lactams 1a–f were prepared in good yields from the corresponding imides according to literature procedure8 after LiBEt₃H reduction to the corresponding ethoxylactams, followed by BF₃·OEt₂ promoted addition of allyltrimethylsilane. Our first choice of reaction conditions for the intramolecular Heck reaction with 1a included the use of 5 mol% palladium acetate as catalyst, (which is assumed to be reduced in situ to palladium(0) species by the solvent, amine or the added ligand)⁹ degassed DMF as solvent,

Scheme 1

ISSN 0039-7881
triphenylphosphine (10 mol%) and potassium carbonate (10 equiv) or triethylamine (1.2 equiv) as base. Under these conditions, a smooth reaction ensued upon heating at 115 °C under an inert atmosphere and indolizidinone 3a was isolated in 56% yield after column chromatography. The same results were observed when tri-o-tolyolphosphine or DIPHOS were employed whereas attempts to carry out the cyclization in acetonitrile were unsuccessful (Table).

The reaction product was characterized by the absence of the stretching of the C–Br at 920 cm⁻¹ in the IR spectrum and by significant changes in the δ 3.50–5.70 region of its ¹H NMR spectrum as compared to the same region for 1a: H–8a appeared at δ 4.26 as a broad triplet (J = 6.0 Hz), the olefinic protons of the exocyclic methylene as doublets (J = 1.5 Hz) at δ 4.99 and 5.09 and the endocyclic hydrogen H–8 as a singlet at δ 5.63. The presence of a methyl group at δ 1.86 as a singlet and of the two methylene hydrogens at C–5 as doublets (J = 15.4 Hz) at δ 3.57 and 4.70 were diagnostic for the assignment of structure 3a to the isolated indolizidinone (HRMS m/z: [M⁺] calcd for C₁₀H₁₃NO, 163.0997; found, 163.0994). The downfield shift observed for one of the hydrogens at C-5 (Δδ 1.13) was assigned to the anisotropic shift of the carboxyl group as inspection of molecular models and geometry optimization by ab initio method (HF/6-31g(d)) revealed the coplanar orientation of one of the hydrogens at C-5 and the carbonyl group. ¹¹

The isolation of 3a as the sole product was rationalized as involving the initial formation of the exo-bismethylene 2a followed by prototropic shift promoted either thermally or through a sequence of β-hydride elimination, re-addition of a hydridopalladium species and elimination as observed in the arylation of allylic alcohols. ¹²

In our case, changing the base from triethylamine to potassium carbonate did not avoid prototropic shift. Attempts to carry out the reaction at lower temperatures using the conditions described by Jeffery (tetrabutyl ammonium chloride as phase-transfer catalyst and potassium carbonate as base) were unsuccessful and the intramolecular coupling with this catalytic system was only observed above 100 °C with exclusive formation of 3a in 52% yield.

A final attempt to preclude double bond migration during cyclization of 1a involved the use of silver carbonate as a halide scavenger but no reaction was observed in the presence of either triphenylphosphine or DIPHOS even after 7 d at 115 °C. The lack of reactivity with these catalytic systems contrasts with the results by de Meijere and coworkers for the 5-exo-trig cyclization of 2-bromo-4-aza-1,6-dienes and was rationalized through the intervention of a stable cationic palladium intermediate (Figure).

An analogous reactivity pattern emerged for 2-allylactam 1b. No cyclization was observed when silver carbonate was employed but a 5:1–6:4:1 diastereomeric mixture of quinolizidinones 3b–4b was formed when potassium carbonate or triethylamine was used as the base (Table). This mixture is readily separable by silica gel column chromatography. The ¹H NMR spectrum of the major regiosomer 3b closely resembled that of 3a with the major differences being the downfield shift of H-6 (δ 5.22 and 3.28) and an upfield shift of H-9a (δ 4.04) that appeared as a broad doublet (J = 5.0 Hz). The structural assignment of 4b emerged from its ¹H NMR spectrum, which

Table Intramolecular Heck Reaction of 1a and 1b (Scheme 1)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Method</th>
<th>Ratio (3:4)</th>
<th>Yield (%)</th>
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<td>1a</td>
<td>A, B, E</td>
<td>1:0</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>C, I, L</td>
<td>–</td>
<td>–</td>
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<td>3</td>
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<td>1:0</td>
<td>56</td>
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<td>4</td>
<td>1a</td>
<td>F, J</td>
<td>1:0</td>
<td>52</td>
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<td>1a</td>
<td>G, K</td>
<td>1:0</td>
<td>50</td>
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<td>H</td>
<td>1:0</td>
<td>53</td>
</tr>
<tr>
<td>7</td>
<td>1a</td>
<td>I</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>1b</td>
<td>A</td>
<td>5:2:1</td>
<td>74</td>
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<td>9</td>
<td>1b</td>
<td>B</td>
<td>6:1:1</td>
<td>70</td>
</tr>
<tr>
<td>10</td>
<td>1b</td>
<td>C, I, L</td>
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<td>–</td>
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<tr>
<td>12</td>
<td>1b</td>
<td>E</td>
<td>6:4:1</td>
<td>52</td>
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<td>F</td>
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<td>1b</td>
<td>G</td>
<td>5:8:1</td>
<td>68</td>
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<tr>
<td>15</td>
<td>1b</td>
<td>H, J, K</td>
<td>5:1</td>
<td>48</td>
</tr>
</tbody>
</table>

* Reaction temperature: 115 °C; reaction time: 12 h.
* Quantitative substrate recovery.
* Isolated yield after column chromatography; Conditions: (A): 0.02 equiv Pd(OAc)₂, 0.04 equiv PPh₃, 10 equiv K₂CO₃, DMF (B): 0.02 equiv Pd(OAc)₂, 0.04 equiv PPh₃, 1.2 equiv Et₃N, DMF (C): 0.02 equiv Pd(OAc)₂, 0.04 equiv PPh₃, 2.0 equiv Ag₂CO₃, DMF (D): 0.02 equiv Pd(OAc)₂, 0.04 equiv P(ο-tol)₃, 10 equiv K₂CO₃, DMF (E): 0.02 equiv Pd(OAc)₂, 0.04 equiv P(ο-tol)₃, 1.2 equiv Et₃N, DMF (F): 0.02 equiv Pd(OAc)₂, 0.04 equiv PPh₃, 10 equiv K₂CO₃, 1.2 equiv Bu₄NCl, DMF (G): 0.02 equiv Pd(OAc)₂, 0.04 equiv PPh₃, 1.2 equiv Et₃N, 1.2 equiv Bu₄NCl, DMF (H): 0.02 equiv Pd(OAc)₂, 0.04 equiv DIPHOS, 10 equiv K₂CO₃, DMF (I): 0.02 equiv Pd(OAc)₂, 0.04 equiv DIPHOS, 2.0 equiv Ag₂CO₃, DMF (J): 0.02 equiv Pd(PPh₃)₂, 0.04 equiv PPh₃, 10 equiv K₂CO₃, DMF (K): 0.02 equiv Pd(PPh₃)₂, 0.04 equiv PPh₃, 1.2 equiv Et₃N, DMF (L): 0.02 equiv Pd(PPh₃)₂, 0.04 equiv PPh₃, 2.0 equiv Ag₂CO₃, DMF.

Figure
featured the strongly deshielded H-6 as a singlet at δ 7.21 and H-9a as a multiplet at δ 3.54. The formation of regioisomers 3b and 4b was not thermally promoted as no interconversion was observed even under extended heating (Condition A, Table: 5 d at 115 ºC).

Despite the elusive nature of the exo bisimethylene intermediates 2a and 2b, we attempted their in situ [4+2] cycloaddition with several dienophiles, such as maleic anhydride, methyl vinyl ketone and diethyl azodicarboxylate under conditions A and B, described in Table. In each case, only indolizidinone 3a (from 2a) and quinolizidinones 3b and 4b (from 2b) were formed.

When double bond isomerization to the C7-C8 position was blocked, intramolecular cyclization of 1e (condition A, Table) afforded exo bisimethylene indolizidinone 2c in 65% yield characterized by the presence of four terminal olefinic hydrogens (δ 5.06, 4.90 and 4.84) in 1H NMR spectrum and two CH2 in the olefinic region (δ 112.3 and 108.5) in 13C NMR spectrum. Interestingly, double bond migration to the C5-C6 position was not observed but attempts to trap 2c in situ with maleic anhydride failed.

An additional example for the preference of 6-exo-trig vs. 7-endo-trig with double bond migration emerged from the intramolecular cyclization of lactam 1d, readily prepared from succinic anhydride after 3 steps. Under condition A, depicted in the Table, a 2:1 molar ratio of indolizidinones 5a and 5b (74% combined yield) were isolated, however they were inseparable by flash chromatography (Scheme 2).

Fortunately, hydrogenation of a 2:1 mixture of regioisomers 5a and 5b in methanol and palladium over carbon as catalyst afforded a 20:1 mixture of stereoisomeric indolizidinones 6a and 6b in quantitative yield (Scheme 2). The cis relationship of the hydrogens at C-5 and C-6a in the major isomer 6a was corroborated by NOE increments observed at H-6a (2.3%) upon irradiation at H-5 and at H-5 (3.4%) upon irradiation at H-6a. No increment in the intensity of the methyl absorption was observed upon irradiation of H-6a. The reason for the high diastereoisomeric ratio, which accompanied hydrogenation of the mixture of regioisomers 5a–5b has not been fully explored but it may be associated with double bond migration from exocyclic to the endocyclic position before reduction.

The study on regioselectivity of the intramolecular Heck reactions was next extended to lactams 1e and 1f, which could conceivably undergo a 7-exo-trig or a 8-endo-trig cyclization. In fact, only products arising from 7-exo-trig cyclization were isolated from 1e (6.5:1 mixture of benzoazepines 7a and 8a, in 80% combined yield) and from 1f (2:1 mixture of 7b and 8b, in 90% combined yield) when condition A was employed (Table, Scheme 3).

The structure of the major isomer formed from 1e was unambiguously established by NMR spectroscopy: the presence of two olefinic hydrogens as doublets (J = 1.5 Hz) at δ 5.25 and δ 5.20 together with the absence of a methyl signal in the 1H NMR spectrum and an olefinic methylene at δ 117.1 in the corresponding 13C NMR spectrum fully agree with 7a as the major benzoazepine.

As before, the mixtures of regioisomers obtained from 1e and 1f were inseparable by flash chromatography on silica gel and benzoazepines 7a–8a and 7b–8b were hydrogenated under the conditions described previously for 5a–5b. In both cases, the cis isomer was obtained preferentially with some erosion of diastereoselectivity observed for 7a–8a (4.5:1 molar ratio of 9a–10a, in 94% yield) while a significant increment in the cis–trans ratio was observed in the hydrogenation of an equimolar mixture of 7b–8b (6.5:1 mixture of 9b–10b, in 98% yield).

The cis configuration of 9a was assigned after NOE experiments with an analytically pure sample obtained after flash chromatography on silica gel: a 3.2% increment in the H-11a signal was observed upon irradiation of H-10 while a 2.6% enhancement in the H-10 signal was observed upon irradiation of H-11a. Only 0.8% increment was observed in the methyl doublet signal when H-11a was irradiated. Even stronger increments were observed when 9b was submitted to NOE studies: irradiation of H-11 led to a 8.4% enhancement of H-12a signal while 4.7% increment of H-11 signal was observed upon irradiation of H-12a.

Allyltrimethylsilane addition to N-acyliminium ions derived from succinimide and glutarimide provided an expedient access to 5-allyl lactams 1a–f in moderate to good yields. The intramolecular Heck cyclization of lactam 1a was extensively investigated and indolizidinone 3a was formed exclusively in moderate yields (50–56%) through a 6-exo-trig pathway. Lactam 1a was recovered when Ag2CO3 was employed as base.

An analogous reactivity pattern was observed in the cyclization of 1b and mixtures (5:1, 6:4:1) of indolizidinones 3b and 4b were isolated in moderate to good yields (48–74%). An additional example of the preference for a

Scheme 2 a) 0.02 equiv Pd (OAc)2, 0.04 equiv PPh3, 10 equiv K2CO3, DMF, 115 ºC (5a:5b, 2:1, 74%); b) H2, Pd/C, MeOH, r.t. (100%).

Synthesis 2002, No. 1, 87–93 ISSN 0039-7881 © Thieme Stuttgart · New York
6-exo-trig vs. 7-endo-trig process came from the intramolecular cyclization of lactam 1d, which provided a 2:1 mixture of indolizidinones 5a and 5b (74% yield). Surprisingly, catalytic hydrogenation stereoselectively converted the above mixture to cis-6a (20:1 ratio) in quantitative yield.

Despite the propensity for double bond migration of the putative exo bisimylene intermediates 2a and 2b, attempts to carry out a one-pot tandem [4+2] cycladdition with maleic anhydride, methylvinylketone and diethyl azodicarboxylate were unsuccessful. When double bond migration was precluded in lactam 1c, the corresponding exo–bisimylene intermediate was isolated in 65% yield. Finally, exclusive 7-exo-trig cyclization was observed for lactams 1e and 1f and benzoazepines 7a–8a (4:5:1 ratio) and 7b–8b (6:5:1 ratio) were formed in good yields. The results described here provide an attractive route to indolizidinones, quinolinizidiones and benzodiazepinones and the utilization of this approach in the total synthesis of alkaloids will be investigated.

**Scheme 3**

6-exo-trig vs. 7-endo-trig process came from the intramolecular cyclization of lactam 1d, which provided a 2:1 mixture of indolizidinones 5a and 5b (74% yield). Surprisingly, catalytic hydrogenation stereoselectively converted the above mixture to cis-6a (20:1 ratio) in quantitative yield.

Despite the propensity for double bond migration of the putative exo bisimylene intermediates 2a and 2b, attempts to carry out a one-pot tandem [4+2] cycladdition with maleic anhydride, methylvinylketone and diethyl azodicarboxylate were unsuccessful. When double bond migration was precluded in lactam 1c, the corresponding exo–bisimylene intermediate was isolated in 65% yield. Finally, exclusive 7-exo-trig cyclization was observed for lactams 1e and 1f and benzoazepines 7a–8a (4:5:1 ratio) and 7b–8b (6:5:1 ratio) were formed in good yields. The results described here provide an attractive route to indolizidinones, quinolinizidiones and benzodiazepinones and the utilization of this approach in the total synthesis of alkaloids will be investigated.

1H and 13C NMR spectra were recorded at 300.1 MHz and 75.4 MHz, respectively, on a Varian Gemini 2000 instrument using CDCl3 as solvent and tetramethylsilane as the internal standard, unless otherwise noted. Chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz. Signal multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), double doublet (dd), double triplet (dt), q (quartet), dq (double quartet), m (multiplet), quint (quintet). Infrared spectra were recorded as film on KBr cells on a Nicolet Impact 410 FT-IR instrument and the wavenumbers are expressed in cm⁻¹. Melting points were measured with an Electrothermal A29900 MK3 apparatus and are uncorrected. GC analyses were recorded on Hewlett-Packard 5890 instrument, and GC-MS analyses were recorded on Hewlett-Packard 5890 coupled to HP-5988. HRMS analyses were recorded on Micromass VGAutoSpec instrument. Column chromatography was performed with silica gel (70–230 Mesh).

### N-2-Bromopropenyl-5-allylpyrrolidin-2-one (1a)

To a solution of N-2-bromopropenyl-5-ethoxy-2-pyrrolidin-2-one (0.412 g, 1.14 mmol) in CH2Cl2 (5.70 mL) at 0 °C was added allyltrimethylsilane (0.262 g, 2.29 mmol). To the resulting solution was added BF3·OEt2 (0.486 g, 0.421 mL, 3.42 mmol). The mixture was stirred at 0 °C for 12 h and quenched by the addition of 1% NaHCO3 solution (5.7 mL). The layers were separated and the aqueous layer was extracted with CH2Cl2 (3 × 5.7 mL). The combined organic layers was dried (MgSO4), filtered and concentrated under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 1:1) to afford 1a in 9% yield as a colorless oil.

IR (KBr): 2973, 2979, 2915, 1700, 1646, 1631, 1443, 1428 and 922 cm⁻¹.  

1H NMR (CDCl3): δ 1.78–1.80 (m, 1 H, CH2CH2CO), 1.80–1.96 (m, 3 H, CH2CH2CO and CH2CH2CO), 2.21–2.39 (m, 3 H, CH2CH2CO), 2.40–2.49 (m, 3 H, CH2CH2CO and CH2CH2CO), 3.46–3.55 (m, 1 H, CHN), 3.67 (d, J = 15.0, 1 H, CHN), 5.00 (d, J = 15.0, 1 H, CHN), 5.10–5.20 (m, 2 H, CH2CH2CH2CH2CO), 5.60–5.78 (m, 3 H, CH2CH2CO and CH2CH2CH2CO).  

HRMS (EI): m/z calcd for C17H18NOBr, 245.0239. Found: 245.0242.  

### N-2-Bromopropenyl-6-allylpiperidin-2-one (1b)

The same procedure as described above for 1a was employed starting from N-2-bromopropenyl-5-ethoxypiperidin-2-one. After evaporation under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 1:1) to afford 1b in 55% yield as a grey oil.

IR (KBr): 2982, 2959, 1650, 1445, 1426 and 922 cm⁻¹.  

1H NMR (CDCl3): δ 1.78–1.80 (m, 1 H, CH2CH2CO), 1.80–1.96 (m, 3 H, CH2CH2CO and CH2CH2CO), 2.21–2.39 (m, 3 H, CH2CH2CO), 2.40–2.49 (m, 3 H, CH2CH2CO and CH2CH2CO), 3.46–3.55 (m, 1 H, CHN), 3.67 (d, J = 15.0, 1 H, CHN), 5.00 (d, J = 15.0, 1 H, CHN), 5.10–5.20 (m, 2 H, CH2CH2CH2CH2CO), 5.60–5.78 (m, 3 H, CH2CH2CO and CH2CH2CH2CO).  

HRMS (CI: iso-butane): m/z calcd for C17H18NOBr, 257.0415. Found: 257.0395, 257.0420 and 259.0400.  

### N-2-Bromopropenyl-5-(1,1-dimethylallyl)pyrrolidin-2-one (1c)

The same procedure as described above for 1a was employed except (3.3–dimethylallyl)tributylstannane (2.0 equiv) was used instead of allyltrimethylsilane. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 1:1) to afford 1c in 40% yield as a grey oil.

IR (KBr): 2982, 2964, 2929, 2875, 1697, 1633, 1415 and 914 cm⁻¹.  

1H NMR (500 MHz, CDCl3): δ 1.01 (s, 3 H, CH3), 1.02 (s, 3 H, CH3), 1.94 (m, 1 H, CH2CH2CO), 2.03–2.10 (m, 1 H, CH2CH2CO), 2.33–2.43 (m, 2 H, CH2CH2CO), 3.10 (dd, J = 7.0 and 7.7, 3 H, CHN), 3.90 (d, J = 15.9, 1 H, CH2CH2CO), 4.78 (d, J = 15.9, 1 H, CHN), 5.06 (dd, J = 16.1 and 1.0, 1 H, CH2CH2CO), 5.10 (dd, J = 10.5, 1.0, 1 H, CH2CH2CO), 5.63 (dd, J = 3.5, 2.0, 1 H, CH2CH2CO), 5.73 (dd, J = 3.5, 2.0, 1 H, CH2CH2CO), 5.83 (dd, J = 17.6, 10.5, 1 H, CH2CH2CO).  

1C NMR (125 MHz, CDCl3): δ 21.8 (CH3), 22.0 (CH2CH2CO), 25.9 (CH3), 30.9 (CH2CH2CO), 42.7 (CH3), 51.2 (CH2CH2CO), 65.5 (CHN), 119.7 (CH2CH2CO), 119.0 (CH2CH2CO), 129.4 (CBr), 134.4 (CH2CH2CO), 171.2 (CO).
N-2-Iodomethyl-5-allylpyrrolidin-2-one (1d)
The same procedure as described above for 1a was employed starting from N-2-iodomethyl-5-ethoxyethoxypyrrolidin-2-one. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography (hexane/ EtOAc, 1:1) to afford 1d in 65% yield as a colorless oil.

IR (KBr): 2945, 2864, 1641, 1442 and 1412 cm⁻¹.

HRMS (EI): m/z calcd for C₁₁H₁₃NO: 177.1154. Found: 177.1152.

7-Methyl-6-methylene-1,2,3,5,6,8a-hexahydroindolizin-3-one (3a)
In a Pyrex flask was added a solution of 1a (0.412 g, 1.14 mmol) in DMF (16.0 mL), followed by Pd(OAc)₂ (0.0011 g, 0.0040 mmol) and K₂CO₃ (0.538 g, 3.90 mmol) under an Ar atmosphere. The mixture was kept at 110 °C for 12 h. Upon completion of the reaction, DMF was carefully evaporated under reduced pressure (0.2 mmHg, 40–50 °C), the residue was dissolved in EtOAc and filtered through a column of celite. Purification by column chromatography (hexane/ EtOAc, 1:1) afforded 3a (36.0 mg, 0.220 mmol) in 56% yield as a pale yellow oil.

IR (KBr): 2925, 2857, 1694, 1606, 1445 and 1423 cm⁻¹.

HRMS (EI): m/z calcd for C₁₂H₁₄NO: 183.0994. Found: 183.0997.

8-Methyl-7-methylene-1,3,4,6,7,9a-hexahydro-2H-indole-2,5-dione (4b)
The same procedure as described above for 3a was employed starting from 1b. Quinolinizidone 3b was obtained in 62% yield as a brown oil and 4b was obtained in 12% yield as a red oil after column chromatography (hexane/EtOAc, 1:1).

IR (KBr): 2945, 2864, 1641, 1442 and 1412 cm⁻¹.

The same procedure as described above for 3a was employed starting from 1a. Indolizidinone 2c was obtained in 67% yield as a yellow oil.

IR (KBr): 2968, 2875, 1689, 1458, 1421, 1284, 1255 and 1182 cm⁻¹.

1H NMR (CDCl₃): 0.84 (s, 3 H, CH₂), 1.11 (s, 3 H, CH₃), 1.81–1.86 (m, 1 H, CH₂CH₂CO), 2.01–2.08 (m, 1 H, CH₂CH₂CO), 2.38 (t, J = 7.2, 2 H, CH₂CO), 3.36 (dd, J = 8.4, 5.5, 1 H, CHN), 3.46 (d, J = 14.6, 1 H, CH₂N), 4.60 (d, J = 14.6, 1 H, CH₂N), 8.48 (s, br, 1 H, CH₂=CHCH₃), 4.90 (s, br, 1 H, CH₂=CHCH₃), 5.06 (s, br, 2 H, CH₂=CHCH₃).

C 31.4 (H Ar ), 173.4 (C=CH₂), 112.3 (CH₂=C), 141.8 (C=CH₃), 155.0 (C=CH₃), 174.0 (CO).

GC-MS: m/z (%) = 213 (78), 198 (5), 184 (5), 170 (8), 156 (4), 130 (100), 115 (54), 102 (4), 91 (7), 84 (28) and 77 (8).

HRMS (EI): m/z calculated for C₉H₈NO: 213.1154. Found: 213.1153.

8a (data from an enriched fraction of the mixture 7a–8a):

1H NMR (CDCl₃): δ = 1.77–1.84 (m, 1 H, CH₂CH₂CO), 2.18 (s, 3 H, CH₃), 2.20–2.34 (m, 1 H, CH₂CH₂CO), 2.35–2.43 (m, 2 H, CH₂CO), 3.81–3.87 (m, 1 H, CHN), 3.90 (d, J = 13.5, 1 H, CHN), 4.69 (d, J = 13.5, 1 H, CHN), 5.74 (d, J = 11.1, 1 H, CH₂=CHCH₃), 7.20–7.26 (m, 1 H, CH-Ar), 7.32–7.37 (m, 3 H, CH₂CH₃).

GC-MS: m/z (%) = 213 (23), 198 (100), 184 (4), 170 (6), 156 (9), 142 (6), 128 (12), 115 (14), 91 (6), 84 (3) and 77 (6).

10-Methyl-2,3,5,10,11,11a-hexahydro-1H-azololo[1,2-a]benzo[e]azepin-3-one (9a)

A 6:1:5 mixture of 7a–8a was dissolved in MeOH (5 mL) and stirred for 10 h under H₂ atmosphere (4 bar) at r.t. After evaporation under reduced pressure and column chromatography (hexane–EtOAc, 1:1), a 4:5:1 mixture of 9a–10a was obtained in 94% yield.

Data for the major isomer: white solid, mp 89–90 °C.

IR (KBr): 2962, 2922, 2875, 2852, 1682, 1489 and 760 cm⁻¹.

1H NMR (CDCl₃): δ = 1.44 (d, J = 7.1, 3 H, CH₃), 1.43–1.58 (m, 1 H, CH₂CH₂CO), 1.74 (m, 1 H, CH₂CH₂CO), 1.88 (dd, J = 14.5, 3.3, 1 H, CH₂=CHCO), 2.19–2.37 (m, 3 H, CH₂CH₂CO and CH₂CO), 3.20–3.29 (m, 1 H, CHN), 3.87–3.93 (m, 1 H, CH₂CH₃), 4.09 (d, J = 14.5, 1 H, CH₂CH₃), 4.97 (d, J = 14.3, 1 H, CH₂CH₃), 7.16–7.32 (m, 3 H, CH₂CH₃), 7.36 (m, 1 H, CH₂CH₃).

13C NMR (125 MHz, CDCl₃): δ 20.6 (CH₂CH₂CO), 29.7 (CH₂CH₂CO), 34.3 (CHCH₃), 44.4 (CHCH₃), 46.9 (CH₂CH₃), 62.1 (CH₂CH₂CO), 124.7 (CH₂CH₂CO), 126.5 (CH₂CO), 128.1 (CH₂CO), 129.9 (CH₂CO), 136.6 (CO), 145.4 (CO), 174.1 (CO).


11-Methyl-1,2,3,4,6,11,12,12a-octahydrobenzo[e]pyrido[1,2-a]azepin-4-one (9b, 10b)

The same procedure as described above for 3a was employed starting from 1f. After evaporation under reduced pressure, the residue was purified by column chromatography (hexane–EtOAc, 5:3:1:1) to afford an inseparable 2:1 mixture of 7b–8b in 90% yield as a colorless oil.

GC-MS: 7b m/z (%) = 227 (76), 212 (5), 198 (3), 184 (5), 170 (10), 156 (16), 144 (7), 130 (100), 115 (54), 98 (5). 8b m/z (%) = 227 (31), 212 (100), 198 (23), 184 (14), 170 (13), 157 (21), 143 (8), 130 (21), 115 (22), 98 (21).

The above mixture was dissolved in MeOH (5.0 mL) and stirred for 10 h under H₂ atmosphere (4 bar). After evaporation under reduced pressure, a 6:5:1 mixture of 9b–10b was obtained in 98% yield.

Column chromatography (hexane–EtOAc, 1:1) afforded the major isomer 9b as a white solid: mp 114–115 °C.

IR (KBr): 3060, 3030, 2983, 2873, 1635, 1446, 1417, 1365, 1259, 1184 and 760 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 1.25 (d, J = 5.0, 3 H, CH₃), 1.56–1.76 (m, 5 H, CH₂CH₂CH₂, CH₂CH₂CH₂ and CH₂CH₂CO), 1.91–2.12 (m, 1 H, CH₂CH₂CO), 2.19–2.25 (m, 1 H, CH₂CH₂CO), 2.29–2.39 (m, 1 H, CH₂CH₂CO), 3.26–3.33 (m, 1 H, CHN), 3.83–3.89 (m, 1 H, CH₂CH₂CO), 3.87 (d, J = 13.9, 1 H, CH₂CH₂CO), 5.30 (d, J = 13.9, 1 H, CH₂CH₂CO), 7.16–7.26 (m, 3 H, CH₂CO), 7.45 (dd, J = 7.4, 1.5, 1 H, CH₂CH₂CO).

13C NMR (125 MHz, CDCl₃): δ 18.3 (CH₃), 20.9 (CH₂CH₂CH₂), 30.5 (CH₂CH₂CO), 32.8 (CH₂CO), 35.4 (CHCH₃), 44.6 (CHCH₂CH₂CO), 49.9 (CH₃), 61.4 (CHN), 124.7 (CH₂CO), 126.4 (CH₂CO), 127.7 (CH₂CO), 130.4 (CH₂CO), 137.7 (CO), 145.0 (CO), 169.3 (C).
Acknowledgements

Fellowships from CAPES (LSS) and CNPq (RAP) are gratefully acknowledged as well as financial support from Fapesp (Brazil) and Volkswagen Stiftung (Germany). The authors wish to thank Professor Timothy J. Brocksom (UFSCar, Brazil), Helena M. C. Ferraz (USP, Brazil) and Armin de Meijere (Georg-August Universität, Göttingen, Germany) for generous gift of reagents.

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(9) For the in situ reduction of palladium(II) to palladium(0) species, see: (a) Trost, B. M.; Murphy, D. J. Organoometallics 1985, 4, 1143. (b) McCrindle, R.; Ferguson, G.; Arsenaault, G. J.; McAlees, A. J. J. Chem. Soc., Chem. Commun. 1983, 2473; and references cited therein.


(17) N-2-iodophenyl succinimide was prepared from succinic anhydride, 2-idoaniline and acetyl chloride according to ref.16.