Organolithium or Heck-type cyclization of N-ortho-iodobenzyl-2-alkenylpyrrolidines to give indolizidines

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Dedicated to Professor Bill Bailey on the occasion of his 65th anniversary

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Abstract

Carbolithiation reactions of 2-alkenyl-substituted pyrrolidines have been studied. An electron-withdrawing group in the alkene (R = CONEt₂) is required for the 6-exo-trig cyclization to afford hexahydropyrrolo[1,2-b]isoquinolines. Alternatively, the cyclization of the unactivated alkene can be performed under Heck conditions.

Keywords: Organolithium, carbanion, carbolithiation, palladium, Heck, heterocycles

Introduction

Cyclization of organometallic species onto alkenes plays a key role in organic synthesis. Perhaps most common is the use of organopalladium species, typically formed by insertion of palladium(0) into an aromatic halide.¹ Cyclization onto an alkene is normally followed by β-elimination (of a palladium hydride species) to regenerate an alkene. An alternative methodology, developed extensively by Bailey and co-workers, makes use of an organolithium species, often formed by halogen–lithium exchange.² For example, treatment of the bromide 1 (R = allyl) with two equivalents of tert-butyllithium promotes the formation of the aryllithium which cyclizes to give, after protonation, the indoline 2 (Scheme 1).³ The same chemistry with bromide 1 (R = H), palladium acetate (3 mol%) and tris(2-tolyl)phosphine (6 mol%) is known to give (after heating for several days) the product 3 (R = H) in 60% yield (or 87% yield from the iodide).⁴
Our research groups have a long-standing interest in using organometallic species for cyclization onto π-systems to give nitrogen-containing heterocycles. One target of interest is the preparation of 5-substituted indolizidines. Coldham and co-workers have shown that intramolecular carbolithiation of the organolithium provides a route for the preparation of the desired indolizidines (Scheme 2, disconnection a). In this chemistry cyclization to give the six-membered ring is competitive with enantiomerization of the organolithium. On the other hand, Lete and co-workers have reported that pyrrolo[1,2-b]isoquinolines can be obtained by intramolecular carbolithiation starting from 2-alkenyl N-(o-iodobenzyl)pyrroles. We wondered whether we could approach such biologically important indolizidine targets by disconnection b (Scheme 2, M = metal). There is precedent for carrying out such chemistry using an intramolecular Heck reaction with 6, R = Me. We decided to explore this reaction for a selection of R groups using either Heck or intramolecular carbolithiation chemistry.

Scheme 2

Results and Discussion

Our first task was the synthesis of the 2-alkenyl substituted N-(o-iodobenzyl)pyrrolidines 11a,b, in which the alkene is unsubstituted or incorporates an electron-withdrawing group. As shown in Scheme 3, aldehyde 8 was obtained by deprotonation of N-Boc-pyrrolidine 7 followed by DMF quench. Wittig reaction with the corresponding phosphorus ylides gave the alkenes 9a,b. Nitrogen deprotection with trifluoroacetic acid (TFA) (quantitative) and alkylation with ortho-iodobenzylbromide gave 11a,b.
Scheme 3. Reagents and conditions: a: s-BuLi / TMEDA, Et₂O, −78 °C, 2 h, then DMF, rt, 2 h. b: Ph₃P(CH₃)Br, n-BuLi, THF, −78 °C, 30 min, then rt, overnight (for 9a); Ph₃P=CHCONEt₂, CH₂Cl₂, rt overnight (for 9b). c: TFA, CH₂Cl₂, rt, overnight. d: KOH, EtOH, rt, 15 h.

We first studied the carbolithiation reactions of N-(o-iodobenzyl)pyrrolidine 11a with n-BuLi/TMEDA (Scheme 4). Although iodine–lithium exchange occurred efficiently, aryllithium 6a failed to undergo the carbolithiation reaction onto the unsubstituted alkene, and only the dehalogenated pyrrolidine 12 was obtained after work-up. However, when 11a was treated with palladium acetate (10 mol%) and triphenylphosphine (20 mol%) in the presence of potassium carbonate, under classical Heck reaction conditions, the hexahydropyrrolo[1,2-b]isoquinoline 13a was obtained in good yield.

Scheme 4

Then, we studied the intramolecular carbolithiation of 11b (Scheme 5). As shown in Table 1, the introduction of the electron-withdrawing group on the alkene moiety favours the 6-exo-cyclization of the intermediate aryllithium, and the hexahydropyrrolo[1,2-b]isoquinoline 14 was obtained in excellent yield. Cyclization took place at low temperature, although the best results were obtained when the reaction mixture was allowed to warm to room temperature. It is noteworthy that both n-BuLi and t-BuLi effected efficient iodine–lithium exchange (in the presence of TMEDA). No products from direct addition of these reagents to the α,β-unsaturated amide group were detected (as reported for related systems). The cyclization took place with...
complete stereoselectivity, affording in all cases product 14 as a single diastereomer.\textsuperscript{11} Attack of the intermediate aryllithium could occur as shown in Figure 1, leading to 14 with a relative 10,10a-\textit{trans} configuration. This model allows possible nitrogen–lithium chelation and subsequent intramolecular carbolithiation. NOESY and COSY experiments confirmed the stereochemistry of 14. The most significant NOESY results obtained are shown in Figure 1. In particular, 2D NOESY experiments showed an enhancement between the protons H-10 and H-1, and between H-10a and the methylenic protons of the substituent at C-10. These data are consistent with a \textit{trans} stereochemistry in the indolizidine system.

Finally, Heck reaction of 11b was studied. However, when 11b was treated with Pd(OAc)\textsubscript{2}, PPh\textsubscript{3} and K\textsubscript{2}CO\textsubscript{3} under the same conditions as used for 11a, no cyclization product could be detected, and a mixture of products was obtained. Other reaction conditions, that have been used successfully in related substrates,\textsuperscript{5a} were tested. Thus, 11b was treated with Pd(PPh\textsubscript{3})\textsubscript{4} (5%), \textsuperscript{n}Bu\textsubscript{4}NCl (1.5 eq), NaHCO\textsubscript{3} (2.5 eq), in refluxing CH\textsubscript{3}CN or with Pd(PPh\textsubscript{3})\textsubscript{4} (30%), Et\textsubscript{3}N (2.2 eq) in toluene. In these cases a cyclized product could be detected by \textsuperscript{1}H NMR spectroscopy of the crude reaction mixtures, but it could not be isolated or characterized, possibly due to instability.

**Scheme 5**

**Table 1. Carbolithiation reactions of 11b**

<table>
<thead>
<tr>
<th>RLi</th>
<th>Conditions</th>
<th>14 Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-BuLi</td>
<td>–78 °C, 10 min</td>
<td>70</td>
</tr>
<tr>
<td>n-BuLi</td>
<td>–78 °C, 10 min; rt, 3 h</td>
<td>90</td>
</tr>
<tr>
<td>t-BuLi</td>
<td>–78 °C, 10 min</td>
<td>63</td>
</tr>
<tr>
<td>t-BuLi</td>
<td>–78 °C, 10 min; rt, 3 h</td>
<td>79</td>
</tr>
</tbody>
</table>

**Figure 1.** Possible transition state and selected NOE enhancements for 14.
Conclusions

Intramolecular carbolithiation reaction of a 2-alkenyl-substituted pyrrolidine leads to a hexahydropyrrolo[1,2-b]isoquinoline via a 6-exo cyclization process, though the alkene needs to be substituted with an electron-withdrawing group (R = CONEt₂). Halogen–lithium exchange takes place efficiently with n-BuLi or t-BuLi, in the presence of the enamide moiety. The Heck reaction constitutes an efficient alternative to these reactions with the unsubstituted alkene.

Experimental Section

**General.** Melting points were determined in unsealed capillary tubes and are uncorrected. IR spectra were obtained on KBr pellets (solids) or in CHCl₃ solution (oils). NMR spectra were recorded at 20–25 °C, running at 300 or 500 MHz for ¹H and 75.5 or 125.7 MHz for ¹³C in CDCl₃ solutions. Assignment of individual ¹³C and ¹H resonances is supported by DEPT experiments and 2D experiments (COSY, HMBC, HSQC, NOESY) when necessary. Mass spectra were recorded under electron impact at 70 eV. Exact mass was obtained using a TOF detector. GC-MS analyses were performed using a TRB-1 column (methyl polysiloxane, 30 m × 0.25 mm × 0.25 µm). TLC was carried out with 0.2 mm thick silica gel plates. Visualization was accomplished by UV light. Flash column chromatography on silica gel was performed with Kieselgel 60 (230-400 mesh). All solvents used in reactions were anhydrous and purified according to standard procedures. Organolithium reagents were titrated with diphenylacetic acid or N-benzylbenzamide periodically prior to use. All air- or moisture-sensitive reactions were performed under argon; the glassware was dried (130 °C) and purged with argon.

**tert-Butyl 2-formylpyrrolidine-1-carboxylate (8).** A 0.5 M solution of N-Boc pyrrolidine 7 (0.315 g, 1.83 mmol) in Et₂O (4 mL) at -78 °C was treated with TMEDA (0.27 mL, 1.83 mmol) and s-BuLi (1.69 mL of a 1.3M solution in hexanes, 2.20 mmol). After 2 h at -78 °C, the resulting solution was added dropwise via syringe over a solution of DMF (0.28 mL, 3.66 mmol) in Et₂O (2 mL). The reaction mixture was warmed up to room temperature for 2 h and quenched by the addition of sat. NH₄Cl solution (10 mL). The organic layer was separated and the aqueous phase was extracted with Et₂O (2 x 20 mL). The combined organic extracts were dried with Na₂SO₄ and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, petroleum ether/AcOEt 20%) to give 8 as an oil (0.323 g, 83%), whose spectroscopic data were identical to those reported:⁸ ¹H NMR (CDCl₃, ratio of rotamers 2:1) 1.42 (s, 9H, major rotamer), 1.50 (s, 9H, minor rotamer), 1.79–2.27 (m, 4H major rotamer, 4H minor rotamer), 3.36–3.68 (m, 2H major rotamer, 2H minor rotamer), 3.98–4.30 (m, 1H major rotamer, 1H minor rotamer), 9.46 (s, 1H, major rotamer), 9.52 (s, 1H, minor rotamer). ¹³C NMR (CDCl₃), 24.0, 26.7, 28.3, 46.7, 65.0, 80.6, 158.2, 200.4.

**N-(tert-Butoxy carbonyl)-2-vinylpyrrolidine (9a).** n-BuLi (5.32 mL of a 1.3 M solution in hexanes, 6.96 mmol) was added to a solution of methyltriphenylphosphine bromide (1.92 g, 5.28 mmol) in THF (15 mL) at 0 °C, and the reaction was stirred for 30 min. The mixture was
The addition of sat. NHCl to the mixture was warmed up to room temperature overnight and quenched by the addition of sat. NH4Cl solution (10 mL). The organic layer was separated and the aqueous phase was extracted with Et2O (2 x 20 mL). The combined organic extracts were dried with Na2SO4 and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, petroleum ether/AcOEt 10%) to give 9a as an oil (0.763 g, 77%) whose spectroscopic data were identical to those reported:14 1H NMR (CDCl3): 1.46 (s, 9H), 1.67–1.76 (m, 1H), 1.77–1.93 (m, 2H), 1.95–2.10 (m, 1H), 3.32–3.49 (m, 2H), 4.21–4.42 (m, 1H), 4.96–5.17 (m, 2H), 5.68–5.84 (m, 1H). 13C NMR (CDCl3): 23.0, 28.5, 31.8, 46.3, 53.9, 59.1, 79.1, 113.7, 138.9, 154.6.

(E)-N,N-Diethyl-3-[(1-tert-butoxycarbonyl)pyrrolidin-2-yl]acrylamide (9b). N,N-diethyl-2-(triphenylphosphorylidene)acetamide15 (4 g, 10.8 mmol) was added in portions to a solution of N-Boc prolinal 8 (0.237 g, 1.191 mmol) in CH2Cl2 (20 mL), and the reaction mixture was stirred at room temperature overnight. The reaction crude mixture was washed with H2O (2 x 10 mL) and the aqueous layer was extracted with CH2Cl2 (2 x 20 mL). The combined organic extracts were washed with H2O (2 x 10 mL) and sat. NaCl solution (2 x 10 mL), dried with Na2SO4 and evaporated under reduced pressure. The crude product was purified by flash column chromatography (neutral alumina, hexane/AcOEt 50%) to give 9b as an oil (0.297 g, 84%). IR (CHCl3): 1609, 1685 cm⁻¹. 1H NMR (CDCl3): 1.10–1.21 (m, 6H), 1.43 (s, 9H), 1.74–1.90 (m, 3H), 1.96–2.10 (m, 1H), 3.30–3.49 (m, 6H), 4.35–4.55 (m, 1H), 6.10–6.30 (m, 1H), 6.60–6.84 (m, 1H). 13C NMR (CDCl3, rotamers): 13.1, 14.9, 22.7, 23.6, 28.5, 31.0, 31.7, 40.8, 42.2, 46.2, 46.5, 57.9, 58.1, 79.5, 119.3, 120.6, 143.9, 145.6, 154.5, 165.7. MS (EI) m/z (rel intensity) 297 ([M+H]+, 7), 241 (100), 223 (6), 196 (10), 195 (5), 124 (13), 96 (6). HRMS Calcd for C16H20N2O3: 297.2178. Found: 297.2172.

2-Vinylpyrrolidine (10a) (trifluoroacetate salt). A solution of N-Boc-2-vinylpyrrolidine 9a (0.327 g, 1.66 mmol) in CH2Cl2 (10 mL) was treated with TFA (1.3 mL, 16.60 mmol) and the mixture was stirred overnight at room temperature. Evaporation of the solvent under reduced pressure afforded 2-vinyl pyrrolidine 10a trifluoroacetate as an oil (0.555 g, quantitative). Data of the free pyrrolidine have been reported:16 1H NMR (CDCl3): 1.78–2.48 (m, 4H), 3.25–3.65 (m, 2H), 4.00–4.30 (m, 1H), 5.30–5.62 (m, 1H), 5.72–6.14 (m, 2H), 7.69–8.34 (bs, 1H), 8.51–9.16 (bs, 1H). 13C NMR (CDCl3): 23.5, 30.4, 45.2, 62.6, 116.9, 122.0, 131.4, 161.4.

(E)-N,N-Diethyl-3-(pyrrolidin-2-yl)acrylamide (10b) (trifluoroacetate salt). According to the procedure described for 10a, N,N-diethyl-3-(1-Boc-2-pyrrolidinyl)acrylamide 9b (0.287 g, 0.97 mmol) and TFA (0.4 mL, 4.85 mmol) gave the product 10b as an oil (0.305 g, quantitative). 1H NMR (CDCl3) 0.96 – 1.19 (m, 6H), 1.64 – 2.16 (m, 4H), 3.09 – 3.41 (m, 6H), 4.05 (q, J = 7.5 Hz, 1H), 6.55 (d, J = 15 Hz, 1H), 6.76 (dd, J = 7.5, 15 Hz, 1H), 8.24 (bs, 2H). When the product was purified by flash column chromatography (neutral alumina, MeOH/AcOEt 50%) 10b was obtained as a free amine (0.124 g, 65%). IR (CH2Cl2) 1609, 1656, 3448 cm⁻¹. 1H NMR (CDCl3): 1.11 (t, J = 7 Hz, 3H), 1.16 (t, J = 7 Hz, 3H), 1.61–1.74 (m, 1H), 1.86–1.94 (m, 2H), 1.94–2.04 (m, 1H), 2.91–2.99 (m, 1H), 3.03–3.11 (m, 1H), 3.22 (s, 1H), 3.32–3.42 (m, 4H), 3.77 (q, J = 6.5 Hz, 1H), 6.38 (dd, J = 15, 1, Hz, 1H), 6.83 (dd, J = 15, 6.5, Hz, 1H). 13C NMR (CDCl3): 13.0, 14.8, 25.0, 31.9, 40.8, 42.1, 46.3, 59.7, 120.3, 145.8, 165.5. MS (Cl) m/z (rel intensity) 197
was separated by (silica gel, petroleum ether/AcOEt 20%) to give as an oil (0.712 g, 74%)
IR (CHCl₃): 1654 cm⁻¹. ¹H NMR (CDCl₃): 1.60–1.90 (m, 3H), 1.93–2.07 (m, 1H), 2.21 (q, J = 8.5 Hz, 1H), 2.96 (q, J = 8.5 Hz, 1H), 3.03 (dt, J = 8.5, 2.5 Hz, 1H), 3.30 (d, J = 14 Hz, 1H), 3.98 (d, J = 14 Hz, 1H), 5.13 (dd, J = 1.5, 10 Hz, 1H), 5.24 (dd, J = 1.5, 17 Hz, 1H), 5.74–5.93 (m, 1H), 6.94 (td, J = 7.5, 1 Hz, 1H), 7.33 (td, J = 7.5, 1 Hz, 1H), 7.48 (d, J = 7.5 Hz, 1H), 7.83 (dd, J = 7.5, 1 Hz, 1H). ¹³C NMR (CDCl₃): 22.3, 31.6, 53.5, 62.1, 68.8, 100.0, 116.5, 128.0, 128.4, 130.2, 139.2, 140.9, 142.0. MS (Cl) m/z (rel intensity) 314 (MH⁺, 41), 313 (M⁺, 100), 186 (40). HRMS Calcd for C₁₃H₁₇IN (MH⁺): 314.0406. Found: 314.0403.

(E)-N,N-Diethyl-3-[1-(o-iodobenzyl)pyrrolidin-2-yl]acrylamide (11b). According to the procedure described for 11a, the pyrrolidine 10b trifluoroacetate (0.150 g, 0.484 mmol), KOH (0.054 g, 0.968 mmol) and o-iodobenzyl bromide (0.150 g, 0.484 mmol) gave, after flash column chromatography (neutral alumina, hexane/AcOEt 20%) the product 11b as an oil (0.120 g, 60%): ¹H NMR (CDCl₃): 1.11 (t, J = 7 Hz, 6H), 1.60–1.90 (m, 3H), 1.98–2.09 (m, 1H), 2.27 (q, J = 8.5 Hz, 1H), 3.01–3.12 (m, 1H), 3.16–3.46 (m, 6H), 3.85 (d, J = 14.5 Hz, 1H), 6.36 (d, J = 15 Hz, 1H), 6.85 (dd, J = 15, 7.5 Hz, 1H), 6.89 (td, J = 8, 1.5 Hz, 1H), 7.29 (td, J = 8, 1.5 Hz, 1H), 7.48 (dd, J = 8, 1.5 Hz, 1H), 7.77 (dd, J = 8, 1.5 Hz, 1H). ¹³C NMR (CDCl₃): 13.2, 14.9, 22.8, 31.6, 40.8, 42.2, 53.8, 62.6, 66.4, 99.6, 121.0, 128.1, 128.4, 130.0, 139.1, 141.7, 147.1, 165.5. IR (CHCl₃): 1661, 1615 cm⁻¹. MS (EI) m/z (rel intensity) 412 (M⁺, 4), 312 (72), 286 (55), 217 (100), 195 (100), 122 (79), 90 (31). HRMS Calcd for C₁₈H₂₆N₂O (MH⁺): 413.1096. Found: 413.1096.

N-benzyl-2-vinylpyrrolidin (12). A solution of N-benzyl-2-vinylpyrrolidine 11a (0.145g, 0.46 mmol) in THF (10 mL) was treated with n-BuLi (0.41 mL of a 1.3M solution in hexanes, 1.02 mmol) and TMEDA (0.15 mL, 1.02 mmol) at −78 °C. After 10 min, the mixture was allowed to warm to room temperature, and stirred for 3 h. The reaction was quenched by the addition of sat. NH₄Cl solution (10 mL). The organic layer was separated and the aqueous phase was extracted with Et₂O (2 x 20 mL). The combined organic extracts were dried with Na₂SO₄ and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, petroleum ether/AcOEt 20%) to give 12 as an oil (0.060 g, 70%), data identical to those reported. ¹H NMR (CDCl₃): 1.55–1.91 (m, 3H), 1.92–2.07 (m, 1H), 2.14 (q, J = 8.5 Hz, 1H), 2.83 (q, J = 8.5 Hz, 1H), 2.96 (td, J = 10, 3 Hz, 1H), 3.11 (d, J = 13 Hz, 1H), 4.07 (d, J = 13 Hz, 1H), 5.19 (dd, J = 10, 1.5 Hz, 1H), 5.24 (dd, J = 17.5, 1.5 Hz, 1H), 5.66–6.01 (m, 1H), 7.19–7.42 (m, 5H). ¹³C NMR (CDCl₃): 22.1, 31.6, 53.3, 58.1, 68.4, 116.5, 126.7, 128.1, 129.0, 139.5, 141.0.
10-Methylidene-1,2,3,5,10a-hexahydropyrrolo[1,2-b]isoquinoline (13a). A solution of pyrrolidine 11a (0.157 g, 0.50 mmol) in DMF (2 mL) was treated with Pd(OAc)$_2$ (0.011 g, 0.05 mmol), PPh$_3$ (0.026 g, 0.10 mmol) and K$_2$CO$_3$ (0.104 g, 0.75 mmol). The resulting mixture was heated at 80 °C for 2 days. The reaction was quenched by the addition of water (10 mL), the organic layer was separated and the aqueous phase was extracted with Et$_2$O (2 x 20 mL). The combined organic extracts were dried with K$_2$CO$_3$ and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, petroleum ether/AcOEt 50%) to give 13a as an oil (0.060 g, 65%). IR (CH$_2$Cl$_2$): 1630 cm$^{-1}$. ¹H NMR (CDCl$_3$): 1.16 (t, $J = 7.1$ Hz, 6H, 2 x CH$_3$), 1.62–1.69 (m, 1H, H-1), 1.71–1.78 (m, 1H, H-2), 1.80–1.93 (m, 1H, H-2), 2.03–2.14 (m, 1H, H-1), 2.17–2.29 (m, 2H, H-3 and H-10a), 2.53 (dd, $J = 15.5$, 6 Hz, 1H, CH/HCONEt$_2$), 2.73 (dd, $J = 15.5$, 6 Hz, 1H, CH/HCONEt$_2$), 3.24 (t, $J = 9$ Hz, 1H H-3), 3.33 (q, $J = 7$ Hz, 2H, NCH$_2$CH$_3$), 3.37–3.48 (m, 3H, NCH$_2$CH$_3$ and H-5), 3.50–3.57 (m, 1H, H-10), 4.05 (d, $J = 14.5$ Hz, 1H, H-5), 7.00–7.23 (m, 4H, H-arom). ¹³C NMR (CDCl$_3$): 13.0 (CH$_3$), 14.5 (CH$_3$), 21.5 (C-2), 30.4 (C-1), 37.9 (CH$_3$), 40.6 (CH$_2$CH$_3$), 41.4 (C-10), 42.1 (CH$_2$CH$_3$), 54.9 (C-3), 56.2 (C-5), 67.1 (C-10a), 125.7 (C-7), 126.5, 126.6 (C-9, C-8), 127.1 (C-6), 135.1 (C-9a), 138.8 (C-5a), 171.0 (C=O). MS (Cl) $m/z$ (rel intensity) 287 (MH$^+$, 100), 286 (M$^+$, 5), 214 (3), 186 (2), 172 (11). HRMS Calcd for C$_{18}$H$_{27}$N$_2$O (MH$^+$): 287.2123. Found: 287.2135.

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References and Notes

10. The failure of 6-exo-trig cyclizations of aryllithiums on non-substituted alkenes has been reported. See refs. 5b and c.
11. The 10SR,10aRS diastereomer was not detected by NMR spectroscopy under the reaction conditions used.