Intramolecular Heck Coupling of Alkenyl 3-Iodoindole-2-carboxamide Derivatives

Lidwine Chacun-Lefèvre, Benoît Joseph, Jean-Yves Mérour*

Institut de Chimie Organique et Analytique, UMR-CNRS 6005, Université d'Orléans, BP 6759, 45067 Orléans Cedex 2, France
Fax (33) 2-38-41-70-81; jean-yves.merour@univ-orleans.fr

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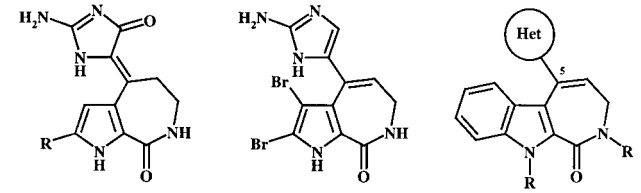
Abstract: Ethyl 2-(1-oxo-1,2,3,4,5,10-hexahydroazepino[3,4-*b*]indol-5-yliden)acetate derivative **1a** has been synthesised in good yield from indole-2-carboxylic acid **2** via a stoichiometric intramolecular Heck reaction.

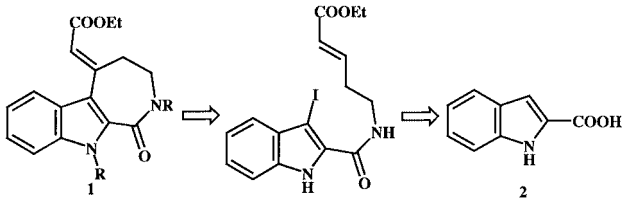
Key words: indole, palladium, cross-coupling, Heck, cyclisation

Several polycyclic natural products possessing a pyrrole moiety have been isolated from marine sponges. Among them, Hymenialdisine **I**, Debromohymenialdisine **II** and Stevensine or Odiline **III** are characterised by a pyrroloazepine skeleton (pyrrolo[2,3-*c*]azepin-8-one) connected to a cyclic hydantoïne or guanidine.[1-3] These compounds display a large number of biological properties.[4-7]

Our interest in seven-membered indolic derivatives[8] arose out of our desire to prepare a diverse set of 5-substituted azepinoindoles **IV** which can be potential building blocks. We have recently described a synthetic method based on Stille or Suzuki reactions between triflate prepared from the azepino[3,4-*b*]indole-1,5-dione moiety and heterocyclic stannyl or boronic acid derivatives.[9] This synthetic approach failed in connecting guanidine or hydantoïne onto the 5-position of seven-membered ring.

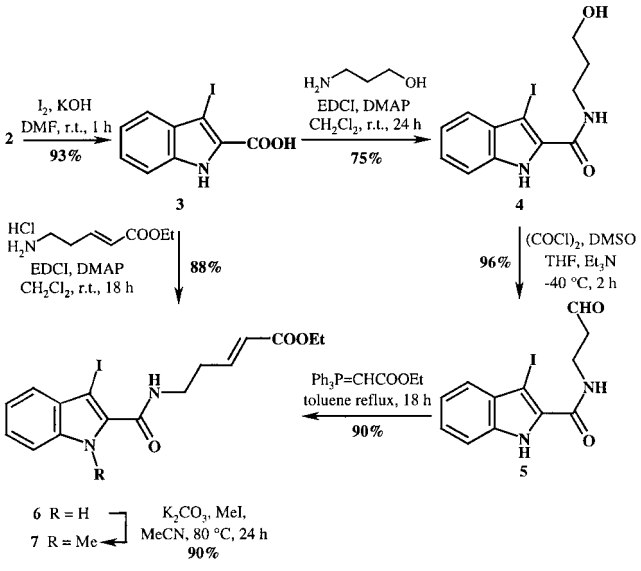


According to the literature,[10] we planned to create the guanidine or hydantoïne moiety from amidine and α-hydroxy ester. This pathway required as a key intermediate preparation of the α,β-unsaturated ester **1** from indole-2-carboxylic acid **2** via an intramolecular Heck reaction[11] as outlined in the retrosynthetic Scheme 1. 7-Exo intramolecular Heck reaction have not been extensively studied.[12] Pioneering works were reported by Trost[13] and Sundberg.[14] As reported previously, an easier synthetic route to obtain **1** from azepino[3,4-*b*]indole-1,5-dione failed (Wittig reaction).[9] We now report our investigations in this area.



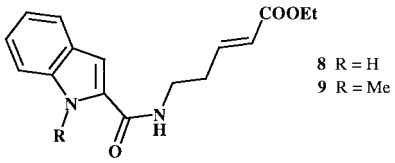
Scheme 1

Treatment of indole-2-carboxylic acid **2** with iodine in the presence of potassium hydroxide provided **3** in 93% yield.[15] Amidification of **3** with the 3-aminopropanol in the presence of EDCI and DMAP in dichloromethane at room temperature gave **4** in 75% yield. The aldehyde **5** was obtained in 96% yield from the alcohol **4** by a Swern oxidation using THF as solvent. The Wittig reaction of **5** with (carbethoxymethylene)triphenylphosphorane in toluene gave the α,β- ethylenic ethyl ester **6** as *E*-isomer in 90% yield. Compound **6** could be also obtained by reacting **3** with ethyl (*E*)-5-amino-2-pentenoate hydrochloride[16] in the presence of EDCI and DMAP in dichloromethane in 88% yield (Scheme 2). Selective *N*-methylation of indolic nitrogen of **6** was carried out in the presence of potassium carbonate as base to afford **7** in 90% yield.

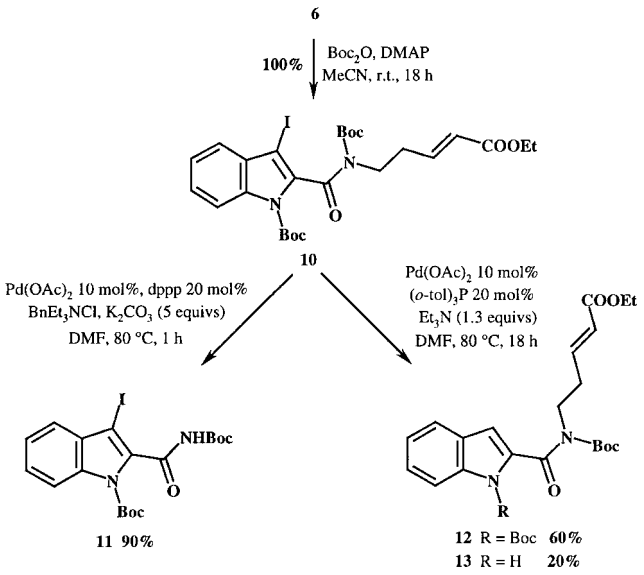


Scheme 2

First we investigated the intramolecular Heck reaction of compounds **6** and **7**. All of them led to the deiodination reaction which gave quantitatively compounds **8** and **9**.



With these results, further experiments were performed on the totally protected derivative **10**. *N*-Boc protection of **6** was achieved with *tert*-butylcarbonate (Boc_2O) in the presence of DMAP in acetonitrile to give **10** in quantitative yield. The latter when treated with $Pd(OAc)_2$ and potassium carbonate afforded unexpectedly compound **11**[17] in 90% yield. Again, use of triethylamine as base resulted in formation of two deiodinated compounds, **12** and the monodeprotected **13** in 60% and 20% yield, respectively (Scheme 3).



Scheme 3

Replacement of triethylamine by silver carbonate (Ag_2CO_3), sometimes used for intramolecular Heck reactions, was envisaged.[18] Pleasingly, this simple experimental modification allowed us to obtain cyclised derivatives **1a**[19] and **1b** in 15% and 33% yield, respectively, and by-products (**12** and **13**). Substitution of DMF by THF increased yields of **1a** and **12** and avoided the formation of deprotected compounds **13** and **1b** (Table). Optimal yield of **1a** (84% yield) was observed by treatment of **10** in the presence of $Pd(OAc)_2$ (1 equiv), Ph_3P (2 equiv) and Ag_2CO_3 (2 equiv) in refluxing THF for 16 h, together with the deiodinated product **12** (10%) (Table, entry 9). An explanation as to why this intramolecular Heck reaction requires stoichiometric amounts of palladium catalyst is not at hand. The main formation of **1a** with the *E*-exo-olefin[20] (determined by 2D NMR data) showed that the Heck reaction proceeded with *cis*-addition of the primarily formed Pd-aryl species on intramolecular C-C double bond followed by *syn*-elimination.[21]

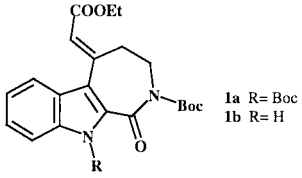


Table Conditions employed for the intramolecular Heck reaction of **10**

Entry	$Pd(OAc)_2$ (mol%)	PPh_3 (mol%)	Ag_2CO_3 (mol%)	Solvent	Temp (°C)	Yield[a] (%) **12**	**13**	**1a**	**1b**
1	10	20	20	DMF	110	10	20	15	33
2	10	20	20	THF	60	30	/	30	/
3	10	20	200	THF	60	20	/	35	/
4	15	30	20	THF	60	20	/	45	/
5	15	30	20	MeCN	80	10	10	30	10
6	20	40	100	THF	60	40	/	30	/
7	20	40	200	THF	60	30	/	48	/
8	50	100	200	THF	60	30	/	60	/
9	100	200	200	THF	60	10	/	84	/
10	100	200	400	THF	60	50	/	/	/

[a] Isolated yield after chromatography.

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(16) Ethyl *(E)*-5-amino-2-pentenoate hydrochloride was prepared from commercially available 3-aminopropanol in four steps (Boc protection, PCC oxidation, Wittig reaction and deprotection) in 64% overall yield.
(17) **Typical procedure**: A suspension of 1,3-bis-(diphenylphosphino)propane (27 mg, 0.65 mmol), palladium acetate (7.5 mg, 0.033 mmol), potassium carbonate (225 mg, 1.63 mmol) and benzyltriethylammonium chloride (75 mg, 0.33 mmol) in anhydrous DMF (5 mL) was stirred at r.t. for 15 min. Ester **10** (200 mg, 0.33 mmol) in DMF (2 mL) was added and the final mixture was stirred at 80 °C for 1 h. After cooling, the catalyst and potassium carbonate were filtered off and the solvent was removed under reduced pressure. Purification of the crude residue by column chromatography on silica gel (PE 35-60 °C/EtOAc 8:2) gave 145 mg (90%) of **11** as an oil. Physical data of **11**: IR (film) 3212, 1730, 1720, 1686 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.11 (d, 1H, *J* = 7.5 Hz, H_7), 7.77 (broad s, 1H, NH), 7.44-7.32 (m, 3H, H_4, H_5, H_6), 1.62 (s, 9H, CH_3), 1.32 (s, 9H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 163.0 (CO), 149.4 (CO), 148.3 (CO), 135.0 (C), 134.5 (C), 137.0 (C), 126.8 (CH), 124.0 (CH), 122.3 (CH), 115.6 (CH), 85.9 (C), 83.4 (C), 68.2 (C), 28.0 (3 CH_3), 27.9 (3 CH_3); MS (IS) m/z 487 (MH^+); Anal. Calcd for $C_{19}H_{23}IN_2O_5$: C, 46.93; H, 4.77; N, 5.76; Found: C, 47.25; H, 4.91; N, 5.62.
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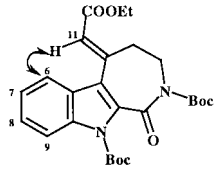
(19) **Typical procedure**: A suspension of triphenylphosphine (525 mg, 2.0 mmol), palladium acetate (225 mg, 1.0 mmol) and silver carbonate (552 mg, 2.0 mmol) in anhydrous THF (20 mL) was stirred at r.t. for 15 min. Ester **10** (613 mg, 1.0 mmol) in THF (10 mL) was added and the final mixture was stirred at 60 °C for 16 h. After cooling, the catalyst and silver carbonate were filtered off and the solvent was removed under reduced pressure. Purification of the crude residue by column chromatography on silica gel (PE 35-60 °C/EtOAc 8:2) gave 405 mg (84%) of **1a** as a gum and 48 mg (10%) of **12**. Physical data of **1a**: IR (film) 1788, 1754, 1722, 1718 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.37 (d, 1H, *J* = 8.0 Hz, H_9), 7.96 (d, 1H, *J* = 8.0 Hz, H_6), 7.47 (td, 1H, *J* = 1.1, 8.0 Hz, H_8), 7.33 (td, 1H, *J* = 1.1, 8.0 Hz, H_7), 6.37 (t, 1H, *J* = 2.5 Hz, H_{11}), 4.24 (q, 2H, *J* = 7.1 Hz, CH_2), 4.16-4.11 (m, 2H, CH_2), 3.51-3.46 (m, 2H, CH_2), 1.61 (s, 9H, CH_3), 1.57 (s, 9H, CH_3), 1.33 (t, 3H, *J* = 7.1 Hz, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 166.1 (CO), 161.0 (CO), 151.2 (CO), 148.8 (CO), 147.3 (C), 138.1 (C), 131.5 (C), 127.6 (C), 125.2 (C), 123.9 (C_7), 122.8 (C), 121.4 (C_{11}), 121.1 (C_6), 114.7 (C_9), 85.3 (C), 83.6 (C), 60.2 (CH_2), 42.8 (C_3), 34.9 (C_4), 28.0 (3 CH_3), 27.6 (3 CH_3), 14.3 (CH_3); MS (IS) m/z 485 (MH^+); Anal. Calcd for $C_{26}H_{32}N_2O_7$: C, 64.45; H, 6.66; N, 5.78; Found: C, 64.10; H, 6.48; N, 5.89.
(20) Connectivities were observed between protons H_6 and H_{11} in an NOE spectrum of **1a**.



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