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Synthesis of fused heterocycles with a benzazepinone moiety via intramolecular Heck coupling

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Abstract—The preparation of fused heterocycles with a benzazepinone moiety was realised via an intramolecular Heck coupling reaction either at position 2 or at position 3 of the heterocyclic system. This method allowed the synthesis of the pyrrolo[2,3-*c*]azepinone core and Paullone derivatives.

1. Introduction

In our ongoing project concerning the development of new cyclin dependent kinase (CDK) inhibitors, we became interested in the preparation of azepinoindole derivatives. Indeed, these structures are closely related to well-known pyrroloazepine moieties which are present in a number of natural and synthetic products such as Hymenialdisine,[1] Latonduine[2] and Paullones[3] (Fig. 1).

Some of these molecules are interesting CDK and/or GSK-3 (glycogen synthase kinase 3) inhibitors.[4] We report in this letter, a general, mild and straightforward procedure for the preparation of the benzazepinone moiety, involving an intramolecular Heck type coupling reaction.

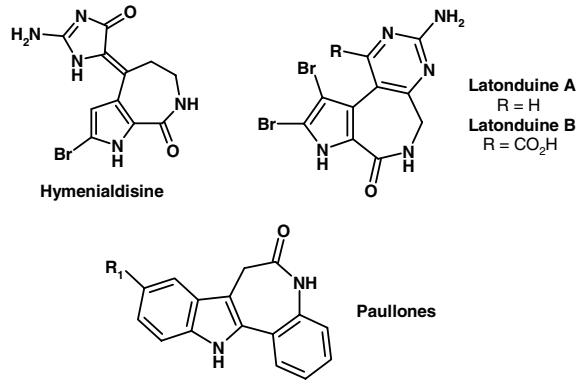
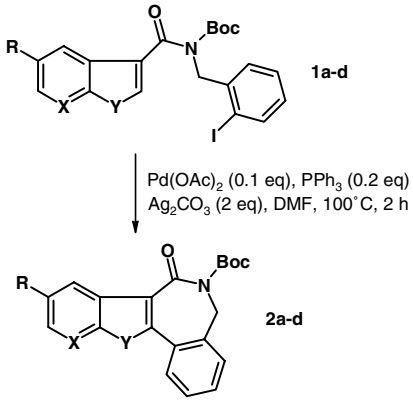


Figure 1.

2. Results and discussion

First, we investigated the cyclisation of compounds **1a**–**d** (Scheme 1), which were easily available by a peptidic coupling (EDCI, DMAP) between the corresponding indole-, pyrrolo[2,3-*b*]pyridine- or benzo[*b*]thiophene-3-carboxylic acids and 2-iodobenzylamine followed by a Boc protection of the amide.



Scheme 1.

Keywords: Benzazepinone; Palladium; Heck; Cyclisation.
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As previously reported by Mérour and co-workers[5] for the preparation of the six-membered ring analogues, the Heck reaction was effective in the presence of a $Pd(OAc)_2/PPh_3$ catalytic system and silver carbonate as base. The reaction was performed in excellent yield (Table 1) with 0.1 equiv of palladium catalyst in 2 h. In the case of **1d**, only 0.05 equiv of $Pd(OAc)_2$ was required to complete the reaction. This was certainly due to a transition state involving a stabilisation of the palladium species by the sulfur atom as suggested by Lemaire and co-workers.[6]

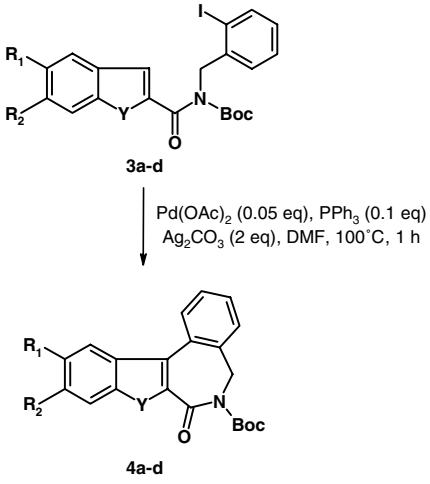
Thus, the 2-regioisomers **3a–d** were synthesised according to the procedure applied for compounds **1a–d**. We attempted to perform the intramolecular Heck coupling on position 3 of heterocycles, as reported in the literature for five- or six-membered rings.[8]

When the cyclisation conditions described above were applied to compound **3a**, the latter underwent a complete degradation after 24 h (Scheme 2). Therefore, we decided to protect the indole nitrogen with an electron donating group (–EOM = $-CH_2OCH_2CH_3$), as reported for the inter- or intramolecular cyclisation of nitrogen heterocycles.[8,9] The resulting protected indole **3b** was then submitted to the Heck coupling reaction and afforded the desired product **4b**[10] in an excellent 96% yield. In addition, we were pleased to observe that the cyclisation occurred with only 0.05 equiv of $Pd(OAc)_2$ in 1 h compared to the reported intramolecular cyclisations of heterocycles.[8]

Table 1. Yield of compounds **2** obtained by Heck coupling reaction

1	R	X	Y	2	Yield (%)
1a	H	CH	*N*-SO_2Ph	**2a**[7]	92
1b	OMe	CH	*N*-SO_2Ph	**2b**	96
1c	H	N	*N*-SO_2Ph	**2c**	86
1d	H	CH	S	**2d**	100[a]

[a] 0.05 equiv of $Pd(OAc)_2$ was used.



Scheme 2.

Table 2. Yield of compounds **4** obtained by Heck coupling reaction

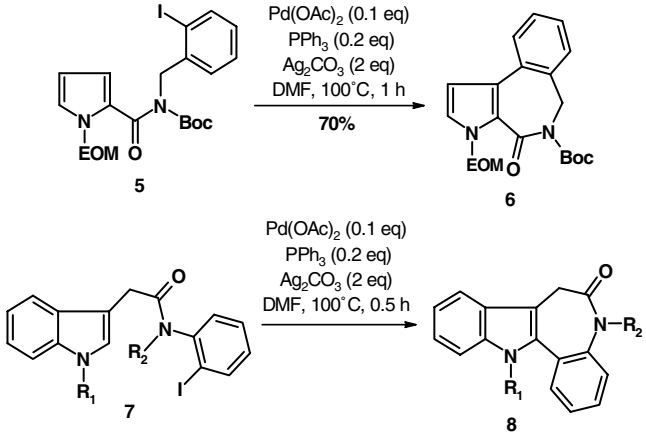
3	R_1	R_2	Y	4	Yield (%)
3a	H	H	*N*-Boc	**4a**	/[a]
3b	H	H	*N*-EOM	**4b**	96
3c	OMe	H	*N*-EOM	**4c**	93
3d	H	OMe	*N*-EOM	**4d**	96
3e	H	H	S	**4e**	82

[a] Degradation of **3a**.

We then extended these conditions to **3c–e** and obtained excellent results (Table 2). For **3e**, an increase from 0.05 to 0.075 equiv of the amount of $Pd(OAc)_2$ did not improve the yield.

As only a few examples of palladium coupling were described on pyrrole derivatives so far,[8b,9] we eventually applied these conditions (0.05 equiv of $Pd(OAc)_2$) to the synthesis of compound **6**, related to the structure of Latonduine (Scheme 3). The cyclisation of **5** afforded **6**[11] in 59% yield (40% of starting material recovered), and was then improved up to 70% (26% of starting material recovered) when 0.1 equiv of $Pd(OAc)_2$ was used.

This methodology can also be extended to the synthesis of Paullone series (Scheme 3).[12] Actually, *N*-electron withdrawing protecting groups such as Boc or SO_2Ph prevented cyclisation (Table 3, entry 1). However, *N*-Me and *N*-EOM compounds **7b** and **7c** allowed the intramolecular cyclisation with excellent yield (Table 3, entry 2–3). As recently reported for palladium-mediated methodologies,[13] our synthetic strategy allows the preparation of *N*-unprotected derivatives (via final deprotection of EOM groups). This represents a convenient



Scheme 3.

Table 3. Yield of compounds **8** obtained by Heck coupling reaction

7	R_1	R_2	8	Yield (%)
7a	Me	Boc	**8a**	/[a]
7b	Me	Me	**8b**	89
7c	EOM	EOM	**8c**	92

[a] Degradation of **7a**.

alternative to Fischer indole synthesis which is the most useful route to Paullones used so far.[3]

3. Conclusion

In summary, we have shown that $Pd(OAc)_2/PPh_3/Ag_2CO_3$ is a mild, fast and efficient high yielding catalytic system for the synthesis of fused heterocycles with a benzazepinone moiety. This methodology can be applied to heterocycles such as indole, pyrrolo[2,3-*b*]pyridine, benzo[*b*]thiophene or pyrrole. In addition, we proposed a simple and novel synthetic route to pyrrolo[2,3-*c*]azepinone and indolo[3,2-*d*]benzazepinone ring systems. Further studies are under investigation in order to obtain new Paullone analogues and will be published in due course.

Acknowledgements

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7. *Example of Heck reaction, preparation of* **2a**: A mixture of **1a** (154 mg, 0.25 mmol), triphenylphosphine (13 mg, 0.05 mmol), palladium acetate (5.6 mg, 0.025 mmol) and silver carbonate (138 mg, 0.5 mmol) in anhydrous DMF (5 mL) was vigorously stirred at 100 °C for 2 h. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was taken up in dichloromethane and filtered over Celite®, rinsed with dichloromethane. The solvent was evaporated in vacuo and the crude residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 9:1) to give **2a** (112 mg, 92%). Mp 154 °C dec. (Et_2O); ^1H NMR (300 MHz, $CDCl_3$): δ 1.51 (s, 9H, $3CH_3$), 3.66 (d, 1H, $J = 14.5$ Hz, CH_2), 5.09 (d, 1H, $J = 14.5$ Hz, CH_2), 7.12 (br d, 2H, $J = 8.5$ Hz, H_{Ar}), 7.20 (t, 2H, $J = 8.5$ Hz, H_{Ar}), 7.37–7.58 (m, 6H, H_{Ar}), 7.97–8.00 (m, 1H, H_{Ar}), 8.16 (br d, 1H, $J = 7.7$ Hz, H_{Ar}), 8.34 (d, 1H, $J = 8.3$ Hz, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.1 ($3CH_3$), 47.8 (CH_2), 83.8 (C), 117.6 (CH), 121.7 (C), 122.8 (CH), 126.0 (CH), 126.5 (2CH), 126.6 (CH), 127.5 (2CH), 128.7 (C+2CH), 129.7 (C), 130.3 (CH), 133.4 (CH), 134.2 (CH), 135.7 (C), 136.5 (C), 138.6 (C), 141.9 (C), 151.1 (CO), 162.7 (CO); HRMS (EI) *m/z* calcd for $C_{27}H_{24}N_2O_5S$: 488.1406; found: 488.1408.
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10. Selected data for **4b**. Mp 104–106 °C (EtOAc/PE); ^1H NMR (300 MHz, DMSO-d_6): δ 1.03 (t, 3H, $J = 7.2$ Hz, CH_3), 1.47 (s, 9H, $3CH_3$), 3.34–3.54 (m, 2H, CH_2), 4.26 (d, 1H, $J = 15.1$ Hz, CH_2), 5.09 (d, 1H, $J = 15.1$ Hz, CH_2), 5.92 (d, 1H, $J = 10.7$ Hz, CH_2), 6.05 (d, 1H, $J = 10.7$ Hz, CH_2), 7.32 (t, 1H, $J = 7.7$ Hz, H_{Ar}), 7.44–7.63 (m, 4H, H_{Ar}), 7.83 (d, 1H, $J = 8.5$ Hz, H_{Ar}), 8.03–8.06 (m, 2H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.2 (CH_3), 28.2 ($3CH_3$), 48.9 (CH_2), 64.2 (CH_2), 74.3 (CH_2), 83.5 (C), 111.9 (CH), 121.3 (C), 122.1 (2CH), 124.6 (C), 126.3 (CH), 127.3 (CH), 128.3 (CH), 128.5 (CH), 128.7 (C), 129.4 (C), 132.9 (C), 136.1 (C), 139.8 (C), 150.8 (CO), 161.6 (CO); HRMS (EI) *m/z* calcd for $C_{24}H_{26}N_2O_4$: 406.1893; found: 406.1894.
11. Selected data for **6**. Mp 77–79 °C (EtOH); ^1H NMR (300 MHz, $CDCl_3$): δ 1.19 (t, 3H, $J = 7.2$ Hz, CH_3), 1.50 (s, 9H, $3CH_3$), 3.55–3.59 (m, 2H, CH_2), 4.24 (d, 1H, $J = 14.7$ Hz, CH_2), 5.11 (d, 1H, $J = 14.7$ Hz, CH_2), 5.54 (d, 1H, $J = 9.5$ Hz, CH_2), 6.09 (d, 1H, $J = 9.5$ Hz, CH_2), 6.55 (d, 1H, $J = 2.8$ Hz, H_{Pyr}), 7.22 (d, 1H, $J = 2.8$ Hz, H_{Pyr}), 7.27–7.69 (m, 4H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.1 (CH_3), 28.1 ($3CH_3$), 48.9 (CH_2), 64.6 (CH_2), 78.3 (CH_2), 82.9 (C), 107.7 (CH), 123.5 (C), 127.0 (CH), 127.3 (CH), 128.2 (CH), 128.6 (CH), 129.2 (CH), 130.8 (C), 133.7 (C), 135.0 (C), 151.2 (CO), 161.2 (CO); HRMS (EI) *m/z* calcd for $C_{20}H_{24}N_2O_4$: 356.1736; found: 356.1735.
12. Selected data for **8b** and **8c**. Compound **8b**: mp 145–146 °C (EtOAc/PE); ^1H NMR (300 MHz, $CDCl_3$): δ 3.07 (d, 1H, $J = 13.9$ Hz, CH_2), 3.35 (s, 3H, CH_3), 3.91 (s, 3H, CH_3), 3.97 (d, 1H, $J = 13.9$ Hz, CH_2), 7.20 (t, 1H, $J = 7.0$ Hz, H_{Ar}), 7.28–7.49 (m, 5H, H_{Ar}), 7.55 (d, 1H, $J = 7.8$ Hz, H_{Ar}), 7.73 (d, 1H, $J = 7.9$ Hz, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.9 (CH_3), 32.4 (CH_2), 37.7 (CH_3), 109.8 (CH), 112.4 (C), 118.8 (CH), 120.1 (CH), 122.9 (CH), 124.4 (CH), 124.8 (CH), 125.1 (C), 125.7 (C), 128.1 (CH), 128.7 (CH), 133.8 (C), 139.3 (C), 141.8 (C), 172.9 (CO); HRMS (EI) *m/z* calcd for $C_{18}H_{16}N_2O$: 276.1263; found: 276.1264. Compound **8c**: mp 102–103 °C (EtOAc/PE); ^1H NMR (300 MHz, $CDCl_3$): δ 1.16 (t, 3H, $J = 7.0$ Hz, CH_3), 1.25 (t, 3H, $J = 7.0$ Hz, CH_3), 3.11 (d, 1H, $J = 13.6$ Hz, CH_2), 3.41–3.51 (m, 1H, CH_2), 3.56–3.70 (m, 3H, CH_2), 3.96 (d, 1H, $J = 13.6$ Hz, CH_2), 4.73 (d, 1H, $J = 10.0$ Hz, CH_2), 5.39 (d, 1H, $J = 10.0$ Hz, CH_2), 5.57 (s, 2H, CH_2), 7.21–7.48 (m, 4H, H_{Ar}), 7.54 (d, 1H, $J = 8.3$ Hz, H_{Ar}), 7.73 (d, 1H, $J = 7.9$ Hz, H_{Ar}), 7.88 (d, 1H, $J = 7.9$ Hz, H_{Ar}), 7.95 (br d, 1H, $J = 7.6$ Hz, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.2 (CH_3), 15.3 (CH_3), 32.6 (CH_2), 64.3 (CH_2), 64.6 (CH_2), 73.9 (CH_2), 78.9 (CH_2), 110.3 (CH), 112.9 (C), 118.9 (CH), 121.0 (CH), 123.5 (CH), 124.8 (CH), 125.3 (C), 126.0 (CH), 126.2 (C), 128.6 (CH), 129.0 (CH), 134.2 (C), 139.2 (C), 140.8 (C), 172.7 (CO); HRMS (EI) *m/z* calcd for $C_{22}H_{24}N_2O_3$: 364.1787; found: 364.1788.
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