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Synthesis of fused rings at a pivotal nitrogen: tandem Heck reactions of *N*-vinyl-2-iodobenzamides

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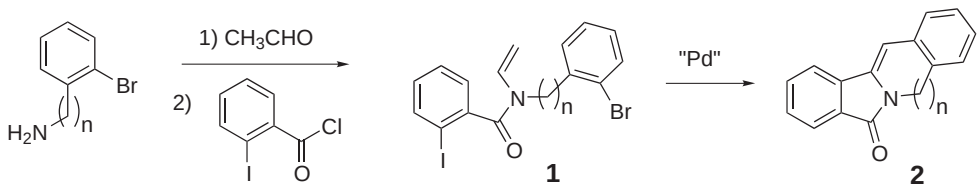
Abstract—A short two-step synthesis of the tetracyclic nitrogen heterocycles **2** (isoindoloneindole, isoindoloneisoquinoline and isoindolone[3]benzazepine) is presented. Condensation of the corresponding *o*-bromoarylamine with acetaldehyde followed by acylation with *o*-iodobenzoyl chloride affords the key dihalo *N*-vinylbenzamides **1**, which are then cyclized by a tandem Heck reaction.

The Heck reaction,[1] the palladium-catalyzed arylation of olefines, is widely used for carbon–carbon bond formation in organic synthesis. The utility of the intramolecular variant of this reaction for the synthesis of carbocyclic and heterocyclic systems is well documented.[2] In particular, a number of nitrogen heterocycles have been synthesized in this way by regiocontrolled cyclization of enamides at both the α and β positions.[3]

Here we report the use of this approach for direct synthetic entry to the (5,5), (5,6) and (5,7) nitrogen heterocycles **2a**–**c** from the corresponding dihalobenzamides **1a**–**c**. The method developed relies on intramolecular tandem Heck reactions, taking advantage of the difference in reactivity between the two aromatic halides of **1**.[1] Specifically, chemoselective oxidative addition of palladium to the more reactive Ar–I bond of **1** triggers a 5-*exo*-*trig* cyclization giving the corresponding methylenephthalimide intermediate, which then undergoes a second *endo* mode Heck cyclization (Scheme 1, Table 1).

A major advantage of the proposed synthetic scheme is the ease of access to the required dihalobenzamides **1a**–**c**, which are prepared in one pot by simply condensing the corresponding *o*-bromoarylamine with acetaldehyde and then acylating the resulting imine with *o*-iodobenzoyl chloride.[4,5]

All cyclizations were carried out in DMF as solvent with 20 mol% of $Pd(OAc)_2$, 40 mol% of Ph_3P, K_2CO_3 (400 mol%) as base and Et_4NBr (200 mol%) as additive.[6] Heating enamide **1b** in DMF for 6 h at 100°C in a sealed tube gave an 87% yield of **2b**, the identity of which supported by comparison of its ^1H NMR spectrum with previously reported data.[7] The alternative isoindoleisoquinolone structure, that would result if a 6-*endo* cyclization of the iodide preceded a 5-*exo* process in the bromide moiety, was ruled out by an HMBC study, which showed a diagnostic 3-bond correlation between the vinyl **C**–H and the corresponding aromatic proton in the non benzamide ring.



Scheme 1.

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Table 1. Pd-catalyzed cyclization of enamides **1**

n	Compound	Time (h)	*T* (°C)	Product	Yield (%)
0	**1a**	24	100	**2a**	40
		2	130	**2a**	81
1	**1b**	6	100	**2b**	87
2	**1c**	24	130	**2c**	47

By contrast, heating enamide **1a** in DMF for 24 h at 100°C as above gave only a 40% yield of the isoindoloneindole **2a**.[8] The yield of **2a** being lower than that of **2b** is attributable to the greater difficulty of oxidative addition to the more electron-rich brominated ring of **1a**, and to the 5-*endo* cyclization being slower than the 6-*endo* cyclization. Interestingly, when the temperature was increased to 130°C an excellent 81% yield was obtained in a shorter reaction time. Finally, in the case of **1c** it was necessary to heat for 24 h at 130°C for the reaction to go to completion, and the yield of **2c**[9] was only 47%, reflecting the greater difficulty of the 7-*endo* versus the 6-*endo* cyclization.[10] As for **2b**, full identities of the cyclized compounds **2a** and **2c** were fully established by 2D-NMR experiments. These results indicate that, as expected, the first Heck cyclization takes place regioselectively in the more favored 5-*exo* mode, leading to the isoindolone nucleus, while the second takes place in the *endo* mode.

In conclusion, the procedure described gives dibenzo fused nitrogen heterocycles in two steps from readily available starting materials. In addition, the presence of a double bond leaves open the possibility of further manipulations. For example, this would allow the synthesis of the unsubstituted aromatic skeleton of the alkaloid chilenine in four steps from the starting phenethylamine (by DMD oxidation[11] of **2c**) or that of lennoxamine in three steps (by reduction[12] of **2c**).[13]

Acknowledgements

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6. **Typical experimental procedure for the Heck reactions**: Enamide **1b** (140 mg, 0.31 mmol), Ph_3P (34 mg, 0.13 mmol), Et_4NBr (133 mg, 0.62 mmol) and K_2CO_3 (175 mg, 1.2 mmol) were suspended in 5 mL of dry DMF and the mixture was flushed with Ar for 10 min. Then, $Pd(OAc)_2$ (14 mg, 0.062 mmol) was added and the mixture heated at 100°C in a sealed tube for 6 h. After reaching rt the crude was poured onto brine, this mixture was extracted with EtOAc (2×15 mL), and the organic phase was washed with brine (3×20 mL). After evaporation of the solvent, the residue was chromatographed on silica gel, affording 1.55 g (87%) of compound **2b** as a yellowish solid, mp 150–152°C (lit.[7] mp 157–158°C). ^{1}H NMR (250.13 MHz, $CDCl_3$) δ 7.85 (d, J=8.2, 1H), 7.59 (d, J=8.0, 1H), 7.48 (t, J=8.1, 1H), 7.48 (t, J=7.9, 1H), 7.21–7.13 (m, 4H), 6.38 (s, 1H), 5.02 (s, 2H).
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