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Formation of cyclic sulfonamides via an unusual 8-*endo*-trig Heck olefination reaction

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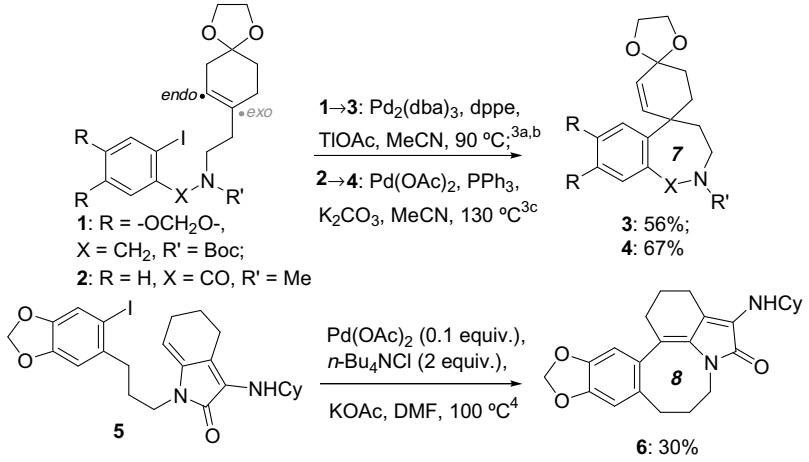
ABSTRACT

The synthesis of the novel benz[*c*]azocines, **11a** and **11b** was achieved following an 8-*endo*-trig selective intramolecular Heck reaction. Optimisation of this reaction demonstrated that inclusion of both tetra-*n*-butylammonium sulfate and water was essential for its success. No products from the corresponding 7-*exo*-trig process were encountered under these conditions.

We have recently become interested in the preparation of cyclic sulfonamide-containing compounds[1] and have employed the palladium-catalysed intramolecular Heck (Heck–Mizoroki) olefination reaction for their synthesis. More generally, it is well appreciated that this reaction represents a useful method for the preparation of 5- and 6-membered cyclic compounds following 5-*exo*-trig and 6-*exo*-trig cyclisation processes.[2] Several literature reports also exist describing the successful 7-*exo*-trig palladium-mediated Heck-type cyclisation (i.e., the conversion of **1** to **3** and **2** to **4**), a noteworthy feature of which is the formation of a quaternary stereogenic centre (Scheme 1).[3] The motivation being that this type of spiro-benz[*c*]azepine architecture is found in several nitrogen-based natural products of biological interest. More rare are examples of 8-*endo*-trig cyclisations, however, in certain instances it appears possible that the corresponding 8-membered ring-containing products may also form competitively. For example, Rigby demonstrated that for one substrate class, 7- and 8-*endo*-trig cyclisations occur in preference to their *exo*-counterparts under Jeffery-type conditions (see **5** to **6**, Scheme 1).[4] This regiochemical outcome is reversed under more standard conditions. Similarly, Gibson has shown that dehydroamino acid derived substrates, in which the intermediate palladium species resulting from *exo*-carbopalladation are unable to undergo β-hydride elimination, generate reasonable to good yields of the products resulting from *endo*-cyclisation.[5] At first sight, these reports appear surprising since, based on a combination of entropic and thermodynamic



Scheme 1. Literature examples of 7-*exo* and 8-*endo*-trig intramolecular Heck reactions.

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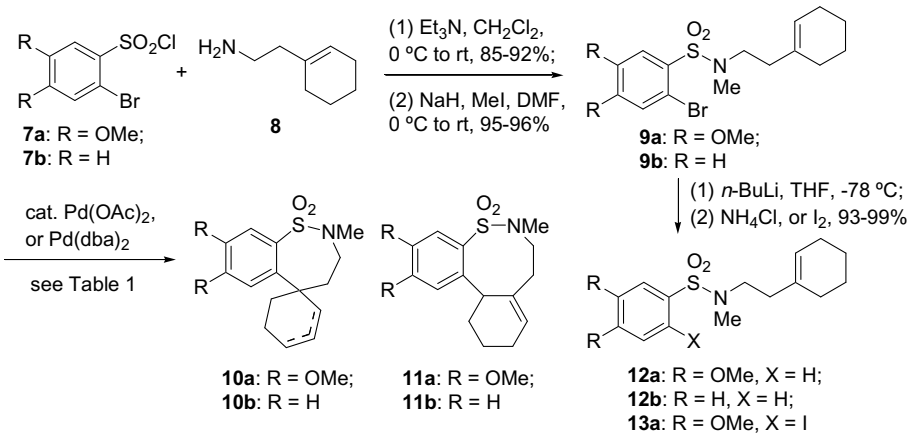


Scheme 2.

considerations, the formation of 'medium' ring-containing heterocycles (8–10 membered) remains a synthetic challenge.[6]

Consequently, we decided to investigate whether an intramolecular Heck reaction might be useful for the synthesis of cyclic sulfonamides containing 7- or 8-membered rings. The alkenyl substrate chosen to test this sequence was the commercially available cyclohexenylethylamine **8**. Thus, sulfonamide formation was performed with both 2-bromo-4,5-dimethoxybenzenesulfonyl chloride[1a] **7a** and 2-bromobenzenesulfonyl chloride **7b**. N-Alkylation under standard conditions then afforded the corresponding *N*-methyl compounds **9a** and **9b** (Scheme 2).

Substrate **9a** was then subjected to standard Heck conditions in the hope that a regioselective cyclisation would occur (Table 1, entry 1). In the event, using catalytic amounts of either $Pd(OAc)_2$ or $Pd(dba)_2$, starting material **9a** was completely consumed. However, although mass spectrometry confirmed the formation of a species with the expected molecular weight, NMR spectroscopy indicated that complex mixtures of products were formed in contrast to the conversion of **2** into **4**[3c] (Scheme 1) that was successfully reported under similar conditions. Furthermore, these species proved to be inseparable by flash column chromatography. It seemed likely that the mixture comprised of 8-membered ring-containing compound **11a** and the corresponding 7-membered ring-containing compound **10a**, probably as mixture of alkene regioisomers (the isomerisation of alkenes following Heck olefination has frequently been encountered[2,7]). Palladium-catalysed hydrogenation, however, failed to significantly simplify these mixtures. Therefore, we set out to systematically screen various alternative conditions in the hope that the selectivity of this reaction might improve. Use of triethylamine as the base led to the formation of the product of bromine-hydrogen exchange **12a** (entry 2) whose structure was confirmed independently on treatment of **9a** with *n*-BuLi followed by aqueous acidic work-up. This result suggested that although the required oxidative addition was occurring, the following cyclisation was slow, consequently enabling 'protonation' of the putative aryl-palladium(II) intermediate. Support for this hypothesis came by way of the X-ray crystal structure of **9a**, which indicates a large distance between the alkene and reactive sp^2-centre in the solid state (Fig. 1). Based on the work of Jeffery[8] and the indication that inclusion of tetraalkylammonium salts drastically altered the regiochemical outcome of a series of related intramolecular Heck processes[4] (see Scheme 1), tetra *n*-butylammonium hydrogensulfate was next investigated. Disappointingly, the formation of complex mixtures of products was observed again (entry 3). However, this situation was improved when water was included. The use of solvent mixtures including water was shown by Genêt and co-workers to lead to significant reversals in the regiochemistry of Heck cyclisation reactions, and even the products of 6-*endo*-trig cyclisation were obtained with reasonable selectivity over their 5-*exo*-trig counterparts.[9] Accordingly, treatment of **9a** in a DMF–water (9:1) mixture (entry 4) led to the formation of two products which proved to be **12a** and the hoped for cyclic species **11a** (ratio 25:75). Sulfonamide **11a** could be obtained in pure form by recrystallisation from a mixture of dichloromethane-pentane (ca. 1:4), and its structure was confirmed by X-ray crystallography.[10]

It should be noted that this reaction proceeded most effectively in a sealed tube in the absence of oxygen. If the amount of the additive was increased (entry 5), then preferential formation of the protonated species **12a** was observed. Conducting the reaction

Table 1

Entry	Substrate	Conditions[a]	Ratio **10**:**11**:**12**	Yield[b] (%)	Conversion[c] (%)
1	**9a**	K_2CO_3 (2 equiv), DMF (or DMSO, or MeCN), 110 °C, 24 h	CM	ND	60–100
2	**9a**	Et_3N (10 equiv), DMF, 110 °C, 24 h	0:0:100	57	88
3	**9a**	K_2CO_3 (2 equiv), *n*-Bu_4NHSO_4(0.3 equiv), DMF, 110 °C, 24 h	CM	ND	87
4[d]	**9a**	K_2CO_3 (2 equiv), *n*-Bu_4NHSO_4 (0.3 equiv), DMF–H_2O (9:1), 110 °C, 24 h	0:75:25	90 (55%)[e]	100
5[d]	**9a**	K_2CO_3 (2 equiv), *n*-Bu_4NHSO_4 (1 equiv), DMF–H_2O (9:1), 110 °C, 24 h	0:15:85	70	100
6[d]	**9a**	K_2CO_3 (2 equiv), *n*-Bu_4NHSO_4 (0.3 equiv), H_2O, 110 °C, 24 h	0:55:45	74	100
7[d]	**9a**	K_2CO_3 (2 equiv), DMF–H_2O (9:1), 110 °C, 24 h	15:60:25	ND	100
8[d]	**13a**	K_2CO_3 (2 equiv), *n*-Bu_4NHSO_4 (0.3 equiv), DMF–H_2O (9:1), 110 °C, 24 h	0:70:30	77	100
9[d]	**9b**	K_2CO_3 (2 equiv), *n*-Bu_4NHSO_4 (0.3 equiv), DMF–H_2O (9:1), 110 °C, 24 h	0:60:40	96	100

[a] $Pd(OAc)_2$ (0.1 equiv) [or $Pd(dba)_2$ (0.1 equiv)], PPh_3 (0.2 equiv), solvent (0.1 M), degassed for 0.5 h under a steady N_2 stream.
[b] After purification by flash column chromatography.
[c] Based on recovered starting material.
[d] Reactions performed under N_2 in a sealed tube.
[e] Isolated yield following recrystallisation; CM = complex mixture; ND = not determined.

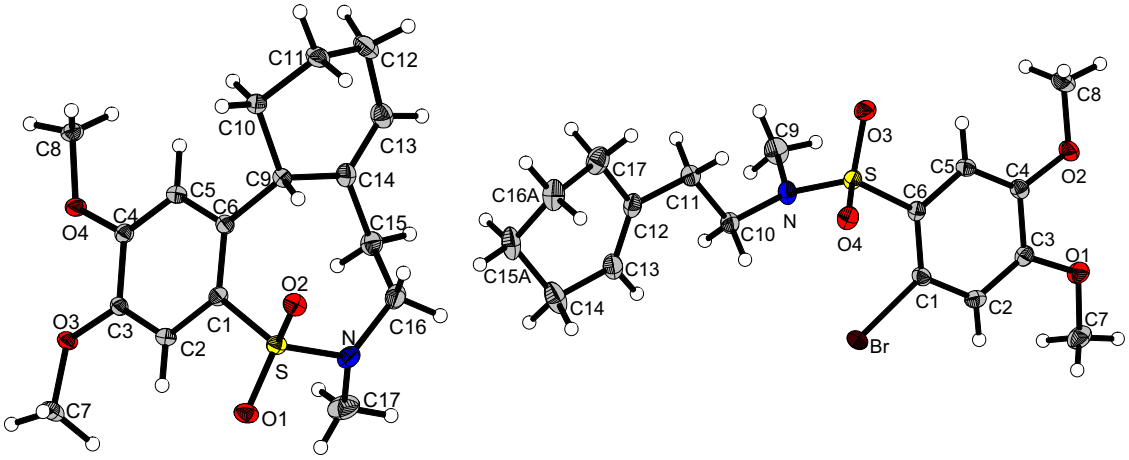
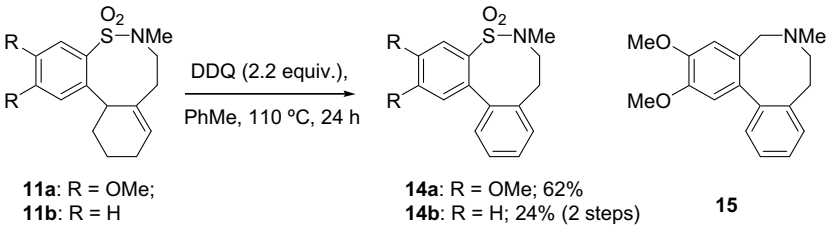


Figure 1. X-ray crystallographic structures of **11a** and its precursor **9a** (Diamond representations).



Scheme 3.

in water as the sole solvent (entry 6) proved to be less selective in terms of formation of **12a**. Omission of the ammonium additive did prove to generate the adduct **11a**, which, as above, was accompanied by **12a**. However, this reaction also formed significant amounts of an impurity attributed to the 7-membered species **10a** (entry 7). Since the rate of halogen-palladium oxidative addition might be expected to alter the ratio of these products, a bromine-iodine exchange was performed to afford **13a** from **9a**. However, it was found that under the optimised conditions, this structural change did not alter the outcome of the Heck reaction in terms of the product ratio (entry 8). Finally, a similar reactivity pattern was observed for substrate **9b**. For example, as entry 9 indicates, under the optimised conditions, the 8-membered species **11b** was formed in conjunction with **12b** (60:40). In this instance, separation of these compounds was not possible since **11b** proved not to be a solid. Notable additional points concerning this cyclisation process are that omission of triphenylphosphine[11] from the reagents in entry 1 resulted in no turnover and **9a** was recovered and that the Heck reactions attempted with the NH sulfonamide precursors to **9a** and **9b** under the optimised, 8-*endo* selective conditions (entry 5) resulted both in only moderate conversion and in the formation of mixtures of products.[12]

The novel benz[*c*]thiaazocine dioxide **11a** was further converted into **14a** following oxidation with DDQ in 62% yield (Scheme 3).[13] This compound can be considered a sulfonamide analogue of the natural product buflavine **15**, a rare example of a naturally occurring *Amaryllidaceae* alkaloid possessing the dibenz[*c*,*e*]azocine skeleton.[14] Similarly, the previously inseparable mixture of **11b** and **12b** was treated with DDQ and **14b** proved now to be isolable (24% yield from **9b**).

In summary, we have discovered that inclusion of both tetra-*n*-butylammonium hydrogensulfate and water is required to facilitate an unusual 8-*endo*-trig intramolecular Heck reaction, which allows the preparation of a novel heterocyclic ring system.[15]

Acknowledgements

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Supplementary data

Full experimental procedures, spectroscopic data and X-ray crystallographic structures of **9a**, **11a** and **12a** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.004.

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