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Synthesis of 2-substituted 1-benzyl-2,3,4,5-tetrahydro-1-benzazepines by palladium catalysis. Observation of a competitive β-hydride elimination pathway

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Abstract—A synthetic route to 1-benzyl-tetrahydro-1-benzazepine is reported, which also permits access to analogous structures with alkyl and aryl substituents at position-2 of the aliphatic ring. Palladium catalysis is utilized in two of the three steps, constructing the seven-membered rings effectively from 2-bromoiodobenzene. Competitive β-hydride elimination was observed in the attempted carbon–nitrogen bond formation with a sterically bulky substrate (when R = *tert*-butyl). © 2003 Elsevier Science Ltd. All rights reserved.

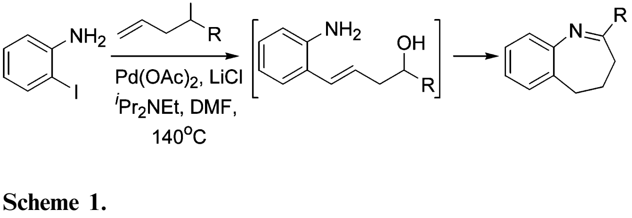
Molecules bearing saturated tetrahydro-1-benzazepine core structures are often found to inhibit selectively certain receptors of the AVP neuropeptide (V_{1A} and V_2) and may have potential applications in the treatment of a number of disorders such as diabetes,[1] congestive heart failure,[2] hypertension,[3] and dysmenorrhea.[4] Orally active V_2 antagonists bearing this fused bicyclic structure have been applied successfully to the treatment of hyponatremia.[5]

Tetrahydro-1-benzazepines are most commonly accessed through reduction of the products of Beckmann[6] or Schmidt[7] ring expansion reactions from derivatives of 1-tetralone. These methods require the use of hazardous reagents (e.g. azides) and are thus not amenable to large-scale synthesis. Moreover, the success of these ring expansion methodologies is highly dependent on the nature of the substrate.

Conversely, formation of the seven-membered ring by the cyclisation of an aliphatic chain often proceeds in low yield.[8,9] An interesting exception is the report of a tandem Heck isomerisation–condensation reaction (Scheme 1), which gave moderate yields of 2-substituted 1-benzazepines from 2-iodoaniline.[10] However, the reaction is limited by the nature of the R substituent, and failed to work when R = H.

Herein we report a milder synthetic route for the synthesis of 1-benzyl-tetrahydro-1-benzazepine **1a** that utilizes palladium catalysed C–C and C–N bond forming steps in the construction of the heterocyclic ring. The scope of the methodology will be demonstrated by the synthesis of structures incorporating alkyl **1b** and aryl substituents **1c** at the 2-position (Fig. 1).

Adopting a reported procedure,[11] the tandem Heck isomerisation reaction proceeded smoothly between 2-bromo-iodobenzene and but-4-en-1-ol under mild reaction conditions, furnishing aldehyde **3a** in high yield (Scheme 2). With slight modifications, the ketones **3b–d** can also be obtained from their corresponding 1-substituted homoallylic alcohols.[12] Even though the conver-



Scheme 1.

Keywords: palladium catalysis; heterocycles; benzazepines; β-hydride elimination.

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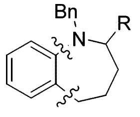

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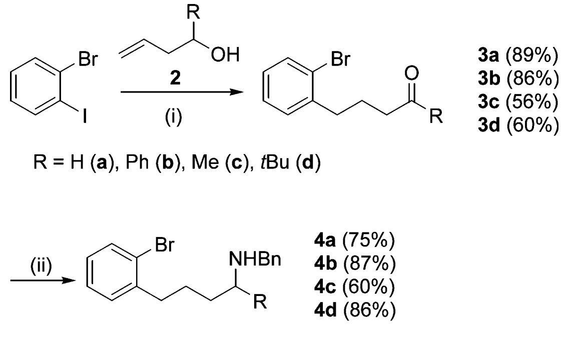
Figure 1. R = H (**a**), Me (**b**), Ph (**c**), *t*-Bu (**d**).

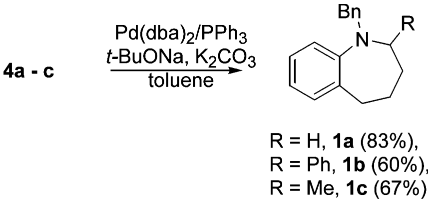


Scheme 2. Synthesis of **4**: (i) when R = H: 2 mol% Pd(OAc)$_2$, ^{n}Bu$_4$NCl, NaHCO$_3$, DMF, 40°C; when R ≠ H: 2 mol% Pd(OAc)$_2$, LiCl, ^{i}Pr$_2$NEt, DMF, 80°C; (ii) a. BnNH$_2$, Ti(O^{i}Pr)$_4$, NaBH$_4$, THF, reflux,[13] b. H$_3$O$^+$.

sions are high, the isolated yields of **3c** and **3d** are lower, as we found these alkyl ketones difficult to purify by conventional column chromatography. Nevertheless, all the carbonyl compounds were isolated as pale yellow oils with varying degrees of thermal stability. If not used immediately, they are best kept at –20°C, where they solidify as cream solids. Subsequent reductive amination under pH-neutral conditions afforded amines **4a–d** in good yields.[13]

A reported procedure for intramolecular aryl amination was adopted for the ring closure step, where a combination of two bases was found to be necessary to attain the optimal yield for **1a**.[14] The method can also be adopted to afford the substituted rings **1b** and **1c** in moderate yields (Scheme 3).

In all cases the formation of the ring was accompanied by a downfield shift of the ^{13}C resonance of the substituted aromatic carbon from 124 to 146 ppm. The connectivity was supported by relevant 2D NMR spectroscopy (HMBC) and the observation of the monomeric M$^+$ ion. Addition of conc. HCl to **1a** yielded the corresponding salt, which was recrystallized from methanol to give colourless prisms suitable for X-ray crystallographic analysis (Fig. 2).[†] The solid-state structure shows that the benzazepine ring adopts a chair-like conformation, with the benzyl substituent in the axial position.[15] The conformation is probably fairly rigid in solution—distinct NMR resonances are observed for each of the nuclei present in the ring, which are not affected by changes in temperature.



Scheme 3. Intramolecular aryl amination.

When the *tert*-butyl substituted amine **4d** was subjected to the ring closure, the major product isolated from the reaction mixture was a dehalogenated imine **5**,[16] the product of a competitive β-hydride reductive elimination pathway (Scheme 4).

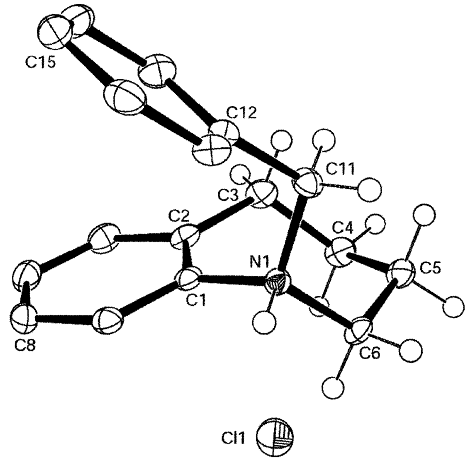
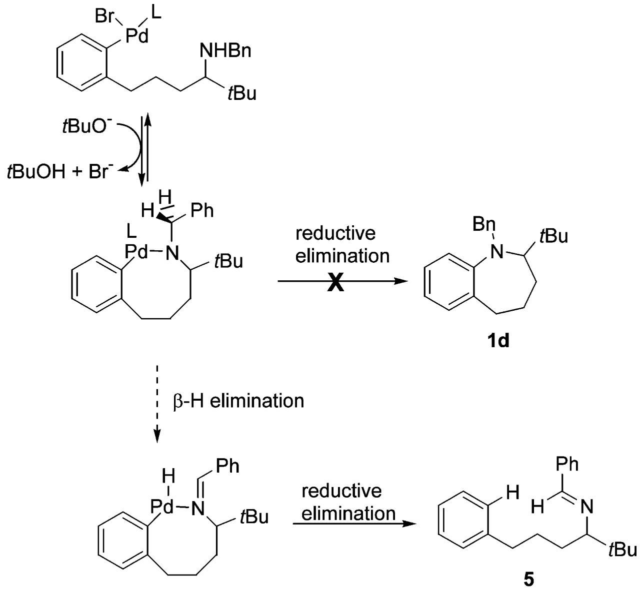


Figure 2. ORTEP drawing for compound **1a**·HCl at 50% probability. Aromatic hydrogen atoms are omitted for clarity.



Scheme 4. Competitive β-H elimination pathway.

[†] Crystallographic data (excluding structure factors) for compounds **1a** and **4d** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 202838 and 202839, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

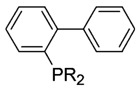


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Figure 3. Bulky ligands for aryl amination reactions.

In a previous study by Hartwig et al., the size of the phosphine ligand, as well as the substitution pattern of the amide ligands and the aryl ring, were found to influence the relative rates for C–N bond-forming reductive elimination and β-hydrogen elimination of amides.[17] With this in mind, we attempted the aryl amination reaction under milder reaction conditions with bulky ligands **6** (Fig. 3, R = *cyclo*-hexyl, **a**; *tert*-butyl, **b**)[18] in the hope of suppressing the β-hydride elimination pathway. However, this resulted only in the recovery of the starting material.

In summary, we have developed a synthetic route to the synthesis of 1-benzyl-tetrahydro-1-benzazepine **1a**, which also permits access to structures **1b** and **1c**, incorporating alkyl and aryl substituents at position-2 of the aliphatic ring. The synthesis constructs the seven-membered ring in three steps from 2-bromo-iodobenzene, utilizing palladium catalysis in two key bond-forming reactions (C–C and C–N). Competitive β-hydride elimination was observed in the C–N bond formation step of a sterically bulky substrate (when R = *tert*-butyl).

Acknowledgements

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12. *Typical procedure*: In a dry, thick-walled, Young's tube was placed $Pd(OAc)_2$ (32 mg), LiCl (1.8 g) and dried DMF (13 mL). The solution was magnetically stirred to afford a yellow suspension, before the addition of diisopropylethylamine (3.8 mL), homoallylic alcohol (14.6 mmol) and 2-bromo-iodobenzene (1.95 mL, 15.0 mmol) successively. The reaction vessel was then sealed via a PTFE tap and placed in a thermostated oil bath at 80°C. After 18 h, the reaction mixture was poured into H_2O and extracted with ether. The combined ether extracts were washed successively with aq. HCl (2N), H_2O, aq. $CaCl_2$ and H_2O. The solution was finally dried over $MgSO_4$, filtered and evaporated. The dark oil was then subjected to column chromatography to furnish the required product.
13. *Typical procedure*: A solution of the corresponding ketone (1 equiv.), $Ti(O\textit{i}Pr)_4$ (1.2 equiv.) and benzyl amine (1.5 equiv.) was stirred in dry THF at ambient temperature overnight, after which time $NaBH_4$ (1.2 equiv.) was added in one portion and the reaction mixture was refluxed for 7 h. In the workup, excess reducing agent was carefully destroyed by the addition of 2 M HCl (aq) at 0°C. The solution was then refluxed for a further 2 h. After cooling, the pH was adjusted to 11 by the addition of 1 M NaOH (aq). The suspension was then filtered through a pad of Celite, and the residue was washed with several portions of CH_2Cl_2. The filtrate was then extracted with CH_2Cl_2 and the combined organic extracts were dried over Na_2SO_4, filtered and evaporated. The residue was subjected to flash column chromatography (silica gel, 20% EtOAc in pentane) to yield the required product as colourless to pale yellow oils. Microanalytically pure samples may be obtained by the precipitation of the compounds as HCl salts, recrystallised from ethanol. However, due to their low solubility in common organic solvents, the NMR spectra and subsequent reactions were carried out using the unprotonated amine.
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16. **Characterisation data for 5**. (EtOAc:*n*-pentane, 1:9, R_f 0.9). Yield 76%. White solid, mp 66.7–66.9°C. IR (KBr disc) ν (*C*=N)1638 cm^{-1}. *m*/*z* (EIMS): 294 (M^+). ^1H NMR ($CDCl_3$, 360 MHz, δ): 0.84 (9H, s, CH_3); 1.19–1.50 (2H, m, CH_2); 1.60–1.64 (2H, m, CH_2); 2.484–2.58 (2H, m,

C*H*$_2$); 2.62 (1H, dd, *J*=4.0, 9.0 Hz, C*H*N); 7.04–7.09 (3H, m, Ph); 7.14–7.18 (2H, m, Ph); 7.31–7.33 (3H, m, Ph); 7.64–7.67 (2H, m, Ph); 8.06 (1H, s, =C*H*N). ^{13}C NMR (CDCl$_3$, 90.5 MHz, δ): 27.0 (C*H*$_3$); 29.4 (C*H*$_2$); 29.5 (C*H*$_2$); 34.4 (*C*Me$_3$); 36.0 (Ar*C*H$_2$); 81.0 (*C*HN); 125.6 (C$_{para}$); 128.1 (*C*H); 128.2 (*C*H); 128.4 (*C*H); 128.5 (*C*H); 130.2 (C$_{para}$); 136.5 (C$_{ipso}$); 142.7 (C$_{ipso}$); 159.1 (*C*=N). Anal. calcd for $C_{21}H_{27}N$ requires 85.95; H, 9.27; N, 4.77%. Found C, 85.93; H, 9.28; N, 4.70%.

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