



Intramolecular palladium mediated π -allyl cyclisation of bis-Cbz- and bis-Boc-protected guanidines



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ABSTRACT

The Pd-mediated π -allyl cyclisation of bis-Cbz- and bis-Boc-protected guanidines **4** and **14b** led to the formation of five- and six-membered heterocycles **5** and **17** in high yields.

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We have previously reported on the synthesis of cyclic guanidines via the epoxide ring opening,¹ iodocyclisation² and Mitsunobu³ condensations and have shown these methods to be effective and predictable for the preparation of five- and six-membered guanidine heterocycles. We were interested in extending this methodology to include palladium catalysed π -allyl cyclisations, and prompted by the report of Miyabe⁴ on intermolecular palladium- and indium-catalysed allylation of substituted guanidines, we now report our initial findings on intramolecular allylation of bis-protected guanidines. It is worthy of note that at the outset of this work the only known cyclisation of this type had been reported by Büchi et al., in 1988, who cyclised an *N*-methoxy-guanidine in their synthesis of alchohaine and isoalchohaine.^{5,6}

Our initially required substrate **4** was easily prepared from commercially available 2-*tert*-butene-1,4-diol (**1**), which on reaction with phthalimide in the presence of PPh₃ and DEAD gave the protected amine **2** in 82% yield. Reaction of **2** with hydrazine hydrate afforded deprotection of the amine, which on treatment with triethylamine and the commercially available guanidylating agent **6a**, gave the guanidine **3** in 56% yield. Acetylation of **3** was achieved by treatment with acetic anhydride in pyridine leading to the required substrate **4** in 72% yield. Cyclisation of **4** was achieved by treatment with Pd(OAc)₂ and PPh₃ in THF to give the five-membered guanidine **5** in 90% yield after chromatography (Scheme 1).

Following this success, we investigated the formation of a six-membered system and set about the preparation of substrate **14a**. The commercially available alcohol **7** was silyl protected using *t*BDMSCl/trisilazole to give **8** in quantitative yield, which in turn was metallated with *n*-BuLi and treated with paraformaldehyde to give on work-up the alcohol **9** in 84% yield. Selective reduction of **9** was achieved using Ni(OAc)₂/NaBH₄ leading to alcohol **10** (88% yield), which was acetylated using pyridine and acetic anhydride affording **11** in 95% yield. The silyl ether was deprotected using TBAF to give alcohol **12** in 84% yield. Reaction of **12** with phthalimide in the presence of PPh₃ and DEAD gave the protected amine **13**, which was treated with hydrazine hydrate to remove the phthalimide protecting group and then guanidylated with **6a** to give the bis-Boc-protected substrate **14a** in 90% yield over 2 steps. Similar treatment of **13** with hydrazine hydrate followed by guanidylating with **6b** gave the bis-Cbz-protected substrate **14b** in 47% yield over 2 steps.

Attempted cyclisation of **14a** using the previously employed conditions of Pd(OAc)₂ and PPh₃ in THF or CH₂Cl₂ failed to give any evidence of cyclisation, and on prolonged reaction the only product isolated was the mono-protected guanidine **15**, which also did not undergo cyclisation under these conditions. Attempts were made to modify the conditions including pre-forming the palladium catalyst *in situ* using Pd(OAc)₂ or PdCl₂(CH₂Cl₂) in acetonitrile or THF, using Pd(dppf)₂ in THF or 1,4-dioxane, but in all cases no cyclisation products were observed and either **14a** was recovered or complete decomposition occurred. We suspected

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