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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.

We have previously reported on the synthesis of cyclic guanidines via the epoxide ring opening,[1] iodocyclisation[2] and Mitsunobu[3] 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 Miyabe[4] on intermolecular palladium- and iridium-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-methoxyguanidine in their synthesis of alchorneine and isoalchorneine.[5,6]

Our initially required substrate **4** was easily prepared from commercially available 2-cis-butene-1,4-diol (**1**), which on reaction with phthalimide in the presence of PPh_3 and DEAD gave the protected amine **2** in 82% yield. Reaction of **2** with hydrazine hydrate affected deprotection of the amine, which on treatment with triethylamine and the commercially available guanylating 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 PPh_3 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)DMSCl/imidazole 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 64% yield. Selective reduction of **9** was achieved using $Ni(OAc)_2/NaBH_4$ loading 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 PPh_3 and DIAD gave the protected amine **13**, which was treated with hydrazine hydrate to remove the phthalimide protecting group, and then guanylated 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 guanylation 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 PPh_3 in THF or CH_3CN 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 $PdCl_2(CH_3CN)$ in acetonitrile or THF, using $Pd(dppe)_2$ 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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