Tetrahedron Letters 54 (2013) 6716–6718

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

Zainab Al-Shuhaib [a,b], Henning Böckemeier [a], Lawrence Coghlan [a], Elina Dörksen [a], Iestyn V. Jones [a], Patrick J. Murphy [a,*], Robert Nash [c], James M. Page [a]

[a] School of Chemistry, University of Wales, Bangor, Gwynedd LL57 2UW, UK
[b] Department of Chemistry, University of Basra, College of Education, Basra, Iraq
[c] Phytoquest Limited, Aberystwyth University, Plas Gogerddan, Aberystwyth, Ceredigion SY23 3EB, UK

ARTICLE INFO

Article history:
Received 26 June 2013
Revised 3 September 2013
Accepted 20 September 2013
Available online 27 September 2013

Keywords:
Guanidine
Palladium allylation
Heterocyclisation
Intramolecular cyclisation

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 1989, who cyclised an N-methoxyguainidine in their synthesis of alchorneine and isoalchorneine.[5,6]

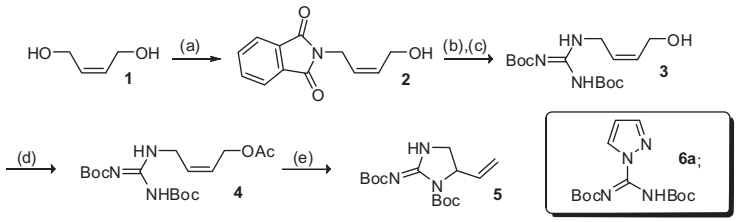
Our initially required substrate **4** was easily prepared from commercially available 2-*cis*-butene-1,4-diol (**1**), which on reaction with phthalimide in the presence of PPh_3 and DEAD gave the protected amine **2** in 82% yield. Reaction of **2** with hydrazine hydrate affected deprotection of the 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*BDMSCl/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 $Ni(OAc)_2/NaBH_4$ 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 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

* Corresponding author. Tel.: +44 01248 382392; fax: +44 01248 370528.
E-mail address: paddy@bangor.ac.uk (P.J. Murphy).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.09.093



Scheme 1. Reagents and conditions: (a) PPh_3, phthalimide, THF, DEAD, 82%; (b) $NH_2NH_2{\cdot}H_2O$, EtOH, reflux, (c) Et_3N, **6a** rt, 24 h, 56%; (d) Ac_2O, py, DMAP, CH_2Cl_2, 0 °C, 30 min, 72% (e) $Pd(OAc)_2/PPh_3$, THF, reflux 3 h, 90%.

the lack of cyclisation might be based on the presence of the bulky Boc-protecting groups and we thus turned our attention to the Z-protected analogue **14b** (Scheme 2).

Reaction of **14b** with $Pd(PPh)_4$ in acetonitrile at reflux led to a rapid consumption of the starting material as evidenced by TLC, and the appearance of a new product at a similar *Rf* to the previously prepared **5**. A small sample was removed from the reaction mixture and ^1H NMR spectroscopy demonstrated the presence of the bis-protected guanidine **16** as evidenced by an ABX signal at δ_H 5.85 (1H, ddd, J = 4.4, 10.4, 17.4 Hz) for the vinylic CH and a complex multiplet at δ_H 5.22–5.00 (6H, m) for the benzyl and vinylic methylene protons. Attempted purification of the reaction product after work-up failed to yield any material at this *Rf* and instead a lower running fraction was obtained which was identified as the mono-Cbz-protected guanidine **17**, and which unfortunately co-eluted with Ph_3PO formed as a by-product in the reaction. In order to circumvent this problem we reacted **14b** with $Pd(OAc)_2$ and LiBr in THF in the presence of Et_3N under phosphine-free conditions and obtained **17** in 39% yield after chromatography. In an attempt to improve this yield we reacted **14b** with a catalytic amount of $Pd(dppe)_2$ in THF in the presence of Et_3N under reflux for 24 h which gave **17** in 84% yield. (Scheme 2) Diagnostic signals in the ^1H NMR spectrum were at δ_H 5.70 (1H, ddd, J = 5.4, 10.3, 17.2 Hz) for the vinylic methine proton and at δ_H 5.19 (1H, d, J = 10.3 Hz, CH) and 5.21 (1H, d, J = 17.2 Hz, CH) for the vinylic methylene protons. Long range HMBC correlations between the guanidine carbon at δ_C 158.2 and the signals at δ_H 3.15 (2H, t, J = 5.8 Hz, CH_2N) and 3.94–3.98 (1H, m, CHN) were also observed.

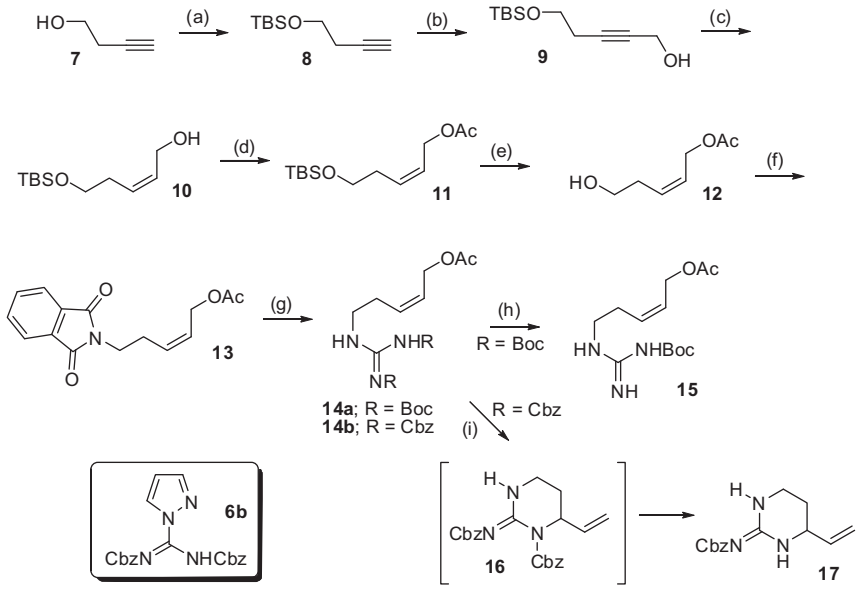
In conclusion we have demonstrated that the Pd-mediated π-allyl cyclisation of bis-Cbz- and bis-Boc-protected guanidines is a feasible and high yielding process, particularly in the case of five-membered ring systems. However, problems exist in the labile nature of the protecting groups and this might be a limiting factor in their use. Despite this, the reaction has potential applications in synthesis[6] and similar reactions of carbamates and ureas[7–10] have been reported with considerable success. We are currently applying our findings to the synthesis of the novel guanidine-containing natural product, nitensidine E,[11] and will report our findings in due course.

Acknowledgements

Thanks are given to the ESF (I.V.J.), the ERASMUS/SOCRATES Program (H.B and E.D) and to the Iraqi government (Z.A.S.) for funding, and also to the EPSRC Mass Spectrometry service at Swansea for analytical data.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.09.093. These data include MOL files and InChiKeys of the most important compounds described in this article.



Scheme 2. Reagents and conditions: (a) DMF, *t*BDMSCl/imid., 0 °C to rt, 16–24 h, 100%; (b) THF, *n*-BuLi, paraformaldehyde, −78 °C to rt, 1 h, 64%; (c) $Ni(OAc)_2{\cdot}4H_2O$, EtOH, H_2, $NaBH_4$, ethylenediamine, 88%; (d) Ac_2O, py, DMAP, CH_2Cl_2, 0 °C, 30 min, 95%; (e) THF, TBAF, 0 °C to rt 4 h, 84%; (f) PPh_3, phthalimide, THF, DIAD; (g) (i) $NH_2NH_2.H_2O$, EtOH, reflux, (ii) Et_3N, **6a** or **6b**, rt, 16–24 h, **14a**: 90% (from **12**); **14b**: 47% (from **12**); (h) $Pd(OAc)_2/PPh_3$, THF, reflux; (i) see text.

References and notes

1. (a) Dennis, M.; Hall, L. M.; Murphy, P. J.; Thornhill, A. J.; Nash, R.; Winters, A. L.; Hursthouse, M. B.; Light, M. E.; Horton, P. *Tetrahedron Lett.* **2003**, *44*, 3075–3080; (b) Albrecht, C.; Barnes, S.; Böckemeier, H.; Davies, D. H.; Dennis, M.; Evans, D. M.; Fletcher, M. D.; Jones, I.; Leitmann, V.; Murphy, P. J.; Rowles, R.; Nash, R.; Stephenson, R. A.; Horton, P. N.; Hursthouse, M. B. *Tetrahedron Lett.* **2008**, *49*, 185–188.
2. Murphy, P. J.; Davies, D. H.; Fletcher, M. D.; Franken, H.; Hollinshead, J.; Kähm, K.; Nash, R.; Potter, D. *Tetrahedron Lett.* **2010**, *51*, 6825–6829.
3. Evans, D. M.; Murphy, P. J. *Chem. Commun.* **2011**, 3225–3226.
4. Miyabe, H.; Yoshida, K.; Reddy, V. K.; Takemoto, Y. *J. Org. Chem.* **2009**, *74*, 305–311.
5. Büchi, G.; Rodriguez, A. D.; Yakushijin, K. *J. Org. Chem.* **1989**, *54*, 4494–4496.
6. Cyclisation of *O*-protected-N-hydroxyguanidines to give five-membered guanidines similar to anatoxin-A(*S*) has been recently reported: Buck, E. E. Ph.D. thesis, University of Pittsburgh, 2012.
7. Trost, B. M.; Patterson, D. E. *J. Org. Chem.* **1998**, *63*, 1339–1341.
8. Hirai, Y.; Watanabe, J.; Nozaki, T.; Yokoyama, H.; Yamaguchi, S. *J. Org. Chem.* **1997**, *62*, 776–777.
9. Kirsch, S. F.; Overman, L. E. *J. Org. Chem.* **2005**, *70*, 2859–2861.
10. Overman, L. E.; Remarchuck, T. P. *J. Am. Chem. Soc.* **2002**, *124*, 12–13.
11. Regasini, L. O.; Castro-Gamboa, I.; Silva, D. H.; Furlan, M.; Barreiro, E. J.; Ferreira, P. M.; Pessoa, C.; Lotufo, L. V.; de Moraes, M. O.; Young, M. C.; Bolzani, V. S. *J. Nat. Prod.* **2009**, *72*, 473–476.