Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Palladium-NHC catalyzed formation of cyclopenta[*b*]benzofurans and their subsequent modification.

Silviya Demerzhan and Scott R. Gilbertson

Leave this area blank for abstract info.

Palladium-NHC catalyzed formation of cyclopenta[*b*]benzofurans and their subsequent modification.

Silviya Demerzhan^a and Scott R. Gilbertson^{a,*}

^aDepartment of Chemistry, University of Houston, Houston TX 77204

ARTICLE INFO

Article history:

Received

Received in revised form

Accepted

Available online

Keywords:

Benzofuran

N-heterocyclic carbene

Palladium

Suzuki

Hydrazine

ABSTRACT

A palladium NHC complex is used to catalyze the addition of *ortho* iodophenols to diazabicyclic alkenes. The product cyclopenta[*b*]benzofurans are then derivitized by Suzuki reaction, and reduction of the N-N bond and followed by conversion of the amines into amides.

2009 Elsevier Ltd. All rights reserved.

Introduction

We have recently reported that palladium NHC complex **1** will catalyze the reaction of bicyclic hydrazines with iodophenols (Scheme 1).¹ The original version of this reaction, using palladium phosphine complexes, was reported by others to required the use of additives such as tetrabutylammonium chloride, lithium chloride and the need to run the reaction in ionic liquids such as 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF₆]).² We have found that palladium NHC complexes such as **1** catalyze the formation of the cyclopenta[*b*]benzofuran structure in good to excellent yields. The reaction can be carried out at 80 °C in a sealed Schlenk tube or using microwave heating.

Given that the cyclopenta[*b*]benzofuran structure is found in a number of biologically active molecules including thromboxane A₂ inhibitors (**6**), and the natural products, beraprost (**7**) aplysin (**8**) and rocaglaol derivatives (**10–13**),^{3–8} we decided to develop this reaction to provide a small collection of molecules for screening.

Two sites were selected for modification on the benzofuran scaffold, the aromatic ring and the nitrogen attached to the allylic position of the five-member ring. The approach taken was to perform the initial reaction with a substrate that would allow for modification of the benzene ring of the benzofuran. This was

accomplished by performing the initial reaction with bromo-iodo phenol **4**. This bromide was then modified by the Suzuki reaction with a variety of different aromatic boranes.

Scheme 1

Figure 1

* Corresponding author. Tel.: +1-832-842-8821; fax: +1-713-743-2709; e-mail: srgilbertson@uh.edu

To make the desired modifications to the nitrogen on the five-member ring, chemistry needed to be developed that allowed for the cleavage of the N-N bond of the hydrazide to an amine. This transformation required considerable optimization. Initial attempts to cleave the bond by hydrogenolysis using Raney nickel,⁹⁻¹² palladium on carbon,¹³⁻¹⁵ platinum oxide,¹⁶⁻¹⁸ Wilkinson's catalyst or palladium hydroxide¹⁹ on carbon at pressures up to 30 bar of hydrogen resulted in only reduction of the double bond (Scheme 2). Using methods that include zinc dust,²⁰ lithium in liquid ammonia²¹ or reduction with titanium tetrachloride with lithium aluminum hydride²² resulted in either decomposition or no reaction in the case for TiCl_4/LAH . The method of Friestad²³ (Scheme 3) requiring the swapping of Cbz protection of a trifluoroacetate group followed by samarium(II)iodide proceeded in good yield however the workup of the reaction mixture proved to be difficult.

Scheme 2

Raney Ni, H_2 (1 bar), AcOH (cat), MeOH, 30 h, no reaction
 Raney Ni, H_2 (20 bar), AcOH (cat), MeOH, 24 h, 89%
 Raney Ni, H_2 (30 bar), AcOH (cat), MeOH, 24 h, 94%
 Raney Ni, H_2 (30 bar), TFA(cat), MeOH, 3 days, 93%

Other catalysts used: Wilkinson's Catalysts, PtO_2 , Pd/C, $\text{Pd}(\text{OH})_2/\text{C}$

Scheme 3

The best method for our purposes proved to be reaction of the hydrazide with methyl bromoacetate and cesium carbonate, followed by heating in the presence of cesium carbonate for up to 48 hours (Scheme 4).²⁴ This method proved effective with isopropyl, *t*-butyl and benzyl carbamates as the protecting group on nitrogen. Given the superior yields and ease of deprotection, *t*-butyl version was carried forward. Removal of the Boc protecting group with TFA provided the desired amine in high yield.

With routes to **27** and **28** in hand, derivatives where the aromatic ring and the amine are modified were synthesized. The bromide of the benzene ring was modified by Suzuki coupling using a collection of boronic acids.²⁵ The Suzuki reaction was run on the Boc protected version of the benzofuran, which was then subsequently deprotected.²⁶ The yields for these reactions range

Scheme 4

Scheme 5

from 89% to 50% for the Suzuki reaction and 88% to 69% for the deprotections. Products with ethers, ketones, esters, sulfonamides, nitro groups and trifluoromethyl groups were all synthesized and fully characterized (Scheme 5).

In addition to modification at the aromatic ring a series of amides was synthesized. Amides possessing aromatic groups, aliphatic groups as well as amino acids were synthesized. In general these molecules were synthesized from the corresponding acid chlorides. One sulfonamide was also made.

Scheme 6

In conclusion, the diastereoselective Pd-NHC catalyzed cyclopentannulation of diazabicyclic alkenes with 2-iodophenols has been used to synthesize cyclopenta[*b*]benzofurans. This reaction readily proceeds in good yield on a variety of substrates under reasonable conditions. The product cyclopenta[*b*]benzofurans offer potential as biologically active molecules and consequently methodology needed to be found to convert the hydrazide products into amines that could then be further elaborated. A number of methods were investigated with two of them providing the desired product. The resulting amine was found to be compatible with amide formation to allow for a series of compounds to be synthesized. Additionally the catalytic reaction tolerates the presence of a bromide on the indophenol used. This allows further modification of the cyclopenta[*b*]benzofurans through the Suzuki reaction. Versions

of the scaffold where either the aromatic ring or amine were modified have been synthesized.

Acknowledgments

This work was supported in part by NSF CHE-0953083 and Robert A. Welch Foundation.

References and notes

1. Prasad, B. A. B.; Buechele, A. E.; Gilbertson, S. R. *Org Lett* **2010**, *12*, 5422.
2. John, J.; Indu, U.; Suresh, E.; Radhakrishnan, K. V. *J. Am. Chem. Soc.* **2009**, *131*, 5042.
3. Engelmeier, D.; Hadacek, F.; Pacher, T.; Vajrodaya, S.; Greger, H. *J. Agric. Food Chem.* **2000**, *48*, 1400.
4. Yamamura, S.; Hirata, Y. *Tetrahedron* **1969**, *19*, 1485.
5. Irie, T.; Suzuki, M.; Kurosawa, E.; Masamune, T. *Tetrahedron* **1970**, *26*, 3271.
6. Ohta, K.; Takagi, M. *Phytochemistry* **1977**, *16*, 1062.
7. Ojika, M.; Shizuri, Y.; Yamada, K. *Phytochemistry* **1982**, *21*, 2010.
8. Shizuri, Y.; Yamada, A.; Yamada, K. *Phytochemistry* **1984**, *23*, 2672.
9. Enders, D.; Schubert, H.; Nußling, C. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1109.
10. Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 6397.
11. Hinman, R. J. *J. Org. Chem.* **1957**, *22*, 148.
12. Hsieh, Y.-T.; Lee, G.-H.; Wang, Y.; Luh, T. Y. *J. Org. Chem.* **1998**, *63*, 1484.
13. Bataille, P.; Paternò, M.; Brown, E. *Tetrahedron Asymm.* **1998**, *9*, 2181.
14. Chandrasekhar, S.; Reddy, C. R.; Rao, R. J. *Synlett* **2001**, 1561.
15. Clive, D. L. J.; Zhang, J.; Subedi, R.; Bouetard, V.; Hiebert, S.; Ewanuk, R. J. *J. Org. Chem.* **2001**, *66*, 1233.
16. Claremon, D. A.; Lumma, P. K.; Phillips, B. T. *J. Am. Chem. Soc.* **1986**, *108*, 8265.
17. Gennari, C.; Colombo, L.; Bertolini, G. *J. Am. Chem. Soc.* **1986**, *108*, 6394.
18. Guerra, F. M.; Mish, M. R.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 4265.
19. Kim, Y. H.; Choi, J. Y. *Tetrahedron Lett.* **1996**, *37*, 5543.
20. Leblanc, Y.; Fitzsimmons, B. *Tetrahedron Lett.* **1989**, *30*, 2889.
21. Denmark, S.; Nicaise, O.; Edwards, J. J. *J. Org. Chem.* **1990**, *55*, 6219.
22. Entwistle, I.; Johnstone, R.; Wilby, A. *Tetrahedron* **1982**, *38*, 419.
23. Ding, H.; Friestad, G. *Org. Lett.* **2004**, *6*, 637.
24. Magnus, P.; Garizi, N.; Seibert, K.; Ornholt, A. *Org. Lett.* **2009**, *11*, 5646.
25. Gong, Y.; Wei, H. *Org. Lett.* **2002**, *4*, 3803.
26. Srinivasan, N.; George, A.; Ganesan, A. *Molecular Diversity* **2005**, *9*, 291.