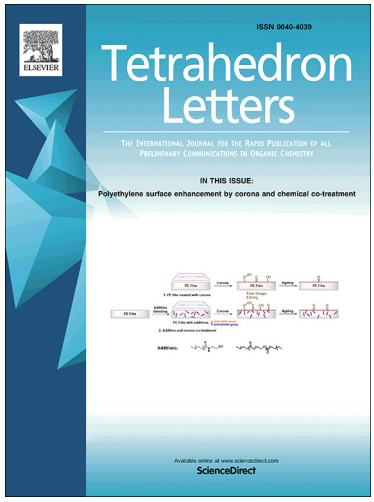



# Synthesis of oxetane/azetidine containing spirocycles

Rosalie Hamill, Benjamin Jones, Christopher M. Pask, Visuvanathar Sridharan

PII: S0040-4039(19)30258-8
DOI: https://doi.org/10.1016/j.tetlet.2019.03.042
Reference: TETL 50683

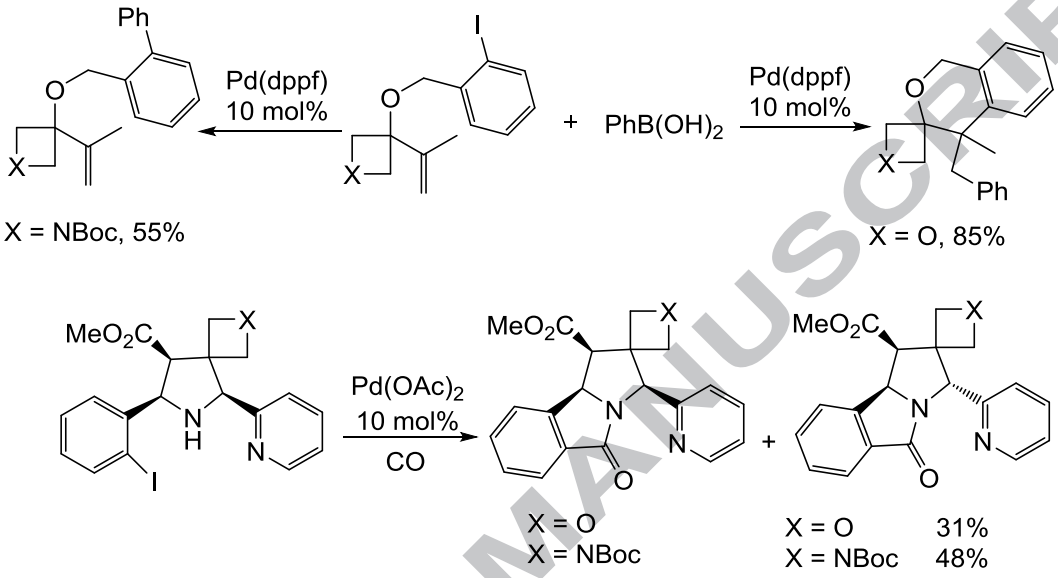
To appear in: *Tetrahedron Letters*

Received Date: 7 January 2019
Revised Date: 12 March 2019
Accepted Date: 15 March 2019

Please cite this article as: Hamill, R., Jones, B., Pask, C.M., Sridharan, V., Synthesis of oxetane/azetidine containing spirocycles, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.03.042

# Synthesis of oxetane/azetidine containing spirocycles

Rosalie Hamill, Benjamin Jones, Christopher M. Pask and Visuvanathar Sridharan*



ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

# Synthesis of oxetane/azetidine containing spirocycles

Rosalie Hamill, Benjamin Jones, Christopher M. Pask, and Visuvanathar Sridharan*

*School of Chemistry, University of Leeds, LS2 9JT, UK.*
*Corresponding author: v.sridharan@leeds.ac.uk; Tel: +44 1133436520

ARTICLE INFO

*Article history:*
Received
Received in revised form
Accepted
Available online

*Keywords:*
Oxetane
Spirocycle
Cycloaddition
Carbonylation

ABSTRACT

Oxetane-benzopyran spirocycles were synthesised *via* a palladium catalysed cyclisation-cross coupling cascade reaction whilst oxetane/azetidine-pyrrolidino isoindolone spirocycles were synthesised *via* a silver catalysed 1,3-dipolar cycloaddition reaction followed by a palladium catalysed carbonylation-amination process.



## Introduction

Oxetane rings in drug molecules have been determined to have an influence on a multitude of different properties, including lipophilicity, aqueous solubility, metabolic stability, and conformational preference; they also greatly improve key pharmacokinetic properties when grafted onto molecular scaffolds.[1] Oxetanes also demonstrate diverse potential as bioisosteres for less desirable functional groups in drug design, such as *gem*-dimethyl and carbonyl groups. The potential for oxetanes to be used as *gem*-dimethyl bioisosteres was introduced by Carreira and co-workers;[2] it is common practice in drug discovery to introduce *gem*-dimethyl groups into metabolically labile methylene units. However, this also adds to the molecules lipophilicity, and can adversely affect its pharmacokinetic properties. Use of an oxetane instead of a *gem*-dimethyl group, bridging the two methyl groups with an electronegative oxygen, has been shown to add the desired bulk without altering the overall lipophilicity.[2] Furthermore, the Van der Waals volume of an oxetane is almost identical to that of the *gem*-dimethyl group, and their partial molar volumes in water are essentially identical.[3]

Benzopyran derivatives have been shown to have notable bioactivities, including anti-inflammatory and anti-hypertensiveproperties.[4] Benzopyrans can be found in a multitude of divergent areas within chemistry; such as the metabolite eriodictyol, which has anti-inflammatory and antioxidant properties,[5] and the phytoalexin xanthyletin, which is found in citrus plants[6] (Fig. 1). Oxetane/pyrrolidine containing spirocycles are important structural motifs, possessing a wide range of medicinal properties including anti-viral[7] and anti-bacterial[8] (Fig. 1).

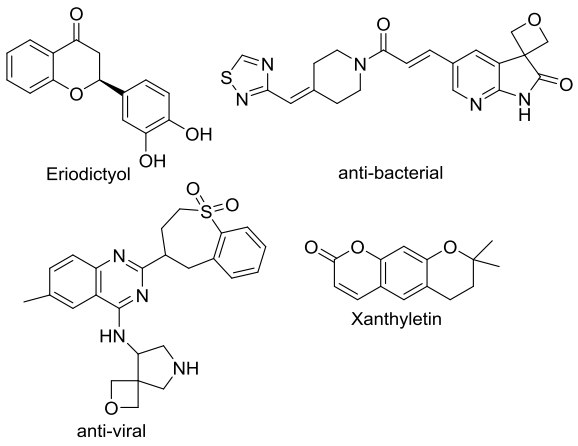


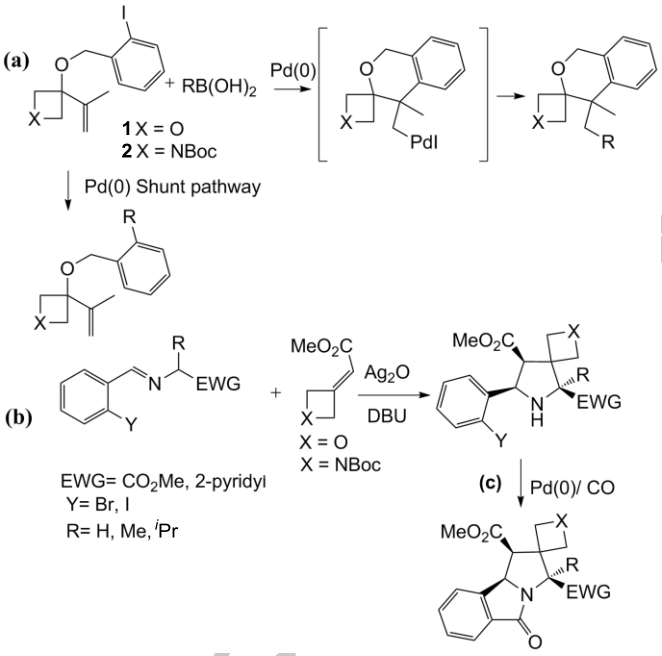

**Figure 1**. Representative examples of drug molecules containing the benzopyran motif and oxetane/pyrrolidine spirocycles.

In this communication we report (i) a palladium catalysed cyclisation-cross coupling cascade reaction for the synthesis of oxetane-benzopyran spirocycles (Scheme 1a) and (ii) a silver catalysed 1,3-dipolar cycloaddition reaction followed by a palladium catalysed carbonylation amination process to afford oxetane/azetidine-pyrolidino isoindolone containing spirocycles (Scheme 1b, c).

Palladium catalysed cyclisation-cross coupling cascade reactions were used to synthesise benzopyran spirocycles with a tethered oxetane moiety.[9] Initially we explored the palladium catalysed cyclisation-cross coupling process using **1** (1 mmol), phenyl boronic acid (2 mmol), $Pd(OAc)_2$ (10 mol%), dppf (10 mol%) and $Cs_2CO_3$ (2 mmol) in dioxane/water (15:1, 3 mL)

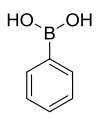
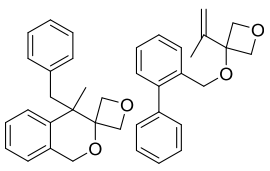
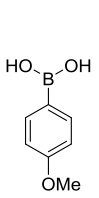
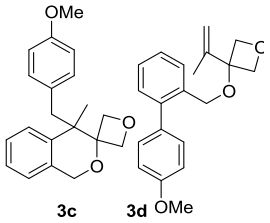
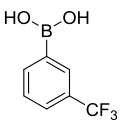
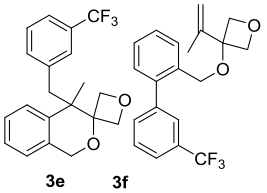
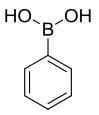
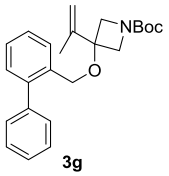
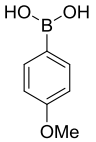
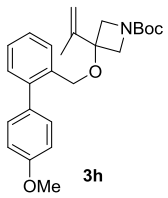
stirred at 90 °C for 16 h, which gave the cyclisation-cross coupling product **3a** together with the direct capture product **3b** in 85% combined yield (Table 1, entry 1) favouring the cyclisation-cross coupling product **3a**. Cyclisation-cross coupling reactions using **1** and *p*-methoxyphenyl boronic acid gave the cyclisation-cross coupling product **3c** together with the direct capture product **3d** in 50% combined yield (Table 1, entry 2) whilst *m*-trifluoromethylphenylboronic acid gave the cyclisation-cross coupling product **3e** and the direct capture product **3f** in 24% combined yield (Table 1, entry 3). The lower yields of products **3c** and **3d** may be partly due to the boronic acid containing an electron withdrawing group and therefore undergoing protodeborylation at a faster rate.

However, when a Boc-protected azetidine was tethered to alkene **2** only the direct capture products **3g** and **3h** were observed (Table 1, entries 4, 5) in moderate yield suggesting that the transmetallation step occurs faster than the carbopalladation step (Scheme 1a). This is proposed to be due to the difference in puckering angle between the azetidine (≈33°) and oxetane (11°) rings.[10]




**Scheme 1.** Palladium and silver catalysed cascade reactions.

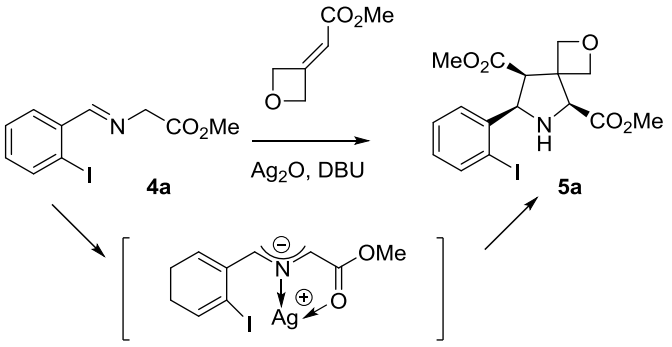
**Table 1.** Palladium catalysed cyclisation-cross coupling cascade.[a]

| Entry | Zipper | Boronic acid | Product | Yield (%)[b] |
|---|---|---|---|---|
| 1 | **1a** |  |  **3a** : **3b** 13 : 1 | 85 |
| 2 | **1a** |  |  **3c** : **3d** 3 : 1 | 50 |
| 3 | **1a** |  |  **3e** : **3f** 3 : 1 | 24 |
| 4 | **1b** |  |  **3g** | 55[c] |
| 5 | **1b** |  |  **3h** | 30[c] |

[a]Reagents and conditions: **1** (1 mmol), boronic acid (2 mmol), $Pd(OAc)_2$ (10 mol%), dppf (10 mol%), $Cs_2CO_3$ (2 mmol), dioxane/water (15:1, 3 mL), 90 °C, 16 h; [b]Isolated yield. [c]The use of $Pd(PPh_3)_4$ (10 mol%) also gave the direct capture product.

Next, we explored a silver catalysed 1,3-dipolar cycloaddition reaction followed by a palladium catalysed carbonylation amination process to afford oxetane/azetidine-pyrolidino isoindolone spirocycles (Scheme 1b). Initially we carried out the silver catalysed 1,3-dipolar cycloaddition reaction using methyl-(*E*)-*N*-[(2-iodophenyl)methylene]glycinate (0.5 mmol), methyl 2-(oxetan-3-ylidene)acetate (0.5 mmol), $Ag_2O$ (10 mol%) and DBU (0.5 mmol) in toluene (10 mL) at room temperature for 16 h, which gave the cycloadduct **4a** in 71% yield (Table 2, entry 1).

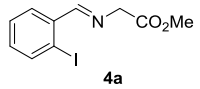
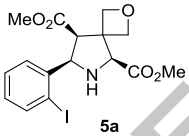
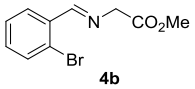
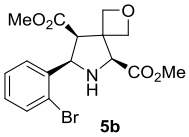
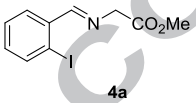
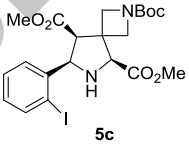
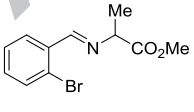
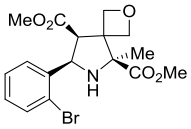
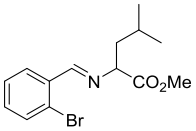
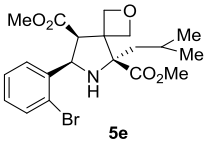
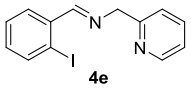
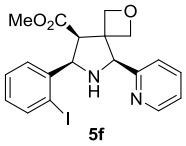
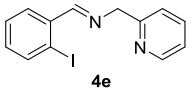
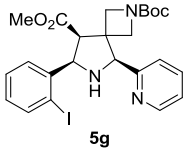
The reaction is stereospecific and regiospecific, affording a single isolated product.[11] One regioisomer is preferentially formed because of the favourable HOMO-LUMO overlap between the dipole and dipolarophile in the *endo*-transition state of the *syn*-dipole (Scheme 2).[12] A single diastereomer was also observed using *tert*-butyl-3-(2-methoxy-2-oxoethylidene)azetidine-1-carboxylate **4c** as a dipolarophile (Table 2, entry 3).




**Scheme 2.** Formation of the metallodipole.

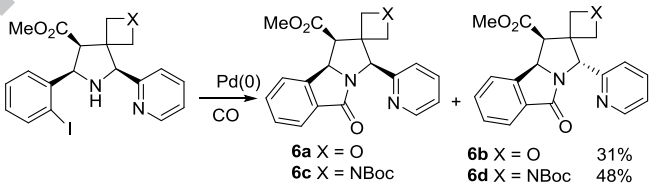
Imines derived from alanine methyl ester/leucine methyl ester also underwent the cycloaddition reaction with oxetane/azetidine dipolarophiles to give cycloadducts **5d** and **5e** in moderate yields (Table 2, entries 4-5). We also varied the activating group in the imine. Thus, the 2-pyridyl activating group resulted in the formation of cycloadducts **5f** and **5g** in moderate yields (Table 2, entries 6-7).

**Table 2.** Silver catalysed 1, 3-dipolar cycloaddition reaction.[a]

| Entry | Imine | Cycloadduct | Yield (%)[b] |
|---|---|---|---|
| 1 |  **4a** |  **5a** | 71 |
| 2 |  **4b** |  **5b** | 53 |
| 3 |  **4a** |  **5c** | 46 |
| 4 |  **4c** |  **5d** | 52 |
| 5 |  **4d** |  **5e** | 25 |
| 6 |  **4e** |  **5f** | 31 |
| 7 |  **4e** |  **5g** | 46 |

[a]Reagents and conditions: imine (0.5 mmol), dipolarophile (0.5 mmol), DBU (0.5 mmol), $Ag_2O$ (10 mol%), toluene (15 mL), room temperature 16-20 h. [b]Isolated yield.

Finally we explored the palladium catalysed carbonylation-amination reaction (Scheme 1c).[13] Thus, **5f** (1 mmol), $Cs_2CO_3$ (2 mmol), $Pd(OAc)_2$ (10 mol%) and tris 2-furyl phosphine (20 mol%) under a carbon monoxide balloon (1 atm.) in toluene at 100 °C for 24 h, afforded the expected carbonylated product **6a** and the epimerised carbonylated product **6b** in a 1:1 ratio and 31% combined yield (Scheme 3). The structure of **6b** was confirmed by single crystal X-ray diffraction (Fig. 3).[14]




**Scheme 3.** Palladium catalysed carbonylation/amination reaction.

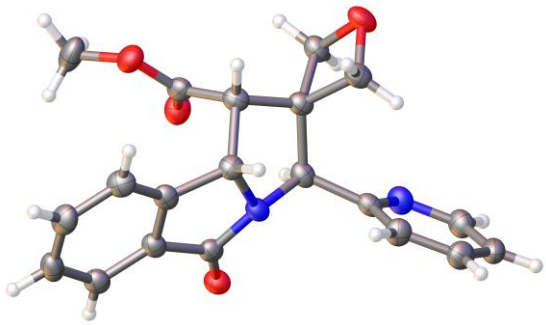


**Figure 2.** Single X-ray crystal structure of compound **6b**.

Epimerisation could occur before or after the carbonylation process. The reaction of cycloadduct **5g** and carbon monoxide (1 atm.) also afforded the expected carbonylated product **6c** and the epimerised carbonylated product **6d** in a 1:1 ratio and 48% combined yield. However, cycloadducts **5a-e** failed to give carbonylated products under the same conditions, possibly due to a sluggish oxidative addition process.

In summary, we report the application of a palladium catalysed cyclisation-cross coupling cascade to synthesise benzopyran/oxetane spirocycles together with biaryl containing oxetane/azetidines in moderate to good yields. Oxetane/azetidine-pyrrolidino isoindolone spirocycles were also synthesised *via* a silver-catalysed 1,3-dipolar cycloaddition reaction followed by a palladium catalysed carbonylation-amination process in good yields.

## Notes and References


1. Burkhard JA, Wuitschik G, Rogers-Evans M, Muller K, Carreira EM. *Angew. Chem. Int. Ed*. 2010; 49: 9052.
2. Wuitschik G, Rogers-Evans M, Muller K, Fischer H, Wagner B, Schuler F, Polonchuk L, Carreira EM. *Angew. Chem. Int. Ed.* 2006; 45: 7736; Wuitschik G, Carreria EM, Wagner B, Fisher H, Parrilla I, Schuler F, Rogers-Evans M, Muller K. *J. Med. Chem.* 2010; 53: 3227.
3. Edward JT, Farrell PG, Shahidi P. *J. Chem. Soc. Farady. Trans.* 1977; 73: 705.
4. You ZY, Wang YH, Zhang ZG, Xu MJ, Xe SJ, Han TS, Feng L, Li XG, Xu J. *Marine Drugs* 2013; 11: 4035.
5. Rossato MF, Trevisan G, Walker CIB, Klafke JZ, de Oliveria AP, Villarinho JG, Zanon RB, Royes LFF, Athayde ML, Gomez MV, Ferrerira J. *Biochem. Pharmacol.* 2011; 81: 544.
6. Magiatis P, Melliou E, Skaltsounis AL, Mitaku S, Leonce S, Renard P, Pierre A, Atassi G. *J. Nat. Prod.* 1998; 61: 982.
7. Chen, L., Feng, L., Feng, S., Gao, L., Guo, T., Huang, M., Liu, C., Liu, Y., Wang, L., Wong, J., J. C. PCT Int. Appl. WO/2013/020993; *Chem. Abstr*. **2013**
8. Mohamed T., Hosahalli S., Panigrahi S.K., PCT Int.Appl. WO/2013/148537A1; *Chem. Abstr*. **2013**
9. Grigg R, Sridharan V. *Pure Appl. Chem*. 1998; 70: 1047; Grigg R, Sridharan V. *J. Organomet. Chem.* 1999; 576: 65; Li Z, Hu C, Guo J, Li J, Cui Y, Jia Y. *Org. Lett.* 2010; 12: 480-483; Petrone DA, Malik HA, Clemenceau A, Lautens M. *Org. Lett.* 2012; 14:4806-4809
10. Smith SA, Hand KE, Love ML, Hill G, Magers DH. *J. Comput. Chem.* 2013; 34: 558; Dorofeeva OV, Mastryukov VS, Vilkov LV, Hargittai I. *J. Chem. Soc. Chem. Commun.* 1973; 20: 772.
11. Stereochemistry confirmed by NOE studies performed by Jones *et al*. on analogous cycloadducts. Results are shown in the ESI.
12. Grigg R, Sridharan V. *Adv. in Cycloaddition* 1993; 3: 161; Coldham I, Hufton R. *Chem. Rev.* 2005; 105: 2765; Najera C, Sansano JM. *J. Angew. Chem. Int. Ed*. 2005; 44: 6272; Pandey G, Banerjee P, Gadre SR. *Chem. Rev*. 2006; 106: 4484; Aldrio J, Carretero JC. *Chem. Comm.* 2014; 50: 12434-12436; Jones B, Proud M, Sridharan V. *Tetrahedron Lett.* 2016; 57: 2811; Grigg R, Sridharan V, Selvaratnam S, Bridge AW. *Tetrahedron* 1995; 51: 295-306.
13. Wu, XF Neumann H, Beller M. Chem. Rev. 2013; 113: 1-35
14. Deposition number for compound **20a** CCDC 1849751 contains the supplementary crystallographic data for this structure. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Highlights

- Oxetane/azetidine containing spirocycles are gaining interest in medicinal chemistry
- Stereo/regio-selective synthesis of oxetane/azetidine containing pyrolidines
- Creating molecular complexity using simple starting material