Pictet-Spengler reactions of oxetan-3-ones and related heterocycles

Benjamin O. Beasley, Abimbola Alli-Balogun, Guy J. Clarkson, Michael Shipman

PII: S0040-4039(13)02024-8
DOI: http://dx.doi.org/10.1016/j.tetlet.2013.11.077
Reference: TETL 43872

To appear in: *Tetrahedron Letters*

Received Date: 28 September 2013
Revised Date: 8 November 2013
Accepted Date: 20 November 2013

Please cite this article as: Beasley, B.O., Alli-Balogun, A., Clarkson, G.J., Shipman, M., Pictet-Spengler reactions of oxetan-3-ones and related heterocycles, *Tetrahedron Letters* (2013), doi: http://dx.doi.org/10.1016/j.tetlet.2013.11.077

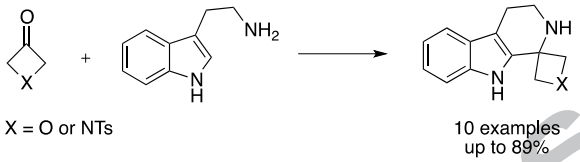
Graphical Abstract

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

Pictet-Spengler reactions of oxetan-3-ones and related heterocycles

Leave this area blank for abstract info.

Benjamin O. Beasley, Abimbola Alli-Balogun, Guy J. Clarkson, Michael Shipman



ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

Pictet-Spengler reactions of oxetan-3-ones and related heterocycles

Benjamin O. Beasley, Abimbola Alli-Balogun, Guy J. Clarkson, Michael Shipman*

Department of Chemistry, University of Warwick, Gibbet Hill Road, Coventry, CV4 7AL, U.K.

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Heterocycles
Oxetanes
Imines
Catalysis
Spiro compounds

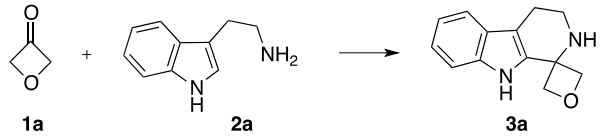
ABSTRACT

Pictet Spengler reactions of oxetan-3-ones and azetidin-3-ones with tryptamine and tryptophan derivatives produce spirocyclic tetrahydro-β-carbolines in good yields. Molecular iodine (5 mol%) is an effective catalyst in most cases and high levels of diastereoselectivity are witnessed using 2-substituted oxetan-3-ones.

There is much current interest in the use of oxetanes in medicinal chemistry. Carreira, Rogers-Evans and coworkers have pioneered their use as bioisosteric replacements for common functional groups such as *gem*-dimethyl or carbonyl groups.[1] Furthermore, the introduction of an oxetane ring can induce profoundly beneficial effects on the aqueous solubility, lipophilicity, metabolic stability and conformational preference of drug candidates.[1] Consequently, there is considerable interest in exploring the benefits of oxetane introduction into various privileged drug scaffolds.[2] With this in mind, we sought to examine if practical methods for oxetane introduction into tetrahydro-β-carbolines (THBC) could be realised. Many bioactive natural products (e.g. harmicine,[3] fumitremorgin C[4]) and approved medicines such as tadafil[5] contain the THBC nucleus, and oxetane introduction would be expected to modulate their physicochemical properties. Since the most direct and straightforward route to THBCs involves Pictet-Spengler cyclization,[6] we reasoned that oxetane-containing THBCs might be efficiently made using this chemistry. In this Letter, we report practical conditions for the synthesis of a range of oxetane-containing THBCs in high yield and stereoselectivity through Pictet-Spengler reactions.

Initially, a range of Brønsted and Lewis acidic conditions were explored for the reaction of commercially available oxetan-3-one (**1a**) with tryptamine (**2a**) (Table 1). Modest conversion into spirocycle **3a** was achieved using trifluoroacetic acid (TFA) at room temperature, with better conversions seen upon heating. Lewis acids such as boron trifluoride and ytterbium triflate proved ineffective. Better results were seen using molecular iodine as the activator[7] although intriguingly, the best yield was achieved in the *absence* of any activator. Simply heating **1a** and **2a** together in acetonitrile provided THBC **3a** in 75% isolated yield after chromatography. Whilst uncatalysed Pictet Spengler reactions have been reported using aldehydes,[8] we are unaware of any reports of uncatalyzed reactions using simple ketones. Presumably the high ring strain associated with the four-membered ring accelerates the Pictet-Spengler cyclization of the intermediate ketimine in this instance.

Table 1.



1a **2a** **3a**

Entry	Activator	Solvent	Temp (°C)	Conversion (%)[a]
1	TFA (2 mol%)	CH_2Cl_2	r.t.	4
2	TFA (2 mol%)	MeCN	82	25
3	TFA (1 mol%)	PhMe	85	73
4	$BF_3{\cdot}OEt_2$ (3 equiv)	CH_2Cl_2	r.t.	0
5	$Yb(OTf)_3$ (10 mol%)	CH_2Cl_2	40	8
6	I_2 (5 mol%)	MeCN	82	48[b]
7	-	MeCN	82	75[b]

[a] Determined from ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b] Isolated yield after chromatography.

Next, we sought to explore the scope of this reaction (Table 2). Using oxetan-3-one (**1a**), THBCs **3a** and **3b** were prepared in good yields without addition of a catalyst (entries 1 and 2). However, in all other cases, iodine catalysis proved beneficial (entries 3-8). The reaction tolerates substitution of the indole

* Corresponding author. E-mail address: m.shipman@warwick.ac.uk; Fax +44(0)24 76524429

nitrogen atom (entry 4), or substituents on the aromatic ring (entries 2 and 6). High yields were obtained using L-tryptophan ethyl ester (**2c**) as the amine component (entries 3 and 7). Chiral shift NMR analysis using Pirkle's reagent[9] confirmed that no measurable racemization occurred during the Pictet-Spengler cyclization to form **3c** (see Supplementary Information). Using oxetanes **1b** and **1c** bearing substituents on the ring, the reactions proceeded in a highly diastereoselective manner. For example, reaction of **1b** with **2a** provided **3e** in 65% yield as a single diastereoisomer. The relative stereochemistry of **3e** was unambiguously determined by X-ray crystallography on a crystal grown from CH_2Cl_2/pentane (Figure 1).[10] This product must arise from nucleophilic attack of the indole nucleus to the least hindered face of the intermediate iminium ion, *i.e.*, the face opposite the phenethyl group on the oxetane ring. The reaction of **1b** with **2c** produced near equal quantities of two diastereomers, **3g** and **3h** (*ca.* 1.1:1), because the starting ketone is racemic. NOE experiments were used to establish that the same sense of stereochemical induction had occurred in spirocycles **3g-i**.[11]

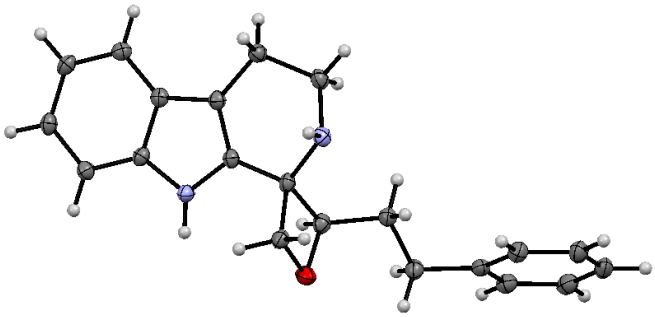
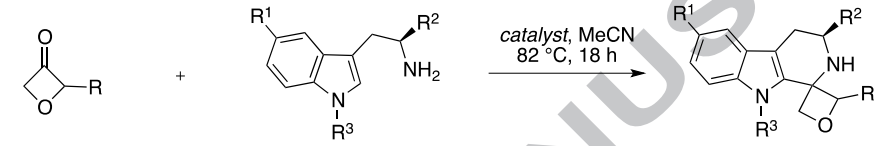


Figure 1. ORTEP representation of the X-ray crystal structure of **3e**

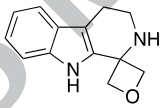
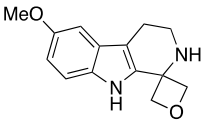
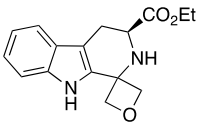
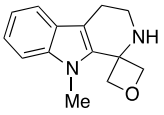
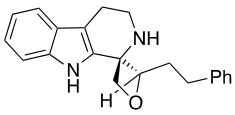
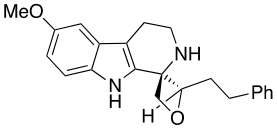
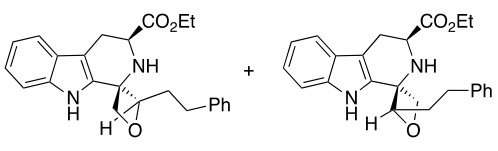
Table 2. Scope of Pictet-Spengler reactions involving oxetan-3-ones

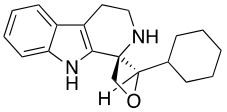


1a (R = H)
1b (R = CH_2CH_2Ph)
1c (R = Cy)

2a (R^1, R^3, R^3 = H)
2b (R^1 = OMe, R^2, R^3 = H)
2c (R^1, R^3 = H, R^2 = CO_2Et)
2d (R^1, R^2 = H, R^3 = Me)

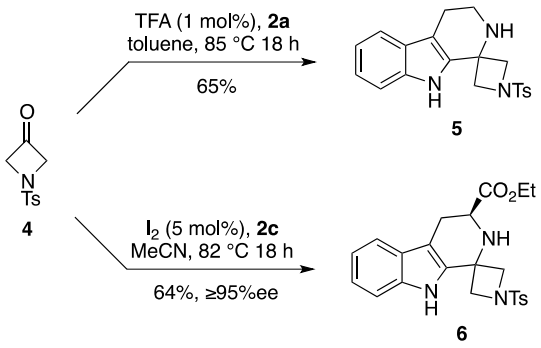
3a-i

Entry	Ketone	Amine	Catalyst	Product	Yield (%)[a]
1	**1a**	**2a**	-	 **3a**	75
2	**1a**	**2b**	-	 **3b**	85
3	**1a**	**2c**	I_2 (5 mol%)	 **3c**	89 ≥95%ee[b]
4	**1a**	**2d**	I_2 (5 mol%)	 **3d**	52
5	**1b**	**2a**	I_2 (5 mol%)	 **3e**	65
6	**1b**	**2b**	I_2 (5 mol%)	 **3f**	72
7	**1b**	**2c**	I_2 (5 mol%)	 **3g** *ca.* 1.1 : 1 **3h**	72

8	**1c**	**2a**	I_2 (5 mol%)	 **3i**	23

[a] Full experimental procedures and characterization data in Supplementary data. [b] Determined using chiral shift NMR employing Pirkle's alcohol.

The chemistry can be extended to azetidin-3-ones. For example, spirocycle **5** can be made in 65% yield from *N*-tosyl azetidin-3-one (**4**) and tryptamine (**2a**) using TFA as the catalyst (Scheme 1). Lower yields (44%) were observed using iodine (5 mol%) in MeCN. Using L-tryptophan ethyl ester (**2c**), compound **6** was produced in good yield without detectable racemization.



Scheme 1

In conclusion, we have developed simple methodology for the synthesis of oxetane- and azetidine-containing tetrahydro-β-carbolines through application of Pictet-Spengler cyclizations. Iodine catalysis proved effective in most cases and the reactions exhibited high diastereofacial selectivity. In the course of this work, we have unearthed what we believe to be the first examples of uncatalysed Pictet-Spengler reactions involving simple ketones. Work to explore the benefits of oxetane introduction into THBCs and other drug-like scaffolds is continuing in our laboratory.

Acknowledgements

This work was supported by the University of Warwick and the Engineering and Physical Sciences Research Council (EPSRC). *N*-Tosyl azetidin-3-one was kindly provided by Nicola Powell. The Oxford Diffraction Gemini XRD system was obtained, through the Science City Advanced Materials project: Creating and Characterizing Next Generation Advanced Materials, with support from Advantage West Midlands.

Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at ******

References and notes

1. For reviews, see: (a) Wuitschik, G.; Carreira, E. M.; Wagner, B.; Fischer, H.; Parrilla, I.; Schuler, F.; Rogers-Evans, M.; Müller, K. *J. Med. Chem*. **2010**, *53*, 3227. (b) Burkhard, J. A.; Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Carreira, E. M. *Angew. Chem. Int. Ed*. **2010**, *49*, 9052.
2. (a) Burkhard, J. A.; Wuitschik, G.; Plancher, J.-M.; Rogers-Evans, M.; Carreira, E. M. *Org. Lett*. **2013**, *15*, 4312. (b) Fujishima, T.; Nozaki, T.; Suenga, T. *Bioorg. Med. Chem*. **2013**, *21*, 5209. (c) Nassoy, A.-C.; Raubo, P.; Harrity, J. P. A. *Tetrahedron Lett.* **2013**, *54*, 3094. (d) Beasley, B. O.; Clarkson, G. J.; Shipman, M. *Tetrahedron Lett.* **2012**, *53*, 2951. (e) Stepan, A. F.; Karki, K.; McDonald, W. S.; Dorff, P. H.; Dutra, J. K.; DiRico, K. J.; Won, A.; Subramanyam, C.; Efremov, I. V.; O'Donnell, C. J.; Nolan, C. E.; Becker, S. L.; Pustilnik, L. R., Sneed, B.; Sun, H.; Lu, Y.; Robshaw, A. E.; Riddell, D.; O'Sullivan, T. J.; Sibley, E.; Capetta, S.; Atchison, K.; Hallgren, A. J.; Miller, E.; Wood, A.; Obach, R. S. *J. Med. Chem.* **2011**, *54*, 7772. (f) Vigo, D.; Stasi, L.; Gagliardi, S. *Tetrahedron Lett.* **2011**, *52*, 565. (g) Burkhard, J. A.; Guérot, C.; Knust, H.; Rogers-Evans, M.; Carreira, E. M. *Org. Lett.* **2010**, *12*, 1944. (h) Wuitschik, G.; Rogers-Evans, M.; Buckl, A.; Bernasconi, M.; Märki, M.; Godel, T.; Fischer, H.; Wagner, B.; Parilla, I.; Schuler, F.; Schneider, J.; Alker, A.; Schweizer, W. B.; Müller, K.; Carreira, E. M. *Angew. Chem. Int. Ed*. **2008**, *47*, 4512. (i) Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Fischer, H.; Wagner, B.; Schuler, F.; Polonchuk, L.; Carreira, E. M. *Angew. Chem. Int. Ed*. **2006**, *45*, 7736.
3. Kam T.-S.; Sim, K.-M. *Phytochemistry* **1998**, *47*, 145.
4. Rabindran, S. K.; Ross, D. D.; Doyle, L. A.; Yang, W.; Greenberger, L. M. *Cancer Res.* **2000**, *60*, 47.
5. (a) Daugan, A.; Grondin, P.; Ruault, C.; Le Monnier de Gouville, A.-C.; Coste, H.; Kirilovsky, J.; Hyafil, F.; Labaudinière, R. *J. Med. Chem.* **2003**, *46*, 4525; (b) Daugan, A.; Grondin, P.; Ruault, C.; Le Monnier de Gouville, A.-C.; Coste, H.; Linget, J.-M.; Kirilovsky, J.; Hyafil, F.; Labaudinière, R. *J. Med. Chem.* **2003**, *46*, 4533.
6. For reviews, see: Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797. (b) Stöckigt, J.; Antonchick, A. P.; Wu, F. R.; Waldmann, H. *Angew. Chem. Int. Ed.*, **2011**, *50*, 8538.
7. (a) Lingam, Y.; Rao, D. M.; Bhowmik, D. R.; Santu, P. S.; Rao, K. R.; Islam, A. *Tetrahedron Lett.*, **2007**, *48*, 7243. (b) Prajapati, D.; Gohain, M. *Synth. Commun.*, **2008**, *38*, 4426.
8. See, for example: Soerens, D.; Sandrin, J.; Ungemach, F.; Mokry, P.; Wu, G. S.; Yamanaka, E.; Hutchins, L.; DiPierro, M.; Cook, J. M. *J. Org. Chem.* **1979**, *44*, 535.
9. Pirkle, W. H.; Hoover, D. J. *Topics Stereochem.* **1982**, *13*, 263.
10. Crystallographic data (excluding structure factors) for **3e** (CCDC 961012) have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.
11. The structural assignment for **3e** deduced by X-ray (Figure 1) was also confirmed by NOE experiments. Specifically, reciprocal NOE enhancements were seen between the indole NH and two oxetane ring hydrogens attached to different ring carbons. These and other relevant NOEs were also seen in **3g**, **3h** and **3i**. These observations are consistent with the oxetane substituent being *anti* to the new C–C bond in all cases.