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Synthesis of diversely functionalised 2,2-disubstituted oxetanes: fragment motifs in new chemical space†

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Di-, tri- and tetra-substituted oxetane derivatives with combinations of ester, amide, nitrile, aryl, sulfone and phosphonate substituents are prepared as fragments or building blocks for drug discovery. The synthesis of these novel oxetane functional groups, in new chemical space, is achieved *via* rhodium-catalysed O–H insertion and C–C bond forming cyclisation.

Recent years has seen considerable enthusiasm for exploring new chemical motifs in medicinal chemistry that enter unexplored chemical and intellectual property (IP) space.[1,2] Oxetanes motifs have gained significant traction as desirable modules for drug discovery.[3] Carreira, Rogers-Evans, Müller and co-workers demonstrated that 3,3-disubstituted oxetanes constitute polar replacements for *gem*-dimethyl groups, and often afford improved solubility and physicochemical properties.[4] Subsequently, oxetane motifs have been adopted widely in medicinal chemistry programs.[5,6] 3-Substituted oxetane motifs have been examined in particular, exploiting oxetan-3-one[3,4] and 3-iodooxetane[7] as building blocks. New spirocycles,[8] peptidomimetics[9] and other oxetane analogues of important compounds have been prepared (*e.g.* Fig. 1).[6,10]

Examples of 2-substituted oxetanes remain less studied; Pfizer reported a class of 2-oxetanyl containing γ-secretase inhibitors that possessed improved properties relative to tetrahydrofuran and carbocyclic derivatives.[6] However, oxetanes bearing functional groups on the ring are unexplored, and could provide fascinating new structural units for use by medicinal chemists. The synthesis of functionalised oxetanes continues to be a challenge. Cyclisation by intramolecular Williamson etherification is most common,[3] but 2-functionality is often precluded due to unstable oxyanionic intermediates. Also, epoxide-opening and ring-closure methods using sulfoxonium ylides are not tolerant of sensitive electrophilic functionality.[11] On the other hand, the photochemical Paterno–Büchi reaction can introduce functionality from an alkene component, but is often restricted to very highly substituted oxetanes, with undesirable properties for medicinal chemistry.[12–14]

We have targeted new oxetane derivatives due their small, polar nature and well-defined 3-D shape.[15] We recently reported the preparation of 2-sulfonyl oxetanes, formed through a novel anionic C–C bond forming cyclisation (Scheme 1A).[16] These fragments displayed good pH stability, and stability to liver microsomes.[16b] We have also established an efficient synthesis of oxetane 2,2-dicarboxylates involving O–H insertion using diazomalonates, and C–C bond forming cyclisation (Scheme 1B).[17]

Here we report the synthesis of unusual oxetane motifs bearing medicinally relevant functional groups directly on the

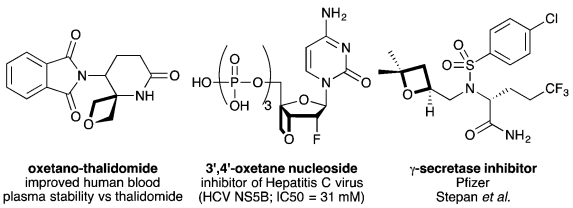
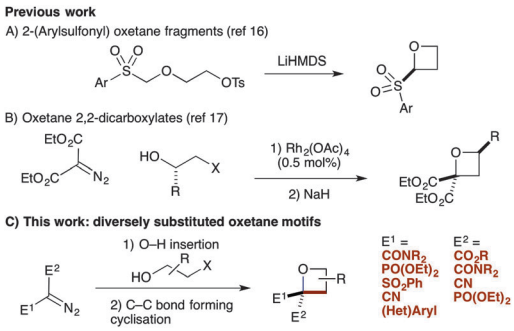


Fig. 1 Biologically active oxetane-containing compounds.



Scheme 1 Synthesis of oxetanes through anionic C–C bond forming cyclisation.

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† Electronic supplementary information (ESI) available: Experimental procedures, characterisation data, ^{1}H and ^{13}C NMR spectra; details of reaction optimisation and calculated molecular properties. See DOI: 10.1039/c5cc05740j

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ring (Scheme 1C). Diversely functionalised oxetanes in new chemical space are prepared in a facile manner from functionalised diazo compounds by O–H insertion and C–C bond forming cyclisation. These simple but highly functionalised motifs provide interesting shape and physicochemical properties for fragments or building blocks for drug discovery that cannot be prepared by other methods.

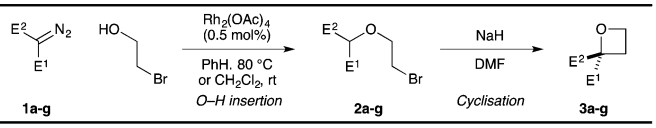
Targeting 2,2-difunctionalised oxetanes, our investigations initially focused on a range of unsymmetrical acceptor–acceptor diazo compounds, with which to examine O–H insertion with 2-bromoethanol (Scheme 1C and Table 1).[18,19] A series of diazo compounds **1a–g** bearing amide, sulfone, phosphonate, and nitrile groups were prepared from the methylene precursors using TsN_3 or TfN_3.[18,20,21] We first examined amide–ester diazo **1a** (entry 1). Pleasingly, using catalytic $Rh_2(OAc)_4$ (0.5 mol%) in benzene at 80 °C successfully mediated O–H insertion of the carbene derived from diazo **1a** into 2-bromoethanol in 75% yield.

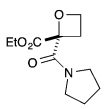
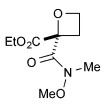
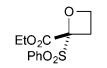
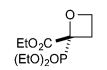
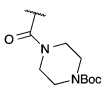
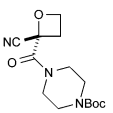
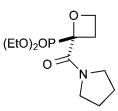
Cyclisation was then effected by treatment of **2a** with NaH (1.2 equiv., 0 °C, 1 h, then 25 °C, 1 h) to afford 2-amido-2-ester-oxetane **3a** in excellent yield forming the C(2)–C(3) bond. Using Weinreb amide **1b** (entry 2), a slightly reduced yield was obtained for the O–H insertion (51%), but an excellent yield was obtained on cyclisation of **2b** to oxetane **3b**. Sulfone–ester diazo **1c** smoothly underwent O–H insertion, followed by cyclisation in just 1 h at 0 °C to provide a new type of sulfonyl oxetane (entry 3).[16] Phosphonate–ester diazo **1d** proceeded similarly, to yield the first example of a 2-oxetanyl phosphonate, **3d**.[22] Interestingly, the use of nitrile–ester diazo **1e** led to side reactions under the conditions for O–H insertion, with the carbenoid undergoing competitive insertion into the benzene solvent (1.2 : 1–2.4 : 1 O–H insertion : π-insertion). To prevent this unwanted side product, the reaction was performed in CH_2Cl_2 (25 °C, 17 h), and bromide **2e** was isolated in 85% yield (entry 5). Cyclisation at 0 °C afforded nitrile oxetane **3e** after 1 h. The sequence was also successful on a larger scale affording >1.5 g of oxetane **3e** in excellent yield (entry 6). Mixed nitrile–amide and phosphonate–amide diazo compounds were also successful under the same conditions, providing oxetanes **3f** and **3g** respectively (entries 7 and 8). The wide variety of substituted oxetanes that can be readily accessed demonstrates the versatility of this approach.

Substituted bromohydrins were then investigated to form tri- and tetrasubstituted oxetane derivatives (Table 2). The reaction sequence successfully formed oxetanes with 4-alkyl (**5a**) and 4-aryl substituents (**5b–e**) in good yields using similar reaction conditions. The additional substituent had little influence on the O–H insertion step. However, elevated temperature and increased reaction times were required for cyclisation of all substituted examples, requiring 16 h at 25 °C for complete conversion.

For oxetanes **5a** and **5b**, a ~1 : 1 mixture of diastereoisomers was obtained due to the sterically similar ester–sulfone or ester–phosphonate groups.[23] Diazo compounds with a less sterically demanding nitrile group (**1e**, **1h**, **1i**) gave increased diastereoselectivity (up to 3 : 1 dr). The incorporation of a 3-Ph group gave the 2,2,3-substituted derivative **5f** (dr = 56 : 44). 2,2,4,4-Tetrasubstituted oxetane **5g** was prepared from the commercially available chlorohydrin (1-chloro-2-methyl-2-propanol)

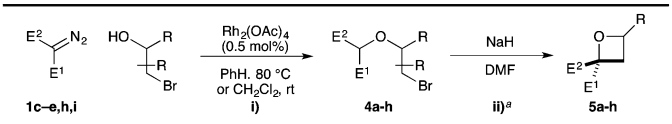
Table 1 Scope of 2,2-disubstituted oxetanes varying diazo **1a–g**

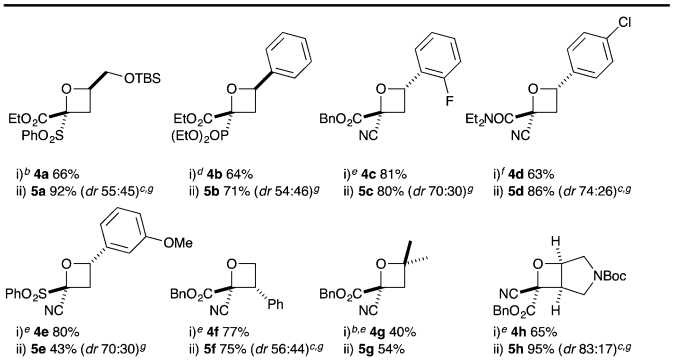


Entry	E^1	E^2		Yield **2**[a] (%)	Yield **3**[b] (%)	Oxetane **3**
1		CO_2Et	**a**	75	93[c]	
2		CO_2Et	**b**	51	96[c]	
3	SO_2Ph	CO_2Et	**c**	92	87[d]	
4	$PO(OEt)_2$	CO_2Et	**d**	77[e]	70[d]	
5	CN	CO_2Bn	**e**	85[f]	88[d]	
6				93[f,g]	93[d,h]	
7		CN	**f**	67[i]	87[d]	
8		$PO(OEt)_2$	**g**	84	72[d]	

[a] O–H insertion: **1** (1.1 equiv.), 2-bromoethanol (1.0–2.0 mmol), $Rh_2(OAc)_4$ (0.5 mol%), PhH, 0.1 M, 80 °C. [b] Cyclisation: **2** (0.3–0.6 mmol), NaH (1.2 equiv.), DMF, 0.025 M. [c] 0 °C for 1 h; then 25 °C for 1 h. [d] 0 °C for 1 h. [e] 1.5 equiv. diazo **1d**. [f] Run in CH_2Cl_2, 0.1 M at 25 °C for 17 h. [g] 10 mmol scale. [h] 8 mmol scale. [i] 1.2 equiv. diazo **1f**.

Table 2 Preparation of 2,2,4-, 2,2,3-tri- and 2,2,4,4-tetrasubstituted oxetanes





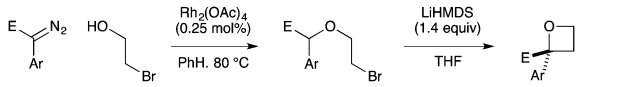
Conditions: (i) O–H insertion: **1** (1.1 equiv.), β-bromohydrin (0.5–1.3 mmol), $Rh_2(OAc)_4$ (0.5 mol%), PhH, 0.1 M, 80 °C. (ii) Cyclisation: **4** (0.3–0.5 mmol), NaH (1.2 equiv.), DMF, 0.025 M, 25 °C, 16 h. [a] dr determined by ^1H NMR of crude reaction mixture. [b] β-Chlorohydrin used. [c] Oxetane isomers separated by silica chromatography. [d] 1.5 equiv. diazo. [e] Run in CH_2Cl_2, 0.1 M at 25 °C for 17 h. [f] 1.2 equiv. diazo. [g] Major diastereoisomer indicated (see ref. 23).

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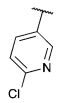
in moderate yields. The synthesis of novel fused bicyclic oxetane scaffold **5h** started by treating *N*-Boc-3-pyrroline with NBS and H_2O to provide 3-bromo-4-hydroxy-pyrrolidine, which gave ether **4h** on O–H insertion. Cyclisation then afforded the bicyclic oxetane **5h** as a 83 : 17 mixture of separable diastereoisomers in 95% combined yield.[21,23]

Next we examined aryl–ester (donor–acceptor) diazo compounds,[24] to generate 2-aryl-oxetane-2-carboxylates (Table 3). Such aryl-substituted heterocycles offer attractive features for fragment screening and are little studied in medicinal chemistry.[25] To our delight, the O–H insertion conditions were effective for the phenyl–ester diazo **6a** with an excellent 86% yield using reduced $Rh_2(OAc)_4$ loading (0.25 mol%, entry 1). The O–H insertion was successful across varied aryl groups (entries 3–8), including the chloropyridyl diazo **6f**. However, using the NaH in DMF conditions for cyclisation gave variable yields and oxetane **8a** and bromide **7a** proved inseparable.

Table 3 Scope of 2-aryl-oxetane 2-carboxylates



6a-g 7a-g 8a-g

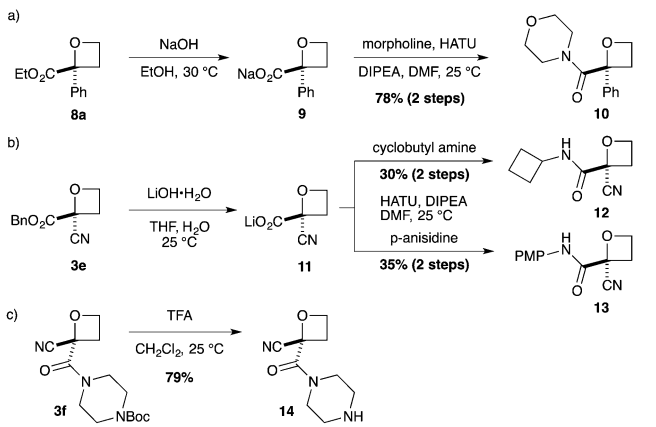
Entry	Ar	E		Yield 7[a] (%)	Yield 8[b] (%)	Oxetane 8
1	Ph	CO_2Et	**a**	86	93	
2				80[c]	76[d]	
3	Ph	CO_2iPr	**b**	87[e]	72	
4	3-ClPh	CO_2Et	**c**	69	97	
5	4-CF_3Ph	CO_2Et	**d**	64	77	
6	4-MeOPh	CO_2Et	**e**	86	22	
7					41[f]	
8		CO_2Et	**f**	54	76	
9	3-ClPh		**g**	73	90	

[a] O–H insertion: **6** (1.1–1.5 equiv.), 2-bromoethanol (0.4–2.0 mmol), $Rh_2(OAc)_4$ (0.25 mol%), PhH, 0.1 M, 80 °C. [b] Cyclisation: **7** (0.3–0.5 mmol), LiHMDS (1.4 equiv.), THF, 0.025 M, 0 °C, 1 h. [c] Reaction on 7.5 mmol scale. [d] Reaction on 5.0 mmol scale. [e] 0.5 mol% $Rh_2(OAc)_4$. [f] 2.0 equiv. LiHMDS.

Alternative bases and conditions were examined,[21] and the use of LiHMDS (1.4 equiv.) in THF was found to give quantitative conversion to oxetane **8a** with a 93% isolated yield (entry 1). This reaction sequence was similarly successful on a larger scale (entry 2). The modified cyclisation conditions worked well for substituted aryl derivatives including halogenated (entries 4 and 5), and pyridyl derivatives (entry 8). However, the electron rich *p*-methoxy phenyl substrate (entry 6) led to low conversion and isolated yield. Using a larger excess of LiHMDS (2 equiv.) gave an improved yield of 41% (entry 7). The cyclisation conditions were also effective for aryl–amide ether **7g** (entry 9). This approach provided direct access to compounds that conform well to fragment guidelines for fragment screening.[21]

As a more divergent approach to similar compounds, hydrolysis of ester oxetane **8a** was examined (Scheme 2a). Using NaOH afforded sodium salt **9** as an attractive oxetane containing building block. Amide coupling with morpholine, directly from the salt,[26] gave amide **10** in a good yield over two steps. Finally, we prepared additional 2-nitrile oxetane derivatives. The nitrile group is receiving considerable attention in drug discovery,[27,28] being metabolically robust and a strong hydrogen bond acceptor. Therefore, we considered that the combination with an oxetane motif could present a fascinating structure for medicinal chemistry.[13,29] From nitrile–oxetane benzyl ester **3e**, ester hydrolysis was best achieved using LiOH to afford lithium salt **11** (Scheme 2b). Amide bond formation gave nitrile amide oxetanes **12** and **13** in 30–35% yields over 2 steps. Importantly, treatment of oxetane **3f** with TFA promoted Boc deprotection, **14**, without other degradation, providing encouraging preliminary information on acid stability (Scheme 2c; 10 equiv. TFA, 22 h).

In summary, we have developed a versatile strategy to prepare diversely functionalised oxetane derivatives, involving O–H insertion and C–C bond forming cyclisation. A wide variety of functional groups have been introduced on the oxetane ring, accessing new chemical space. We believe these oxetane motifs will provide interesting new structural elements for medicinal chemistry programs as well as synthesis. Efforts towards enantioselective synthesis and studies on the stability and medicinal chemistry properties of the new oxetane derivatives will be reported in due course. We gratefully acknowledge EPSRC



Scheme 2 Divergent synthesis of oxetane derivatives.

(CAF, EP/J001538/1; Impact Acceleration Account, EP/K503733/1), and Imperial College London. We thank EPSRC National Mass Spectrometry Facility, Swansea.

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