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Passerini reactions for the efficient synthesis of 3,3-disubstituted oxetanes

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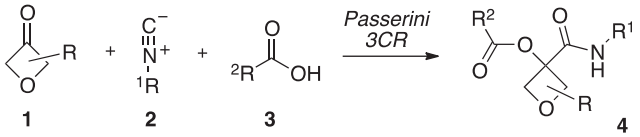
ABSTRACT

Three-component reactions of oxetan-3-ones with isocyanides and carboxylic acids produce 3,3-disubstituted oxetanes in good yields. Good levels of diastereocontrol (dr = 4:1) can be achieved in these Passerini reactions when the oxetane nucleus possesses a bulky cyclohexyl substituent at C–2. The (2*S**,3*R**)-stereochemistry of the major diastereomer was confirmed by X-ray crystallography after ester hydrolysis, and a possible mechanism to account for the diastereofacial selectivity is presented.

Multi-component reactions (MCRs) are one-pot processes that bring together three or more starting materials to form a product that contains most, if not all, elements of the reactants.[1,2] They offer a very attractive and efficient approach to chemical synthesis. The most important examples are those employing isocyanides as one of the components, such as the Passerini[3] and Ugi[4] reactions. These isocyanide based MCRs have been widely used as an avenue to libraries of small drug-like molecules because of their ability to produce compounds with several degrees of structural diversity under mild reaction conditions.[5]

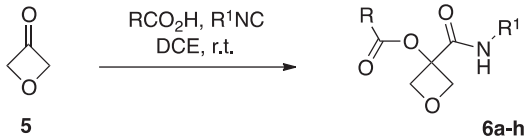
There is much interest in the synthesis of oxetanes for their application in medicinal chemistry.[6] These four-membered oxygen heterocycles are increasingly being used as surrogates for common functional groups such as *gem*-dimethyl or carbonyl groups in drug molecules. This isosteric replacement can induce profoundly beneficial effects on the aqueous solubility, lipophilicity, metabolic stability and conformational preference of such molecules.[7] 3-Substituted oxetanes are especially useful in this regard as no additional stereocentres are introduced into the molecular scaffold of the drug.[6,7] Although, multi-step routes to 3-substituted oxetanes are known,[6] no isocyanide based MCRs have been reported.[8] We imagined that a Passerini reaction involving oxetan-3-one **1**, an isocyanide **2** and a carboxylic acid **3** could provide a simple, flexible route to 3,3-disubstituted oxetanes **4** (Scheme 1). As oxetan-3-ones are readily available,[9] this chemistry offers a practical new method for the synthesis of a wide variety of drug-like molecules containing this important heterocyclic nucleus. In this Letter, we demonstrate the feasibility and scope of this isocyanide based MCR to oxetanes.

The relatively few examples of Passerini reactions involving ketones as the carbonyl component,[3] and the privileged position



Scheme 1. Proposed Passerini MCR to 3,3-disubstituted oxetanes.

Table 1
Passerini reactions of oxetan-3-one (**5**)



5 **6a-h**

Entry	R	R^1	Product	Yield[a] (%)
1	Me	^{t}Bu	**6a**	90
2	Me	Cy	**6b**	79
3	Me	^{n}Bu	**6c**	51
4	Me	Bn	**6d**	62
5	$CbzNHCH_2$	^{t}Bu	**6e**	47
6	Ph	^{t}Bu	**6f**	92
7	2-Thienyl	^{t}Bu	**6g**	85
8	2-(3-Bromo-thienyl)	^{t}Bu	**6h**	52

[a] Full experimental procedures and characterization data are available in the Supplementary data.

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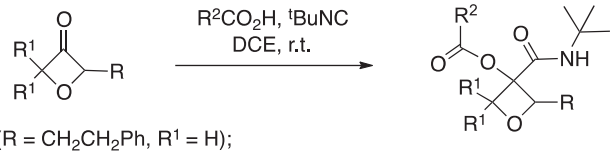
Table 2
Passerini reactions of substituted oxetan-3-ones **7a–c**



7a (R = CH_2CH_2Ph, R^1 = H);
7b (R = Cy, R^1 = H);
7c (R = CO_2Et, R^1 = Me);

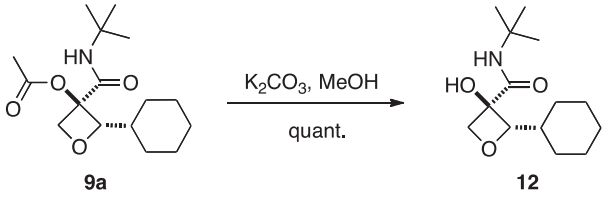
Entry	R	R^1	R^2	Product **a**/**b**	Yield[a] (%)	dr[b]
1	CH_2CH_2Ph	H	Me	**8**	76	1.7:1
2	Cy	H	Me	**9**	97	4:1
3	CO_2Et	Me	Me	**10**	79	2.8:1
4	Cy	H	Ph	**11**	49	3.4:1

[a] Full experimental procedures and characterization data are available in the Supplementary data.
[b] Diastereomeric ratios determined by ^1H NMR analysis on the crude product.

of the 3,3-disubstituted oxetane skeleton, led us to begin our studies using commercially available oxetan-3-one (**5**). Treatment of this ketone with acetic acid (1.2 equiv) and *tert*-butyl isocyanide (1.2 equiv) in dichloroethane (DCE) for 18 h provided the Passerini adduct **6a** in 90% yield (Table 1, entry 1). Other aprotic solvents such as dichloromethane (91%) were equally effective for this transformation, but much lower yields were seen with protic solvents such as MeOH (20%). The structural complexity arising in this MCR was deduced from NMR spectroscopy, and later confirmed by X-ray crystallography on a single crystal of **6a** grown from CH_2Cl_2/pentane (see Supplementary material). [10] The scope of this reaction was readily determined through simple variation in the nature of the isocyanide (Table 1, entries 1–4) and the carboxylic acid (Table 1, entries 4–8). Good to excellent yields were observed in most cases.

Next, this chemistry was applied to more hindered oxetan-3-ones bearing 2- and 2,4-substituents. Known oxetanes **7a–c** were readily made using the method of Zhang and co-workers.[8] Despite the fact that bulky substituents were introduced close to the reacting C=O bond, good yields of the Passerini products were obtained (Table 2). However, the use of benzoic acid led to a lower yield (Table 2, entry 4). It was found that good levels of stereoselectivity were seen in these reactions when the substituent at C–2 was relatively large. For example, **7b** with a cyclohexyl group at C–2 gave much better levels of diastereocontrol than **7a** bearing the phenylethyl substituent (Table 2, entry 1 cf. entry 2). For entry 2, we separated **9a** and **9b** by column chromatography, and deduced their relative stereochemistry in the following ways. For minor diastereomer **9b**, crystals were grown from CH_2Cl_2/pentane, and the structure solved by X-ray crystallography.[10] For **9a**, the acetate group was first removed via simple ester hydrolysis with K_2CO_3 in MeOH (Scheme 2). The resultant α-hydroxyamide **12** was sufficiently crystalline that its structure could also be solved by X-ray crystallography (Fig. 1). Knowing the relative stereochemistry of **12**, that of **9a** could be deduced with confidence.

The formation of **9a** as the major stereoisomer from **7b** was not anticipated. One might expect that **9b** would predominate as a result of addition of the isocyanide to the opposite face of the C–2 substituent on the oxetane ring (Scheme 3).[11] However, the Passerini reaction is a multi-step process in which the steps are often considered reversible prior to the final acyl migration, and considerable uncertainty remains about the precise mechanistic details.[3,12] To account for the favoured production of **9a**, we



Scheme 2. Ester hydrolysis of Passerini product **9a**.

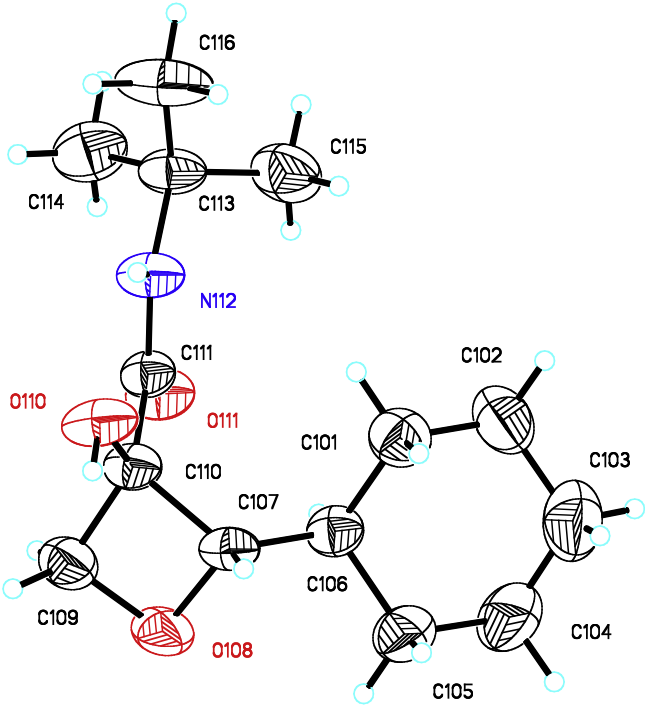
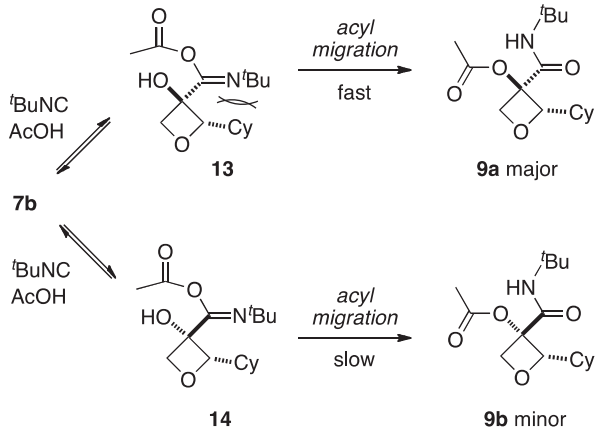


Figure 1. ORTEP representation of one of the crystallographically independent molecules in the asymmetric unit of the solid-state structure of **12**.



Scheme 3. Possible mechanism to account for observed stereoselectivity.

propose that both **13** and **14** are produced under equilibrating conditions through the addition of ^{t}BuNC and AcOH to both faces of **7b**. The diastereoselectivity then arises from differences in the relative rates of acyl migration from **13** to **9a**, and from **14** to **9b**. The observed preference for **9a** is explained by suggesting that increased steric crowding between the cyclohexyl and imidoyl substituents

in **13** encourages faster acyl transfer than that seen for **14** where these substituents are on opposite faces of the four-membered ring.

To conclude, oxetan-3-ones have been shown to be excellent substrates for Passerini reactions providing a simple, direct route to the pharmaceutically important 3,3-disubstituted oxetane scaffold. This three-component reaction proceeds in high yields with a range of isocyanides and carboxylic acids, and useful levels of diastereocontrol are witnessed with oxetanes bearing bulky ring substituents at C–2. Ongoing work is focused on the development of other MCRs of the oxetane nucleus, and their application to drug discovery.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.065.

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8. We are aware of just one example of an MCR involving an oxetane. Zhang and co-workers describe a single example of a Strecker reaction using oxetan-3-one (**5**) in Ref. 9.
9. Ye, L.; He, W.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 8550–8551 and references cited therein.
10. Crystallographic data (excluding structure factors) for **6a** (CCDC 863326), **9b** (CCDC 863327) and **12** (CCDC 863328) 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. Indeed, this stereochemical preference has been reported in the addition of ^{t}BuNC to 2-phenoxycyclopentanone, albeit under somewhat different reaction conditions, see: Lumma, W. C. *J. Org. Chem.* **1981**, *46*, 3668–3671.
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