Asymmetric Heterocycle Synthesis

1,2,4-Oxadiazolidinones as Configurationally Stable Chiral Building Blocks**

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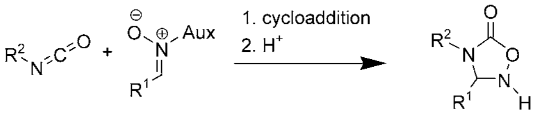
Heterocycles are ubiquitous in drug discovery and development by virtue of the fact that they can serve as scaffolds incorporating multiple points of diversification and thereby facilitate library synthesis. Nonaromatic heterocycles can impart added benefits in drug design, because they define out-of-plane vectors from a central core. One of the more recent examples of such a scaffold is the antibacterial linezolid, an optically active oxazolidinone.[1,2] Chiral 1,2,4-oxadiazolidinones **3** [Eq. (1)] constitute a structurally intriguing scaffold, which bear structural similarity to oxazolidinones. However, they have rarely been employed as biologically active agents and then only in racemic form.[3] Their absence in the medicinal chemistry literature likely stems from the lack of synthetic methodology for their preparation in enantiomerically pure form and, consequently, the fact that it is unclear whether they would be configurationally stable. In this communication we document the convenient asymmetric synthesis of a wide range of substituted 1,2,4-oxadiazolidinones by cycloaddition. Access to the enantiomerically pure compounds allows us to ascertain for the first time the configurational stability of this class of compounds, including that of the unsubstituted, previously unknown parent heterocycle **3**.

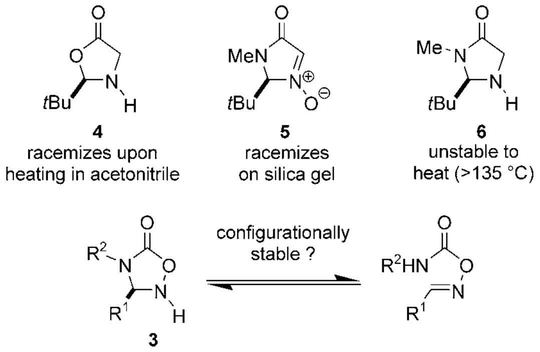


1 **2** **3**

up to > 99% *ee*
configurationally stable

(1)

The cycloaddition of isocyanates and nitrones was first reported by Goldschmidt and Beckmann in 1890, but it was not until almost 100 years later (1987) that the structure of the cycloadducts was firmly established as 1,2,4-oxadiazolidinones.[4] In order to exploit these heterocycles as potentially useful, versatile building blocks, two key criteria must be met: 1) methodology must be available for the convenient synthesis of oxadiazolidinones in optically active form,[5] and 2) the heterocycle **3** (intermediates and end products) must be configurationally stable. Examination of related heterocycles casts into question the configurational stability, especially under acidic and alkaline conditions (Scheme 1). In this respect, oxazolidinone **4** racemizes upon heating in acetonitrile[6] and the cyclic nitrone **5** was found to undergo rapid racemization during chromatography on silica gel through putative ring opening to the acyl imminium ion and subsequent recyclization.[7] The imidazolidinone scaffold **6** was reported to undergo degradation to the Schiff base upon vacuum distillation (135 °C, 0.05 torr).[8]



Scheme 1. Configurational stabiliy of heterocycles related to oxadiazolidinones.

Our recent work in alkynylzinc additions to mannosyl- and erythrosyl- (Aux^1 and Aux^2, respectively) derived nitrones[9] led us to explore these substrates[10] in the cycloaddition reaction for the preparation of oxadiazolidinones. The starting nitrones are conveniently accessed from readily available starting materials (mannose, hydroxylamine, aldehyde) in three steps.[11]

Simply mixing a range of commercially available isocyanates **1** with mannosyl-derived nitrones **2** in CH_2Cl_2 led to smooth cycloaddition at 23 °C to afford oxadiazolidinones **7** in 69–87 % yield [Eq. (2), Table 1]. The diastereoselectivity of the cycloaddition ranges from 4:1 to 12:1 for the products isolated directly upon evaporation of the solvent. We were pleased to observe that simple trituration of the products with methanol generally furnished the desired substituted 1,2,4-oxadiazolidinones in up to >99:1 d.r. in analytically pure form. Electron-deficient and -rich aromatic and heteroaromatic nitrones, alkenylnitrones, as well as alkylnitrones participate in this cycloaddition, with the *C*-alkylnitrones most and the electron-deficient aromatic least reactive. Electron-deficient isocyanates react more readily than those substituted with electron-releasing groups, consistent with frontier orbital control. Reactions of substrates that are less reactive can be carried out successfully in refluxing acetonitrile.

The enantiomeric oxadiazolidinones can be accessed by using the erythrose-derived auxiliary [Eq. (3)] and removing the auxiliary from the heterocyclic product [Eq. (4)]. In analogy to the cycloadditions described above, concentration

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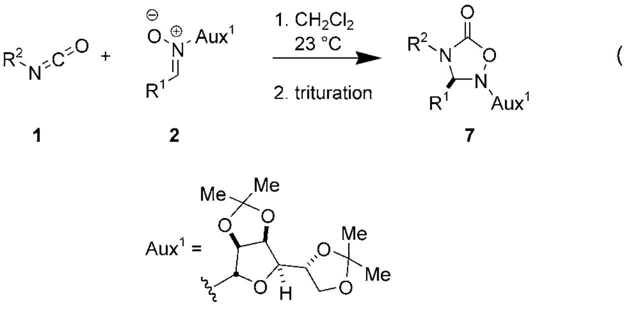
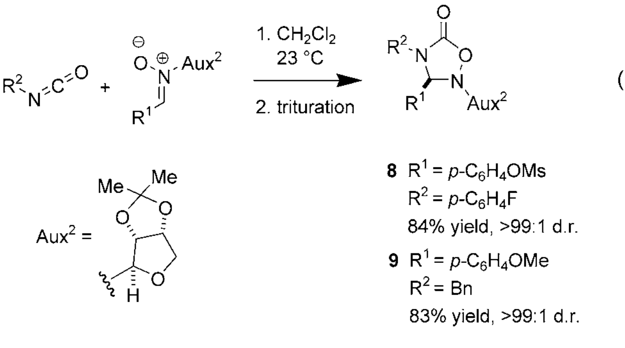


(2)

Table 1: Diastereoselective nitrone cycloaddition [Eq. (2)].[a]

R^1	R^2	d.r. (crude prod.)	d.r. (isolated prod.)	Yield [%][b]
p-$C_6H_4NO_2$	p-$C_6H_4NO_2$	11:1	>99:1	84
p-C_6H_4Br		10:1	>99:1	87
p-$C_6H_4CF_3$	p-$C_6H_4CF_3$	10:1	>99:1	85
Ph	p-C_6H_4F	8:1	>99:1	83
p-C_6H_4OMe		12:1	>99:1	81
p-C_6H_4OMs		8:1	>99:1	84
3-Py	p-C_6H_4F	8:1	>99:1	80
2-C_4H_3S		8:1	19:1	79[c]
2-furyl	Ph	7:1	13:1	82[c]
E-styryl		10:1	>99:1	76
p-$C_6H_4NO_2$	Bz	5:1	24:1	71
1-Naph		10:1	>99:1	79
p-C_6H_4Br	Bn	7:1	>99:1	74[d]
p-C_6H_4OMe		10:1	>99:1	76[c]
Me	p-$C_6H_4NO_2$	4:1	>99:1	69
Cy		5:1	19:1	84
*t*Bu	p-C_6H_4OMe	6:1	>99:1	70
	2,6-$Cl_2C_6H_3$	6:1	>99:1	70

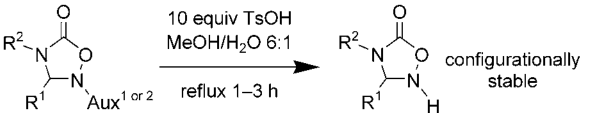
[a] Reaction conditions: CH_2Cl_2, 23 °C. Abbreviations used: Cy = cyclohexyl, Ms = methanesulfonyl, Naph = naphthyl, Py = pyridyl. [b] Yield of the isolated, analytically pure material. [c] Reaction conducted at reflux. [d] Reaction conducted in acetonitrile at reflux.



(3)

of the reaction mixture and simple trituration of the resulting solids (MeOH) generally affords the desired heterocycles in analytically pure form (> 99:1 d.r.).

Auxiliary removal is readily accomplished under acidic conditions (0.5 M toluenesulfonic acid (TsOH), aq. MeOH) [Eq. (4)]. We found that in the course of this reaction the isopropylidene protecting groups on the auxiliary first undergo hydrolysis followed by release of the heterocycle. Consequently, the water-soluble carbohydrate remnant of the auxiliaries is removed in the aqueous workup, leading to the isolation of the N2-unsubstituted heterocycles in > 99% *ee* as determined by HPLC.



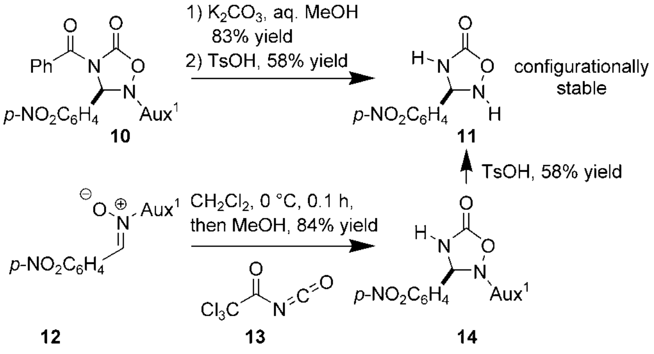
(4)

The results in Table 2 make apparent that the optically active oxadiazolidinones are stable towards acid, even when conc. aq. HCl in MeOH is used.[12] Additionally, the heterocycles have also been shown to be stable under alkaline conditions. Thus, as exemplified for **10**, cleavage of the *N*-benzoyl group with K_2CO_3 in aq. MeOH leads to monosubstituted oxadiazolidinone **11** in > 99% *ee* after auxiliary removal (Scheme 2).

Table 2: Cleavage of the chiral auxiliary [Eq. (4)].

R^1	R^2	Yield [%]	*ee* [%]
from Aux1			
p-C_6H_4OMe	Bn	88	>99
p-C_6H_4OMs	p-C_6H_4F	87	>99
p-C_6H_4OMs	p-C_6H_4F[a]	87	>99
Ph	p-C_6H_4F	81	>99
3-Py	p-C_6H_4F	65	>99
Me	p-$C_6H_4NO_2$	65	>99
1-Naph	H[b]	35	>99
from Aux2			
p-C_6H_4OMe	Bn	86	>99
p-C_6H_4OMs	p-C_6H_4F	91	>99

[a] Reaction conditions: MeOH/aq HCl conc. 5:1, 15 h, 23 °C. [b] Reaction conditions: 40 °C, 6 h.



Scheme 2. Synthesis of oxadiazolidinone **11**.

Trichloroacetyl isocyanate (**13**) participates in rapid cycloaddition (6 min) with the least reactive nitrone investigated (**12**). An added advantage is that product **14** is produced directly, since the trichloroacetyl group is cleaved during workup. Subsequent acid treatment affords **11**. These observations collectively underscore the fact that the oxadiazolidinones are inherently configurationally stable, even in their least substituted form.

In conclusion, we report the first general synthesis of enantiomerically pure oxadiazolidinones including the previously unknown optically active N2-unsubstituted parent structures. The salient features of this process include the convenient experimental protocol (simple dissolution of the two reactants in CH_2Cl_2) and the isolation of analytically pure products upon trituration with methanol in up to $>99{:}1$ d.r. Of additional importance, we document that this class of optically active heterocycles is configurationally stable. These compounds should find application as building blocks for pharmaceutical and other biologically relevant substances in industry and academia.

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[12] The configurational stability of these heterocycles may be related to the low basicity of the N2 nitrogen. Preliminary investigations with the oxadiazolidinone derived from *p*-fluorophenyl isocyanate and *p*-mesyloxyphenyl-derived nitrone provide an estimate of the pK_a as ≤ 2 for the corresponding conjugate acid.