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Synthesis of *syn*- and *anti*-1,2-Amino Alcohols by Regioselective Ring Opening Reactions of *cis*-3-Aminooxetanes#

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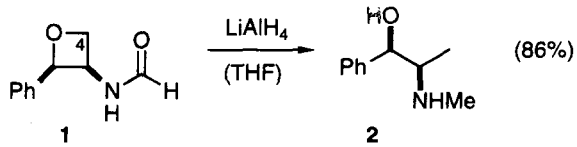
Abstract: *N*-*t*-Butyloxycarbonyl (Boc) substituted *cis*-2-phenyl-3-aminooxetanes **3** undergo a ring expansion to oxazolidinones **5** upon treatment with trifluoroacetic acid. The reaction occurs at the C(2) position under inversion of configuration. Alternatively, 3-aminooxetanes can be ring-opened at the less substituted C(4) position with retention of the relative configuration between C(2) and C(3) as exemplified by the synthesis of (±)-pseudoephedrine (**2**). The *cis*-3-aminooxetanes serve as precursors for either *syn*- or *anti*-1,2-amino alcohols.

Cis-2-aryl-3-aminooxetanes can by obtained in excellent yields by the [2+2]-photocycloaddition of aromatic aldehydes to α-unsubstituted *N*-acyl enamines.[1,2] These compounds represent 1,2-difunctional building blocks which can be transformed into biologically relevant *syn*-1,2-amino alcohols[3] by a regioselective ring opening at C(4). A yet unpublished example for such a reaction is depicted in scheme 1. Upon treatment with $LiAlH_4$ (THF, 25°C) the *N*-formyl protected oxetane **1** is converted to (±)-pseudoephedrine (**2**) in very good yield. The hydride attack occurs selectively at the less hindered position of the oxetane and it is presumably intramolecularly directed by the amino group.[4] Other known methods[5] should favor the ring opening at C(4) in a similar manner leading to *syn*-1,2-amino alcohols.

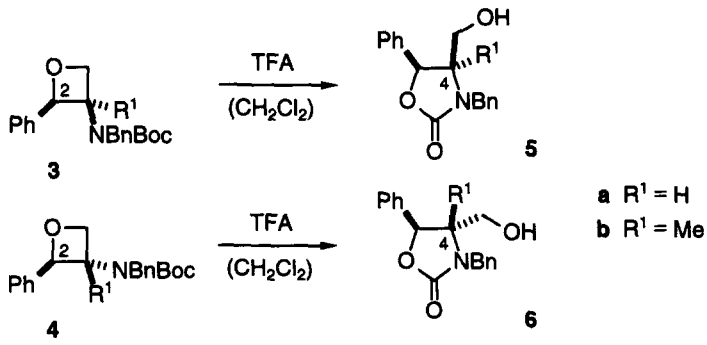


1 **2**

Scheme 1

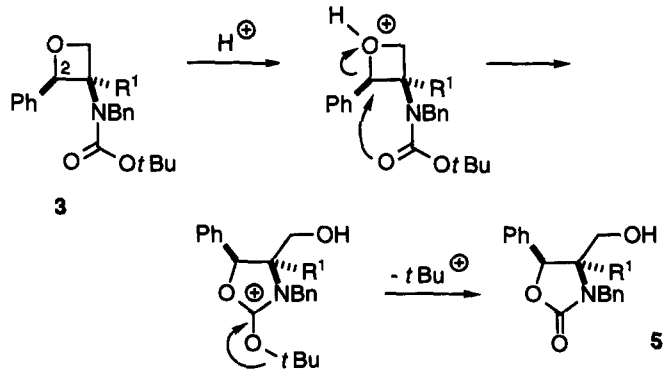
The ultimate goal of a stereoselective method is the production of either stereosisomer with high selectivity. Starting from *N*-acyl enamines it is unfortunately impossible to make *anti*-1,2-amino alcohols[6] accessible by a photochemical C-C-bond forming reaction. A possible remedy for this lack of versatility was envisaged by attack of an oxygen nucleophile at the higher substituted carbon atom C(2) under inversion. Accidently, we have found a simple method which facilitates the described transformation.

In an attempt to deprotect the *N*-*t*-butyloxycarbonyl (Boc) substituted oxetane **3a** with trifluoroacetic acid (TFA) according to a standard procedure,[7] we did not observe the formation of the corresponding 3-*N*-benzylaminooxetanes. Instead, we isolated the oxazolidinone **5a** (scheme 2). In experiments which were aimed at the optimization of the reaction conditions we also obtained and identified a small amount of the diastereomeric oxazolidinone **6a**. Since the oxetane **3a** could not be separated by conventional chromatography from its diastereoisomer **4a** the latter is always contained in the starting material in an amount of roughly 10%. Provided the reaction proceeds stereospecifically a product ratio **5a/6a** of 90/10 ist to be expected. Under optimized reaction conditions (2 equiv. TFA, -78 °C, CH_2Cl_2)[8] we isolated oxazolidinone **5a** in 75% yield starting from the diastereomeric mixture of oxetanes **3a** and **4a** combined with an additional 5% of oxazolidinone **6a**. The regioisomeric ring opening product was not observed.



Scheme 2

In the case of the fully separable oxetanes **3b** and **4b** the reactions yielded for each run under the conditions given above a single oxazolidinone formed by attack at C(2) (scheme 2). The oxazolinone **5b** is formed exclusively from oxetane **3b** whereas oxetane **4b** is converted to oxazolidinone **6b**. The relative configuration of the products was proven by NOE experiments. The reaction clearly proceeds under inversion at the former oxetane carbon atom C(2).

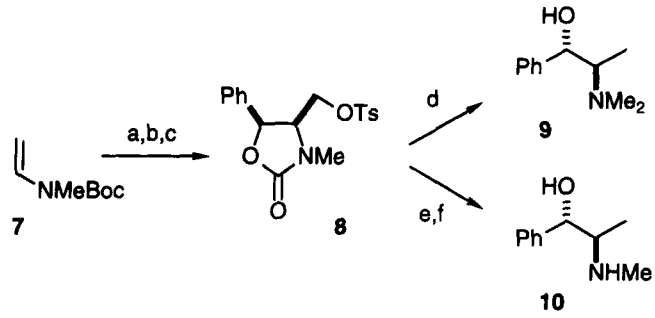


Scheme 3

From a mechanistic point of view the reaction is initiated most likely by protonation of the basic ring oxygen atom[9] and subsequent attack of the carbamate at C(2).[10,11] The *t*-butyl moiety acts as an electrophilic leaving

group (scheme 3). At higher temperature an epimerization can occur due to the formation of a carbenium ion (S_N1 mechanism). At low temperatures this pathway is successfully suppressed.

In scheme 4 shown below an application of the oxetane ring opening for the preparation of *anti*-1,2-amino alcohols is outlined. Starting from *N*-acyl enamine **7** the oxazolidinone **8** is generated by photocycloaddition, ring expansion and tosylation. It can be readily reduced with $LiAlH_4$ to (±)-*N*-methylephedrine (**9**). Alternatively, the oxazolidinone can be reduced in a formal hydro-de-tosylation with $NaBH_4$ in DMSO[12] and subsequently hydrolyzed to (±)-ephedrine (**10**).



a) PhCHO (MeCN), hv, 30 °C; 15 h; 56%. b) TFA (CH_2Cl_2), -78 °C; 2 h; 58%.
c) TsCl (py), 25 °C; 15 h, 86%. d) $LiAlH_4$ (THF), reflux; 2 h; 97%. e) $NaBH_4$ (DMSO), 150 °C; 1 h, 81%. f) KOH ($EtOH/H_2O$), reflux; 2 h, 77%.

Scheme 4

The comparison of the syntheses of (±)-*N*-methylephedrine (**9**) and (±)-ephedrine (**10**) with the preparation of (±)-pseudoephedrine (**2**) depicted in scheme 1 reveals the complementary character of the oxetane ring opening at C(2) and C(4). Often, the hydroxymethyl group at C(4) of the oxazolidinones **5** and **6** (scheme 2) may serve as a functional group which can be employed for further reactions.

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This paper is dedicated to Professor Hans Jürgen Schäfer on the occasion of his 60th birthday.

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