Synthetic Methods

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Ring Expansion of 3-Oxetanone-Derived Spirocycles: Facile Synthesis of Saturated Nitrogen Heterocycles**

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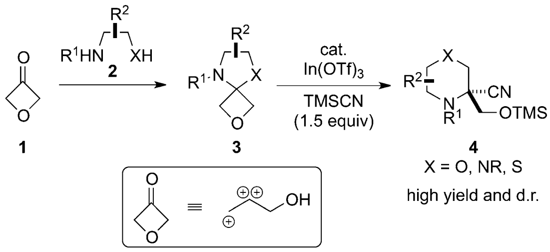
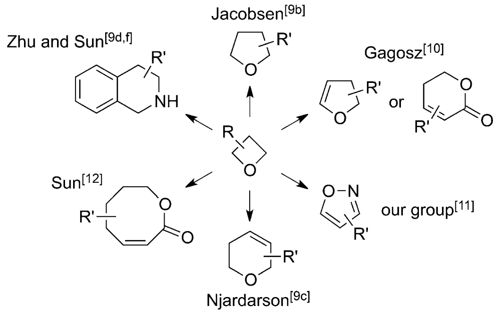
In recent years, oxetanes have received attention among medicinal chemists as they can improve key physicochemical and metabolic properties of potential drugs.[1] As a result, new synthetic methods to incorporate oxetanes in biologically active scaffolds have been developed[2] and a variety of oxetane building blocks have become commercially available.[3] However, the potential of these novel structures to serve as synthetic intermediates remains less thoroughly explored. Herein, we report a novel strategy for the facile synthesis of biologically important saturated nitrogen heterocycles which is based on the unique reactivity of 3-oxetanone (**1**) derived aminals, hemiaminal ethers, and thio ethers **3** (Scheme 1). The method provides convenient access to a variety of functionally rich morpholines (X = O), thiomorpholines (X = S), and piperazines (X = NR) in a stereocontrolled manner and good yields.



Scheme 1. The catalytic ring expansion of 3-oxetanone (**1**) derived spirocycles **3** to biologically important heterocycles **4**.

Oxetan-3-one (**1**) has become an important starting point for the synthesis of oxetane-containing molecules by exploiting the excellent electrophilicity of the carbonyl group.[1a,c,2,4] Inter- and intramolecular ring-opening reactions have successfully been achieved using Brønsted acids[5] as well as strong Lewis acids such as Et_2AlCl,[6] $TiCl_4$,[7] and $BF_3{\cdot}OEt_2$,[8] and elegant enantioselective processes relying on these activation modes have also been realized.[9] In particular, methods involving oxetane opening have recently emerged for the synthesis of valuable heterocycles, including tetrahydrofurans,[9b] dihydrofurans and dihydropyranones,[10] isoxazoles,[11] dihydropyrans,[9c] eight-membered-ring lactones,[12] and tetrahydroisoquinolines (Scheme 2).[9d,f] However, preparation of the appropriate substrates for ring-opening reactions often necessitate multistep sequences, thus somewhat limiting the overall efficiency of these methods.



Scheme 2. Recent examples of oxetane-opening reactions in the synthesis of heterocycles.

3-Oxetanone (**1**) has become commercially available at reasonable prices;[3] consequently, we have on-going efforts to examine its reactivity profile. This ketone ether can be considered a hydroxy-substituted C_3-synthon with two vicinal electrophilic carbon atoms (Scheme 1). The combination of the two inherent reactivity modes of 3-oxetanone (**1**) synergistically coupled to and accentuated by the ring strain and pronounced Lewis basicity of the ether[13] provide opportunities for the development of novel reaction cascades.

We have observed that ketone **1** readily undergoes condensation with β-heteroatom-substituted amino compounds **2** to form spirocycles **3** in high yields. We hypothesized that following activation by a Lewis acid a sequence of events would be triggered enabling access to saturated nitrogen heterocycles of relevance to drug discovery[14] possessing an underrepresented substitution pattern. Furthermore, it would constitute a rare example of a ring expansion of oxazolidines,[15] thus underscoring the potential of **1** to serve as a versatile reagent for organic synthesis.

Our studies commenced with oxazolidine **3a** (R^1 = H, R^2 = *i*Pr, X = O), readily prepared from 3-oxetanone (**1**) and valinol. Screening of various Lewis acid catalysts in the presence of trimethylsilyl cyanide (TMSCN) led to the identification of optimal conditions for the formation of morpholines (for a full description of optimization studies, see the Supporting Information). Accordingly, when hemiaminal ether **3a** was treated with indium(III) triflate (2 mol%) in acetonitrile in the presence of TMSCN, morpholine **4a** was obtained in 92% yield with excellent diastereoselectivity of > 20:1 (Scheme 3). A variety of oxazolidines derived from

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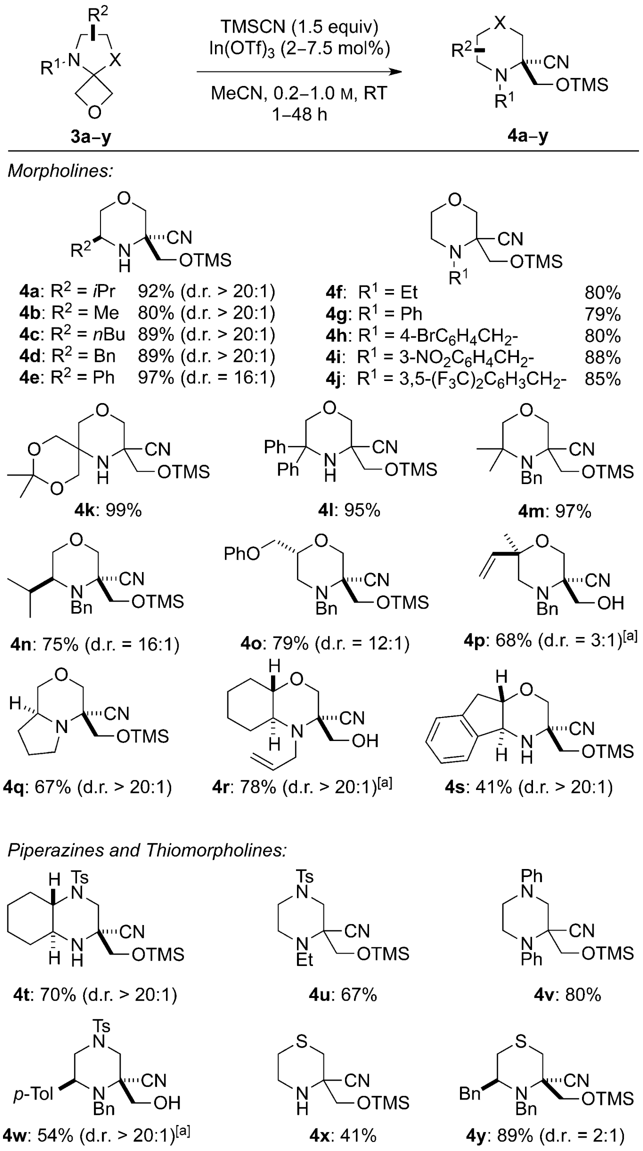
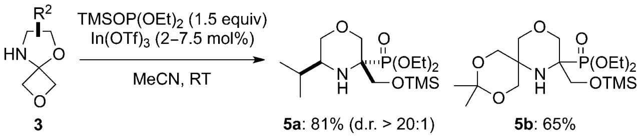


Scheme 3. Scope of the catalytic ring expansion of **3**. Reactions were conducted with **3** (0.50 mmol), TMSCN (0.75 mmol), and In(OTf)$_3$ (2–7.5 mol%) in MeCN (0.2–1.0 M) at RT. Yields refer to the isolated products after chromatographic purification. Diastereomeric ratios were determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture. [a] After complete consumption of the starting material, the mixture was diluted with MeCN to a concentration of 0.1 M and BF$_3$·OEt$_2$ (0.75 mmol) was added.

corresponding substituted amino alcohols were well tolerated and the products were obtained in high yields. Oxazolidines derived from primary amines, as well as substrates incorporating N-alkylated, arylated, and benzylated groups were successfully converted into the corresponding morpholines **4b–j**.

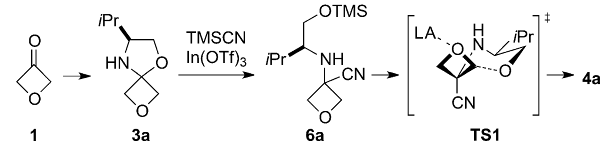
The presence of an acid-labile acetonide had no influence on the reaction outcome, and morpholine **4k** was obtained in quantitative yield. Furthermore, oxazolidines with various substitution patterns could be employed, leading to morpholines **4l–p** with equally good yield and diastereoselectivity (Scheme 3). The use of substrates derived from cyclic amino alcohols led to the formation of annulated morpholines **4q–s**. The method could also be extended to the ring expansion of imidazolidines and thiazolidines featuring cyclic, monosubstituted or unsubstituted backbones. Accordingly, piperazines **4t–w** and thiomorpholines **4x** and **4y** could be synthesized. The formation of products **4p**, **4r**, and **4w** required the addition of stoichiometric amounts of BF$_3$·OEt$_2$ to effect rearrangement of the Strecker intermediates. The ring expansion generally proceeded with high diastereoselectivity (d.r. = 12:1 to > 20:1) with the exception of **4p** and **4y** (d.r. = 3:1 and d.r. = 2:1, respectively). Notably, the unusual substitution pattern of the products is the result of the unique inherent reactivity of 3-oxetanone (**1**), and general routes to access similarly decorated morpholines, piperazines, and thiomorpholines have not been reported.[16] In this respect, a substructure search on SciFinder revealed that 68% of all morpholines are merely substituted at the nitrogen, and less than 1% feature geminal carbon substituents next to the ring nitrogen (see the Supporting Information for details). Consequently, the method provides access to new saturated heterocycles.

We have found that the process is amenable to the use of nucleophiles other than cyanide. For example, the use of diethyl trimethylsilyl phosphite leads to the formation of phosphonates **5a** and **5b** (Scheme 4).



Scheme 4. Synthesis of phosphonates **5**.

We speculate that the process proceeds as described in Scheme 5. Following condensation of **1** with valinol, oxazolidine **3a** undergoes Strecker reaction with trimethylsilyl cyanide to afford nitrile **6a**. After activation of the oxetane by Lewis acid (LA), intramolecular 6-*exo*-tet cyclization ensues, leading to morpholine **4a**. In the proposed transition state **TS1** the nitrile group (A-value of 0.21)[17] occupies an axial position and the side chain (isopropyl) resides equatorially. This scenario is in accordance with the configuration of the products as established by X-ray crystal structure analysis of two representative morpholines (see the Supporting Information).[18]

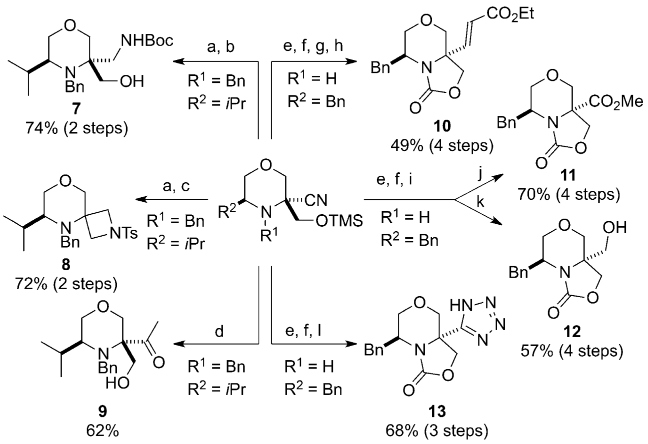


Scheme 5. Proposed mechanism for the formation of morpholine **4a**.

We have conducted additional experiments that suggest an unusual role for In^{III} as the Lewis acid. When the Strecker product **6a** was synthesized separately and treated with In(OTf)$_3$ (2 mol%), no reaction except slow decomposition of the starting material was observed. However, when In-

(OTf)$_3$ (2 mol %) and catalytic amounts of TMSCN (20 mol %) were added, morpholine **4a** was obtained cleanly in 91 % yield and d.r. > 20:1. The same outcome was observed when InCl$_3$ (3 mol %) was used instead of In(OTf)$_3$, although in this case the reaction was significantly slower. The role of TMSOTf as an active catalyst, potentially formed in situ under the reaction conditions, could also be ruled out, because treatment of Strecker product **6a** with TMSOTf (10 mol %) led only to a complex mixture of products. The combination of TMSOTf (10 mol %) and TMSCN (20 mol %) produced morpholine **4a** along with its O-desilylated derivative in diminished yield of 58 %. Additionally, TMSCN (20 mol %) alone was also unable to promote the desired rearrangement. These observations raise an interesting question as to the true nature of the catalytically active species generated over the course of the reaction. Further investigations to provide insight into the mechanism of this intriguing process are currently underway.

The high functional group density of the products provides diverse handles for their interconversion into a variety of other valuable building blocks. Accordingly, morpholine **4n** can be converted into protected amine **7** by nitrile reduction and subsequent Boc protection. In a similar fashion, azetidine **8** was formed after nitrile reduction, N-tosylation, and ring closure. Treatment of **4n** with methyllithium gave methyl ketone **9**. Furthermore, morpholine **4d** was desilylated and converted into the corresponding oxazolidinone, which was further elaborated into α,β-unsaturated ester **10** through reduction of the nitrile to the aldehyde and subsequent Wittig olefination. Nitrile hydrolysis of the same oxazolidinone intermediate and ester formation or reduction of the resulting acid gave ester **11** and alcohol **12**, respectively, whereas treatment of the oxazolidinone with sodium azide produced tetrazole **13** (Scheme 6).



Scheme 6. Representative transformations of the morpholine products. Reagents and conditions: a) LiAlH$_4$, THF, 0 °C; then 70 °C. b) Boc$_2$O, NEt$_3$, CH$_2$Cl$_2$/MeOH, 0 °C to RT. c) TsCl, NEt$_3$, DMAP, THF, 0 °C to RT; then KOH, TsCl, THF, 75 °C. d) MeLi, THF, 0 °C to RT; then 2 M HCl. e) TBAF, THF, 0 °C. f) COCl$_2$, toluene, 0 °C. g) Raney Ni, NaH$_2$PO$_2$·H$_2$O, py/H$_2$O/AcOH, 50 °C. h) Ph$_3$PCHCO$_2$Et, CH$_2$Cl$_2$, RT. i) 6 M HCl, AcOH, 80 °C. j) TMSCHN$_2$, benzene, MeOH, RT. k) *i*BuOC(O)Cl, *N*-methyl morpholine, THF; then NaBH$_4$, H$_2$O, 0 °C. l) NaN$_3$, ZnBr$_2$, H$_2$O/*i*PrOH, 110 °C.

In summary, we have discovered an efficient method for the catalytic ring expansion of 3-oxetanone-derived aminals, hemiaminal ethers, and thio ethers to provide heterocycles relevant to drug discovery. The unique reactivity of 3-oxetanone provides rapid entry to valuable morpholines, piperazines, and thiomorpholines with an otherwise difficult-to-access substitution pattern. The cascade reaction reported herein is broad in scope and the substrates are readily prepared, mostly in one step from commercially available starting materials. Given the fundamental importance of these heterocycles in bioactive agents and the fact that densely functionalized morpholines, piperazines, and thiomorpholines have been scarcely reported, we believe that the method enhances the medicinal chemist's toolbox and, at the same time, stimulates further developments toward the use of oxetan-3-one as a versatile C$_3$ synthon in organic synthesis. As new methods for the synthesis of oxetanes continue to be reported, applications on the use of oxetanes as synthetic intermediates are revealing the untapped potential of this small heterocycle. Consequently, oxetanes as an epoxide homologue may attain the general utility that is enjoyed by epoxides as synthetic modules.

Experimental Section

Representative procedure: To a solution of oxazolidine **3a** (79 mg, 0.50 mmol, 1.0 equiv) in MeCN (1.2 mL) were added In(OTf)$_3$ (5.6 mg, 0.01 mmol, 2 mol %) and TMSCN (101 μL, 0.75 mmol, 1.5 equiv) and the mixture was stirred at RT for 1 h. The reaction was poured into sat. NaHCO$_3$ solution and the aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic fractions were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/ethyl acetate 4:1) to afford morpholine **4a** (119 mg, 0.46 mmol, 92 %) as a colorless oil.

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Keywords: cascade reactions · heterocycles · homogeneous catalysis · oxetanes · ring expansion

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[18] CCDC 951984 (**14a**, see the Supporting Information) and 952032 (**4n**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.