Lewis Acid Catalyzed Annulation of Nitrones with Oxiranes, Aziridines, and Thiiranes

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Supporting Information

ABSTRACT: A highly selective Lewis acid catalyzed annulation of three-membered heterocycles with nitrones has been developed. Oxiranes, aziridines, and thiiranes were used as substrates for the synthesis of various six-membered heterocycles using Al or In catalysts. This catalytic protocol demonstrates a broad substrate scope and provides access to new structural motifs in high yields and in excellent selectivity under mild reaction conditions.

F unctionalized nitrogen-containing heterocycles are common structural motifs in natural products, pharmaceuticals, and agrochemicals. In particular, the importance of saturated heterocycles (high sp3-content) in drug discovery has recently been highlighted.1 One important strategy for the synthesis of a diverse range of heterocyclic (and carbocyclic) compounds is based on transformations of strained rings such as cyclopropanes, oxiranes, and aziridines.2 For example, the Lewis acid catalyzed formal cycloaddition of donor−acceptor cyclopropanes to nitrones (Scheme 1), olefins, and other unsaturated reaction partners has been extensively explored for the synthesis of a variety of cyclic structures.3 Furthermore, oxiranes4 and aziridines5 have been utilized as analogous heteroatom-containing building blocks for the construction of heterocycles by the selective cleavage of the C−C or the C−heteroatom bond. As a part of our research program based on catalysis with main-group elements, we envisioned that the catalytic activation of strained heterocycles such as oxiranes would enable the synthesis of N,O-linked heterocycles such as 1,4,2-dioxazinane derivatives by a catalytic annulation reaction with nitrones (Scheme 1).

The 1,4,2-dioxazinane and 1,2,4-oxadiazinane products represent a largely unexplored class of saturated heterocycles; only a few multistep preparative methods have been reported for the purpose of conformational studies and for an evaluation of their pharmaceutical activities.6 Various dioxazine and oxadiazine derivatives have been shown to exhibit high activity as γ-secretase modulators9a for potential use in the treatment of Alzheimer’s disease (Figure 1).

Herein, we report a new catalytic method for the synthesis of 1,4,2-dioxazinanes (with oxiranes), 1,2,4-oxadiazinanes (with aziridines), and 1,4,2-oxathiazinanes (with thiiranes). At the outset of this study, our focus was directed toward finding an appropriate catalyst and suitable reaction conditions for the annulation of oxirane 1a with nitrone 2a. More specifically, we screened for a catalyst and reaction conditions that would suppress the Meinwald rearrangement10 and the competitive nucleophilic ring opening11 of the oxirane component. Our initial experiments, using InCl3 (20 mol %) in CH2Cl2,a afforded the dioxazinane product 3a in 52% isolated yield after 24 h at 20 °C (Table 1, entry 1).

Interestingly, the product 3a was obtained as a single diastereomer. The two phenyl groups were found to be positioned in a trans relationship (vide infra). When the temperature was increased to 40 °C in the presence of 10 mol % of InCl3, the yield of 3a increased to 69% after 4 h reaction time.
We then applied a selection of substituted oxiranes in the annulation reaction (Table 3). Under the standard reaction conditions, the para-substituted phenyl oxiranes 1b–d were all less efficient compared to their nonsubstituted analogue 1a. The electron-rich oxiranes 1c and 1d were found to undergo a rapid rearrangement and/or polymerization when AlCl3 was used as the catalyst. However, upon changing the solvent to CH2Cl2 and the catalyst to InCl3 for 1c, moderate yields of dioxazinanes 3n–p were obtained (Table 3, entries 1–3). In contrast, vinylxirane 1e and cyclohexene oxide 1f reacted with high selectivity using AlCl3 as the catalyst; vinyl-substituted dioxazinanes 3q–r and trans-fused bicyclic products 3s,t were isolated in excellent yields (Table 3, entries 4–7). The use of cyclohexyl nitrore 2n with oxirane 1f and the reaction of chloro-substituted oxirane 1g required a prolonged reaction time (24 h) for completion and resulted in lower yields (Table 3, entries 8 and 9). For all of the monosubstituted oxiranes, a single diastereomer of the dioxazinane products 3 was obtained. Thus, we were interested in exploring the selectivity with trans- and cis-disubstituted oxiranes 1h and 1i. The reaction of 1h with nitrore 2a furnished the fully substituted dioxazinane 3w in a 3:1 diastereomeric ratio (by crude 1H NMR). Upon isolation by silica gel chromatography, the ratio changed to 2:1 (Table 3, entry 10). When InBr3 was used in place of AlCl3, a 2:1 ratio of 3w was observed by crude 1H NMR analysis. The ratios varied slightly over time though, indicating a rapid epimerization process.

For cis-oxirane 1i with nitrore 2a, a 2:1 diastereomeric ratio of 3x was observed by crude 1H NMR with AlCl3 as catalyst. However, with InBr3, a single isomer of 3x was isolated in 98% yield (Table 3, entry 11). We speculate that the stereochemical outcome (i.e., the C3 configuration) for 3w and 3x is dependent...
on the relative stabilities of the two diastereomers (the all-equatorial arrangement of 3x is energetically favored).

Having established a procedure for the annulation of oxiranes with nitrones, we then investigated the possibility of using aziridines as substrates. In comparison with the oxiranes, we found that the annulation with aziridines required modified reaction conditions with respect to reaction temperature and catalyst. Additionally, aziridines 4a and 4b reacted with the applied nitrones also in the absence of a catalyst, albeit in lower yields. As shown in Table 4, both the phenyl-substituted and aliphatic N-benzylaziridines 4a and 4b led to a selective formation of the 1,2,4-oxadiazinanes 5a−c in high yields with InCl3 as catalyst. In the absence of a catalyst, 40% of product 5a and 16% of 5c were obtained. The use of AlCl3 as catalyst led to a lower yield, 35%, of 5c at 80 °C, whereas no reaction was observed at 40 °C (Table 4, entries 1−3). N-Ethyl-substituted aziridine 4c did not react without a catalyst; InCl3 furnished the product 5d in 51% yield (Table 4, entry 4). N-Tosyl-substituted aziridines were unreactive under the applied conditions. This lack of reactivity may be explained by a less efficient Lewis acid activation or a low nucleophilicity of the N-tosyl group, which impedes the annulation reaction.

Furthermore, we were pleased to find that not only oxiranes and aziridines but also thiranes 6 could be employed in the annulation with nitrones (Scheme 2, eqs 1 and 2). The reaction of nitrone 2a with thiranes 6a and 6b furnished the 1,4,2-oxathiazinane products 7a,b in moderate yields as single diastereomers. A rapid decomposition of the thirane was observed that only partly could be avoided by the use of InCl3 in toluene.

In order to gain insight into the mechanism of the presented transformation, reactions of enantiopure oxirane (2R)-1a with nitrones 2a and 2g were performed (Scheme 3).

The corresponding dioxazinanes 3a and 3g were obtained in high yields with only a slight erosion of the enantiomeric excesses. Single-crystal X-ray analysis was used to determine the absolute configuration of 3g (Figure 2).15

**Table 3. Oxirane Substrate Scope**

<table>
<thead>
<tr>
<th>entry</th>
<th>oxirane, 1</th>
<th>nitrone, 2</th>
<th>product, 3</th>
<th>yield [%]</th>
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<tr>
<td>1</td>
<td>p-CPh</td>
<td>2a</td>
<td>3n</td>
<td>65f</td>
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<tr>
<td>2</td>
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<td>2a</td>
<td>3o</td>
<td>4444</td>
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<td>3</td>
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<td>3p</td>
<td>25c</td>
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<td>4</td>
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<td>6</td>
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<td>3e</td>
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<td>7</td>
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<tr>
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<tr>
<td>11</td>
<td>2a</td>
<td>3x</td>
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**Table 4. Annulation of Aziridines and Nitrones**

<table>
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<th>nitrone, 2</th>
<th>product, 5</th>
<th>yield [%]</th>
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<tr>
<td>1</td>
<td>4a</td>
<td>2a</td>
<td>5a</td>
<td>8740</td>
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<td>2</td>
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<td>2a</td>
<td>5b</td>
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<td>3</td>
<td>4b</td>
<td>2j</td>
<td>5c</td>
<td>8546434f</td>
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<tr>
<td>4</td>
<td>4c</td>
<td>2a</td>
<td>5d</td>
<td>5144</td>
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**Scheme 2. Reactions with Thiiranes**

**Scheme 3. Transfer of Chirality in the Annulation Reaction**

**Figure 2. Ellipsoidal representation of compound 3g.**

From these experiments, it can be concluded that the stereocenter of the oxirane was inverted upon reaction with the nitrone. Most likely, these results indicate that the reaction is initiated by an SN2-opening of the oxirane followed by a selective cyclization.16 Alternatively, a rapid epimerization of the second stereocenter, leading to the most stable conformer of the dioxazinane product, can be envisioned on the basis of the results in Table 3, entries 10 and 11.

In summary, we have established an efficient catalytic method for the selective annulation of nitrones with oxiranes, aziridines, and thiranes. The products were, in almost all cases, obtained as single diastereomers comprising a wide variety of functional
groups. Thus, this straightforward method provides ready access to structural motifs with a potential biological importance with inexpensive and readily available catalysts and reagents.

**ASSOCIATED CONTENT**

Supporting Information

Experimental procedures, compound characterization data, and crystallographic data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02195.

Experimental procedures, compound characterization data, and crystallographic data (PDF)

X-ray crystallographic data of 3g (CIF)

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Notes

The authors declare no competing financial interest.

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**REFERENCES**


(12) A Brønsted acid-mediated pathway at lower temperatures cannot be ruled out.

(13) For a helpful discussion on aziridine opening, see ref2g. (a) CCDC 1051506 contains 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. For compounds 3a, 3s, 3w, 3x, 5a, and 7a, the relative stereochemistry was established by dNOE experiments; see the Supporting Information for details.