Heterocycle Synthesis via Radical Addition-Cyclization of Oxime Ethers

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Abstract: Oxime ethers connected by a tether to aldehydes or ketones efficiently cyclized via stannyl radical addition-cyclization to give a new entry to heterocyclic amino alcohols. The SmI2-induced radical cyclization was found to be effective for preparing cyclic trans-amino alcohols. These radical reactions provide a novel method for the synthesis of (−)-balanol, aminocyclitols, 1-deoxynojirimycin, 2-substituted 5-amino-4-piperidinol, and nucleoside analogs. The sulfanyl radical addition-cyclization-elimination reaction was developed, which was successfully applied to the synthesis of (−)-kainic acid. The sulfanyl radical addition-cyclization of oxime ethers gave a method for synthesis of rigidified cyclic β-amino acids. The carbon radical addition-cyclization reaction of substrates having two different radical acceptors such as acrylate and aldoxime ether moieties proceeded even in aqueous media via a diastereoselective tandem C-C bond-forming process, providing a method for asymmetric synthesis of γ-butyrolactones and γ-amino acids.

1. Introduction

Strategies involving radical reactions have become preeminent tools in organic synthesis.1 Free radical-mediated cyclization has developed as a powerful method for preparing various types of cyclic compounds via carbon-carbon bond-forming processes. Although a number of extensive investigations into the radical reaction were reported in recent years, the majority of these employ methods utilizing conventional radical acceptors such as alkenes or typical radical precursors such as alkynes, selenides, and xanthates. One drawback in the traditional procedures using such radical acceptors and precursors is the loss of the inherent functional groups. Our laboratory is interested in developing effective and convenient methods for the synthesis of highly functionalized cyclic compounds. For this purpose, we have focused our efforts on radical reactions using aldehydes, ketones, and C-C multi bonds as a radical precursor and/or an oxime ether group as a radical acceptor.2

2. Synthesis of Functionalized Heterocycles via Radical Reaction of Oxime Ethers

2.1 Stannyl Radical Addition–Cyclization Reaction

We have explored a new carbon–carbon bond-forming reaction based on the stannyl radical addition-cyclization of oxime ethers 1 tethered to a carbonyl group (Scheme 1).3 The newly found radical reaction provides a synthetically useful method for the construction of cyclic amino alcohols 2 widely found in biologically active natural products.

To disclose the scope and limitation of the stannyl radical addition–cyclization of oxime ethers, we focused our attention on a systematic study employing readily available starting compounds 3a−g in which two functional groups, oxime ether and carbonyl groups, are connected with a nitrogen atom with different carbon chains. The compounds 3a−g were prepared as an E/Z mixture concerning the geometry of the oxime group. A solution containing tributyltin hydride (Bu3SnH) and 2,2′-azobisisobutyronitrile (AIBN) in benzene was added dropwise to a solution of the oxime ether in boiling benzene while stirring under nitrogen (Table 1). In the case of 3a, a 2.3:1 mixture of the cyclized trans- and cis-product 4a was obtained in 54% yield (entry 1). The ketoxime ether 3b gave a similar result (entry 2). In the case of 3c having a ketone carbonyl group, the reaction took place slowly compared with the substrates 3a,b having a formyl group (entry 3). The ketoxime ether 3d connected with a ketone carbonyl group underwent a highly stereoselective reaction to afford amino alcohol 4d having two adjacent quaternary carbons in a 14:1 trans: cis ratio (entry 4). These reactions were extended to the cyclization of the oxime ethers 3e−g to give the six- and seven-membered cyclic products 4e−g (entries 5−7). However, attempted formation of an eight-membered product was unsuccessful. In every case, the reactions took place exclusively in exo-trig manner, and no endo-trig products were formed. The stannyl radical is known to be oxygenphilic4 and, therefore, attacks the carbonyl group to form the ketyl radical A, which would be trapped intramolecularly with the oxime ether moiety. The preferential formation of trans-4 could be explained by assuming both the electronic and steric repulsions between the ketyl radical moiety and the oxime ether group.

We also investigated the effect of the E/Z-geometry of the...
oxime group on either the chemical yield or trans/cis selectivity in the formation of a seven-membered ring (Table 2). However, no remarkable effect was observed by employing geometrically pure E-5a and Z-5a. A similar trend has been recently reported by Bartlett in a tributyltin hydride-induced coupling of phenyl thionocarbonates with oxime ethers.

2.2 Samarium Diiodide-Induced Radical Cyclization

In recent years, samarium diiodide (SmI2) has evolved as a unique single-electron reducing reagent that is well suited for highly chemo- and stereoselective radical reactions. We next investigated the SmI2-induced reaction of oxime ethers 5a, b (Table 3). Cyclizations were performed in the presence of t-BuOH as a proton donor in THF at from -78°C to room temperature using a 0.1 M solution of SmI2 in THF. The addition of HMPA, which was recognized to increase the reaction rate by SmI2, was found to be essential for successful seven-membered ring-forming cyclization of 5a to afford a 6.6:1 mixture of the trans- and cis-product 6a in 53% yield (entries 1 and 2). In contrast to seven-membered ring formation, the five-membered ring-forming reaction of 5b proceeded even in the absence of HMPA to give 8a after refluxing for 120 min (entry 1). In the case of triphenylborane (Et3B), the cyclic product 8a was obtained in 82% yield after refluxing for 15 min (entry 2). Although the reaction using Et3B (2.5 eq) as a radical initiator proceeded moderately even at 20°C, the use of a catalytic amount of Et3B (0.2 eq) was less effective for the reaction. These results indicate that Et3B acts as not only a radical initiator but also a Lewis acid and a radical trapping-terminator; therefore, more than a stoichiometric amount of Et3B is required. Thus, the major reaction pathway is that the stannyl radical adds to the Et3B-activated oxime ether 7 to form the aminyl radical G, which is trapped with Et3B as a radical chain terminator (Scheme 3). High chemical yields were also observed in the radical cyclization using triphenyltin hydride and tris(trimethylsilyl)silane (entries 3 and 4). These reactions were successfully applied to solid-phase radical reactions.

2.4 Stannyl Radical Addition-Cyclization of Vinylogous Systems

We have investigated stannyl radical addition-cyclization of the vinylogous systems involving the oxime ether and carbonyl group, providing a novel synthetic method for the bifunctionalized pyrrolidines (Scheme 4). The reaction of oxime ether 9 connected with the α,β-unsaturated ketone group proceeded smoothly to afford trans-product 10 as a...
single isomer in 58% yield. In the reaction, a stannyl radical added to an oxygen atom of the \( \alpha,\beta \)-unsaturated ketone group to form allylic \( O \)-stanyl ketyl radical \( H \), which was trapped with the oxime ether group to give an aminyl radical \( I \). Since the stable allylic ketyl radical \( H \) would be equilibrated with trans- and cis-aminyl radicals \( I \), the preferential formation of stable trans-product \( 10 \) was observed. We also investigated the radical addition-cyclization of \( \alpha,\beta \)-unsaturated oxime ether \( 11 \) connected with a formyl group, which was prepared as \( E- \) and \( Z- \)olefinic isomers. The reaction of both \( E-11 \) and \( Z-11 \) proceeded slowly compared with that of \( 9 \) to give a mixture of trans- and cis-isomers \( 12 \) in a different ratio. These results indicate that there would be no equilibration between ketyl radical \( J \) and allylic aminyl radical \( K \). In the case of \( \alpha,\beta \)-unsaturated oxime ether \( 13 \) connected with the \( \alpha,\beta \)-unsaturated ketone group, the reaction proceeded more slowly than those of \( 9 \), \( E-11 \), and \( Z-11 \) to give a mixture of trans- and cis-isomers \( 14 \) in 59% yield.

### 2.5 Synthetic Applications to Natural Compounds

The radical cyclization of oxime ethers connected with the formyl group provides a synthetically useful method for the construction of cyclic amino alcohols found in biologically active natural products such as \((-\)-balanol, pseudodistomin, amino cyclitols, dysiherbaine, and amino sugars (Figure 1).

\((-\)-Balanol, a potent protein kinase C inhibitor, consists of a benzophenone fragment \( 16 \) and a hexahydroazepine fragment \( 17 \) (Scheme 5). The total synthesis of \((-\)-balanol \( 18 \) was achieved via the preparation of a benzophenone frag-

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### Table 4. Radical addition-cyclization by using triethylborane

<table>
<thead>
<tr>
<th>Entry</th>
<th>XH</th>
<th>Initiator (eq)</th>
<th>Time (min)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bu$_3$SnH</td>
<td>AlBN (1.0)</td>
<td>120</td>
<td>8a</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>Bu$_3$SnH</td>
<td>Et$_3$B (2.5)</td>
<td>15</td>
<td>8a</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>Ph$_3$SnH</td>
<td>Et$_3$B (2.5)</td>
<td>15</td>
<td>8b</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>(TMS)$_3$SH</td>
<td>Et$_3$B (2.5)</td>
<td>15</td>
<td>8c</td>
<td>79</td>
</tr>
</tbody>
</table>

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### Scheme 3. Possible reaction pathway

Scheme 3 shows the possible reaction pathway involving the radical addition-cyclization of oxime ethers. The reaction proceeds via the formation of ketyl radical \( J \) and aminyl radical \( K \), leading to the formation of stable trans-products. The yields and reaction conditions are summarized in Table 4.
Pseudodistomins and an enantiomer of neuraminidase inhibitor can be synthesized via radical reaction of oxime ether 19 prepared from L-aspartic acid (Scheme 6). Treatment of 19 with SmI₂ in the presence of t-BuOH underwent smooth cyclization to give a 2.5:3.6:1 mixture of three cyclized products 20-22. The 6-exo-trig cyclization as well as 5-exo-trig cyclization took place smoothly even in the absence of HMPA, in contrast to 7-exo-trig cyclization as shown in Table 3. Conversion of anti-cis-20 to 2-substituted 5-amino-4-piperidinol 23, which is regarded as a synthetic precursor of pseudodistomins, was readily achieved. The isomer anti-trans-22 could be converted to the trisubstituted piperidine 24, which is an enantiomer of the synthetic intermediate of neuraminidase inhibitor.

Stannyl radical addition-cyclization of oxime ethers derived from d-glucose, d-galactose, and d-xylene proceeded smoothly to afford alkoxyamino alcohols (Table 5), which were effectively converted into two types of glycosidase inhibitors or its candidates such as aminocyclitols, 1-deoxynojirimycin, and 1-deoxygalactostatin via reductive ring-expansion of trans-alkoxyamino alcohols (Scheme 7). As a related synthetic application, we achieved the synthesis of 5-pyrimidinyl- and 5-purinylpyrrolidin-3-ol nucleoside analogues from trans-amino alcohol (Scheme 8). We have recently studied the radical cyclization of oxime ethers derived from monosaccharides aiming at the synthesis of (-)-dyisierbaine and related stereoisomers.

3. Synthesis of Cyclic Compounds via Sulfanyl Radical Reactions

3.1 Sulfanyl Radical Addition–Cyclization Reaction

Most radical reactions are carried out using Bu₃SnH. However, because of the toxicity of Bu₃SnH, an area of continuing and important research is to develop new methods for radical generation that avoid the use of tin reagents. Therefore, we have also explored the reactions based on sulfanyl radical addition – cyclization. A combination of sulfanyl radical addition – cyclization of diene 31 connected to the trisubstituted piperidine 24, which is an enantiomer of the synthetic intermediate of neuraminidase inhibitor.

Table 5. Radical cyclization of oxime ethers derived from sugars

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>4-H</th>
<th>E.Z</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25a</td>
<td>β</td>
<td>5:1</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>25b</td>
<td>α</td>
<td>3:1</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>25c</td>
<td>β</td>
<td>3:1</td>
<td>27</td>
</tr>
</tbody>
</table>
with hydroximate and subsequent conversion of the resulting cyclic hydroximate 32 to the lactone provides a novel method for the construction of \( \alpha, \beta \)-disubstituted \( \gamma \)-lactones (Scheme 8). The \( Z-O \)-methylhydroximate 31 would exist in conformer 31A, preferable for intramolecular cyclization over the less favored conformer 31B, as a result of steric repulsion between the substituents on the nitrogen and oxygen atoms. This method was successfully applied to a practical synthesis of \((\pm)\)-oxo-parabenzlactone.

The sulfanyl radical addition–cyclization of diene 33 derived from \( \alpha \)-serine or (S)-glycidol proceeded smoothly to afford a 1:3 \( \text{trans/cis} \) mixture of the cyclized product 34 in 85\% yield. Both \( \text{trans} \)- and \( \text{cis} \)-isomers 34 were effectively converted into the known key intermediate for the synthesis of \((\pm)\)-\( \alpha \)-allokainic acid via conversion of the phenylsulfanyl-methyl group into an isopropenyl group.

The sulfanyl radical addition–cyclization–elimination of diallylamine 35 in the presence of a catalytic amount of thiophenol and AIBN gave a 1:1.5 \( \text{trans/cis} \) mixture of the 2,3,4-trisubstituted pyrrolidines 36 in 95\% yield. The synthesis of \((-)\)-kainic acid was achieved by conversion of the \( \text{cis} \)-isomer of 36 to the target compound.

3.2 Sulfanyl Radical Addition–Addition–Cyclization and Addition–Cyclization–Addition Reactions

The reaction of unbranched diyne 37 with the sulfanyl radical proceeded smoothly to give the cyclized \( \text{exo-olefin} \) 38 in 70\% yield via a sulfanyl radical addition–addition–cyclization process, accompanied with the cyclized \( \text{endo-olefin} \) 39 in 26\% yield via a sulfanyl radical addition–cyclization–addition process (Scheme 9). Since unbranched diyne 37 would exist in a stable zig-zag conformer, the addition–addition–cyclization process is major reaction pathway (Scheme 10). In contrast, the reaction of diyne 40 having a quaternary carbon gave the cyclized \( \text{endo-olefin} \) 41 in 86\% yield via a sulfanyl radical addition–cyclization–addition process, because diyne 40 would exist in a suitable conformer for intramolecular cyclization. These reactions were applied to the synthesis of the A–ring fragment of \( \text{la,25-dihydroxyvitamin D} \).

3.3 Sulfanyl Radical Addition–Cyclization Reaction of Oxime Ethers

We also investigated the sulfanyl radical addition–cyclization of the alkenyl–tethered–oxime ethers 43a–d and hydrazones 43e–g for the synthesis of rigidified \( \beta \)-amino acids (Table 6). In these reactions, the \( \text{cis} \)-isomers were preferentially formed, probably due to the effect of orbital symmetry reported by Beckwith. The synthesis of cyclic \( \beta \)-amino acid 45, cispentacin, from the cyclopentylamines cis-44b,e and \( \text{trans-44b,e} \), was readily achieved by conversion of the phenylsulfanyl methyl group into a carboxyl group.
4. Tandem C–C Bond-Forming Radical Addition-Cyclization Reaction

We examined the radical addition-cyclization reaction of substrate 46 having two different radical acceptors such as acrylate and aldoxime ether moieties (Table 7). A remarkable feature of this reaction is the construction of two C–C bonds and two chiral centers via a tandem process. The reaction in refluxing toluene proceeded smoothly to give major diastereomers 47a-d in good yields along with a small amount of the other diastereomers (entries 1, 3, 5, and 7). A favorable experimental feature of this method is that the reaction proceeds smoothly even in the absence of toxic tin hydride or heavy metals via a route involving an iodine atom-transfer process (Scheme 11). From the viewpoint of elucidating the reaction mechanism, it is important to note that the tandem reaction proceeded even in aqueous media (entries 2, 4, and 6). These observations suggest that the major reaction pathway is not a route involving the conversion of water-unstable boryl enolate N into cyclic product O but a tandem radical route involving the conversion of water-resistant radical intermediate M into cyclic product O.

Table 7. Tandem C–C bond-forming radical reaction of oxime ethers

<table>
<thead>
<tr>
<th>Entry</th>
<th>( R^2 )</th>
<th>Solvent</th>
<th>Product</th>
<th>cis/trans</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>benzene</td>
<td>47a</td>
<td>12:1</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>( \text{H}_2\text{O} + \text{MeOH}=1:4 )</td>
<td>47a</td>
<td>9:1</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>( \beta\text{-Pr} )</td>
<td>benzene</td>
<td>47b</td>
<td>12:1</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>( \beta\text{-Pr} )</td>
<td>( \text{H}_2\text{O} + \text{MeOH}=1:4 )</td>
<td>47b</td>
<td>7:1</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>c-Hexyl</td>
<td>benzene</td>
<td>47c</td>
<td>12:1</td>
<td>64</td>
</tr>
<tr>
<td>6</td>
<td>c-Hexyl</td>
<td>( \text{H}_2\text{O} + \text{MeOH}=1:4 )</td>
<td>47c</td>
<td>8:1</td>
<td>56</td>
</tr>
<tr>
<td>7</td>
<td>c-Pentyl</td>
<td>benzene</td>
<td>47d</td>
<td>12:1</td>
<td>70</td>
</tr>
</tbody>
</table>

Scheme 11. Possible reaction pathway

As shown in Scheme 12, the \( \gamma \)-butyrolactone 47a was easily converted to a \( \beta \)-amino acid derivative 48 by standard methods. These reactions were successfully applied to the solid-phase radical reaction of oxime ethers.

Scheme 12. Synthesis of \( \beta \)-amino acid

4. Tandem C–C Bond-Forming Radical Addition-Cyclization Reaction

Table 6. Sulfanyl radical addition-cyclization of imines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate X=CO(_2\text{Et}_2), R=OEt</th>
<th>Product Cispentacin</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>43a</td>
<td>44a</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>43b</td>
<td>44b</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>43c</td>
<td>44c</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>43d</td>
<td>44d</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>43e</td>
<td>44e</td>
<td>73</td>
</tr>
<tr>
<td>6</td>
<td>43f</td>
<td>44f</td>
<td>75</td>
</tr>
<tr>
<td>7</td>
<td>43g</td>
<td>44g</td>
<td>84</td>
</tr>
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5. Conclusion

We have shown new, free radical-mediated cyclization reactions of oxime ethers for the synthesis of heterocycles via the construction of a C–C bond. In addition to previously reported intermolecular reactions of oxime ethers, the intramolecular reactions disclosed a broader aspect of the utility of oxime ethers as a radical acceptor for the synthesis of various types of amino compounds.

References

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