Synthetic and Computational Study of Tin-Free Reductive Tandem Cyclizations of Neutral Aminyl Radicals

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Supporting Information

ABSTRACT: 5-exo, 5-exo Cyclizations of conformationally unbiased propargylic aminyl radicals proceed with excellent yield, chemoselectivity, and diastereoselectivity under tin-free reductive cyclization conditions, regardless of the electronic environments and intermediate radical stabilization resulting from various olefin substituents. These conditions avoid the need for slow addition of initiator and reductant. By contrast, analogous 6-exo, 5-exo cyclizations require substituents capable of intermediate radical stabilization to avoid premature reduction products. These experimental results are corroborated by computations that further establish the reactivity of these aminyl radicals upon exposure to tin-free cyclization conditions.

Tertiary amines are privileged structures in pharmaceutical lead targets because they improve solubility and decrease lipophilicity, while maintaining potency.¹ Polycyclic molecules bearing tertiary amines are of special interest because they possess the rigid structural framework, high density of sp³ centers, and low molecular weight profile associated with “drug-like” molecules.² We were attracted to the potential utility of neutral aminyl radicals to construct these frameworks because radical cascades have well-established reactivity with predictable bond construction outcomes. While amidyl,³ iminyl,⁴ and aminium⁵ radicals are more reactive and tend to cyclize more efficiently⁶ than the more stable neutral aminyl radicals,⁷ the latter are strategically appealing because their cyclization reactions lead directly to aliphatic amine-containing products.⁸ In this work, we demonstrate the utility of our recently reported¹¹ tin-free conditions for the cyclization of neutral aminyl radicals. We obtained good yields of 5-exo-initiated twelve tandem cyclization products employing electronically differentiated olefins and demonstrated the electronic dependence of 6-exo cyclizations of conformationally unbiased substrates. Lastly, we computed the barrier heights and thermodynamics of these cyclizations in the gas phase, toluene, and tetrahydrofuran (THF).

We recently reported the development of tin-free conditions to access the ABC core of the calyciphylline A alkaloids via tandem cyclization of a neutral aminyl radical.¹¹ In these cyclizations, an existing six-membered ring (ring A) reduced the conformational degrees of freedom in the substrate (Scheme 1). The cyclization of N-chloroamine 1 is initiated via 6-exo cyclization, which is a rare mode of reactivity for aminyl radicals. An electron-deficient olefin was required in these cyclizations as allylic alcohol derivatives led only to N–Cl reduction products.¹² Finally, our experiences indicated that internal and terminal alkynes performed differently in otherwise analogous tandem cyclizations. Because of the unique features of this substrate relative to known cyclizations of aminyl radicals, we sought to establish the utility of these tin-free cyclization conditions, which also avoid slow addition of initiator and H atom donor, in conformationally unbiased systems.

We hypothesized that cascades beginning with cyclization of the relatively nucleophilic¹⁶ aminyl radicals would have lower barriers when cyclizing with electron-deficient olefins than with nonactivated olefins.¹⁷ Findings that enones analogous to substrate 1 cyclized efficiently while the corresponding allylic alcohol¹⁴ led only to N–Cl reduction (R₂N–Cl → R₂N–H) were consistent with our hypothesis but were insufficient to provide insight into 5-exo and 6-exo cyclizations of conformationally unbiased substrates. Thus, we selected representative unactivated and activated olefin substituents to investigate...
under these conditions. For convenience, we retained the terminal alkyne in the second cyclization, thus minimizing potential complications arising from the formation of multiple diastereomers. We found that unactivated substrates 3a–3b afforded good to excellent yields of cyclized products 4a–4b when treated with azobisisobutyronitrile (AIBN) and the weak H-atom donor ([Pr],SiH) at 100 °C in THF.14,19 Bicyclic amine 4b was formed as a single diastereomer. The relative stereochemistry is consistent with previous stereoc hemical studies of 5-exo, 5-exo tandem cyclizations.20 Enone substrate 3c also cyclized efficiently, and following thermal isomerization of the exocyclic olefin, bicyclic amine 4c was isolated in 87% yield. Cyclization of trans-3d led to a 69% yield of 4d with 95:5 dr (Scheme 2). The cis-isomer of the styrenyl substrate (cis-3d) performed similarly to enone 3c with an isolated yield of 86% and 91:9 dr. Isomerization of the exocyclic olefin was not observed in either case, and the major product diastereomer was trans for both cyclizations.21

Previously, we observed that cyclization of N-chloroenoone 1 in THF with ([Pr],SiH) as an H atom donor led to fewer reduction products than did the same cyclization in toluene with Bu3SnH.11 We presumed that the change in H atom donor was the primary contributor to this reactivity; however, both solvents can also donate hydrogen atoms. The calculated energy barrier for intermolecular H atom transfer from the solvent to radical 8a was 13.4 kcal/mol in implicit THF and 15.4 kcal/mol in implicit toluene (calculations were performed using the Gaussian 09 software22 and the oB97X-D level of theory and 6-31+G(d,p) basis set at 100 °C).23 The barrier to hydrogen atom transfer from each reducing agent to radical 8a was also calculated at 100 °C. For Et3SnH, the barrier is 4.8 kcal/mol in implicit THF and 5.0 kcal/mol in implicit toluene. For ([Pr],SiH), the barrier is 13.7 kcal/mol in implicit THF and 14.4 kcal/mol in implicit toluene. Thus, the reduction products observed in toluene/tin hydride conditions likely arise due to H atom transfer from the stannane, not toluene. These labeling experiments and computational data support our hypothesis that a weaker H atom donor should favor tandem cyclization products in preference to N–H bond formation.21

We next calculated the energetics of the cyclization pathway from the aminyl radicals 5a–8a to vinylcyclopropyl radicals 5d–8d via the Beckwith–Houk transition states of each substrate (Table 1).25,26 For 5-exo-initiated cyclizations, the initial cyclization barriers (i.e., barrier 1 = ΔG° for 5b–8b → 5c–8c) range from 9.3 to 14.2 kcal/mol in implicit solvent, with the barrier for 7b in THF as an apparent outlier. These data are consistent with published computational results for aminyl radical monocyclization.7a The reverse reaction barriers range from 15.4 to 26.9 kcal/mol depending on the substrate and solvent. These data suggest that the first 5-exo cyclization event is likely irreversible for most of these substrates. These results are consistent with some27,28 previous experimental rate studies.29 For all evaluated substrates, the transformation of the N-centered radical (5a–8a) to the vinylcyclopropyl radical (5d–8d) is exothermic owing to the formation of two C–C bonds and a fused bicyclic system.

As expected, barrier 1 tracks the stability of the intermediate radicals 5c–8c. The barrier for the terminal olefin (5b) was 1.4–1.9 kcal/mol higher in energy than for methoxymethyl-substituted 6b. The barrier for enone 7b was 1.8–2.5 kcal/mol lower than for 5b in the gas phase or implicit toluene, while in THF, the gap is larger than expected at 6.9 kcal/mol. The barrier for styrenyl substrate 8b was 2.5–3.5 kcal/mol lower than for 5b. While these energy differences follow the expected trend, they are relatively small, and the high temperature for cyclization is sufficient to enable cyclization even in the highest barrier case (R = H). Interestingly, barrier 1 is higher in THF than in toluene for 5b and 6b and lower for 7b and 8b. For substrates capable of generating a stabilized C-centered radical intermediate (i.e., 7c and 8c), the barrier height for the second cyclization (barrier 2) is significantly larger than for radicals 5c and 6c. α-Keto radical 7c is 7.3–7.4 kcal/mol more stabilized than primary radical 5c in implicit THF and toluene solvent, respectively. For styrenyl substrate 8c, these values increase to 9.6–13.3 kcal/mol, respectively.

On the basis of the computational results outlined above, we hypothesized that 6-exo-initiated cyclizations would be more sensitive to substitution changes because of the significantly reduced reactivity of these substrates. We selected H and Ph groups as representative electron-normal and electron-withdrawing substituents. Attempted cyclization of N-hexenyl-N-

### Table 1. Activation Barriers and Relative Energies of Radical Intermediates in the 5-exo, 5-exo Pathway

<table>
<thead>
<tr>
<th>R</th>
<th>solvent</th>
<th>S–8b</th>
<th>barrier 1</th>
<th>int S–8c</th>
<th>barrier 2</th>
<th>int S–8d</th>
</tr>
</thead>
<tbody>
<tr>
<td>H (5)</td>
<td>(gas)</td>
<td>0.0</td>
<td>13.2</td>
<td>6.2</td>
<td>12.4</td>
<td>26.6</td>
</tr>
<tr>
<td>H</td>
<td>PhMe</td>
<td>0.5</td>
<td>13.9</td>
<td>4.2</td>
<td>11.6</td>
<td>24.5</td>
</tr>
<tr>
<td>H</td>
<td>THF</td>
<td>0.9</td>
<td>14.2</td>
<td>3.1</td>
<td>10.8</td>
<td>23.0</td>
</tr>
<tr>
<td>CH3OMe</td>
<td>(gas)</td>
<td>2.3</td>
<td>11.8</td>
<td>6.3</td>
<td>6.5</td>
<td>26.4</td>
</tr>
<tr>
<td>CH3OMe</td>
<td>PhMe</td>
<td>2.4</td>
<td>12.0</td>
<td>5.8</td>
<td>6.9</td>
<td>24.8</td>
</tr>
<tr>
<td>CH3OMe</td>
<td>THF</td>
<td>3.1</td>
<td>12.7</td>
<td>6.8</td>
<td>7.2</td>
<td>20.9</td>
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<tr>
<td>COEt(7)</td>
<td>(gas)</td>
<td>1.0</td>
<td>11.4</td>
<td>12.6</td>
<td>12.4</td>
<td>25.6</td>
</tr>
<tr>
<td>COEt</td>
<td>PhMe</td>
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<td>11.4</td>
<td>11.6</td>
<td>13.9</td>
<td>23.3</td>
</tr>
<tr>
<td>COEt</td>
<td>THF</td>
<td>0.8</td>
<td>7.3</td>
<td>10.4</td>
<td>13.3</td>
<td>21.5</td>
</tr>
<tr>
<td>Ph(8)</td>
<td>(gas)</td>
<td>1.2</td>
<td>10.1</td>
<td>15.0</td>
<td>15.6</td>
<td>24.4</td>
</tr>
<tr>
<td>Ph</td>
<td>PhMe</td>
<td>0.7</td>
<td>10.1</td>
<td>17.5</td>
<td>16.2</td>
<td>21.7</td>
</tr>
<tr>
<td>Ph</td>
<td>THF</td>
<td>0.6</td>
<td>9.3</td>
<td>12.7</td>
<td>16.3</td>
<td>20.4</td>
</tr>
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</table>

αoB97X-D functional and Gibbs free energies were calculated at 100 °C. All values in kcal/mol. Barrier 1 is calculated from the prearranged conformation (S–8b). All intermediate values are relative to the energy of the fully elongated, staggered aminyl radical (5–8a).
propargyl chloroamine 9 with THF/[(iPr)2SiH] conditions led to recovery of 77% reduced amine 11 (Scheme 3A). Bicycle 10 was not observed in the crude NMR. For the styrenyl analogue of this substrate (12), cyclization product 13 was isolated in 40% yield after an acetic anhydride workup, which was required to facilitate isolation of 14 (44% yield, Scheme 3B). Presumably, formation of the reduced products (pre-11, pre-14) in these cases occurs via both intramolecular and intermolecular H-atom transfer. This is particularly true in the styrenyl system where the allylic radical is highly stabilized.20a

The computational analysis for these two cyclizations is consistent with the drop in both overall reactivity for 6-exo cyclizations and in the relative success of the two substrates (Table 2). Interestingly, once the substrate (9a and 12a) adopts the appropriate conformation for cyclization (9b and 12b), the barrier 1 values for 6-exo cyclization are not significantly different from the 5-exo substrates. However, the energy required to adopt these precyclization conformations is significant. In THF, combining the uphill conformational change with the activation barrier gives an overall transition state energy (∆G‡) of 15.3 kcal/mol. Thus, it is unsurprising that the reduction pathway, which had a barrier of 13.4 kcal/mol for H atom transfer from THF to 8a, outcompetes the cyclization. However, for the styrenyl substrate, the ∆G‡ is 12.3 kcal/mol. It is thus expected to be competitive with reduction, and a mixture of products (13 and 14) is observed. As expected, the barrier 2 heights and overall thermodynamics are similar to the 5,5-cyclization pathway. Overall, these computational data suggest that the rate differences between these 5-exo and 6-exo radical cyclizations are primarily derived from entropic factors associated with substrate prearrangement rather than an inherent decrease in reactivity for 6-exo cyclization resulting from an issue with alignment of the participating molecular orbitals.

We also investigated the applicability of these conditions to the 5-exo, 6-exo substrate chloroamine 15 (Scheme 4). The desired product was formed in 39% yield and 77:23 dr. The lower dr here presumably arises from competitive rotation of the Ph group to the pseudoequatorial position in the transition state. Interestingly, despite the initial formation of a 5-membered ring, significant amounts of reduction product (isolated as the acetate, 17) were observed (35% yield). The dependence of the formation of reduced amine on the size of the second ring suggests reversibility in the first cyclization. Meanwhile, our computational results from Table 1 support irreversible cyclization of the N-centered radical with a reverse barrier of ~23 kcal/mol for 8c → 8b. The retention of stereochemistry in reduction product 17 suggests that intermolecular H-atom transfer to the aminyl radical is faster than 5-exo cyclization in this substrate. By contrast, no reduction is observed in any of our 5-exo, 5-exo tandem cyclizations. Combining previous rate studies with these new computational and experimental data, one can conclude that the reversibility of neutral aminyl cyclizations is dependent on the intermediate radical stability, the reaction conditions, and the effects of impurities in the reaction.

In summary, kinetically favorable 5-exo, 5-exo cyclizations of propargyl-appended aminyl radicals proceed efficiently in tin-free conditions employing a weak H atom donor in THF, regardless of the electronic nature of the substitution on the olefin. Importantly, these conditions avoid kinetic tricks such as slow addition of the radical initiator and reducing agent. By contrast, a radical stabilizing group is essential to facilitate cyclization in 6-exo, 5-exo cyclizations of propargyl aminyl radicals. These results are supported by computational data. Finally, application to a 5-exo, 6-exo cyclization reveals a dependence on the size of the second ring in determining the ratio of cyclization to reduction. Overall, the weak H atom donating ability of [(iPr)2SiH] and THF results in an unusual, if apparently synergistic, solvent/H atom donor combination that is effective for a range of tandem cyclizations. We anticipate that these experimental and computational data will be useful for future synthetic design using neutral aminyl radicals. Further investigation into the factors influencing reversibility is ongoing in our laboratories.

Table 2. Activation Barriers and Relative Energies of Radical Intermediates in the 6-exo, 5-exo Pathway\textsuperscript{a,b}

<table>
<thead>
<tr>
<th>R</th>
<th>solvent</th>
<th>9b</th>
<th>12b</th>
<th>barrier \textsuperscript{b}</th>
<th>int 9c</th>
<th>12c</th>
<th>barrier 2</th>
<th>int 9d, 12d</th>
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</thead>
<tbody>
<tr>
<td>H</td>
<td>(gas)</td>
<td>3.1</td>
<td>10.5</td>
<td>–8.3</td>
<td>8.9</td>
<td>–29.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>PhMe</td>
<td>2.1</td>
<td>12.3</td>
<td>–7.1</td>
<td>8.7</td>
<td>–28.3</td>
<td></td>
<td></td>
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<tr>
<td>H</td>
<td>THF</td>
<td>2.6</td>
<td>12.7</td>
<td>–5.8</td>
<td>8.6</td>
<td>–26.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>(gas)</td>
<td>1.0</td>
<td>8.4</td>
<td>–17.4</td>
<td>12.9</td>
<td>–28.3</td>
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<tr>
<td>Ph</td>
<td>PhMe</td>
<td>2.9</td>
<td>8.1</td>
<td>–16.2</td>
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</table>

\textsuperscript{a}ωB97xD functional and Gibbs free energies were calculated at 100 °C. All values in kcal/mol. \textsuperscript{b}Barrier 1 is calculated from the rearranged conformation (9b, 12b). All intermediate values are relative to the energy of the fully elongated, staggered aminyl radical (9a, 12a).

Scheme 3. Sensitivity of 6-exo, 5-exo Initiated Cyclizations to Olefin Electronics

A) AIBN (0.2 equiv) THF (0.01 M), 100 °C sealed vessel, 3 h

B) AIBN (0.2 equiv) THF (0.01 M), 100 °C sealed vessel, 3 h

Scheme 4. Sensitivity of 6-exo, 5-exo Initiated Cyclizations to Olefin Electronics

Table 2. Activation Barriers and Relative Energies of Radical Intermediates in the 6-exo, 5-exo Pathway\textsuperscript{a,b}
ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or- glett.8b02456.

Experimental procedures and spectroscopic data (PDF)

Computational methodology and Cartesian coordinates (PDF)

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REFERENCES

(18) See the Supporting Information for experimental details and substrate syntheses.
(19) The cyclization of 3a was performed on a 1.1 molm scale, resulting in 81% yield of 4a. See the Supporting Information for details.


(23) See the Supporting Information for computational details.

(24) Ethyl is employed to expedite the computation.


