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Radical heterocyclization and heterocyclization cascades triggered by electron transfer to amide-type carboxyls

Huan-Ming Huang and David J. Procter*

Abstract: Radical heterocyclizations triggered by electron transfer to amide-type carboxyls using SmI₂-H₂O provides straightforward access to bicyclic heterocyclic scaffolds containing bridgehead nitrogens. Furthermore, the first radical heterocyclization cascades triggered by reduction of amide-type carboxyls deliver novel, complex tetracyclic architectures containing five contiguous stereocenters with excellent diastereoselectivity.

Polycyclic, heterocycle-containing architectures possessing bridgehead nitrogen atoms are found widely in natural and unnatural compounds of biological significance, including nucleic acids, drug molecules and natural products (Figure 1).11,12 Developing expedient new methods to construct such systems is an important goal in synthetic and medicinal chemistry.2 For example, recent advances in the one-step construction of polycyclic systems possessing bridgehead nitrogens include the [4+2][3+2] cycloaddition cascades of Boger,3 the Rh(II)-catalyzed cyclization/3+2 cycloaddition cascades of Padwa4 and Zhai,5 and Movassaghi’s double intramolecular trapping of iminium ions.6 Perhaps due to the challenge associated with the control of selectivity in the reactions of highly reactive open shell intermediates, the otherwise desirable use of radical cyclizations and cyclization cascades to assemble such systems is rare.7-9

Radical cyclizations are a powerful synthetic approach for the construction of carbo- and heterocyclic systems.7 Samarium diiodide (SmI₂, Kagan’s reagent) is a selective, versatile, and commercially available or readily-prepared electron transfer (ET) reductant.8 It is particularly adept at mediating radical carboacyclization processes involving ketyl radicals but this is largely limited to radicals generated from ketones or aldehydes (Scheme 1A).10 Recently, we described how SmI₂, when activated by H₂O, can execute the challenging ET reduction of cyclic esters, and have exploited the unusual ketyl radicals formed in new radical carboacyclizations.11 The ubiquitous amide moiety10 is even more resistant to ET reduction and the development of new radical cyclization methods based on the reduction of amide derivatives presents a significant challenge. Inspired by the pioneering work of Reissig,11 Skyrdstrup,12 Py,13 and Huang14,15 on SmI₂-mediated nitrogen heterocycle synthesis (Scheme 1A),15-16 herein, we describe radical heterocyclizations16-18 and the first radical heterocyclization cascades of amide-type substrates. The SmI₂-H₂O mediated radical processes involve the coupling of amide carboxyls and amines, tethered through an sp²-hybridized nitrogen, and provide expedient access to important polycyclic heterocycles possessing bridgehead nitrogen atoms (Figure 1 & Scheme 1B).

Radical cyclization involving ketyl radicals (Scheme 1A): Treatment of 1a, possessing an alkene radical trap attached via nitrogen, was readily synthesized in one step from commercial barbituric acid and 4-phenylbut-3-en-1-ol. After careful optimization (see Supporting Information),17 slow addition of SmI₂ (3 equivalents over 1 hour) to 1a and water (100 equiv) gave heterocyclization/dehydration product 2a in 78% isolated yield. Various substituents, including fluoro (2c and 2e), methyl (2d), methoxy (2f and 2l), chloro (2g), bromo (2h), trifluoromethyl (2i), thienyl (2k) and naphthyl (2l), were compatible with the radical heterocyclization and products were obtained in good to excellent isolated yield (Table 1). Larger alkyl groups at C2 of the barbituric acid unit were also tolerated: 2b was obtained in 50% isolated yield. A larger scale experiment (2 mmol, 0.84 g of 1a) gave the product 2a in 70% yield after 2 h (0.56 g). Treatment of 1a with D₂O in combination...
with SmI$_2$ gave the labeled product 2a-D in 65% isolated yield, thus confirming that the process is terminated by protonation of a benzylid organosamarium.

### Table 1. Scope of the radical heterocyclization to form bicyclic enamines containing bridgehead nitrogens $^{2,14}$

<table>
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<th>Compound</th>
<th>Yield</th>
<th>Note</th>
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<tr>
<td>2a</td>
<td>78%</td>
<td>2 mmol scale = 0.56 g, 70%$^e$</td>
</tr>
<tr>
<td>2a-D</td>
<td>65%$^d$</td>
<td>(97% D incorp.)</td>
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[a] Reaction conditions: To the substrate (0.1 mmol, in THF) under N$_2$ was added H$_2$O (100 equiv), followed by slow addition of SmI$_2$ in THF (3 equiv) over 1 h. The reaction was then quenched after a further 1 h. [b] Isolated yields. [c] Result of a larger scale experiment (2 mmol). [d] D$_2$O was used rather than H$_2$O. [e] 4 equiv SmI$_2$ was used.

Alkyne radical traps could also be used in the radical amide heterocyclization. In this approach, unusual bicyclic hemiaminals were obtained in good isolated yield and as single double bond isomers (Table 2). Notably, a 5-exo-dig radical heterocyclization was also possible and 2p was obtained in 44% yield. An alkynylsilane acceptor also proved compatible with the process and vinylsilane 2q was obtained in 52% yield. X-ray crystallographic analysis confirmed the structure of product 2n.$^{16}$ E-alkene isomers are thought to arise from selective formation and protonation of vinyl samarium intermediates in which samarium coordinates to the oxygen of the hemiaminal moiety.$^{16}$ With the exception of 1q, the presence of an aryl substituent on the alkenyl or alkyne has so far proved important for efficient cyclization.

### Table 2. Scope of the radical heterocyclization to form bicyclic hemiaminals containing bridgehead nitrogens $^{2,14}$

<table>
<thead>
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</tr>
</tbody>
</table>

[a] Reaction conditions: To the substrate (0.1 mmol, in THF) under N$_2$ was added H$_2$O (80 equiv), followed by slow addition of SmI$_2$ in THF (4 equiv) over 1 h. The reaction was quenched after a further 1 h. [b] Isolated yields.

The radical heterocyclization of 1a proceeds by reductive ET to the amide-type carbonyl to generate radical 3.$^{15,16}$ 5-Exo-dig cyclization and dehydration via acyl iminium ion intermediate 4 delivers bicyclic amine 2a. 5-exo-dig cyclization of the radical derived from 1m gives vinyl radical intermediate 5 that upon further reduction and protonation gives bicyclic hemiaminal 2m (Scheme 2).

**Scheme 2.** Proposed mechanism for the radical heterocyclizations.

The bicyclic hemiaminal products are versatile building blocks for synthesis.$^{19}$ Treatment of 2m with Et$_3$SiH and BF$_3$·OEt$_2$ gave 1,2-addition product 6 (90% yield) while exposure of 2m to allylTMS and BF$_3$·OEt$_2$ gave 1,4-addition product 7 (82% yield) (Scheme 3).
Cyclization cascades have the potential to convert simple starting materials to complex polycyclic molecular frameworks in one step. Barbiturate 8a was synthesized in three straightforward steps from diethyl 2,2-diallylmalonate and was used to explore the feasibility of a radical hetero-carbocyclization cascade to construct complex, polycyclic hemiaminals containing bridgehead nitrogens (cf. Scheme 1B). Exposure of 8a to SmI₂·H₂O gave tetracyclic hemiaminal 9a, containing five contiguous stereocenters in 58% isolated yield with high diastereorecontrol (>95:5 dr) (Table 3). Assessing the scope of the process, a wide variety of substituents including bromo (9b), methoxy (9c and 9f), trifluoromethyl (9d), chloro (9e and 9g), naphthyl (9h) and benzo[b]thiophenyl (9i) were tolerated and products were obtained in moderate to good isolated yield and with universally high diastereorecontrol. Finally, 8j bearing a methyl substituent on the cyclopentene unit underwent cascade heterocyclization to give 9j possessing six contiguous stereocenters. The structure of 9a was confirmed by X-ray crystallographic analysis.

Unsymmetrical substrates bearing different groups on nitrogen are easily prepared and can also be used in the cascade. For example, unsymmetrical substrates 9k–m bearing recognized protecting groups on nitrogen (vide infra) gave the expected tetracyclic hemiaminal products 9k–m in moderate yield with complete diastereorecontrol (Table 3). Interestingly, unsymmetrical N-methyl barbiturate 8n underwent radical heterocyclization to give enamine 9n: the hemiaminal product appears to be particularly prone to dehydration in this case. The structure of 9n was confirmed by X-ray crystallographic analysis. Reversible reduction of the amide-type carbonyls likely accounts for the selectivity seen in the reactions of unsymmetrical substrates.

The radical heterocyclization cascade of 9a proceeds by reductive ET to generate radical 10 (Scheme 4). Such radicals bearing α-allylsubstituents typically undergo radical fragmentation and deallylation, however, the choice of the cyclopentene moiety is likely to render such a process reversible and ensures radical 10 persists. Diastereoselective 5-exo-trig cyclization then gives rise to secondary benzyl radical intermediate 12 that undergoes a highly selective 6-exo-trig cyclization via a chair transition structure in which the phenyl substituent adopts a pseudoequatorial orientation.

Table 3. Scope of the radical heterocyclization cascade of symmetrical and unsymmetrical amides 8 to form hemiaminals 9a-m or enamine 9n.

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[a] Reaction conditions: To the substrate (0.1 mmol) in THF under N₂ was added H₂O (100 equiv), followed by slow addition of SmI₂ in THF (4 equiv) over 1 h. The reaction was quenched after 1 h. [b] Isolated yields. [c] Diastereoisomeric mixture at highlighted stereocenter. [d] Based on recovered starting material. [e] Dehydrated product was isolated. TMS = trimethylsilyl.
The cinnamyl protecting group in the radical heterocyclization product 91 could be removed to give the corresponding N-H tetracyclic hemialdiam 13 in 55% isolated yield (Wacker oxidation\textsuperscript{121} followed by elimination) (Scheme 5A). Finally, upon treatment of 8a with the more reducing Sml\textsubscript{2}-H\textsubscript{2}O- LiBr system,\textsuperscript{122} polycyclic amine 14 was obtained in 40% isolated yield with high diastereoccontrol (Scheme 5B). Thus, the cascade cyclization of 8a could be selectively switched to form either hemiaminal 9a or amine 14 simply through the choice of LiBr as an additive under otherwise identical reaction conditions. The structure of 14 was confirmed by X-ray crystallographic analysis\textsuperscript{123} and arises from a sequence involving radical heterocyclization cascade, acyl iominium formation and reduction.

![Scheme 4. Proposed mechanism for the radical heterocyclization cascade.](image)

In conclusion, radical heterocyclizations triggered by electron transfer to amide-type carbonyls using Sml\textsubscript{2}-H\textsubscript{2}O provide straightforward access to bicyclic heterocyclic scaffolds containing bridgehead nitrogen atoms. Furthermore, the first radical heterocyclization cascades triggered by reduction of amide-type carbonyls deliver complex tetracyclic architectures containing five contiguous stereocenters with excellent diastereoccontrol.

Acknowledgements

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Keywords: radical • samarium diiodide • heterocyclization • cascade • amides


For the first example of radical carboxylation of amide-type carbonyls, see: M. Szostak, B. Sautier, M. Spain, M. Behlendorf, D. J. Procter, Angew. Chem., Int. Ed. 2013, 52, 12559; Angew. Chem. 2013, 125, 12791.


See the Supporting Information for details.

See supporting information for X-ray structures and CCDC numbers (CCDC 1536045 for 2h, CCDC 1545501 for 9a, CCDC 1545502 for 9n, CCDC 1545503 for 14). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre. 


Radical heterocyclization and heterocyclization cascades triggered by electron transfer to amide-type carbonyls provides straightforward access to heterocyclic scaffolds containing bridgehead nitrogen atoms. The radical cascade cyclizations deliver novel tetracyclic architectures containing five contiguous stereocenters with excellent diastereoccontrol.