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Radical Anions from Urea-type Carbonyls: Radical Cyclizations and Cyclization Cascades

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Abstract: Radical anions generated from urea carbonyls by reductive electron transfer are exploited in carbon-carbon bond formation. New radical cyclizations of urea radical anions deliver complex nitrogen heterocycles and, depending upon the proton source used in the reactions, a chemoselective switch between reaction pathways can deliver two heterobicyclic scaffolds. A computational study has been used to investigate the selectivity of the urea radical processes. Furthermore, radical cyclization cascades involving urea radical anions deliver unusual spirocyclic aminal architectures.

Carbon-carbon bond formation is integral to almost any synthetic endeavor and provides a focal point for contemporary synthetic method development.[1] Radical reactions constitute one of the most important and attractive tools to achieve carbon-carbon bond formation.[2] In particular, radical cyclizations and cyclization cascades are prized for their ability to construct carbons and heterocyclic motifs, including those found in complex natural products, biologically-active molecules, and materials.[3]

Within radical chemistry, ketyl radicals, typically derived by single electron transfer (SET) reduction of aldehydes and ketones, hold high status as one of the most important and versatile classes of open shell intermediates for use in synthesis.[4] Cyclization reactions involving ketyl radicals inherently give oxygenated cyclic products, often possessing valuable three-dimensional shape, and have been achieved by deploying reagents based on Sm(II),[5] Ti(III),[6a-e] Ru(II),[6f,g] Ir(III),[6h] and electrochemistry.[6i] In particular, samarium(II) iodide (SmI₂) is the reagent most frequently used to generate ketyl radicals and the reactive intermediates formed in this way have found widespread application in myriad cyclization and cyclization cascade strategies,[5] thus establishing both reagent and reaction as standard tools for synthesis.[7]

Unfortunately, the formation of ketyl-type radicals is typically limited to aldehyde or ketone substrates, regardless of the reagent used for radical generation. Recently, we and others have begun to extend the rich chemistry of ketyl-type radicals to the reductive cyclizations of carboxylic acid derivatives,[8a] including cyclic esters,[8b-d] and cyclic amide derivatives,[8e-i] possessing more electron-rich carbonyls. However, engaging carbonyl-containing substrates in which the carbonyl is flanked by two heteroatom substituents in ketyl-type radical chemistry, until now, has not proved possible, despite the promise of new reaction space for exploration.

From the birth of organic synthesis in 1828,[9] ureas, possessing carbonyls flanked by two nitrogen atoms, have remained an important compound class with members widely used as catalysts, ligands, drugs, and materials, and exhibiting roles in nature.[10] From a synthetic perspective, the electron-rich character of the urea carbonyl typically exempts them from the signature reactions of the carbonyl group. Furthermore, their resistance to SET reduction[11] ensures that there are no examples of ketyl-type radical generation from urea carbonyls and therefore no examples of carbon-carbon bond formation using the hypothetical radical anions (Scheme 1A).[11] Herein, we report the first examples of reductive cyclizations and cyclization cascades involving ketyl-type radicals derived from the carbonyl groups of urea derivatives by reductive SET (Scheme 1B). SmI₂ activated by a protic additive (e.g., H₂O) and LiBr is used to mediate SET and the choice of protic additive can be used to switch cleanly between two reaction pathways that deliver bicyclic scaffolds resembling those found in numerous natural products.[12] Furthermore, radical cyclization cascades are described in which both radical anion intermediates formed during the sequential SET reduction of ureas are harnessed for multiple carbon-carbon bond formation.

During our studies on reductive SET to important heterocyclic substrates, we prepared barbiturates 1a,b in three steps from the corresponding substituted malonate esters. Treatment of 1a (R = CH₃) with SmI₂ in the presence of H₂O and LiBr gave bicyclic enamine 2a. The process involves cyclization of a radical anion from the amide-type carbonyl followed by dehydration (Scheme 2). Surprisingly, when the starting material 1b (R = Et) was treated under identical conditions, novel bicyclic...
aminal 3b was obtained in 64% yield and with complete diastereoccontrol. Surprisingly, 3b results from cyclization involving a radical anion derived from the urea carbonyl (Scheme 2).

Optimization studies\(^{13}\) using substrate 1c revealed that LiBr and H\(_2\)O were essential for the cyclization to form bicyclic aminals and 3c was obtained in 75% yield and as a single diastereoisomer (Conditions A); no urea cyclization was seen in the absence of the additives. The use of LiI and LiCl in the place of LiBr resulted in lower conversions. Interestingly, the use of tBuOH as a proton source in place of H\(_2\)O gave 3c\(^*\) in 60% yield, the enediamine product of urea radical cyclization followed by dehydration (Conditions B). Thus, the urea radical cyclization could be switched between products of differing oxidation state by a simple change in protic cosolvent (Scheme 3).

Scheme 3. Optimized reaction conditions allow switching between cyclization outcomes upon a change ofprotic cosolvent.

It is known that the use of H\(_2\)O as a protic additive with SmI\(_2\) gives rise to a more reducing reagent system.\(^{14}\) Thus, Conditions A deliver more-reduced products than Conditions B. The role of LiBr is also crucial. Flowers has demonstrated that adding LiBr to SmI\(_2\) (−0.9 V vs SCE) generates more reducing SmBr\(_3\) (−1.55 V vs SCE) in situ.\(^{15}\) In the presence of H\(_2\)O (Conditions A), SmBr\(_3\) is even more reducing and has recently shown unique properties in radical cyclization and cyclization cascades.\(^{16,18,19}\)

With optimized conditions established, the synthesis of a range of bicyclic aminals 3 was achieved using SmI\(_2\)-H\(_2\)O-LiBr (Scheme 4). In all cases, urea radical cyclizations proceeded efficiently and with complete diastereoccontrol (>95:5 dr). Furthermore, changing to the SmI\(_2\)-tBuOH-LiBr reagent system switched the chemoselectivity of the radical process to give bicyclic enediamines 3\(^*\) in good to excellent yield (Scheme 5).
The reductive processes are compatible with various alkyl substituents (3b-d) and a wide range of functional groups including fluoro (3e and 3e'), bromo (3g, 3j, and 3g', 3j'), chloro (3i and 3i'), methoxy (3h, 3k, and 3h', 3k'), trifluoromethyl (3i and 3i') and acetal (3o and 3o'). The reductive radical cyclizations were also compatible with important heteroaromatic rings including indole (3q and 3q'), benzothienyl (3r, 3s and 3r', 3s'), thiophenyl (3t, 3u and 3t', 3u') and furanyl (3v and 3v'). X-ray crystallographic analysis of 3h, 3j and 3m confirmed the structures and, where relevant, the relative stereochemistry of the radical cyclization products. Interestingly, bicyclic enediamine 3w was obtained by 5-exo-trig cyclization of an alkynylsilane 1w in moderate isolated yield. An attempted 6-exo-trig cyclization was unsuccessful.

We next investigated radical cyclization cascades in which both radical intermediates (I and II, Scheme 1) formed during reduction of the urea carbonyl were trapped. Substrates 4 bearing alkene radical traps on both nitrogen atoms were prepared in three steps from commercially available diethyl 2,2-diphenylethanone. Upon exposure to SmI₂–H₂O–LiBr, spirocyclic aminal cyclization cascade products 5 were obtained in moderate isolated yield as a mixture of diastereoisomers. The structure of the major diastereomer of 5a was confirmed by X-ray crystallographic analysis. The urea radical cyclization cascade was found to be compatible with chloro (5b), naphthyl (5d), and benzothienyl (5e) motifs (Scheme 6).

Larger scale transformations of 1c (2 mmol, 0.96 g) gave bicyclic products 3c (70%, 0.66 g) and 3c' (51%, 0.47 g), respectively (Scheme 7A). Experimental and computational studies have been used to explore the mechanism of the urea radical cyclizations (Scheme 7B,C). A labeling study confirms that anions are generated and protonated during the formation of aminal 3c from 1c using SmI₂–H₂O–LiBr: Use of D₂O with SmI₂ and LiBr converted 1c to deuterated bicyclic aminal 3c-D₂ in 69% yield. The labeling pattern in 3c-D₂ suggests that final stage of aminal formation proceeds by reduction of an iminium ion intermediate rather than by formation and reduction of enediamine 3c'.

The nature of the radical anion formed upon SET to the barbituric acid system has been explored computationally. Calculations suggest that the spin density is delocalized although the highest spin density can be found on the amide-type by 0.19 total spin density on C=Oamide and 0.14 on the urea carbonyl in the radical anion derived from 1a; 0.18 total spin density on C=Oamide and 0.15 on the urea carbonyl in the radical anion derived from 1b). Thus, the switch from amide radical cyclization (observed for 1a) to urea radical cyclization (observed for 1b) is likely the result of selective trapping of a delocalized radical at two different sites. Calculated relative transition state energies support the experimental observations (Scheme 7C): the transition state energy for the amide cyclization of the radical anion derived from 1a (R = Me) (amide TS-1a) is calculated to be 3.6 kJmol⁻¹ lower in energy than that of the analogous urea cyclization. Conversely, the transition state energy for the urea cyclization of the radical anion derived from 1b (R = Et) (urea TS-1b) is calculated to be 16.3 kJmol⁻¹ lower in energy than that of the analogous amide cyclization. The switch likely arises from an increased barrier to amide cyclization in the radical anion derived from 1b relative to the
urea radical cyclization due to the greater steric demands of the proximal ethyl groups.\textsuperscript{[19]} As expected, anti-transition states were found to be lowest in energy in all cases.\textsuperscript{[20]}

A proposed mechanism for the urea radical cyclization is shown in Scheme 8. SET to substrates 1 and 4 gives delocalized radical anion 6. When \( \text{R} \) is larger than Me, carbon-carbon bond formation takes place at what was the carbon of the urea carbonyl and 5-exo-trig cyclization gives the corresponding bicyclic \( \text{Sm(III)} \) alkoxy intermediates 7 (Scheme 8).

![Scheme 8. Proposed mechanism for the urea radical cyclizations.](image)

When \( \text{BuOH} \) is used as the proton source, bicyclic enediamines 3' are obtained upon elimination. In contrast, when \( \text{H}_2\text{O} \) is used, the more reducing reagent system forms aminal radicals \( 8 \) and further reduction and protonation delivers bicyclic aminals 3. When the \( \text{R} \) group in \( 8 \) contains a radical trap, the aminal radicals undergo cyclization to give cascade products 5, after further reduction and protonation.

In summary, ketone-type radical anions derived from the urea carbonyl by reductive SET undergo, intramolecular carbon-carbon bond formation. Depending upon the proton source used in the radical reactions, a chemoselective switch between reaction pathways delivers two important heterobicyclic scaffolds. Computational studies have been employed to explore the natural of the radical anion intermediates and their selective radical cyclization. Furthermore, radical cyclization cascades involving radicals derived from ureas by SET deliver unusual spirocyclic aminal architectures.

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**Keywords:** urea • radical • cyclization • samarium • nitrogen heterocycles


See supporting information.

[16] See the Supporting Information for X-ray structures. CCDC 1586111 (3h), CCDC 1586112 (3i), CCDC 1586113 (3q), CCDC 1586114 (3m'), CCDC 1586115 (3a) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

For an early EPR and computational study, see: H. C. Box, E. E. Budzinski, J. Chem. Phys. 1973, 59, 1588–1591. Although our calculations do not involve samarium, two Sm(III) ions could be incorporated in the resonance forms set out in Scheme 7, one associated with the ketyl radical anion and one with the other carbonyl.
Radical anions generated from urea carbonyls by reductive electron transfer are exploited in carbon-carbon bond formation. New radical cyclizations of urea radical anions deliver complex nitrogen heterocycles and, depending upon the proton source used in the reactions, a chemoselective switch between reaction pathways can deliver two heterobicyclic scaffolds. A computational study has been used to investigate the selectivity of the urea radical processes. Furthermore, radical cyclization cascades involving urea radical anions deliver unusual spirocyclic aminal architectures.