Reductive cyclisations of amidines involving aminal radicals†

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Amidines bearing simple alkenes undergo aminal radical cyclisation upon treatment with SmI2. The mild, reductive electron transfer process delivers medicinally-relevant, polycyclic quinazolinone derivatives in good to excellent yield and typically with complete diastereoselectivity.

Nitrogen-containing heterocycles are ubiquitous components in the molecular architectures of natural products, materials and drug candidates. As a feature in biologically active alkaloids, the quinazolinone ring system is a significant member of the family and its presence in nature has inspired the search for synthetic quinazolinones with medicinal potential (Scheme 1A). Although various approaches to these polycyclic scaffolds have been described, expedient, stereoselective synthetic strategies to quinazolinones that operate under mild conditions on simple, readily accessible substrates, are of high value.

Radical cyclisations have emerged as an important tool for the efficient generation of complex polycyclic products. However, few radical cyclisation strategies have been developed for the synthesis of quinazolinone analogues. Of these, Malacria, Courillon and Fensterbank have described an elegant radical cyclisation approach using tributyltin hydride and applied the method to a synthesis of Luotonin A. Weaver and Bowman have also reported a radical cyclisation approach to quinazolinones using tributyltin hydride. Recently, Chiba reported an elegant oxidative radical rearrangement that constructs quinazolinones. Finally, quinazolinone scaffolds have been accessed using radical processes involving Ag(i) and Cu(i), visible-light photoredox catalysis, and DTBP in a metal-free process. Despite these reports, there remains a need for a straightforward method that constructs polycyclic quinazolinones under mild conditions.

We recently reported the first radical reduction, cyclisations and cyclisation cascades involving radical anions generated from urea-type carbonyls by single electron transfer (SET). During the study, we found that the aminal radical intermediates could be generated and trapped by tethered alkenes to form heterocyclic products.Related aminal radicals were formed and trapped, in an intermolecular sense, by Beaudry in his highly effective cross-coupling of amidines with electron-deficient alkenes. Both processes are mediated by the reductive SET reagent, samarium iodide (SmI2, Kagan’s reagent). This highly versatile, commercially available or readily prepared reagent often proves to be the only viable mediator of challenging radical cyclisations and cyclisation cascades designed to deliver high value products not easily accessible by alternative means. Crucially, in Beaudry’s study, only two intramolecular examples of amidine–alkene coupling were described and in all examples, both inter- and intramolecular, alkenes bore strongly electron-withdrawing groups. We recognised that the intramolecular SmI2-mediated coupling of amidines with simple unactivated alkene radical acceptors could provide expedient access to important quinazolinones. Herein, we describe the first general study of aminal radical cyclisations triggered by SET reduction of amidines using

Scheme 1

(A) Selected biologically-active quinazolinone natural products

(B) this work: the cyclisation of aminal radicals, formed from amidines by SET, provides efficient access to quinazolinones.

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SmI₂ (Scheme 1B). The radical cyclisations deliver quinazolinones in good yield and typically with complete diastereocontrol.

We began our studies by optimising the cyclisation of 1a; efficiently synthesised in one step from commercial 4-hydroxyquinazoline. Pleasingly, the desired cyclisation product 2a was obtained in 50% yield upon treatment with SmI₂ (Table 1, entry 1). The fact that SmI₂, in the absence of additives that increase the reducing power of the reagent, can reduce 1a highlights the reactive nature of the N-acyl amidine functional group relative to, for example, amides, acids, esters, and nitriles.

Drawing on the observations of Beaudry, NH₄Cl proved to be an effective proton source in the reductive coupling, and its use gave 2a in 57% yield (entry 2). Using the more established proton sources, H₂O and t-BuOH, resulted in the formation of 2a in 61% and 60% yield, respectively (entries 3 and 4). When the amount of H₂O was reduced, the yield of 3a did not improve (entries 5 and 6). The use of LiBr as an additive in combination with H₂O gave 2a in a lower 26% yield (entry 7). The key to further improvement in the yield of 2a proved to lie in the rate of addition of the SET reagent; slow addition of SmI₂ gave 2a in 81% isolated yield (entry 8). It is likely that slow addition prevents the over-reduction of aminal radical I that would compete with radical cyclisation. The combination of SmI₂ and H₂O was clearly too reducing for the amidine substrate (even with slow addition of SmI₂) and thus Beaudry’s NH₄Cl additive was used in further studies.

Using the optimised conditions, we have explored the generality of the amidine–alkene radical cyclisation (Scheme 2). In all cases, the desired quinazolinone products of cyclisation were obtained with complete diastereocontrol (>95:5 dr) and in good to excellent yield. Various functional groups on the alkenyl aryl ring were found to be compatible with the reductive conditions, including methoxy (2c, 2d), bromo (2e), chloro (2h), trifluoromethyl (2f), and acetal (2g). Furthermore, the presence of medicinally-relevant heteroaromatic rings including indole (2k), benzothienyl (2l and 2m), and thienyl (2n) did not impede radical cyclisation. Finally, various functional groups on the benzenoid ring of the 4-quinazolinone motif, including bromo (2o and 2p), fluoro (2q and 2r) and methoxy (2s), were also tolerated in the radical cyclisation. The relative configuration of the quinazolinone products was assigned after X-ray crystallographic analysis of 2a and 2g.

The radical cyclisation could be carried out on gram-scale with no loss of efficiency: Using the optimised conditions, 1a...
the cyclisations of ketyl radical anions that often proceed to give anti-products,\textsuperscript{16} the cyclisation of neutral aminal radical \( I \), formed by protonation of a radical anion after SET or by protonation of the aminal prior to SET, favours cyclisation via syn-transition structure \( 3 \).

In summary, reductive amidine–alkene radical cyclisations, involving the intramolecular addition of aminal radicals to simple alkenes, deliver polycyclic quinazolinones. The radical process is mediated by single electron transfer from commercially available SmI\( _2 \), operates under mild conditions on readily-available substrates, proceeds with complete diastereocONTrol, and delivers a range of medicinally-relevant, quinazolinone derivatives in good to excellent yield.

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**Conflicts of interest**

There are no conflicts to declare.

**Notes and references**


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9 Selected leading reviews on Sm(II)-mediated radical cyclisations and cyclisation cascades. For example, see: (a) C. N. Rao, D. Lentz and H.-U. Reissig, Angew. Chem., Int. Ed., 2015, 54, 2750; (b) C. N. Rao, C. Bentz and H.-U. Reissig, Chem. – Eur. J., 2015, 21, 15951; And ref. 10e-g.


8 (a) D. A. Schiedler, Y. Lu and C. M. Beaudry, Org. Lett., 2014, 16, 1160; (b) D. A. Schiedler, J. K. Vellucci, Y. Lu and C. M. Beaudry, Tetrahedron, 2015, 71, 1448. Aminal radicals could also be generated under Bu₃SnH or (TMS)₃SiH conditions, and have been applied in the carbon-carbon bond forming reaction, see: (c) D. A. Schiedler, J. K. Vellucci and C. M. Beaudry, Org. Lett., 2012, 14, 6092.