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Radical Dearomatising Spirocyclisation of Benzisoxazole-Tethered Ynones

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Dedicated to Prof. Dennis P. Curran on the occasion of his 70th birthday.

The dearomative spirocyclisation of benzisoxazoles through a radical chain mechanism is described. Densely functionalised spirocycles were prepared in high yields by reacting benzisoxazole-tethered ynones with aryl thiols in 1,2-dichloroethane (DCE) at 60 °C. The identification of stabilising three-electron interactions was key to the development of this new radical cascade reaction. The obtained spirocyclic products were converted into other spirocyclic scaffolds through a two-step hydrogenolysis-cyclisation sequence.

Introduction

Radical dearomatising spirocyclisation cascade reactions enable simple aromatic substrates to be converted into densely functionalised and highly prized molecular scaffolds in a single step.[1] The effectiveness of this reaction strategy to quickly access complex 3-dimensional chemical space has inspired significant progress and a number of substrate systems have been developed to explore this approach.[2] However, a significant proportion of systems developed to date are based on a simple design principle: tether an electron-rich (hetero)arene to a reactive radical acceptor or precursor.

In addition to polarity effects lowering the barrier to spirocyclisation,[3] we hypothesised that one reason electron-rich (hetero)arenes have proven so effective is their ability to form partially stabilised radical intermediates upon spirocyclisation. For example, indole-tethered ynones **2** were proposed to rapidly react with a variety of different radical species to form spirocyclic α-amino radicals **2**,[4,5] which are stabilised by two-centre three-electron (2c,3e) bonding interactions (Scheme 1a).[6] Based on this rationale, we reasoned that the elusive radical dearomative spirocyclisation of comparatively electron-deficient heteroarenes might be realised if similar interactions could be incorporated into the substrate. Thus, we identified benzisoxazole-tethered ynones **3** as promising candidates for study (Scheme 1b). Here, the addition of a transient vinyl radical to the C=N bond of the adjacent benzisoxazole ring would form nitrogen-centred radical **4**,[7] which would be stabilised by 2c,3e bonding with the lone-pair on the adjacent oxygen atom.

Herein, we describe validation of this design rationale and, to the best of our knowledge, the first dearomative spirocyclisation of benzisoxazoles. The straightforward conversion of the products into other spirocyclic scaffolds through a divergent, two-step ring expansion sequence is also reported.

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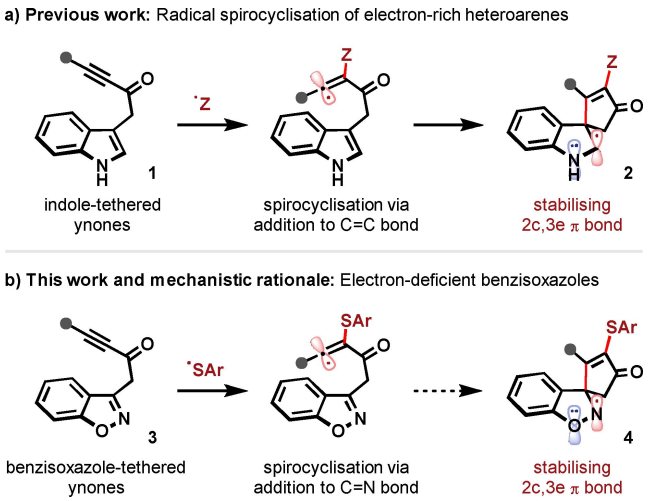

Scheme 1. Radical dearomatising spirocyclisation cascades.

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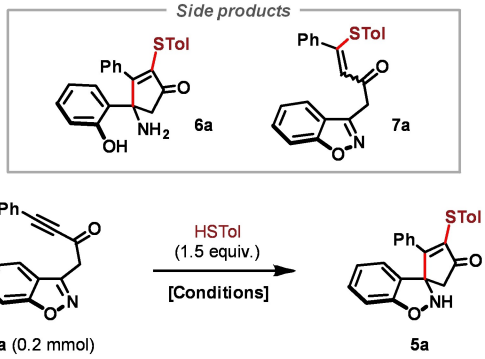
Results and Discussion

Our studies began by reacting ynone **3a** with *p*-toluenethiol (HSTol) in MeCN at 60 °C for 20 h (Table 1, entry 1), which led to the formation of a complex mixture of: i) the desired spirocycle **5a** in 4% yield; ii) amino alcohol **6a** in 11% yield, which was presumed to form via the cleavage of the weak N–O bond of spirocycle **5a**; and iii) a ~3:7 mixture *E*/*Z* alkenes **7a** in 65% yield, which presumably formed via conjugate addition of the thiol to the electrophilic ynone. Fortunately, a solvent screen (entries 2–4) revealed that the formation of both side-products **6a** and **7a** could be completely supressed by using DCE, which produced the desired spirocycle **5a** as the sole product in quantitative yield (entry 4).[8] Attempts to accelerate this reaction under photochemical conditions led to the unwanted formation of amino alcohol **6a** (entry 5). Interestingly, the addition of basic additives, such as triethylamine, completely switched the selectivity to favour formation of conjugate addition product **7a** (entry 6). The addition of TEMPO completely inhibited the formation of spirocycle **5a** and only conjugate addition products **7a** were observed (entry 7). Moreover, a thiyl radical TEMPO adduct was observed by HRMS (see the supporting information). Finally, the formation of spirocycle **5a** was also strongly inhibited by the addition of 9,10-dihydroanthracene (DHA), which is an excellent hydrogen atom donor (entry 8).[9]

Table 1. Reaction optimisation studies.

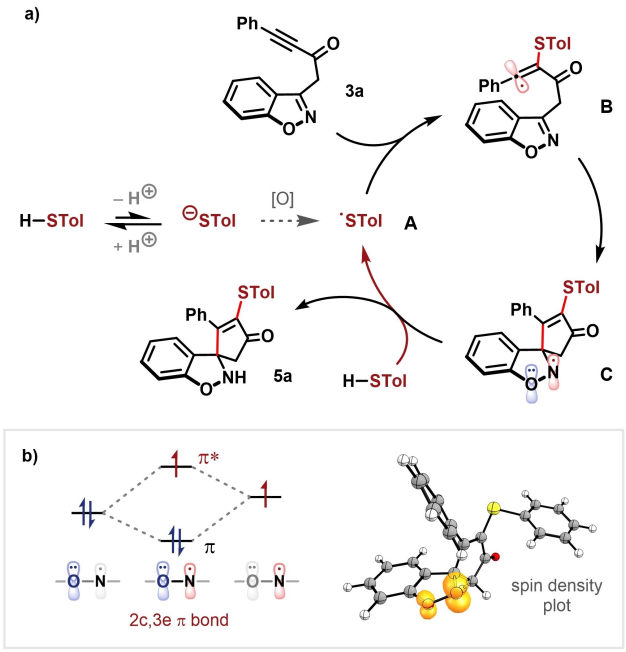


Entry[a]	Reaction conditions	Yield[b] **5a**/%	Yield[b] **6a**/%	Yield[b] **7a**/%
1	MeCN, 60 °C, 20 h	4	11	65
2	THF, 60 °C, 20 h	42	18	–
3	PhMe, 60 °C, 20 h	85	4	–
4	DCE, 60 °C, 20 h	100	–	–
5	DCE, blue LEDs, rt, 21 h	36	34	–
6	Et_3N (1 equiv.), DCE, 60 °C, 20 h	–	–	95
7	TEMPO (1 equiv.), DCE, 60 °C, 20 h	–	–	83
8	DHA (1 equiv.), DCE, 60 °C, 20 h	trace	–	35

[a] All reactions were performed with 0.2 mmol of ynone **3a** and 0.3 mmol of HSTol in the stated solvent (2 mL) under argon. [b] Determined by ^{1}H NMR spectroscopy against an internal standard (dibromomethane).

Based on these observations and previous work in this area, we propose that a radical chain mechanism is likely operative and is initiated by the generation of thiyl radical **A** (Scheme 2a).[10] We propose that thiyl radical **A** is likely formed by the facile single electron oxidation of the corresponding thiolate anion present in solution; the oxidant may simply be adventitious oxygen, and/or a cationic organic oxidant formed in situ.[11] The regioselective addition of radical **A** to ynone **3a** forms vinyl radical **B**, which undergoes rapid spirocyclisation to form nitrogen-centred radical **C**. Intermediate **C** may then abstract a hydrogen atom from HSTol to regenerate thiyl radical **A** and afford spirocycle **5a**. Computational studies support the viability of this radical chain, and the idea that intermediate **C** is stabilised by 2c,3e bonding interactions (Scheme 2b, see the Supporting Information for details).[12]

The scope of this dearomative spirocyclisation cascade was next explored using the optimised reaction conditions (Scheme 3). First, different thiols were examined and pleasingly a wide variety of alkylated benzenethiols could be used to afford spirocycles **5a–f** in near quantitative yields. It should be noted that these reactions were easily scalable as spirocycle **5a** could be isolated in 93% yield when the reaction was performed with 1.0 mmol of ynone **3a**. More electron-rich aryl thiols, including unprotected 4-hydroxybenzenethiol, were similarly compatible and used to obtain spirocycles **5g–i** in excellent yields. Halogenated benzenethiols were also readily incorporated into spirocycles **5j–l** and the structure of **5l** was unambiguously confirmed by X-ray crystallography.[13] More acidic electron-deficient aryl thiols primarily afforded conjugate addition products **7m,n**, with spirocycles **5m,n** only obtained in low yield, presumably due to there being a higher concentration of thiolate anions in solution. Unfortunately, very



Scheme 2. a) Proposed radical chain mechanism; b) Orbital illustration and calculated spin density plot to support the proposed 2c,3e π bonding interaction.

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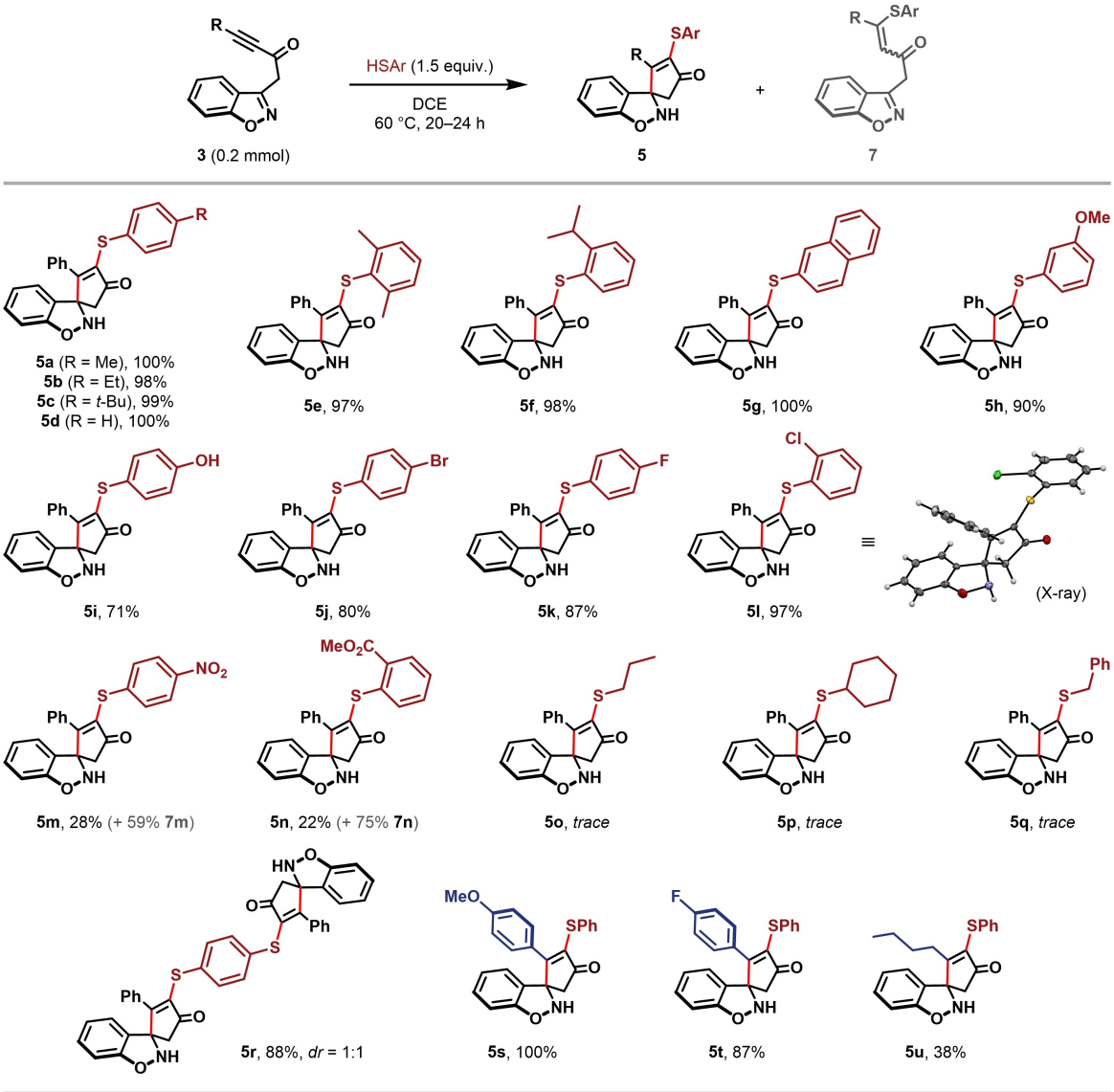

Scheme 3. Scope of the radical dearomative spirocyclisation cascade. Reactions performed on a 0.2 mmol scale in 2 mL of DCE.

limited reactivity was observed when alkyl thiols were used (spirocycles **5o**–**q** were only formed in trace amounts or low yields), which is likely due to the higher bond-dissociation energy (BDE) of the alkyl thiol S–H bonds.[14] However, dithiols such as 1,4-benznedithiol were compatible and could be used to form spirocycle **5r** in excellent yield, as a ~1:1 mixture of diastereoisomers. Other methoxy- and fluoro- substituted aromatic ynones were prepared and converted into spirocycles **5s**,**t** in excellent yields. Finally, an alkyl ynone substrate was also prepared and converted into spirocycle **5u** in 38% yield. The reduced reactivity of this alkyl ynone may be due to the lack of resonance stabilisation of the intermediate vinyl radical,[15] which could change the geometry of the vinyl radical (from linear to bent) and make thiyl radical addition to the ynone less thermodynamically favourable.

The synthetic utility of this novel spirocyclic framework was next explored, by testing a series of divergent reactions to convert spirocycle **5a** into other spirocyclic products. Guided by our previous observation that the N–O bond could be readily cleaved, hydrogenolysis was performed to selectively obtain amino alcohol **6a** in quantitative yield (Scheme 4a). This procedure was also compatible with other spirocycles and the structure of amino alcohol **6j** was unambiguously confirmed by confirmed by X-ray crystallography.[13] Amino alcohol **6a** was then readily cyclised under simple reaction conditions to access a variety of novel spirocycle frameworks **8**–**10** in 39–84% yield. To confirm that other spirocycles could be derivatised similarly, spirocyclic carbamates **11**–**14** were also prepared in the same way, in excellent yields (Scheme 4b).

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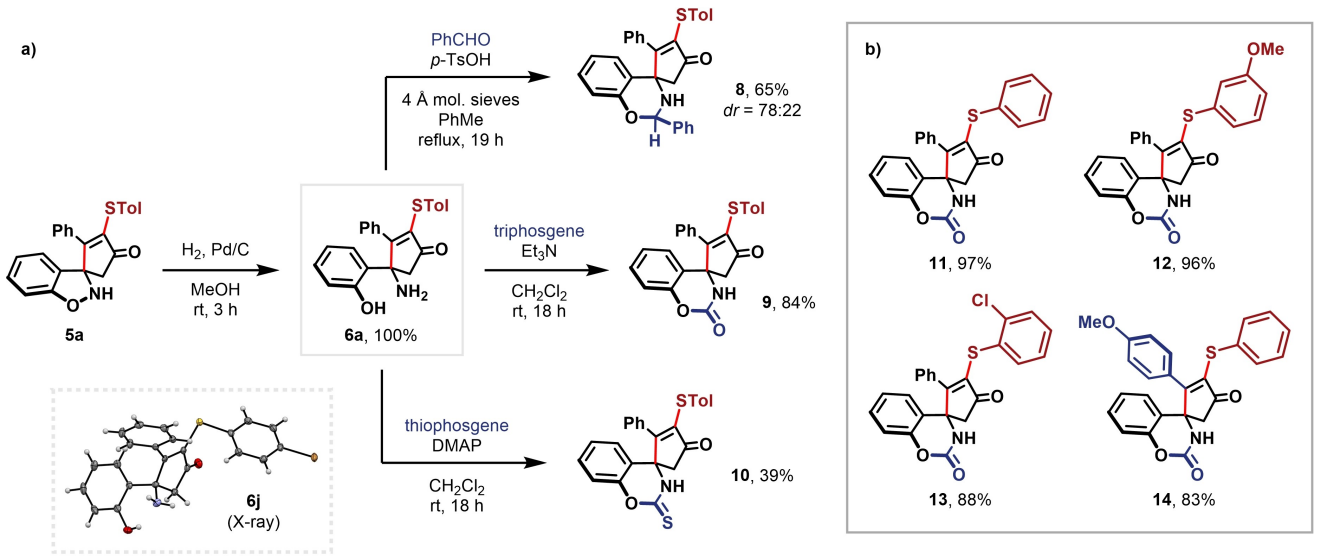

Scheme 4. Diversification of the spirocycle products through a two-step ring expansion sequence.

Conclusions

In conclusion, the first radical dearomative spirocyclisation cascade with benzisoxazoles has been developed. The reactions are proposed to proceed via a thiyl radical-based chain mechanism, which is initiated under operationally simple thermal conditions. Thanks to the synthetic versatility of the weak N–O bond, the densely functionalised spirocyclic products obtained with this method could be used to access other novel spirocyclic scaffolds, via divergent, two-step ring expansion reaction sequences. Considering the prominence of both benzisoxazoles and spirocycles in medicinal chemistry,[16,17] this work will enable diverse libraries of medicinally relevant spirocyclic molecules to be rapidly generated. The discovery that ynones tethered to electron deficient arenes undergo dearomative spirocyclisation should also encourage the exploration of analogous reactions with other arenes in future studies.

Experimental Section

General procedure for the synthesis of spirocycles 5: To a solution of benzioxazole-tethered ynone (0.2 mmol) in DCE (2 mL) in a sealed vial was added thiol (0.3 mmol). The reaction mixture was degassed with argon for 5 minutes, before being stirred at 60 °C for 20–24 h in a preheated metal heating block. The crude mixture was quenched with sat. aq. $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3×5 mL). The organic layers were combined, dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography to afford the spirocycle product.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: cascade · dearomatisation · radical · ring expansion · spirocyclisation

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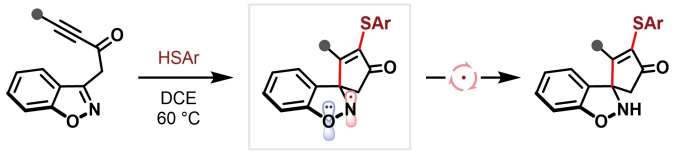

The synthesis of densely functionalised spirocyclic products through a radical dearomative spirocyclisation chain mechanism is described. The spirocyclic products were converted into other spirocyclic scaffolds through a two-step ring expansion sequence.

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