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Radical Cyclization Approach to Spirocyclohexadienones†

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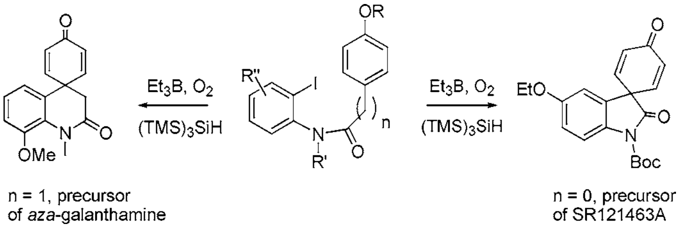
ABSTRACT



Cyclization of an aryl radical at the *ipso* position of a *p*-*O*-aryl-substituted acetamide or benzamide generates oxindoles or quinolones bearing spirocyclohexadienone rings. This versatile reaction is applied to formal syntheses of the vasopressin inhibitor SR121463A and *aza*-galanthamine.

Spirocyclohexadienones such as spirooxindole **1** and spirodihydroquinolone **4** are pivotal intermediates in the preparation of biologically active compounds (Figure 1). Reduction of spirocyclohexadienone **1** provides spirocyclohexanone **2**, a key intermediate in the synthesis of the potent and selective vasopressin inhibitor SR121463A **3**.[1] Spirodihydroquinolone **4** is a key intermediate in the preparation of *aza*-galanthamine **5**.[2] Structures such as the spirooxindole **2** have been synthesized starting from 4-oxo-protected cyclohexyl derivatives,[3] oxindoles,[4] or substituted indolones.[5] Reports on the synthesis of spirodihydroquinolones such as **4** are less abundant and involve the use of organometallic chemistry to install the key quaternary center in a protected 4-oxo cyclohexyl derivative.[2]

The formation of spirocyclohexadienones in radical cyclizations was first described by Hey in reactions of radicals generated by photolysis of iodides or reduction of diazonium salts,[6] but the synthetic potential of this reaction has yet to be recognized. We hypothesized that a radical cyclization could be used to construct both the spirooxindole **1** and the spirodihydroquinolone **4** starting from generalized cyclization precursor **6** (Figure 2).

Aryl radical **7** derived from **6** can cyclize at the *ortho* position (path a) to give **8a** or the *ipso* position (path b) to give **8b**.[7] These radicals might be in equilibrium through a

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† This paper is dedicated to Prof. Amos B. Smith, III, in honor of his 60th birthday.

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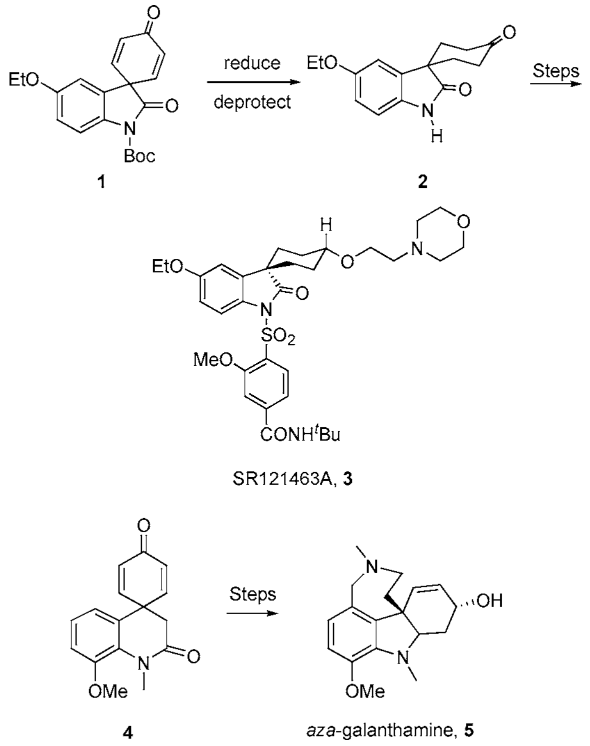

Figure 1. Examples and uses of key spirocyclohexadienone intermediates.

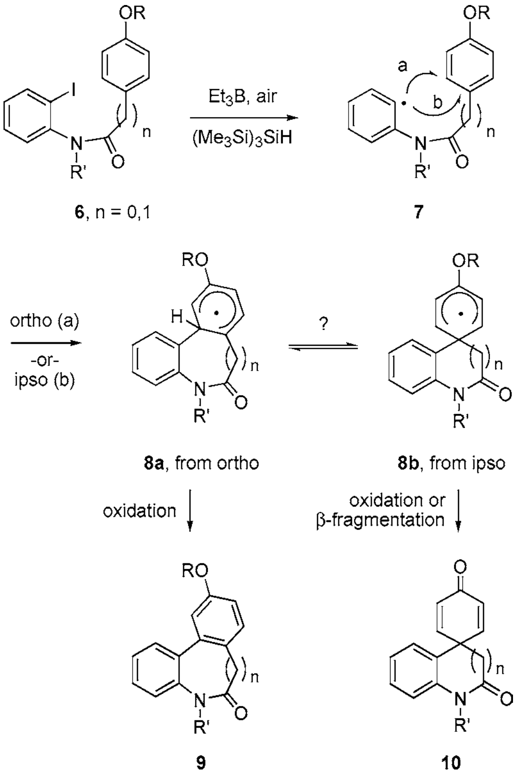

Figure 2. *Ortho* and *ipso* cyclization pathways.

formal 1,2-shift.[8] Oxidation[9] of **8a** gives **9** with the OR group intact, while either oxidation or β-fragmentation[10] of **8b** should give the target spirocyclohexadienone **10**.

To test the viability of this approach, precursors **14a−d** and **15b** were synthesized by coupling readily available 2-iodoanilines **11** and **12** and acyl chloride **13** (Scheme 1).[11] Treatment of the TBS-protected phenols **14a** and **15a** with TBAF gave alcohols **16** and **17**. These were tritylated, benzoylated, or methylated to give precursors **14b−d** and **15b**.

With these precursors in hand, the key cyclization reactions were tested employing the $(Me_3Si)_3SiH/Et_3B$ method.[12] In a typical experiment, a solution of **14a** in benzene (0.15 M) was treated with 1.2 equiv of $(Me_3Si)_3SiH$ and 1.2 equiv of Et_3B, and the resulting mixture was stirred at room temperature open to air until the starting material was consumed (typically 3 h). Subsequent evaporation and ^{1}H NMR spectroscopic analysis showed spirocyclic compound **18** and the phenanthridinone **20a** as the only products (entry 1, Table 1). These were isolated by flash chromatography in 13 and 57% yields, respectively.

Interestingly, we found that the ratios of spirocyclic to phenanthridinone products were different depending on the group attached to the phenol. With the trityl or benzoyl precursors **14b**,**c** and **15b**, the desired spirocyclic compounds **18** and **19** were the main products (entries 2, 3, and 5, Table 1), and purification by column chromatography allowed isolation of the spirocyclic compounds in yields ranging from

Scheme 1

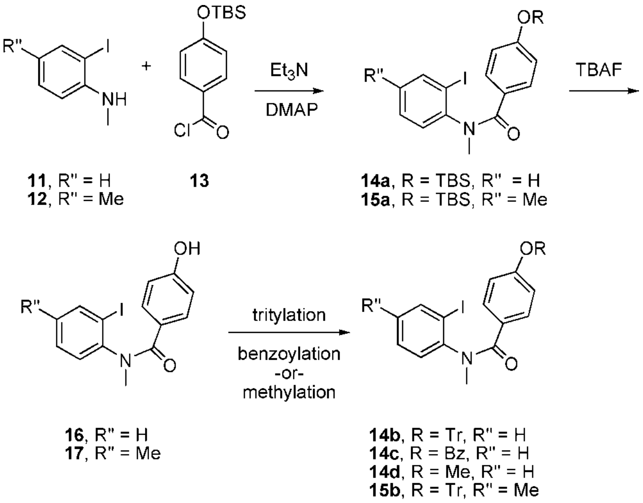

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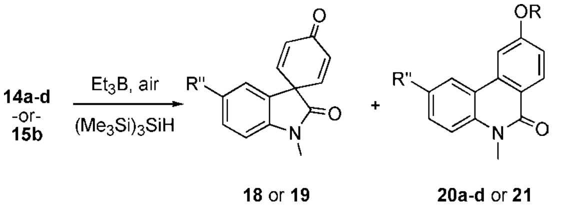
Table 1. Synthesis of Spirooxindoles **18/19** and Phenanthridinones **20/21**



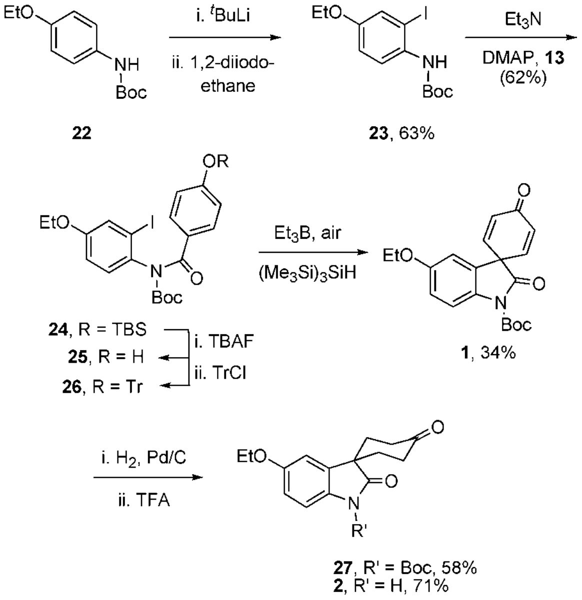
precursor	R″	R	product	ratio[a]	yield[b]
14a	H	TBS	**18/20a**	1/4.4	13%/57%
14b	H	Tr	**18/20b**	2.2/1	43%/nd[d]
14c	H	Bz	**18/20c**	1.5/1[c]	29%/nd[d]
14d	H	Me	**18/20d**	1/2.6	15%/38%
15b	Me	Tr	**19/21**	1/0	53%

[a] Ratio determined by ^{1}H NMR spectroscopy. [b] Isolated yield after column chromatography. [c] Reaction did not go to completion. [d] Not determined (purification was not possible by column chromatography).

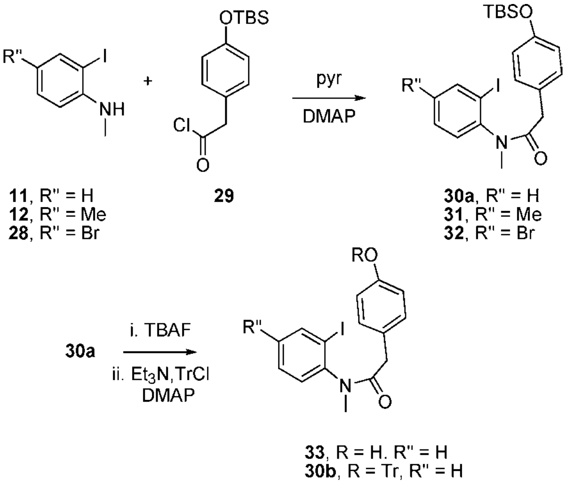
29 to 53%. In contrast, when the cyclization was performed with the TBS- or methyl-protected precursors **14a**,**d**, the main products were the phenanthridinones **20a**,**d**, which were isolated in yields ranging from 38 to 57% (entries 1 and 4, Table 1). Importantly, these experiments revealed suitable precursors for the selective formation of either the spirocyclic (**18**, **19**) or phenanthridinone (**20a**–**d**, **21**) products, setting the stage for the synthesis of the spirocyclic compound SR121463A **3**.

The approach to vasopressin inhibitor **3** started with the readily available protected aniline **22** (Scheme 2).[11] Directed *ortho* lithiation of **22**, followed by treatment of the resulting anion solution with 1,2-diiodoethane, gave iodoaniline **23** in 63% yield. Coupling of the protected aniline **23** and the acyl chloride **13** gave the amide **24**, which was deprotected with TBAF to give alcohol **25**. Treatment of this alcohol with trityl chloride in the presence of Et$_3$N and DMAP provided the key cyclization precursor **26**. Gratifyingly, cyclization of **26** under the standard conditions (0.15 M in benzene, (Me$_3$Si)$_3$SiH, Et$_3$B, open to air) gave the desired spirocyclic compound **1** in 34% yield. Subsequent Pd-mediated hydrogenation of dienone **1** and removal of the Boc group with TFA gave the desired spirocyclohexanone **2**, an intermediate previously reported in the synthesis of SR121463A.[1b]

Scheme 2. Formal Synthesis of SR121463A



Scheme 3. Synthesis of Cyclization Precursors



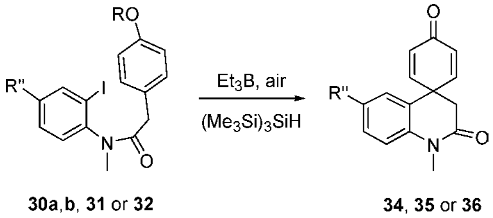
Having established the viability of this approach in the synthesis of spirooxindoles, we turned our attention to the preparation of spirodihydroquinolones. The required cyclization precursors **30a**, **31**, and **32** were synthesized by the coupling reaction of the readily available iodoanilines **11**, **12**, or **28** with acyl chloride **29** (Scheme 3).[11] Subsequent deprotection of the TBS group in **30a** provided alcohol **33**, which was reacted with trityl chloride in the presence of DMAP and Et$_3$N to give precursor **30b**.

The key cyclization reactions were performed under the previous reaction conditions with precursors **30a**,**b**, **31**, and **32**. Evaporation of the crude reaction mixture after the starting material was consumed (typically 2 h) and purification by column chromatography provided the desired spirodihydroquinolones **34**, **35**, and **36** in yields shown in Table 2. All the products resulted from the *ipso* cyclization, and there was no evidence for products of *ortho* cyclization.

Interestingly, the target spirohydroquinolines **34**–**36** were isolated in acceptable yields starting from the corresponding TBS-protected precursors **30a**, **31**, and **32**. The trends of yields in these reactions were typically between 40 and 65% depending on the substitution of the aromatic ring of the cyclization precursors. These experiments allowed us to identify suitable precursors for the synthesis of spirodihydroquinolones, prompting us to consider application of this method to a formal synthesis of *aza*-galanthamine **5**.

The approach toward *aza*-galanthamine **5** started with the readily available trisubstituted aromatic ring **37**,[11] which was

Table 2. Synthesis of Spirodihydroquinolones



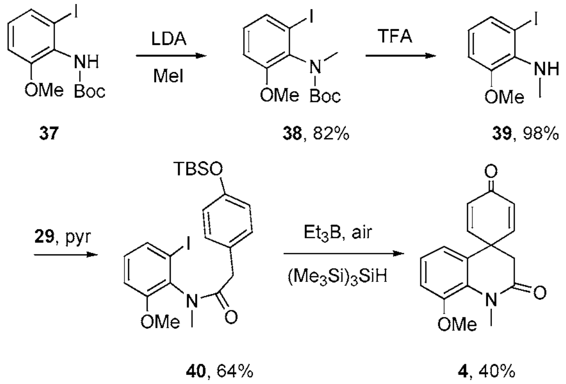
precursor	R″	R	product	yield[a]
30a	H	TBS	**34**	49%
30b	H	Tr	**34**	65%
31	Me	TBS	**35**	53%
32	Br	TBS	**36**	40%

[a] Isolated yield after column chromatography.

protected by deprotonation with LDA and treatment of the resulting anion solution with methyl iodide. Boc deprotection of **38** by using TFA, followed by condensation with the corresponding acyl chloride **29**, gave the desired cyclization precursor **40** in 64% yield. Gratifyingly, we found that when precursor **40** was treated under the radical cyclization conditions, the desired spirodihydroquinolone **4** was isolated in 40% yield (Scheme 4).[13]

In summary, we have introduced a new procedure for the synthesis of spirooxindoles and spirodihydroquinolones through *ipso* cyclization of aryl radicals to oxygen-substituted aromatic rings. The reaction allows quick access to a variety of spirocyclic structures starting from simple cyclization precursors. The usefulness of the method is shown by the synthesis of a number of spirocyclic compounds, including key intermediates in the synthesis of both SR121463A and *aza*-galanthamine. In some cases, the products of *ortho* substitution (phenanthridinones) are also observed, and the ratio of *ortho*- to *ipso*-substituted products can be controlled by the oxygen substituent. Substituents favoring β-fragmentation (trityl) give more *ipso*-substitution product, while substituents disfavoring it (methyl) give more *ortho*-substitution product.

Scheme 4. Formal Synthesis of *aza*-Galanthamine



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Supporting Information Available: Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Compound **4** showed ^{1}H NMR data identical to that reported in the literature (see ref 2). The published ^{13}C NMR data lack the quaternary carbon that resonates at $\delta = 43.6$ ppm.