Synthetic Methods

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Approach to Spirocyclohexadienimines and Corresponding Dienones through Radical *ipso* Cyclization onto Aromatic Azides**

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Spirocyclohexadienones, such as **1** and **3**, are pivotal intermediates in the synthesis of important biologically active compounds (Figure 1). In particular, reduction and deprotection of **1** provides spirooxindole **2**, an intermediate in the synthesis of the vasopressin inhibitor SR121463A,[1–4] whereas spirodihydroquinolone **3** is a key intermediate in the preparation of azagalanthamine[5a] and other indole alkaloids.[5b]

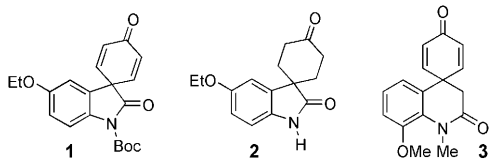
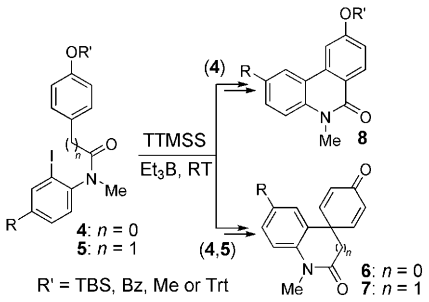


Figure 1. Spirooxindoles (**1**, **2**) and spirohydroquinone (**3**) intermediates in the preparation of biologically active compounds.



Scheme 1. Synthesis of spirooxindoles and spirodihydroquinolones by five- and six-membered *ipso*-cyclization of aryl radicals. TTMSS = tris(trimethylsilyl)silane; TBS = *tert*-butyldimethylsilyl; Trt = triphenylmethyl.

In a recent study, Curran and co-workers devised an elegant radical procedure for the synthesis of both spirooxindoles and spirodihydroquinolones, entailing five- and six-membered *ipso* cyclization of aryl radicals arising from deiodination of *p*-alkoxy-substituted anilides **4** and **5**: the resulting spirocyclohexadienyl radicals afford dienones **6** and **7** upon β cleavage of the O–R′ bond with elimination of the alkyl/silyl R′ radical (Scheme 1).[6] The effectiveness of this method is, however, somewhat limited by the efficiency of the β-elimination process, which was especially effective only when a highly stable species, such as a triphenylmethyl (trityl, Trt) radical, could be eliminated. Furthermore, the construction of the trityloxy precursors **4** and **5** (R′ = Trt) was not trivial, as it entailed deprotection and tritylation of preliminary silyloxy anilides **4** and **5** (R′ = *tert*-butyldimethylsilyl, TBS), which in turn required the rather longwinded preparation of TBS-protected 4-hydroxybenzoyl and, especially, 2-(4-hydroxyphenyl)acetyl chloride (four steps). Moreover, the production of spirooxindole **6** (from benzanilides **4**) was significantly limited by the concomitant generation of phenanthridinone **8**, arising from cyclization at the aromatic *ortho*-position.

In previous studies, we discovered that α-azidoalkyl radicals can form iminyl radicals by extrusion of dinitrogen.[7] In principle, suitable azidocyclohexadienyl radicals, which would arise from radical *ipso* attack at the *para* position of aromatic azides, might behave similarly to afford cyclohexadieniminyl radicals. We therefore considered that spirocyclohexadienyl radicals, analogous to those devised by Curran, but bearing a *p*-azido rather than a *p*-alkoxy substituent, should be very attractive candidates for testing our assumption. Indeed, spirocyclic azidocyclohexadienyl radicals, such as **13** and **14** (Scheme 2), might afford the corresponding iminyl radicals **15** and **16**, which, under reductive conditions, would yield cyclohexadienimines **17** and **18** in an efficient fashion. Since those imines should undergo easy hydrolytic conversion into dienones, we envisioned that our study might eventually lead to an alternative synthetic route to spirocyclohexadienones **6** and **7**, based on the primary radical reaction of *p*-azido-substituted 2-iodoanilides **9** and **10** with tris(trimethylsilyl)silane (TTMSS) and Et_3B.

Aromatic azides are widely known to undergo smooth radical attack at the azido moiety to give aminyl radicals[8] but, to our knowledge, their potential use as alternative precursors of cyclohexadieniminyl radicals is to date totally unprecedented.

The use of azidoanilides **9** and **10** as radical cyclization precursors was also encouraged by our expectation that such compounds should be more easily accessible than the oxygen-

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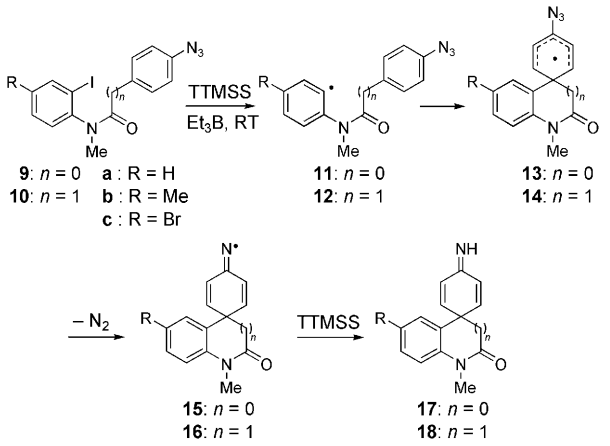
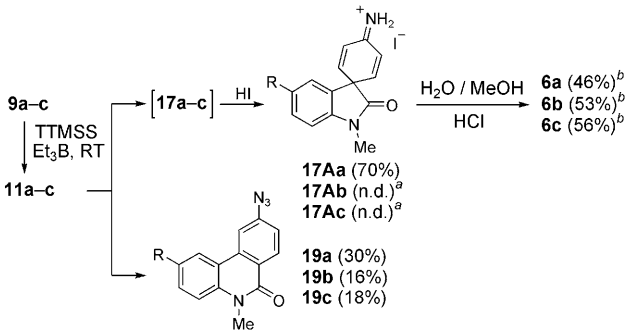


Scheme 2. Radical approach to cyclohexadienimines from *p*-azido-substituted 2-iodoanilides.



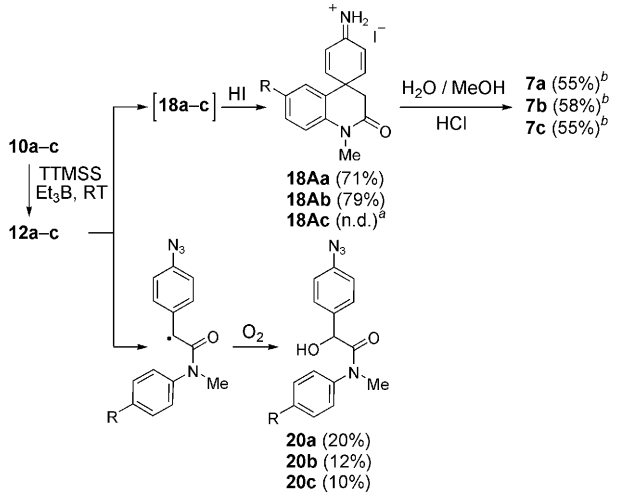
Scheme 3. Route to indolones by five-membered radical spirocyclization, and concurrent formation of phenathridinone by-products. **a** R = H; **b** R = Me; **c** R = Br. [*a*] Yield not determined, owing to unsatisfactory purification; [*b*] yield based on starting azides **9a–c**.

substituted counterparts **4** and **5**. Furthermore, previous results from this group suggested that tris(trimethylsilyl)silyl radicals, rather than adding to the azido moiety, would effect selective iodine abstraction from the azidoiodides **9** and **10** to give aryl radicals **11** and **12**.[7a,8a,9] Finally, the azido functionality is known to effect stronger radical stabilization than an alkoxy group[10] and, in the case of **9**, this effect should favor the five-membered ring-closure ratio of aryl radical **11**, hence disfavoring the competing formation of the phenanthridone.

Herein we report the highly rewarding results provided by our preliminary studies, using azides **9a–c** and **10a–c** (Scheme 2), and the congener **21** (Scheme 5). As anticipated, compounds **9a–c** and **10a–c** were prepared in good yields (65–85%) by coupling the appropriate *N*-methyl-2-iodoaniline with 4-azidobenzoyl or 2-(4-azidophenyl)acetyl chloride. These acyl chlorides were, in turn, readily prepared through conversion of the corresponding commercially available amino acids into azides.

All azides were reacted by adopting experimental conditions strictly comparable with those previously employed for alkoxyanilide substrates **4** and **5**.[6] After 16 h, the reaction of benzamide **9a** gave rise to extensive precipitation of an orange solid, which was isolated by filtration and found to be sparingly soluble in the common nonpolar solvents, and more soluble in polar solvents, such as acetone, methanol, and, to a lesser extent, water. The spectroscopic data were consistent with the structure of imine **17a**, in the form of its hydroiodide salt **17Aa** (Scheme 3). This salt (70% yield) presumably arose from the initial formation of **17a** through subsequent reaction with hydrogen iodide, possibly produced upon hydrolysis of tris(trimethylsilyl)iodosilane, and/or direct reaction with the iodosilane followed by fast hydrolysis of the ensuing *N*-silyliminium iodide. Column chromatography of the filtrate remaining after removal of **17Aa** afforded the minor product azidophenanthridinone **19a** (30% yield), that is, the product of the competing six-membered cyclization of aryl radical **11a**. In a similar fashion, direct filtration of the reaction mixture from the radical reactions of benzanilides **9b** and **c** furnished comparable amounts of the analogous crude imine hydroiodides **17Ab** and **Ac**. Chromatographic separation of the filtrate gave the respective phenanthridinone by-products **19b** and **c** (Scheme 3).

Analogous radical reactions of acetanilides **10a–c** also led to satisfactory results, giving rise to the precipitation of large amounts of quinolone imine hydroiodides **18Aa–Ac**, which were again isolated by filtration. In each case, column chromatography of the filtrate furnished modest amounts of the respective 2-hydroxy-substituted acetanilides **20a–c**, which conceivably arose from the 1,5-H-transfer reaction of aryl radicals **12a–c**, followed by trapping of the translocated benzyl radicals by oxygen (Scheme 4).[7a,11]



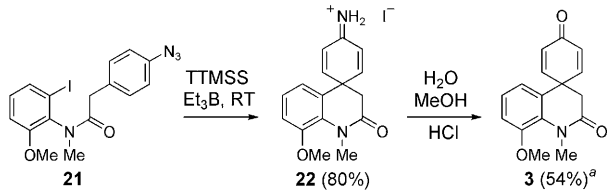
Scheme 4. Route to quinolones by six-membered radical spirocyclization, and concurrent formation of 2-hydroxy-substituted acetanilide by-products. **a** R = H; **b** R = Me; **c** R = Br. [*a*] Yield not determined, owing to unsatisfactory purification; [*b*] yield based on starting azides **10a–c**.

The above overall results confirmed our original assumptions that aryl radicals **11** and **12** could undergo both five- and six-membered spirocyclization reactions onto the internal aromatic azide, and that the resulting intermediate spirocyclic azidocyclohexadienyl radicals **13** and **14** could extrude

molecular nitrogen in a highly efficient fashion to afford cyclohexadieniminyl radicals **15** and **16**, and thence the corresponding imines **17** and **18**. The yields of the latter compounds were significantly higher than those of cyclohexadienones **6** and **7**, arising from silyloxy- and trityloxy-substituted amides **4** and **5** (R′ = TBS or Trt).[6] This fact validated our additional hypothesis that the azido substituent promotes aryl radical spirocyclization more effectively than an alkoxy group. These interesting results might pave the way to important future applications of aromatic azides for the construction of uncommon spirocyclic cyclohexadienimines.[12,13]

Gratifyingly, upon brief heating at 60 °C in methanol/water in the presence of a few drops of hydrochloric acid, **17A** and **18A** afforded the respective spirocyclohexadienones **6** and **7**, in satisfactory yields based on the original azides **9** and **10** (Scheme 3 and 4).

We finally attempted the synthesis of spiroquinolone **3**, a valuable intermediate in the preparation of indole alkaloids. Coupling of *N*-methyl-2-iodo-6-methoxyaniline with 2-(4-azidophenyl)acetyl chloride gave azidoacetamide **21** in high yield (82%). Treatment of **21** with TTMSS/Et_3B led to imine hydroiodide **22** (80%), which was hydrolyzed to afford the target quinolone **3** in 54% overall yield (Scheme 5). Compound **3** had previously been prepared in moderate yield through a long-winded, expensive multistep sequence based on intramolecular Heck cyclization of a protected 2-(4-oxocyclohexenyl)acetanilide[5a] and, subsequently, in 40% yield, through direct radical cyclization of the TBSO analogue of azide **21**.[6]



Scheme 5. Synthesis of spirodihydroquinolone **3.** [*a*] Yield based on starting azide **21**.

In conclusion, we have shown that aromatic azides can provide an unprecedented straightforward synthetic entry to cyclohexadieniminyl radicals that can be suitably exploited in the valuable production of indolones and quinolones bearing spirocyclohexadienimine/spirocyclohexadienone rings. As far as the dienones are concerned, our new synthetic protocol is evidently superior to both Curran's radical procedure[6] and other reported nonradical methods.[4,5] Our procedure, in fact, while giving rise to comparable or even better yields of those dienones, employs very easy to prepare azido precursors, entails very simple workup,[14] and results in highly minimized atom waste. Our present discovery could allow novel, highly appealing applications of radical chemistry in the synthesis of biologically active compounds.

Experimental Section

All azides (0.5 mmol) were treated in either benzene or toluene (8 mL) with TTMSS (1.2 equiv) and Et_3B (1.2 equiv) and the resulting mixtures were stirred at RT under air until total consumption of the starting material. Filtration of the reaction mixtures afforded crude imine hydroiodides, which were then hydrolyzed, whereas chromatography of the filtrates yielded the by-products (phenanthridones or hydroxyanilides).

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[14] Imine hydroiodides are recovered by filtration of the reaction mixtures and can be subjected to hydrolysis without any need for further purification by column chromatography.

