Radical-Reaction Mechanism

The Mechanism of Bu_3SnH-Mediated Homolytic Aromatic Substitution

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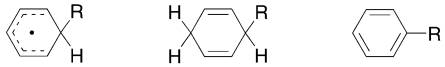
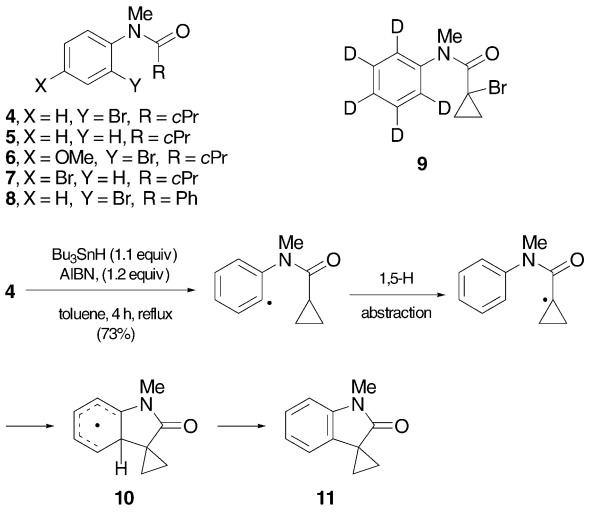
A large and growing number of Bu_3SnH-mediated cyclization reactions which proceed in modest to good yields[1–6] involve intramolecular homolytic aromatic substitution of arenes and heteroarenes. These and similar intermolecular reactions proceed by addition of the initial radicals R$^\bullet$, generated by $Bu_3Sn^\bullet$ radicals, to the aromatic rings (ArH) to yield intermediate substituted cyclohexadienyl radicals ArRH$^\bullet$ **1**. The mechanistic question is how the fully aromatic products ArR **3** are formed in what is formally an oxidation reaction.



1 **2** **3**

There are a number of possible mechanisms by which the conversion of a substituted cyclohexadienyl radical ArRH$^\bullet$ **1** into a substituted arene **3** might occur. Herein we report our attempts to distinguish between them. The first and most obvious possible mechanism involves disproportionation of **1** or hydrogen-atom transfer from Bu_3SnH to afford the intermediate $ArRH_2$ (e.g., **2**) and its isomers, which can then undergo oxidation by the initiator or oxygen on workup. Whilst oxidation during workup may be plausible, dihydro-type systems, such as **2**, are not oxidized rapidly in air.[7] The yields are also higher than 50%, and this rules out disproportionation as the main mechanism.

As a test for H transfer from Bu_3SnH to the π radical **1**, bromo compound **4** (Scheme 1) was converted into the spiro-oxindole **11** by treatment with Bu_3SnD. Under these circumstances any cyclohexadiene derivative formed would bear a deuterium substituent and would be expected to give at least some partially deuterated analogue of the product **11**. In the event, careful D NMR spectroscopy of the crude product showed no detectable signal for deuterium attached to an arene, a result that precludes the formation of a dihydro intermediate and suggests that homolytic aromatic substitution is not directly dependent on the use of Bu_3SnH as radical carrier. This conclusion agrees with that of Crich and Hwang,[7] who found that intermediate π radicals in Bu_3SnH-mediated cyclizations could be effectively intercepted by the efficient hydrogen-atom donor PhSeH (with the formation of a dihydro spiro-cyclized product) but not by Bu_3SnH.



Scheme 1. Synthesis of oxindoles by homolytic aromatic substitution; AIBN = azobisisobutyronitrile.

Two possible mechanisms are characterized by the production of dihydrogen. One involves the induced decomposition of Bu_3SnH [Eq. (1)], a reaction which has no precedent but appears to be thermodynamically feasible. The other mechanism that we proposed earlier[1,2] involves Bu_3SnH acting as a hydride donor and ArRH$^\bullet$ as a protic acid to give the arene radical anion $[Ar{-}R]^{\bullet-}$ [Eq. (2)]. This can undergo single-electron transfer (SET) to the precursor halide to propagate the chain [Eqs. (3) and (4)], that is, a $S_{RN}1$-type mechanism. The possible occurrence of these reactions was probed by treating the deuterated radical precursor **9** (Scheme 1) with Bu_3SnH to give the corresponding tetradeutero analogue of **11** (66% yield). If the mechanism involves the reactions of either Equation (1) or (2), HD should be formed. However, careful examination of the gaseous products by mass spectrometry, NMR, and Raman spectroscopy failed to detect any HD. We therefore conclude that the mechanism does not involve either of the steps given in Equations (1) and (2).

$$ArRH^{\bullet} + Bu_3SnH \rightarrow Ar{-}R + Bu_3Sn^{\bullet} + H_2 \quad (1)$$

$$ArRH^{\bullet} + Bu_3SnH \rightarrow [Ar\text{-}R]^{\bullet-} + Bu_3Sn^{+} + H_2 \quad (2)$$

$$[Ar{-}R]^{\bullet-} + Ar{-}Br \rightarrow Ar{-}R + [Ar{-}Br]^{\bullet-} \quad (3)$$

$$[Ar{-}Br]^{\bullet-} \rightarrow Ar^{\bullet} + Br^{-} \quad (4)$$

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In a further test for the intermediacy of $[Ar{-}R]^{\bullet-}$ an equimolar mixture of **4** (X = H) and its *p*-methoxy derivative **6** was treated with 0.5 molar equivalents of Bu_3SnH in the usual way. If the reaction involves chain-propagating electron transfer from the intermediate arene radical anion $[Ar{-}R]^{\bullet-}$ to Ar–Hal [Eq. (3)], the more readily reduced substrate **4** should be preferentially consumed. In the event, GC analysis of the reaction mixture showed that the two substrates had been consumed to an equal extent. This experiment further confirms that these reactions do not involve the mechanism given in Equations (2)–(4).

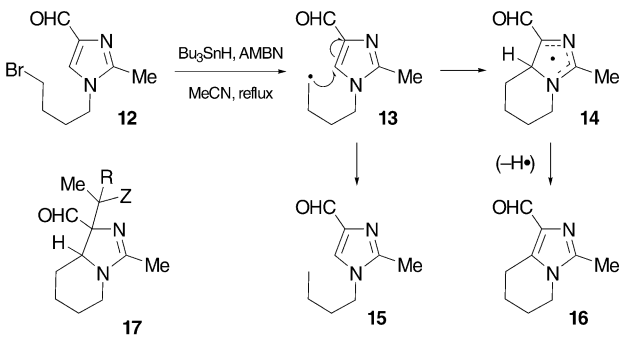
Hydrogen-atom transfer to other radicals present in the reaction mixture [Eq. (5)] is another possibility. If disproportionation between $Bu_3Sn^{\bullet}$ and $ArRH^{\bullet}$ occurs, the reaction should be catalytic in Bu_3SnH. However, when a series of experiments on the cyclization of **12** was conducted with a constant quantity of azobismethylisobutyronitrile (AMBN, 1.0 equiv) and decreasing amounts of Bu_3SnH, the yield of cyclized material dropped steadily (e.g., 2.2 equiv of Bu_3SnH: **16** (92%) and **12** (0%); 0.5 equiv of Bu_3SnH: **16** (0%) and **12** (75%)). These results clearly indicate that Bu_3SnH is not regenerated during the reaction.

$$ArRH^{\bullet} + X^{\bullet} \rightarrow Ar{-}R + XH \qquad (5)$$

Further experiments were conducted to determine whether radicals $X^{\bullet}$ formed directly from initiators can abstract hydrogen from $ArRH^{\bullet}$ [Eq. (5)]. One involved azobisisobutyronitrile (AIBN)-initiated conversion of the deuterated precursor **9** into the tetradeutero analogue of **11**. Examination of the reaction mixture by GC-MS and D NMR spectroscopy revealed the formation of Me_2CDCN in 23% yield. In another experiment involving di-*tert*-butyl peroxide as initiator and an excess of Bu_3SnH, D NMR spectroscopy of the mixture indicated the presence of both Bu_3SnD and *tert*-BuOD. Both $Bu_3Sn^{\bullet}$ radicals[8] and 2-cyanoprop-2-yl radicals (from AIBN)[9] rapidly quench any traces of oxygen present with formation of the corresponding peroxy radicals, $Bu_3SnOO^{\bullet}$ and $Me_2C(CN)OO^{\bullet}$, which might act as H abstractors. Although all the reaction mixtures were thoroughly deoxygenated with nitrogen gas, studies have shown that traces of oxygen remain unless very special conditions are used.[9] The conversion of **12** into the cyclization product **16** (see Scheme 2) in similar yields when di-*tert*-butyl peroxide or triethylborane (> 1 equiv) was used as the initiator in place of AIBN suggests that *tert*-butoxyl or ethyl radicals, respectively, can carry out the required H abstraction [Eq. (5)].

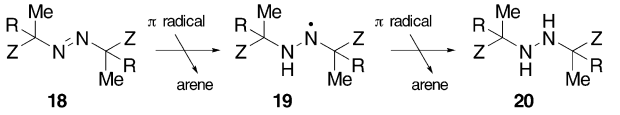
Intermediate π radicals (e.g., **14**) may also couple with other radicals (e.g., to give **17**). For cyclization onto indoles,[6] products from the addition of $Me_2C^{\bullet}CN$ from AIBN breakdown to the π radicals have been isolated and shown to undergo elimination to give the aromatic product.

Common to many[1–4] but not all[5,13] reactions involving radical addition to aromatic systems is the reported need for stoichiometric amounts of initiator. We also found this to be the case by conducting a series of experiments involving the cyclization of **12**[10] (Scheme 2), in which the amount of AMBN (**18**; R = Et, Z = CN; see Scheme 3) was varied while other conditions were kept constant. Analysis of the products by ^{1}H NMR spectroscopy with an internal standard revealed a clear relationship between the yield of cyclized product and the amount of AMBN used (e.g., AMBN: 1.0 equiv, **16** (92%), **12** (0%); 0.5 equiv, **16** (43%), **12** (53%); 0.25 equiv, **16** (8%), **12** (92%)).[10]



Scheme 2. Synthesis of bicyclic imidazole **16**.

Further confirmation of the role of the initiator was obtained when **4** was treated under the standard conditions (110 °C, 240 min) with Bu_3SnH/AIBN (1.2 equiv). The evolution of only 0.3 equivalents of nitrogen indicated that 0.9 equivalents of AIBN was not consumed by breakdown to nitrogen gas and 2-cyano-2-propyl radicals. Nevertheless, careful analysis of reaction mixtures of the Bu_3SnH/AMBN-mediated reaction of **12** by GC-MS and ^{1}H NMR spectroscopy showed no signs of the expected reduction product **20** (R = Et, Z = CN; Scheme 3). An explanation for the non-detection of **20** (R = Et, Z = CN) was obtained when independent synthesis showed it to be extremely unstable. The diester AIBMe (**18**; R = Me, Z = CO_2Me) was also used as initiator, but its reduced form **20** (R = Me, Z = CO_2Me), although a stable compound, also decomposed under our reaction conditions. Further studies on this problem are continuing. Recently the isolation of **20** (R = Me, Z = CO_2Me) from a Bu_3SnH-mediated cyclization onto pyrazole with AIBMe as initiator was reported.[3b]



Scheme 3. Reduction of azo initiators.

These results suggest that in these reactions (Schemes 2 and 3) the initiator is acting as the oxidizing agent. Curran et al.[11] previously reached the same conclusion. Furthermore, dialkyldiazenes (R–N=N–R) have been shown to abstract hydrogen from benzhydryl radicals to yield benzophenone and the corresponding hydrazines,[12] and this supports the possibility that AIBN/AMBN may have a similar role. The intimate details of the mechanism remain obscure. Possibly, a two-step process via an intermediate hydrazyl radical (Scheme 3) is involved, but an SET reaction between AMBN or AIBN and the intermediate cyclohex-

adienyl π radical to yield the radical anion of AMBN or AIBN or AIBN and a π cation, which would rapidly aromatize with loss of a proton, cannot be ruled out.

The above results indicate that the mechanism of Bu_3SnH-mediated homolytic aromatic substitution does not involve the electron-transfer processes of Equations (3)–(4). It appears therefore that the predominant, although probably not the sole, reaction sequence[6,13] for processes initiated by azo compounds (R′−N=N−R′) is given by Equations (6)–(9)

$$R'' + Bu_3SnH \rightarrow R'H + Bu_3Sn^{\cdot} \quad (6)$$

$$Bu_3Sn^{\cdot} + R{-}Br \rightarrow Bu_3SnBr + R^{\cdot} \quad (7)$$

$$R^{\cdot} + ArH \rightarrow ArRH^{\cdot} \quad (8)$$

$$2\,ArRH^{\cdot} + R'{-}N{=}N{-}R' \rightarrow 2\,ArR + R'NHNHR' \quad (9)$$

When the reaction is initiated by RO· radicals the last step is most likely replaced by that of Equation (5), where X· = RO·. Both types of reaction involve the conversion of ArRH· into product in a chain-terminating step.

If these sequences are correct then homolytic aromatic substitution reactions, both intra- and intermolecular, should retard alternative radical processes. This hypothesis was tested in a series of experiments involving stannane-mediated reduction of bromooctane in the presence of **8** (see Scheme 1), which undergoes cyclization. In the absence of other radical processes reduction of bromooctane is first-order in Bu_3SnH and half-order in initiator. However, kinetic analysis of the system involving both reduction of bromooctane and cyclization of **8** with chain termination according to the above mechanism indicated that the initial reaction rate should be proportional to $[\text{initiator}]_{\text{initial}}$ and inversely proportional to $[\mathbf{8}]_{\text{initial}}$. The results of a series of experiments involving mixtures of **8**, 1-bromooctane, Bu_3SnH, and di-*tert*-butyl hyponitrite (BONNOB) in cyclohexane at 45 °C were in full accord with this hypothesis. For example, when the concentrations of the other reactants were kept constant, reactions involving $[\text{BONNOB}]_{\text{initial}} = 4.5$ mM and 1.5 mM gave initial rates of formation of octane of 4.3 and 1.4 $\mu M\,s^{-1}$, respectively. However, when $[\text{BONNOB}]_{\text{initial}}$ was kept at 1.5 mM, initial concentrations of **8** of 11 and 22 mM gave initial rates of formation of octane of 2.8 and 1.5 $\mu M\,s^{-1}$, respectively. The conformity of the observed rates to those expected supports the notion that most, if not all, of the intermediate, substituted cyclohexadienyl radicals formed during the cyclization of **8** undergo termination directly with the initiator or with radicals derived from it.

Finally, the effect of substituted cyclohexadienyl-radical intermediates on the course of a typical stannane-mediated chain reaction was explored by determining the rates of reduction of two typical substrates with Bu_3SnH in benzene and cyclohexane. In the first series of experiments the progress of the AIBN-initiated ($[\text{AIBN}]_{\text{initial}} = 0.1$ mM) reduction of methyl *p*-bromobenzoate with Bu_3SnH at 70 °C in benzene was compared with that of the reaction under the same conditions in cyclohexane. The results revealed that the reaction rate was dramatically retarded in benzene. For example, after heating for 2 h in cyclohexane the yield of methyl benzoate was 97 %; in benzene the yield was 6.5 %. In a second series of experiments with $[\text{AIBN}]_{\text{initial}} = 0.5$ mM it was found that the reduction of 1-bromooctane also occurs more slowly in benzene than in cyclohexane. Thus, after 40 min at 70 °C the yields of octane in cyclohexane and benzene were 80 and 28 %, respectively.

These results, which indicate that the intermediacy of substituted cyclohexadienyl radicals results in chain termination, have implications concerning the choice of conditions for the use of Bu_3SnH and other radical carriers in synthesis. Reactions involving intramolecular homolytic substitution will require larger amounts of initiator and more forcing conditions than usual. More significantly, it appears that arenes, such as benzene, toluene, and *tert*-butylbenzene, are not necessarily the best solvents for reactions involving very low concentrations of substrate, under which conditions homolytic addition to the solvent may compete effectively with the desired chain-transfer processes. In such cases the use of alternative, nonaromatic solvents could be advantageous. Also, it should be noted that although relatively large amounts of initiator are required, the methods described in our earlier reports[1–3] provide efficient routes to compounds such as **11** and **16** that are not easily accessed by other means. In these reactions, the initiator should be regarded as an expendable reagent. Although good chain reactions are desirable, they do not necessarily equate with good synthetic methods. Initial studies with alternative hydride sources to Bu_3SnH, for example, tris(trimethylsilyl)silane and tributylgermanium hydride, implicate the same mechanistic considerations.

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Keywords: azo compounds · cyclization · radical reactions · radicals · reaction mechanisms

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