Sulfur-Controlled *Exo* Selective Aryl Radical Cyclization onto *Exo*-Methylenecycloalkanes

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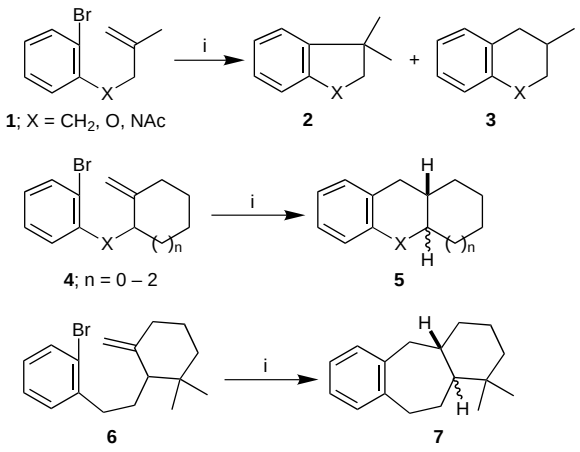
Abstract: The Bu_3SnH-mediated aryl radical cyclization of vinyl sulfides **9** proceeds in an *exo* selective manner to give fused aromatic compounds **10** which contain a benzylic quaternary carbon center.

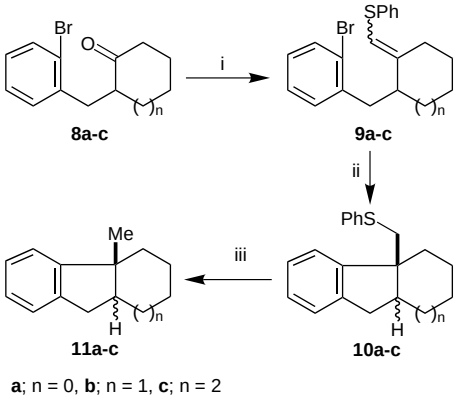
Key words: aryl radical, neophyl rearrangement, vinyl sulfide, radical cyclization, tributyltin hydride

The control of the regiochemistry of radical cyclizations is a subject of intense investigation.[1] In principle, the ring-closure of *o*-bromo-(3-methyl-3-butenyl)benzene (**1**, X = CH_2) and its related species can occur in an *exo* or in an *endo* manner to give **2** and **3**, respectively, under the Bu_3SnH-mediated conditions. The literature indicated that the product distribution of the cyclizations depended upon the nature of atom X of **1** or the reaction conditions employed. The aryl bromides **1** where X = CH_2[2a,b] or O,[2c] in general, gave a mixture of the *exo* and the *endo* cyclization products **2** and **3**, whereas the corresponding aza analog (**1**, X = NAc) gave only the *exo* cyclization product **2**.[2d] On the other hand, the bromides **4** having an *exo*-methylenecycloalkane exclusively gave the *endo* cyclization products **5**.[3a,b] This was also the case for the homologous system **6** which gave the *endo* cyclization product **7**.[3c,d,4] Herein we report that the *endo* selectivity of the cyclizations of **4** and **6** can be shifted to the *exo* mode by introducing a phenylthio group at the terminus of their *exo*-methylene bonds.



Scheme 1 i, Bu_3SnH, AIBN, benzene, reflux

The radical precursors **9a–c** were prepared from the ketone **8a–c**[3b] by the Horner-Emmons reaction with the lithium salt of $Ph_2P(O)CH_2SPh$.[5] A solution of Bu_3SnH (1.2 equiv.) and a catalytic amount of azoisobutyronitrile (AIBN) in benzene was slowly added to a boiling solution of **9a** over a period of 1 h and the mixture was further heated for 3 h to give the *exo* cyclization product **10a** in 75% yield as a single stereoisomer. The stereochemistry of the ring-juncture of **10a** proved to be *cis* based on the nOe experiments of the corresponding desulfurized compound **11a.**

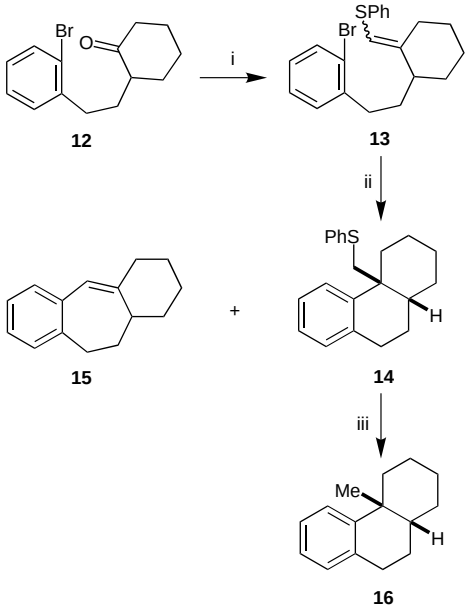


Scheme 2 i, $Ph_2P(O)CH_2SPh$, BuLi, THF, then H_3O^+; ii, Bu_3SnH, AIBN, benzene, reflux; iii, Raney Ni, EtOH, reflux.

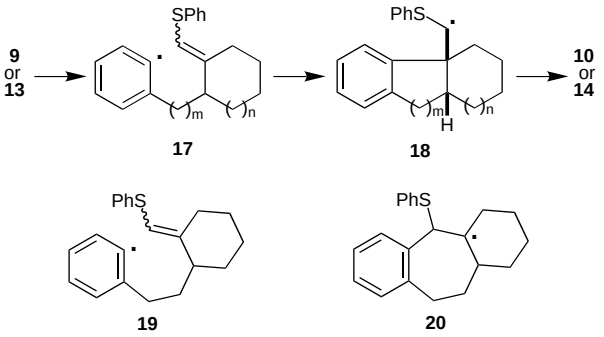
The cyclization of the cyclohexyl congener **9b** proceeded more smoothly to give the *exo*-cyclization product **10b** in 91% yield, whose *cis*-stereochemistry was confirmed by its desulfurization to the known compound **11b**.[6] Compound **9c** also gave the *exo* cyclization product **10c** in 82% yield as a mixture of the *cis* and the *trans*-isomers in a ratio of 4.3:1 (determined by the nOe experiments of **11c**).

The reaction of the homologous compound **13**, prepared from the ketone **12**,[7] gave also the *exo* cyclization product **14** in 40% yield along with a trace amount of the *endo*-cyclization product **15.** The *cis*-stereochemistry of the ring-juncture of **14** was established by the transformation to the known compound **16.**[8]

The formation of the *exo* cyclization products **10** (from **9**) and **14** (from **13**) may be best explained by assuming that the intermediate radicals **18** formed by an *exo* cyclization of the aryl radicals **17** are highly stabilized by an adjacent sulfur atom.[9,10]



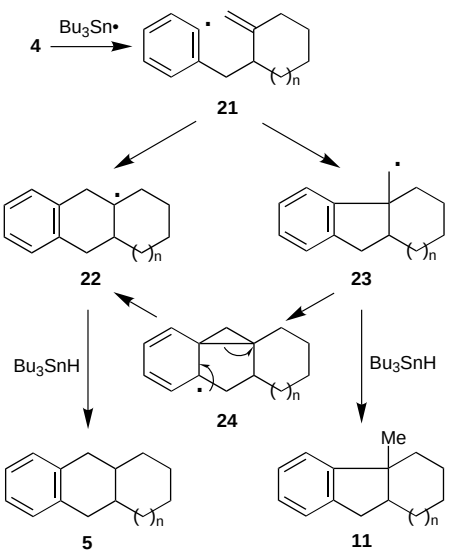
Scheme 3 i, $Ph_2P(O)CH_2SPh$, BuLi, THF then H_3O^+; ii, Bu_3SnH, AIBN, benzene, reflux; iii, Raney Ni, EtOH, reflux



Scheme 4

The formation of **15** from **13** may be rationalized in terms of a partial *endo* cyclization of the aryl radical **19** followed by an elimination of the benzenethiyl radical from the resulting intermediate radical **20**.

The present results suggest that the *endo* selective cyclization of the aryl bromides **4** may be explained by considering the difference in the stability between the intermediate radicals **22** and **23** formed by an *endo* or by an *exo* cyclization of the aryl radicals **21**. The former might be more stable than the latter based on stereoelectronic reasons, thereby resulting in the formation of the *endo* cyclization products **5**. However, the possibility of the consecutive *exo* cyclization of the aryl radicals **21** and the neophyl rearrangement[2c] of the resulting radical **23** (*via* **24**) could not be excluded for the formation of **22**. We then reinvestigated the reaction of **4** (n = 1).



Scheme 5

Ghatak and his coworkers reported that the bromide **4** (n =1) gave **5** (n = 1) in 95% yield as a mixture containing a debrominated product in a ratio of 9:1 under the conditions where the concentration of Bu_3SnH in benzene was maintained at 0.007–0.02 M.[3a,b] In our laboratory, the compound **4** (n = 1) was treated with Bu_3SnH at a 0.1 M concentration, which was higher than that employed by Ghatak, to give a small amount of the *exo* cyclization product **11b** (n = 1) as a mixture containing the reported *endo* cyclization product **5** (n = 1) in a ratio of 1:7. This result strongly suggests that the *exo* cyclization of **21** giving **23** might be the kinetically favored process over the *endo* cyclization giving **22**. The radicals **23** formed from **21** might rapidly undergo a neophyl rearrangement at a low Bu_3SnH concentration to give the *endo* cyclization products **5** *via* the radical **22**.

In summary, the whole sequence of the reactions herein described can be regarded in a formal sense as an *exo* cyclization of **4** and **6** giving **11** and **16**, respectively, since the sulfur atom of the cyclization products **10** and **14** can easily be removed by reductive desulfurization. The present method provides a new synthesis of fused aromatic compounds containing a benzylic quaternary carbon atom. An extended application of the method to the synthesis of natural products is now in progress.

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