Radical Cyclization of Mesitylsulfonylhydrazones

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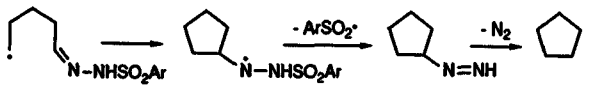
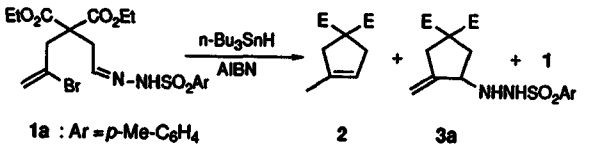
Abstract: Radical cyclization of mesitylsulfonylhydrazones provides a useful method for the formation of unsubstituted five- and six-membered cyclic compounds. Thus, diethyl 3-methyl-3-cyclopentene-1,1-dicarboxylate (2) was formed by reaction of diethyl 5-bromo-1-mesitylsulfonylhydrazono-5-hexene-3,3-dicarboxylate (1b) with tributyltin hydride and 2,2'-azobisisobutyronitrile in benzene.

Radical cyclizations have rapidly emerged as a powerful synthetic tool for the formation of five- and six-membered rings.[1] Recently, we have reported a novel radical cyclization of N-aziridinyl imines for the formation of five- and six-membered ring radicals from acyclic precursors.[2] As the extension of this work, we have studied radical cyclizations using arenesulfonylhydrazones[3] as radical acceptors. As shown in Scheme 1, our approach is based on (i) the previously known addition of alkyl radicals to C=N double bonds,[4] (ii) β-fragmentation of the arenesulfonyl radical,[5] and (iii) the known decomposition pathway of the diazene.[6]



Scheme 1

Radical cyclization of arenesulfonylhydrazones was initially examined with the tosylhydrazone 1a as shown in Scheme 2.



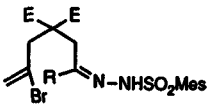
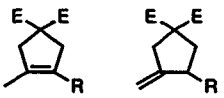
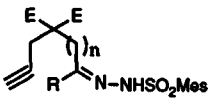
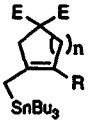
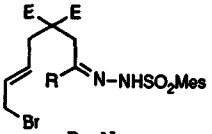
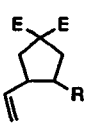
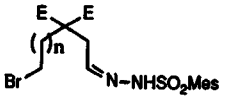
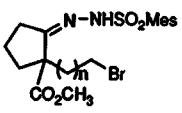
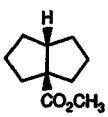
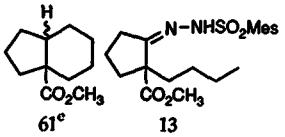
1a : Ar = *p*-Me-C_6H_4 2 3a
1b : = 2,4,6-Me_3-C_6H_2 3b

Scheme 2

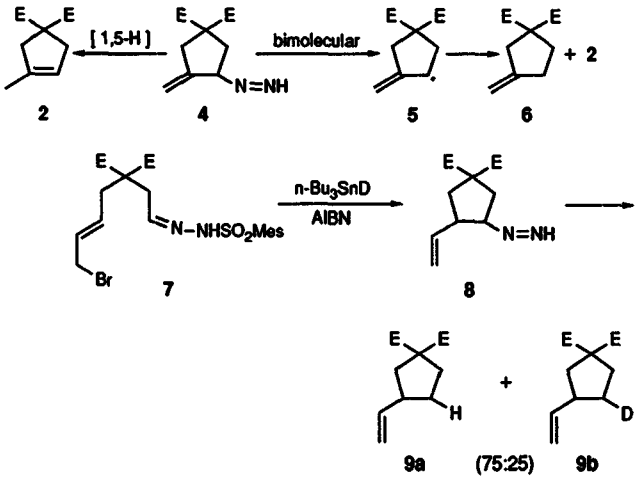
The addition of 0.1 M benzene solution of n-Bu_3SnH (2.4 equiv) and AIBN (0.2 equiv) by a syringe pump over 4 h to a 0.1 M refluxing benzene solution of the tosylhydrazone 1a with additional stirring for 1 h afforded a mixture of 2 (35%)[7], 3a (17%), and 1a (10%) and Stork method using n-Bu_3SnCl/$NaBH_3CN$/AIBN gave no improvements.[8] In order to obviate the formation of 3a, we have investigated the possibility of increasing the β-fragmentation rate by modifying the structure of arenesulfonylhydrazones. The radical cyclization of *p*-methoxyphenyl- and *o*-nitrophenylsulfonylhydrazone with n-Bu_3SnH /AIBN under high dilutions gave similar results without any improvements. However, the use of 1b gave the best result, yielding 70% of 2 along with 10% of the starting material without the formation of 3b. Thus, remaining reactions were carried out with mesitylenesulfonylhydrazones. Mesitylenesulfonylhydrazones were prepared in good yields by treatment of aldehydes and ketones in ethanol with mesitylenesulfonylhydrazine and a mixture of syn and anti isomers was used in this study.

The formation of 2 from the diazene 4 deserves a few comments on possible mechanisms and two possible mechanisms may be considered as shown in Scheme 3, although the intermediacy of 4 could not be determined by spectroscopic methods due to the instability of 4.[6] One is that 4 may undergo [1,5] sigmatropic hydrogen shift to yield 2. The other is that decomposition of 4 in a bimolecular process may give the intermediate 5 which

Table 1. Radical Cyclization of Mesitylenesulfonylhydrazones

Entry	Substrate[a]	Time, h	Product Yield, %
			
1	R = H	8	77 (96 : 4)[b]
2	R = CH_3	13	88 (100 : 0)[b]
			
3	n = 1, R = H	21	59
4	n = 1, R = CH_3	14	67
5	n = 2, R = H	10	45
			
6	R = H	9	65
7	R = CH_3	5	60[c]
			
8	n = 1	6	38
9	n = 2	6	58
10	n = 3	7	27(58)[d]
			
11	n = 2	13	40
12	n = 3	10	 61[e] 13

[a] E = COOEt, Mes = 2-mesityl. [b] The ratio was determined by ^{1}H-NMR. [c] The ratio of cis and trans isomer was 3:1 by ^{1}H-NMR. [d] Yield of the reduction product. [e] a 78 : 22 mixture of stereoisomers.



Scheme 3

yields a mixture of **2** and **6**. In order to elucidate the mechanism, radical cyclization of **1b** was carried out with n-Bu_3SnD/AIBN and **2** was found to contain almost no deuterium (<4%) by ^{1}H-NMR but incorporation of deuterium was detected in mass spectrum. This finding suggests that the formation of **2** would proceed mainly via [1,5] hydrogen shift along with a radical process to a small extent as shown in Table 1 (entry 1).[9] However, radical cyclization of **7** with n-Bu_3SnD/AIBN afforded a mixture of **9a** and **9b** in a ratio of 3 : 1, suggesting that the decomposition of **8** may proceed in a bimolecular radical process.[6b,6c]

Table 1 summarizes some of our experimental results. Radical cyclization of the alkynes proceeded smoothly, yielding allyltin compounds (entries **3**, **4** and **5**). Their structures were confirmed by ^{1}H-NMR analysis of the destannylated products after treatment with DCl. Similarly, allyl bromides and alkyl bromides underwent radical cyclization (entries **6** ~ **12**) and relatively low yields of five-membered rings were obtained due in part to the thermal instability of the starting mesitylenesulfonylhydrazones (entries **8** and **11**). Furthermore, the formation of the seven-membered ring was much less efficient, yielding only 27% of the cyclized product along with 58% of the reduction product (entry **10**). It is noteworthy that intermolecular addition of n-Bu_3Sn radical to a sulfonylhydrazone group did not occur.

A typical procedure is as follows. A 0.05 M benzene solution of n-Bu_3SnH (2.4 equiv) and AIBN (0.2 equiv) was added to a 0.05 M refluxing benzene solution of the mesitylenesulfonylhydrazone over 4 h by a syringe pump and the solution was stirred until the starting material disappeared on the TLC plate. For radical cyclization of the alkynes, Stork procedure was adopted.[10]

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References and Notes

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(7) A small amount of **6**(<5%) was contained in the reaction product.

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(9) Quenching **5** with n-Bu_3SnH afforded **2** and **6** in a ratio of 87 : 13. See reference 2.

(10) Stork, G.; Mook, R. *J. Am. Chem. Soc.* **1987**,*109*, 2829.