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A New Free Radical-Based Method for the Synthesis of Spiroannulated Medium Rings

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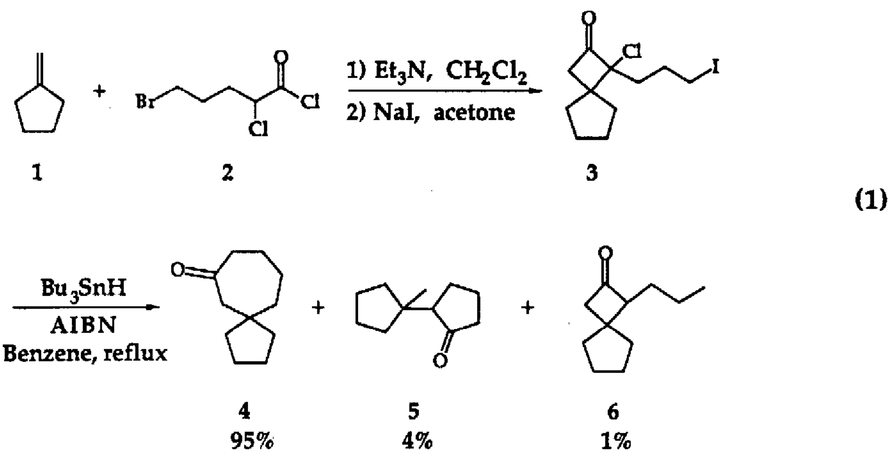
Abstract Free radical promoted cyclobutanone ring expansion provides a new entry to a variety of spiroannulated ring systems.

Direct methods of spiroannulation starting from alkene precursors, particularly those suitable for the preparation of medium rings, are limited in number. This makes it attractive to extend our ring-expansion method[1] to include the spiro carbon-skeleton class.[2,3]

Regiospecific cycloaddition[4] of ω-bromoalkylchloroketenes to methylenecycloalkanes takes place readily, yielding spirocyclobutan-2-ones. Treatment of the adducts with tri-*n*-butyltin hydride, under standard free radical-generating conditions leads to smooth cyclization and ring expansion. An example is shown in eq 1 in which methylenecyclopentane **1** is



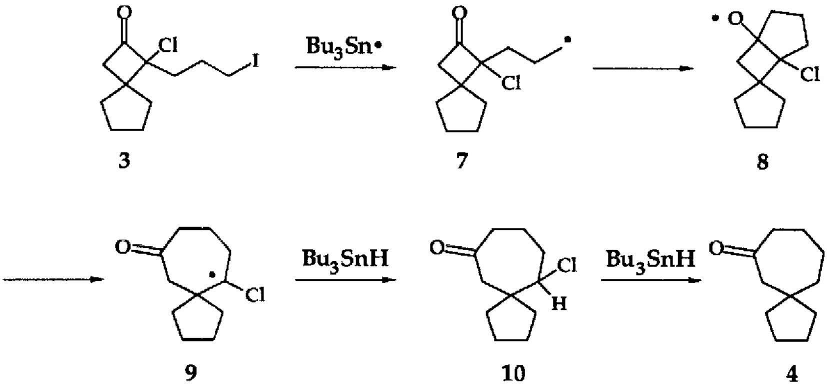
1 **2** **3**

(1)

4 95% **5** 4% **6** 1%

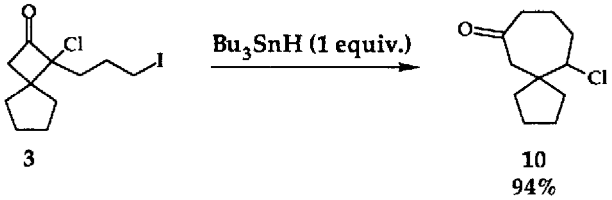
condensed with 2-chloro-5-bromopropyl ketene, generated from **2**. The adduct is transformed to the iodide **3**, which then undergoes smooth ring expansion to the spiroketone **4**. Small amounts of by-products **5** and **6** were also detected.

We suggest, as a working scheme, that initial free radical formation of **7** (eq 2) is followed by attack on the cyclobutanone carbonyl group. Regioselective ring opening of the resulting oxy radical **8** is assisted by the chlorine substituent; the chlorine is then reductively removed in the latter stage of the reaction.



(2)

That chlorine is removed at the end of the sequence was established when it was shown that the chlorine-bearing ring expansion product **10** can be isolated by limiting to one equivalent the tin hydride reagent. Thus, treatment of the halogenated cyclobutanone **3** with one equivalent of tri-*n*-butyltin hydride leads in excellent yield to the ring expanded spiro chloroketone **10** (eq 3).

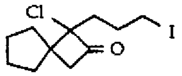
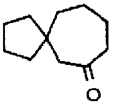
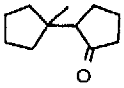
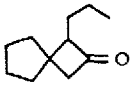
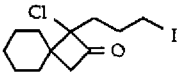
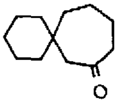
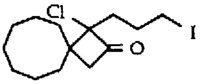
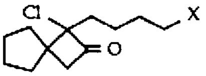
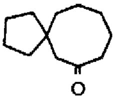
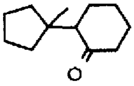
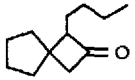
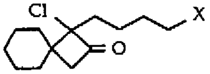
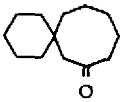
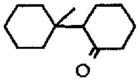
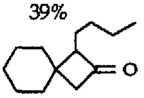
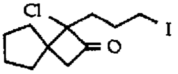
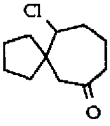
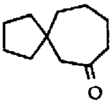
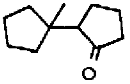
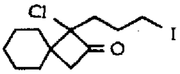
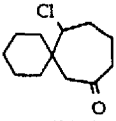
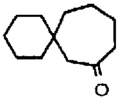


(3)

The free radical method provides good yields of seven and eight-membered spiro annulated rings (Table 1) and is complementary to the Diels-Alder reaction, used to convert alkenes to spiro compounds containing six-membered rings.[5] We found it highly advantageous to use the terminal iodide in the ring expansion step. Indeed, the results in entries 4 and 5 of Table 1, show clearly that the iodide is more effective than the bromide,[6,7] presumably in chain

Table 1

Products and Yields of Spiroannulation

Entry	Starting Materials	Conditions[a]	Products and Relative Yields[b,c]		
1.		A	 95% (90%)	 4%	 1%
2.		A	 100% (95%)		
3.		A	 (86%)		
4.	 X=I X=Br	A	 61% (58%) 52%	 11% 4%	 17% 39%
5.	 X=I X=Br	A	 70% (66%) 20%	 6% <1%	 24% 80%
6.		B	 94% (91%)	 2%	 4%
7.		B	 97% (93%)	 3%	

[a] (A) 5-7 h slow additon of 2.5 equiv of Bu$_3$SnH with AIBN to refluxing benzene. (B) 4 h slow addition of 1.05 equiv Bu$_3$SnH with AIBN to refluxing benzene. [b] Relative yields refer to normalization on GC-MS. Figures in parentheses are isolated yields after flash column chromatography. [c] All major products had satisfactory ^{1}H-NMR, ^{13}C-NMR, IR and mass spectra, including exact mass determination.

propagation at the alkyl iodide stannyl radical stage.[6a]

The free radical method can be employed to prepare spiro ring systems of considerable variety starting from readily available methylenecycloalkanes.

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