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Intramolecular Cyclization Reactions of Enone Radicals

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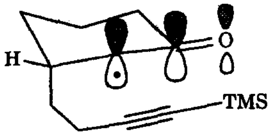
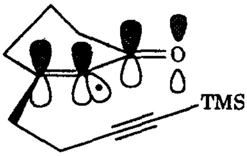
Abstract: Enone radicals, generated from the corresponding iodo enones, or vinylogous esters and amides, undergo intramolecular cyclization to the tethered trimethylsilyl acetylenic side chain to give the carbo- or heterobicyclic enones.

Intramolecular radical cyclization reaction has emerged as one of the most useful synthetic methods for the formation of carbon-carbon bonds.[1] We recently reported the intramolecular cyclization of α-carbonyl radicals, e.g. **1**, and the application to the total synthesis of (±)-modhephene.[2] In this letter, we disclose the result of a related study, that is the intramolecular cyclization reaction of enone radicals, e.g. **2**.

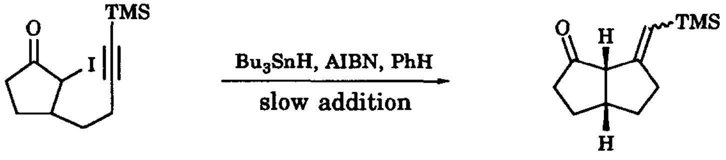


1

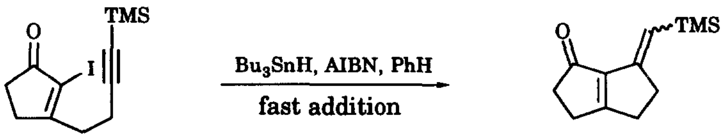


2

In our previous study, iodo ketone **3** was treated with tributyltin hydride by slow addition to produce vinylsilane ketone **4**.[2] Radical **1**, generated from the corresponding α-iodo ketone, is presumably stabilized by the carbonyl π system via resonance, and therefore is not very nucleophilic and cyclizes slowly. On the other hand, we reason that enone radical **2**, which has a radical orthogonal to the enone π system, should be of higher nucleophilicity and cyclizes more rapidly. Toward that end, iodo enone **5** was prepared[3] and treated with tributyltin hydride and 2,2'-azobisisobutyronitrile (AIBN) by fast one-shot addition. We found that iodo enone **5** indeed cyclized smoothly to give **6** in 70% yield (*Z* : *E* = 2 : 1).[4] The slow addition of tributyltin hydride was avoided. In order to understand the generality and limitation of this enone radical cyclization reaction, we investigated this reaction systematically. A typical procedure for the radical cyclization of iodo enones is as follows : To a solution of iodo enone (1 mmol) and AIBN (0.05 mmol) in dry benzene (40 mL) was added a solution of tributyltin hydride (1.2 mmol) in dry benzene (10 mL) rapidly. The mixture was heated to reflux for 1h. After cooling to room temperature, the reaction mixture was concentrated. Potassium fluoride ($KF \cdot 5H_2O$, 1.2 mmol) and ether (20 mL) were added to the residue.[5] The mixture was stirred for 30 min and dried with anhydrous potassium carbonate. Filtration, concentration, and silica gel column chromatography gave the bicyclic enone.

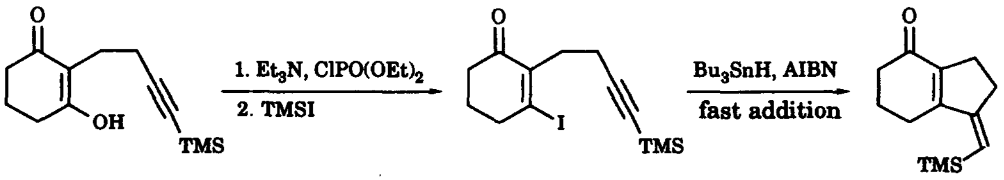


3 **4** 81% (*Z*:*E* = 7 : 3)



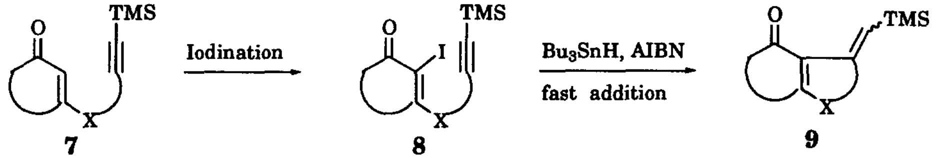
5 **6** 70% (*Z*:*E* = 2 : 1)

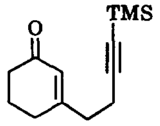
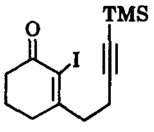
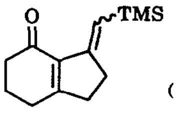
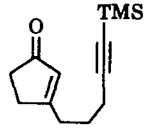
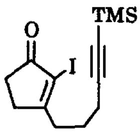
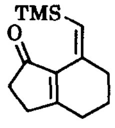
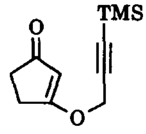
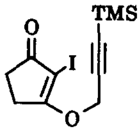
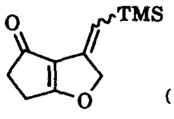
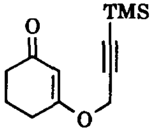
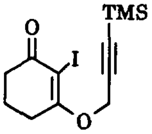
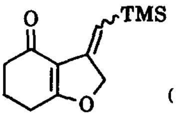
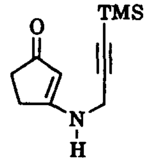
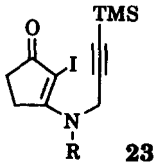
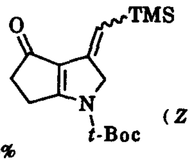
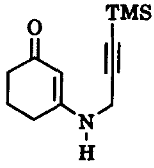
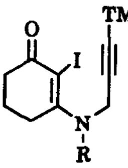
The results are summarized in Table 1. The starting iodo enones **5**, **11**, and **14** were prepared by the method of McIntosh (Method A in Table 1).[3] Iodo vinylogous esters **17**, **20** and amides **23**, **27** were synthesized by Johnson's procedure (Method B or C in Table 1) from vinylogous esters **16**, **19** and amides **22**, **26**.[6] In Entry 1, treatment of iodo enone **11** by tributyltin hydride gave product **12** via a 5-*exo* cyclization.[7] In Entry 2, iodo ketone **14** cyclized via a 6-*exo* radical cyclization[7] to give **15** only in low yield even by the slow addition of tributyltin hydride. In Entries 3 and 4, iodo vinylogous esters **17** and **20** cyclized to give products **18** and **21** in good yields. However when iodo vinylogous amides **23** and **27** (Entries 5 and 6) were treated with tributyltin hydride, the reaction failed. Only the starting compounds and decomposed products were isolated. After protecting the NH groups in **23** and **27** with a *t*-butoxycarbonyl group,[8] compound **24** cyclized to give product **25** upon treatment with tributyltin hydride (Entry 5). However, iodo vinylogous amide **28**[8] was unstable and decomposed under the same reaction condition (Entry 6). Furthermore, β-iodo enone **30** was prepared from 1,3-diketone **29**[9] by Wiemer's method,[10] and treated with



29 **30** 65% **31** 85%

Table 1. Intramolecular Cyclization Reactions of Enone Radicals



Entry	Enone	Iodination Method and Condition	Iodo Enone[a]		Bicyclic Enone[a]	
1	 **10**	(A) NaN$_3$, ICl CH$_3$CN, 24h	 **11**	52%	 **12**	81% ($Z:E = 8:7$)[b]
2	 **13**	(A) NaN$_3$, ICl CH$_3$CN, 24h	 **14**	50%	 **15**	18%[c]
3	 **16**	(B) I$_2$, DMF 2h	 **17**	88%	 **18**	84% ($Z:E = 2:5$)[b]
4	 **19**	(B) I$_2$, DMF 2.5h	 **20**	85%	 **21**	81% ($Z:E = 5:4$)[b]
5	 **22**	(C) I$_2$, CH$_3$CN 40 min	 **23** R = H **24** R = *t*-Boc	90%	 **25**	89% ($Z:E = 11:1$)[b]
6	 **26**	(C) I$_2$, CH$_3$CN 40 min	 **27** R = H **28** R = *t*-Boc	95%	—	

a. Isolated yield. b. The structures of *Z* and *E* isomers were determined by NOE experiments. The ratios were determined by ^{1}H NMR integration. c. By slow addition of tributyltin hydride, there was still a 51% yield of reduction product formed.

tributyltin hydride to give **31** in excellent yield presumably via a β-enone radical cyclization.

In conclusion, we have described an efficient intramolecular cyclization reaction of enone radicals. This method is complementary to the palladium-catalyzed coupling reaction of vinyl halides[11] and provides a new entry to the carbo- and heterobicyclic enones. These enones, which are otherwise difficult to prepare, can serve as important intermediates for natural products synthesis. The applications of these bicyclic enones to the total syntheses of natural products are currently under investigation in our laboratories.

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References and Notes

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