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Radical-Induced Epoxide Fragmentation Chemistry, V. Formation of Medium-Sized Rings via β-Scission of Alkoxy Radicals

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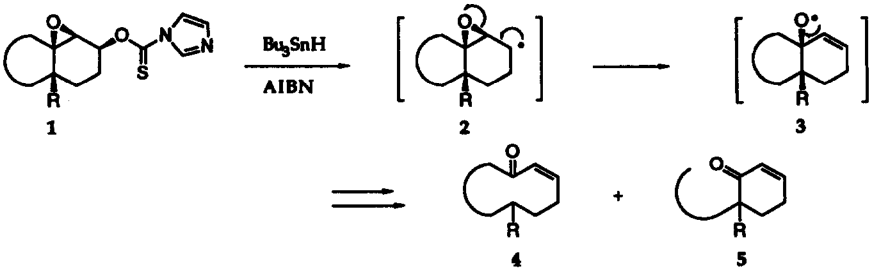
Abstract: Functionalized medium-sized rings can be prepared from simple Robinson annulation derived precursors having a suitably placed stabilizing group. The key step is a radical-induced epoxide fragmentation reaction followed by β-scission of the resulting alkoxy radical.

The prevalence of complex natural products with a medium ring carbon backbone,[1] such as the potent sex attractant and sex excitant pheromone of the American cockroach, periplanone B,[2] has spawned the development of new strategies to such ring systems. It has long been recognized that medium-sized rings can be formed through the β-scission of bridgehead alkoxy radicals, which can be generated by various, novel methods.[3-5] Indeed, several synthetically useful ring expansions have been developed that rely on the β-scission of an alkoxy radical as a key step.[6] Mcdonald has shown that presence of an olefin in the bicyclic precursor can significantly influence the outcome of β-scission reactions.[7] For example, the β-scission of the olefin containing decalinoxy radical (e.g., 3, R = Me), generated via the hypohalite, gives the corresponding cyclohexenone (e.g., 5) in high yield, with none of the medium ring product. By contrast, fragmentation of the saturated compound under kinetic conditions gives the medium ring product.[7,6a]

Our interest in the radical-induced epoxide fragmentation,[8] which can provide ready access to allyloxy radicals such as 3 (Scheme I), prompted us to examine the β-scission of several olefin containing bicycles. Based on previous work in this area,[6] we expected to be able to promote scission of the central bond by appropriate placement of a radical stabilizing group on the bicyclic precursor.[6] We describe here the outcome of the epoxide fragmentation/β-scission of several bicyclic compounds, all of which are easily available from Robinson annulation derived precursors.[9] We have found that this process can provide access to functionalized ten membered ring compounds. Moreover, the conditions for the epoxide fragmentation can be selected to favor formation of either a medium ring, a hydrazulene, or the simple epoxide fragmentation-reduction product.

Scheme I

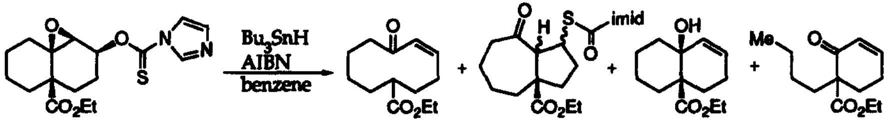


An important advantage of the present strategy is that the required precursors are easily prepared in three steps and in good yield from Robinson annulation derived enones. Reduction of the enones under the Luche conditions[10] afforded in quantitative yield a mixture of the α and β-allylic alcohols, favoring the latter (2.2:1 to >10:1). After epoxidation the hydroxyl group was converted to the thionoimidazolide under standard conditions and in high overall yield.[8a] At this stage the major diastereomer was easily separated by chromatography and used to test the fragmentation step.

We have carried out extensive studies on the epoxide fragmentation/β-scission chemistry of the carboethoxy substituted substrate **1a**. The results, summarized in Table I, show that the outcome of the fragmentation can be altered dramatically by varying the reaction conditions. When tin hydride and AIBN were added in one portion to a solution of **1a** and the resulting solution heated to reflux (Entry 1), a fast reaction occurred to afford the desired medium-ring enone **4a** in good yield.[11,13] Also formed during the reaction were thioimidazolide containing hydroazulene **6a** and allylic alcohol **7a**. The former, which is formed as a single diastereomer, presumably arises from a transannular cyclization of the intermediate stabilized radical followed by trapping of the resulting radical by **1a**, thereby continuing the radical chain.[12,14] The medium-ring product formed even more cleanly when AIBN and tin hydride were added over 3h and the reaction conducted at a lower temperature (Entry 2). Furthermore, at room temperature none of the the hydroazulene product was observed.

The transannular cyclization onto the *cis*-enone evidently requires higher temperature and is maximized by decreasing the available hydride source (Entry 4). Indeed, when the fragmentation was initiated under photochemical conditions, in the absence of tin hydride, a clean reaction took place to give hydroazulene **6a** as the sole isolable product. Further refinement of the reaction conditions allowed us to minimize the β-scission and increase the amount of allylic alcohol **7a**. Thus at room temperature and under an excess of the hydrogen source **7a** was formed as the major product in good yield. It should be noted that in contrast to previous reports on olefin containing substrates, the ester substituted substrate gave none of the alternate β-scission product, **5a**.[7]

Table I — Tin Hydride Induced Epoxide Fragmentation/Alkoxy Radical β-Scission of 1a

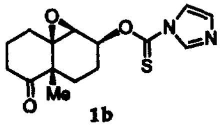
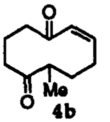
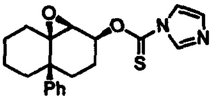
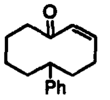
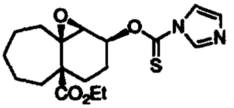
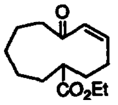
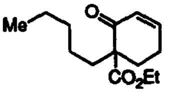
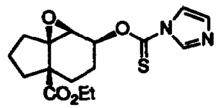
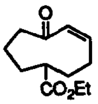
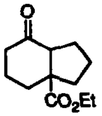
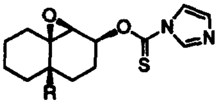
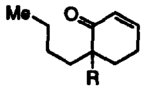
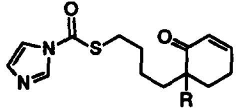


1a **4a** **6a** **7a** **5a**

Entry	Conditions, Bu$_3$SnH (1.2 eq) AIBN (0.1 eq) Addn Method	Final Conc	Temp	Total Rxn Time	Isolated Yields (%) 4a	6a	7a	5a
1	one portion addition	0.02M	reflux	5 min	59	9	14	—
2	syringe pump, 3h	0.02M	60 °C	6 h	69	5	10	—
3	syringe pump, 3h	0.02M	rt	15 h	64	—	20	—
4	syringe pump, 12h	0.02M	reflux	12 h	48	42	5	—
5	sun lamp, no Bu$_3$SnH/AIBN	0.02M	reflux	6 h	—	50	—	—
6	(Bu$_3$Sn)$_2$, AIBN, one portion sun lamp	0.05M	reflux	10 h	—	59	—	—
7	Bu$_3$SnH(5 eq), AIBN (0.1 eq)	0.02M	rt	15 h	18	—	56	—

In an effort to better understand the scope and usefulness of this process, we have examined the epoxide fragmentation/β-scission chemistry of several related substrates (Table II). The first entry shows that cleavage of the central C-C bond is also promoted by a carbonyl in the adjacent ring. The product of this reaction is relatively well functionalized, containing differentiated carbonyls. The next entry shows that besides the two traditional electron withdrawing groups shown so far, an aryl group can also favor the desired β-scission. The fragmentation of the ester substituted substrate **1d** gave the expected eleven membered ring product, albeit accompanied by a considerable amount of the alternate β-scission product **5d**. Scission of the central bond is again the major path for **1e**. The yield of the nine membered ring product is low as the intermediate radical readily undergoes a transannular addition to afford the hydrindane product (Entry 4). In agreement with Macdonald's hypohalite mediated fragmentations, scission of the central bond does not take place in the absence of a good radical stabilizing group (Entries 6 and 7).[7] Overall, these results show that simple, Robinson annulation-derived precursors can be transformed into functionalized medium sized rings by way of the radical induced epoxide fragmentation/β-scission.

Table II— Epoxide Fragmentation/Alkoxy Radical β-Scission of Related Substrates

Entry	Substrate	Reaction Conditions	Products (isolated yield)
1	**1a**	A	**4a** (69%) **6a** (5%) **7a** (10%)
2	 **1b**	A	 **4b** 60%
3	 **1c**	A	 **4c** 46%
4	 **1d**	A	 **4d** 35%  **5d** 25%
5	 **1e**	A	 **4e** —  44%
		B	14% **6e** 43%
6	 **1f** R = H	A	 **5f** 44% 
7	**1g** R = Me	A	**5g** 44% **6g** 27%

A: 0.02M soln, 60°C, 3h addn of 1.2eq Bu_3SnH/0.1eq AIBN by syringe pump and upto 10h additional reaction time.
B: 0.02M soln, reflux, fast addition of 1.2eq Bu_3SnH/0.1eq AIBN and 1h additional reaction time.

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