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Radical cyclizations of 2-(ω-haloalkylthio)enones to thiapolycycloalkanones

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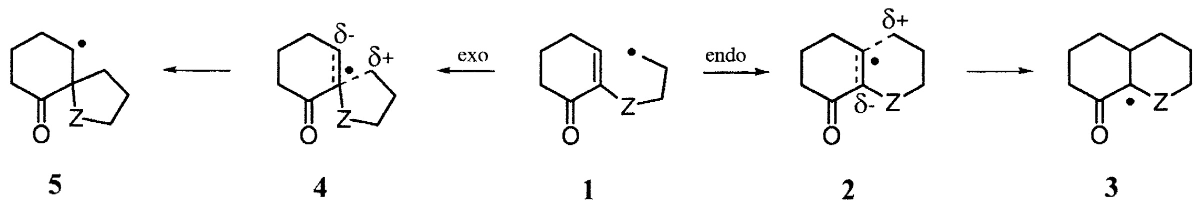
Abstract

Radical cyclization of 2-(ω-haloalkylthio)enones gives predominantly *fused*-thiapolycycloalkanones. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: heterocyclic compounds; polyheterocyclic compounds; sulfur heterocycles; radicals and radical reactions; cyclization; enones; α-sulfenyl ketones.

We have previously prepared oxapolycycloalkanones via cyclization of radicals (e.g., **1**, Z=O) generated from diosphenol ω-haloalkyl ethers.[1] We decided to examine radical cyclization of analogous sulfur-tethered systems for several reasons. First, due to the high nucleophilicity of thiols and thiolates, the cyclization substrates can be prepared efficiently from a variety of precursors.[2] Second, thiacycloalkanones,[3] the expected products, are of interest in mechanistic and conformational analysis studies,[4] and should be useful in the preparation of heterocyclic analogues of physiologically-active substances.[5–7] Third, mechanistic considerations suggested that, since sulfur stabilizes adjacent radical centers more than oxygen,[8] replacement of oxygen by sulfur would result in a greater preference for fused products. Polarized[9] transition state **2** is strongly influenced by Z; polarized[9] transition state **4** is less strongly influenced by Z, since Z is one atom further removed from the developing radical center (Scheme 1).



Scheme 1.

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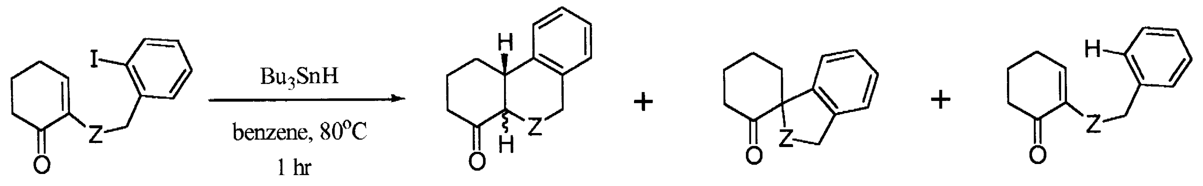
The experiments described below suggest that this hypothesis is correct. For example, when **6s**[2,10] was subjected to the same cyclization conditions as **6o**, the exclusive product was the *trans*-fused **7s** (Scheme 2).[11]



6o, Z=O
6s, Z=S

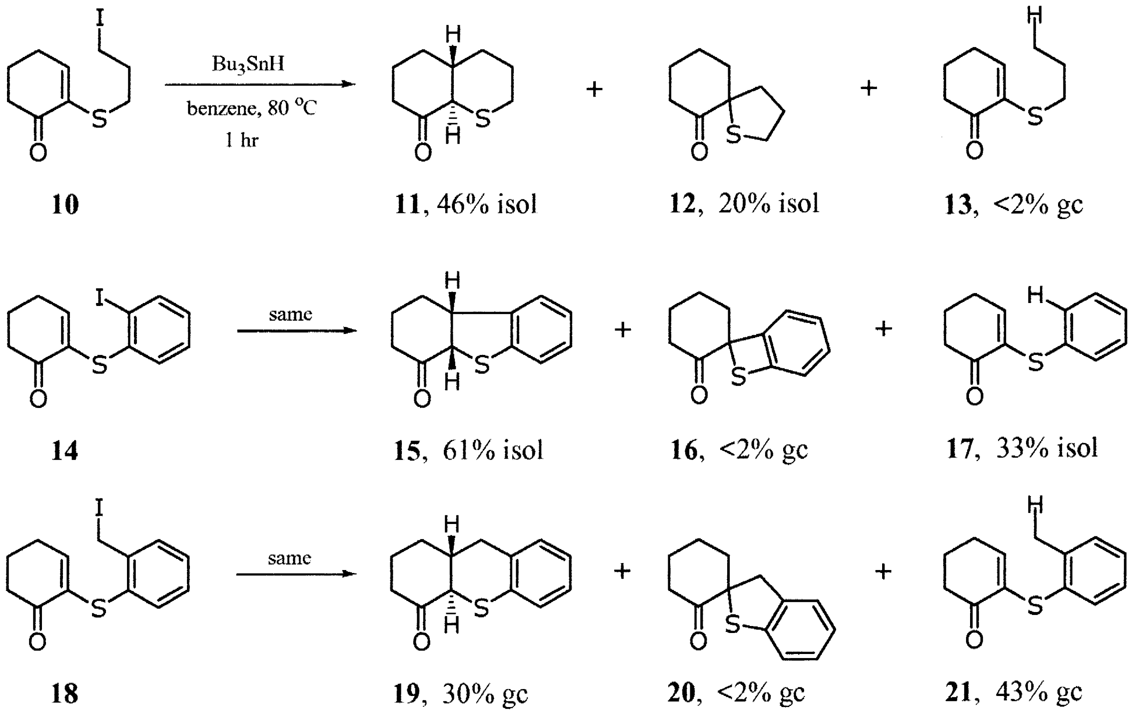
7o, 38% (*trans*/*cis* = 5:1)
7s, 80% (all *trans*)

8o, 24%
8s, <2%

9o, 15%
9s, <2%

Scheme 2.

Results with three other systems are presented in Scheme 3 (yields by isolation or gas chromatography).[12]



10 — **11**, 46% isol — **12**, 20% isol — **13**, <2% gc

14 — **15**, 61% isol — **16**, <2% gc — **17**, 33% isol

18 — **19**, 30% gc — **20**, <2% gc — **21**, 43% gc

Scheme 3.

It is notable that for each thia-substrate there is more fused product than in the oxa-series and, with the exception of **14**, less uncyclized (reduced) product.[13] The increased amount of 5-*endo* cyclization in **14** (compared to its oxa analogue) can also be attributed to the longer C–S bond length.[14] As previously noted,[1] aryl radicals (cf. **6s**) cyclize well, whereas benzyl radicals (cf. **18**) cyclize poorly.

Application of transformations typical of α-sulfenylketones[15] leads to further possibilities. For example, Raney nickel desulfurization of **11** and **12** gives 3-propylcyclohexanone **22** and 2-propylcyclohexanone **23**, respectively, thereby providing a method to distinguish *fused*- from *spiro*-cyclization (Scheme 4).

11 **22** **12** **23**

Scheme 4.

Reductive alkylation or sulfur-directed regioselective enolate formation followed by alkylation are other attractive sequences.[16] We are continuing to explore the synthetic possibilities of these cyclizations.

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10. All new compounds were fully characterized: 60 MHz ^{1}H NMR ($CDCl_3$) and IR (film) data are presented below. Compound **6s**: NMR δ 1.7–2.7 (m, 6H), 3.98 (s, 2H), 6.79 (t, J=4.5 Hz, 1H), 6.9–8.0 (m, 4H); IR 1678, 1589, 1245, 1160 cm^{-1}. Compound **7s**: NMR δ 1.4–3.1 (m, 7H), 3.46 (d, J=12 Hz, 1H), 3.68 (s, 2H), 6.9–7.5 (m, 4H); IR 1715, 1654, 1541, 1489, 1456 cm^{-1}. Compound **10**: NMR δ 1.7–3.0 (m, 10H), 3.27 (t, J=6.5 Hz, 2H), 6.80 (t, J=4.5 Hz, 1H); IR 1677, 1589, 1210, 1125 cm^{-1}. Compound **11**: NMR δ 1.1–2.1 (m, 9H), 2.1–2.6 (m, 4H), 3.19 (d, J=9 Hz, 1H); IR (KBr) 1699, 1454, 1318, 1122 cm^{-1}. Compound **14**: NMR δ 1.8–2.8, (m, 6H), 6.63 (t, J=4.5 Hz, 1H), 6.9–7.9 (m, 4H); IR 1680, 1590, 1421, 1330, 1125, 1007 cm^{-1}. Compound **15**: NMR δ 1.6–2.7 (m, 6H), 3.4–4.0 (m, 1H), 4.27 (d, J=7, 1H), 6.7–7.4 (m, 4H); IR 1708, 1665, 1446, 1233 cm^{-1}. Compound **17**: NMR δ 1.6–2.7 (m, 6H), 6.53 (t, J=4.5 Hz, 1H), 7.1–7.6 (m, 4H); IR 1676, 1592, 1440, 1346, 1262, 750 cm^{-1}. Compound **18**: NMR δ 1.7–2.8 (m, 6H), 4.63 (s, 2H), 6.28 (t, J=4.5 Hz, 1H) 6.9–7.5 (m, 4H);

IR 1674, 1593, 1234, 1159 cm^{-1}. Compound **19**: NMR (90 MHz) δ 1.4–3.0 (m, 9H), 3.96, (d, *J*=12 Hz, 1H), 6.9–7.3 (m, 4H); IR 1704, 1567, 1474, 1436, 1417 cm^{-1}. Compound **21**: NMR δ 1.6–2.7, (m, 6H), 2.36 (s, 3H), 6.12 (t, *J*=4.5, 1H), 6.9–7.5 (m, 4H); IR 1676, 1590, 1470, 1329 cm^{-1}.

11. Only the *trans*-fused **7s** could be detected. In analogy with **7o**, it is presumed that both *cis* and *trans* are initially formed and that *cis* isomerizes to *trans* under the reaction and/or workup conditions.
12. Typical experimental procedure: a 0.407 g (1.4 mmol) portion of tributyltin hydride was added all at once under nitrogen to a magnetically stirred solution of 0.330 g (1 mmol) of **14** and 0.01 g azobisisobutyronitrile in 5 mL dry benzene. The mixture was heated at reflux for 1 h, then solvent was removed under vacuum. The residue was dissolved in 10 mL of ether and stirred with 10 mL of 10% aq. potassium fluoride solution for 30 min. The white precipitate (presumably tributyltin fluoride) was separated by filtration and the aqueous phase extracted with 10 mL of ether. The combined ether extracts were washed with brine, dried over anhyd. magnesium sulfate, and evaporated, giving 0.325 g residue. This residue was dissolved in a minimum amount of chloroform and chromatographed on 40 g silica gel (Davisil grade 643, 200–425 mesh) packed in benzene:ethyl acetate (19:1) giving 0.125 g (61%) of **15**[10] followed by 0.067 g (33%) of **17**.[2,10] In a parallel experiment, the crude reaction mixture was desulfurized with Raney nickel in ethanol, giving 3-phenylcyclohexanone but no 2-phenylcyclohexanone, thus establishing the absence of **16**.
13. Reactions were typically conducted with substrate concentrations of 0.2 M. It is likely that greater dilution would diminish the amount of uncyclized (reduced) product.
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