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FREE RADICAL RING-EXPANSION LEADING TO NOVEL SIX- AND SEVEN-MEMBERED HETEROCYCLES

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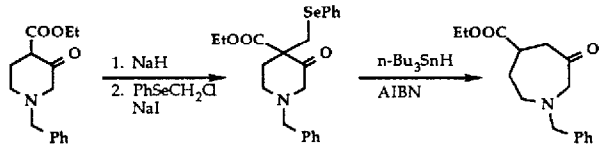
Summary: Free radical ring-expansion of a variety of heterocycles is described.

The regioselective, free radical ring-expansion of β-keto esters[1,2,3] has broad potential applicability in organic synthesis.[4] The synthetic utility of the ring-expansion reaction will be further enhanced by the inclusion of heterocyclic compounds[5] in the ring-expansion process.

Thus, a convenient synthetic sequence is illustrated by the one-carbon ring-expansion of the six-membered, ethyl 1-benzyl-3-oxo-4-piperidinecarboxylate (**1**) to the seven-membered azepine derivative **3** (eq 1). Alkylation of **1** with chloromethyl phenyl selenide[6] and sodium

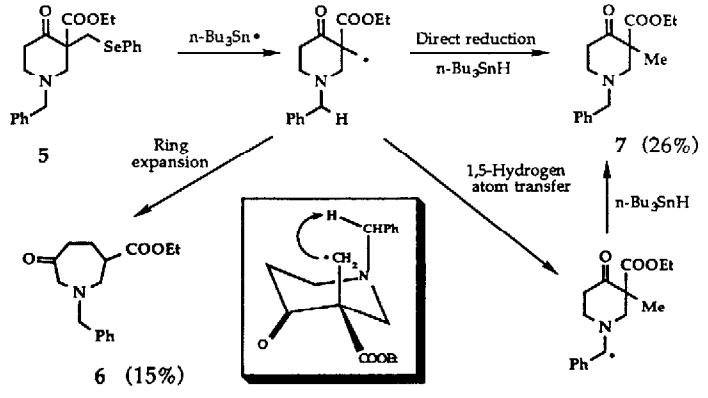


(1)

1 **2** **3**

hydride in the presence of sodium iodide in refluxing tetrahydrofuran yielded the phenylseleno adduct **2** (18%). Tri-*n*-butyltin hydride reduction of **2** in refluxing benzene, containing a catalytic amount of AIBN, led to smooth rearrangement to the ring expanded product **3** (71% isolated yield).

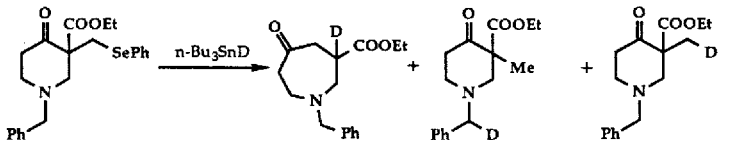
By contrast, when ring expansion of **5** was attempted, the direct reduction product **7** predominated over the rearranged product **6** by a 2:1 ratio (Scheme 1; see also Table 1, entry a). The



Scheme 1

ratio of **6** to **7** does not depend on the tin hydride concentration nor does the ratio change upon ten-fold dilution of the reactants. Thus, the reduction probably involves intramolecular 1,5-hydrogen atom transfer[7] (Scheme 1, Inset) in competition with bimolecular hydrogen atom transfer from n-Bu_3SnH.

When **5** was treated with tri-*n*-butyltin deuteride, the ring-expansion product **6-d$_1$** was



(2)

5 **6-d$_1$** **7-d$_1$** **7'-d$_1$**

obtained in 17 % yield together with reduction products **7-d$_1$** and **7'-d$_1$** (33%) in a ratio of 3:7 (eq 2). The location of deuterium in the products was established by NMR and mass spectrometry. The observation of reduction product **7-d$_1$**, with deuterium at the benzylic carbon establishes the occurrence of 1,5-hydrogen atom transfer during the reaction of **5** with tin hydride. This undesired reduction process can be suppressed by replacing the benzyl group in **5** with the triphenylmethyl group, shown by a comparison of entries **a** and **b** in Table 1.

Six-membered, sulfur- and oxygen-containing β-keto esters **12**[8] and **16**[9] undergo regioselective ring-expansion to the seven-membered thiepane and oxepane derivatives **14** and **18** in good yield (Table 1, entries **c** and **d**). Functionalized heterocycles such as **3**, **6**, **10**, **14**, and **18**

Table 1. Free Radical Ring-Expansion of Heterocyclic β-Keto Esters (% Isolated Yield)

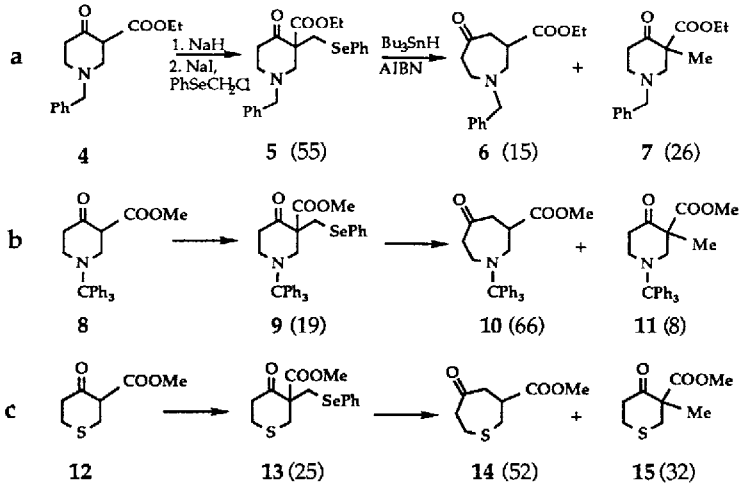
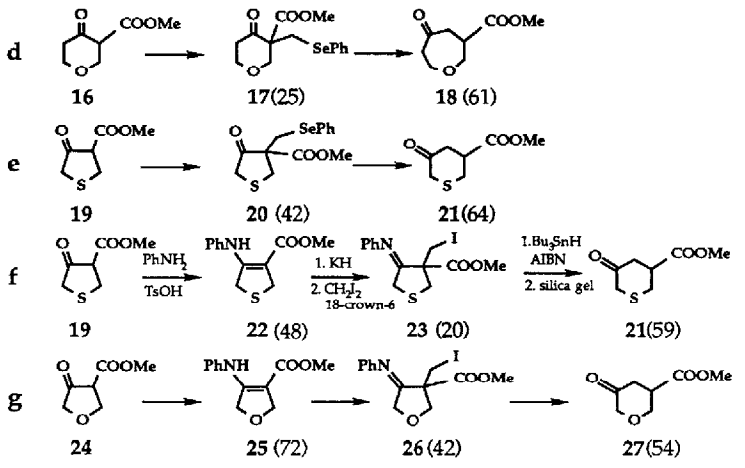


Table 1 (continued)

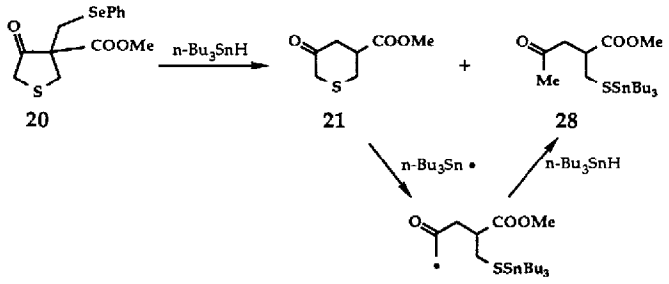


*All new substances had satisfactory NMR, IR, and mass spectra including exact mass determination.

in the azepine, oxepane, and thiepane series are not easily prepared by other means.[5]

The five-membered β-keto ester **19**[10] and the enamines **22** and **25**[11] rearrange readily to the novel, six-membered heterocyclic compounds **21** and **27** (Table 1, entries **e**, **f** and **g**). The five-membered heterocyclic compounds rearrange more easily than their six-membered ring counterparts as judged by the negligible amount of direct reduction products formed.[1]

The open-chain product **28** was obtained in 39% yield together with the ring-expansion



Scheme 2

product **21** (17 % yield) when **20** was treated with 2.0 equiv of n-Bu_3SnH (Scheme 2). The reduction product **28** apparently arises from attack of excess tin radical on the sulfur atom of the rearranged product **21** followed by tin hydride reduction of the resulting stabilized radical adjacent to the carbonyl group. The formation of **28** was completely suppressed by using 1.1 equiv of tin hydride (Table 1, entry **e**).

The free radical ring-expansion reaction has been extended to oxygen-, nitrogen-, and sulfur-containing heterocyclic β–keto esters. The sequential alkylation and ring-expansion of

heterocyclic β-keto esters, readily available by Dieckmann condensation, provides a rapid and efficient route to new and unusual heterocyclic compounds.

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(5) For the pertinent reviews and references see: Smalley, R. K. In *Comprehensive Heterocyclic Chemistry*; W. Lwowski, Ed.; Pergamon: Oxford, 1984; Vol. 7, pp 491-546. D. R. Boyd, *Ibid*, Vol. 7; pp 547-592. Hassenrück, K.; Martin, H. D. *Synthesis* **1988**, 569.

(6) For the preparation of this reagent see: Beckwith, A. L. J.; Pigou, P. R. *Aust. J. Chem.* **1986**, *39*, 77.

(7) For a recent interesting example see: Curran, D. P; Kim, D.;Liu, H. T.; Shen, W. *J. Am. Chem. Soc.* **1988**, *110*, 5900, and references on hydrogen atom transfer in free radical reactions cited therein.

(8) β–Keto ester **12** was prepared by one-pot reaction of methyl 3-mercaptopropionate with methyl acrylate and sodium hydride in dimethylsulfoxide by a modification of the procedure of Flavin, M. T.; Lu, M. C. *Tetrahedron Lett.* **1983**, *24*, 2335.

(9) Condensation of terahydro-4*H*-pyran-4-one with dimethyl carbonate in the presence of sodium hydride and a catalytic amount of potassium hydride in refluxing benzene provided **16**.

(10) Compound **19** was prepared by piperidine catalyzed Michael addition of methyl thioglycolate to methyl acrylate, followed by Dieckmann cyclization of the resulting adducts according to the procedure of Woodward, R. B.; Eastman, R. H. *J. Am. Chem. Soc.* **1946**, *68*, 2229.

(11) Following the procedure of reference 8, condensation of methyl glycolate and methyl acrylate afforded **24**, the precursor of enamine **25**.

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