

Hexenyl Radical Cyclization *via* Phenyl Selenide Transfer

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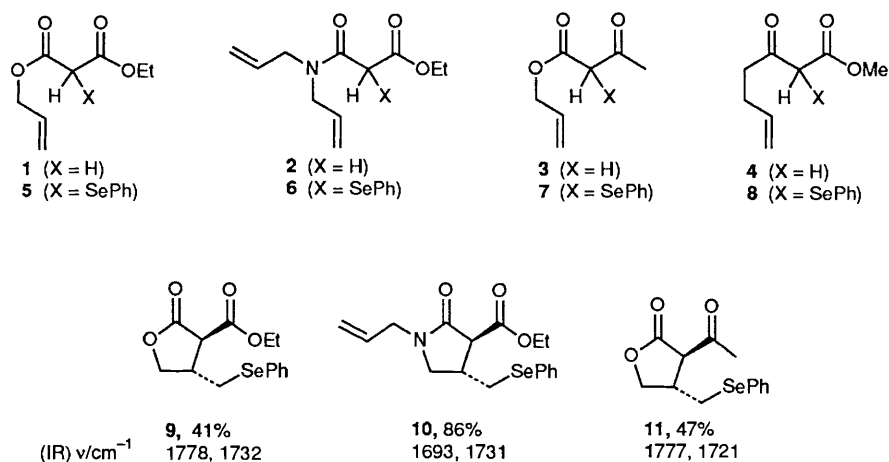
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Several 2-phenylseleno-1,3-dicarbonyl compounds have been shown to undergo radical cyclization accompanied by phenyl selenide transfer upon photolysis.

In a recent article we described the free-radical addition of diethyl 2-(phenylseleno)propanedioate to alkenes.¹ The novel mechanistic feature of this reaction involved the first example of phenyl selenide transfer in a carbon-carbon bond forming radical reaction. We now describe an analogous process in which the synthetically important hexenyl radical cyclization² is accompanied by phenyl selenide transfer, leading to highly functionalized heterocycles and carbocycles.

The dicarbonyls **1-4**[†] were routinely converted to the corresponding phenyl selenides **5-8** upon addition of NaH

[†] Precursors **1** and **2** were prepared upon reaction of ethyl malonyl chloride (Aldrich) with allyl alcohol and diallylanine respectively. Allyl acetoacetate **3** is commercially available (Aldrich), and keto-ester **4** can be prepared by reaction of the dianion of methyl acetoacetate with allyl bromide, as described in ref. 3.

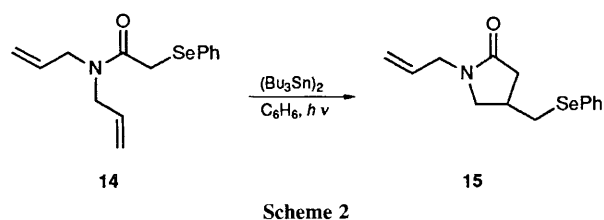
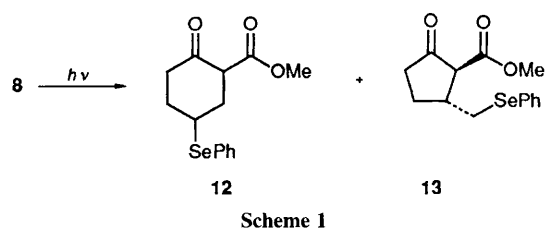


followed by quenching of the resulting anion with phenylselenenyl chloride or *N*-(phenylseleno)phthalimide at -20°C .⁴ It is interesting to note that there appear to be no literature references to radical cyclizations of β -dicarbonyl compounds of this type, in which the carbonyl groups are situated such that one of them will be endocyclic after cyclization, other than metal ion-promoted cyclizations in which the intermediacy of radicals is not known with certainty.⁵

We have found that phenyl selenides **5–7** will undergo cyclization upon photolysis to generate products **9–11** in the yields shown, arising from 5-*exo* cyclization accompanied by phenyl selenide transfer. Typical reaction conditions are as follows. A solution of the selenide (1 mmol) in freshly distilled benzene (2 ml) was degassed with bubbling Ar for 15 min, and was then irradiated overnight with a 250 W sunlamp. Products were purified by flash chromatography or medium pressure liquid chromatography and were characterized by IR and ^1H and ^{13}C NMR spectroscopy, and combustion analysis.

The carbonyl stretching frequencies in the IR spectrum proved to be a valuable probe of ring size⁶ in these cyclized products. These compounds all showed the carbonyl stretching absorptions at higher wavenumbers characteristic of carbonyls in five-membered rings. We are proposing the *trans*-stereochemistry, as shown, for several reasons. The $\text{Mn}(\text{OAc})_3$ promoted cyclization of compounds similar to **4**, which may proceed through radical intermediates, has been shown to generate primarily the *trans*-product.^{5a} *trans*-2-Ethoxycarbonyl-3-methylbutanolide and closely related compounds have been shown to have coupling constants of 7–8 Hz between the ring methine protons.⁷ Similar coupling constants of 9.4, 6.9 and 7.9 Hz, were obtained for the ring methine protons in the cyclized products **9–11**, respectively. These reactions showed an exceptional degree of regioselectivity and stereoselectivity. Analysis of the crude reaction mixtures by GC-MS failed to indicate any significant amounts (less than 1% in these examples) of any other isomeric products. While one could envisage the formation of six-membered ring products arising from 6-*endo* cyclization, as well as *cis*-disubstituted 5-membered ring products, they were not identified or isolated. Most of the byproducts appeared to be very polar, with only minor quantities of unidentified, but non-isomeric, chromatographable products. It is also important to note that radical cyclizations of unconstrained esters such as **5** and **7** are quite rare, owing to the large barrier to rotation about the CO–O bond which inhibits the formation of the proper conformer for cyclization.⁸

The cyclization of the ketoester **8** (Scheme 1), yielded a more complex product mixture. Photolysis of **8** generated a 60% yield of the cyclohexanone **12** and a 20% yield of the cyclopentanone **13** (ring methine coupling of 6 Hz). Cyclized



ketoester **13** showed the expected carbonyl stretching frequencies at 1755 and 1729 cm^{-1} . Owing to the high degree of enolization in **12**, as indicated by an NMR signal at δ 12.1 and a complex carbonyl stretching region, the IR spectrum could not be used with confidence to gauge ring size. However, upon saponification and decarboxylation⁹ of **12**, a 61% yield of 4-phenylselenocyclohexanone, which possessed a normal cyclohexanone stretching frequency at 1713 cm^{-1} was obtained, thus proving that **12** did indeed possess a 6-membered ring. This is in contrast to the metal ion-promoted cyclization of similar ketoesters, which generated primarily 5-membered ring products.⁵

The conversion of **8** to **12** has previously been performed under conditions involving Lewis acid catalysis, presumably *via* an ionic mechanism.⁴ Therefore, the cyclization of **8** was attempted by simply refluxing **8** in benzene solution with exclusion of light. As expected, no reaction occurred, thus proving that the reaction is indeed photo-initiated, and providing further evidence for the proposed radical process.

In contrast to the iodine-transfer radical cyclizations,¹⁰ these cyclizations of 2-phenylseleno-1,3-dicarbonyl compounds do not necessarily require addition of a catalytic portion of a hexaalkylditin. This is because they seem to proceed well only when the initially formed radical is stabilized by two adjacent carbonyl groups, thus decreasing the need for additional initiator. However, when the cyclization of amide **14** was attempted (Scheme 2), only a 7% yield of cyclized product **15** was obtained. In order to achieve any cyclization it was necessary in this case to add hexabutyltin as catalyst and photolyse for 24 h with a 450 W Hanovia lamp.

When the cyclization of **8** was attempted in the presence of hexabutylditin as catalyst, the reaction proceeded more quickly than in its absence, but the isolated chemical yield of cyclized products dropped significantly, to 20–30%. Some of this product loss may have occurred during the more elaborate workup procedures used to remove stannane byproducts.¹¹

The results obtained from the radical cyclization of **8** also bring up the interesting question as to whether the cyclohexanone **12** was arising *via* thermodynamic or kinetic control. Julia¹² has reported that certain well stabilized hexenyl radicals, generated by hydrogen abstraction, are capable of undergoing reversible cyclization, leading to significant quantities of the 6-*endo* cyclohexyl product. In these examples, the regiochemistry of ring closure was shown to be the result of the stabilization available to the initially formed carbon-centred radical. Curran,^{10d} on the other hand, has shown that the product arising from 6-*endo* cyclization of iodomalones, when accompanied by iodine transfer, is formed for kinetic reasons.

If the formation of cyclohexanone **12** was the result of equilibrating cyclized intermediates, the radicals generated from ketoesters **7** and **8** would be expected to cyclize with similar regioselectivities. This clearly was not the case. Additionally, we were unable to interconvert **12** and **13** upon photolysis of the purified isomers, even upon the addition of hexabutylditin as catalyst. Thus we feel that the regiochemistry of the products arising from the photolysis of **8** was the result of kinetically controlled cyclization, not a thermodynamically controlled reversible cyclization.

We feel that radical cyclizations accompanied by phenyl selenide transfer present a promising and potentially versatile approach to the formation of cyclic compounds possessing a wide variety of functionality.

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