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Tandem homolytic addition/substitution sequences and their application to tin-free radical chemistry

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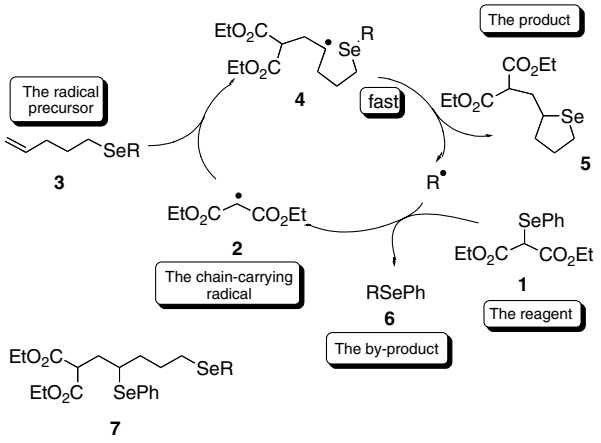
Abstract—Alkyl pent-4-enyl selenides (**3a**, **b**, **e** and **f**), pent-4-enylseleno benzoate (**3c**) and phenyl (pent-4-enylseleno)formate (**3d**) act as precursors of alkyl, acyl and oxyacyl radicals by reaction with diethyl 2-phenylselenomalonate (**1**) under photochemical conditions in a process involving tandem homolytic addition/substitution to afford tetrahydroselenophenes (**5**, **11**) and the corresponding phenylselenides (**6**).

There is a desire to remove stannane-based reagents from the chemical armoury available to the synthetic chemist because these reagents and reaction byproducts are toxic[1] and are not readily removed from reaction mixtures by chromatographic techniques.[2,3] The reader is referred to an excellent recent review by Walton in which the 'tyranny of tin' is discussed in some detail.[3] Stannanes, however, possess several features which are desirable from the viewpoint of the free-radical chemist; these include the ability to sustain chain reactions due to well-matched rate constants for the transfer of a hydrogen atom to alkyl and other radicals,[3] and for the reaction of the ensuing stannyl radical with a wide variety of radical precursors.[3]

With our considerable experience in the use of intramolecular homolytic substitution chemistry for the preparation of selenium-containing heterocycles,[4] and with the knowledge that radicals derived from diethyl 2-phenylselenomalonate (**1**) undergo efficient intermolecular addition chemistry,[5] we began to explore the possibility of sustaining the radical chain depicted in Scheme 1. The use of intramolecular homolytic substitution chemistry to trigger the formation of radicals is not new. Crich reported that intramolecular attack of aryl radicals at sulfur can be used to generate acyl radicals;[6] however, since homolytic substitution at sulfur is a relatively slow process,[7] this technique is limited to the use of reactive



Scheme 1.

aryl radicals and substituents on sulfur devoid of abstractable hydrogens. In a preliminary experiment, a solution of pent-4-enyl benzyl selenide (**3a**) (112 mg) and **1** (5 equiv) in benzene (2 mL) was irradiated for 12 h with a 250 W sun lamp at a distance of about 10 cm. To our delight, tetrahydroselenophene **5** was isolated in 88% yield after flash chromatography. This transformation clearly demonstrates the viability of the proposed radical chain (Scheme 1). The success of this tandem homolytic addition/substitution protocol from such simple precursors under stannane-free conditions represents an important new procedure for the preparation of selenium-containing rings and for the generation

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of radicals which may be further manipulated to provide interesting new synthetic targets. To demonstrate the scope of this chemistry, we subjected a range of radical precursors **3** to the reaction conditions listed in Table 1. The yields of **5** ranged from 28% to 88%, while the alkyl phenyl selenide product **6** was isolated in yields of 28–61% after chromatography.[8]

We also examined the synthetic utility of alkynes (**8**) as radical precursors. The data listed in Table 1 demonstrate clearly that **8** is less effective than **3** as a radical precursor.

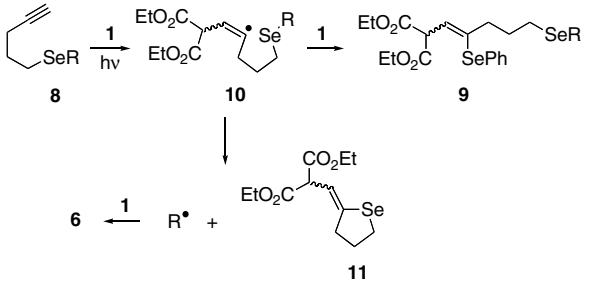
It should be noted that other than the reaction involving **3a**, the remaining precursors failed to react to completion; varying amounts of starting material were always observed by ^{1}H NMR spectroscopy. Increasing the reaction time did not appear to improve the outcome. We speculate that the addition of the diethyl malonyl radical (**2**) to alkene **3** or alkyne **8** is reversible and, as a consequence, the success of the overall transformation relies on the leaving ability of radical (R). When R is a poor leaving group (R = Bu), we observed poorer yields as well as the formation of the trapped (uncyclized) products **7** and **9** (Scheme 2).

Table 1. Yields of products arising from the photolysis of precursors **3** and **8** in the presence of diethyl 2-(phenylseleno)malonate (**1**)

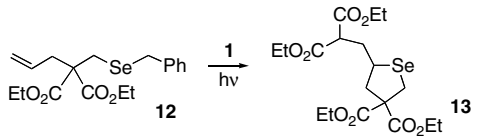
Precursor	Conc. (M)	Solvent	Yield (%)		
			5 or **11**	**6**	**7** or **9**
3a (R = benzyl)	0.18	PhH	88	Nd	—
3b (R = CH_2CO_2Et)	0.18	PhH	74	61	—
3c (R = COPh)	0.18	PhH	55	54	—
3c	0.125	PhMe	80	70[a]	
3d (R = CO_2Ph)	0.18	PhH	32	28	40
3e (R = *iso*-propyl)	0.07	PhH	56[a]	47[a]	11[a]
3f (R = *n*-butyl)	0.18	PhH	—	—	55
3f	0.07	PhH	47[a]	Nd	20[a]
3g (R = Ph)	0.07	PhMe	—	—	46
8a (R = benzyl)	0.18	PhH	60	52	—
8b (R = CH_2CO_2Et)	0.18	PhH	28	36[a]	—
8b	0.07	PhH	39	37[a]	—
8c (R = COPh)	0.18	PhH	51	Nd	—
8c	0.07	PhH	59	Nd	—

Nd = yield not determined.

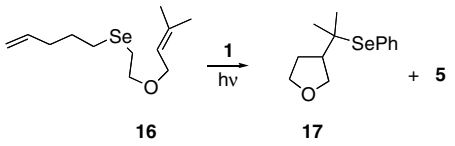
[a] Yield determined by ^{1}H NMR spectroscopy of the crude reaction mixture.



Scheme 2.



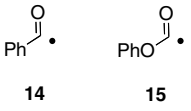
Scheme 3.



Scheme 4.

In an attempt to increase the overall reaction rate, the benzyl selenide **12**, bearing geminyl ester substituents, was prepared and subjected to similar reaction conditions. The cyclized product **13** was isolated in 68% yield after photolysis in toluene (0.125 M) for 5 h (Scheme 3). A similar yield of **5** was obtained from **3a** after 17 h under identical reaction conditions.

It is also interesting to note that precursor **3c** leading to acyl radical **14** afforded the phenylseleno ester **6c** in 54% yield under the conditions described, while precursor **3d** leading to the oxyacy radical **15** afforded the analogous phenylseleno formate **6d** in considerably lower yield. These results suggest that despite obvious structural similarities, the oxyacyl radical **15** is less stable than the analogous acyl radical **14**. These observations are consistent with our previous report[9] that (phenyltelluro)formates are more stable than (phenyltelluro)esters and are supported by ab initio calculations.[10]



Finally, we examined the analogous reaction of precursor **16**. To our delight, when **16** (0.07 M in benzene) was subjected to the previously described reaction conditions, tetrahydrofuran (**17**) was isolated in 69% yield (Scheme 4),[11] demonstrating the synthetic potential of this protocol.

Acknowledgement

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