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A radical cyclization route to pyrrolidines based on conjugate addition to electron deficient phenylselenenylalkenes

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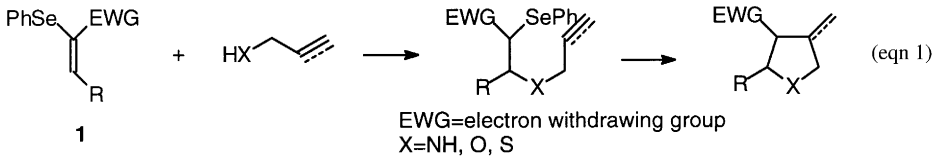
Abstract

α-Phenylselenenyl-α,β-unsaturated esters, amides, ketones, nitriles and sulfones were prepared by zinc chloride promoted chloroselenation/dehydrochlorination of the corresponding α,β-unsaturated compounds. After Michael addition of allyl or propargylamine and triethylborane initiated reductive radical cyclization in the presence of tris(trimethylsilyl)silane, pyrrolidine and dihydropyrrole derivatives, respectively, were obtained.

Keywords: selenium and compounds; radicals and radical reactions; pyrrolidines; addition reactions.

Vinylic selenides can be easily prepared by a variety of methods.[1] Their usefulness in synthesis stems from the ability of the heteroatom to stabilize both negative[2] and positive[3] charges and from the inherent weakness of the carbon–selenium bond. Thus, under the proper reaction conditions, vinylic selenides undergo Michael addition with alkyllithiums whereas sterically hindered bases deprotonate them α to selenium. Under acidic conditions, vinylic selenides are hydrolyzed to carbonyl compounds.[4] Cross-coupling with various organometallic reagents is catalyzed by transition metals.[5] In addition, certain vinylic selenides undergo vinylic substitution[6] and cycloaddition and ene reactions.[7]

Piancatelli and co-workers recently reported the conjugate addition of nucleophiles (alkyllithiums[8] and amines[9]) to α-phenylselenenyl-α,β-unsaturated esters. It occurred to us that a tandem conjugate addition–radical cyclization as shown in eqn 1 could provide a useful entry to a variety of heterocyclic compounds. Vinylic selenides **1** are most conveniently[10] accessed by addition of phenylselenenyl chloride to electron deficient olefins, followed by base-induced dehydrochlorination.[11,12] However, in contrast to



1 (eqn 1)

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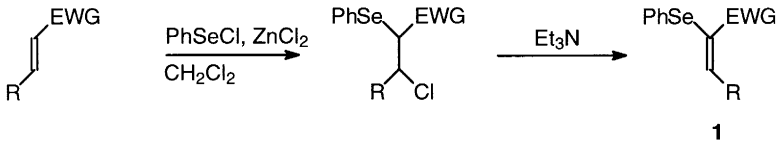
simple alkenes, electron deficient ones react slowly and sometimes incompletely with phenylselenenyl chloride.[13,14] Some time ago, zinc chloride was shown to greatly promote addition of phenylselenenyl chloride to α,β-unsaturated esters.[14] We have found that the binary reagent PhSeCl–$ZnCl_2$ adds essentially instantaneously to a variety of electron deficient olefins (Table 1, eqn 2). After removal of zinc residues, the crude addition product can be treated with triethylamine[12] to obtain good overall yields of a variety of electron deficient phenylselenenylalkenes **1**. For some reason, triethylamine induced reversal of the chloroselenation reaction with the adducts derived from crotonic acid, *N*,*N*-dimethylacrylamide and ethyl cinnamate (Table 1, entries 5, 6 and 12).

Table 1
Preparation of phenylselenenylalkenes **1** from electron deficient olefins by PhSeCl–$ZnCl_2$ addition/dehydrochlorination



(eqn 2)

1

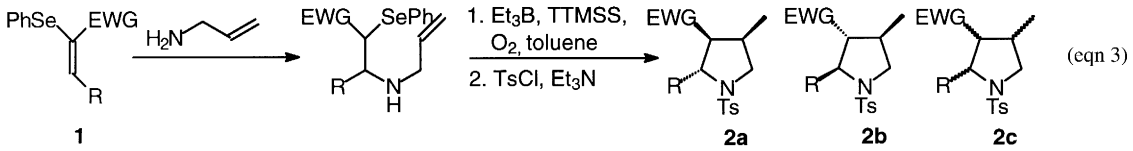
entry	EWG	R	Yield[a] (%)	entry	EWG	R	Yield[a] (%)
1	CO_2Me	H	82	7	CN	H	84
2	$CONH_2$	H	85	8	SO_2Ph	H	86
3	COMe	H	69	9	CO_2Me	(*E*)-CO_2Me[b]	65
4	CHO	H	53	10	CO_2Me	(*E*)-Me[c]	90
5	CO_2H	H	0	11	CO_2Me	Pent[d]	82
6	$CONMe_2$	H	0	12	CO_2Et	(*E*)-Ph	0

[a] Isolated yield after flash chromatography.[b] Assigned as *E* (see ref. 14).[c] Assigned as *E* (see ref. 12). [d] One isomer. Stereochemistry not determined.

Conjugate addition of allylamine to vinylic selenides **1** proceeded best in a neat solution of the amine (Table 2, eqn 3). After 30 min at ambient temperature, ^1H NMR analysis indicated complete consumption of the starting material. In the case of β-substituted compounds, a diastereomeric mixture (ca 3:1) of Michael adducts was obtained and used in the following cyclization reactions. Dimethyl phenylselenenylfumarate and dimethyl phenylselenenylmaleate afforded the same mixture of Michael addition products when treated with allylamine. This shows that the configuration of the vinylic selenide is of little significance in the preparation of the radical precursor. Reductive radical cyclization was conveniently effected in toluene at ambient temperature with triethylborane initiation and tris(trimethylsilyl)silane (TTMSS) serving as the hydrogen atom donor (Table 2, eqn 3). Since chromatographic purification of the pyrrolidines formed was difficult, the crude reaction product was routinely treated with tosyl chloride/triethylamine before isolation. As seen in Table 2, β-unsubstituted vinylic selenides **1** afforded *N*-tosyl-3,4-disubstituted pyrrolidines **2** in fair to good yields as mixtures of *cis*- and *trans*-isomers. Here, it should be noted that epimerization to the thermodynamically favoured *trans*-isomer is possible. Thus, treatment of compound **2a** (Table 2, entry 1) with sodium methoxide in refluxing methanol afforded compound **2b**. The unstable[12] α-phenylselenenylacrolein failed to undergo a clean conjugate addition with allylamine. Unfortunately, the two diastereomers formed in the conjugate addition of allylamine to the β-substituted vinylic selenides could not be separated and cyclized separately. However, in view of the radical stabilizing effect of the electron withdrawing substituent, the radical formed prior to cyclization

is expected to be planar/rapidly inverting. Thus, the diastereoselectivity in the cyclization is probably unrelated to the configuration of the radical precursor.

Table 2
Preparation of *N*-tosylpyrrolidines **2** from vinylic selenides **1** by tandem allylamine conjugate addition–radical cyclization

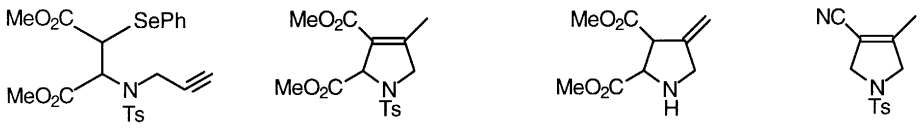


1 **2a** **2b** **2c** (eqn 3)

entry	EWG	R	Yield[a] (%)	Isomeric ratio (**2a/2b/c**)[b]
1	CO_2Me	H	89	40/60/0
2	$CONH_2$	H	47	38/62/0
3	COMe	H	54	43/57/0
4	CN	H	69	40/60/0
5	SO_2Ph	H	36	38/62/0
6	CO_2Me	(*E*)-CO_2Me	83	65/28/7
7	CO_2Me	(*E*)-Me	77	64/33/3
8	CO_2Me	*n*-Pent	68	71/29/0
9	CO_2Et	Ph[c]	73	88/12/0

[a] Isolated overall yield after flash chromatography. [b] Ratio determined from the crude ^1H NMR spectra and stereochemistry from NOE experiments. [c] 1:1 mixture (according to HMBC experiment) of *E* and *Z* isomers prepared by PhSeH addition to ethyl phenylpropiolate (see ref 15).

Michael additions of propargylamine to compounds **1** proceeded as readily as those employing allylamine. However, product yields after radical cyclization/*N*-tosylation were not as good as those obtained with allylamine adducts. Thus, the addition product of propargylamine and dimethyl α-phenylselenenylfumarate (**3**) afforded only a 31% yield of *N*-tosyldihydropyrrole **4**. The initially formed *exo*-methylene pyrrole **5** was clearly the primary product of the reaction (47% yield as determined by ^1H NMR using an internal standard), but it isomerized during *N*-tosylation. Attempts to isolate compound **5** by chromatography or distillation also caused migration of the exocyclic double bond. The addition product of propargylamine and α-phenylselenenylacrylonitrile similarly afforded the dihydropyrrole derivative **6** in 36% yield.



3 **4** **5** **6**

Acknowledgements

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