Synthetic Applications of 2-Phenylselenenyl Enones. Selective Formation of Exocyclic or Endocyclic Enones from a Common Intermediate

Summary: 2-Phenylselenenyl enones are versatile species which can be selectively converted into a number of different ketones and enones (e.g., **5**, **6**, **9**, **10**, or **11**) in high overall yields.

Sir: 2,3-Dialkylated ketone and enone sub-units are present in a broad spectrum of naturally occurring substances. In the past 10 years there has been intense interest in the synthesis of many of these compounds, most notably in the field of prostaglandins.[1] In principle, these compounds are accessible via the conjugate addition of a cuprate to an enone, followed by alkylation of the resulting enolate. In practice, however, the yield of the alkylation step is often quite variable.[2]

Since selenium-stabilized enolates are known to undergo relatively facile alkylation reactions,[3] we felt that the problem of variable yields could be overcome by incorporating a phenylselenenyl group in the 2-position of the enone. Moreover, since the phenylselenenyl group can be removed either reductively or oxidatively, one would have the extra flexibility of generating either the 2,3-dialkylated ketone or a new dialkylated enone from the same intermediate (vide infra).

In this communication we demonstrate the synthetic utility of mono- and dialkylation of 2-phenylselenenyl enones[4] and describe a general method for the selective high-yield conversion of these compounds into a number of different ketones and enones. An illustration of the types of transformations effected is given in Scheme I. Specific results are listed in Table I.

Addition of a cuprate to **1** in ether, followed by quenching with a saturated ammonium chloride solution, results in the high-yield formation of a mixture of *cis*- and *trans*-2-(phenylselenenyl)-3-alkyl ketone. Oxidation/elimination of these variously substituted mixtures (**3** and **4**) proceeds in good yield to their corresponding 3-alkyl enones, **5**, despite the fact that the cis isomer (**3**) is present in substantial amounts in each of the three mixtures given in Table I.[5]

Under the conditions given above, alkylations of enolates **2** with alkyl halides at room temperature completely fail.

Table I

substrate	R	R'	products[d,e] A	% yield	B	% yield	C	% yield
1a	CH_3	H	5a	77				
1a	*n*-Bu	H	5a	94				
1b	CH_3	H	5b	76				
1a	CH_3	CH_3	9a	55	9a	68	9a	4
			11a	14			11a	64
1a	*n*-Bu	CH_3	9a	50	9a	77	9a	<1
			11a	33			11a	74
1b	CH_3	CH_3	9b	51	9b	58	9b	60
			11b	22			11b	14
1a	CH_3	allyl	9a	13			9a	<1
			11a	53			11a	65
1a	CH_3	benzyl	9a	9		56	9a	<1
			11a	53			11a	69

[a] Reaction sequence A: (1) LiR_2Cu, Et_2O, -20 °C; (2) R'X, Et_2O, THF, HMPA, 25 °C or satd NH_4Cl; (3) O_3; (4) Et_2NH, CH_2Cl_2, Δ. [b] Reaction sequence B: (1) LiR_2Cu, Et_2O, -20 °C; (2) R'X, Et_2O, THF, HMPA, 25 °C; (3) O_3; (4) Et_2NH, CH_2Cl_2, Δ; (5) HCl, *n*-BuOH, 90 °C. [c] Reaction sequence C: (1) LiR_2Cu, Et_2O, -20 °C; (2) R'X, Et_2O, THF, HMPA, 25 °C; (3) LiSePh, THF; (4)O_3; (5) Et_2NH, CH_2Cl_2, Δ. [d] Products were identified by analysis of their IR, NMR, and mass spectra and by comparisons with authentic samples. [e] All reported yields are isolated yields.

However, addition of an equal volume of THF and at least 2 molar equiv of hexamethylphosphoramide (HMPA) after the cuprate addition is complete allows for the smooth alkylation of these enolates at room temperature to yield mixtures of **7** and **8**. The oxidation/elimination of these mixtures is complicated by the fact that two different enones, **9** and **11**, can be formed, depending upon the relative availability of a cis β-hydrogen. We have found that the oxidation/elimination of cis-dialkyl compounds like **7** gives predominantly endocyclic enones (**9**). On the other hand, oxidation/elimination of trans-dialkyl compounds like **8** necessarily yields only exocyclic enones (**11**).

On the basis of this, the relative amounts of endocyclic and exocyclic enones produced from mixtures of **7** and **8** are almost totally dependent upon the isomer distribution obtained in the original 2-phenylselenenyl enone dialkylation reaction (**1** → **7** + **8**) (see Table I, reaction sequence A). Since this reaction sequence leads in all cases to mixtures of endocyclic and exocyclic enones, the overall synthetic utility of this procedure in its current form is necessarily limited. Clearly, a more desirable situation would be one in which mixtures of **7** and **8** could be converted selectively to either **9** or **11** without resorting to isomer separations. We describe herein an effective approach for accomplishing this.

Oxidation/elimination of mixtures of **7** and **8**, followed by treatment of the crude enone mixtures with HCl/*n*-BuOH at 90 °C,[8] results in the complete isomerization of the mixture to the thermodynamically more stable endocyclic enones (**9**) in good yields (see Table I, reaction sequence B). While these reaction conditions are clearly not suitable for substrates which are acid sensitive, most of the systems studied are smoothly isomerized under these conditions.

Our approach to the production of **11** in a synthetically viable fashion has focused on isomerizing mixtures of **7** and

(1) Mitra, A. "Prostaglandins"; Wiley-Interscience: New York, 1977.
(2) (a) Davis, R.; Untch, K. G. *J. Org. Chem.* **1979**, *44*, 3755. (b) Boeckman, R. K. *Ibid.* **1973**, *38*, 4450. (c) Posner, G. H.; Sterling, J. J.; Whitten, C. E.; Lentz, C. M.; Brunelle, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 107. (d) Stork, G.; Isobe, M. *Ibid.* **1975**, *97*, 4745. (e) Stork, G.; Isobe, M. *Ibid.* **1975**, *97*, 6260. (f) Stork, G.; d'Angelo, J. *Ibid.* **1974**, *96*, 7114. (g) Han, Y.; Paquette, L. A. *J. Org. Chem.* **1979**, *44*, 3731.
(3) For example, see: Grieco, P. A.; Nishezawa, M.; Oguiri, T.; Burke, S.; Marinovic, N. *J. Am. Chem. Soc.* **1977**, *99*, 5773.
(4) (a) 2-Phenylselenenyl enones are readily synthesized from their corresponding enone via reaction with phenylselenenyl chloride/pyridine. See: Zima, G.; Liotta, D. *Synth. Commun.* **1979**, *9*, 697. For an alternate synthesis, see: Shumizer, M.; Takeda, R.; Kuwajima, I. *Tetrahedron Lett.* **1979**, 3461. (b) For papers dealing with reactions of 2-(phenylthio)-cyclopentenone, see: Monterio, H. J. *J. Org. Chem.* **1977**, *42*, 2324; Kurozumi, S.; Toru, T.; Tanaka, T.; Kobayashi, M.; Miura, S.; Ishimoto, S. *Tetrahedron Lett.* **1976**, 4091.
(5) Since it is well-established that selenoxide eliminations occur in a syn fashion,[6] epimerization at the α-carbon must be occurring prior to or during the elimination reaction.[7] This is significant since both epimers can be simultaneously converted to product without any additional synthetic manipulations.
(6) Sharpless, K. B.; Young, M. W.; Lauer, R. F. *Tetrahedron Lett.* **1973**, 1979.
(7) To our knowledge this important observation has only been mentioned in one other instance in the literature. This involved the oxidation/elimination of 3-phenyl-2-(phenylselenenyl)cyclopentanone for which it was noted that both the cis and trans isomers appeared to give enone. See Scheme II, footnote b, of Reich, H. J.; Renza, J. M.; Reich, I. L. *J. Org. Chem.* **1974**, *39*, 2133.
(8) (a) Caton, M. P. L.; Coffee, E. C. J.; Watkins, G. L. *Tetrahedron Lett.* **1972**, 773. (b) Abdulla, R. F.; Fuhr, K. H. *J. Org. Chem.* **1978**, *43*, 4248. (c) Wakamatsu, T.; Hashimoto, K.; Ogura, M.; Ban, Y. *Synth. Commun.* **1978**, *8*, 319.

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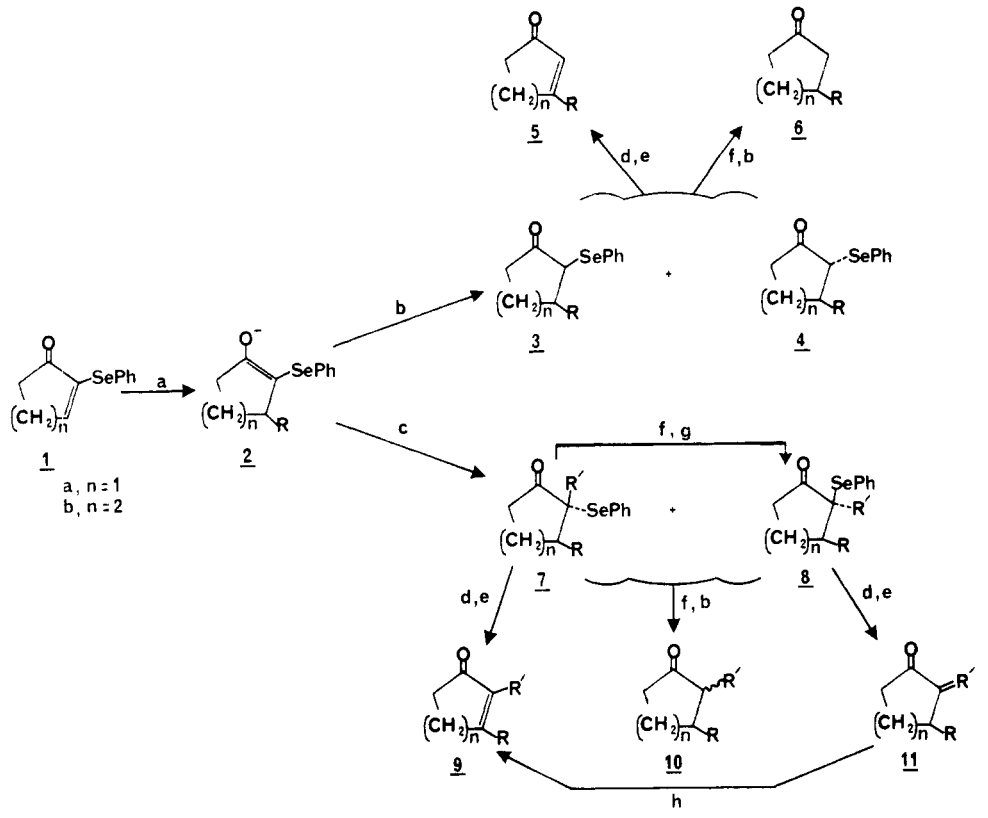
Scheme I[a]



[a] (a) LiR_2Cu, Et_2O, -20 °C; (b) satd NH_4Cl; (c) R'X, Et_2O, THF, HMPA, 25 °C; (d) O_3; (e) Et_2NH, CH_2Cl_2, Δ; (f) LiSePh, THF; (g) PhSeCl; (h) HCl, *n*-BuOH, 90 °C.

8 entirely to 8, prior to the oxidation/elimination process. We envisioned effecting this isomerization in a relatively straightforward, two-step process: first, a nucleophilic cleavage of the carbon–selenium bond, followed by reselenation of the resulting enolate from the less hindered side yielding the trans isomer 8. In practice, the nucleophilic cleavage of the carbon–selenium bonds in 7 and 8 is readily accomplished by exposing a mixture of these compounds to lithium phenyl selenide in THF at -78 °C.[9] The resulting enolate can then be protonated (saturated NH_4Cl solution) to give **10** or directly selenated.[10] The use of this method (LiSePh, then PhSeCl)[11] produces mixtures of 7 and 8 in which 8 is by far the major component. In fact, in three of the cases reported here, the epimerized mixtures contain only trace amounts of 7. Even in the worst case studied, a mixture of **7b** and **8b** which was originally 7:3 is transformed by this method to a 1:4 mixture of **7b** and **8b**, respectively. Once isomerized, these mixtures can then be oxidized and eliminated under standard conditions to give excellent overall yields of 11.

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(9) Cleavage of the carbon–selenium bond of α-(phenylselenenyl)-propiophenone by lithium phenyl selenide has been previously noted; see: Reich, H. J.; Renza, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

(10) Although not specifically listed in tabular form, these protonation reactions in all cases lead to deselenated ketones **6** and **10** in essentially quantitative yields.

(11) This transformation may also be accomplished by using LiSePh, followed by CH_3I.

Supplementary Material Available: Experimental details for the preparation of representative compounds (3 pages). Ordering information is given on any current masthead page.

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Copper(II)-Induced Cleavage of Carbon–Carbon Bonds. Mononitriles of Muconic Acids from *o*-Benzoquinones, Catechols, and Phenols by Reaction with Copper(II) in the Presence of Ammonia

Summary: *o*-Benzoquinones, catechols, and phenols react with certain copper(II) reagents to give, in one step, mononitriles of muconic acids.

Sir: Recently we reported on the oxidative cleavage of *o*-benzoquinones, catechols, and phenols to the corresponding monoesters of muconic acids.[1-3] In discussing the nature of the active copper(II) species responsible for the carbon–carbon bond cleavage, we suggested that in pyridine solution the active component of the reagent was dimeric cupric methoxy hydroxide complexed with pyridine.[2,3] We demonstrated[2,3] that this active component

(1) M. M. Rogić, T. R. Demmin, and W. B. Hammond, *J. Am. Chem. Soc.*, **98**, 7441 (1976).

(2) M. M. Rogić and T. R. Demmin, *J. Am. Chem. Soc.*, **100**, 5472 (1978).

(3) M. M. Rogić and T. R. Demmin, "Aspects of Mechanism and Organometallic Chemistry", J. H. Brewster, Ed., Plenum Press, New York, 1978, p 141.

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