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REACTIONS INVOLVING SELENIUM METAL AS AN ELECTROPHILE.
THE ENOLATE - SELENOLATE TRANSFORMATION

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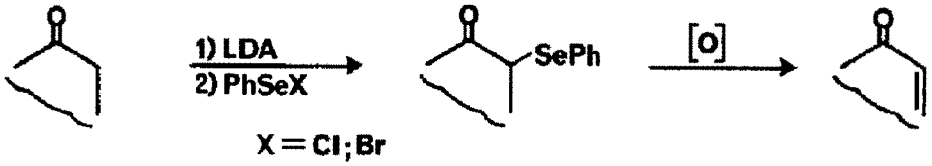
Abstract: When enolate ions are allowed to react with selenium metal, followed by methyl iodide, the corresponding α-methylselenenyl derivatives are produced in high yield.

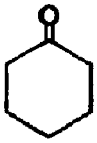
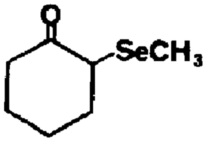
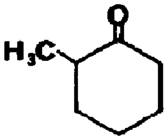
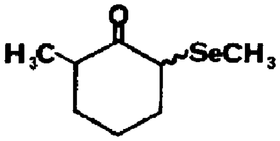
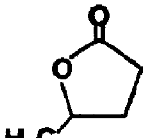
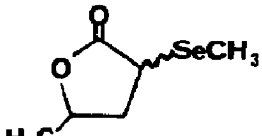
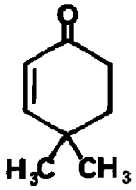
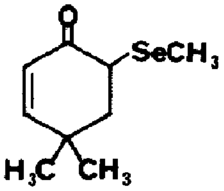
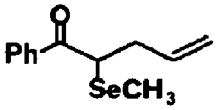
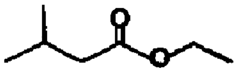
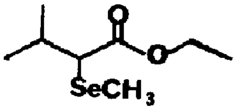
In a classic paper Reich et al described a simple procedure for the conversion of ketones to enones via the sequence of reactions shown below[2] (see Scheme I). Although some minor problems have been noted in both the selenation step[2] and the oxidation/elimination step[3], this reaction sequence can usually be carried out in high overall yield and, as such, represents the best general method for effecting ketone → enone conversions.

Scheme I.



Perhaps the major drawback of this procedure is the high cost associated with the various PhSeX reagents (X = Cl, Br, SePh), which are often prohibitively expensive to use in moderate or large scale reactions. In this communication we wish to report an alternative procedure for effecting the selenation of ketone (or ester) enolates which can be performed in yields comparable to enolate/PhSeX reactions, but at a greatly reduced cost. The key feature of this procedure involves the reaction of a lithium enolate with selenium metal to form a selenolate (selenide) ion[4,5]. The resulting selenolate can then be directly alkylated to give the corresponding α-alkylselenenyl derivative (see Scheme II). The results of our investigation are given in Table I.

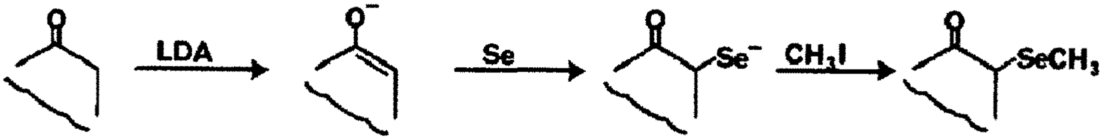
TABLE I

SUBSTRATE	PRODUCT	TEMP. (°C)	% YIELD[a,b]
 **1**	 **2**	-20	80
 **3**	 **4**	-20	80
 **5**	 **6**	-10	90
 **7**	 **8**	-10	90
 **9**	 **10**	-20	83
 **11**	 **12**	-15	85

a. Isolated yields.

b. Products were identified on the basis of their ir, nmr and high resolution mass spectra.

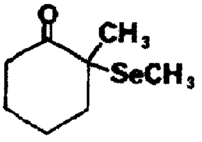
Scheme II



We have identified three factors which are critical to the success of the above reaction sequence: (a) the amount of HMPA used, (b) the reaction temperature of the selenation step and (c) the reaction time allowed for the alkylation reaction. With regard to (a), we have found that three molar equivalents of HMPA is optimal. Smaller quantities of HMPA result in sharply decreased yields (substantial amounts of unreacted starting materials are recovered); large quantities of HMPA lead to complex mixtures of products which are difficult to separate.

With regard to (b), temperatures of -20 to -10°C appear to give the best results. Reactions of enolates with selenium metal do not occur below -40°C and are quite slow even at -30°C. If the temperature is allowed to rise much above 0°C, complex mixtures again result. Usually, 30-60 min. is sufficient time for complete selenation. The uptake of selenium metal is easily monitored visually. With regard to (c), it is important to keep the alkylation reaction time brief (5 to 10 min.), since the desired products can be further alkylated on selenium in the presence of excess alkylating agents (thus lowering the isolated yields).

Some general points regarding the examples reported here are noteworthy. For example, generation of the kinetic enolate of 3 (LDA, -78°C) and subsequent reaction with selenium metal and methyl iodide leads exclusively to a cis/trans mixture of 4. No trace of 13, the product derived from reaction of selenium metal with the thermodynamic enolate of 3 is observed. Thus, enolate exchange is insignificant under the conditions employed here. Furthermore, although selenolates have previously been used to cleave esters by S_N2 - type reaction[6,7], the reaction rate of the cleavage process is very slow at -20°C and therefore does not interfere with the overall methylselenation sequence (e.g., 11 → 12). Finally, a side reaction which apparently does not occur under these reaction conditions is the 2,3-sigmatropic rearrangement of selenlate 14, i.e., none of the product derived from the methylation of 15 is observed.



13

14 15

A typical experimental procedure is illustrated below for the conversion of 11 to 12. A three neck, 250 ml round bottom flask, containing 125 ml dry THF and a few crystals of α,α′-dipyridyl, is equipped with an alcohol thermometer, a serum cap and an Erlenmeyer flask (connected via Gooch tubing), which contains 0.88g (11 mmole) of finely ground black selenium. To this is added 1.32g of diisopropylamine (freshly distilled from CaH_2). After cooling to -78°C, 8.0 ml n-BuLi (1.5 M, 12 mmole) is added. After allowing the reaction mixture to stir for 15 min., 1.30 g (10 mmole) 11 in 4 ml of dry THF is added. After 15 min., 3.60 ml (30 mmol HMPA and the selenium metal in the Erlenmeyer flask are added and the dry ice/acetone bath is replaced with a dry ice/CCl_4 bath. The reaction mixture is allowed to remain in the cooling bath for one hour after which time the temperature is allowed to briefly rise to -15°C, and the returned to -20°C. At this point 2.80 g CH_3I (20 mmole) is added in one portion. After an additional 5 min. the reaction is quenched with 2 ml of sat. NH_4Cl solution. After standard work-up and chromatography on silica gel, 1.95 g of pure 12 is isolated (85% yield).

In conclusion, we believe that this procedure represents a unique and efficient method for converting ketones and esters into their corresponding α-methylselenenyl derivatives. Moreover α-methylselenenyl ketones and esters are well-behaved compounds and can be efficiently converte to the corresponding enones via the same type of oxidation/elimination procedures commonly employed for their α-phenylselenenyl counterparts. Further studies involving the selenation of anions with selenium metal are in progress and will be the subject of future reports.

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References

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2. H. J. Reich, J. M. Renga and I. L. Reich, J. Amer. Chem. Soc., 97, 5434 (1975).
3. H. J. Reich, S. Wollowitg, J. E. Trend, F. Chow and D. F. Wendelborn, J. Org. Chem., 43, 1697 (1978).
4. Selenium metal is the basic starting material for all organoselenium reagents, and, as such, is necessarily much less expensive to use.
5. For some examples of other anions reacting with selenium metal, see: (a) K. B. Sharpless and M. W. Young, J. Org. Chem., 40, 947 (1975); (b) D. L. Klayman and T. S. Griffin, J. Amer. Chem. Soc., 95, 197 (1973).
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