

REACTIONS INVOLVING SELENIUM METAL AS AN ELECTROPHILE. 2.

A GENERAL PROCEDURE FOR THE PREPARATION OF UNSATURATED β -DICARBONYL COMPOUNDS

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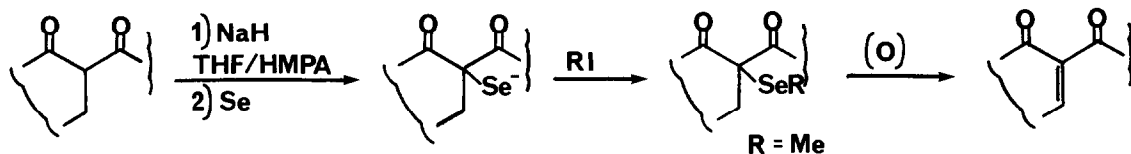
Summary: A variety of β -dicarbonyl compounds can be converted to the corresponding unsaturated derivatives in high yields. The process involves reaction of the β -dicarbonyl carbanion with Se metal, followed by alkylation with methyl iodide to form the methylseleno derivative and subsequent oxidative elimination.

Unsaturated β -dicarbonyl compounds are useful intermediates for a variety of synthetic transformations. However, since many of these compounds are relatively unstable, they are often not accessible by the traditional approaches used to introduce unsaturation in carbonyl compounds (e.g., halogenation - dehydrohalogenation or DDQ oxidation²). In 1975, Reich et al reported the first viable solution to this problem³. More recently, we reported a modification of the Reich procedure which we believe represents the simplest and most efficient method available for the synthesis of unsaturated β -dicarbonyl compounds⁴. Both processes involve the conversion of a β -dicarbonyl compound to its corresponding 2-phenylselenenyl derivative, followed by oxidative elimination of the seleno group to form the unsaturated derivative.

Although both of these sequences generally proceed in high overall yields, they are generally unsuitable for large scale preparations, primarily due to the prohibitively high cost of the various PhSeX reagents (X = Cl, Br, SePh). Recently, we reported a procedure for the methylselenation of enolates which makes use of the relatively inexpensive electrophile, selenium metal (the enolate-selenolate transformation)^{5,6}. In this communication we report that after suitable modification this selenium metal methodology can be successfully used in large-scale syntheses of unsaturated β -dicarbonyl compounds. The reaction sequence employed is shown

in Scheme I. Experimental results are listed in Table I.

Scheme I



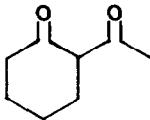
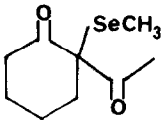
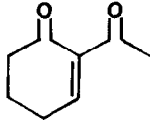
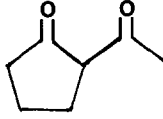
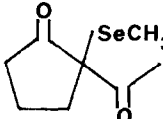
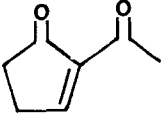
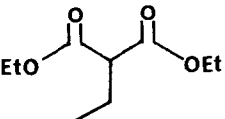
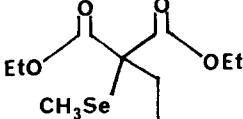
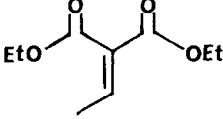
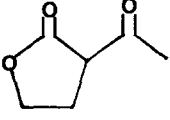
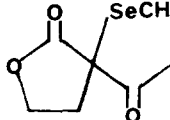
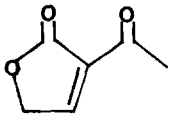
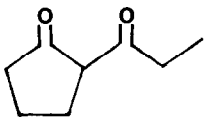
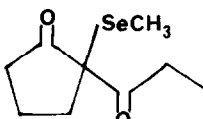
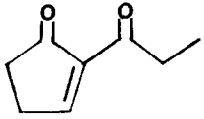
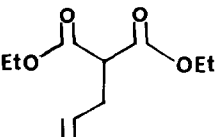
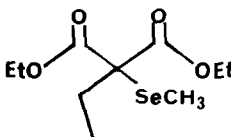
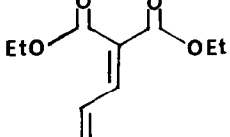
In our preliminary report involving reactions of simple enolates with selenium metal three factors were identified which are critical to the success of the reaction⁵. These include (a) the amount of HMPA used, (b) the reaction temperature of the selenation step and (c) the reaction time allowed for the alkylation step. In the reactions reported here only factors (a) and (c) appear to be of great importance. In general, 3-6 molar equivalents of HMPA were found to be optimal, i.e., these reactions apparently require enough HMPA to solubilize the enolate and make it reactive to selenium metal, but not so much as to permit significant competition from side reactions (e.g., polyselenide formation).

Not surprisingly, reactions of stabilized carbanions with selenium metal require higher reaction temperatures and longer reaction times than those employed for simple lithium enolates (25°C for 12-24 hours vs. -10°C for 1 hour). Longer reaction times do not significantly alter the results. Finally, as previously noted for the enolate-selenolate transformation, it is important to keep the selenide methylation time brief in order to minimize further alkylation of selenium.

With regard to the substrates which were examined, some points are noteworthy. Although selenides have been previously used to cleave esters and lactones by S_N2-type reaction,⁷ no products derived from ester cleavage processes are observed in the conversions 7→8, 10→11, and 16→17. Moreover, none of the methylation product of 20, formed from a [2,3] sigmatropic rearrangement of 19, is observed. Finally, under the reaction conditions described here⁸, β-keto aldehydes, such as 21 or 22, form complex product mixtures from which only trace amounts of the desired methylselenation products can be isolated.

In most cases, oxidative eliminations of methyl selenide derivatives are most conveniently accomplished using a two phase oxidation system composed of 30% hydrogen peroxide solution and methylene chloride. This method is not effective for converting 2 to 3, presumably because hydration of the intermediate selenoxide further retards what is an already slow elimination

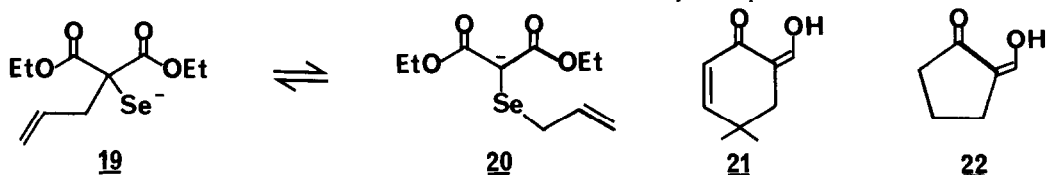
TABLE I

<u>Substrate</u>	<u>Selenide</u>	<u>% Yield</u>	<u>Unsaturated Product</u>	<u>% Yield</u>
 <u>1</u>	 <u>2</u>	75	 <u>3</u>	83 ^a
 <u>4</u>	 <u>5</u>	72	 <u>6</u>	69 ^b
 <u>7</u>	 <u>8</u>	97	 <u>9</u>	98 ^b
 <u>10</u>	 <u>11</u>	82	 <u>12</u>	98 ^b
 <u>13</u>	 <u>14</u>	84	 <u>15</u>	96 ^b
 <u>16</u>	 <u>17</u>	78	 <u>18</u>	96 ^b

(a). Oxidant = *m*-chloroperbenzoic acid (MCPBA)(b). Oxidant = 30% H₂O₂

reaction⁹. However, if *m*-chloroperbenzoic acid is used in place of hydrogen peroxide, the process proceeds smoothly.

In conclusion, the methodology described here represents a simple, and relatively inexpensive approach to the synthesis of unsaturated β -dicarbonyl compounds.



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References:

1. Fellow of the Alfred P. Sloan Foundation, 1980-84.
2. The yields of unsaturated β -dicarbonyl compounds obtained from DDQ oxidations of their saturated counterparts depend heavily on the substrate in question. In general, the yields obtained from this procedure are only modest.
3. H. J. Reich, J. M. Renga and I. L. Reich, *J. Amer. Chem. Soc.*, **97**, 5434 (1975).
4. D. Liotta, C. Barnum, R. Puleo, G. Zima, C. Bayer and H. Kezar, *J. Org. Chem.*, submitted.
5. D. Liotta, G. Zima, C. Barnum and M. Saindane, *Tetrahedron Lett.*, 3643 (1980).
6. Selenium metal is the basic starting material for all organoselenium reagents and, as such, is necessarily much less expensive to use.
7. a. D. Liotta, W. Markiewicz and H. Santiesteban, *Tetrahedron Lett.*, 4365 (1977); b. D. Liotta and H. Santiesteban, *Tetrahedron Lett.*, 4369 (1977).
8. A representative experimental procedure for the conversion of **4** to **6** is as follows: To a suspension of 265 mg (11 mmole) of pentane-washed NaH in 20 ml of THF was added 5.2 ml (5.36 g, 3 mmole) of HMPA. The solution was cooled to 0°C and 1.26 g (10 mmole) of **4** in 5 ml of THF was added. The ice bath was removed and the solution was stirred an additional 15 minutes. The solution was transferred (under N₂) to a flask containing 850 mg (10.7 mmole) of Se metal. The dark red solution was stirred for 24 hrs at 20°C and then cooled to 0°C. Methyl iodide (0.75 ml, 1.7 g, 12 mmole) was added and the reaction was stirred for 2 min at 0°C, at which time the reaction was quenched by the addition of 5 ml of saturated NH₄Cl solution. The reaction mixture was diluted with 100 ml of 4:1 petroleum ether-ethyl acetate and washed twice with 100 ml of water. The organic layer was separated, dried and evaporated. On flash chromatography it afforded **5** (1.58 g, 7.2 mmole, 72%): IR (neat) 1728 (C=O), 1688 (C=O) cm⁻¹; NMR (CDCl₃) 1.90-2.75 (m, 6H), 2.06 (s, 3H, Se-CH₃), 2.45 (s, 3H, C-CH₃); ¹³C NMR (CDCl₃) ppm 208.7 (C=O), 200.6 (C=O), 59.7 (C-Se), 37.9, 32.2, 26.4 (CH₂C), 18.4, 5.6 (SeCH₃). A solution of 1.10 g (5.0 mmole) of **5** in 50 ml of CH₂Cl₂ was cooled to 0°C and 1.1 ml (10.6 mmole) of 30% H₂O₂ was added dropwise. The water bath was removed and the solution was kept below 25° by intermittent cooling for 15 minutes. Five ml of water was added and the organic layer was dried and evaporated at 0°C to give **6** (428 mg, 3.5 mmole, 69%): IR (neat) 1705 (C=O), 1600 (C=C) cm⁻¹; NMR (CDCl₃) 2.25-2.87 (m, 4H), 2.44 (s, 3H, C-CH₃), 8.40 (t, J=2.7 Hz, 1H, =CH).
9. Selenoxide eliminations are slow in six-membered rings. See: H. J. Reich, S. Wollowitz, J. Trend, F. Chow and D. Wendelborn, *J. Org. Chem.*, **43**, 1697 (1978).

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