

Communications to the Editor

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A NEW 1,2-CARBONYL TRANSPOSITION METHOD VIA PHENYLSELENYNYLATION.
HIGH YIELD TRANSFORMATION OF O-METHYLESTRONE TO O-METHYLISOESTRONE

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Acidic phenylselenenylation of O-methylestrone with PhSeCl and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ gave an α -phenylselenenylketone and an α -chloro- α -phenylselenenylketone, both of which were converted to the same α, α -dimethoxyketone on treatment with mercury(II) perchlorate in methanol. Hydride reduction of this, dithiocarbonylation of the resulting product followed by acid hydrolysis, and treatment with tributyltin hydride gave O-methylisoestrone, the 1,2-carbonyl transposed product, in overall yield of 75%.

KEYWORDS—1,2-carbonyl transposition; mercury(II) perchlorate; α -phenylselenenylketone; α -chloro- α -phenylselenenylketone; α, α -dimethoxyketone; O-methylestrone; O-methylisoestrone

1,2-Carbonyl transposition reaction is one of the important procedures in organic synthesis, and a number of methods have been hitherto proposed for this purpose.¹⁾

We previously reported that, in the course of total synthesis of Erythrina alkaloids, an α -phenylselenenylketone was smoothly converted to an α, α -dimethoxyketone on treatment with mercury(II) perchlorate (MPC) in methanol.²⁾ This observation and the succeeding findings that an α -chloro- and an α -methoxy- α -phenylselenenylketone similarly give the same α, α -dimethoxyketone on a similar treatment disclosed a new 1,2-carbonyl transposition method described below, which would be generally applicable particularly to base-sensitive compounds. In this communication we describe transformation of O-methylestrone to O-methylisoestrone as an example.

Phenylselenenylation of O-methylestrone **1** with PhSeCl in presence of a catalytic amount of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ gave the α -phenylselenenylketone **2**,^{3,4)} mp 134–137°C, and the α -chloro- α -phenylselenenylketone **3**,³⁾ mp 110–111°C. The yields and the ratio of **2** and **3** varied depending on the reaction condition as shown in Table I.

Table I. Phenylselenenylation of O-Methylestrone **1**
by PhSeCl/ $\text{BF}_3 \cdot \text{Et}_2\text{O}$

PhSeCl(eq)	Time (h)	Product ratio (2:3)	Isolated yield (%)
1.2	2	3:1	69
2.0	1.5	9:7	81
7.5	3	2<<3	77

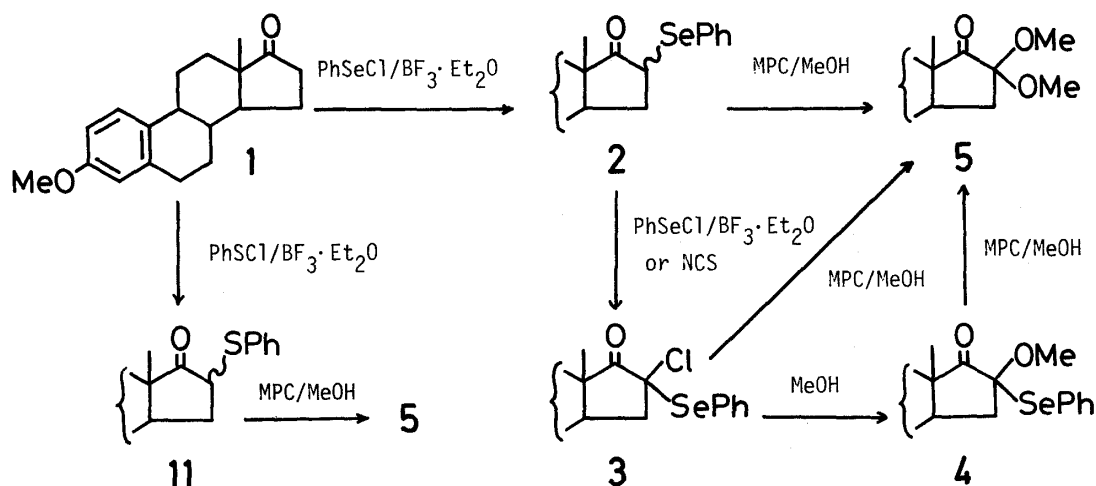
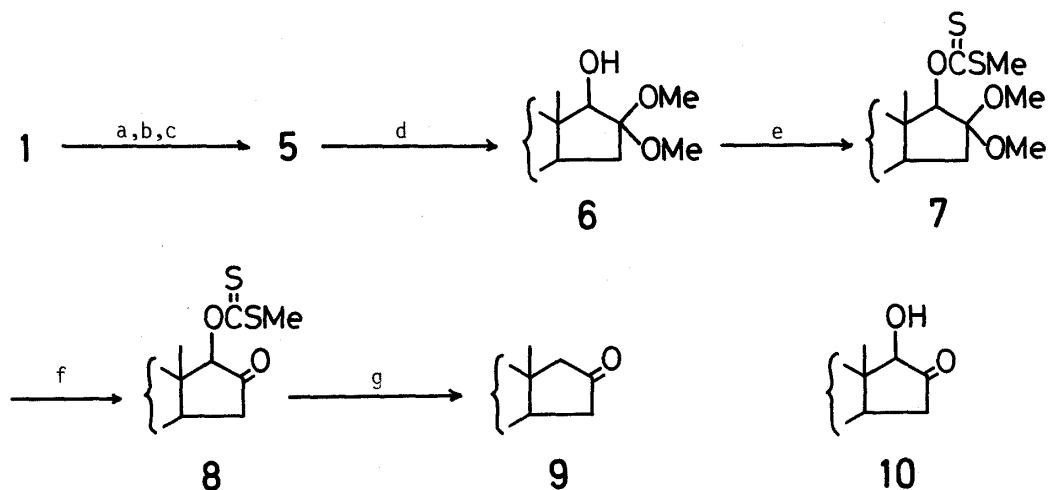


Chart 1



- a. $\text{PhSeCl}/\text{BF}_3 \cdot \text{Et}_2\text{O}$, b. MeOH, c. MPC/MeOH, d. NaBH_4 , e. $\text{NaH}/\text{CS}_2/\text{CH}_3\text{I}$,
f. $\text{HCl}/\text{H}_2\text{O}$ -acetone, g. $\text{Bu}_3\text{SnH}/\Delta$.

Chart 2

The α -chloro- α -phenylselenenylketone 3 is also prepared from 2 on reaction with an excess of PhSeCl or with N-chlorosuccinimide,⁵⁾ which was smoothly converted to the α -methoxy- α -phenylselenenylketone 4, gum, when treated in methanol (r.t., 12 h).

All of the above three α -phenylselenenyl derivatives, 2, 3, and 4, on treatment with MPC in methanol, were converted to the same α,α -dimethoxyketone 5, mp 143–146 °C, in yields of 83%, 98%, and 100%, respectively.⁶⁾

Based on the above knowledge, O-methylestrone 1 was converted to 5 in 81% yield on successive treatments with $\text{PhSeCl}-\text{BF}_3 \cdot \text{Et}_2\text{O}$, MeOH, and MPC in methanol as

shown in the example. The resulting α,α -dimethoxyketone was reduced by NaBH_4 to the alcohol **6**³⁾ which was converted to the dithiocarbonate **7**, mp 163–164°C, on treatment with NaH followed by CS_2 and CH_3I . Heating of **7** with tributyltin hydride in toluene afforded, after acid hydrolysis of the resulting product, two compounds, O-methylisoestrone **9** and the keto-alcohol **10**,^{3,7)} mp 174–178°C, in yields of 45% and 33%, respectively.

However, when **7** was hydrolysed first to **8** and then treated with tributyltin hydride, the desired O-methylisoestrone **9** was obtained as a sole product (92%). Apparently the carbonyl group created is stabilizing the intermediate radical at the α -position. Overall yield of the above 1,2-carbonyl transposition from O-methylestrone to O-methylisoestrone was 75%.⁸⁾

We have to emphasize that the above method is applicable not only to α -phenylselenenylketones but also to α -phenylsulfenylketones. In fact, α -phenylsulfenylketone **11**⁹⁾ obtained by the reaction of **1** with PhSeCl and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ was smoothly converted to the α,α -dimethoxyketone **5** on treatment with MPC in methanol. Fujita et al.¹⁰⁾ reported a similar transformation of various α -alkylsulfenylketones on treatment with thallium trinitrate (TTN) in methanol. Since α -phenylselenenyl (or α -phenylsulfenyl)-ketones are easily available from the ketones by the above acidic phenylselenenylation (or phenylsulfenylation) or on treatment with base and diphenyl diselenide (or diphenyl disulfide), the present 1,2-carbonyl transposition method must provide a useful alternative to the hitherto known methods.

Example: Transformation of O-Methylestrone to O-Methylisoestrone.

O-Methylestrone (1.12 g), PhSeCl (1.52 g, 2.0 eq), and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (5 drops) in THF (50 ml) were heated under reflux in Ar atmosphere for 2.5 h and then 3.5 h after addition of another portion of PhSeCl (0.58 g, 0.7 eq). The mixture was poured into NaHCO_3aq , extracted with CHCl_3 , and the organic layer was washed with water, dried, concentrated, and the residue chromatographed over silica gel. The mixture of **2** and **3** thus obtained was stirred in methanol (50 ml) at 50°C for 2 h, then MPC (2.7 g, 1.5 eq) was added and stirring was continued for a further 10 min, and then made slightly acidic by addition of solid Na_2S . The precipitate was removed by filtration through a filter-aid, and the filtrate was diluted with CHCl_3 , washed with brine, dried, and concentrated to give **5**, mp 143–146°C, (1.10 g, 81%) after chromatography. The α,α -dimethoxyketone **5** (172 mg) in methanol (30 ml) was reduced with NaBH_4 (76 mg) for 30 min at room temp. to give the alcohol **6** (232 mg, 100%) as a gum. The compound **6**, NaH (195 mg of 60% oil-dispersion), and imidazole (4 mg) in THF (20 ml) were refluxed under Ar for 3 h, then CS_2 (1 ml) and (after a further 30 min) CH_3I (1 ml) were added successively and refluxing was continued for a further 30 min. After decomposition of excess NaH with acetic acid, the mixture was poured into water, extracted with CHCl_3 , and the extract was dried and concentrated to give **7**, mp 163–164°C, (218 mg, 100%) after chromatography. This was hydrolysed in 5% HCl -acetone(1:2) (30 ml) on heating at 50°C for 30 min and the resulting gum **8** (182 mg) was heated under reflux in toluene (20 ml) with Bu_3SnH (660 mg) and a catalytic amount of azobis-isobutyronitrile for 1 h. Chromatography of the product gave O-methylisoestrone **9**, mp 125–129°C (lit.¹¹⁾ mp 123–124°C), (132 mg, 92%).

REFERENCES AND NOTES

- 1) V.V. Kane, V. Singh, A. Martin, and D.L. Doyle, *Tetrahedron*, 39, 345 (1983) and references therein.
- 2) Y. Tsuda, S. Hosoi, A. Nakai, T. Ohshima, Y. Sakai, and F. Kiuchi, *J. Chem. Soc., Chem. Commun.*, 1984, 1216.
- 3) The stereochemistry is not established.
- 4) All new compounds in this communication gave satisfactory spectral and/or analytical data.
- 5) The only preparative method of α -chloro- α -phenylselenenylketones that has been reported is that of the reaction of α -diazoketones and PhSeCl (D.J. Buckley, S. Kulkowit, and A. McKervey, *J. Chem. Soc., Chem. Commun.*, 1980, 506).
- 6) An interesting selectivity between reagent and substrate was observed for this reaction. TTN was superior to MPC for **2**, while MPC was superior to TTN for **3**. Other salts such as AgNO₃ and Hg(OAc)₂ were practically useless. Details will be published in a full paper.
- 7) The same compound was obtained by acid hydrolysis of **6**.
- 8) To our knowledge, the best method of this transformation so far known is that of Trost et al., who gave 70% overall yield (B.M. Trost, K. Hiroi, and S. Kurozumi, *J. Am. Chem. Soc.*, 97, 438 (1975)).
- 9) A mixture of two stereoisomers.
- 10) Y. Nagao, K. Kaneko, and E. Fujita, *Tetrahedron Lett.*, 1978, 4115.
- 11) M.N. Huffman, M.H. Lott, and A. Tillotson, *J. Biol. Chem.*, 217, 107 (1955).

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