Communications to the Editor

Chem. Pharm. Bull.
33(4)1745—1748(1985)

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

Yoshisuke Tsuda* and Shinzo Hosoi
Faculty of Pharmaceutical Sciences, Kanazawa University,
13-1, Takara-machi, Kanazawa 920, Japan

Acidic phenylselenenylation of O-methylestrone with PhSeCl and $BF_3.Et_2O$ 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 $BF_3.Et_2O$ 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 $PhSeCl/BF_3.Et_2O$

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

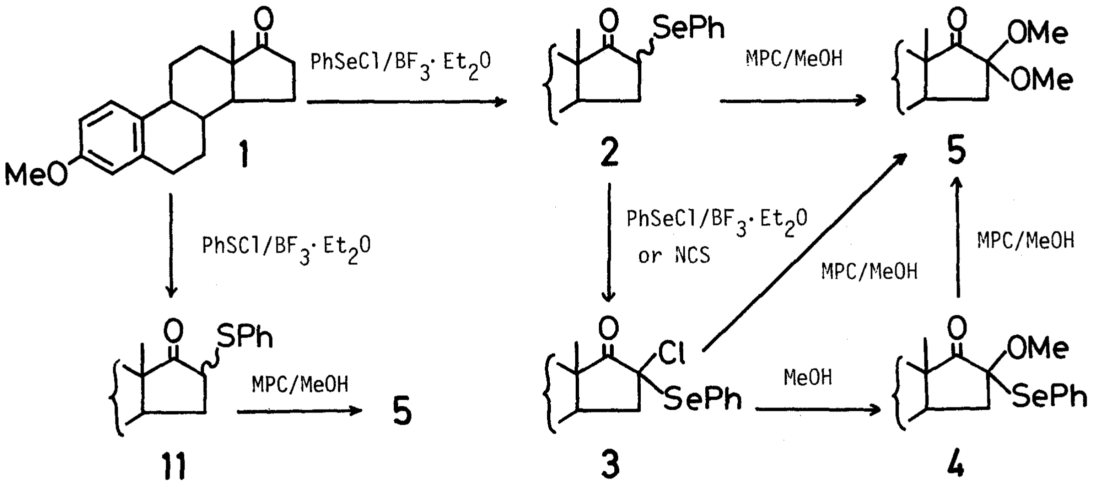
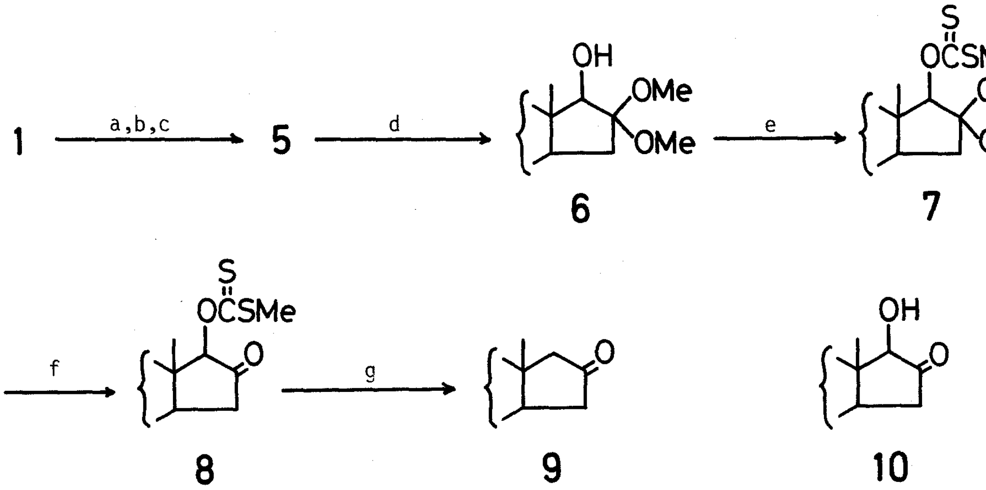


Chart 1



a. $PhSeCl/BF_3 \cdot Et_2O$, b. MeOH, c. MPC/MeOH, d. $NaBH_4$, e. $NaH/CS_2/CH_3I$,
f. HCl/H_2O-acetone, g. Bu_3SnH/Δ.

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 $PhSeCl-BF_3.Et_2O$, 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 PhSCl and $BF_3.Et_2O$ 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 $BF_3.Et_2O$ (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 $NaHCO_3$aq, 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 $AgNO_3$ 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).

(Received February 4, 1985)