BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 50 (1), 325—326 (1977)

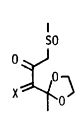
Various Acceleration Conditions of Pummerer Reaction Observed in the Total Synthesis of Illudins[1]

Takeshi MATSUMOTO, Haruhisa SHIRAHAMA, Fujio SAKAN,* and Kazuko TAKIGAWA*
Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060
**Chemical Laboratory, Faculty of Education, Fukui University, Fukui 910*

(Received August 2, 1976)

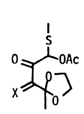
Synopsis. Pummerer reaction of highly functionalized sulfoxides were examined under various modified conditions. The results indicated that added base and/or neighboring acetoxyl group accelerated the reaction.

In the course of our synthetic work on illudins,[2] we found a base catalyzed and a neighboring group participated acceleration of Pummerer reaction whose utility for organic synthesis increased recently.[3]



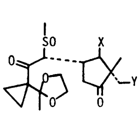
1 X = ◁

3 X = $<^{CH_3}_{CH_3}$

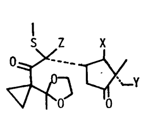


2 X = ◁

4 X = $<^{CH_3}_{CH_3}$



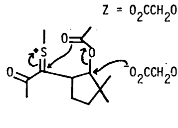
5 X = Y = H
6 X = OAc, Y = H
8 X = Y = OAc



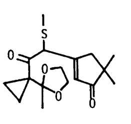
7 X = Z = OAc, Y=H
9 X = Y = OAc
Z = O$_2$CCH$_2$OCH$_3$

PhCOCH$_2$SOCH$_3$
10

PhCOCH(OAc)SCH$_3$
11



12



13

According to the mechanism proposed by Oae and Kise,[4] the acceleration of the reaction by base was expected and in fact effect of pyridine on simple sulfoxides was recently reported.[5] In our work highly functionalized sulfoxides, **1**, **3**, **6**, and **8** smoothly underwent Pummerer reaction by addition of pyridine, while without pyridine they did not undergo the reaction under mild reaction conditions or gave no normal reaction products, which were key intermediates for our synthesis,[2] even under more drastic conditions.

Another new observation is an acceleration of the reaction by neighboring group participation. The reaction with sulfoxides **5** and **6** showed clearly the effect of acetoxyl group on their cyclopentane rings. The mode of participation is not clear at present but migration of acetoxyl group through transition like **12** was excluded by the experiment employing methoxyacetic anhydride (**8**→**9**). The results were summarized in Table 1.

Further study revealed that the Pummerer reaction was markedly accelerated by the addition of mercuric chloride as shown in the Table 1.[6]

Experimental

Sulfoxide (**10**) was obtained from ethyl benzoate according to Corey's procedure[11]. Other sulfoxides were synthesized during our synthetic work and their physical and analytical data appeared in the references indicated.

NMR spectra were measured at 100 MHz on a JEOL Model JNM-4H-100 spectrometer using TMS as an internal standard. IR spectra were taken on a HITACHI Model EPI-G3 spectrometer with NaCl optics.

Acetic anhydride used in this work was purified by fractional distillation. Pyridine was dried over potassium hydroxide and distilled before use.

Pummerer Reaction without Pyridine. A mixture of 100 mg of sulfoxide and 2.8 ml of acetic anhydride was heated to reflux for 2 h. The mixture was concentrated in vacuo and the residue was dissolved in chloroform. The solution was washed with saturated sodium hydrogencarbonate solution and brine and dried over anhydrous sodium sulfate. Removal of the solvent gave a practically pure product.—**2**, **4**, and **11**.

The Reaction with Pyridine. A mixture of 100 mg of sulfoxide, 2.8 ml of acetic anhydride and 4.0 ml of pyridine was allowed to stand for 1 week at room temperature. The mixture was concentrated in vacuo at ambient temperature and the residue was stirred with water for 30 min and extracted three times with chloroform. The combined extracts were washed with sodium hydrogencarbonate solution and brine and dried over sodium sulfate. After removal of

TABLE 1. VARIOUS CONDITIONS OF THE PUMMERER REACTION

Sulfoxides	Products	Yields (%) under various conditions			
		Ac$_2$O/r.t./1 week	Ac$_2$O/reflux/2 h	Ac$_2$O–Py/r.t./1 week	Ac$_2$O–HgCl$_2$/r.t./3 h
1[7]	**2**[7]	recovered	79[a]	85[a,g]	75[a]
3[8]	**4**	recovered	>95[b]	>90[b,g]	>90[b]
5[2b]	—	recovered	complex mixture[9]	recovered	—
6[2c]	**7**[2c]	recovered	complex mixture	70[a,g]	—
8[2e]	**9**[2e]	—	—	65[a,c,d]	—
10	**11**	recovered[f]	>95[b]	>95[b,e]	95[b]

a) Isolated yield (by column chromatography on silica gel). b) Based on NMR analysis. c) Methoxyacetic anhydride was used instead of Ac$_2$O. d) The reaction was completed in 2 days. e) The reaction was completed in 3 days. f) After 3 days. g) The starting sulfoxide remained in shorter reaction time (TLC analysis).

the solvent the product obtained was practically pure.—**2**, **4**, and **11**.

In the case of the reactions with **6** and **8** the product was purified by chromatography on silica gel.

In the reaction with sulfoxide **8** methoxyacetic anhydride was used instead of acetic anhydride and in this case the reaction was completed in 2 days. The reaction time was 3 days with **10**.

The Reaction with Mercuric Cholride. A mixture of 100 mg of sulfoxide, 2.8 ml of acetic anhydride and 180 mg of mercuric chloride was stirred at room temperature for 3 h. The mixture was then poured into large volume of water with vigorous stirring and extracted with chloroform. The extracts were washed with 2% aqueous EDTA solution and water and dried over sodium sulfate. Removal of the solvent gave a practically pure product.—**4** and **11**.

A pure sample of **2** was obtained through chromatography on silica gel.

1-Methylthio-1-acetoxy-3,3-dimethyl-4-ethylenedioxy-2-pentanone (4). IR(neat) 1745, 1705, 1220, and 1035 cm^{-1}; NMR δ (CCl_4) 1.18, 1.19 (each 3H, s., $C(CH_3)_2$), 1.31 (3H, s., $OCCH_3$), 2.05, 2.09 (each 3H, s., SCH_3, and $OCOCH_3$), 3.94 (4H, b.s., OCH_2CH_2O), and 6.56 (1H, s., SCHO); Anal. Found: C, 52.37; H, 7.26%. Calcd for $C_{12}H_{20}O_5S$: C, 52.16; H, 7.30%.

2-Methylthio-2-acetoxyacetophenone (11). IR (neat) 3050, 1745, 1685, 1595, 1580, 1225, 750, and 690 cm^{-1}; NMR δ (CCl_4) 2.01, 2.13 (each 3H, s., SCH_3 and $OCOCH_3$), 6.70 (1H, s., SCHO), centered at 7.45 and 7.95 (3H, and 2H respectively, m., arom. H); Anal. Found: C, 58.93; H, 5.35%. Calcd for $C_{11}H_{12}O_3S$: C, 58.93; H, 5.40%.

Physical and analytical data of other compounds appeared in the references indicated.

References

1) Large part of this work was read at Winter Meeting of Hokkaido Division of Chemical Society of Japan, Feb. 1, 1971, Sapporo.

2) a) Total synthesis of illudin M; T. Matsumoto, H. Shirahama, A. Ichihara, H. Shin, S. Kagawa, F. Sakan, S. Matsumoto, and S. Nishida, *J. Am. Chem. Soc.*, **90**, 3286 (1968); b) Synthesis of illudane skeleton; T. Matsumoto, H. Shirahama, A. Ichihara, H. Shin, S. Kagawa, N. Ito, T. Hisamitsu, T. Kamada, and F. Sakan, *Tetrahedron Lett.*, **1967**, 4097; c) Synthesis of functionalized illudane; T. Matsumoto, H. Shirahama, A. Ichihara, H. Shin, S. Kagawa, N. Ito, T. Hisamitsu, T. Kamada, F. Sakan, K. Saito, S. Nishida, and S. Matsumoto, *Tetrahedron Lett.*, **1968**, 1925; d) Alternative synthesis of illudin M; T. Matsumoto, H. Shirahama, A. Ichihara, H. Shin, S. Kagawa, and F. Sakan, *Tetrahedron Lett.*, **1970**, 1171; e) Total synthesis of illudin S; T. Matsumoto, H. Shirahama, A. Ichihara, H. Shin, S. Kagawa, F. Sakan, and K. Miyano, *Tetrahedron Lett.*, **1971**, 2449.

3) a) G. A. Russell and G. J. Mikol, *J. Am. Chem. Soc.*, **88**, 5498 (1966); b) R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *ibid.*, **91**, 1401 (1969); c) Y. Oikawa, and O. Yonemitsu, *Tetrahedron Lett.*, **1972**, 3393; *J. Org. Chem.*, **41**, 1118 (1976); D. Connor and M. von Strardtmann, *J. Org. Chem.*, **39**, 1549 (1974); d) K. Ogura, and G. Tsuchihashi, *J. Am. Chem. Soc.*, **96**, 1960 (1974); S. Iriuchijima, K. Maniwa, and G. Tsuchihashi, *ibid.*, **96**, 4280 (1974); e) H. Kosugi, H. Uda, and S. Yamagiwa, *J. Chem. Soc., Chem. Commun.*, **1975**, 192; **1976**, 71.

4) M. Kise, and S. Oae, *Bull. Chem. Soc., Jpn.*, **43**, 1421 (1970).

5) G. E. Wilson, and G. J. Strong, *J. Org. Chem.*, **37**, 2376 (1972). More recently Uda *et al.* observed acceleration effect of pyridine in Pummerer type reaction.[3e)]

6) K. Takigawa, Graduation Thesis, Fukui Univ., 1974.

7) T. Matsumoto, H. Shirahama, A. Ichihara, H. Shin, S. Kagawa, T. Hisamitsu, T. Kamada, and F. Sakan, *Bull. Chem. Soc., Jpn.*, **45**, 1136 (1972).

8) T. Matsumoto, H. Shirahama, A. Ichihara, H. Shin, and S. Kagawa, *Bull. Chem. Soc., Jpn.*, **45**, 1144 (1972).

9) From the complex products only enone **13** could be isolated.[10)]

10) T. Matsumoto, H. Shirahama, A. Ichihara, H. Shin, S. Kagawa, N. Ito, T. Hisamitsu, T. Kamada, F. Sakan, K. Saito, S. Nishida, and S. Matsumoto, 11th Symposium on the Chemistry of Natural Products, Kyoto, Oct., 1967, Symposium Paper, p. 120.

11) E. J. Corey, and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1345 (1965).