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2-(PHENYLTHIO)-2-PENTEN-5-OLIDE, A NEW BUILDING BLOCK FOR THE SYNTHESIS OF 3-SUBSTITUTED δ-LACTONES

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2-(Phenylthio)-2-penten-5-olide, readily accessible from δ-valerolactone, showed high electrophilic reactivities toward some typical carbon nucleophiles to give 3-substituted 2-(phenylthio)pentanolides, which were convertible to a variety of 3-substituted pentan-5-olides and 2-penten-5-olides.

In our synthetic projects we required an efficient synthetic method of 3-substituted 2-penten-5-olides. Although a variety of methodologies for the syntheses of 3-substituted butenolides have been reported,1) mostly in connection with natural product synthesis, those for the 3-substituted pentenolides are, to our knowledge, not well defined. In spite of this disadvantage, however, the 3-substituted pentenolides have been used as building block of some organic compounds.2)

We wish to report herein that 2-(phenylthio)pentenolide 1 can act as a versatile Michael acceptor to give 3-substituted 2-(phenylthio)-2-pentan-5-olides 2, and that the phenylthio group of the latter serves to derive other related δ-lactones as shown in Fig. 1; firstly, thermolysis of the sulfoxides 3 obtained by oxidation of 2 would give 3-substituted pentenolides 4 (Route A); secondly the

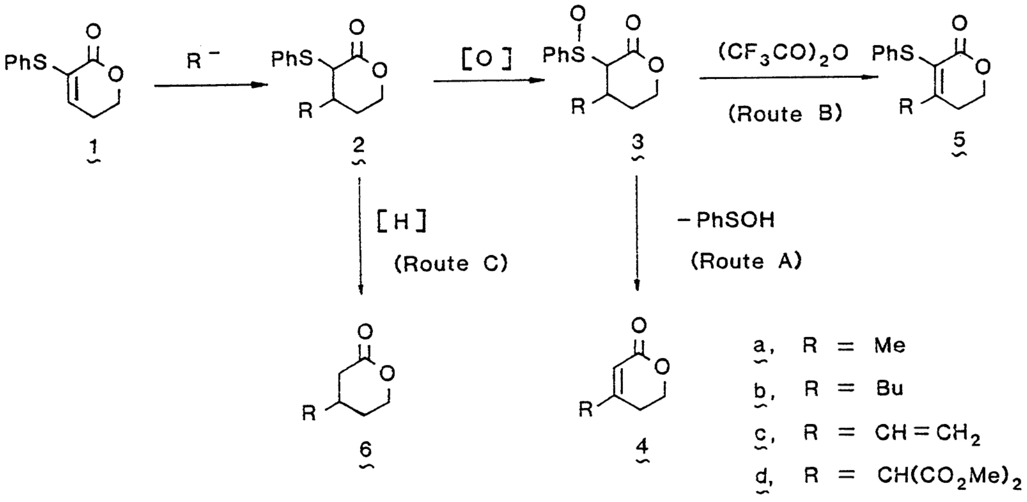
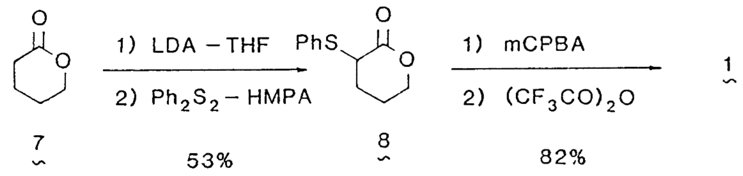


Fig. 1.

Pummerer rearrangement would lead the above sulfoxides to 3-substituted 2-(phenylthio)pentenolides 5 (Route B), and finally, the phenylthio function of 2 would be reductively cleaved to give 3-substituted pentanolides 6 (Route C).

2-(Phenylthio)pentenolide 1 was prepared from δ-valerolactone 7 as follows; 7 was treated with LDA (2.4 equiv.) in THF at -75 °C for 0.5 h, and addition of a solution of diphenyl disulfide (2 equiv.) in HMPA was followed at -70 °C. Then the temperature was gradually raised to room temperature (rt) to give 2-(phenylthio)pentanolide 8.3) The product 8 was oxidized with equimolar mCPBA (CH_2Cl_2, 0 °C, 1 h) and after usual workup, the resultant crude sulfoxide was treated with trifluoroacetic anhydride (0 °C to rt, overnight) to afford the desired 1.4)



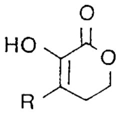
Having 1 in hand, we investigated the scope of conjugate addition to 1 with several reagents; (a) lithium dimethylcuprate (1.1 equiv., THF-Et_2O-Me_2S, -25 to -17 °C, 0.5 h); (b) lithium dibutylcuprate (1.05 equiv., Et_2O, -20 to -17 °C, 0.5 h); (c) vinylmagnesium bromide-cuprous iodide 1:1-complex (2 equiv., THF-Et_2O, -45 to 8 °C, 7 h), and sodium dimethylmalonate (2.2 equiv., THF-Et_2O, ca. 0 °C, 1.5 h). All reactions proceeded smoothly and 3-substituted 2-(phenylthio)pentanolides 2a-d5) were isolated in good to excellent yields as indicated in Table 1.

Table 1. Yields (%)a) of 3-substituted pentanolides and pentenolides.

Product	2	4	5	6
a	91	72	52b)	-
b	80	79	49c)	76
c	82	73	10d)	42f)
d	73	80	0e)	-

a) Isolated yield.
b) As a minor product, 2-hydroxy-3-methylpentenolide 9a was isolated (18% yield).
c) Formation of a trace of 3-butyl-2-hydroxypentenolide 9b was observed.
d) The major product (74% yield) was 4c.
e) Isolated 3d was used in this run and 2-hydroxypentenolide 9d was obtained in 34% yield as the sole isolable product.
f) W-4 Raney nickel deactivated with acetone was employed.

The lactones 2a-d were then oxidized with equimolar mCPBA (CH_2Cl_2, -15 °C), respectively, and the sulfoxides 3a-d obtained in quantitative yields were treated under thermal elimination conditions (benzene containing catalytic pyridine, reflux) to give 3-substituted pentenolides 4a-d[6)] in good yields. The sulfoxides 3a-d, on the other hand, were exposed to Pummerer rearrangement conditions [$(CF_3CO)_2O$, -15 °C to rt, 2 to 3 days, and quenching with aqueous $NaHCO_3$ solution], respectively. While 3a and 3b gave the expected 2-(phenylthio)pentenolides 5a and 5b in fair yields, the major product derived from 3c was 4c, and the yield of the expected 5c was only 10%. Formation of 4c may be rationalized by surmising that elimination of sulfenic acid easily had occurred before the Pummerer rearrangement initiates, because of high acidity of the allylic β-hydrogen in 3c. It is interesting to note that when the substrate was 3d, 2-hydroxy-3-bis(methoxycarbonyl)-methylpentenolide 9d was obtained as the sole isolable product, whereas 9a[7)] and 9b, products of this type, were obtained as minor products from 3a and 3b.[8)]



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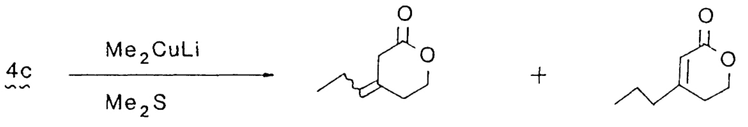
a, R = Me
b, R = Bu
d, R = $CH(CO_2Me)_2$

Reductive desulfurization of 2b and 2c, employed as the representative, was also examined with W-4 Raney nickel (EtOH, rt, 1 to 3 h). While 2b was led to the expected product 6b[9)] in good yield, 2c afforded 3-ethylpentanolide[10)] in 86% yield as a result of concomitant hydrogenation of the vinyl group. In the case where the Raney nickel deactivated with acetone was employed, however, the reaction was somewhat sluggish, 2c gave the desired 6c in moderate yield.

Finally, as a preliminary examination to know the regioselectivity in the Michael addition to 4c, lithium dimethylcuprate (1.1 equiv., Et_2O-Me_2S, -30 °C, 25 min) was allowed to react. Product obtained was a mixture of 10a and 10b and no formation of regioisomers arising from 1,2- and 1,4-additions was observed, indicating that the addition took place only in the 1,6-conjugate addition mode.



10a 51%

10b 8%

Further studies are in progress.

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2) For example, H. Kosugi, S. Sekiguchi, R. Sekita, and H. Uda, Bull. Chem. Soc. Jpn., 49, 520 (1976); J. D. White, J. P. Carter, and H. S. Kezar, III, J. Org. Chem., 47, 929 (1982).

3) NMR, IR, and high resolution mass spectra of all new compounds are consistent with the proposed structures.

4) The phenylthio group was introduced as an activator for the Michael acceptor with the α,β-unsaturated carbonyl system. In our initial studies, in fact, reactions of pentenolide 4 (R=H) with lithium dibutylcuprate and vinylmagnesium bromide-cuprous iodide 1:1-complex yielded 6b and 6c only 45 and 13% yields, respectively. For the effect of the phenylthio group, see: K. Iwai, H. Kosugi, and H. Uda, Chem. Lett., 1974, 1237; H. J. Monterio, J. Org. Chem. 42, 2324 (1977); F. Kido, Y. Noda, and A. Yoshikoshi, J. Am. Chem. Soc., 104, 5509 (1982).

5) The δ-lactones 2a-d were inseparable diastereomeric mixtures, in which trans-isomers were contained undoubtedly in much larger quantities judging from their NMR spectra.

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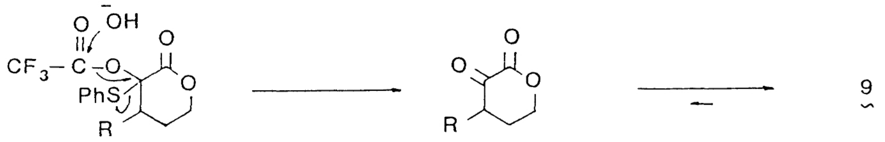
8) Formation of 5 and/or 9 is considerably affected by reaction temperature as well as the presence or types of β-substituents in the substrates. In fact, treatment with trifluoroacetic anhydride at low temperature (<0 °C) led the sulfoxides 3 (R=H) derived from 8 smoothly to 1 in the nearly same yield as previously described. The sulfoxide 3a, on the contrary, yielded 9a as the major product (59% yield) accompanied with 5a (14% yield). 2-Hydroxypentenolide 9 would be formed through hydrolysis of the Pummerer rearrangement product i and subsequent tautomerization of the resultant α-ketolactone ii.



i ii

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