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A NEW SYNTHETIC METHOD FOR β-SUBSTITUTED $\Delta^{\alpha,\beta}$-BUTENOLIDES

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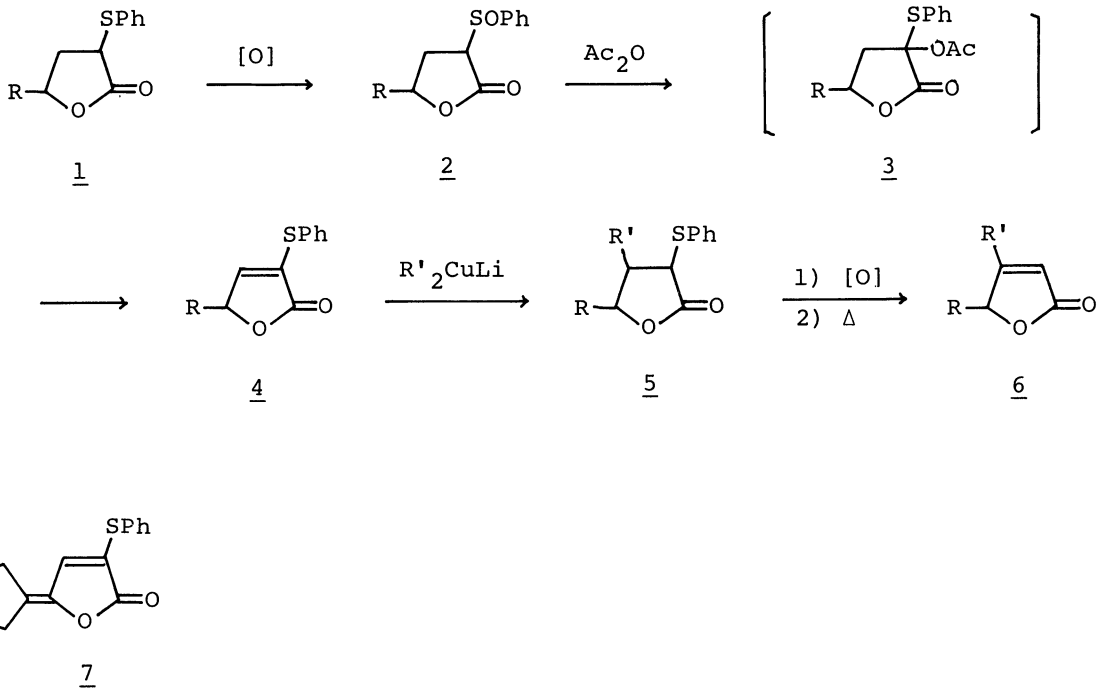
α-Phenylsulfinyllactones 2 underwent the Pummerer rearrangement and subsequent elimination of acetic acid by treating with hot acetic anhydride to give α-phenylthiobutenolides 4. Conjugate addition reaction of 4 with organocopper reagents or malonic ester followed by oxidation to sulfoxides and pyrolysis afforded β-monosubstituted or β,γ-disubstituted butenolides 6 in moderate overall yields.

We recently reported[1] a convenient method for the synthesis of γ-monosubstituted and α,γ-disubstituted butenolides (γ-crotonolactones) via α-phenylthiolactones 1 by the reaction of lithium lithio(phenylthio)acetate or its α-alkyl derivatives with terminal epoxides.[2,3] As an extension of the reaction of 1 a new synthetic method for β-monosubstituted or β,γ-disubstituted butenolides 6 was described in this communication.[6] The reaction sequence involves the Pummerer rearrangement of α-phenylsulfinyllactones 2, the subsequent elimination of acetic acid, and the conjugate addition of organocopper reagents or malonic ester to the resulting α-phenylthiobutenolides 4 as the key steps.

The Pummerer rearrangement[7] of α-phenylsulfinyllactone 2 (R = H[8] or CH_3[1]) and simultaneous elimination of acetic acid from the rearrangement product 3 proceeded smoothly by heating in acetic anhydride at 60 – 70°C overnight (for avoiding the competitive elimination of phenylsulfenic acid from 2 occurred over 100°C) and then at 150°C (refluxing) for 2 hr to give α-phenylthiobutenolide 4 in high yield. The intermediate 3 was isolated as a minor product when the reaction mixture was worked up without refluxing.

Treatment of a solution of 4 in ether with 2 equiv of dimethyl- (0°C, 2 – 3 hr), di-n-butyl- (-78°C, 3 – 4 hr), or divinylcopper lithium (-60 – -50°C, 1.5 – 2 hr)[10] gave the conjugate addition product, β-monosubstituted or β,γ-disubstituted α-phenylthiolactone 5, in excellent yield. Oxidation of 5 followed by pyrolysis of the

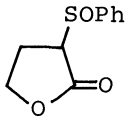
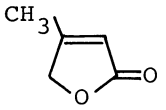
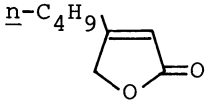
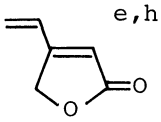
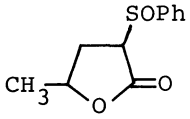
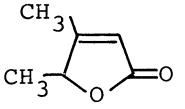
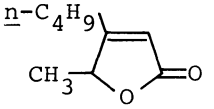
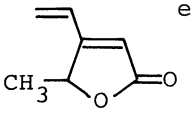


resulting sulfoxide as reported previously afforded β-monosubstituted or β,γ-disubstituted butenolide 6 in good yield.

Successful introduction of a vinyl group at the β-position of a butenolide system would provide an alternative process for preparation of synthetically useful butenolides,[11,12] and the results of this process are summarized in Table I.

Furthermore, we have attempted an examination of the reactivity of α-phenylthiobutenolide 4 (R = H) as a Michael or enamine receptor to extend the method for introduction of specially functionalized substituents at the β-position.[14] Addition of 4 (R = H) to a tetrahydrofuran solution containing 1 equiv of diethyl lithiomalonate, prepared from lithium hydride and diethyl malonate, at 25°C for 3 hr and then at 65°C for 0.5 hr and quenching the reaction with cold aqueous ammonium chloride led to 60% yield of the adduct 5 (R = H, R' = $-CH(CO_2Et)_2$), which could be also transformed into β-[bis(ethoxycarbonyl)methyl]butenolide 6 (R = H, R' = $-CH(CO_2Et)_2$)[15] in 68% yield. On the other hand, reaction of 4 (R = H) with 1 equiv of 1-morpholino-1-cyclopentene in acetonitrile at room temperature for 3 hr afforded an unexpected condensation product, γ-cyclopentylidenebutenolide 7, mp 138 – 139°C,[15] in 50% yield, rather than a conjugate addition product. The formation of 7 would be accounted for by the following reaction sequence: a proton abstraction from the γ-position of 4 (R = H) with the enamine, the

Table I. β-Monosubstituted and β,γ-Disubstituted $\Delta^{\alpha,\beta}$-Butenolides[a]

Phenylsulfinyl-lactone 2	Phenylthio-butenolide 4	%	Phenylthio-lactone 5[b] R'	%	Butenolide 6[c]	%
	R = H[d]	86	CH_3-[e]	91	 [f]	87
			n-C_4H_9-	92		73
			CH_2=CH-[g]	quant.	 [e,h,i]	51
 [j]	R = CH_3	93	CH_3-[e]	82		80
			n-C_4H_9-	86		82
			CH_2=CH-[g]	75	 [e,h]	89

(a) Yields given are for isolated products and not necessarily optimum. Satisfactory infrared and nuclear magnetic resonance spectra were obtained for isolated samples of all compounds. Unless otherwise indicated, purified samples gave satisfactory elemental analyses.
(b) Stereochemistries of these compounds have not been established.
(c) Oxidation was carried out in methylene chloride with m-chloroperbenzoic acid (0°C, 0.5 – 1 hr), except in the case of 5 (R = H, R' = CH_2=CH-) (sodium metaperiodate in dilute methanol, room temperature, 15 hr). Pyrolysis was performed in refluxing toluene.
(d) Mp 57.5 – 59.0°C from ethanol.
(e) Elemental analytical result was unsatisfactory even if a purified sample (homogeneous by tlc and nmr) was used. The reason was not clarified.
(f) This compound was also identified with the authentic sample.
(g) This compound was immediately subjected to oxidation.
(h) This compound seemed to be slightly sensitive to heat or air.
(i) This compound was synthesized through an alternative reaction route by Professor Yoshikoshi, et al.[16] in this Institute.
(j) A mixture of cis and trans isomers.

addition between the resulting γ-carbanion of 4 (R = H) and the protonated enamine and finally the elimination of morpholine from the adduct.

As is clear from the examples cited above the procedure should be useful for the synthesis of a variety of β-substituted butenolide including natural products.

References and Notes

1) K. Iwai, M. Kawai, H. Kosugi, and H. Uda, Chem. Lett., 385 (1974).
2) For a review of butenolides, see Y. S. Rao, Chem. Rev., 64, 353 (1964).
3) Similar reaction sequence from α-methylthio-[4] or α-phenylseleno-[5]γ-butyrolactone to butenolide has been reported.
4) B. M. Trost and T. N. Salzmann, J. Amer. Chem. Soc., 95, 6840 (1973).
5) K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, J. Amer. Chem. Soc., 95, 6137 (1973).
6) For recently reported alternative processes leading to β-monosubstituted and α,β-disubstituted butenolides, see (a) fused pyrazoline γ-butyrolactone thermolysis: M. Franck-Neumann, Angew. Chem., 80, 42 (1968), and β,γ-disubstituted butenolides, see (b) organocopper-ynoic ester addition: E. J. Corey, C. U. Kim, R. H. K. Chen, and M. Takeda, J. Amer. Chem. Soc., 94, 4395 (1972); (c) β-ketosulfoxide condensation: M. Kurono, K. Imagi, T. Tanikawa, and M. Watanabe, Abstracts of Papers of the 26th Annual Meeting of the Chemical Society of Japan, Hiratsuka, Kanagawa Pref., April, 1972, Series III, p. 1623.
7) (a) R. Pummerer, Ber., 42, 2282 (1909); 43, 1401 (1910); L. Horner and P. Kaiser, Ann., 626, 19 (1959), (b) W. E. Parham and L. D. Edwards, J. Org. Chem., 33, 4150 (1968), and references cited therein.
8) Parent α-phenylsulfinyl-γ-butyrolactone 2 (R = H), mp 100 – 104°C, was easily prepared in good overall yield by the reaction of α-bromo-γ-butyrolactone[9] and sodium thiophenolate in tetrahydrofuran, followed by sodium metaperiodate oxidation of the resulting α-phenylthio-γ-butyrolactone 1 (R = H) in dilute methanol.
9) C. C. Price and J. M. Judge, "Organic Syntheses", Coll. Vol. V, p. 255 (1973).
10) Attempts for conjugate addition of 4 with a combination of Grignard reagent and cuprous iodide gave unsatisfactory results (low yield of 5, formation of considerable amounts of by-products).
11) Cf. Ref. 6b.
12) An important point of this process is the synthesis of β-monosubstituted derivatives because of the very limited availability of them.[13]
13) Cf. Refs. 2 and 6a.
14) For the reactions of methyl (α-methylthio)acrylate with enolates and enamines, see R. J. Cregge, J. L. Herrmann, and R. H. Schlessinger, Tetrahedron Lett., 2603 (1973).
15) Spectral and analytical results were consistent with the assigned structure.
16) Presented in the 30th Annual Meeting of the Chemical Society of Japan, April, 1974, Osaka.

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