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

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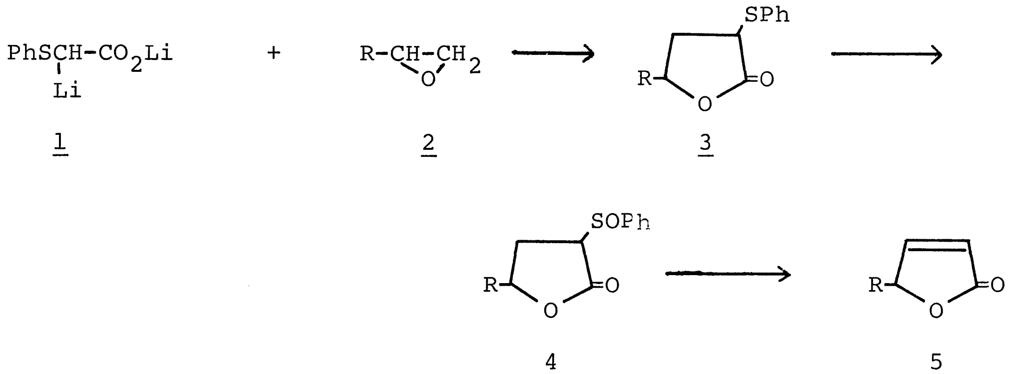
Reaction of the dilithio derivative of phenylthioacetic acid with terminal epoxides gave γ-substituted α-phenylthio-γ-butyrolactones, which were oxidized to sulfoxides and then pyrolyzed to give γ-substituted $\Delta^{\alpha,\beta}$-butenolides in moderate overall yields.

In connection with the synthetic studies of natural products, we require a synthesis of variously substituted $\Delta^{\alpha,\beta}$-butenolides for model experiments. We outline here a new convenient method for the synthesis of γ-substituted $\Delta^{\alpha,\beta}$-butenolides using phenylthioacetic acid.[1,2]

Treatment of phenylthioacetic acid in dry tetrahydrofuran at 0° for 1 hr with 2 equiv of lithium diisopropylamide in tetrahydrofuran gave a solution of the dianion 1, which is stable at that temperature. The formation and stability of the dianion 1 was verified by quenching with deuterium oxide, incorporating one deuterium atom at the methylene position of the starting material. Slow addition of a solution of an excess of freshly purified terminal epoxide 2 in tetrahydrofuran to the solution of the dianion 1 at -60° followed by stirring at -60° for 1 hr and then gradually warming to room temperature within ca. 15 hr afforded after usual work-up crude addition product, which



was completely lactonized by heating in refluxing benzene containing a trace of concentrated sulfuric acid (3 hr, employing a water-separator) to give a mixture of *cis* and *trans* γ-substituted α-phenylthio-γ-butyrolactone 3 . Oxidation of 3 with either sodium metaperiodate (in aqueous methanol, room temperature, *ca.* 12 hr), 30% hydrogen peroxide (in aqueous methanol, room temperature, 4 days), or *m*-chloroperbenzoic acid (in methylene chloride, 0°, 30 min) gave the sulfoxide 4 . Elimination of the α-phenylsulfinyl group of 4 was accomplished by pyrolysis at *ca.* 110° in toluene or pyridine to yield the γ-substituted $\Delta^{\alpha,\beta}$-butenolide 5 in moderate overall yields.[3,5]

This procedure was also effectively applicable to a synthesis of $\Delta^{\alpha,\beta}$-butenolide having the same substituents at β and γ positions starting with a symmetrical epoxide (for example cyclohexene oxide). The typical examples of this process are summarized in Table I.

The dianion 1 was easily alkylated by treatment with alkyl halides (-60° – room temperature, overnight) to give the homologous α-phenylthiocarboxylic acids, which also form the dianions in the same manner. Thus, application of the method to these dianions provides a synthetic process leading to the α,γ-disubstituted $\Delta^{\alpha,\beta}$-butenolides as depicted in Table II.[6] In these examples, an unsaturation was exclusively introduced to an endocyclic α,β-position.[8,9]

Furthermore, we have examined the analogous reaction using the ester of phenylthioacetic acid. Ethyl phenylthioacetate was also lithiated in the same manner (1 equiv lithium diisopropylamide) as its free acid.[11] At present, however, the reaction of the lithio derivative with an epoxide (propylene oxide) gave an unsatisfactory result, yielding γ-methyl-α-phenylthio-γ-butyrolactone (3, $R=CH_3$) in low yield (36%).

Further works on the reactivities of the dianion 1 and the convenient processes for the preparation of other variously substituted $\Delta^{\alpha,\beta}$-butenolide derivatives are in progress.

References

1) For a review of butenolides, see Y. S. Rao, Chem. Rev., 64, 353 (1964).

2) Recently alternative processes leading to γ-substituted $\Delta^{\alpha,\beta}$-butenolides have been reported. (a) For the synthesis of γ-substituted $\Delta^{\alpha,\beta}$-butenolides *via* ynoic ester hydrogenation, see A. Nobuhara, Agr. Biol. Chem., 34, 1745 (1970). See also Ref. 10. (b) For the synthesis of β,γ-disubstituted $\Delta^{\alpha,\beta}$-butenolides *via* organocopper - ynoic ester addition, see E. J. Corey, C. U. Kim, R. H. K. Chen, and M. Takeda, J. Amer. Chem. Soc., 94, 4395 (1972). (c) For the synthesis of γ-substituted and β,γ-disubstituted $\Delta^{\alpha,\beta}$-butenolides *via* β-ketosulfoxide condensation, see M. Kurono, K.

Table I. γ-Substituted $\Delta^{\alpha,\beta}$-Butenolide[a]

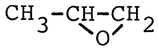
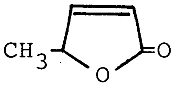
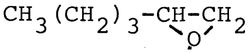
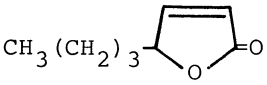
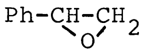
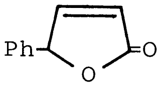
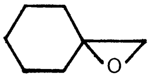
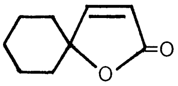
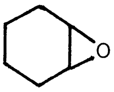
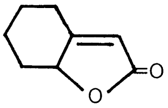
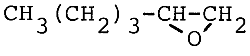
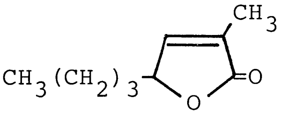
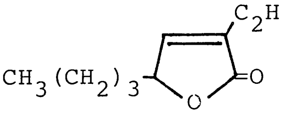
Epoxide[b]	Phenylthio-lactone[c,d,e]	Sulfoxide lactone[f]	Butenolide[c,e]	
	%	%		%
 $CH_3\text{-}\underset{O}{CH\text{-}CH_2}$	70	quant[e]	 [g]	74
 $CH_3(CH_2)_3\text{-}\underset{O}{CH\text{-}CH_2}$	94	"	 [g]	82
 $Ph\text{-}\underset{O}{CH\text{-}CH_2}$	94	"	 [h]	80
	90	"		83
	68	" [e]		82

Table II. α,γ-Disubstituted $\Delta^{\alpha,\beta}$-Butenolide[a]

Alkylating Reagent		b	e,i			e,j
	%[c]					
CH_3I	93	 $CH_3(CH_2)_3\text{-}\underset{O}{CH\text{-}CH_2}$	88	k		63
C_2H_5Br	quant	"	73	k	 [l]	78

(a) Yields are not necessarily optimum. Satisfactory infrared and nuclear magnetic resonance spectra were obtained for purified samples of all compounds. (b) About 1.2 equiv of epoxides were employed except propylene oxide (somewhat large excess). (c) Yields are for isolated pure products. (d) Yields are based on phenylthioacetic acid used. (e) Pure samples gave the satisfactory analytical results. (f) Yields are for total crude products. (g) This compound was also identified with the authentic sample. (h) Isolated total crude product was almost pure $\Delta^{\alpha,\beta}$-isomer as determined by nmr spectrum but partially isomerized to the $\Delta^{\beta,\gamma}$-isomer during purification by chromatography on silica gel. When pyrolysis was performed in pyridine the $\Delta^{\beta,\gamma}$-isomer was obtained as a sole product. (i) Yields are based on the alkylated phenylthioacetic acids. (j) Yields are based on phenylthiolactones. (k) Elimination of the phenylsulfinyl group occurred partially during work-up and complete elimination was accomplished by heating at 60°–70°. (l) In this case, pyrolysis was carried out in refluxing carbon tetrachloride in the presence of 2-mercaptobenzothiazole for removing sulfur-containing by-products,[12] because of difficulty of separation by simple column chromatography.

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, p1623.

3) Trost and Salzmann[4] have recently developed the same reaction sequence as 3 ⟶ 5, thio ether ⟶ oxidation to sulfoxide ⟶ elimination of sulfinyl group, as a method for introduction of unsaturation α,β to carbonyl groups including ketone, ester, and lactone, starting from α-sulfenylation of these substrates.

4) B. M. Trost and T. N. Salzmann, J. Amer. Chem. Soc., 95, 6840 (1973).

5) See also Ref. 10.

6) Recently, the α,γ-dialkylsubstituted $\Delta^{\alpha,\beta}$-butenolides were isolated from natural sources.[7] The procedure recorded above would be applicable to the synthesis of these natural products.

7) N. N. Gerber, Tetrahedron Lett., 771 (1973).

8) Cf. Ref. 4.

9) In contrast with these observations, exclusive formation of an exocyclic double bond (an α-methylene-γ-butyrolactone system) by similar elimination of a methylsulfinyl group in a fused bicyclic α-methyl-α-methylsulfinyl-γ-lactone derivative has been recently reported.[10]

10) J. L. Herrmann, M. H. Berger, and R. H. Schlessinger, J. Amer. Chem. Soc., 95, 7923 (1973).

11) For formation and reaction of an α-lithio-α-methylthiocarboxylate, see Ref. 10.

12) T. Kamiya, T. Teraji, Y. Saito, M. Hashimoto, O. Nakaguchi, and T. Oku, Tetrahedron Lett., 3001 (1973).

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