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CARBANION OF *O*-ETHYL *S*-(TETRAHYDRO-2-OXO-3-FURANYL) THIOCARBONATE: A NEW REAGENT FOR THE STEREOSELECTIVE SYNTHESIS OF α-ALKYLIDENE-γ-BUTYROLACTONES FROM CARBONYL COMPOUNDS

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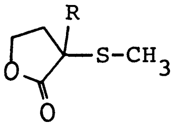
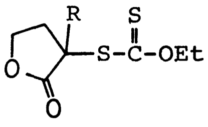
The lithium salt of *O*-ethyl *S*-(tetrahydro-2-oxo-3-furanyl) thiocarbonate was found to be an efficient reagent for the stereoselective synthesis of α-alkylidene-γ-butyrolactones from carbonyl compounds.

Synthetic routes to α-alkylidene-γ-butyrolactones have received considerable attention in recent years$^{1)}$ because of their biological activity.$^{2)}$ Since carbonyl compounds are readily available in organic synthesis, direct procedure for the preparation of α-alkylidene-γ-butyrolactones from carbonyl compounds is very attractive. There are, however, only a few reports on the one-step synthesis of these compounds.$^{3)}$ We wish to report here the new synthetic methodology for stereoselective synthesis of α-alkylidene-γ-butyrolactones using sulfur-stabilized carbanion. A difficulty encountered in the reaction of the above carbanion lies in the lack of nucleophilic reactivity toward carbonyl groups. For example, it is reported that anion II of α-methylthio-γ-butyrolactone (I) did not react with cyclohexanone.$^{4)}$

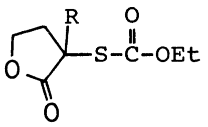
We have found that the carbanion IV derived from *O*-ethyl *S*-(tetrahydro-2-oxo-3-furanyl) dithiocarbonate (III) is a convenient reagent for the preparation of α-alkylidene-γ-butyrolactones from carbonyl compounds.



I, R=H
II, R=Li

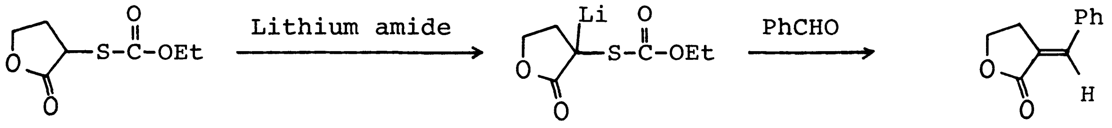


III, R=H
IV, R=Li



V, R=H
VI, R=Li

Treatment of III (20 mmol) with lithium diisopropylamide (22 mmol) at -78°C in dry THF (40 ml) produced a yellow solution of anion IV. After 40 min, a solution of benzaldehyde (22 mmol) in 3 ml of dry THF was added dropwise during 2 min. After stirring for 2 h at -78°C, the bath was removed and the reaction mixture allowed to warm to room temperature for 1 h, during which time the solution became deep red. Aqueous workup gave a 60% yield of (*E*)-α-benzylidene-γ-butyrolactone, mp 117.5-118.5°C (lit,[3b]) mp 118.5°C). Unfortunately, an attempt to purify the starting material III by vacuum distillation failed due to its decomposition. In order to avoid the redundant operation by column chromatography, the corresponding monothiocarbonate V was prepared in 91% yield by the addition of triethylamine to a solution of α-mercapto-γ-butyrolactone[5]) and ethyl chloroformate in benzene. Compound V was easily purified by distillation, bp 122°C/0.6 mmHg. Therefore, this monothiocarbonate is the preferred reagent for synthetic purpose.



VII

Table 1. Effect of lithium amide structure on product yields

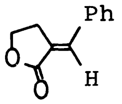
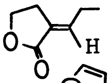
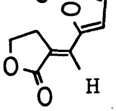
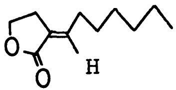
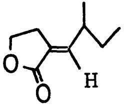
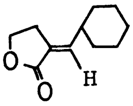
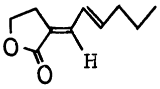
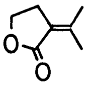
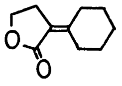
Lithium amide[a)]	Yield of VII[b)] %
(*i*-Pr)$_2$NLi	53
(*i*-Pr)$_2$NLi-TMEDA[c)]	54
(Me$_3$Si)$_2$NLi	39
Et$_2$NLi	84

a) Reactions were carried out on a 20 mmol scale.
b) Isolated yields based on V.
c) N,N,N',N'-Tetramethylethylenediamine.

Among the various amide examined, lithium diethylamide (LDEA) was found to be the most effective base for the generation of anion VI from V as indicated in

Table 1. The generation and reaction of VI with electrophiles is as follows. Into a solution of LDEA (22 mmol) in dry THF (40 ml) at -78°C was added dropwise monothiocarbonate V (20 mmol) in 5 ml of dry THF. After stirring for 1 h at -78°C, aldehyde (25 mmol) in 3 ml of dry THF was added over 2 min. After a reaction time of 2 h at -78°C, the cooling bath was removed and the mixture stirred for an additional 1 h. Workup and purification gave mainly *E*-geometry of α-alkylidene-γ-butyrolactone in a high yield as shown in Table 2.

Table 2. Reaction of carbanion VI with carbonyl compounds

Carbonyl compound	Product	Yield[a) %]	E/Z[b)]
Benzaldehyde		84	100/0
Propionaldehyde		78	94/6
2-Furaldehyde		75	100/0
Heptanal		83	94/6
2-Methylbutyraldehyde		93	85/15
Cyclohexanecarboxaldehyde		82	92/8
(*E*)-2-Hexenal		76	91/9
Acetone		75	--
Cyclohexanone		65	--

a) Yield of isolated product. b) Determined by NMR and GLPC.

The effectiveness of this novel anion as a powerful nucleophile was demonstrated for the reaction with ketones. These findings indicate the anion VI to be a highly efficient reagent for the stereoselective introduction of a new carbon-carbon double bond on the α-position of γ-butyrolactone under mild conditions, where the desulfurizing agents such as heavy metals or trivalent phosphine compounds are not required.[6)]

Research on the scope and limitation of these reactions is currently being investigated.

References and Notes

1) R. B. Grammill, C. A. Wilson, and T. A. Bryson, Synth. Commun., 5, 245 (1975), and references cited therein.

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6) For the mechanistic pathway of this reaction, see K. Tanaka, R. Tanikaga, and A. Kaji, Chem. Lett., 1976, 917.

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