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DIANION OF α-MERCAPTO-γ-BUTYROLACTONE: AN EFFICIENT REAGENT FOR THE STEREOSELECTIVE SYNTHESIS OF α-ALKYLIDENE-γ-BUTYROLACTONES FROM CARBONYL COMPOUNDS

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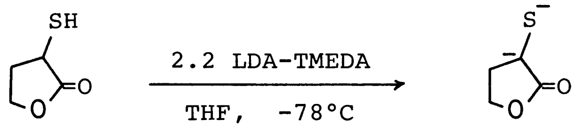
Dianion of α-mercapto-γ-butyrolactone was successfully generated by treating α-mercapto-γ-butyrolactone with lithium diisopropylamide-N,N,N',N'-tetramethylethylenediamine at -78°C in THF. This dianion was found to be highly reactive toward electrophilic reagents. A new methodology for the stereoselective synthesis of α-alkylidene-γ-butyrolactones by one-pot procedure has been developed.

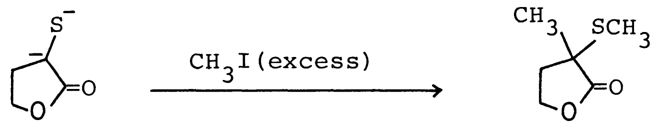
The utilization of dianions in organic synthesis might provide a very useful method for the construction of complex molecules, if the reaction of dianions with two different electrophiles proceeds regioselectively.1) In the previous communication, we have reported the efficient reagents for the synthesis of α-alkylidene-γ-butyrolactones,2) which have recently received considerable attention because of their biological activity.3) A recent survey indicates that there are no general and direct methods for preparing α-alkylidene-γ-butyrolactones from carbonyl compounds with high stereoselectivity.3) We now wish to report the successful generation of the heretofore unknown dianion of α-mercapto-γ-butyrolactone and its application to the stereoselective synthesis of α-alkylidene-γ-butyrolactones.

Treatment of the readily available α-mercapto-γ-butyrolactone4) (I) with 2.2 molar equiv of lithium diisopropylamide (LDA) in the presence of N,N,N',N'-tetramethylethylenediamine (TMEDA) in dry THF at -78°C resulted in formation of dianion II.



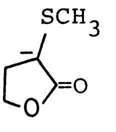
I   II

The presence of dianion II was ascertained by treating II with excess of CH_3I to afford an excellent yield of dimethylation product III, which is an important precursor of α-methylene-γ-butyrolactone, Tulipalin A.5)



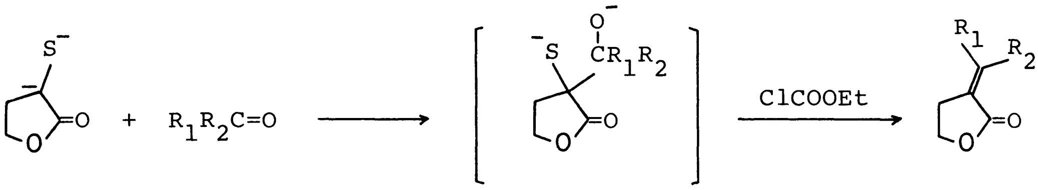
II III (93%)

Comparison of this result with the yield (37%) obtained using monoanion (IV) of α-methylthio-γ-butyrolactone[5)] illustrates the efficiency of this new dianion.



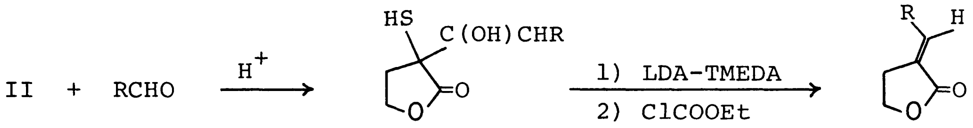
IV

The dianion II was condensed with aldehydes to give adducts V which were subsequently converted to *E*-isomer of α-alkylidene-γ-butyrolactones (VII) upon treatment with ethyl chloroformate. The generality of this new procedure is apparent from the results summarized in Table.



II V VII

The intermediate addition product VI could be readily isolated by quenching the reaction mixture of dianion and aldehyde with aqueous NH_4Cl at low temperature. Similar treatment of adducts VIa and VIb with LDA-TMEDA followed by treatment of the resulting dianions Va and Vb with ethyl chloroformate in THF gave α-alkylidene-γ-butyrolactones VIIa and VIIb in 35% and 42% yields, respectively.[6)]



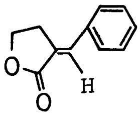
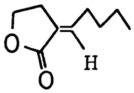
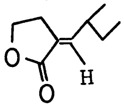
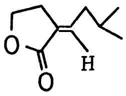
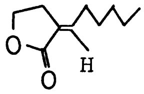
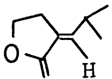
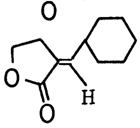
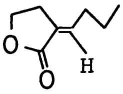
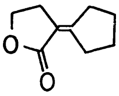
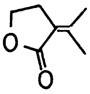
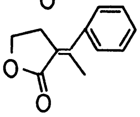
a: R=Ph VIa: 76% VIIa: 35% (*E*-isomer only)

b: R=$CH_3(CH_2)_3$ VIb: 87% VIIb: 42% (*E*/*Z*=96/4)

The effectiveness of this dianion as a highly reactive nucleophile is further demonstrated for the facile reaction even with highly enolizable ketones such as cyclopentanone (Table).

A typical experiment consisted of adding α-mercapto-γ-butyrolactone (20 mmol) in 7 ml of dry THF dropwise to the mixture of LDA (44 mmol) and TMEDA (44 mmol) in 40 ml of dry THF at -78°C. After stirring for 1 h, a solution of valeraldehyde (40 mmol) in 5 ml of dry THF was added and the reaction mixture was stirred at -78°C for 2 h. Ethyl chloroformate (20 mmol) in 5 ml of dry THF was then added portionwise to the above solution with stirring and the resulting mixture was maintained at -78°C for 30 min and at room temperature for 1 h. Usual workup and distillation and/or silica gel chromatography gave a 95:5 mixture of *E*-isomer and *Z*-isomer of α-pentylidene-γ-butyrolactone in 69% isolated yield, bp 83-85°C/0.35 mmHg; Anal. Found: C, 69.80; H, 9.03%. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15%.

Table. Product yields obtained by reaction of dianion II with carbonyl compounds

Carbonyl compound	Product[a)]		Yield[b)] %	E/Z[c)]	Bp or mp, °C
Benzaldehyde		(VIIa)	54	100/0	117.5-118.5[d)]
Valeraldehyde		(VIIb)	69	95/5	83-85(0.35mmHg)
2-Methylbutanal		(VIIc)	51	93/7	85-87(0.7mmHg)
Isovaleraldehyde		(VIId)	64	95/5	93-94(0.8mmHg)
Hexanal		(VIIe)	67	92/8	115-117(1.1mmHg)
Isobutyraldehyde		(VIIf)	61	95/5	83-84(1.0-1.1 mmHg)
Cyclohexanecarboxaldehyde		(VIIg)	59	95/5	131-134(1.0mmHg)
Butyraldehyde		(VIIh)	61	97/3	88-94(0.8mmHg)
Cyclopentanone		(VIIi)	43	--	110-135(1.1-1.3 mmHg)
Acetone		(VIIj)	50	--	71-73(0.9mmHg)
Acetophenone		(VIIk)	40	100/0	123(0.5mmHg) 75-78

a) All products gave satisfactory analytical results and spectral data (IR, NMR, and mass).[7)]

b) Isolated yields.

c) Determined by NMR and GLPC.

d) Lit.[3c)] mp 118.5°C.

In conclusion, the present method represents a new and general method for the introduction of alkylidene functionality with a high degree of stereoselectivity on the α-position of γ-butyrolactone under exceedingly mild conditions where no redundant desulfurization procedure using heavy metals is necessary.[8]

Additional experiments are underway to determine the full potential of this new reagent.

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References and Notes

1) E. M. Kaiser, J. D. Petty, and P. L. A. Knutson, Synthesis, 1977, 509.

2) K. Tanaka, N. Yamagishi, H. Uneme, R. Tanikaga, and A. Kaji, Chem. Lett., 1978, 197.

3) a) R. B. Grammil, C. A. Wilson, and T. A. Bryson, Synth. Commun., 5, 245 (1975), and references cited therein.
   b) P. A. Grieco, Synthesis, 1975, 67.
   c) T. Minami, I. Niki, and T. Agawa, J. Org. Chem., 39, 3236 (1974).
   d) P. A. Grieco, C-L. J. Wang, and S. D. Burke, J. Chem. Soc., Chem. Commun., 1975, 537.

4) G. Fucks, Ark. Kemi, 26, 111 (1966); Chem. Abstr., 66, 28363g (1967).

5) B. M. Trost, T. N. Salzmann, and K. Hiroi, J. Am. Chem. Soc., 98, 4883 (1976).

6) VIa: mp 125-125.5°C. VIb: bp 128-131°C/2.0mmHg.

7) VIIa: NMR($CDCl_3$) δ=3.22 (dt, J=3.3 and 7.4Hz, 2H), 4.44 (t, J=7.5Hz, 2H, -CH_2O-), 7.2-7.6 (m, 6H, aromatics and =CH-). VIIb: NMR(CCl_4) δ=0.95 (t, 3H, -CH_3), 1.1-1.6 (m, 4H), 1.9-2.3 (m, 2H), 2.82 (m, 2H), 4.24 (t, J=7.1Hz, 2H, -CH_2O-), 6.47 (m, 1H, -CH= of *E*-isomer). VIIc: NMR(CCl_4) δ=0.89 (t, 3H, CH_3-), 1.06 (d, 3H, CH_3-), 1.45 (m, 2H), 2.1-2.4 (m,1H), 2.87 (dt, J=3 and 7.4Hz, 2H), 4.31 (t, J=7.4Hz, 2H, -OCH_2-), 6.41 (td, J=3 and 10Hz, 1H, -CH= of *E*-isomer), 6.02 (td, 0.05H, -CH= of *Z*-isomer). VIId: NMR(CCl_4) δ=0.95 (d, J=6.8Hz, 6H), 1.6-2.2 (m, 3H), 2.81 (m, 2H), 4.24 (t, J=7.4Hz, 2H, -OCH_2-), 6.48 (m, 1H, -CH= of *E*-isomer), 6.10 (m, 0.04H, -CH= of *Z*-isomer). VIIe: NMR(CCl_4) δ=0.89 (t, J=5.9Hz, 3H), 1.1-1.7 (m, 6H), 1.9-2.3 (m, 2H), 2.83 (m, 2H), 4.23 (t, J=7.6Hz, 2H, -OCH_2-), 6.46 (m, 1H, -CH= of *E*-isomer), 6.10 (m, 0.04H, -CH= of *Z*-isomer). VIIf: NMR(CCl_4) δ=1.06 (d, 6H), 2.3-2.7 (m, 1H), 2.87 (dt, J=2.6 and 7.1Hz, 2H), 4.27 (t, J=7.1Hz, 2H, -OCH_2-), 6.34 (td, 1H, -CH= of *E*-isomer), 5.94 (td, 0.05H, -CH= of *Z*-isomer). VIIg: NMR(CCl_4) δ=0.8-2.4 (m, 11H), 2.82 (dt, 2H), 4.22 (t, J=7.1Hz, 2H, -OCH_2-), 6.34 (td, 1H, -CH= of *E*-isomer), 5.94 (td, 0.04H, -CH= of *Z*-isomer). VIIh: NMR(CCl_4) δ=0.98 (t, 3H), 1.2-1.7 (m, 2H), 2.18 (m, 2H), 2.84 (m, 2H), 4.27 (t, J=7.6Hz, 2H, -OCH_2-), 6.53 (m, 1H, -CH= of *E*-isomer), 6.12 (m, 0.05H, -CH= of *Z*-isomer). VIIi: NMR(CCl_4) δ=1.70 (m, 4H), 2.26 (m, 2H), 2.70 (m, 4H), 4.15 (t, J=7.6Hz, 2H, -OCH_2-). VIIj: NMR (CCl_4): δ=1.88 (br s, 3H, CH_3-), 2.20 (br s, 3H, CH_3-), 2.84 (m, 2H), 4.20 (t, J=7.6Hz, 2H, -OCH_2-). VIIk: NMR($CDCl_3$) δ=2.57 (t, 3H, CH_3-), 2.88 (m, 2H, -CH_2-), 4.22 (t, J=7.1Hz, 2H, -OCH_2-), 7.1-7.5 (m, 5H, aromatics).

8) For the mechanistic pathway of this reaction, see K. Tanaka, N. Yamagishi, R. Tanikaga, and A. Kaji, Chem. Lett., 1977, 471.

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