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# Lithiated Dimethylketene Diisopropyl Dithioacetal as a Synthon of Homoenolate Dianion of Isobutyric Ester. An Application to the Synthesis of α-Methylenelactones

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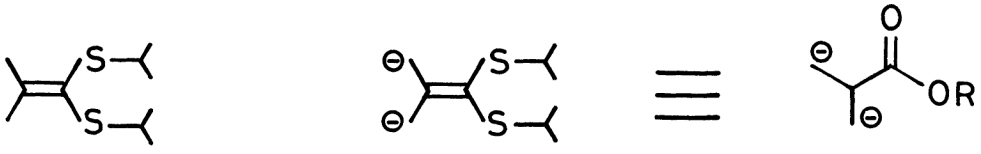
Lithium anion of dimethylketene diisopropyl dithioacetal reacted with various kinds of electrophiles to afford γ-substituted products with high regioselectivity. The utility of the lithiated ketene dithioacetal, a novel homoenolate dianion equivalent of isobutyric ester, was demonstrated in the synthesis of α-methylenelactones.

Ketene dithioacetals have recently been introduced as a useful acyl or homoenolate anion equivalent.[1] In the reaction of their lithium anions with electrophiles, however, it has remained an important problem to control the ratio of α vs. γ substitution. In general their lithium anions preferentially react at the "harder" α-site with alkyl halides and at the "softer" γ-site with carbonyl compounds.[1] The regioselectivity appears to depend on a number of factors,[1c] one of which is the steric bulkiness of the substituents on the ketene dithioacetals.[2] The regioselectivity can be controlled by utilizing the steric effect, that is, γ-regioselectivity increases with increasing the steric congestion of α-site. To demonstrate this effect, dimethylketene diisopropyl dithioacetal (1) having sterically congested α-site was chosen as a starting substrate in this research. If 1 is able to undergo successively the above lithiation-substitution sequence at the both γ-sites, it will be available as a synthon of homoenolate dianion (2) of isobutyric ester. We wish to describe here the high regioselectivity in the reaction of 1 with various kinds of electrophiles, and the utility of 1 as the homoenolate dianion equivalent.

The compound 1, prepared easily from lithium salt of trimethylsilylformaldehyde diisopropyl dithioacetal and acetone,[3] was lithiated by lithium diisopropylamide (LDA) (1.5 equiv.) in THF and 3 equiv. of hexamethylphosphoric triamide (HMPA). Then the resulting anion (3) was treated with electrophiles (1.1 equiv.) to give the γ-substituted products (4) and the α-substituted products (5). These two regioisomers could be easily separated from each other by preparative TLC. The result of the reaction of 3 with various kinds of electrophiles is summarized in




1 2

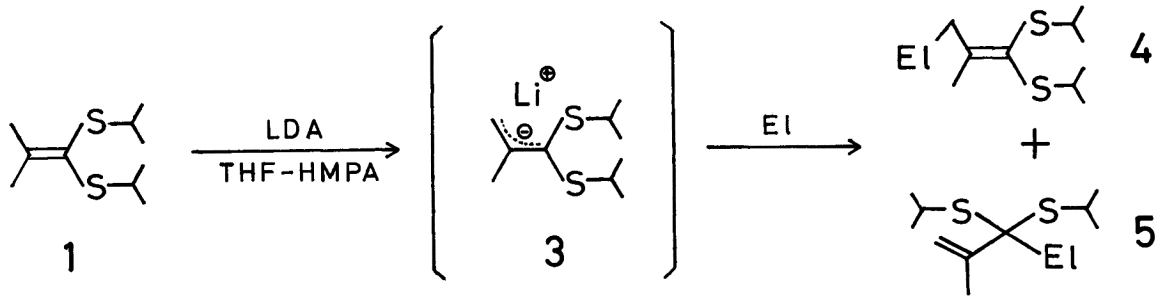


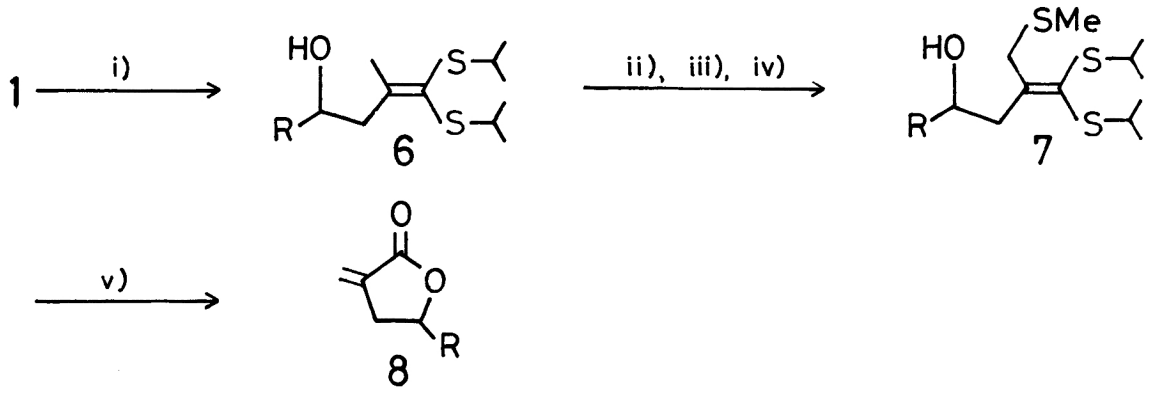

Table 1.

Alkylation with various alkyl halides took place at the γ-site with over 90% regioselectivity to give the ketene dithioacetals 4 (entries 1—4). The high γ-regioselectivity in the present reaction may be attributed to the steric congestion caused by the two isopropyl and two β-methyl groups in 1. Compared to the lack of regioselectivity (γ to α ratio of 45 : 55) in the allylation of lithiated methylketene diisopropyl dithioacetal bearing only one methyl group,[2] the presence of two β-methyl groups caused the high γ to α ratio of 90 : 10 (entry 3). Surprisingly the reaction with alkyl or aryl disulfides gave only the γ-sulfenylated products 4 (entries 5 and 6), in contrast to α-sulfenylation of 2-pentylidene-1,3-dithiane[1e] or 2-styryl-1,3-dithiane[4] with methyl disulfide. The high regioselectivity of the sulfenylation can be reasonably explained by the hard and soft acids and bases principle that the accepter property of disulfide is softer than that of alkyl halide.[5] The lithium anion 3 reacted with carbonyl compounds to give exclusively γ-substituted products 4 (entries 7—10). Thus the lithium anion 3 was found to give γ-substituted products 4 regardless of the kind of electrophiles.

Table 1. Reaction of the lithium anion 3 with various kinds of electrophiles[a]

| Entry | Electrophile | Yield/%[b] 4 + 5 | Ratio[c] 4 : 5 |
|---|---|---|---|
| 1 | $CH_3I$ | 79 | 93 : 7 |
| 2 | $(CH_3)_2CH(CH_2)_3I$ | 65 | 91 : 9 |
| 3 | $CH_2=CHCH_2Br$ | 74 | 90 : 10 |
| 4 | $C_6H_5CH_2Br$ | 77 | 96 : 4 |
| 5 | $CH_3SSCH_3$ | 69 | 100 : 0 |
| 6 | $C_6H_5SSC_6H_5$ | 34[d,e] | 100 : 0 |
| 7 |  | 40 | 100 : 0 |
| 8 | HCHO | 42 | 100 : 0 |
| 9 | $CH_3CH_2CHO$ | 57 | 100 : 0 |
| 10 | $C_6H_5CHO$ | 80 | 100 : 0 |

a) All reactions were performed on 0.5 mmol scale with the same procedure as described in the text. b) All products were identified by NMR and IR spectra. c) The regioisomers 4 and 5 were easily separated by preparative TLC. d) By-product was disulfenylated product. e) Lithium anion 3 was added to the disulfide.




i) LDA, THF-HMPA, RCHO, -78 °C → rt. ii) DHP, Pyridinium *p*-toluenesulfonate, $CHCl_3$, rt. iii) LDA, THF-HMPA, $CH_3SSCH_3$, -78 °C → rt. iv) *p*-TsOH, MeOH, rt. v) $4CuCl_2$-6CuO, aqueous 99% acetone reflux.

Moreover, another β-methyl group can also be altered according to the analogous pathway involving lithiation and the subsequent γ-regioselective substitution. This suggests a possibility that the lithium salt of 1 is equivalent to the homoenolate dianion 2 of isobutyric ester. The possibility was realized in the following α-methylenelactone synthesis. The frequent occurrence of α-methylenelactone structure in sesquiterpenes and the other natural products has resulted in a continued development of synthetic methods for them.[6] Our synthetic route is shown in the above scheme. The hydroxyketene dithioacetal (6) was protected with 2,3-dihydro-4*H*-pyran (DHP), followed by sulfenylation with methyl disulfide and deprotection affording hydroxysulfide (7) without any other regioisomers. Lactonization of 7 (R = $C_2H_5$) with trifluoroacetic acid[1a] gave a mixture of α-methylthiomethyl- and α-isopropylthiomethyl-γ-ethyl-γ-butyrolactones in 73% yield, which was oxidized with $NaIO_4$, followed by desulfinylation to give γ-ethyl-α-methylene-γ-butyrolactone (8) in 85% yield. However, this three-step method could not be applied to the case of 7 (R = $C_6H_5$), because the dehydration occurred preferentially to produce 2-methylthiomethyl-4-phenyl-1,1-bis(isopropylthio)-1,3-butadiene under the acidic conditions on the lactonization step. On the contrary, hydrolysis of 7 (R = $C_6H_5$) under neutral conditions using cupric chloride and cupric oxide[7] gave α-methylenelactone 8 in 69% yield in one step. The result of α-methylenelactone synthesis using the one-step procedure is listed in Table 2. α-Methylene-γ-butyrolactone (entry 1) is a natural product, tulipalin A, isolated from tulip bulbs.[8] α-Methylene-γ-phenyl-γ-butyrolactone (entry 3) has been reported to exhibit

Table 2. Synthesis of α-methylenelactones[a]

| Entry | R | Yield of 7 % | Yield of 8 % |
|---|---|---|---|
| 1 | H | 37 | 34 |
| 2 | $C_2H_5$ | 79 | 52 |
| 3 | $C_6H_5$ | 57 | 69 |

a) All products were identified by NMR and IR spectra.

the same degree of plant growth inhibitory activity as that of heliangine, a sesquiterpene lactone isolated from *Helianthus tuberosus L.*[9]

A typical procedure is described for the reaction of the lithium anion of 1 with allyl bromide. To a solution of lithium diisopropylamide (0.75 mmol) in THF (2 ml) was added HMPA (1.5 mmol) and a solution of 1 (0.50 mmol) in THF (2 ml) at -25 °C, successively. After stirring for 2 h at the same temperature, the reaction mixture was cooled to -78 °C and a solution of allyl bromide (0.55 mmol) in THF (2 ml) was added. Then, the reaction mixture was warmed slowly to room temperature over a period of 13 h, and quenched with a saturated aqueous solution of ammonium chloride at 0 °C. The organic layer was extracted with ether, and dried over anyhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on silica gel (hexane) to give 1,1-bis(isopropylthio)-2-methyl-1,5-hexadiene and 3,3-bis(isopropylthio)-2-methyl-1,5-hexadiene in 67% and 7% yields, respectively.

In conclusion, the lithium anion of 1 reacted regioselectively at γ-site with various electrophiles, and its utility as a homoenolate dianion equivalent of isobutyric ester was demonstrated in the synthesis of α-methylenelactones.

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