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THE HIGHLY SELECTIVE REACTION OF LITHIUM DITHIOESTER ENOLATES WITH β-ALKENYL-β-PROPIOLACTONES: A SIMPLE METHOD FOR THE SYNTHESIS OF 6-(METHYLTHIO)THIOCARBONYL-(E)-3-ALKENOIC ACIDS

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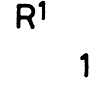
Lithium dithioester enolates were found to react with β-alkenyl-β-propiolactones highly regio- and stereoselectively at the terminal vinyl carbon to give 6-(methylthio)thiocarbonyl-(*E*)-3-alkenoic acids, masked 1,7-dicarboxylic compounds.

Displacement reaction of allylic esters with carbon nucleophiles has provided a useful method for regio- and stereoselective olefin synthesis by a carbon-carbon bond formation.[1)] Lactones with unsaturated substituent at the ω-position, one of allylic esters, are much useful as a building block for the natural product syntheses.[2)] Recently, β-ethynyl- and β-vinyl-β-propiolactones have been found to be useful five-carbon blocks for the syntheses of several natural products.[3)] In these reactions organocopper reagents have been generally employed as carbon nucleophiles. If ester enolates or their equivalents successfully work as carbon nucleophiles, it enlarges the scope of the building blocks of the lactones. Herein, we report an efficient way to synthesize 6-(methylthio)thiocarbonyl-(*E*)-3-alkenoic acids (3) by a highly regio- and stereoselective S_N2' type reaction of β-vinyl- and β-isopropenyl-β-propiolactones (1) with lithium dithioester enolates (2).

When β-vinyl-β-propiolactone (1; R^1 = H) was treated with lithiated methyl dithioacetate (2; R^2,R^3 = H) in THF at -78 °C, 6-(methylthio)thiocarbonyl-3-hexenoic acid (3) was obtained in 80% yield. This reaction exclusively took place at the terminal vinyl carbon of 1 without any formation of isomers 4 and 5, yielded



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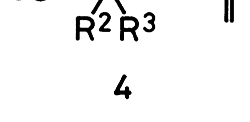

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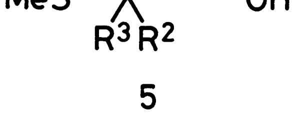

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Table 1. Yields of 6-(Methylthio)thiocarbonyl-(*E*)-3-alkenoic Acids (3) by the Reaction of β-Vinyl- and β-Isopropenyl-β-propiolactones (1) with Lithiated Dithioesters (2)[a)]

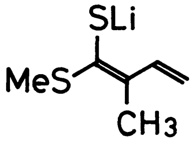
Entry	R^1	R^2	R^3	Yield of 1/% [b)]
1	H	H	H	80
2	H	CH_3	H	87
3	H	C_6H_5	H	63
4	H	CH_3	CH_3	75[c)]
5	H	$-CH_2(CH_2)_3CH_2-$		28
6	CH_3	H	H	84
7	CH_3	CH_3	H	88
8	CH_3	C_6H_5	H	72[c)]
9	CH_3	CH_3	CH_3	50
10	CH_3	$-CH_2(CH_2)_3CH_2-$		34

a) All reactions were carried out on 1 mmol scale with the same procedure as described in the text. All products were identified by IR and NMR spectra. b) Isolated by distillation (Kugelrohr). c) Isolated by TLC on silica gel.

by the addition to the acyl carbon and the S_N2 type reaction at the β-carbon, respectively. In contrast to the effect of a copper catalyst in the reaction of 1 with Grignard reagent,[3)] increasing the ratio of S_N2' product rather than S_N2 product, the addition of copper(I) iodide (2 mol%) in the present reaction decreased the yield of the S_N2' product 3 to 38% along with polymeric products.

Our previous result[4)] shows that the reaction of soft nucleophiles regioselectively occurs at the soft reaction site of the terminal vinyl carbon of 1. The present results suggest that lithium dithioester enolates are one of the soft nucleophiles as equal as organocopper reagent.[5)]

Table 1 summarizes some of the results obtained by the reaction of β-vinyl- and β-isopropenyl-β-propiolactones with various kinds of lithiated dithioesters.[6)] Both of methyl dithioacetate (entries 1 and 6) and methyl propanedithioate (entries 2 and 7) gave the corresponding carboxylic acids in high yields. However, bulky dithioesters, such as methyl 2-methylpropanedithioate (entry 9) and methyl cyclohexanecarbodithioate (entries 5 and 10) gave poor results. It has suggested that the stereochemistry of newly formed double bond in these products should be E isomer fairly predominant from strong IR absorption at 950 cm^{-1} and capillary GLPC



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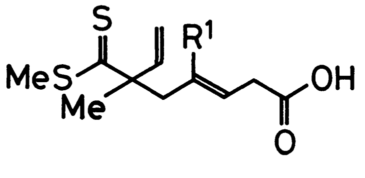
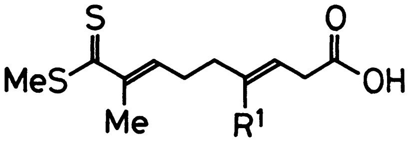


7 (α-adduct)

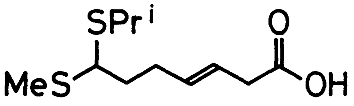


8 (γ-adduct)

(FFAP, 50 m) analysis.[7)]

The reaction of β-vinyl- and β-isopropenyl-β-propiolactones with lithiated methyl 2-methyl-3-butenedithioate (6), which has two reaction points on α- and γ-carbons, was also successfully carried out with high regioselectivity in THF at -78 °C. Both of the lactones gave exclusively the corresponding α-adducts 7 in yields of 80% and 78%, respectively, without any formation of γ-adducts 8.

The brief survey for the synthetic potential of the products obtained in the present reaction was examined as follows. Thiophilic addition[8)] of alkyl Grignard reagent to dithioester is well recognized to give a dithioacetal carbanion which is alkylated by various electrophiles.[9)] When 3 (R^1,R^2,R^3 = H) was treated with 3 equiv. of isopropylmagnesium bromide in THF at -40 °C for 40 min, dithioacetal 9 was obtained in 46% yield after treatment of 2 M aqueous HCl solution. It is also well known that dithioacetals are easily converted into carbonyl compounds, such as ketone, and aldehyde.[10)] The carboxylic part of 3 was selectively reduced to the corresponding alcohol 10 in 88% yield by lithium aluminum tri-*t*-butoxyhydride using *N*,*N*-dimethylchloromethyleniminium chloride as an activating reagent of carboxylic acid, that was developed in our laboratory.[11)] Thus, the selective conversion either of the carboxylic or dithioester moiety into other functional groups such as ketone, aldehyde or alcohol was successfully achieved.



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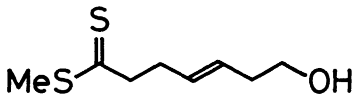

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The following procedure for the synthesis of 6-(methylthio)thiocarbonyl-3-hexenoic acid (3; R^1,R^2,R^3 = H) is representative for the present reaction; Methyl dithioacetate (1.1 mmol) was lithiated by lithium diisopropylamide (1.2 mmol) in THF (2 ml) at -78 °C under argon. β-Vinyl-β-propiolactone (1.0 mmol) was slowly added at the same temperature. The mixture was stirred at -78 °C for 2 h and quenched by adding 2 M aqueous HCl solution, and the organic layer was extracted with ether. Purification by Kugelrohr distillation gave 3 in 80% yield; NMR (60 MHz, CCl_4) δ 2.5 (2H, m), 2,6 (3H, s, CH_3S), 3.0 (4H, m), 5.6 (2H, m), 10.6 (s, COOH); IR (neat, cm^{-1}) 2850, 1710, 950, 890; bp 150 °C/0.5 mmHg (Kugelrohr).

Thus the following advantages render the present reaction attractive; 1) The product has a characteristic structure of two kinds of carboxylic function at the both terminals, one of which is a masked carbonyl function. 2) Highly stereoselective double bond formation at the 3 position of the acid. 3) Dithioester have recently been introduced as synthetically useful functional group.[5,6,8,10,12)] It should be expected that this reaction could afford a new useful building block for constructing natural products.

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7) ^{13}C NMR of 3, R^1,R^3 = H, $R^2 = CH_3$; ($CDCl_3$) δ 244.66 ($CSSCH_3$), 177.84 (C-1), 131.68 (C-4), 123.46 (C-3), 54.57 (C-6), 41.04 (C-5), 37.76 (C-2), 22.17 (CH_3), and 19.19 (CH_3S-). We thank Professor Katsumasa Sakanishi, Suzuka Technical College, for helpful suggestion and measurement of ^{13}C NMR.

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