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DIANIONS OF ETHYL α-MERCAPTOACETATE AND ETHYL α-MERCAPTOPROPIONATE: A NEW METHOD FOR AN EFFICIENT SYNTHESIS OF α,β-UNSATURATED ESTERS FROM CARBONYL COMPOUNDS

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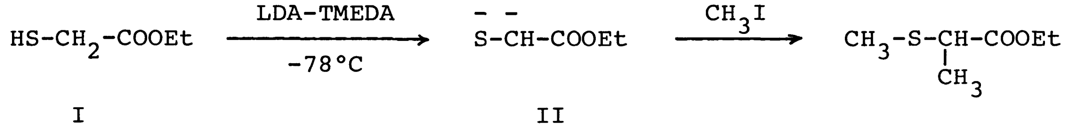
Ethyl α-mercaptoacetate and ethyl α-mercaptopropionate dianions were found to be useful reagents for the synthesis of α,β-unsaturated esters from carbonyl compounds by a single operation under mild conditions. Highly substituted α,β-unsaturated esters could be prepared by this method. The application to the synthesis of a component of ant mandibular gland secretions was described.

The reaction of dianions has been a topic of recent interest in synthetic chemistry as well as physical organic chemistry,[1,2] however much of the efforts has been concentrated on the reaction of 1,1- and 1,3-dianions.[3] The utilization of 1,2-dianions might provide a very useful method for constructing new carbon framework, if the reaction of 1,2-dianions with electrophilic reagents proceed regioselectively. In this communication we wish to report a new single operation for the synthesis of α,β-unsaturated esters using 1,2-dianions derived from the readily available ethyl α-mercaptoacetate[4] and ethyl α-mercaptopropionate.[5]

Treatment of ethyl α-mercaptoacetate with 2.2 equivalents of lithium diisopropylamide(LDA) in the presence of 2.2 equivalents of N,N,N',N'-tetramethylethylenediamine(TMEDA) in THF at -78°C for 1 hr resulted in formation of anion II which was stable at -78°C for at least several hours. The dianion II was trapped by an excess of methyl iodide to give an excellent yield of ethyl α-methylthiopropionate (III).

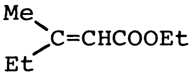
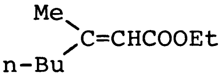
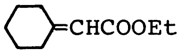
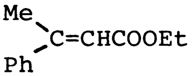
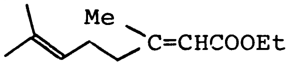
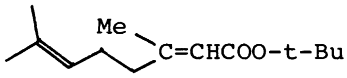
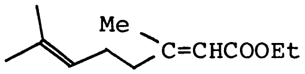
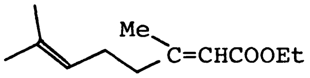


$$\mathrm{HS\text{-}CH_2\text{-}COOEt} \xrightarrow[-78\,°\mathrm{C}]{\mathrm{LDA\text{-}TMEDA}} \overset{-}{\mathrm{S}}\text{-}\overset{-}{\mathrm{C}}\mathrm{H\text{-}COOEt} \xrightarrow{\mathrm{CH_3I}} \mathrm{CH_3\text{-}S\text{-}}\underset{\substack{|\\ \mathrm{CH_3}}}{\mathrm{CH}}\mathrm{\text{-}COOEt}$$

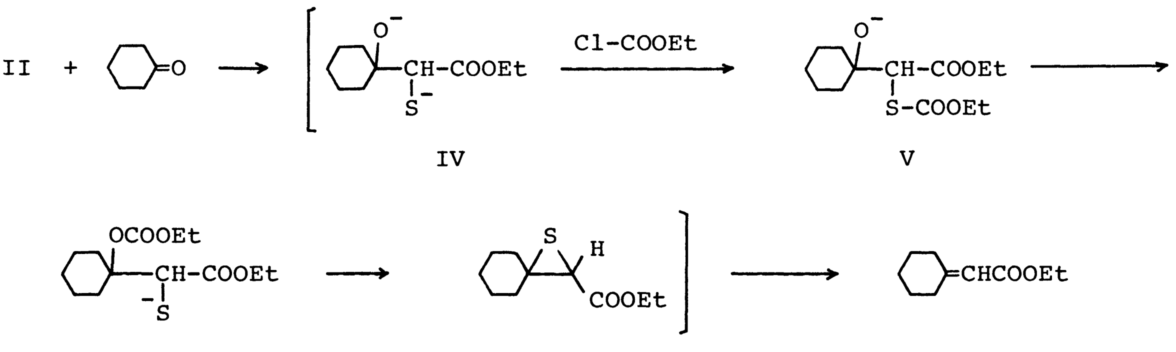
I II III (86%)

When a THF solution of dianion II was successively treated with cyclohexanone for 2 hr and with ethyl chloroformate at -78°C for 0.5 hr, then at room temperature for 1 hr, ethyl cyclohexylideneacetate was obtained in 60% yield after usual work-up. The results of similar one-step preparation of several α,β-unsaturated esters from ketones are summarized in the Table.

Table. Preparation of α,β-Unsaturated esters from Dianion, $\overset{-}{\mathrm{S}}\text{-}\overset{-}{\mathrm{C}}\mathrm{H}\text{-COOR}$ and Ketones.

Dianion R	Ketone	Product[a]	Yield[b] %	E/Z[c]
Et	2-Butanone	 $\mathrm{(Me)(Et)C{=}CHCOOEt}$	64	43/57
Et	2-Hexanone	 $\mathrm{(Me)(\textit{n}\text{-}Bu)C{=}CHCOOEt}$	67	38/62
Et	Cyclopentanone		74	
Et	Cyclohexanone		60	
Et	Acetophenone	 $\mathrm{(Me)(Ph)C{=}CHCOOEt}$	58	97/3
Et	6-Methyl-5-hepten-2-one		70	38/62
t-Bu	6-Methyl-5-hepten-2-one		56	40/60
Et	6-Methyl-5-hepten-2-one		62	51/49[d]
Et	6-Methyl-5-hepten-2-one		55	51/49[e]

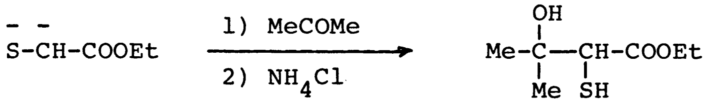
a) The structure was assigned on the basis of elemental analysis, and NMR and IR data. b) Isolated yields. c) Determined by NMR and GLPC. d) The dianion was generated in dry ether. After stirring for 4 hr at -78°C, ketone was added. e) The dianion was generated in dry n-hexane. After stirring for 4 hr at -78°C, ketone was added.



IV V

VI VII (60%)

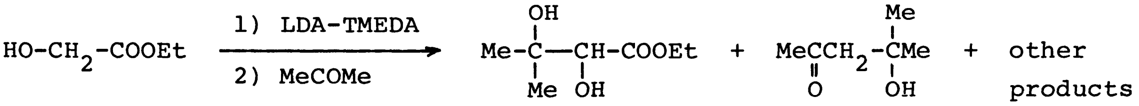
As shown above, the adduct IV should react with ethyl chloroformate to form *S*-ethoxycarbonylated intermediate(V), since a thiolate anion is a more powerful nucleophile than an alcoholate anion.[6] The subsequent ethoxycarbonyl group migration of V to VI followed by the elimination of sulfur has been established in the previous paper.[7] The presence of the adduct dianion, such as IV, could be demonstrated by quenching of the corresponding reaction mixture from acetone with saturated aqueous NH_4Cl at -78°C from which VIII was obtained in 82% yield.



II

VIII (82%)

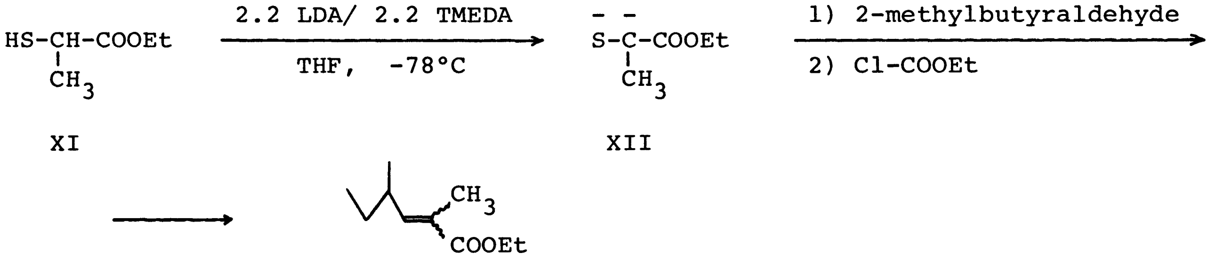
In contrast to the facile reaction of ethyl α-mercaptoacetate, when ethyl glycolate(IX) was treated in the similar manner as described above, the adduct X was obtained only in *ca.* 15% yield in addition to the aldol and other unidentified products. These results suggest that dianion II is far more selective to the electrophilic reagents than the corresponding ethyl glycolate dianion.



IX

X (*ca.* 15%)

Next, this technique was applied to the synthesis of (*E*)-2,4-dimethyl-2-hexenoic acid, a component of ant mandibular gland secretions from ethyl α-mercaptopropionate(XI)[5] and 2-methylbutyraldehyde.[4] Successive treatment of 1,2-dianion XII generated *in situ* with the aldehyde and ethyl chloroformate at -78°C afforded ethyl 2,4-dimethyl-2-hexenoate(XIII) in 67% isolated yield as a mixture of *E* and *Z* isomers in the ratio of 55:45, b.p. 100-115°C/68mmHg; Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.65, Found: C, 70.42; H, 10.79. The *Z*- and *E*-isomers of XIII were separated by GLPC in 98% and 95% purity, respectively and exhibited the NMR and IR spectra identical to the reported data.[8] Hydrolysis of ethyl (*E*)-2,4-dimethyl-2-hexenoate to the desired carboxylic acid has been established.[8]



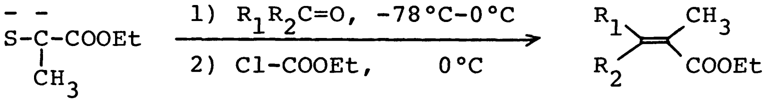
XI

XII

XIII (67%)

Conversion of ketones into tri-substituted acrylates has been difficult to achieve.[9,10] Recently, it was reported that aryl methyl ketones and dicyclohexyl ketone reacted with α-methyl triethylphosphonoacetate anion to afford tri-substituted α,β-unsaturated esters in good yields under much vigorous conditions.[11]

We have found that dianion XII also smoothly reacts with ketones under the mild conditions to give highly substituted α,β-unsaturated esters (XIV) after treatment with ethyl chloroformate; the yields have not been optimized.



$R_1 = R_2 =$ Me, 57%

$R_1 = R_2 = -(CH_2)_5-$, 43%

XII XIV

As the conditions of the reaction are extremely mild and the process very simple, it is expected to be applicable to the synthesis of α,β-unsaturated esters containing polyene systems which are known to be thermally labile. Other advantages of this new method are that work-ups are simpler, reagents are readily available, and by-products (CO_2 and sulfur) are easily separated. Investigation on the scope and limitation of these reaction is currently being continued.

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