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THE SYNTHESIS OF ETHYL 2-ETHOXYCARBONYL-3,5-DIOXOHEXANOATE

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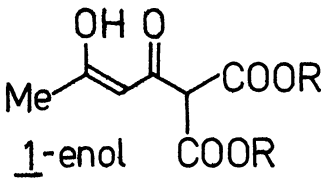
Ethyl 2-ethoxycarbonyl-3,5-dioxohexanoate (1-b) was synthesized by the hydrogenolysis and hydrolysis of diethyl (3-methyl-5-isoxazolyl)-malonate (3-b), which was obtained by the di-carboxylation of 3,5-dimethylisoxazole (4) with ethyl cyanoformate in the presence of butyllithium.

In the biosynthesis of various natural compounds by acetyl co-enzyme or malonyl co-enzyme, β-polyketo acids such as triacetic acid and dehydroacetic acid, have been much interested as intermediates. Authors suppose that 2-carboxy-3,5-dioxohexanoic acid (1-a) is also the intermediate of biosynthetic route of the natural products. The lactone form of 1-a, 2,4-dioxo-2,3-dihydropyran-3-carboxylic acid (2-a), was isolated from the urine of rabbit.[1] But the synthesis of 1-a, 2-a and their esters has never been reported. This paper will communicate the synthesis of ethyl 2-ethoxycarbonyl-3,5-dioxohexanoate (1-b) by the hydrogenolysis and hydrolysis of diethyl (3-methyl-5-isoxazolyl)malonate (3-b), which is obtained by the di-carboxylation of 3,5-dimethylisoxazole (4).

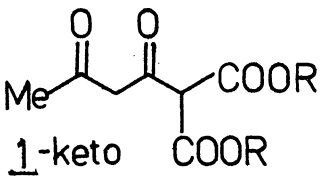
Previously, authors described that the mono-, di- and tri-alkylation reactions occurred on the C-5 methyl group of 4 in the presence of sodium amide in liquid ammonia.[2] Similarly, 4 reacts with alkyl halides by butyllithium in ether.[3] On the other hand, in the reaction of ethyl cyanoformate with ethylmagnesium bromide, 3-ethyl-3-pentanol is obtained by the substitution of cyano group with ethyl group.[4] From these facts, cyanoformic esters as the carboxylating reagent were used to synthesize the (3-methyl-5-isoxazolyl)malonic esters by di-carboxylation of 4.

3,5-Dimethylisoxazole (4) was lithiated by butyllithium in THF and this lithio compound was treated with ethyl cyanoformate. The NMR of the reaction product shows 3-methyl and 4-methine of 3-methylisoxazolyl group at δ 2.27 and 6.21, respectively. The methyl and methylene signals of two ethoxycarbonyl groups at δ 1.30 and 4.22, and

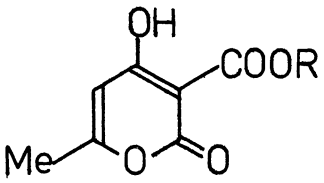
a methine singlet at δ 4.72 were observed. The IR absorption bands of isoxazole at 3140 and 1610 cm^{-1} and those of malonic ester at 1755 and 1735 cm^{-1} were observed. From these data and the elemental analysis, the reaction product was deduced to be diethyl (3-methyl-5-isoxazolyl)malonate (3-b). The ethanol solution of 3-b was hydrogenated in the presence of platinum oxide. The resulting needles were confirmed to be ethyl 5-amino-2-ethoxycarbonyl-3-oxo-4-hexenoate (5-b) by the NMR spectrum showing C-6 methyl at δ 1.99, C-2 methine at δ 4.33 and C-4 methine at δ 5.06. The methyl and methylene protons of ethoxycarbonyl were observed at δ 1.30 and 4.24, respectively. The amino protons appear at δ 9.6 and 5.8. The elemental analysis and the IR spectrum supported the structure of 5-b. The hydrolysis of 5-b was carried out by treating with dilute hydrochloric acid in ethanol at room temperature. The structure of hydrolyzed product was supposed to be ethyl 2-ethoxycarbonyl-3,5-dioxohexanoate (1-b) from the IR spectrum and the elemental analysis. In the NMR spectrum, the methyl and methylene protons of ethoxycarbonyl groups were observed at δ 1.30 and 4.25. Two singlets at δ 2.27 and 2.10 were assigned to the C-6 methyl protons of keto and enol tautomers. These assignments were supported by the fact that ethyl 3,5-dioxohexanoate shows C-6 methyl singlets at δ 2.18 and 2.03 assigned to those of keto and enol tautomers, respectively.[5] The enol content of 1-b calculated from the peak intensity was about 45% in chloroform.



1-enol



1-keto



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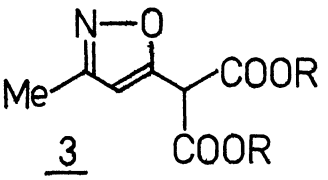

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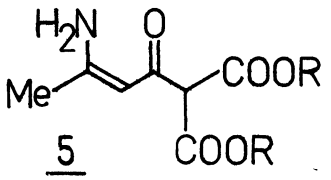

5

a : R = H
b : R = Et

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