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A DIRECTION CONTROLLED DIECKMANN TYPE CYCLIZATION OF HALF-THIOL DIESTERS

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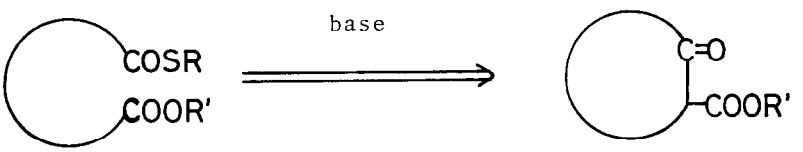
Summary: A direction controlled Dieckmann type cyclization was performed on treatment of the half-thiol diesters(1) with base to give exclusively the β-keto esters(2).

The Dieckmann condensation[1] is known as one of the most successful methods for the formation of carbocyclic and heterocyclic compounds. However, the cyclization of dissymmetric diester usually takes place in two ways forming two isomeric β-keto esters[1-4]. Recently, H.J.Liu and his co-worker[5] have reported a dithiol ester version of the Dieckmann condensation and showed that the cyclization of dithiol ester occurred under milder condition compared with the case of ordinary diesters. The fact prompted us to investigate a Dieckmann type cyclization of half-thiol diester (Scheme). In this method, the direction of the cyclization is expected to be controlled by the location of the thiol ester in the

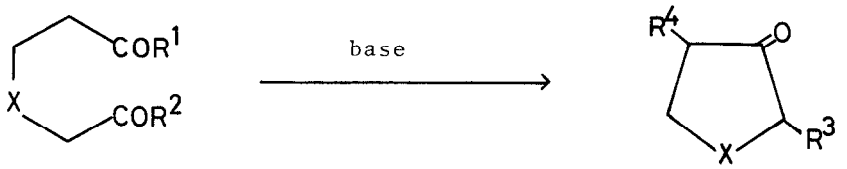


Scheme

half-thiol diesters. We now wish to describe a direction controlled cyclization of the half-thiol diesters(1) with base leading to the β-keto esters(2).

The half-thiol diesters(1)[6] were prepared as follows. The compounds(1a) and (1c) were obtained on treatment of 5-ethoxycarbonylvaleroyl chloride and (2-ethoxycarbonylethylthio)acetyl chloride with lead ethylmercaptide, respectively, in THF at room temperature. The compounds(1b) and (1d) were prepared by the Michael addition of methyl thioglycolate and ethyl glycinate, respectively, to ethyl thioacrylate.

Ethyl 5-thioethoxycarbonylvalerate(1a) was treated with 1.5 equivalents of lithium diisopropylamide in dry THF (0.1 mol solution of 1a) at -30°C for 3 hr. After acidification of the reaction mixture followed by usual work-up procedure, the crude product was purifide by column chromatography on silica gel giving exclusively the β-keto ester(2a)[7] in 74% yield.



1 2

a. $X=CH_2$, R^1=SEt, R^2=OEt
b. X=S, R^1=SEt, R^2=OMe
c. X=S, R^1=OEt, R^2=SEt
d. $X=NCO_2Et$, R^1=SEt, R^2=OEt

a. $X=CH_2$, $R^3=CO_2Et$, R^4=H
b. X=S, $R^3=CO_2Me$, R^4=H
c. X=S, R^3=H, $R^4=CO_2Et$
d. $X=NCO_2Et$, $R^3=CO_2Et$, R^4=H

In the case of heteroatom(S or N) containing half-thiol diesters(1b-d), the cyclization also proceeded smoothly with sodium hydride at room temperature giving the corresponding β-keto esters(2b-d). Treatment of methoxycarbonylmethyl thioethoxycarbonylethyl sulfide(1b) with 1.3 equivalents of sodium hydride in dry THF (0.01 mol solution of 1b)[8] gave the 2-methoxycarbonyl derivative(2b)[2] in 74% yield. On the contrary, ethoxycarbonylethyl thioethoxycarbonylmethyl sulfide(1c) was cyclized to the other isomer 4-ethoxycarbonyl derivative(2c)[2] in 70% yield under the same condition. Similarly, treatment of ethyl N-ethoxycarbonyl-N-(2-thioethoxycarbonylethyl)glycinate(1d)[9] with sodium hydride in dry THF(0.1 mol solution of 1d) afforded 2-ethoxycarbonyl derivative(2d)[4] in 77% yield.

This method provides wide synthetic utility for the formation of carbocyclic and heterocyclic compounds.

References and Notes

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4. J.Blake,C.D.Willson, and H.Rapoport, J.Amer.Chem.Soc., 86,5293 (1964).
5. H.J.Liu, and H.K.Lai, Tetrahedron Lett., 1193 (1979).
6. Elemental analyses and spectral data for these new compounds(1)were satisfactory.
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8. Low concentration is favorable to avoid side reaction.
9. The Dieckmann condensation of corresponding diester,ethyl N-ethoxycarbonyl-N-(2-ethoxycarbonylethyl)glycinate(1, $X=NCO_2Et$, $R^1=R^2$=OEt),was reported to yield a mixture of 2d and 4-ethoxycarbonyl derivative(2, $X=NCO_2Et$, R^3=H, $R^4=CO_2Et$)[3,4].

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