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AUTOXIDATION OF 4H-5-OXAZOLONE

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α-Methoxy-N-(phenylacetyl)phenylglycine methyl ester was obtained in 37% yield by the treatment of N-(phenylacetyl)phenylglycine with dicyclohexylcarbodiimide in methanol under an oxygen atmosphere. The mechanism and the generality of this oxidative alkoxylation are discussed.

It is well known that the treatment of N-acyl-α-amino acids with dehydrating agent, such as acetic anhydride, dicyclohexylcarbodiimide(DCC)[1] or ethyl chloroformate, gives 4H-5-oxazolone($\underline{2}$), which are converted to N-acyl-α-amino acid esters, N-acyl-α-amino acid amides or N-acyl-α-amino acids, respectively by further reactions with nucleophiles, such as alcohols, amines or water.

From these facts, it was expected that the reaction of N-(phenylacetyl)phenylglycine($\underline{1a}$) with DCC in methanol would afford N-(phenylacetyl)phenylglycine methyl ester($\underline{3a}_1$) via 4H-5-oxazolone($\underline{2a}$). However, it was found that the reaction gave α-methoxy-N-(phenylacetyl)phenylglycine methyl ester($\underline{12a}_1$) together with $\underline{3a}_1$ and that this oxidative alkoxylation did not occur under an argon atmosphere.

Then, the same reaction was tried under an oxygen atmosphere as follows ; two molar amounts of DCC was added to $\underline{1a}$ in methanol at -18°C. The mixture was stirred at room temperature for 20 hr. After separation of N,N'-dicyclohexylurea(DCU) (138% per mole), the residue was chromatographed on silica gel to give $\underline{12a}_1$ in 37% yield : mp 126°C, lit. mp 126~127°C[2] along with $\underline{3a}_1$ (7%), $\underline{8a}_1$ (trace), $\underline{9a}$ (10%), $\underline{10a}$ (17%) : mp 136.5°C, lit. mp 133.5~135°C[3], and $\underline{11a}$ (10%) : mp 211~214°C (calcd. for $C_{29}H_{35}N_3O_3$: C,73.50% ; H,7.40% ; N,8.88%. found : C,73.69% ; H,7.75% ; N,8.94%.). The structures of these compounds were confirmed by i.r. and n.m.r.

When the same reaction was carried out in ethanol, α-ethoxy-N-(phenylacetyl)phenylglycine ethyl ester($\underline{12a}_2$) was obtained in 27% yield : mp 151~152°C (calcd. for $C_{20}H_{23}NO_4$: C,70.38% ; H,6.74% ; N,4.11%. found : C,70.13% ; H,6.52% ; N,4.11%.).

In this case, DCU was obtained in 130% per mole, and 10a (26.5%) and 11a (32%) were obtained.

However, in 2,2,2-trichloroethanol or ethanethiol the oxidative alkoxylation did not occur and esters of N-(phenylacetyl)phenylglycine were obtained as sole products.

And, it was found that the treatment of N-(phenylacetyl)phenylglycine methyl ester ($3a_1$) with DCC in methanol under an oxygen atmosphere did not give $12a_1$, and $3a_1$ (97%) was recovered.

Based on the results, it was assumed that the mechanism of the oxidative alkoxylation involves autoxidation of 4H-5-oxazolone(2a), which is expected to be formed in the early stage, to give the active intermediate(4a). And 4a may form the addition compound(6a) with DCC, and 6a may be attacked by methanol or ethanol to give 12a. 8a, 9a and 10a might be given from 4a through routes shown in the scheme, and intramolecular acyl transfer of 6a might give 11a.

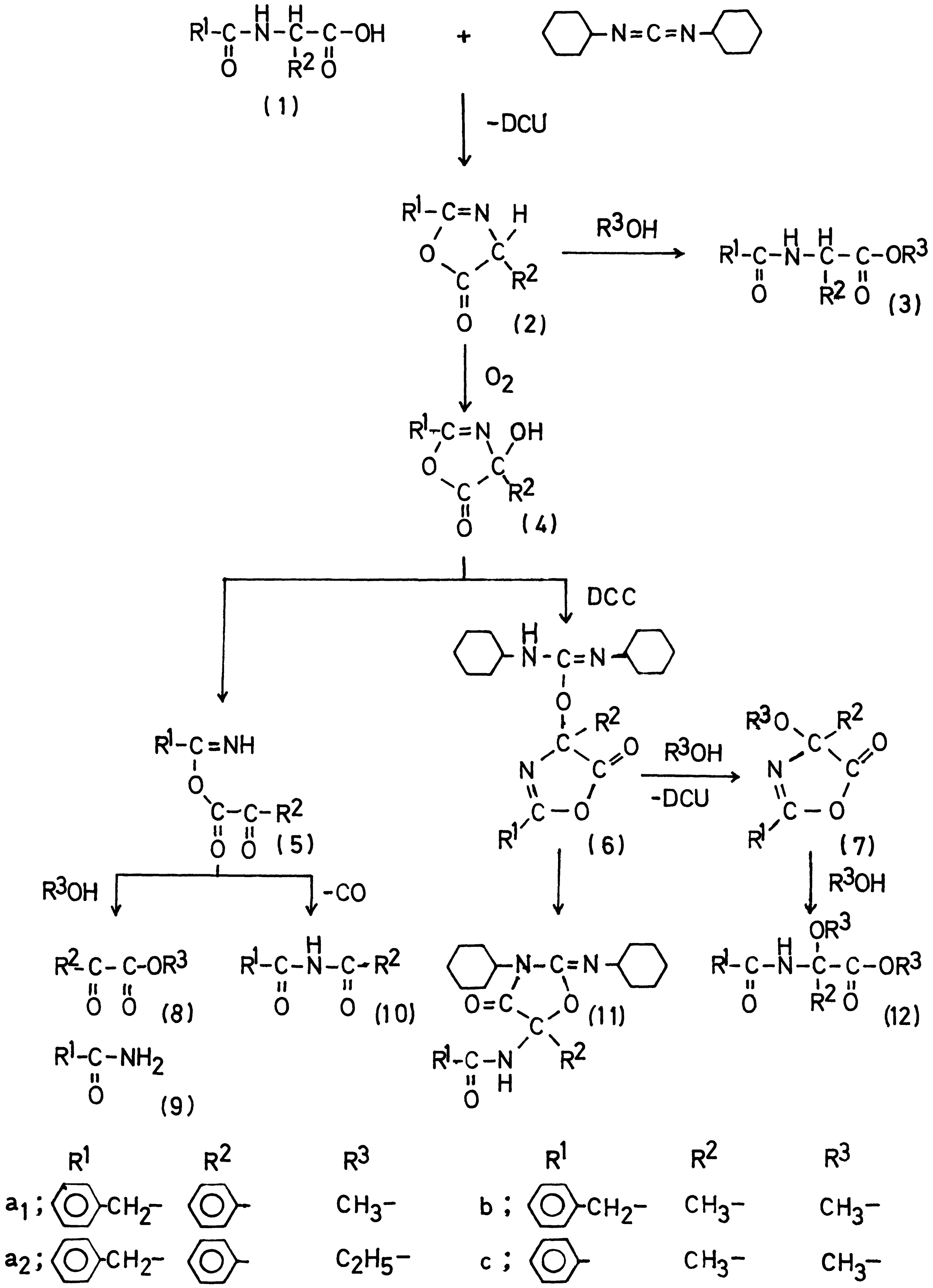
Concerning the autoxidation of active hydrogen compounds, Russel and coworkers have reported that the best results were obtained by base-catalyzed autoxidation. For instance, triphenylmethanol was obtained by the t-BuOK-catalyzed autoxidation of triphenylmethane$^{4)}$.

On the other hand, the present non base-catalyzed oxidative alkoxylation is assumed to proceed through 4H-5-oxazolone(2a) which has an active hydrogen at C-4.

Concerning ether bond formation using DCC as dehydrating agents, Vowinkel has reported that alkyl aryl ethers were obtained from alkyl alcohols and phenols$^{5)}$, and Shemyakin and coworkers have reported that treatment of N-benzoyl-α-hydroxyalanine with DCC in methanol gave N-benzoyl-α-methoxyalanine methyl ester(12c) in 17% yield accompanying with 26% N-benzoyl-α-hydroxyalanine methyl ester$^{6)}$.

Then, the present oxidative alkoxylation was applied to various N-acyl-α-amino acids. When N-(phenylacetyl)alanine(1b) was treated with DCC in methanol under an oxygen atmosphere, N-(phenylacetyl)alanine methyl ester(3b) was obtained in 88% yield, and the oxidatively alkoxylated product could not be detected. Contrary to the above result, the reaction of N-benzoylalanine(1c) with DCC in methanol under an oxygen atmosphere gave N-benzoyl-α-methoxyalanine methyl ester(12c) in 9% yield : mp 128~130°C, lit. mp 128~130°C$^{7)}$, along with 44% N-benzoylalanine methyl ester(3c) and 12% benzamide (9c). The yield of DCU was 115% per mole.

And then, 4-methyl-2-phenyl-5-oxazolone(2c) was synthesized separately and treated with DCC in methanol under an oxygen atmosphere in order to elucidate the mechanism of this oxydative alkoxylation. After usual work-up, N-benzoyl-α-methoxyalanine methyl ester(12c) was obtained in 9% yield along with 3c and 9c. DCU was obtained in 10.3%


(1)
-DCU
(2)
R3OH
(3)
O2
(4)
DCC
(5)
R3OH
-CO
(6)
R3OH
-DCU
(7)
R3OH
(8)
(9)
(10)
(11)
(12)
R1
R2
R3
a1 ;
-CH2-
CH3-
a2 ;
-CH2-
C2H5-
b ;
-CH2-
CH3-
CH3-
c ;
CH3-
CH3-

yield.

By these results, a sequence, 1) initial formation of 2, 2) autoxidation to the active intermediate 4 by molecular oxygen, 3) dehydration between 4 and alcohol by DCC, and 4) nucleophilic attack of alcohol, has been supported as the course of this oxidative alkoxylation.

Further work on autoxidation of 4H-5-oxazolones is in progress and the results will be reported later.

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