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The Carboxylation of Active Methylene Compounds with Carbon Dioxide in the Presence of 18-Crown-6 and Potassium Carbonate

Koji CHIBA,* Hideyuki TAGAYA, Syunji MIURA,* and Masa KARASU
Department of Applied Chemistry, Faculty of Engineering,
Yamagata University, Yonezawa, Yamagata 992

Active methylene compounds were carboxylated with the reagent system, 18-crown-6, potassium carbonate and carbon dioxide, in dimethyl sulfoxide at room temperature and atmospheric presssure. The concentration of the carbonate ion is important for carboxylation.

In previous papers[1,2] dealing with a model reaction for the biotin-promoted carboxylation, we have reported that a number of active methylene compounds are carboxylated with the reagent system, 1,3-diphenylurea or diphenylcarbodiimide, potassium carbonate and carbon dioxide. In these reactions, carbon dioxide is activated by forming the complex with 1,3-diphenylurea or diphenylcarbodiimide.

On the other hand, experimental investigations were carried out to carboxylate active methylene compounds by carbon dioxide in the presence of a strong organic base such as 1,8-diazabicyclo[5.4.0]-7-undecene.[3]

We have recently found that various active methylene compounds were effectively carboxylated with the reagent system, 18-crown-6, potassium carbonate and carbon dioxide, in dimethyl sulfoxide (DMSO) at room temperature and atmospheric pressure.

Fluorene was used as an active methylene compound, since 9-fluorenecarboxylic acid is stable and therefore easy to treat after reaction. The results are summarized in Table 1. Fluorene was effectively carboxylated by carbon dioxide in the presence of potassium carbonate and 18-crown-6. The longer time than 2 h only leads to the little increase of 9-fluorenecarboxylic acid. But, when the amounts of 18-crown-6 was doubled, the

Table 1. Carboxylation of fluorene[a)]

(Fluorene, 5 mmol; Crown ether, 5 mmol;
Alkali carbonate, 30 mmol; DMSO, 25 ml)

Crown ether	Atmosphere (1 atm)	Alkali carbonate	Reaction time / h	9-Fluorene-carboxylic acid mol%[b)]
———	CO_2	K_2CO_3	2	6.4
18-Crown-6	〃	〃	2	64.5
〃	〃	〃	5	66.3
〃 (10 mmol)	〃	〃	2	82.0
〃	〃	〃	2	0.0[c)]
〃	〃	〃	2	0.0[d)]
〃	〃	Na_2CO_3	2	0.0
〃	N_2	K_2CO_3	2	0.0
15-Crown-5	CO_2	Na_2CO_3	2	0.0

a) The reaction was carried out at room temperature.
b) Isolated yield.
c) Benzene was used as a solvent.
d) Ethanol was used as a solvent.

yield of the carboxylic acid largely increased. The 15-crown-5-Na_2CO_3 system was not effective for the carboxylation.

The solubility of potassium carbonate in DMSO is about 0.1 mmol/100 ml. In the presence of 18-crown-6 (20 mmol), the solubility increases to 0.5 mmol/100 ml. But, even in the presence of 18-crown-6, potassium carbonate was virtually insoluble in benzene. Thus, the concentration of carbonate ion is important for the successful carboxylation.

By similar procedure, a number of active methylene compounds were treated. The results are given in Table 2. When cyclohexanone and indene were used, 2-oxo-1,3-cyclohexanedicarboxylic acid and 1,3-indenedicarboxylic acid were obtained respectively, though the yields were low. From these results, it is found that second carboxyl group is introduced on the other α-carbon atom under the suitable conditions. Acetophenone was effectively carboxylated to produce benzoylacetic acid and benzoylmalonic

Table 2. Carboxylation of active methylene compounds in carbon dioxide atmosphere[a)]

(Substrate, 5 mmol; 18-Crown-6, 5mmol; K_2CO_3, 30 mmol; DMSO, 25 ml; Reaction time, 2 h)

Substrate	pKa	Product	Yield[b)] mol%
4,4'-Dinitrodiphenylmethane	16	Bis(p-nitrophenyl)acetic acid	5.3
Cyclohexanone	17	2-Oxo-1-cyclohexanecarboxylic acid	10.2
		2-Oxo-1,3-cyclohexanedicarboxylic acid	0.1
Acetophenone	19	Benzoylacetic acid	50.7
		Benzoylmalonic acid	3.2
3,4-Dihydro-1(2H)-naphthalenone (α-Tetralone)		1-Oxo-2,3,4-trihydro-2-naphthalenecarboxylic acid	85.6
Indene	21	3-Indenecarboxylic acid	87.5
		1,3-Indenedicarboxylic acid	12.5
Fluorene	23	9-Fluorenecarboxylic acid	64.5
Phenylacetonitrile		Cyanophenylacetic acid	65.1
Acetonitrile	25	———	0.0
Xanthene	29	———	0.0
Diphenylmeyhane	35	———	0.0

a) The reaction was carried out at room temperature and atmospheric pressure.

b) Isolated yield. When the product was a mixture of carboxylic acids, the yields were determined by GLC after esterification with diazomethane.

acid. It was considered that a methylene proton of benzoylacetic acid was easily abstracted, and the resulting carbanion reacted with carbon dioxide to form benzoylmalonic acid. Although 9-fluorenecarboxylic acid, 1-oxo-2,3,4-trihydro-2-naphthalenecarboxylic acid and cyanophenylacetic acid were obtained in good yields, respectively, from fluorene, α-tetralone and phenylacetonitrile, the corresponding dicarboxylic acids were not obtained.

Inspection of the results shown in Table 2 suggests that the organic compounds whose pKa's are in the range from about 19 to 23 can readily be carboxylated; the reason is obscure.

The extensive study on this carboxylation reaction under pressure at elevated temperatures and also the carboxylation using other crown ether-alkali carbonate system are now in progress in our laboratory.

References

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