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The Carboxylation of Active Methylene Compounds with Diphenylcarbodiimide and Potassium Carbonate

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Active methylene compounds were carboxylated by employing the reagent system, diphenylcarbodiimide and potassium carbonate, in dimethyl sulfoxide at room temperature and atmospheric pressure. The reaction proceeded even in the absence of carbon dioxide, but the carboxylation easily proceeded in carbon dioxide atmosphere.

It has been well established that biotin is required as a cofactor in a number of enzymatic carboxylation reactions. In these carboxylations, carbon dioxide is activated by transference perhaps to the imidazolone moiety of enzyme-bound biotin.[1)] But, although the activation has been suggested to occur on the nitrogen of the imidazolone moiety (N-carboxylation), there is still some controversy about whether the carboxylation is a N-carboxylation or an O-carboxylation.

We have undertaken to construct a model reaction for the biotin-promoted carboxylations whereby the chemical mechanism of the reaction may be elucidated. In the meanwhile, one of us has reported that active methylene compounds are carboxylated by employing the reagent system, 1,3-diphenylurea, potassium carbonate and carbon dioxide.[2,3)] Also, Otsuji and co-workers[4)] have reported that a number of active methylene compounds are carboxylated by employing the reagent system, Triton B (benzyltrimethylammonium hydroxide) - dicyclohexylcarbodiimide and carbon dioxide, or a lithium salt of urea derivatives and carbon dioxide.

We have recently found that active methylene compounds were effectively carboxylated with potassium carbonate and diphenylcarbodiimide in dimethyl sulfoxide (DMSO) at room temperature and atmospheric pressure. The reaction proceeded even in the absence of carbon dioxide. But the carboxylation proceeded more efficiently when the reaction was carried out in carbon dioxide atmosphere.

In a typical procedure, fluorene (0.831 g, 5 mmol) and diphenylcarbodiimide (3.26 g, 16.8 mmol) were dissolved in DMSO (25 ml). To this solution, powdered potassium carbonate (4.10 g, 30 mmol) was added. Dry carbon dioxide was then passed into the mixture for 2 h. The reaction mixture was poured into ice-cold water (150 ml) and the precipitate was filtered off (precipitate 1). The filtrate was extracted with ether. Acidification of the aqueous solution with hydrochloric acid gave white precipitate. The precipitate was collected by

Table 1. Carboxylation of fluorene[a]

(Fluorene, 5 mmol; Imine, 16.8 mmol;
Alkali carbonate, 30 mmol; DMSO, 25 ml)

Imine	Atmosphere (1 atm)	Alkali carbonate	Reaction time / h	Fluorene-9-carboxylic acid mol%[b]
———	CO_2	K_2CO_3	2	4.8
———	N_2	"	2	0.0
Dicyclohexyl-carbodiimide	CO_2	"	2	4.8
Diphenyl-carbodiimide	"	"	0.5	15.2
"	"	"	1	28.7
"	"	"	2	35.2
"	"	"	5	26.6
"	air	"	1	8.6
"	"	"	2	18.1
"	N_2	"	5	5.7
"	CO_2	"	2	10.3[c]
"	CO_2[d]	"	2	26.6
"	CO_2	Li_2CO_3	2	trace
"	"	Na_2CO_3	2	1.9
"	"	Rb_2CO_3	2	26.8
Phenylisocyanate	"	K_2CO_3	5	5.2

a) The reaction was carried out at room temperature.
b) The yields were calculated on the basis of fluorene used.
c) Dimethylformamide was used as a solvent.
d) The pressure of carbon dioxide was 25 kg / cm^2.

filtration (precipitate 2, 0.349 g, 33.2 mol% as fluorene-9-carboxylic acid). The filtrate was again extracted with ether. The ether extract was dried over anhydrous sodium sulfate and then the solvent was evaporated (the residue, 0.021 g, 2.0 mol% as fluorene-9-carboxylic acid). Precipitate 2, and the residue were identified by comparisons of IR spectrum and melting point with those of fluorene-9-carboxylic acid. Precipitate 1 was shaken with benzene (100 ml), and then an insoluble material was collected by filtration (0.810 g, 3.81 mmol as 1.3-diphenylurea). From the filtrate, a mixture of unreacted fluorene and unknown materials was recovered by evaporation (3.32 g).

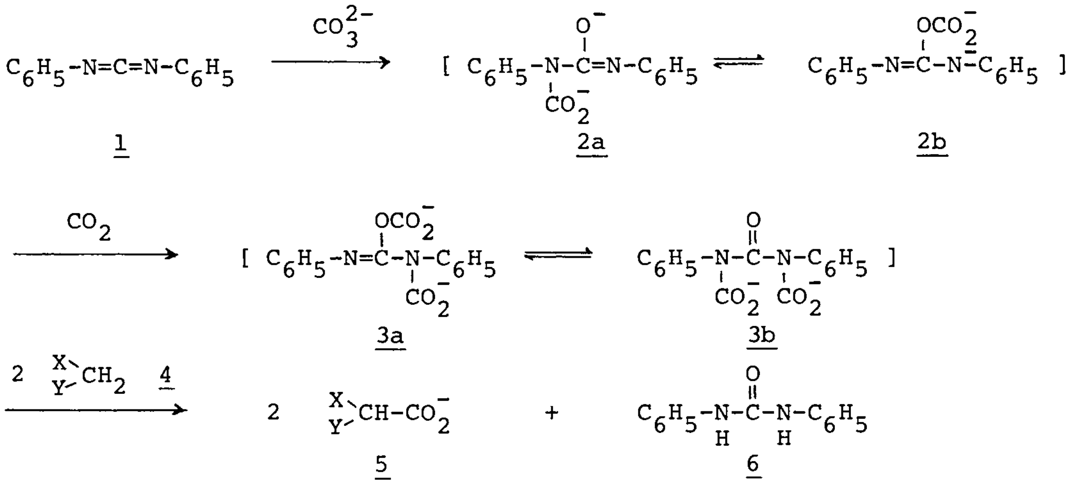
When dimethylformamide was used instead of DMSO, the yield of fluorene-9-carboxylic acid was much poorer (10.3 mol%).

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

(Substrate, 5 mmol; Diphenylcarbodiimide, 16.8 mmol; K_2CO_3, 30 mmol; DMSO, 25 ml; Reaction time, 2 h)

Substrate	pKa	Product[b)]	Yield[c)] mol%
4,4'-Dinitrodiphenylmethane	16	———	0.0
Cyclohexanone		Cyclohexanone-2-carboxylic acid	14.0
Acetophenone	19	Benzoylacetic acid	28.7
Indanone		Indanone-2-carboxylic acid	45.5
Indene	21	Indenemonocarboxylic acid[d)]	53.8
Fluorene	23	Fluorene-9-carboxylic acid	35.2
Acetonitrile	25	Cyanoacetic acid	trace
Xanthene	29	Xanthene-9-carboxylic acid	″
Diphenylmethane	35	———	0.0

a) The reaction was carried out at room temperature and atmospheric pressure.
b) The products were identified by comparison of IR spectra with those of the authentic samples, after esterification with diazomethane, if necessary.
c) The yields were calculated on the basis of amounts of the substrate used.
d) Main product was indene-3-carboxylic acid.



Scheme 1.

At first detailed experimental investigations were carried out to carboxylate fluorene in the absence or the presence of carbon dioxide at room temperature and atmospheric pressure. The results are summarised in Table 1. Fluorene was carboxylated even in the absence of carbon dioxide. But, the higher yield of fluorene-9-carboxylic acid was obtained in the presence of carbon dioxide. The longer reaction time than about 2 hours resulted in a lowering of the yield of the carboxylated product. The reason is still obscure. When dicyclohexylcarbodiimide was used instead of diphenylcarbodiimide, no carboxylation was observed even in carbon dioxide atmosphere.

By a similar procedure, indene, indanone, acetophenone and cyclohexanone were carboxylated. But, acetonitrile and xanthene were scarcely carboxylated. Diphenylmethane and 4,4'-dinitrodiphenylmethane were not carboxylated. The results are given in Table 2.

Inspection of the Table 2 may lead one to suggest that the organic compounds whose pKa's are in the range from about 19 to 23 can readily be carboxylated.

The reaction probably proceeds through the sequence in Scheme 1. The intermediate (2a or/and 2b) may react with an active methylene compound (4) to produce the carboxylated product (5) without carbon dioxide. The similar reaction sequence was previously reported by Otsuji and co-workers.4)

Further work is under way to determine the mechanism of this reaction.

References

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