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CARBOXYLATION OF ACTIVE METHYLENE COMPOUNDS USING 1,3-DIPHENYLUREA, POTASSIUM CARBONATE AND CARBON DIOXIDE

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Indene, and fluorene were effectively carboxylated by employing the reagent system, 1,3-diphenylurea, potassium carbonate and carbon dioxide, in organic solvent at room temperature and atmospheric pressure, to produce indenemonocarboxylic acid and fluorene-9-carboxylic acid, respectively. Diphenylurea was almost quantitatively recovered unchanged. Cyclohexanone was slightly carboxylated by the similar procedure. But acetonitrile, acetophenone, dibenzylketone, diphenylmethane, and xanthene were scarcely carboxylated.

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]. Otsuji and co-workers[2] have reported, as a model reaction for the biotin-promoted carboxylations, that a number of active methylene compounds are slightly carboxylated by employing the reagent system, Triton B - dicyclohexylcarbodiimide and carbon dioxide or a lithium salt of urea derivatives and carbon dioxide.

We have recently found that indene, and fluorene were effectively carboxylated by employing the reagent system, 1,3-diphenylurea, potassium carbonate and carbon dioxide, in organic solvent at room temperature and atmospheric pressure.

In a typical procedure, fluorene (0.831 g, 5 m mol) and 1,3-diphenylurea (3.57 g, 16.8 m mol) were dissolved in DMSO (25 ml). To this solution, powdered potassium carbonate (4.10 g, 30 m mol) was added. Dry carbon dioxide was then passed into the mixture for 5 hr. 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 (precipitate 2). The precipitate was collected by filtration (0.498 g). 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). 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 (3.58 g, 100 % recovery as 1,3-diphenylurea). The material was identified by comparing its IR spectrum with that of 1,3-diphenylurea. From the filtrate, unreacted fluorene was recovered by evaporation (0.41 g, 49 % recovery).

Table 1. Carboxylation of fluorene

(Fluorene, 5 m mol; Urea derivative, 16.8 m mol;
Solvent, 25 ml; Alkali carbonate, 30 m mol)

Urea derivative	Solvent	Alkali carbonate	Reaction time hr.	Fluorene-9-carboxylic acid mol %[1]
———	DMSO	K_2CO_3	5	7.4
1,3-Diphenylurea	"	"	2	20.0
"	"	"	5	49.8
"	"	"	7.5	70.9
"	DMF	"	5	24.8
"	DMSO	Li_2CO_3	5	0.0
"	"	Na_2CO_3	5	0.0
"	"	K_2CO_3	24 (in N_2)	trace
"	"	K_2CO_3 (10 m mol)	5	50.5
" (8.4 m mol)	"	K_2CO_3	5	39.2
" (2.5 m mol)	"	"	5	29.0
" (0.5 m mol)	"	"	5	10.7
1,1-Diphenylurea	"	"	5	0.0
1-Phenylurea	"	"	5	0.0
1,3-Dimethyl-1,3-diphenylurea	"	"	5	6.4
1,3-Dicyclohexylurea	"	"	5	7.8
1,3-Dimethylurea	"	"	5	0.0
1,1,3,3-Tetramethylurea	"	"	5	7.7
1-(3,4-Dichlorophenyl)-3,3-dimethylurea	"	"	5	18.5
1,3-Diphenylthiourea	"	"	5	10.0
Phenylisocyanate	"	"	5	5.2
Phenylurethan	"	"	5	8.6[3]
Acetoanilide[2]	"	"	5	19.6
Propionanilide[2]	"	"	5	21.7
N-methylacetamide[2]	"	"	5	6.4

1) The yields were calculated on the basis of fluorene used.
2) The amount of the compound used was 33.6 m mol.
3) Aniline was isolated from the reaction mixture.

Table 2. Carboxylation of active methylene compounds

(Substrate, 5 m mol; 1,3-Diphenylurea, 16.8 m mol; DMSO, 25 ml; K_2CO_3, 30 m mol)

Substrate	pK_a	Reaction time hr.	Product[1]	Yield[2] mol %
Dibenzylketone		5	———	0.0
Acetophenone	19	10[3]	———	0.0
Cyclohexanone		7.5[3]	Cyclohexanone-2-carboxylic acid	11.8
Indene	21	5	Indenemonocarboxylic acid[4]	95.4
Fluorene	23	7.5	Fluorene-9-carboxylic acid	70.9
Acetonitrile	25	5	———	0.0
Xanthene	29	5	———	0.0
Diphenylmethane	35	5	———	0.0

1) The products were identified by comparison of IR spectrum and melting point with those of the authentic sample.
2) The yields were calculated on the basis of amounts of the substrates used.
3) The amount of 1,3-diphenylurea used was 33.6 m mol.
4) Main product was indene-3-carboxylic acid.

Experimental investigations were carried out to carboxylate fluorene by carbon dioxide in the presence of alkali carbonate and various urea derivatives or analogous compounds at room temperature and atmospheric pressure.

The results are summarized in Table 1.

Fluorene was effectively carboxylated by carbon dioxide in the presence of potassium carbonate and 1,3-diphenylurea. 1-(3,4-Dichlorophenyl)-3,3-dimethylurea, acetanilide, and propionanilide were able to be used instead of 1,3-diphenylurea even though their effects were smaller. But 1,3-dimethyl-1,3-diphenylurea, 1,3-dicyclohexylurea, and 1,1,3,3-tetramethylurea were shown to be ineffective for the carboxylation. Furthermore, 1,1-diphenylurea, 1-phenylurea, and 1,3-dimethylurea were shown to be inhibitory.

These results indicate that the carboxylation is promoted by a urea derivative in which phenyl or substituted phenyl group is replaced for one hydrogen atom of the group $-(C=O)-NH_2$.

By the similar procedure, indene is effectively carboxylated. But acetonitrile, acetophenone, dibenzylketone, diphenylmethane, and xanthene were scarcely carboxylated. The results are given in Table 2.

Inspection of the Table 2 may lead one to suggest that the organic compounds whose pK_a's are in the range from about 21 to 23 can readily be carboxylated while those smaller or larger than the range cannot.

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

Refferences

1) T. C. Bruice and S. J. Benkovic, " Bioorganic Mechanism ", Vol. II, W. A. Benjamin Inc., New York, N. Y. (1966), Chapter 11.
2) Y. Otsuji, M. Arakawa, N. Matsuyama, and E. Haruki, Chem. Lett., 1193 (1973).

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