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# THE CARBOXYLATION OF ACTIVE METHYLENE COMPOUNDS WITH UREA DERIVATIVES AND $CO_2$. A MODEL REACTION FOR THE BIOTIN-PROMOTED CARBOXYLATIONS

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A variety of active methylene compounds was carboxylated by employing the reagent system, dicyclohexylcarbodiimide-tetraalkylammonium hydroxide-$CO_2$ or lithium salts of urea derivatives-$CO_2$ in DMF at room temperature.

It has been well established that biotin is required as a cofactor in a number of enzymatic carboxylation reactions. In these carboxylations, $CO_2$ is first transfered to the imidazolone moiety of enzyme-bound biotin to form a $CO_2$-enzyme-biotin complex and thence to a substrate to effect the carboxylations[1]. The detailed chemical mechanism of these carboxylations remains, however, unclarified[2].

We have undertaken to construct a model reaction for the biotin-promoted carboxylations whereby the chemical mechanism of the reaction may be elucidated. Thus, we have recently found that some sort of urea derivatives effectively promotes the carboxylation of a variety of active methylene compounds. The results are outlined in this communication. In the meanwhile, Kwan and co-workers[3] have found that N-potassium pyrrolidone also promotes the carboxylation of cyclohexanone. This reaction as well as our reaction seem to constitute a model reaction for the biotin-promoted carboxylations.

In a first model reaction we utilized the dicyclohexylcarbodiimide(DCC)-tetraalkylammonium hydroxide-$CO_2$ as a reagent system for the carboxylation of active methylene compounds. We anticipated that this reagent system would produce the complex (4) by way of (3) through the sequence depicted in Scheme 1 (see next page) and that (4) thus produced carboxyates active methylene compounds(5). The carboxylation actually took place using this reagent system.

A typical procedure employed is shown in an example of the carboxylation of indene. A methanol solution containing 1.622g(9.7 mmol) of benzyltrimethylammonium hydroxide(Triton B) was evaporated under reduced pressure at room temperature and then the residue was dissolved in 35ml of DMF. To this solution, an excess of DCC (7.3g, 35 mmol) in DMF was added at 0-5°C. A dry $CO_2$ was then passed into the mixture for 1 hr to obtain the $CO_2$-saturated mixture, and finally a slightly excess of indene(2.349g, 20.2 mmol) was added. The reaction mixture was stirred for 2 hr by bubbling nitrogen at room temperature, and then poured into an ice-hydrochloric acid mixture. The resulting mixture was extracted with ether and the ether layer was washed with 10% aqueous solution of sodium carbonate. The aqueous solution was acidified with an ice-cooled dilute hydrochloric acid. The acidified solution was again extracted with ether. The ether extract was dried over magnesium sulfate and then the solvent

Scheme 1

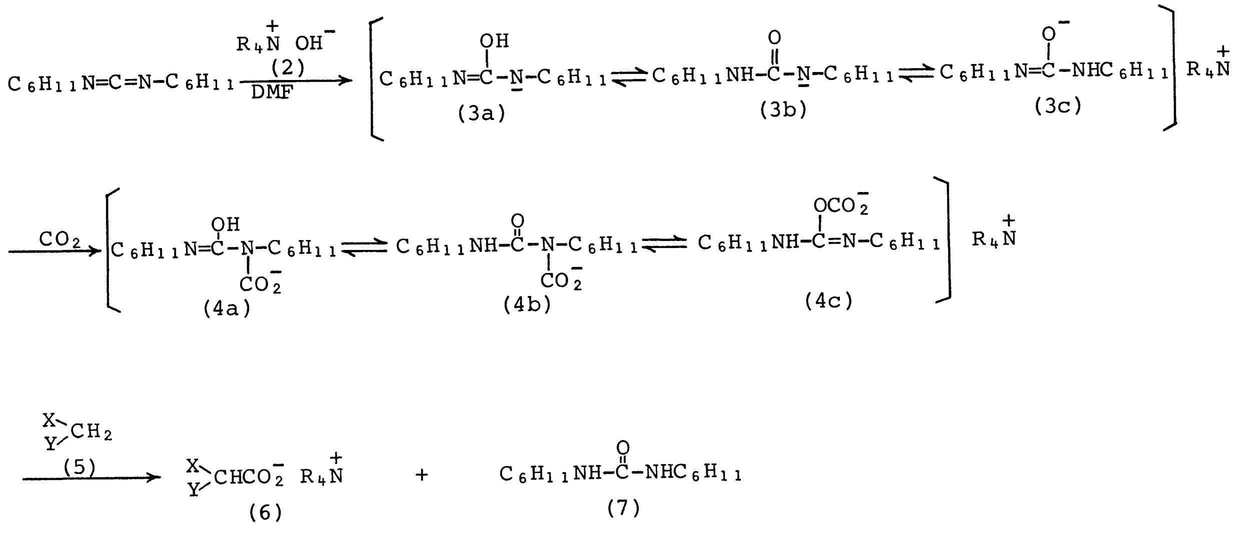


Table 1. The carboxylation of active methylene compounds with DCC-tetraalkylammonium hydroxide-$CO_2$ system

| Active methylene compounds | Product(s) | Yield of product(s)[a) %] A[b)] | B[c)] |
|---|---|---|---|
| Cyclohexanone | Cyclohexanone-2-carboxylic acid | 2 | 2 |
| Acetophenone | Benzoylacetic acid | 9 | 7 |
| Indanone | Indanone-2-carboxylic acid | 13 | 6 |
| Indene | Indene-1-carboxylic acid<br>+<br>Indene-3-carboxylic acid | 35 | 18 |

a) The yields were calculated on the basis of amounts of Triton B initially added.

b) DCC-Triton B-$CO_2$ system was used.

c) DCC-$(CH_3)_4\overset{+}{N}\ OH^-$

was carefully evaporated below 30°C. The IR spectrum indicated that the residue consisted of a mixture of indene-1- and indene-3-carboxylic acids. A mixture of the carboxylic acids thus produced weighed 0.55g.

By the similar procedure, several other active methylene compounds were carboxylated. Furthermore, tetramethylammonium hydroxide was found to be used instead of Triton B. The results are summarized in Table 1. The yields indicated in Table 1 (also Table 2) are based on the amounts of the products isolated. The low yields may partly be attributable to experimental difficulties in isolating the products which are relatively unstable under the experimental conditions.

In a controll experiment, indene was treated with a $CO_2$-saturated solution of Triton B in DMF. However, it was found that the carboxylation of indene does not take place in the absence of DCC.

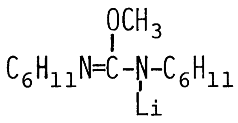
We then investigated the carboxylation of indene using lithium salt of some urea derivatives and $CO_2$. The structure of the salts examined are shown in Table 2. The salt (8) was obtained by the reaction of DCC with lithium methoxide in DMF. The salts, (9), (10) and (11), were prepared by treating the respective ureylene compounds with butyllithium in THF. The carboxylation using these reagents was performed according to the following procedure. $CO_2$ was passed into a solution of the salt in DMF at 0-5°C until a $CO_2$-saturated solution was obtained (in the case of the salts, (9), (10) and (11), the THF solutions of the salts were first evaporated to dryness under a reduced pressure, and the residues were dissolved in DMF to prepare the DMF solutions). A slightly excess of indene was then added, and the mixture was stirred by bubbling nitrogen for 2 hr at room temperature. The resulting mixture was worked up by the method similar to that described above to yield a mixture of indene-1- and indene-3-carboxylic acids. The results are summarized in Table 2.

Table 2. The carboxylation of indene with lithium salt of urea derivatives and $CO_2$

| Salta) | (8) | (9) | (10) | (11)) |
|---|---|---|---|---|
| Yield of indenecarboxylic acids, %b) | 1.3 | trace | 17 | 15 |

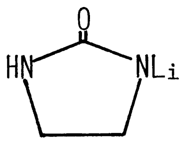
a) Structure of the salts:

(8)

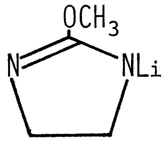


$C_6H_{11}N{=}\overset{\displaystyle OCH_3}{C}-\underset{\displaystyle Li}{N}-C_6H_{11}$

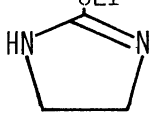
(9)



(10)

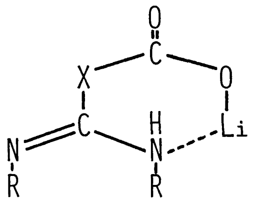


(11)

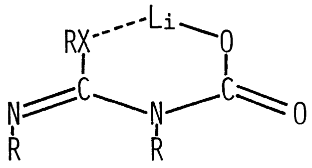


b) The yields were calculated on the basis of amounts of the salts added.

The results of Table 2 suggest that active forms of the carboxylating reagents have the structures of (12) and (13) in which X represents oxygen or sulfur. The detailed mechanism of the carboxylation reported in this communication is now under study in our laboratory4).



(I2)



(I3)

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3) T. Kwan, H. Yamamoto, H. Mori, and H. Samejima, Kagaku-kogyo(Chemical Industry), 23, 1618(1970).

4) During this study , we found that methylsulfinyl carbanion in DMSO promoted the carboxylation of indene; i.e., treatment of indene with this reagent and $CO_2$ gave a mixture of indenecarboxylic acids in 12% yield. The mechanism of this carboxylation is unclear.

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