Carboxylation of Active Methylene Compounds Using Anilide, Potassium Carbonate, and Carbon Dioxide

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(Received June 21, 1993)

Active methylene compounds were effectively carboxylated with carbon dioxide in the presence of anilide (acetanilide or formanilide) and potassium carbonate at 20—40 °C for 0.5—10 h. In the carboxylation of fluorene, a high yield (48%) was obtained at 20 °C for 4 h. The yield of carboxylic acid using 2,6-dimethylacetanilide was 8.9%, and smaller than 26.6% when using acetanilide at 20 °C for 2 h, indicating the interference of a methyl group for the carboxylation.

The fixation of carbon dioxide has been attempted by many researchers since carbon dioxide is a considerable natural source of carbon.[1—3] Carbon dioxide can be converted by coupling with organic substances into useful forms of organic compounds such as acids, esters, lactones, carbonates, and carbamates. Natural carboxylation reactions require a nucleophilic attack at the carbon dioxide carbon by electron-rich species such as a carbanion or an amine. The well-known reaction of carbon dioxide with a Grignard reagent followed by the reaction with water to afford an organic acid is reminiscent of natural carboxylations. However, the practical application of this reaction is limited by the fact that one mole of magnesium is consumed per each mole of acid produced.[4] We have already reported that active methylene compounds were carboxylated by employing a reagent system, 1,3-diphenylurea (DPU) or diphenylcarbodiimide (DPC), potassium carbonate, and carbon dioxide giving carboxylic acids.[5—8] The important role of nitrogens in the urea structure was suggested.

In this study we found that although active methylene compounds could be carboxylated under mild conditions by using a new reagent system, anilide (acetanilide and formanilide) and potassium carbonate, benzanilide was not effective for carboxylation. Mainly, we used fluorene as an active methylene compound because 9-fluorenecarboxylic acid (9-FLC) was easy to treat after the reaction.

Experimental

N-Phenylcyclohexanecarboxamide was synthesized from aniline and cyclohexanecarboxylic acid. Mp 128—130 °C (lit,[9] 130—131 °C). 2,6-Dimethylacetanilide was synthesized from 2,6-xylidine and acetic anhydride. Mp 176—178 °C (lit,[10] 176 °C). Other commercially available chemicals were used as received.

An active methylene compound and an additive were dissolved in predried DMSO (25 ml); to this solution powdered alkali carbonate was added. Dry carbon dioxide was then passed into the mixture. The reaction mixture was poured into ice-cold water and a precipitate filtered off. The filtrate was extracted with ether. Acidification of the aqueous solution with hydrochloric acid gave a white precipitate of carboxylic acid. The ether extract was dried over anhydrous sodium sulfate and the solvent was evaporated. The residue and above-mentioned precipitate were identified by a comparison of the IR spectra and melting points with those of the corresponding carboxylic acids. The yields of 9-FLC, except for the yield at 20 °C for 4 h, were measured by gravimetric analysis. The yields of other carboxylic acids were measured by gas chromatography after esterification.

The amounts of carbon dioxide adsorption in a DMSO solution containing anilide were determined by measuring the weight both before and after carbon dioxide bubbling.

Results and Discussions

Carboxylation of Fluorene with Anilides and Carbon Dioxide. Benzanilide and *N*-phenylcyclohexanecarboxamide were not effective for the carboxylation of fluorene (Table 1). However, we found that formanilide and acetanilide were effective for the carboxylation of fluorene in the presence of potassium carbonate.[11] Figure 1 shows the effects of the reaction temperature and time on the yield of 9-FLC when formanilide was used. 9-FLC was not obtained under a nitrogen atmosphere. This indicated that the carbon source was carbon dioxide and not a carbonate ion. The gravimetric yield of carboxylic acid agreed with the gas chromatographic yield determined after esterification. The yields at 20 °C were higher than those at 40 and 60 °C. The highest yield at 20 °C was 14% and the elongation of the reaction time did not lead to an increase in the yield of 9-FLC. In the case of acetanilide the yield of 9-FLC increased along with an increase in the reaction

Table 1. Carboxylation of Fluorene with Carbon Dioxide in the Presence of Potassium Carbonate[a)]

Additive	Yield of 9-FLC/%[b)]
None	4.8
1,3-Diphenylurea	46.4
1-Methyl-3-phenylurea	0.0
Benzanilide	8.4
4′-Acetylbenzanilide	8.5
N-Phenylcyclohexanecarboxamide	6.9
Formanilide	12.3
Acetanilide	26.6

a) Fluorene, 5 mmol; additive, 33.6 mmol; potassium carbonate, 30 mmol; DMSO, 25 ml; reaction temp, 20 °C; reaction time, 2 h. b) The yields were calculated on the basis of fluorene used.

time; it reached 48% at 20 °C for 4 h (Fig. 2). However, further elongation of the reaction time was detrimental. The same tendencies were observed in reactions at 40 and 60 °C. No reaction was observed when 9-FLC alone was reacted in DMSO. However, when 9-FLC was reacted in the presence of potassium carbonate, 65.5% of the 9-FLC reacted to give fluorene. This suggested the presence of decarboxylation of 9-FLC under the reaction conditions. Furthermore, the yield of 9-FLC at 40 °C for 6 h was 31.3%, and unreacted fluorene was 51.7%. As undesirable side reactions, the dimerization reaction of fluorene and the oxidation reaction to fluorenone were suggested. However, we could not confirm the presence of such products.

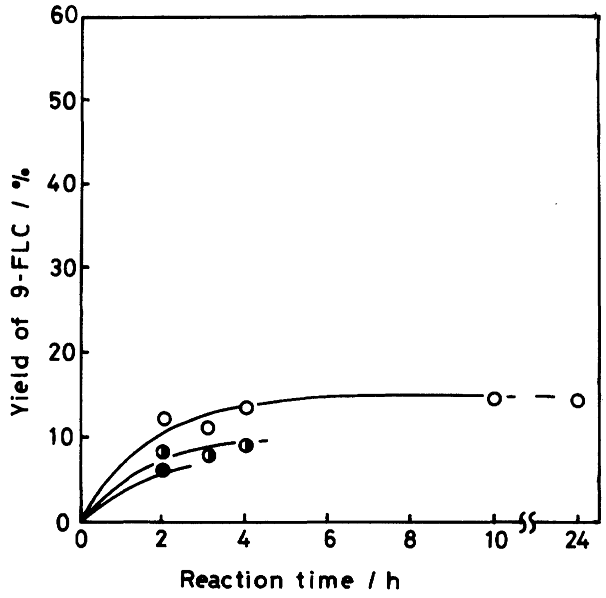


Fig. 1. Carboxylation of fluorene using formanilide and potassium carbonate. Reaction temperature/°C; 20 (○), 30 (◑), 40 (●).

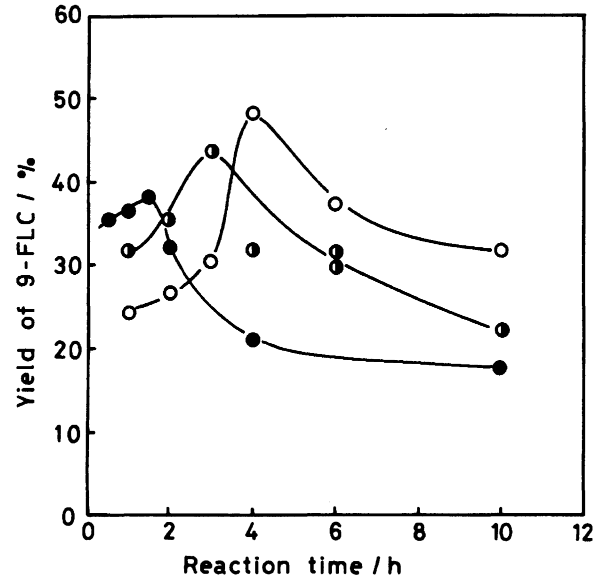


Fig. 2. Carboxylation of fluorene using acetanilide and potassium carbonate. Reaction temperature/°C; 20 (○), 30 (◑), 40 (●).

Although 1,3-diphenylurea was effective for the carboxylation of fluorene, ureas having an aliphatic moiety attached to amido nitrogen, such as 1-methyl-3-phenylurea, 1,3-diethylurea, and 2-imidazolidinone, were not effective. However, in the case of acetanilide, an aliphatic moiety attached to amido nitrogen was not detrimental.

Lithium carbonate, sodium carbonate, and potassium hydrogencarbonate were not effective bases for carboxylation using acetanilide. Their solubilities in DMSO were not large. Since a carbonate ion plays an important role as a base, the concentration of the carbonate ion in DMSO may be critical.[12)]

Carboxylation of Fluorene with Substituted Acetanilide. Here, carboxylation reactions of fluorene were carried out by using phthalimide, aniline, benzimidazole, and 2-hydroxybenzimidazole. They were not effective for the carboxylation of fluorene, indicating the important role of a carboxyl group adjacent to amido nitrogen.

To clarify the role of nitrogen in acetanilide, fluorene was carboxylated by using substituted acetanilides. The yield of 9-FLC decreased upon the substitution of acetanilide (Table 2). Especially, *o*-substitution was more detrimental than were *m*- and *p*-substitutions.

DMSO (25 ml) adsorbed 5.4 mmol of carbon dioxide in the presence of potassium carbonate. Upon the addition of acetanilide, the value increased to 5.8 mmol. It was considered that carbon dioxide attached to amido nitrogen while producing *N*-carboxyanilide. Further, the intermediate may be active for the carboxylation of fluorene. Upon the addition of 2-methylacetanilide and 2,6-dimethylacetanilide, the adsorbed carbon dioxide was 5.9 and 6.3 mmol, respectively. This indicated that the reaction of carbon dioxide with anilide was not interfered with by the substitution. It was considered that the reaction of the active intermediate with fluorene was interfered with by a methyl group. Certainly upon substitution at the 2 and 6 positions the yield of

Table 2. Carboxylation of Fluorene with Carbon Dioxide Using Substituted Acetanilides in the Presence of Potassium Carbonate[a)]

Substituted acetanilide	Yield of 9-FLC/%[b)]
None	4.8
Acetanilide	26.6
2-Methylacetanilide	13.8
3-Methylacetanilide	18.1
4-Methylacetanilide	15.4
2,6-Dimethylacetanilide	8.9

a) Fluorene, 5 mmol; substituted acetanilide, 33.6 mmol; potassium carbonate, 30 mmol; DMSO, 25 ml; reaction temp, 20 °C; reaction time, 2 h. b) The yields were calculated on the basis of fluorene used.

Table 3. Carboxylation of Active Methylene Compounds in a Carbon Dioxide Atmosphere[a)]

Substrate	Yield of carboxylic acid/%[b)]
Indene	53.2
Indanone	41.6
Fluorene	45.1
Phenylacetonitrile	5.9
Acetophenone	13.6
1-Tetralone	19.1
Cyclohexanone	14.0

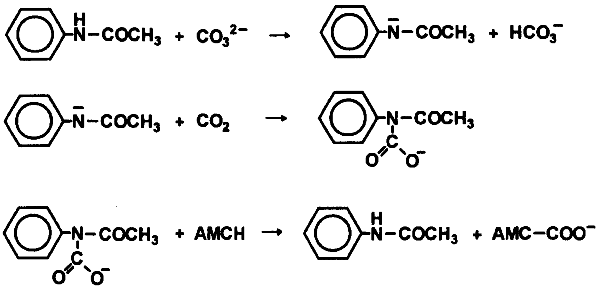
a) Substrate, 5 mmol; acetanilide, 33.6 mmol; potassium carbonate, 30 mmol; DMSO, 25 ml; reaction temp, 20 °C; reaction time, 4 h. b) The yields of carboxylic acids were calculated on the basis of substrate used. The products were monocarboxylic acids. They were identified by comparison of IR spectra with those of the authentic samples after esterification with diazomethane.

9-FLC decreased to 8.9%, which was close to 4.8% for no additive.

We could not confirm the presence of an active intermediate, *N*-carboxylanilide. However, such an active structure was suggested in the case of carboxylation by a biotin enzyme.[13)] The reaction mechanism shown in the scheme was suggested.

Carboxylation of Active Methylene Compounds with Acetanilide and Carbon Dioxide. Seven active methylene compounds were carboxylated with carbon dioxide in the presence of acetanilide and potassium carbonate (Table 3). The yields of the carboxylic acids were determined by gas chromatography, because some of the carboxylic acids were soluble in acid and the reproducibility of the gravimetric yields by ether extraction was poor. Though the yields varied from 5.9 to 53.2%, there was no correlation between pK_a[14,15)] and the yield. The highest yield (53%) was obtained in the carboxylation of indene.

We have clearly indicated that acetanilide and formanilide were effective for the carboxylation of active methylene compounds. The amounts of carbon dioxide in DMSO increased upon the addition of acetanilide, as mentioned above. *o*-Substitution of acetanilide was detrimental for the carboxylation. These results show that anilido nitrogen plays an important role. By the reaction of 3 mmol of acetanilide with 30 mmol of indene at 20 °C for 2 h, 14.8% of indene was carboxylated. The amounts of acid corresponded to 148% of the acetanilide used. As shown in the Scheme 1, a catalytic function of acetanilide was suggested.



Scheme 1.

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