

# CARBOXYLATION OF ACTIVE METHYLENE COMPOUNDS WITH CARBON DIOXIDE AND ALKALI SALTS OF OXIMES

by

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## SYNOPSIS

A number of active methylene compounds including indene, 1-indanone, and cyclohexanone were carboxylated with carbon dioxide in the presence of potassium salt of benzophenone oxime at room temperature. The yield of indene-3-carboxylic acid was as good as 72%. Various organic solvent systems were examined on the effect for the increase of the yields, and dimethylformamide appeared to be the best as a single solvent. The addition of triethylamine was effective. A number of salts of aliphatic and aromatic oximes were also examined in order to find the structural requirement as the carbon dioxide carrier. Aromatic oxime salts effected on the carboxylation more than the aliphatic ones.

## 1. INTRODUCTION

The preparation of carboxylic acid from carbon dioxide has an advantage in ready availability of the starting materials. The well-known Kolbe-Schmidt reaction produces hydroxybenzoic acids including salicylic acid from carbon dioxide and potassium phenoxide in various organic solvents.<sup>1)</sup> The profitable synthesis of 4-hydroxybenzoic acid was achieved by the use of potassium alkylcarbonate as carbon dioxide carrier to phenoxide under the mild condition.<sup>2)</sup> Polycarboxylation of phenoxide with alkylcarbonate was also reported from this laboratory on the synthesis of trimesic acid.<sup>3)</sup>

However, the application of the alkali alkylcarbonate to the carboxylation of active methylene compounds resulted in low yields in various conditions. In the literatures<sup>4-8)</sup>, several so-called carbon dioxide carriers have been reported. The Stiles' reagent, Mg·(OMe)OCOMe is reactive with a number of active methylene compounds such as 1-indanone, acetophenone, and cyclohexanone at 110–130°C in dimethylformamide (DMF). Haruki et al. reported that 1, 8-diazabicyclo(5.4.0)-7-undecene is useful to carboxylate active methylene compounds with carbon dioxide at room temperature.

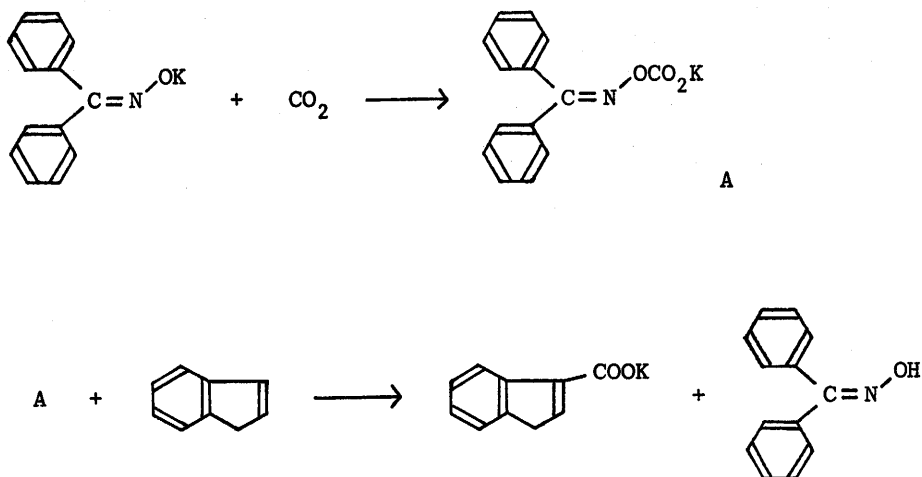
In the search for a practical carbon dioxide carrier usable in mild condition, we found that alkali salts of oximes were easy to prepare and useful for the carboxylation reaction in organic solvents. In the present paper, the carboxylation of indene and other compounds with carbon dioxide and potassium salts of oximes such as benzophenone oxime is described. The effectiveness of the variety of oximes and solvents are also compared in the respect of the production yields.

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## 2. RESULTS AND DISCUSSION

The carboxylation of phenylacetonitrile with sodium methylcarbonate was first tried in various solvents. The reaction required strong base such as phenyllithium to produce phenylcyanoacetic acid in 29% yield. Thus alkali alkylcarbonate appeared to be a poor carboxylation reagent for the non-aromatic active methylene substrate.

*Carboxylation of Indene with Carbon Dioxide and Potassium Salt of Benzophenone Oxime.* Secondly, potassium salt of benzophenone oxime was chosen as the carbon dioxide carrier. Production of indene-3-carboxylic acid from indene and carbon dioxide in the presence of this reagent was achieved at room temperature for 2 hr in good yield (see Scheme). Though the mechanism is not shown in the Scheme, the isomerization of the initial product, indene-1-carboxylic acid to indene-3-carboxylic acid occurred as known in the literature.<sup>9)</sup> Thus it appeared that oxime salt is useful in the reaction of active methylene compound and carbon dioxide in fairly mild condition and in short reaction time.



Scheme. Carboxylation of indene with carbon dioxide and potassium salt of benzophenone oxime. A, proposed structure for the complex of carbon dioxide and oxime salt.

*Solvent Effect.* As the solvent effect was observed in the yield in the modified Kolbe-Schmidt reaction,<sup>1)</sup> several organic solvents were examined for this carboxylation system. Among the solvents listed in Table 1, DMF was the best, even to dimethylsulfoxide (DMSO), and followed by diglyme. The addition of triethylamine increased the yield

Table 1. Carboxylation of Indene with Carbon Dioxide in the Presence of Potassium Salt of Benzophenone Oxime in Various Solvents

Solvent	Yield (%)
DMF	72
DMSO	71
diglyme	20
DMF/NEt <sub>3</sub> (10: 1)	80
DMF/light petroleum (1: 1)	83
Dioxane	0
Methanol	0

Reaction at 25-30°C for 2 hr.

probably due to its basic effect. Light petroleum too was effective in increase of the yield of indene-3-carboxylic acid.

From dioxane was quantitatively precipitated the complex of the potassium salt of benzophenone oxime and carbon dioxide, probably the structure being as given in the Scheme (structure A). When the complex was added to the solution of indene in DMF under nitrogen atmosphere, indene-3-carboxylic acid was obtained in 65% yield. This fact suggests that the complex is the very chemical species which transfer carbon dioxide to the active methylene of indene (second step in the Scheme).

The reaction of oxime salt and carbon dioxide in methanol produced alkali methylcarbonate which has no capability to pass carbon dioxide to indene without strong base.

*Carboxylation of Various Active Methylene Compounds.* As the reactivity of so-called active methylenes differs in various compounds, the usefulness of this oxime salt-carbon dioxide system was examined for several substrates such as 1-indanone, cyclohexanone, acetophenone, and so on. The results are summarized in Table 2. A little difference was observed between the yields in DMF and DMSO. The similar tendency has been seen in the carboxylation by the aid of 1, 8-diazabicyclo(5.4.0)-7-undecene in the relation of the reactivity of the active methylene and the yield of carboxylated product.<sup>8)</sup> The higher temperature and proper selection of the solvent may increase the yield of the carboxylation of less reactive compound. In addition at more vigorous condition, dicarboxylation of cyclohexanone, which was not detected this time may occur.

Table 2. Carboxylation of Various Active Methylene Compounds with Carbon Dioxide and Potassium Salt of Benzophenone Oxime

Substrate	Product	yield (%)
indene	indenemono-carboxylic acid	72 (71) <sup>a)</sup>
1-indanone	1-indanone-2-carboxylic acid	46 (42) <sup>a)</sup>
cyclohexanone	cyclohexanone-2-carboxylic acid	52 (56) <sup>a)</sup>
acetophenone	benzoylactic acid	18 (26) <sup>a)</sup>
p-nitrotoluene	p-nitrophenylacetic acid	12
phenylacetone	phenylcyanoacetic acid	19 (28) <sup>a)</sup>

Reaction at 15–30°C for 6 hr in DMF. <sup>a)</sup> yield in DMSO.

*Comparison of Various Oximes.* Furtherly, a number of aliphatic and aromatic oximes were prepared and applied for carbon dioxide transfer to indene. The results were given in Table 3. Among the oximes compared together, there was not much difference in production yields of indene-3-carboxylic acid. However, aromatic oximes showed a distinct tendency in higher carboxylation than the aliphatic ones. Interestingly, 2-methylbenzaldehyde oxime salt was much better than its 4-methyl isomer. The reason is unclear, but the steric instability of the carbon dioxide complex might relate to the efficiency in carbon dioxide transfer.

Table 3. Carboxylation of Indene with Carbon Dioxide and Potassium Salts of Various Oximes

$\begin{matrix} R_1 \\ R_2 \end{matrix} > C = N - OK$	(R <sub>1</sub> )	H	CH <sub>3</sub>	CH <sub>3</sub>	H	H	H	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>
	(R <sub>2</sub> )	CH <sub>3</sub>	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	2-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>
Yield (%) of indene-3-carboxylic acid		38	48	39	38	31	74	56	71 <sup>a)</sup>

Reaction at 15–30°C for 6 hr in DMSO. <sup>a)</sup> 2 hr in DMF.

### 3. EXPERIMENTAL

Melting points are uncorrected. IR spectra were obtained on JASCO Model IR A-2 spectrometer. Proton NMR spectra were obtained on Japan Electron Optics JNM-C60-HL spectrometer using tetramethylsilane as internal reference.

Potassium salt of benzophenone oxime was prepared as follows. Potassium hydroxide (11.2 g, 0.2 mol) was dissolved in methanol (100 ml). Slightly excess amount of benzophenone oxime was added to the solution, which was then concentrated to dryness. Remaining solid was washed with ether to remove the excess oxime and dried *in vacuo*. Other oxime salts were also prepared similarly.

*Carboxylation of Phenylacetonitrile with Phenyllithium and Sodium Methylcarbonate.* Lithium (4 g, 0.5 mol) was reacted with bromobenzene (0.25 mol) in ether (100 ml) at reflux temperature for 1 hr. Phenylacetonitrile (0.25 mol) was then added to the solution and the mixture was refluxed for 8 hr. Sodium methylcarbonate (0.25 mol) was added to the solution at room temperature. After 3 hr the reaction mixture was diluted with water. The aqueous layer was separated and acidified with hydrochloric acid under cooling. The product was extracted into ether, the solution being washed with water and dried over  $MgSO_4$ . Evaporation of the ether remained crystalline phenylcyanoacetic acid which was recrystallized from ether-hexane. Yield 15.6 g (29%). mp 91–92°C. IR:  $\nu_{C=O}$  1720  $cm^{-1}$ ,  $\nu_{C\equiv N}$  2250  $cm^{-1}$ . Mass. m/e 161, Calcd. 161.

Analysis. Found: C, 61.26; H, 4.42; N, 7.24%. Calcd. for  $C_9H_7O_2N$ : C, 61.57; H, 4.90; N, 7.98%.

*Synthesis of Indene-3-carboxylic Acid. Method A.* Into a solution of indene (2.16 g, 18.6 mmol) and potassium salt of benzophenone oxime (7.05 g, 35 mmol) in DMF (30 ml) was passed dry carbon dioxide at 25–30°C for 2 hr. The reaction mixture was diluted with water, and shaken with ether to remove the unreacted starting material and oxime. The aqueous portion was acidified with hydrochloric acid under cooling with ice. The product, indene-3-carboxylic acid was extracted into ether, the organic solution being washed with water, dried over  $MgSO_4$  and concentrated. Crystallization from chloroform gave 2.14 g (72%) of pale yellow needles. mp 157–158°C. lit.<sup>10)</sup> 157–158°C. IR:  $\nu_{C=O}$  1690  $cm^{-1}$ .

Analysis. Found: C, 75.00; H, 4.98%. Calcd. for  $C_{10}H_8O_2$ : C, 74.99; H, 5.01%.

*Method B.* Carbon dioxide was introduced into a solution of potassium salt of benzophenone oxime (7.05 g, 35 mmol) in dioxane (30 ml) for 2 hr. The white precipitate was collected by filtration, washed with anhydrous ether, and dried. The potassium oxime carbonate was added to the solution of indene (2.16 g, 18.6 mmol) in DMF (30 ml) and reacted under nitrogen for 2 hr at room temperature. After the completion of the reaction, the product was isolated as described above. Yield 1.92 g (65%).

*1-Indanone-2-carboxylic Acid.* Carboxylation of 1-indanone (2.38 g, 18.0 mmol) was achieved as described above (Method A). Crystallization from acetone-chloroform afforded 1.46 g (46%) of the corresponding carboxylic acid with mp 101–102°C. lit.<sup>11)</sup> 102°C.

*Cyclohexanone-2-carboxylic Acid.* This compound was prepared from cyclohexanone (1.76 g, 18.0 mmol) in the same manner as described above. Yield 1.33 g (52%). mp 78–79°C. lit.<sup>12)</sup> 80°C.

*Others.* Acetophenone, 4-nitrotoluene, and phenylacetonitrile were carboxylated in the similar manner as described above to give corresponding carboxylic acids, benzoylacetic acid (18%, mp 97–98°C. lit.<sup>11)</sup> 98–99°C), 4-nitrophenylacetic acid (12%, mp 152–153°C), and phenylcyanoacetic acid (19%).

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