δ 2.19 (s, 3), 2.30 (s, 3), 5.95 (m, 1), 6.20 (m, 2), 7.2 (d, J = 1.5 Hz, 1). The compound was air sensitive, and a satisfactory combustion analysis could not be obtained.

Acknowledgment. We are grateful to the National Institutes of Health for financial support of this study. A.I.M., the recipient of an Alexander von Humboldt Senior Scientist Award, expresses his gratitude to the faculty of the University of Wurzburg for their hospitality and stimulating discussions.

Registry No. 1, 86046-93-7; **5**, 98761-33-2; **10a**, 98761-34-3; **10b**, 98761-35-4; **10c**, 98761-36-5; **10d**, 98761-37-6; **10e**, 98761-38-7; **10f**, 98761-39-8; **10g**, 98761-40-1; **10h**, 98761-41-2; **10i**, 98777-27-6; **11**, 98761-42-3; **12g**, 98761-43-4; **13**, 98761-44-5; **14**, 98761-45-6; **15**, 98761-46-7; **16**, 98761-47-8; **17**, 53774-21-3; **18**, 98761-48-9; **19**, 98761-49-0; **20**, 98761-50-3; **22**, 98777-28-7; **23**, 74055-95-1; **24**, 66002-49-1; **25**, 98761-51-4; **26**, 98761-52-5; **27**, 10160-87-9; **30**, 55454-22-3; **31**, 41453-56-9; **32** (R = Ph), 98761-58-1; **34**, 98761-53-6; **35**, 30078-92-3; **36**, 98761-54-7; **37**, 98761-55-8; **40**, 98761-56-9; **41**, 98761-57-0; $Me(CH_2)_5I$, 21369-64-2; D_2O, 7789-20-0; PhCHO, 100-52-7; $Ph(CH_2)_2CHO$, 104-53-0; $PhCOCH_3$, 98-86-2; Me_3CCOMe, 75-97-8; methyl iodide, 74-88-4; 1-naphthaldehyde, 66-77-3; trimethylacetaldehyde, 630-19-3; furfural, 98-01-1; 2-cyclohexen-1-one, 930-68-7; 2-acetylthiophene, 88-15-3; 2-acetylpyridine, 1122-62-9; 1-iodobutane, 542-69-8.

Carboxylation of Ketones Using Triethylamine and Magnesium Halides

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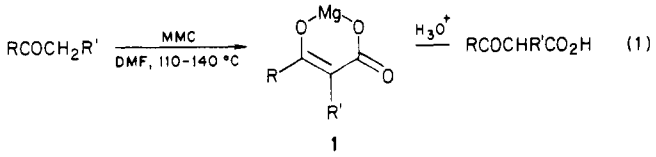
Procedures for the carboxylation of ketones with carbon dioxide at atmospheric pressure in the presence of magnesium halides and triethylamine are described. A variety of ketones are converted to the corresponding β-keto acids in satisfactory yields by using magnesium chloride–sodium iodide mixtures in acetonitrile. This carboxylation reaction exhibits little regioselectivity with 2-butanone.

A variety of procedures have been reported for the conversion of ketones to the corresponding β-keto acids.[1] Perhaps the most widely used procedure is that developed by Stiles and Finkbeiner using the reagent magnesium methyl carbonate (MMC), eq 1.[2] This method often gives

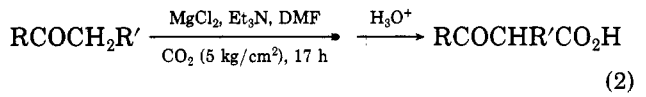


(1)

1

good yields of β-keto acids but has a number of disadvantages including the high reaction temperature, the inconvenient preparation of MMC (usually taken in 4–10× excess), and the difficulty of isolating the product from a large volume of dimethylformamide (DMF) solvent. The formation of the magnesium chelate **1** is probably an essential feature of the reaction. Thus, the reaction has never been reported for ketones possessing only one α hydrogen and fails in a similar situation[3] where a chelate structure analogous to **1** cannot be formed.

More recently, Matsumura has described a direct reaction of ketones with carbon dioxide at elevated pressure which is promoted by a mixture of triethylamine and magnesium chloride in DMF solution (eq 2).[4] We have examined this carboxylation reaction at atmospheric pressure using a variety of solvents and magnesium halides with the results reported here.



(2)

(1) For leading references, see: Haruki, E. In "Organic and Bio-organic Chemistry of Carbon Dioxide"; Inoue, S., Yamayaki, N.; Eds.; Wiley: New York, 1982; pp 5–78.

(2) (a) Stiles, M.; Finkbeiner, H. L. *J. Am. Chem. Soc.* **1959**, *81*, 505. (b) Stiles, M. *Ibid.* **1959**, *81*, 2598.

(3) For example, MMC reacts readily with 3-phenylhydantoin but not with 3-phenyl-5-methylhydantoin: Finkbeiner, H. *J. Am. Chem. Soc.* **1964**, *86*, 961.

(4) Matsumura, N.; Yagyu, T.; Imoto E. *Nippon Kaguku Kaishi* **1977**, *1344*.

Table I. Carboxylation of Cyclohexanone with $MgCl_2$ in a Variety of Solvents[a]

solvent	$T_{50\%}$[b]	$T_{90\%}$[c]
acetonitrile	7 min	45 min
THF	12 min	80 min
methylene chloride	30 min	160 min
dimethoxyethane	2 h	10 h
DMF	3 h	12 h

[a] Reaction at 25 °C; 0.5 M in ketone in each solvent; cyclohexanone/$MgCl_2$/Et_3N (1:1:2). [b] Time for absorption of 0.5 mol of CO_2/mol of cyclohexanone. [c] Time for absorption of 0.9 mol of CO_2/mol of cyclohexanone.

Table II. Carboxylation of Cyclohexanone with a Variety of Magnesium Halides[a]

MgX_2	$T_{50\%}$,[b] min	$T_{90\%}$,[c] min
$MgCl_2$	7	45
$MgBr_2$	3	17
"MgI_2"	1	6

[a] Cyclohexanone/MgX_2/Et_3N (1:1:2); 0.5 M in acetonitrile at 25 °C. [b] Time for absorption of 0.5 mol of CO_2/mol of cyclohexanone. [c] Time for absorption of 0.9 mol of CO_2/mol of cyclohexanone.

Results and Discussion

Our initial experiments were aimed at achieving maximum rates of carbon dioxide absorption. To this end, the carboxylation of cyclohexanone was examined in a variety of solvents in the presence of 2 equiv of triethylamine and 1 equiv of $MgCl_2$. The rate of absorption of CO_2 at atmospheric pressure was followed by using a gas buret. Reaction mixtures were heterogeneous in all cases and the absorption of carbon dioxide was accompanied by formation of additional insoluble material. In general, initial concentrations 0.5 M or less in ketone were necessary to maintain magnetic stirring. As shown in Table I, the fastest rates are obtained in acetonitrile, and the reaction is exceptionally slow in DMF. Presumably, DMF neutralizes the Lewis acidity of Mg^{+2}, accounting for the slow rate in this solvent.

Using acetonitrile solvent, the carboxylation of cyclohexanone was examined in the presence of 2 equiv of

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Table III. Carboxylation of Acetophenone in the Presence of "MgI_2" and Triethylamine

"MgI_2", mmol	Et_3N, mmol	yield,[a] %	"MgI_2", mmol	Et_3N, mmol	yield,[a] %
0	2	0[b]	2	2	52
2	0	0[b]	2	4	75
1	1	15	2	6	67
1	2	46	3	4	65
2	1	27			

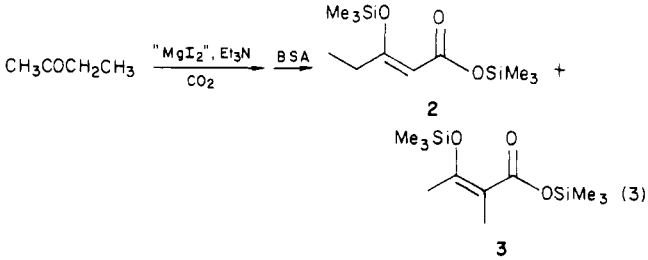
[a] Isolated yield of 3-oxo-3-phenylpropanoic acid. [b] No CO_2 was absorbed.

triethylamine and 1 equiv of a variety of magnesium halides (a mixture of 2 equiv of NaI and 1 equiv of $MgCl_2$ was used to prepare "MgI_2"). The rate of absorption of CO_2 increases in the order $MgCl_2$ < $MgBr_2$ < "MgI_2" (Table II). Carboxylation in the presence of "MgI_2" is remarkably fast, absorption of 1 equiv of CO_2 requires less than 15 min.

In the above studies, the β-keto acid of cyclohexanone was isolated by quenching with cold, dilute acid after 12 h of reaction. Yields of this unstable material were variable even for duplicate reactions but ranged from 15% to 40%. To determine optimum conditions for the preparations of β-keto acids, the carboxylation of acetophenone, which forms a relatively stable β-keto acid, was examined. Maximum yields of 3-oxo-3-phenylpropanoic acid were obtained with 4 equiv of triethylamine and 2 equiv of "MgI_2" (Table III). Under these conditions, the reaction mixtures absorbed 1 equiv of CO_2 rapidly (~30 min) and this was followed by a slower absorption of an additional 0.5–1.1 equiv (12–24 h). The excess CO_2 over 1 equiv was evolved on quenching the reaction mixtures with acid. Part, if not all, of the excess absorption of CO_2 is due to a slow carboxylation of the solvent (see Experimental Section).[5]

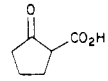
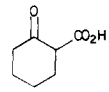
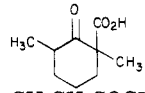
The generality of this method for preparing β-keto acids was examined with a variety of ketones (Table IV). Significantly, the procedure gives excellent yields of the β-keto acid derived from isobutyrophenone, a ketone that has only one α hydrogen. Clearly, the formation of a magnesium chelate of structure **1** is not an essential feature of the reaction.

The regioselectivity of the reaction was examined with 2-butanone. Carboxylation of this ketone gave a mixture of two acids. Silylation with bis(trimethylsilyl)acetamide (BSA), followed by GLC analysis, indicated a 45:55 mixture of the two regioisomers **2** and **3** (eq 3). In contrast, the



MMC procedure is reported to be highly selective for carboxylation at the terminal methyl group of 2-alkanones.[6] A likely explanation for this difference is that carboxylation is reversible[7] at the high temperatures (refluxing DMF) used in the MMC procedure and regiochemistry is then controlled by the relative stability of magnesium chelates of structure **1**.

Table IV. Preparation of β-Keto Acids from a Variety of Ketones[a]

ketone	β-keto acid	yield, %[b]
acetophenone	$C_6H_5COCH_2CO_2H$	75
propiophenone	$C_6H_5COCH(CH_3)CO_2H$	85
isobutyrophenone	$C_6H_5COC(CH_3)_2CO_2H$	90
cyclopentanone		35
cyclohexanone		70
2,6-dimethylcyclohexanone		65
3-pentanone	$CH_3CH_2COCH(CH_3)CO_2H$	58
4-heptanone	$CH_3CH_2CH_2COCH(CH_2CH_3)CO_2H$	75
2,4-dimethyl-3-pentanone	$(CH_3)_2CHCOC(CH_3)_2CO_2H$	65

[a] Reaction times, 3 h in CH_3CN at 25 °C; ketone/"MgI_2"/Et_3N (1:2:4). [b] Isolated yield of β-keto acid.

Experimental Section

Tetrahydrofuran was distilled from sodium and benzophenone. Acetonitrile, DMF, dimethoxyethane, and triethylamine were distilled from calcium hydride and stored under argon. Methylene chloride, reagent grade, was stored over 4A molecular sieves. All ketones were obtained commercially (Aldrich Chemical Co.) and distilled from calcium hydride. Sodium iodide (Aldrich, anhydrous, 99+%) was dried in a vacuum oven and stored in a glovebag under argon. Magnesium chloride (Aldrich, anhydrous, 98+%) was stored in a glovebag and used directly. Magnesium bromide was prepared by a literature procedure[8] from ethylene dibromide and magnesium. Carbon dioxide was generated from dry ice and dried by passage through a tube containing anhydrous $CaSO_4$. BSA was prepared by a literature procedure.[9] ^1H NMR spectra were recorded on a Varian T-60 spectrometer and are reported in parts per million relative to an internal Me_4Si standard. Mass spectra were obtained with a Finnigan 4000 GC/MS. Gas chromatographic analyses were performed with a Varian 920 chromatograph equipped with a 6 ft × 0.25 in. column packed with 15% SE-30 on Chromasorb W.

Rate Studies. The following procedure for the reaction of cyclohexanone with CO_2 in THF is representative of the procedure used to obtain the results of Tables I and II: a flame-dried 50-mL round-bottom flask equipped with septum, gas inlet, and magnetic stirrer was charged with 20 mL of dry THF. Magnesium chloride (0.95 g, 10 mmol), and Et_3N (2.8 mL, 20 mmol) were added to the flask, and stirring was initiated. The flask was connected to a gas buret containing dry CO_2 and flushed with this gas. The flask was immersed in a water bath at 25 °C. After the fluid level in the buret had stabilized, cyclohexanone (1.04 mL, 10 mmol) was injected, and the rate of CO_2 uptake was monitored. A total of 250 mL of CO_2 (10.1 mmol) was absorbed in 70 min, and this value remained constant overnight.

Preparation of β-Keto Acids: 2,2-Dimethyl-3-phenyl-3-oxopropanoic Acid. The following procedure for the reaction of isobutyrophenone with CO_2 is representative of the procedures used to obtain the results of Tables III and IV.

Anhydrous magnesium chloride (20 mmol, 1.9 g) and dry sodium iodide (40 mmol, 6.0 g) were stirred in a 100-mL flask for 0.5 h with 30 mL of acetonitrile at room temperature under argon. At that time, Et_3N (40 mmol, 5.6 mL) was added to the reaction. The flask was flushed with carbon dioxide and connected to a

(5) The excess absorption of CO_2 is probably not due to carboxylation of an initial chelate analogous to **1** because the carboxylation of isobutyrophenone also consumes excess CO_2.

(6) (a) Whitlock, B. J.; Whitlock, H. W., Jr. *J. Org. Chem.* **1974**, *39*, 3144. (b) Crombie, L.; Hemesley, P.; Pattenden, G. *Tetrahedron Lett.* **1968**, 3021.

(7) Pelletier, S. W.; Parthasarathy, P. C. *Tetrahedron Lett.* **1964**, *103*.

(8) Ashby, E. C.; Arnott, R. C. *J. Organomet. Chem.* **1968**, *14*, 1.

(9) Klebe, J. F.; Finkbeiner, H.; White, D. M. *J. Am. Chem. Soc.* **1966**, *88*, 3390.

gas buret. After the gas volume in the buret had stabilized, isobutyrophenone (10 mmol, 1.5 mL) was introduced into the mixture. Absorption of CO_2 ensued immediately, and the reaction mixture became excessively pasty, making stirring difficult. In some cases, small amounts of solvent, in addition to the original 30 mL, were added to maintain effective stirring. The resulting mixture was stirred for 2.5 h, at which time approximately 300 mL of CO_2 had been absorbed. The mixture was quenched with 50 mL of ice–water and extracted with ether. The aqueous layer was cooled to 0 °C in an ice bath and acidified to pH 3–4 with 0.7 M aqueous HCl at 0 °C. Vigorous stirring was maintained throughout this process. The aqueous solution was extracted with two portions of ether (30 mL each). The resulting organic layer was dried with magnesium sulfate. Removal of the solvent in vacuo provided 1.73 g (90%) of 2,2-dimethyl-3-phenyl-3-oxopropanoic acid:[10] 93–95 °C; ^1H NMR ($CDCl_3$) δ 1.58 (1 H, s), 7.3–7.5 (3 H, m), 7.65–7.9 (2 H, m); IR ($CHCl_3$ solution) 3400–2500 (br), 1710 (s), 1635 (s) cm^{-1}; MS, m/e 192 (M^+), 148 ($M^+ - CO_2$), 105, 77.

Benzoylacetic acid was prepared from acetophenone and CO_2 by the procedure described above: 73% yield; mp 101–102 °C (lit. mp 101–102 °C);[11] ^1H NMR (C_3D_6O) δ 4.05 (2 H, s), 5.7 (vinyl H, s), 7.25–7.6 (3 H, m), 7.7–8.05 (2 H, m); IR ($CHCl_3$ solution) 3500–2600 (br), 1730 (s), 1680 (s) cm^{-1}; MS, m/e 165 (M^+), 120 ($M^+ - CO_2$), 105, 77.

2-Methyl-3-phenyl-3-oxopropanoic acid was prepared from propiophenone and CO_2 by the procedure described above: 85% yield; mp 76–78 °C (lit. mp 77–78 °C);[11] ^1H NMR δ 1.5 (3 H, d), 4.2 (1 H, q), 7.3–7.55 (3 H, m), 7.8–8.05 (2 H, m), 10.1 (1 H, s); IR ($CDCl_3$ solution) 3500–2400 (br), 1720 (s), 1680 (s) cm^{-1}; MS, m/e 178 (M^+), 134 ($M^+ - CO_2$), 105, 77.

2-Oxocyclopentane-1-carboxylic acid was prepared from cyclopentanone and CO_2 by the procedure described above: 38% yield obtained as an oil;[12] ^1H NMR ($CDCl_3$), δ 1.5–1.9 (2 H, m), 2.1–2.6 (4 H, m), 8.9 (1 H, br, s); IR ($CHCl_3$ solution) 3400–2500 (br), 1730 (s), 1700 (s) cm^{-1}; MS, m/e 128 (M^+), 84 ($M^+ - CO_2$).

2-Oxocyclohexane-1-carboxylic acid was prepared from cyclohexanone and CO_2 by the procedure described above: 70% yield; mp 79–80 °C, (lit. mp 78–80 °C);[13] ^1H NMR ($CDCl_3$) δ 1.4–2.0 (4 H, m), 2.0–2.6 (4 H, m), 3.2 (1 H, m), 10.3 (1 H, br, s), 11.65 (1 H, br, s, from enol); IR ($CHCl_3$ solution) 3400–2500 (br), 1710 (s), 1660 (s) cm^{-1}; MS, m/e 142 (M^+), 124 ($M^+ - H_2O$), 98 ($M^+ - CO_2$), 68, 55.

1,5-Dimethyl-2-oxocyclohexane-1-carboxylic acid was prepared from 2,6-dimethylcyclohexanone and CO_2 by the procedure described above: 65% yield; mp 58–61 °C;[10] 1H NMR ($CDCl_3$) δ 1.05 (3 H, d), 1.35 (3 H, s), 1.4–2.7 (7 H, m), 10.65 (1 H, s); IR ($CHCl_3$ solution) 3500–2500 (br), 1720 (shoulder), 1700 (s) cm^{-1}; MS, m/e 170 (M^+), 152 ($M^+ - H_2O$), 126 ($M^+ - CO_2$), 111, 97, 87.

2-Methyl-3-oxopentanoic acid was prepared from 3-pentanone and CO_2 by the general procedure described previously:[14] 56% yield obtained as a viscous oil; ^1H NMR ($CDCl_3$) δ 1.1 (3 H, t), 1.4 (3 H, d), 1.6 (2 H, q), 3.6 (1 H, q), 11.85 (1 H, s); IR ($CHCl_3$ solution) 3400–2500 (br), 1750–1710 cm^{-1}; MS, m/e 130 (M^+), 101 ($M^+ - C_2H_5$), 86 ($M^+ - CO_2$), 57.

2-Ethyl-3-oxohexanoic acid was prepared from 3-heptanone and CO_2 by the procedure outlined above.[15] 75% yield isolated as a viscous oil; ^1H NMR ($CDCl_3$) δ 0.95 (6 H, overlapping t), 1.75 (4 H, m), 2.55 (2 H, t), 3.45 (1 H, t), 11.1 (1 H, s); IR ($CHCl_3$ solution) 3500–2500 (br), 1725–1700 cm^{-1}; MS, m/e 158 (M^+), 115 ($M^+ - C_3H_7$), 114 ($M^+ - CO_2$), 71, 43.

2,2,4-Trimethyl-3-oxopentanoic acid was prepared from 2,4-dimethyl-3-pentanone and CO_2 by the procedure described above: 65% yield; mp 25 °C (lit. mp 24 °C);[16,17] ^1H NMR ($CDCl_3$) δ 1.15 (6 H, d), 1.45 (6 H, s), 3.0 (1 H, septet), 11.2 (1 H, s); IR ($CHCl_3$ solution) 3400–2700 (br), 1690 (s) cm^{-1}; MS, m/e 158 (M^+), 140 ($M^+ - H_2O$), 114 ($M^+ - CO_2$), 99 ($M^+ - CO_2Me$), 71, 43.

Carboxylation of 2-Butanone. 2-Butanone (10 mmol, 0.9 mL) was carboxylated by the method described above. A yellow oil (0.55 g, 47%) was isolated and appeared, by ^1H NMR, to be a mixture of two β-keto acids. The oil was dissolved in 5 mL of diethyl ether and treated with BSA according to the procedure of Kleve, Finkbeiner, and White.[9] The resulting solution, containing the bis(silylated) acid derivatives, was subjected to GLC analysis employing tetradecane as an internal standard. The silylation yield was 26%. Two products were present in approximately equal amounts with compound **2** eluting first followed closely by **3**. Compound **2**: ^1H NMR ($CDCl_3$) δ 0.27 (9 H, s), 0.29 (9 H, s), 1.06 (3 H, t), 2.69 (2 H, q), 5.02 (1 H, s); MS, m/e 260 (M^+), 245 (C^+CH_3), 171, 147, 75. Compound **3**: ^1H NMR ($CDCl_3$) δ 0.20 (9 H, s), 0.35 (9 H, s), 1.9 (3 H, m), 2.30 (3 H, s).

Reaction of acetonitrile with CO_2. In a control experiment, the rate of absorption of CO_2 by acetonitrile solvent was examined. A flask containing acetonitrile (30 mL) and Et_3N (2.8 mL, 20 mmol) was saturated with CO_2 and charged with $MgCl_2$ (0.95 g, 10 mmol) and NaI (3.0 g, 20 mmol). The flask was immersed in a water bath at 25 °C and the rate of absorption of CO_2 was monitored: 1 mmol (6 h); 2 mmol (2 days); 4 mmol (6 days). After 6 days, the reaction mixture was quenched with dilute acid at 0 °C. A total of 4 mmol of gas was evolved.

Registry No. **2**, 98779-01-2; **3**, 98779-02-3; NaI, 7681-82-5; $MgCl_2$, 7786-30-3; $C_6H_5COCH_2CO_2H$, 614-20-0; $C_6H_5COCH(CH_3)CO_2H$, 4767-01-5; $C_6H_5COC(CH_3)_2CO_2H$, 38744-73-9; $CH_3CH_2COCH(CH_3)CO_2H$, 14925-93-0; $CH_3(CH_2)_2COCH(CH_2CH_3)CO_2H$, 4384-00-3; $(CH_3)_2CHCOC(CH_3)_2CO_2H$, 98779-00-1; Et_3N, 121-44-8; acetophenone, 98-86-2; propiophenone, 93-55-0; isobutyrophenone, 611-70-1; cyclopentanone, 120-92-3; cyclohexanone, 108-94-1; 2,6-dimethylcyclohexanone, 2816-57-1; 3-pentanone, 96-22-0; 3-heptanone, 106-35-4; 2,4-dimethyl-3-pentanone, 565-80-0; 2-cyclopentanonecarboxylic acid, 50882-16-1; 2-cyclohexanonecarboxylic acid, 18709-01-8; 1,3-dimethyl-2-cyclohexanonecarboxylic acid, 98778-99-5; 2-butanone, 78-93-3.

(10) Compound decomposes on standing.
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(17) In all cases, the products were pure and uncontaminated by by-products.