

$\alpha$ -CARBOXYLATION REACTION OF CARBONYL COMPOUNDS  
WITH BROMOMAGNESIUM UREIDE-CARBON DIOXIDE ADDUCTS

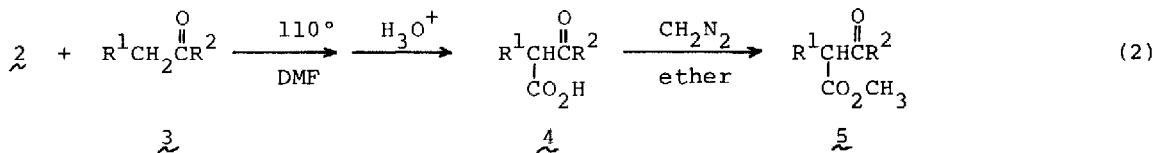
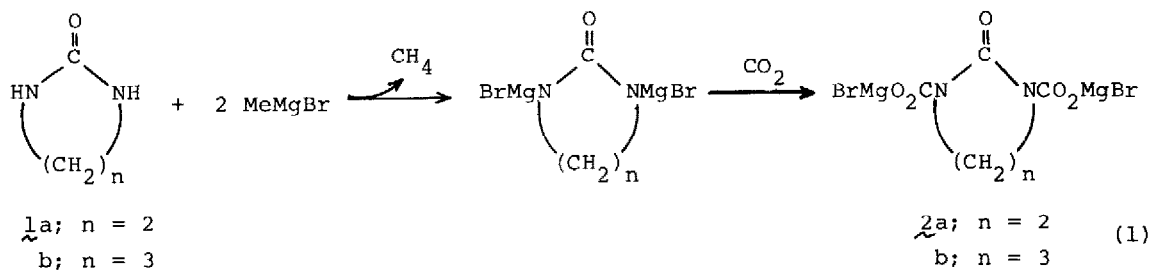
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Summary: Bromomagnesium ureide-carbon dioxide adducts, models of the carboxylated biotin complex, undergo carboxylation of a variety of carbonyl compounds in good yield.

Carboxylation of organic substances with carbon dioxide or bicarbonate ion mediated by biotin-enzymes is one of the most interesting carbon-dioxide fixation reactions found in biological systems.<sup>1</sup> Acetyl CoA carboxylase<sup>2</sup> and pyruvate carboxylase<sup>3</sup> are the typical enzymes which catalyze the carboxylation of the corresponding methyl keto compounds. However, the detailed chemical mechanism of these carboxylations remains uncertain,<sup>4</sup> and little success has been reported in attempts to transfer the carbon dioxide moiety from a carboxy-biotin analogue to an appropriate acceptor.<sup>5</sup> We now wish to show a novel carbon dioxide transfer from bromomagnesium ureide-carbon dioxide adducts (2) to a variety of carbonyl compounds, to afford the corresponding  $\alpha$ -carboxylated ketone in high yields. The chemical structure of these carbon dioxide adducts containing a urea moiety resembles partly that of the biotin-CO<sub>2</sub>-enzyme complexes which are the intermediates formed in the first step of the carbon dioxide transfer reaction catalyzed by biotin enzymes.

The bromomagnesium ureide-carbon dioxide adducts (2), prepared by the carboxylation of the reaction mixture from a cyclic urea (1) and methylmagnesium bromide with gaseous carbon dioxide in tetrahydrofuran, were isolated as white solids.<sup>6</sup> To a solution of 2 (15 mmol) dissolved in dry dimethylformamide (DMF) (30 mL), a ketone (5 mmol) was added with a syringe under argon. The mixture was stirred at 110°C for 3h, cooled with ice, and then poured dropwise onto a stirred solution of 1N hydrochloric acid (40 mL) in ether (20 mL) with ice-cooling. The ethereal layer was separated and the aqueous layer was extracted with ether (20 mL x 2). The combined ethereal solution was washed with cold 1N hydrochloric acid (30 mL). The  $\alpha$ -keto acid (4), without isolation, was esterified with a small excess of diazomethane in ether. After evaporation of the solvent, the residue was subjected to distillation yielding an  $\alpha$ -methoxycarbonyl ketone (5).



The products, which were usually pure enough to give correct analyses, were characterized by GLC, NMR, and IR spectra. Yields of products are satisfactory when more than two equivalents of  $\underline{2}$  to the ketone were used. The results are shown in Table 1.

Yields of the carboxylation of ketones with  $\underline{2b}$  derived from trimethylene urea ( $\underline{1b}$ ) are generally better than those with  $\underline{2a}$  from ethylene urea ( $\underline{1a}$ ). It is noteworthy that with unsymmetrical ketones the site of the carboxylation is directed by relative steric hindrance at the  $\alpha$ -carbon of the ketone (run 2, 4, and 5). On the other hand, in cases of mesityl oxide and isophorone (run 7 and 9), products (15 and 18) carboxylated at the vinylic carbon ( $\text{sp}^2$ ) with  $\underline{2}$  were obtained together with products (14 and 17) carboxylated at the  $\alpha$ -methyl carbon ( $\text{sp}^3$ ) of the ketones.

Although the detailed mechanism of the reaction is not clear, it is suggested that a magnesium (II) metal ion plays an important role as an intermediate in the reaction. When an alkyl halide such as methyl iodide or allyl bromide was added into the reaction mixture of  $\underline{2}$  and cyclohexanone in DMF, a mixture of cyclohexanones mono- and dialkylated at the  $\alpha$ -carbon was obtained. This shows participation of the magnesium chelate ( $\underline{6}$ ) in the reaction as suggested also in the reaction of methylmagnesium carbonate (MMC) with ketone.<sup>7</sup> Carboxylation of other substrates together with mechanistic studies will be reported later.

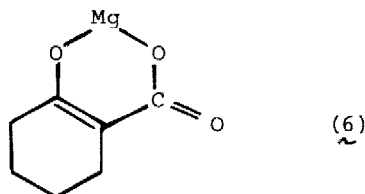

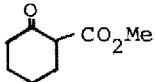
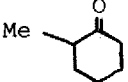
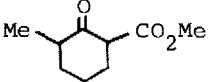

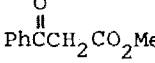
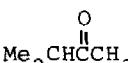
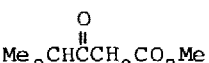
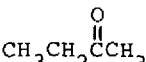
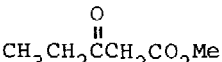
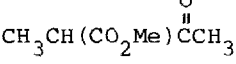
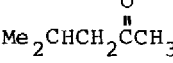
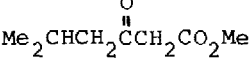
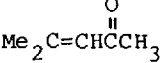
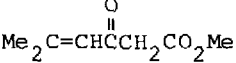
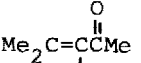
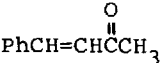
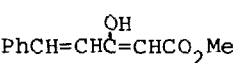
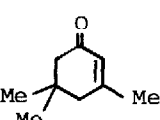
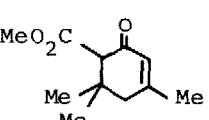
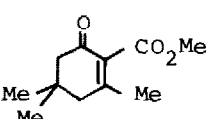
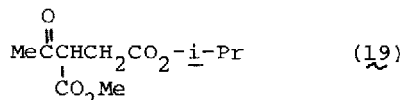
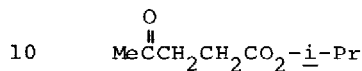


Table 1. Carboxylation of ketones with magnesium ureide-carbon dioxide adducts in DMF.

Run	Ketone	Product <sup>a)</sup>	% Yield <sup>b)</sup>	
			from 2a <sup>c)</sup>	from 2b <sup>d)</sup>
1		 (7) ~	44.8	74.3
2		 (8) ~	30.6	54.1
3		 (9) ~	39.6 <sup>e)</sup>	51.7 <sup>e)</sup>
4		 (10) ~	19.4	55.8
5		 (11) ~		22.1
		 (12) ~		17.0 (11/12=1.3) <sup>f)</sup>
6		 (13) ~	36.7	73.7
7		 (14) ~	30.7 (14/15=9) <sup>f)</sup>	66.6 (14/15=9) <sup>f)</sup>
		 (15) ~		
8		 (16) ~	32.4 <sup>e)</sup>	71.8 <sup>e)</sup>
9		 (17) ~		43.8 (17/18=3/7) <sup>f)</sup>
		 (18) ~		

(Continued on the next page)



77.0

a) Products after treatment with diazomethane. b) Isolated yield based on the starting carbonyl compound unless noted otherwise. c) 6h at 110°C. d) 3h at 110°C. e) Determined by NMR. f) Determined by GLC.

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#### References and Notes

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- (3) H. G. Wood, "The Enzymes", vol. VI, P. D. Boyer, Ed., Academic Press, New York, N. Y., 1972, p. 83.
- (4) Considerable controversy still exists concerning the nature of the enzyme-biotin-CO<sub>2</sub> intermediate. See, (a) T. C. Bruice and A. F. Hegarty, *Proc. Nat. Akad. Sci. U. S.*, **65**, 805 (1970); (b) A. F. Hegarty and T. C. Bruice, *J. Am. Chem. Soc.*, **92**, 6568 (1970); (c) *idem*, *ibid.*, **92**, 6575 (1970); (d) M. Caplow, *ibid.*, **87**, 5774 (1965); (e) *idem*, *ibid.*, **90**, 6795 (1968); (f) M. Caplow and M. Yager, *ibid.*, **89**, 4513 (1967).
- (5) (a) H. J. Schaeffer and P. S. Bhargava, *J. Pharm. Sci.*, **51**, 1116 (1962); (b) *idem*, *ibid.*, **53**, 137 (1964); (c) Y. Otsuji, M. Arakawa, N. Matsumura, and E. Haruki, *Chem. Lett.*, 1193 (1973); (d) Y. Akasaki and A. Ohno, *J. Am. Chem. Soc.*, **96**, 1957 (1974); (e) Y. Akasaki, M. Hatano, and M. Fukuyama, *Tetrahedron Lett.*, 275 (1977); (f) H. Kohn, *J. Am. Chem. Soc.*, **98**, 3690 (1976); (g) T. Kwan, H. Yamamoto, H. Mori, and H. Samejima, *Kagaku-Kogyo (Chemical Industry)*, **23**, 1618 (1970); (h) N. Matsumura, H. Kawai, Y. Otsuji and E. Imoto, *Bull. Chem. Soc. Jpn.*, **50**, 2417 (1977).
- (6) As a typical example, 15g (0.15 mol) of tetrahydro-2-pyrimidinone (1a) was added portionwise to a THF (300 mL) solution of methylmagnesium bromide (0.36 mol) with stirring. After gas evolution ceased, carbon dioxide was bubbled into the solution sufficiently to precipitate the adduct (2a). The latter was isolated by decantation, washed, and dried under reduced pressure to give 77g (95.2 %) of analytically pure 2a·2THF, mp 240-242°C (dec.). The adduct contains 2 mole THF. 2b·2THF was also prepared by a similar procedure, mp 135-140°C.
- (7) M. Stiles and H. L. Finkbeiner, *J. Am. Chem. Soc.*, **81**, 506 (1959).

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