

COPPER CATALYZED REACTION OF GRIGNARD REAGENTS  
WITH CHLOROMAGNESIUM SALTS OF  $\omega$ -BROMOACIDS

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(Received in USA 14 October 1976; received in UK for publication 11 November 1976)

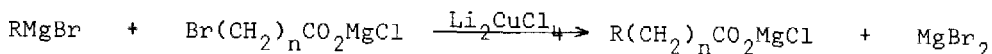
Bergbreiter and Whitesides<sup>1</sup> recently reported a useful method for the synthesis of fatty-acid esters based upon the reaction of organocopper(I) ate complexes with esters of 11-iodoundecanoic acid. The present communication describes a related, though catalytic, process whereby alkyl (fatty) acids may be prepared directly from  $\omega$ -bromoacids.

Whereas at low temperature Grignard reagents react slowly with carboxylate anions, as evidenced by the success of the Grignard carbonation reaction to yield carboxylic acids,<sup>2</sup> they readily undergo copper-catalyzed coupling with alkyl bromides.<sup>3</sup> This differential reactivity suggested the possibility of preparing alkylacids from Grignard reagents and  $\omega$ -bromoacids, provided suitably soluble salts of the latter could be obtained. Chloromagnesium salts, prepared by reaction to the  $\omega$ -bromoacid with methylmagnesium chloride, are quite soluble (ca. 1M) in tetrahydrofuran at -20°, and this property has been used to prepare a variety of alkylcarboxylic acids. The net reaction is as follows:

Dilithium Tetrachlorocuprate-Catalyzed Coupling Reactions of Grignard Reagents  
With Chloromagnesium Salts of  $\omega$ -Bromoacids

<u>Acid (mmoles)</u>	<u>Mole %</u>		<u>Major Product (Yield)*</u>	<u>Minor Product (Yield)</u>
	<u>Grignard (mmoles)</u>	<u>Catalyst</u>		
11-Bromoundecanoic (60)	<u>n</u> -pentyl (63)	2	Palmitic acid (94) mp 62-63°C bp 156-157°/0.45mm	Docosanedioic acid (2) mp 121.5-123.5°C
5-Bromovaleric (30)	<u>sec</u> -butyl (33)	4	6-Methyloctanoic acid (88) bp 146-147°C/13mm	Decanedioic acid (3.6) mp 130-132°C
3-Bromopropionic (40)	<u>n</u> -pentyl (44)	4	Octanoic acid (78) bp 144-146°C/20mm	3-Bromopropionic acid (7)
3-Bromopropionic (40)	2-phenethyl (44)	4	5-Phenylvaleric acid (77) mp 58-59°C bp 113-114°C/0.02mm	3-Bromopropionic acid (13)
Bromoacetic (40)	<u>n</u> -pentyl (44)	4	Succinic acid (40) mp 183-185°C	Heptanoic acid (26) Bromoacetic acid (6)

\* All yields, except that of heptanoic acid, are based upon purified products, the pmnr spectra of which are in accord with those expected. Melting points and boiling points are uncorrected.



The synthesis of palmitic acid is typical of the procedure. To a solution of 60 mmoles of 11-bromoundecanoic acid in 75 ml of tetrahydrofuran under argon is added at  $-20^\circ\text{C}$  61 mmoles of methylmagnesium chloride (2.7M) in tetrahydrofuran. At the cessation of gas evolution, 1.2 mmoles of 0.20M dilithium tetrachlorocuprate<sup>3</sup> is added to the solution, followed then by the addition, over a 30-minute period, of 63 mmoles of n-pentylmagnesium bromide (1.58M)<sup>4</sup> in tetrahydrofuran. The mixture is stirred at  $-20^\circ\text{C}$  until a negative Gilman test is obtained and then poured into a mixture of dilute sulfuric acid-benzene. After removal of the aqueous solution, the product is extracted into aqueous potassium hydroxide. Concentration of the organic layer affords 0.11 g of neutral material. The aqueous layer is acidified, and the liberated product collected. Distillation yields 14.59 g (94%) of palmitic acid, bp  $156-157^\circ/0.45$  mm, mp  $62-63^\circ\text{C}$ . The pot residue, after recrystallization, affords 0.23 g (2%) of docosanedioic acid, mp  $121.5-123.5^\circ\text{C}$ .

The accompanying table summarizes similar experiments. In most reactions, small amounts of the diacid derived from the w-bromoacid were obtained. Residual 3-bromopropionic acid was present in all the products derived therefrom, but was easily removed by means of a hexane-water partition.<sup>5</sup>

The method is applicable to most w-bromoacids, bromoacetic being an obvious exception. Fatty acids are particularly accessible by this route, and mole-scale syntheses have been accomplished in yields exceeding 90%.<sup>6</sup> Furthermore, reagents which might be of limited stability as stoichiometric organocuprates, for example, secondary Grignard reagents, undergo the reaction with no apparent decomposition.

Acknowledgment. The support of the Department of Medicinal Chemistry, University of Kansas, is gratefully acknowledged.

## REFERENCES AND NOTES

- (1) D.E. Bergbreiter and G.M. Whitesides, J. Org. Chem., 40, 779 (1975).
- (2) M.S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-Metallic Substances," Prentice-Hall Co., New York, 1954, p 913.
- (3) M. Tamura and J. Kochi, Synthesis, 1971, 303.
- (4) Grignard concentrations were determined by the method of S.C. Watson and J.F. Eastham, J. Organometal. Chem., 9, 165 (1967).
- (5) This method has also been employed with the chloromagnesium alkoxide of 3-bromopropanol. The reaction is similar to that of 3-bromopropionic acid in both yield and recovery of residual starting material. An analogous transformation using trimethylene oxide has recently been reported by J. Millon and G. Linstrumelle, Tetrahedron Letters, 1976, 1095.
- (6) R.L. Carney and T.A. Baer, Zoecon Corporation, unpublished work.