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COPPER CATALYZED REACTION OF GRIGNARD REAGENTS WITH CHLOROMAGNESIUM SALTS OF ω-BROMOACIDS

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Bergbreiter and Whitesides[1] 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 ω-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,[2] they readily undergo copper-catalyzed coupling with alkyl bromides.[3] This differential reactivity suggested the possibility of preparing alkylacids from Grignard reagents and ω-bromoacids, provided suitably soluble salts of the latter could be obtained. Chloromagnesium salts, prepared by reaction to the ω-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 *ω*-Bromoacids

Acid (mmoles)	Grignard (mmoles)	Mole % Catalyst	Major Product (Yield)*	Minor Product (Yield)
11-Bromoundecanoic (60)	*n*-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)	*sec*-butyl (33)	4	6-Methyloctanoic acid (88) bp 146-147°C/13mm	Decanedioic acid (3.6) mp 130-132°C
3-Bromopropionic (40)	*n*-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)	*n*-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 pnmr spectra of which are in accord with those expected. Melting points and boiling points are uncorrected.

$$RMgBr \quad + \quad Br(CH_2)_nCO_2MgCl \xrightarrow{Li_2CuCl_4} R(CH_2)_nCO_2MgCl \quad + \quad MgBr_2$$

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°C 61 mmoles of methylmagnesium chloride (2.7M) in tetrahydrofuran. At the cessation of gas evolution, 1.2 mmoles of 0.20M dilithium tetrachlorocuprate[3] is added to the solution, followed then by the addition, over a 30-minute period, of 63 mmoles of n-pentylmagnesium bromide (1.58M)[4] in tetrahydrofuran. The mixture is stirred at -20°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°/0.45 mm, mp 62-63°C. The pot residue, after recrystallization, affords 0.23 g (2%) of docosanedioic acid, mp 121.5-123.5°C.

The accompanying table summarizes similar experiments. In most reactions, small amounts of the diacid derived from the ω-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.[5]

The method is applicable to most ω-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%.[6] Furthermore, reagents which might be of limited stability as stoichiometric organocuprates, for example, secondary Grignard reagents, undergo the reaction with no apparent decomposition.

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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.