

tive starch iodide test; mp 178–181°, bubbling; $[\alpha]_D -29^\circ$; λ_{\max} 233 m μ (ϵ 15,000); λ_{\max} 3.02, 3.05, 5.69, 5.98 (shoulder), 6.02, 6.07 (shoulder), 7.95, and 8.08 μ ; nmr, δ (ppm) (TMS = 0): 0.85 ($C_{13}CH_3$), 1.98 ($C_{17}OCOCH_3$), 3.47 ($C\equiv CH$), 5.88 (C_4H), 11.28 ($C_{10}-O-OH$).

Anal. Calcd for $C_{22}H_{28}O_3$: C, 70.94; H, 7.58. Found: C, 71.11; H, 7.45.

Generation of 3-Methoxy-2,5(10)-estradien-17-one (II) from 3-Methoxy-17 α -ethynyl-2,5(10)-estradien-17 β -ol (III, R = H).—To a solution consisting of 0.2 g of III (R = H) in 10 ml of dimethylformamide under nitrogen was added 0.1 g of potassium *t*-butoxide. After 5 min at room temperature, 0.11 ml of acetic anhydride was added. One minute later the reaction mixture was poured into 200 ml of water. The pH was adjusted to about 3 with dilute HCl, and the insolubles, which were collected by filtration and dried at 60° under vacuum, weighed 140 mg. The infrared spectrum matched that of authentic II.

Registry No.—I (R = CH_3CO), 13236-11-8; III (R = CH_3CO), 13251-69-9; V (R = CH_3CO), 51-98-9.

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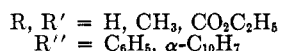
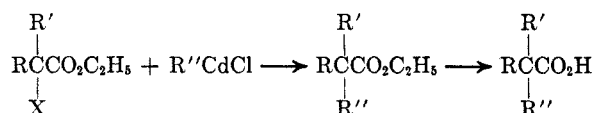
Organocadmium Reagents. V. Reaction with α -Halo Esters and Ketones^{1a,b}

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In view of the diminished reactivity of organocadmium compounds as compared to lithium or magnesium reagents,² it is attractive to consider new syntheses of compounds containing functional groups which would not survive treatment with the more reactive organometallic reagents. Since organocadmium reagents are known to displace halogens in a few instances³ but do not appear to decompose esters,^{2,4} we undertook an investigation of the behavior of some α -halogenated esters with these reagents. If displacement of halogen were to occur in preference to reaction at the ester site, the reaction would be potentially useful as a synthetic route to more complex acids and derivatives.



(1) (a) Abstracted in part from the Ph.D. Thesis of J. R. Y., University of New Hampshire, 1967; (b) P. R. Jones and J. D. Young, Abstracts, 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, p 894; (c) National Defense Education Act fellow, 1963–1966.

(2) J. Cason, *Chem. Rev.*, **40**, 15 (1947); D. A. Shirley, *Org. Reactions*, **8**, 27 (1943).

(3) (a) R. K. Summerbell and L. N. Bauer, *J. Amer. Chem. Soc.*, **58**, 759 (1936); (b) C. D. Hurd and R. P. Holysz, *ibid.*, **72**, 2005 (1950); (c) R. C. Fuson, S. B. Speck, and W. R. Hatchard, *J. Org. Chem.*, **10**, 55 (1945); (d) P. Chancel, *Bull. Soc. Chim. Fr.*, 228 (1951); (e) D. V. Nightingale, W. S. Wagner, and R. H. Wise, *J. Amer. Chem. Soc.*, **75**, 4701 (1953); (f) P. R. Jones and A. A. Lavigne, *J. Org. Chem.*, **25**, 2020 (1960); (g) F. N. Jones and C. R. Hauser, *ibid.*, **27**, 3364 (1962); (h) P. R. Jones, R. G. Nadeau, and G. A. Crosby, Abstracts A of IUPAC Congress, London, 1963, p 267; (i) P. R. Jones, C. J. Jarboe, and R. Nadeau, *J. Organometal. Chem.*, **8**, 361 (1967).

(4) H. Gross and J. Freiberg, *Chem. Ber.*, **99**, 3260 (1966).

This hypothesis was borne out by experiment to a limited extent. We found the reaction to be sensitive to the structure of the halo ester, solvent, and temperature, as can be seen from the results summarized in Table I. The bromo esters of acetic and propionic acids could be converted, respectively, into arylacetic and α -arylpropionic acids in yields of 40–62% under certain experimental conditions. Bromoisobutyrate did not form displacement product in ether or THF but was recovered partially or completely. We found no trace of a Claisen product, ethyl 2,2,4-trimethyl-3-oxopentanoate, as reported by Cason and Fessenden⁵ from a similar reaction with the *n*-butylcadmium reagent in benzene.

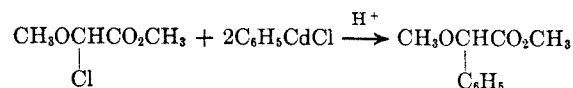
From the two chloro esters examined, only starting material, solvolysis product, or dehalogenative coupling products could be isolated.

The striking effect of solvent on the displacement was unexpected. Thus the conversion of bromoacetate into arylacetic acid was four to five times greater in THF than in ether. Under similar reaction conditions bromopropionate reacted efficiently in ether but failed completely in THF.

Optimum temperature for reactions in THF appears to depend on the cadmium reagent. Highest conversions with the phenylcadmium reagent in THF were realized at ice-bath temperature, while the α -naphthylcadmium reagent was considerably more reactive at room temperature. At least two factors may account reasonably for this temperature effect: increased coupling of phenyl reagent at the higher temperature and lower reactivity of the α -naphthylcadmium reagent, as well as its observed precipitation in THF at ice-bath temperature. By-products from the two cadmium reagents were biphenyl and naphthalene in every case, although the amounts of these hydrocarbons were not usually determined.

The reaction with α -halo ketones proceeded similarly, but the yields were generally lower than those from esters. Deoxybenzoin could be isolated only in 3–31% yield from phenacyl bromide and phenylcadmium reagent, along with the coupling products, biphenyl and 1,2-dibenzoylthane.

To our knowledge, a displacement of halogen in simple α -halo esters has not been reported up until now. Although Gross and Freiberg⁴ recently effected the displacement of the chloro group in methyl chloromethoxyacetate, this substrate is both an ether and an ester; and the replacement of halogen in α -halo ethers by organocadmium reagents is well known.^{3a,3b}



Of great interest is an apparent halogen-metal exchange, which occurs between diethyl bromomalonate and the phenylcadmium reagent. Both malonic ester and bromobenzene were isolated in equal amounts, roughly 75% yield. Thus the displacement method is not applicable to the synthesis of substituted malonic acids.

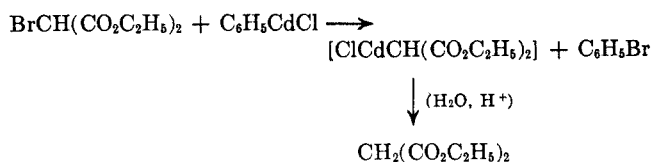
A similar halogen-metal exchange reaction was proposed earlier to explain Reformatsky and Claisen products from organocadmium reagents.⁵

(5) J. Cason and R. J. Fessenden, *J. Org. Chem.*, **22**, 1326 (1957).

TABLE I
 REACTION OF ORGANOCADMIUM REAGENTS WITH α -HALO ESTERS

Ester			Cd reagent		Solvent	Reaction temperature (time, hr)	Yield, % RC(R')(R'')COOH(C ₂ H ₅)
R	RC(R')(X)COOEt R'	X	R''	Ratio ^a			
H	H	Br	α -C ₁₀ H ₇	1	Ether	Reflux (10)	16
H	H	Br	α -C ₁₀ H ₇	2	THF	Ice bath (10)	9 ^b
H	H	Br	α -C ₁₀ H ₇	2	THF	Room temperature (8)	62
H	H	Br	C ₆ H ₅	1	Ether	Reflux (10)	11
H	H	Br	C ₆ H ₅	2	THF	Ice bath (10)	53, 46
H	H	Br	C ₆ H ₅	2	THF	Room temperature (8)	26
CH ₃	H	Br	C ₆ H ₅	2	Ether	Reflux (10)	40, 58
CH ₃	H	Br	C ₆ H ₅	2	THF	Ice bath (10)	0 ^c , 0 ^d
CH ₃	CH ₃	Br	C ₆ H ₅	2	Ether	Reflux (10)	0 ^e
CH ₃	CH ₃	Br	C ₆ H ₅	2	THF	Ice bath (10)	0 ^f
H	H	Cl	C ₆ H ₅	2	THF	Ice bath (10)	0 ^g
CH ₃	H	Cl	C ₆ H ₅	2	Ether	Reflux (10)	0 ^h

^a Molar ratio of organocadmium reagent (R''CdCl) to halo ester. ^b Naphthalene (89%) recovered. ^c Starting material recovered (50%). ^d 2,3-Dimethylsuccinic acid isolated (11%). ^e Starting material recovered quantitatively. ^f Starting material, biphenyl, and unidentified acid obtained. ^g Starting material recovered (30%) along with biphenyl. ^h Lactic acid isolated after saponification.



Sufficient experimental results are lacking at the present time to provide a meaningful evaluation of substrate, solvent, and temperature effects and their relationship to possible mechanisms for the reaction. It is hoped that forthcoming experiments will indicate whether the reaction conforms to the addition-rearrangement pathway, proposed by Ando for the analogous reaction with Grignard reagents.⁶

Observations to date, however, warrant the view that the displacement reaction with organocadmium compounds is a potentially valuable route to α -substituted acids and their derivatives from α -bromo esters where the site of displacement is primary or secondary.

Experimental Section

Infrared and nuclear magnetic resonance spectra, consistent for the compounds examined, are on file in the Department of Chemistry, University of New Hampshire. The following represent typical reaction and isolation procedures.

Preparation of the Organocadmium Reagents.—The Grignard reagent was prepared from equimolar amounts (0.1 or 0.2 mol, as noted) of magnesium and organic bromide and enough dry ether or tetrahydrofuran (THF) to make a 1.0–1.5 *M* solution. After all of the organic bromide had been added, the reaction mixture was allowed to reflux for 0.5 hr and was then filtered from excess magnesium if any remained. The cadmium reagent, assumed to be the unsymmetrical RCdCl or ArCdCl, was prepared by the addition of an equimolar portion of anhydrous cadmium chloride over a period of 15 min. When THF was the solvent, the solution of Grignard reagent was cooled to room temperature or to ice-bath temperature before addition of cadmium chloride was started. Cooling was provided during the addition. In every case a Gilman test⁷ showed the absence of Grignard reagent as soon as all of the cadmium chloride had been added.

(6) T. Ando, *Yuki Gosei Kagaku Kyokai Shi*, **17**, 777 (1959); *Chem. Abstr.*, **54**, 4492b (1960).

(7) H. Gilman and F. Schulze, *J. Amer. Chem. Soc.*, **47**, 2002 (1925).

Reaction of α -Naphthylcadmium Reagent with Ethyl Bromoacetate.—To 0.2 mol of α -naphthylcadmium reagent in THF at room temperature was added 16.7 g (0.1 mol) of ethyl bromoacetate in 15 ml of THF. When about one-half of the bromo ester had been added, the mixture thickened so that stirring was difficult. The mixture was warmed only sufficiently to keep it semifluid. After 8 hr the mixture was hydrolyzed with 100 ml of 3 *N* hydrochloric acid. The organic portion was removed, concentrated, and saponified by prolonged reflux with 100 ml of 10% sodium hydroxide in 50% ethanol. The basic solution was treated with Norit, acidified with concentrated hydrochloric acid, and cooled. There was obtained 11.5 g (62%) of α -naphthylacetic acid, mp 110–120° (recrystallized from benzene-ligroin, mp and mmp 130–132°).

Reaction of Phenylcadmium Reagent with Ethyl Bromoacetate.—A solution of 16.7 g (0.1 mol) of ethyl bromoacetate in 15 ml of THF was added dropwise, with stirring, to 0.2 mol of phenylcadmium reagent in THF, which was cooled in an ice bath. After 10 hr at ice-bath temperature, the mixture was hydrolyzed with an excess of saturated ammonium chloride and then steam distilled.

A first fraction of about 150 ml contained THF exclusively; evaporation on a steam bath left no residue. About 400 ml more of distillate was collected; additional distillate contained no carbonyl compound but did contain biphenyl. By ether extraction of the second distillate there was obtained 8.6 g (53%) of ethyl phenylacetate, bp 66–71° (0.6–1.0 mm), identified by its spectra, properties, and by conversion into α -phenylacetamide, mp 154–154.5° and mmp 155–156°.

Reaction of Phenylcadmium Reagent with Diethyl Bromomalonate.—A solution of 23.9 g (0.1 mol) of diethyl bromomalonate in 25 ml of ether was added dropwise, with stirring, to 0.2 mol of phenylcadmium reagent in refluxing ether. After 10 hr at reflux the mixture was cooled in an ice bath and hydrolyzed with 100 ml of 3 *N* hydrochloric acid. The dark oil (34.1 g) obtained by ether extraction was shown to contain diethyl malonate, bromobenzene, and a trace of diethyl bromomalonate. The amount of diethyl malonate was estimated to be 12 g (75%) by nmr analysis with toluene added to the sample as a standard. Analysis of the mixture by glpc showed diethyl malonate and bromobenzene to be present in equimolar amounts. Similar results were obtained with THF as the solvent.

Registry No.— α -Naphthylcadmium reagent, 15924-34-2; phenylcadmium reagent, 15924-35-3; RC(R')(X)COOEt (R = R' = H; X = Br), 105-36-2; (R = CH₃; R' = H; X = Br), 535-11-5; (R = R' = CH₃; X = Br), 600-00-0; (R = R' = H; X = Cl), 105-39-5; (R = CH₃; R' = H; X = Cl), 535-13-7.