

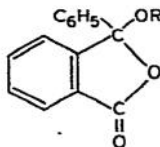
Organocadmium reagents

III. Displacement of acyloxy at saturated carbon¹

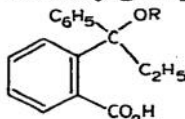
Organocadmium reagents are known to effect displacement of substituents at saturated carbon atoms, where the carbon atom is also attached to an acyl², alkoxy^{3,4}, or acyloxy¹ group. Instances of a similar displacement in carbonyl compounds by Grignard reagents are rare^{9,10}, and this is most likely a reflection of the higher reactivity of the magnesium compounds, which react preferentially at the carbonyl site. Organozinc⁹ and organomercury¹¹ reagents have been reported to effect the displacement in two isolated instances.

In the case of α' -substituted esters, the group displaced by organocadmium reagents has been chloro-^{2,6,7,8}, bromo-^{1,9}, hydroxy-^{1,5}, and alkoxy-¹. From previous experiments it was questionable whether the acyloxy group belonged in the category of displaceable substituents.

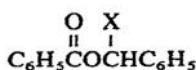
We have accumulated several examples in which the acyloxy group is displaced by organocadmium reagents, either along with the displacement of another group or in preference to another group. In each instance the organocadmium reagent was prepared from equimolar amounts of magnesium, organic halide, and cadmium chloride by way of the Grignard reagent and used without removal of by-products^{1,5}. All of our previous experiments had been carried out with lactones, specifically phthalides, where the substituent is in the 3-position. Those of type (I) react with the ethylcadmium reagent to give (II), the result of acyloxy displacement. The products (IIa) and (IIb), of considerable interest because of their novelty, were identified by analysis and infrared and NMR spectroscopy. A similar displacement in 3-isopropoxyphthalide by the mesityl Grignard reagent was observed by Newman¹⁰, who found that the reaction took alternate courses when conditions were modified. We also found evidence for displacement of the ethoxy group in (Ia).



(Ia), R = C₂H₅
 (Ib), R = CH(CH₃)₂



(IIa), R = C₂H₅
 (IIb), R = CH(CH₃)₂



(IIIa), X = Cl
 (IIIb), X = OCOC₆H₅
 (IIIc), X = C₆H₅



(IV)



(V)

Displacements by organocadmium reagent have now been observed as well in compounds of type (IIIa), (IIIb) and (IV), the acyclic counterparts of 3-substituted phthalides. Either the chloro group or the benzoyloxy group or both are displaced by phenylcadmium reagent; we have found no case where the benzoyloxy is displaced

in preference to chloro. From both (IIIa) and (IIIb) we have obtained benzhydryl benzoate (IIIc). With the α' -chloroester (IV) as substrate we have isolated the hydrocarbon (V), which arises by displacement of both groups. The fact that conversions in the acyclic series are low is not surprising because of the instability of the α' -chloroesters. Another factor may be the use of ether instead of benzene as solvent. No attempt was made to maximize yields, however.

It will be noted that the site of displacement in all cases, (I), (III), (IV), is a benzylic carbon. When we examined the behavior of esters not containing a benzylic site (chloromethyl and α -chloroethyl esters), we recovered the starting esters and found no evidence for displacement.

Experimental

Microanalyses were performed by Galbraith Laboratories, Knoxville, Tennessee. Melting points are uncorrected. Infrared spectra were determined as halocarbon and Nujol mulls with either a Perkin-Elmer 21 spectrophotometer or a Perkin-Elmer 337 grating spectrophotometer. The NMR spectra were determined with a Varian A-60 spectrometer and are reported as ppm downfield from tetramethylsilane as internal standard. Coupling constants (J) are expressed in cps.

3-Ethoxy-3-phenylphthalide (Ia). Considerable ambiguity concerning the physical properties of the normal and pseudo ethyl esters of *o*-benzoylbenzoic acid exists in the literature¹³. The pseudo ester prepared in 31% yield according to Egerer and Meyer¹² was recrystallized first from aqueous ethanol and then repeatedly from 95% ethanol; mp 76–78°. A single carbonyl band in the infrared spectrum appeared at 1760 cm^{-1} . The NMR spectrum (carbon tetrachloride) exhibited a triplet at 1.19 ($J = 7$) and a multiplet centered at 3.4.

3-Isopropoxy-3-phenylphthalide (Ib). Preparation of the pseudo isopropyl ester¹⁴ was modeled after that of Egerer and Meyer for the pseudo ethyl ester. All fractions of crystals were washed with distilled water and recrystallized from ethanol, 21.5 g (45%), m.p. 68–70°. (Found: C, 76.02; H, 6.02. $\text{C}_{17}\text{H}_{16}\text{O}_3$ calcd.: C, 76.09; H, 6.01%.) The infrared spectrum contains a typical lactone carbonyl band at 1775 cm^{-1} . The NMR spectrum (carbon tetrachloride) exhibits a triplet (apparently two overlapping doublets) at 1.16 ($J = 6$) and a quintet at 3.70 ($J = 6$).

o-Benzoylbenzoic acid was recovered to the extent of 5% (2.1 g).

o-(α -Ethyl- α -ethoxybenzyl)benzoic acid (IIa). The ethylcadmium reagent was prepared from 2.72 g (0.112 mole) of dry magnesium turnings, 12.2 g (0.112 mole) of dry ethyl bromide, and 22.3 g (0.112 mole) of dry cadmium chloride. Because the Gilman test¹⁵ was negative, the mixture was stirred only briefly after addition; then the ether was replaced with 125 ml of dry benzene by distillation. To the benzene solution was added, with stirring, over 0.5 h, 14.1 g (0.056 mole) of 3-ethoxy-3-phenylphthalide in 25 ml dry benzene and the mixture heated under reflux for 6 h. The cooled reaction mixture was hydrolyzed in ice cold *ca.* 1.4 *M* sulfuric acid. The resulting mixture was filtered, the filtrate separated, and the aqueous layer extracted with benzene. The benzene layers were combined, extracted with 10% sodium carbonate, dried over anhydrous sodium sulfate, and the benzene distilled. Infrared and TLC analysis of the residue indicated it to be a mixture of 3-ethyl-3-phenylphthalide and 3-ethoxy-3-phenylphthalide. The 10% sodium carbonate extract was acidified slowly with conc. hydrochloric acid, producing a white solid, 13.9 g (87%). A portion (6.95 g)

of the solid was recrystallized from benzene and then ethanol, yielding 2.68 g (39% recovery), m.p. 156–159°. (Found: C, 75.88; H, 6.90; N.E., 285, 289, 290, 291. $C_{18}H_{20}O_3$ calcd.: C, 76.03; H, 7.09%; N.E. 284.) Infrared bands appeared at 2860–2960 cm^{-1} (aliphatic C–H) and at 1700 cm^{-1} (CO_2H). The NMR spectrum (chloroform) exhibited triplets at 0.78 ($J = 7.5$) and 1.23 ($J = 7$) and quartets at 2.41 ($J = 7.5$) and 3.28 ($J = 7$).

o-(α -Ethyl- α -isopropoxybenzyl)benzoic acid (I**b**). The ethylcadmium reagent was prepared as described above, the ether being replaced with 200 ml of dry benzene. A solution of 15.0 g (0.056 mole) of 3-isopropoxy-3-phenylphthalide in 25 ml of dry benzene was added dropwise, with stirring, over a period of 0.5 h. Refluxing and stirring were continued for an additional 6 h. The mixture was poured into *ca.* 1.4 *M* sulfuric acid in ice and water. The reaction mixture was filtered and the filtrate separated into layers. The aqueous layer was extracted with benzene. The benzene layers were combined and extracted with 10% sodium carbonate, dried over anhydrous sodium sulfate, and the benzene distilled. The residue was not examined further. In four successive fractions a white solid separated out of the basic solution. The free acid from each fraction was liberated by suspension in water and slow, dropwise addition of concentrated hydrochloric acid. The fractions were dried, combined (3.2 g, 19%), and recrystallized from ethanol, m.p. 135–137°. (Found: C, 76.31; H, 7.53. $C_{19}H_{22}O_3$ calcd.: C, 76.48; H, 7.43%.) The infrared spectrum contains typical aliphatic C–H absorption and a carbonyl band at 1690 cm^{-1} . The NMR spectrum (chloroform) exhibited a triplet at 0.77 ($J = 7$), a doublet at 1.05 ($J = 6.5$), a quartet at 2.45 ($J = 7$), and an apparent septet at 3.83 ($J = 6.5$).

Preparation of α -chloroalkyl benzoates (IIIa) and (IV). The chloroalkyl esters were made by allowing equimolar quantities of benzoyl chloride and the appropriate, freshly distilled aldehyde to interact in the presence of a catalytic amount of freshly fused zinc chloride^{16,17,18}. The reactions were carried out at room temperature under nitrogen. Because the esters are unstable, reverting on standing to starting materials, they were used with only partial purification. Infrared spectra in both cases indicated the absence of aldehyde and acid chloride in the products.

α -Chlorobenzyl benzoate (IIIa). White, fluffy crystalline solid, m.p. 51–52° (from hexane).

α -Chlorocinnamyl benzoate (IV). The crude, black, solid product was washed repeatedly with cold, anhydrous ether until the ester was white; yield 52%, m.p. 131–140°. Recrystallization from warm, anhydrous acetone raised the melting point a few degrees.

Benzhydryl benzoate from (IIIa). To the phenylcadmium reagent in ether, prepared step-wise from 2.2 g magnesium, 14.2 g bromobenzene, and 16.7 g cadmium chloride, was added 10 g (IIIa) in small portions. The mixture was heated under reflux for 4 h and then decomposed with dilute acid and ice. The ether layer, combined with ether washings of the water layer, was extracted with 10% sodium carbonate. After most of the ether had been removed by distillation, 25 ml of alcohol was added to the residue; distillation was continued until about 25 ml remained, and the residual solution was allowed to cool. The solid collected by filtration amounted to 4.41 g; after two recrystallizations from alcohol there remained 3.38 g (29%), m.p. 86–88°. The ester was shown to be identical to an authentic sample¹⁹ of benzhydryl benzoate by mixture melting point and comparison of infrared spectra.

*Benzhydryl benzoate from benzylidene dibenzoate (IIIb)*¹⁶. The displacement with the phenylcadmium reagent was carried out as above. The residual dark oil after removal of ether was separated by chromatography on neutral alumina into biphenyl (eluted with pentane) and benzhydryl benzoate (eluted with 10:1 pentane/ether), the ester being isolated after one recrystallization from alcohol in 13% yield.

1,3,3-Triphenylpropene (V) from (IV). To the phenylcadmium reagent, prepared in ether from 3.57 g magnesium, 23.1 g bromobenzene, and 27.0 g cadmium chloride, was added 21.2 g (IV) in small portions. The mixture was heated under reflux for 4 h and worked up as above. After removal of the ether, there remained a viscous dark oil, which was subjected to column chromatography on acidic alumina. Bromobenzene was recovered with pentane as eluent; the hydrocarbon (V) was eluted with 15:1 pentane/anhydrous ether (v/v); it was recrystallized from alcohol, 5.3 g (25%), m.p. 96–97°. (Found: C, 93.26; H, 6.80. C₂₁H₁₈ calcd.: C, 93.29; H, 6.71%.) A mixture melting point with a sample of (V) prepared according to Ziegler, Richter, and Schnell²⁰ showed no depression. The NMR spectrum* determined in deuteriochloroform contains a singlet (15 protons) at 7.22, a multiplet (2 protons) centered at 6.5, and a doublet (1 proton) at 4.85 ($J = 7$).

Further elution from the column with eluent richer in anhydrous ether gave a mixture of at least two compounds, one of which, according to the infrared spectrum, is most likely 1,3-diphenylallyl benzoate.

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Department of Chemistry,
University of New Hampshire,
Durham, New Hampshire 03824 (U.S.A.)

PAUL R. JONES
CARI J. JARBOE
RON NADEAU**

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