change in the yield of biphenyl was observed if the reaction was run in the presence of a large excess of cumene.

3 and Phenyllithium.—Under the same conditions used for the reaction of **3** with phenylmagnesium bromide, phenyllithium gave only a 13% yield[13] of biphenyl. This same low yield of coupling product was obtained when phenyllithium was allowed to react with **3** in the presence of N,N,N′,N′-tetramethylethylenediamine.

3 and 4-Biphenylylmagnesium Bromide.—A solution of 4-biphenylylmagnesium bromide was prepared from 7.76 g (0.0333 mol) of 4-bromobiphenyl, 10 g (0.41 g-atom) of magnesium turnings, and a trace of iodine in 200 ml of THF. To this solution was added 6.80 g (0.0167 mol) of **3** in 200 ml of THF (*ca.* 15 min, same color changes as noted in the "C_6H_5MgBr" experiment). During the addition, a solid precipitated. The system was filtered and the solid obtained was triturated with three 250-ml portions of 2 *N* hydrochloric acid, two 250-ml portions of water, and two 100-ml portions of diethyl ether. After traces of solvent had been removed, 4.01 g (79%) of *p*-quaterphenyl was obtained, mp 313–316° (lit.[14] mp 312–313°). The ir spectrum (KBr) of this material was identical in all respects with that of an authentic sample of *p*-quaterphenyl. No change in the yield of *p*-quaterphenyl was noted if the reaction was carried out with a large excess of cumene.

3 and (2-Methoxy-3-phenyl)phenylmagnesium Chloride.—A solution of 20.00 g (0.0916 mol) of 2-chloro-6-phenylanisole in 50 ml of THF was converted into a Grignard reagent by refluxing for 12 hr with 2.43 g (0.100 g-atom) of magnesium. The resulting solution was cooled to *ca.* 15°. Then, with continuous stirring, a solution of 18.70 g (0.0458 mol) of **3** in 175 ml of THF was added dropwise (1 hr). (Each red-colored drop rapidly decolorized as it was added to the Grignard solution until *ca.* 85% of the reagent had been added. A precipitate began to appear after *ca.* 35% of the reagent had been added.) The usual work-up afforded 36.1 g of a mixture of products (vpc). This mixture was recrystallized twice from 98% ethanol; 9.36 g (56%) of 2′,2″-dimethoxy-*m*-quaterphenyl was obtained, mp 137.3–138.8°. Vpc (2-ft 20% SE-30, isothermal at 240°, helium flow 72 ml/min) showed this compound to be homogeneous (t_r = 24.9 min). The ir spectrum showed strong absorptions as 1223 (aryl ether vibration[15]), 1459, 1454, 1409, 1007, 1001, 993, 800, 768, 759, and 695 cm^{-1} (monosubstituted benzene[15]). The nmr spectrum ($CDCl_3$) was consistent with the assigned structure: τ 2.2–3.0 (m, 16 H, ArH), and 6.75 (s, 6 H, OCH_3).

Anal. Calcd for $C_{26}H_{22}O_2$: C, 85.23; H, 6.01. Found: C, 85.3; H, 6.1.

3 and 1-Naphthylmagnesium Bromide.—A sample of 1-bromonaphthalene (2.07 g, 0.0100 mol) in 100 ml of THF was stirred overnight with 1.22 g (0.0500 g-atom) of magnesium turnings and a trace of iodine.[16] A solution of 2.04 g (0.0050 mol) of **3** in 40 ml of THF was added at room temperature. The red color of **3** completely disappeared. Following the usual work-up, 3.26 g of a dark yellow solid was obtained. This solid was stirred overnight at room temperature with 150 ml of isopropyl alcohol and then filtered, giving 0.56 g (44%) of 1,1′-binaphthyl, mp 156–158° (lit.[17] mp 157°). The ir spectrum of this compound and an authentic sample of 1,1′-binaphthyl were superimposable.

3 and 2-Naphthylmagnesium Bromide.—Using the same method as in the case of 1-bromonaphthalene, 2-bromonaphthylmagnesium bromide[16] gave 0.42 g (33%) of 2,2′-binaphthyl, mp 184.5–186.5° (lit.[18] mp 187°). The ir spectrum of this compound was superimposable on that of authentic 2,2′-binaphthyl.

3 and 4-Phenoxyphenylmagnesium Bromide.—By using the identical method as was used for 1-bromonaphthalene, 4-phenoxyphenylmagnesium bromide[16] gave 0.48 g (29%) of 4,4′-diphenoxybiphenyl, mp 152.5–154.5° (lit.[19] mp 151°). The ir spectrum of this compound contained many of the same intense absorption bands as an authentic sample of 4-phenoxybiphenyl: 690, 747 ± 3, 835 ± 7, 1256 ± 1, 1269 ± 1, 1490, and 1588 ± 1 cm^{-1}.

Anal. Calcd for $C_{24}H_{18}O_2$: mol wt 338. Found: mol wt 336.

(14) K. Brand and H. W. Stephen, *Ber.*, **72**, 2175 (1939).

(15) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons, Inc., New York, N. Y., 1958.

(16) When an identical organometallic preparation was worked up by hydrolysis, vpc showed that no aryl bromide remained. Only the corresponding debrominated aromatic hydrocarbon was present.

(17) C. S. Schoepfle, *J. Amer. Chem. Soc.*, **45**, 1566 (1923).

(18) J. Loevenich and A. Leoser, *Ber.*, **60**, 320 (1927).

(19) J. van Alphen, *Rec. Trav. Chim. Pays-Bas*, **50**, 415 (1931).

3 and 1-Dibenzofuranylmagnesium Bromide.—The dimer 1,1′-bisdibenzofuranyl, mp 187–189.5° (lit.[20] mp 191°), was obtained in 11% yield from 1-dibenzofuranylmagnesium bromide[16] and **3** (same method as used for 1-bromonaphthalene except for trituration with 2-propanol). The ir spectrum of this compound contained many of the same intense absorption bands as a sample of dibenzofuran: 726 ± 3, 743 ± 3, 753, 840, 850 ± 2, 1196 ± 1, 1446 ± 2, 1452, and 1470 ± 1 cm^{-1}. It also contained prominent bands at 612, 1050, 1106, 1174, 1262, and 1395 cm^{-1}.

Anal. Calcd for $C_{24}H_{14}O_2$: mol wt 334. Found: mol wt 337.

Registry No.—**1**, 4906-22-3; **2**, 3550-01-4; **3**, 2455-14-3.

(20) H. Gilman, L. C. Cheney, and H. B. Willis, *J. Amer. Chem. Soc.*, **61**, 951 (1939).

Improved Procedure for the Reformatsky Reaction of Aliphatic Aldehydes and Ethyl Bromoacetate

JOHN W. FRANKENFELD AND JAMES J. WERNER

New Investments Research Laboratory, Esso Research and Engineering Company, Linden, New Jersey 07036

Received April 25, 1969

Recently, we required a series of homologous, straight-chain β-hydroxy esters in large quantities and in a high state of purity. Because of its simplicity and the ready availability of the requisite reagents, the Reformatsky reaction appeared to be the best route to these compounds. Our early attempts with this well-known synthesis, however, were disappointing, not only because of the low yields obtained (10–40%), but also because of the difficulty we experienced in purifying the products. An examination of the literature revealed that our results were by no means unique; poor yields are generally the rule when the classical Reformatsky reaction is applied to aliphatic aldehydes.[1–3] Several investigations on the nature of the reaction[4] and on the side reactions encountered[1,5] help to explain the low yields. These workers and others[5,6] have proposed numerous variations of the Reformatsky reaction which have value in certain situations. However, none of these appeared attractive when applied to the large-scale syntheses we required. Consequently, we undertook a study of conditions for the Reformatsky reaction in hopes of improving the yields and quality of the products and with the view of tailoring the reaction for large-scale syntheses. We wish to report the results

(1) R. L. Shriner, *Org. Reactions*, **1**, 1 (1942).

(2) F. Adickes and G. Andresen, *Ann. Chem.*, **555**, 41 (1943).

(3) G. A. H. Buttle and J. D. Bower, *J. Pharm. Pharmacol.*, **10**, 477 (1958).

(4) W. R. Vaughan, S. C. Bernstein, and M. E. Lorber, *J. Org. Chem.*, **30**, 1790 (1965); H. E. Zimmerman and M. D. Traxler, *J. Amer. Chem. Soc.*, **79**, 1920 (1957); J. F. J. Dippy and J. C. Perkins, *J. Chem. Soc.*, 1570 (1951).

(5) A. S. Hussey and M. S. Newman, *J. Amer. Chem. Soc.*, **70**, 3024 (1948); M. S. Newman, *ibid.*, **64**, 2131 (1942).

(6) J. Cason and K. L. Rinehart, Jr., *J. Org. Chem.*, **20**, 1591 (1955); R. Willstätter and D. Hatt, *Ann. Chem.*, **418**, 148 (1919); N. Zelinsky and J. Gutt, *Ber.*, **35**, 2140 (1902); T. Moriwake, *J. Org. Chem.*, **31**, 983 (1966); J. Cason and R. J. Fessenden, *ibid.*, **22**, 1326 (1957); E. H. Charlesworth and P. Charleson, *Can. J. Chem.*, **46**, 1843 (1968); R. E. Miller and F. F. Nord, *J. Org. Chem.*, **16**, 728 (1951); J. A. Nieuwland and S. F. Daly, *J. Amer. Chem. Soc.*, **53**, 1842 (1931); D. Lipkin and T. D. Stewart, *ibid.*, **61**, 3295 (1939); C. A. Grob and P. Brenneisen, *Helv. Chim. Acta*, **41**, 1184 (1958).

TABLE I
TYPICAL IMPROVED YIELDS IN REFORMATSKY REACTIONS WITH ETHYL BROMOACETATE AND ALIPHATIC ALDEHYDES

$CH_3(CH_2)_nCHO$, n	Registry no.	No. of runs	Yield of hydroxy ester, % Range	Avg	Bp, °C (mm)	Ref	Yields with standard[a] procedure, %
0	75-07-0	4	67–74	72	58–60 (2)	*b*	
1	123-38-6	4	48–59	55	63–66 (1)	*b, c*	34[f]
2	123-72-8	16	61–80	69	82–84 (2)	*b, c*	29[g]
3	110-62-3	18	64–84	75	74–75 (0.5)	*b, c, h*	49[h]
4	66-25-1	9	50–80	74	85–88 (0.5)	*c*	37
5	111-71-7	4	47–72	59	93–95 (0.5)	*c, d*	30[i]
6	124-13-0	4	76–85	80	101–102 (0.5)	*e*	
7	124-19-6	2	51–72		112–115 (0.5)	*c*	*j*

[a] Average yields obtained in our laboratories using procedures given by Shriner[1] and Rinehart and Perkins.[7] [b] H. Vieregge and J. F. Arens, *Rec. Trav. Chim.*, **78**, 921 (1959). [c] See ref 2. [d] V. J. Harding and C. Weizmann, *J. Chem. Soc.*, **97**, 302 (1910). [e] H. Thaler and G. Geist, *Biol. Z.*, **302**, 369 (1939). [f] Shriner[1] lists a 39% yield. [g] Shriner[1] lists 25%. [h] Buttle and Bower[3] obtained a 47% yield and give a wide boiling point range. [i] Shriner lists 54%. [j] Adickes and Andresen[2] obtained a 40% "crude yield," apparently about the best in a series of Reformatsky runs.

of these studies and to suggest some modifications in the classical Reformatsky procedure.

The use of large excesses of zinc and ethyl bromoacetate (EBA) to improve yields based on the carbonyl component have been recommended frequently.[1,6,7] However, on the large scale (3–5 mol) on which we wished to operate, the large surplus of highly lacrymatory EBA made the work-up procedure very tedious and unpleasant. We now use only a slight excess of EBA (5–10%) along with a 20–30% excess of zinc. We use zinc dust, activated as described by Shriner,[1] as the condensing agent. Zinc that is not activated is erratic and gives generally lower yields. The zinc must be *neutral* and *dry*. During several runs with *n*-butyraldehyde, an annoying by-product was obtained in large quantities. This was identified as 2,4,6-tri-*n*-propyl-1,3,5-trioxane, which apparently resulted from acid-catalyzed[8] self-condensation of the aldehyde. None of this impurity was found when the zinc was washed until neutral. The zinc must be air dried carefully before use. Colored by-products and lower yields result when traces of moisture are present.

The critical aspect of the reaction conditions is the temperature. We found that, with straight-chain aldehydes and EBA, the optimum temperature lies between 80 and 85°. Below this range, it is difficult to avoid adding the reagents faster than they are consumed. This results in a buildup of reactants to a dangerous level, and the reaction, a highly exothermic one, may accelerate with almost explosive violence. In addition, at the lower temperatures, self-condensation of the aldehyde becomes an important competing reaction. On the other hand, if the temperature exceeds 85°, higher boiling, colored by-products are produced, along with some unsaturated ester, the product of dehydration. The best technique for regulating the temperature is to heat a rapidly stirred suspension of the zinc in benzene to vigorous reflux; cautiously add a small amount of a mixture of the aldehyde and EBA, providing heat, if necessary, until a vigorous reaction is apparent from the reflux rate; and maintain the reaction temperature at 80–85° by controlling the rate of addition of the reagents. Initiating the reaction requires some practice. The important factor is keeping the solvent boiling vigorously while the first few milliliters of reagents are added. We found that adding iodine as an aid in initiating the reaction was unavailing. To maintain a high reaction temperature in the cases of lower boiling aldehydes (C_3 and below), we employ a Dry Ice condenser to trap volatilized aldehyde and return it to the reaction flask. This technique affords surprisingly good yields.

The common techniques for decomposing the intermediate complex involve either rapid addition of acid to the complex[1,7] or pouring the reaction mixture into ice-cold aqueous acid.[1] We found that these procedures invariably afforded a dark-colored mixture which was difficult to purify. The hydroxy ester often boiled over a wide temperature range and was light yellow in color even after repeated distillation (*cf.* ref 3). However, dropwise addition of 50% sulfuric acid to the well-chilled, stirred reaction mixture affords a colorless product in greatly improved yield. Care must be taken to ensure that temperature of the solution does not exceed 35° during work-up and that no local warming occurs. We omit the usual base wash of the organic phase whenever possible to avoid emulsions. Water washing usually proves sufficient to neutralize the solution. With the lower molecular weight hydroxy esters, which are appreciably water soluble, excessive water washing may be replaced by neutralization with 5% potassium carbonate. Extraction of the water washings with an appropriate solvent is important for hydroxy esters from aldehydes of four carbon atoms or less. In the case of acetaldehyde, for example, about half of the ester is recovered from the aqueous phase by extracting with chloroform. Chloroform is about twice as efficient for this extraction as benzene or ether. For hydroxy esters derived from valeraldehyde or higher aldehydes, this extraction may be omitted without noticeably affecting the yield.

The major impurities we have encountered vary somewhat with the molecular weight of the hydroxy ester. In the case of esters derived from the lower aldehydes (C_4 and below), the major by-products are the corresponding α,β-unsaturated esters. In extreme cases, they have amounted to as much as 15% of the product, and they are difficult to remove, since the product mixtures, when significant amounts of impu-

(7) K. L. Rinehart, Jr. and E. G. Perkins, "Organic Syntheses" Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 444.

(8) R. O. C. Norman, "Principles of Organic Synthesis," Methuen and Co., London, 1968, pp 266–267.

rities are present, have indistinct boiling points.[1,3] The higher esters tend to form high-boiling ester interchange products as the major impurities. These byproducts do not present purification problems, but they have reduced yields by as much as 30%. They are, apparently, formed during distillation and can be minimized by keeping the distillation temperatures below 100° by use of reduced pressure. For example, parallel runs of ethyl β-hydroxyheptanoate yielded 50% hydroxy ester and 25% pot residue when distilled at 118–120° (6.0 mm) and 75% hydroxy ester with less than 5% residue at 85–88° (0.5 mm).

The Reformatsky reaction is extremely vigorous[1] and, even under the most controlled conditions, can get out of hand. To avoid a hazardous situation and the loss of expensive reagents, we employ the apparatus shown in Figure 1. This system has virtues in its simple construction and ready adaptability to large-scale reactions. If the reaction becomes so violent that the contents of the reactor are expelled, the effluent is effectively contained in the receptacle H. This can be poured back into the flask A and the reaction can be continued with negligible reduction of yield provided the effluent is kept dry during spillage and transfer. The apparatus may be modified conveniently to accommodate lower boiling aldehydes by replacement of condenser E with a Dry Ice condenser.

The hydroxy esters we prepared are summarized in Table I. The yields given represent isolated materials of 98% or better glpc purity. The modified procedures we recommend are described fully in the two examples given below. Method A is used for aldehydes of four carbons or higher; method B is used for propionaldehyde and acetaldehyde.

Experimental Section

Materials.—Ethyl bromoacetate (Eastman) was used without purification, provided it was colorless. Colored material was discarded or distilled. The aldehydes were obtained from various sources and were the highest grade available. They were distilled under reduced pressure, dried over $MgSO_4$,[9] and used as soon as possible. Certified zinc metal dust (assay 98.8%; Fisher Scientific Co.) was activated by washing, successively, with 20% hydrochloric acid, water until neutral, acetone, and anhydrous ether. It was thoroughly air dried and used immediately.

Method A. Ethyl β-Hydroxyoctanoate.[2]—To the apparatus pictured in Figure 1 was charged 250–300 g (3.8–4.6 g-atoms) of activated zinc dust and 750 ml of dry benzene. The suspension was stirred rapidly and heated to vigorous reflux. The heat was removed and a mixture of 517 g (3.1 mol) of ethyl bromoacetate and 300 g (2.9 mol) of hexanal was added, dropwise, at a rate consistent with maintaining the reaction temperature at 80–85°.[10] The addition required 1.5–2 hr. The reaction mixture was cooled in a Dry Ice–isopropyl alcohol bath and stirred vigorously while 600 ml of 50% sulfuric acid was added dropwise. The temperature of the reaction mixture was kept below 35° during the addition. The layers were separated and the organic phase was washed twice with 1-l. portions of water[11] and dried. Distillation under reduced pressure afforded 285–470 g (50–80%) of colorless ester, bp 85–88° (0.5 mm).

(9) Water may be formed, from dehydration of aldol contaminants, during distillation and pass over with the aldehyde. This can be removed, either by drying in solution or by passing the distilled aldehyde rapidly through a cake of $MgSO_4$ on a suction filter.

(10) Some care is required in starting the reaction. It is important that the benzene be *refluxing vigorously* when the initial addition of aldehyde and EBA is made. A slight surge in the reflux rate is indicative of reaction. Once started, the reaction is easy to maintain.

(11) It is best to make sure that the reaction mixture is neutral after the water wash. If not, the benzene layer may be washed with a little 5% potassium carbonate and, finally, with water. Delaying the base wash until this point, or, if possible, omitting it altogether, reduces chances of emulsions forming and facilitates the separation of layers.

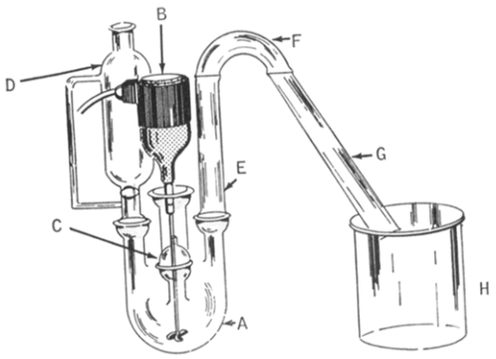


Figure 1.—Apparatus for large-scale Reformatsky reactions. A, 2-l., four-neck flask; B, electric or air-driven stirrer; C, thermometer for reading reaction temperature; D, 500-ml pressure-equalizing dropping funnel; E, Liebig condenser (may be replaced by Dry Ice condenser for lower aldehydes); F, curved adapter; G, Liebig condenser; H, 2-l. beaker.

Method B. Ethyl β-Hydroxybutyrate.[12]—The apparatus shown in Figure 1 was modified to the extent that a Dry Ice condenser was substituted for the condenser E. The reaction was carried out on the same scale and in the same way as described above, using acetaldehyde in place of hexanal. The volatilized unreacted aldehyde was condensed and returned to the reactor continuously. The reaction mixture was hydrolyzed as in method A and washed twice with 500 ml of water. The water washings were extracted twice with 500 ml of chloroform. The combined chloroform and benzene solutions were dried over magnesium sulfate and distilled. The main fraction, bp 58–60° (2.0 mm), weighed 255–283 g (67–74%).

Registry No.—EBA, 105-36-2.

Acknowledgments.—The authors wish to thank Mr. C. W. Drastura for suggesting some of the essential features of the reactor design. In addition, the technical assistance of Mr. F. M. Cornman and Mr. R. C. Hanna is gratefully acknowledged.

(12) See footnote *b*, Table I.

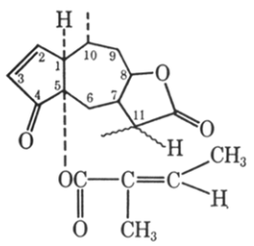
Solvent Shift Studies on Pseudoguaianolides of the Helenalin Series[1,2]

WERNER HERZ, P. S. SUBRAMANIAM, AND N. DENNIS

Department of Chemistry, The Florida State University, Tallahassee, Florida 32306

Received April 11, 1969

The pseudoguaianolide brevilin A was formulated as angeloylmexicanin C (1) recently.[3] However, in view



1, H-11 β
2, H-11 α

(1) Constituents of *Helenium* Species. XXIV. Previous paper: W. Herz, P. S. Subramaniam, and N. Dennis, *J. Org. Chem.*, **34**, 2915 (1969).

(2) Supported in part by grants from the National Science Foundation (GP-6362) and the National Institutes of Health (GM-05814).

(3) W. Herz, C. M. Gast, and P. S. Subramaniam, *J. Org. Chem.*, **33**, 2780 (1968).