method of Kwart and Kaplan.[19] The endo isomer was prepared by the method described by Roberts et al.[20] 5-Chloro-2-norbornene was obtained by the addition of hydrogen chloride to norbornadiene.[19] 3-Chloronortricyclene was prepared by the addition of chlorine to norbornene.[21]

3-Iodonortricyclene was prepared by the following modification of the procedure of Diner and Lown.[22] Silver nitrate (61.1 g, 0.36 mol) was dissolved in 300 mL of chloroform and 150 mL of pyridine. Iodine monochloride (66.8 g, 0.40 mol) in 150 mL of pyridine was added dropwise to the stirred solution. The resultant mixture was filtered and washed with 100 mL of pyridine. Norbornene (36.0 g, 0.38 mol) was added at once to the filtrate. After the mixture was stirred for 4 h, 200 mL of ether was added, the mixture was filtered, the filtrate was washed repeatedly with water, dried over magnesium sulfate, and concentrated, and the product was distilled: bp 40 °C (0.6 torr); 40% yield.

(Trimethyltin)sodium was prepared in THF solution and its concentration determined as previously described.[11]

Reaction of (Trimethyltin)sodium with Halides. In a typical trapping experiment appropriate amounts of halide and DCPH or TBA were added to THF to form solutions of the desired concentrations which were cooled in ice at least 15 min under nitrogen. A THF solution of (trimethyltin)sodium at 0 °C was added in approximately 2-fold excess over halide. Reactions with bromides and the iodide were complete almost upon mixing; 5-chloro-2-norbornene required about 1 h for completion. Yields of isomeric organotin substitution products and of hydrocarbons were determined by GLC.

(Norborn-2-en-5-yl)trimethyltin was isolated from reactions of 3-bromonortricyclene and 5-chloro-2-norbornene with (trimethyltin)sodium: NMR δ 0.06 ($^2J(^{119}SnC-H)$ = 49.5 Hz, 9 H, $(CH_3)_3Sn$), 5.9 (m, 2 H, HC=CH), 0.83-1.43 (m, 7 H, C_5H_7).[23] 3-Nortricyclyltrimethyltin was isolated from the reaction of 3-bromonortricyclene: NMR δ 0.048 ($^2J(^{119}SnC-H)$ = 50.7 Hz, 9 H, $(CH_2)_3Sn$), 0.83-1.43 (m, 9 H, C_7H_9).[23]

Acknowledgment. We are grateful for support of this research by the National Science Foundation and to Cincinnati Milacron, Inc., for gifts of organotins.

Registry No. NI-I, 36071-35-9; NT-Br, 695-02-3; *exo*-NB-Cl, 3721-19-5; *exo*-NB-Br, 5889-54-3; *endo*-NB-Br, 5810-82-2; NT-Sn, 21942-28-9; *exo*-NB-Sn, 21957-51-7; NB-H, 498-66-8; NT-H, 279-19-6; *Sn*, 16643-09-7; iodine monochloride, 7790-99-0.

(19) Kwart, H.; Kaplan, L *J. Am. Chem. Soc.* **1955**, *77*, 2821.
(20) Roberts, J. D.; Trumbull, E. R.; Bennett, W.; Armstrong, R. *J. Am. Chem. Soc.* **1950**, *72*, 3116.
(21) Poutsma, M. L. *J. Am. Chem. Soc.* **1965**, *87*, 4293.
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o-Benzoylbenzoic Acids by the Reaction of Lithium 2-Lithiobenzoates with Acid Chlorides. A Contribution to the Chemistry of Alizarin and Podophyllotoxin

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Although aryllithium reagents usually react with acid chlorides to yield tertiary alcohols, the addition at -100 °C of aroyl chlorides to lithium *o*-lithiobenzoate and its congeners affords a useful route to *o*-benzoylbenzoic acids. The usefulness of this new method is illustrated by the synthesis of four *o*-benzoylbenzoic acids which experience has shown to be difficult or impossible to prepare by previously available methods. These acids include 2-benzoyl-5-methoxybenzoic acid, 2-(3-methoxybenzoyl)-5-methoxybenzoic acid, 2-(2,3-dimethoxybenzoyl)benzoic acid (a new intermediate for the preparation of alizarin dimethyl ether), and 2-(3,4,5-trimethoxybenzoyl)-4,5-(methylenedioxy)benzoic acid, a degradation product of podophyllotoxin.

With certain exceptions the reaction of an organolithium reagent with an acid chloride can be expected to lead to a tertiary alcohol.[3] Wakefield[4] states that "Halide ions are such good leaving groups that elimination from the complex...must take place almost synchronously with addition to the carbonyl group. Thus it is almost impossible to avoid a situation where the ketone and organolithium reagent are present together so that the final product is a tertiary alcohol". The few intances[5] in which satisfactory yields of ketones have been obtained by the reaction of organolithium reagents with acid chlorides appear to be those in which the ketone formed is so sterically hindered as to limit further reaction.

The purpose of the present work was to discover whether satisfactory yields of keto acids could be obtained by reaction of acid chlorides with lithium 2-lithiobenzoate and its congeners.[6] We have found that direct addition of benzoyl chloride to lithium 2-lithiobenzoate (1) at -100 °C affords a 62% yield of pure 2-benzoylbenzoic acid (**5a**). Similar yields were obtained with *p*-anisoyl and *m*-anisoyl chlorides (Table I), but the more sterically hindered ortho isomer gave only a 40% yield of the desired keto acid (**5d**). Analysis of the reaction mixture from the *o*-methoxybenzoyl chloride reaction showed, after hydrolysis, the presence of anisic acid and the absence of high molecular weight byproducts, even after the reaction mixture had been allowed to warm to room temperature, suggesting that the rate of anionic decay for 1 is greater than the rate of addition to the ortho-substituted carbonyl group of the acid chloride. In each experiment the acid chloride was added *directly* to the organolithium reagent (1); hence all but the last increment must be exposed to the action of

(1) Deceased May 21, 1976.
(2) Pharmacological Research Trainee.
(3) Gilman, H.; Van Ess, P. R. *J. Am. Chem. Soc.* **1933**, *55*, 1258.
(4) Wakefield, B. J. "The Chemistry of Organolithium Compounds"; Pergamon Press, Ltd.: Oxford, 1974; pp 21-25.
(5) For example, see: Locksley, H. D.; Murray, I. G. *J. Chem. Soc. C* **1970**, 392; Fuson, R. C.; Tull, R. *J. Am. Chem. Soc.* **1949**, *71*, 2543.
(6) Parham and Sayed (*J. Org. Chem.* **1974**, *39*, 2053) have reported preliminary experiments in which unsatisfactory yields were obtained when lithium 2-lithiobenzoate was allowed to react with ortho-substituted benzoyl chlorides.

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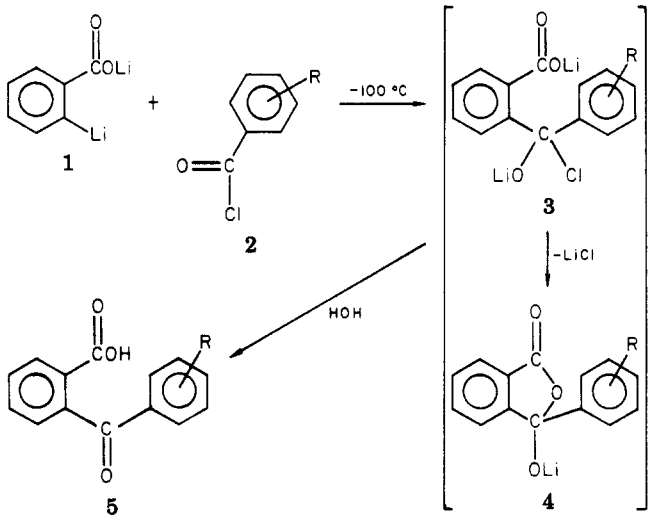
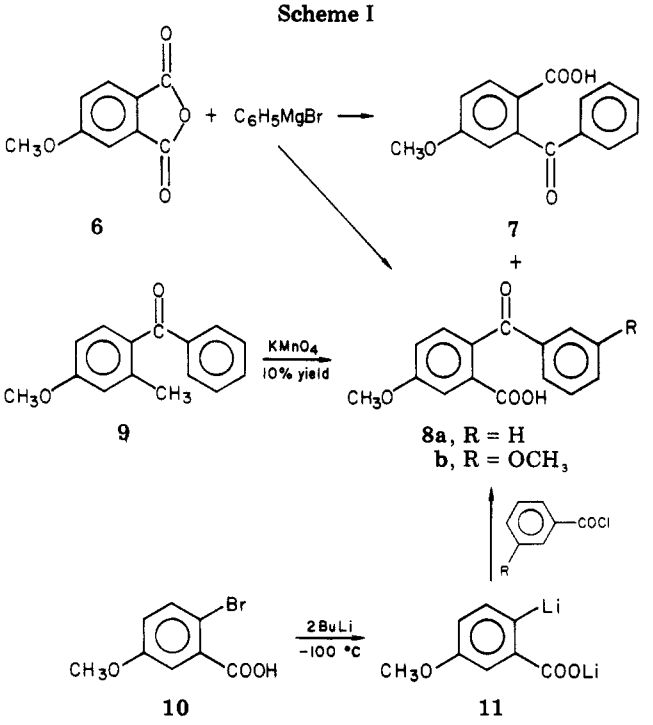


a, R = H; b, R = p-OCH_3; c, R = m-OCH_3; d, R = o-OCH_3

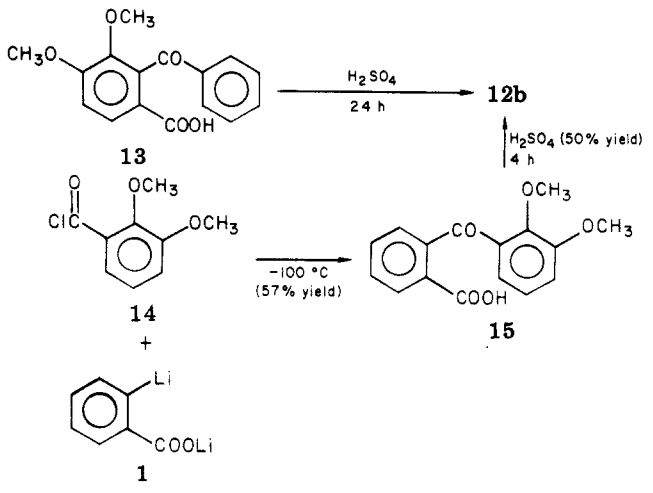
an excess of the organolithium reagent. The failure to obtain a triarylcarbinol under these circumstances can not be attributed to the low temperature alone for we have found that phenyllithium at −100 °C, on addition of benzoyl chloride, affords a 78% yield of triphenylcarbinol. It is not the presence of an ortho substituent per se that prevents the formation of a tertiary carbinol, for addition of benzoyl chloride to o-tolyllithium at −100 °C gives a 78% yield of the carbinol albeit with a 10% yield of 2-methylbenzophenone. Satisfactory yields of ketone appear to be related to the electronic nature of the ortho substituent, for addition of benzoyl chloride to o-lithiobenzonitrile[7] gives 2-cyanobenzophenone in 79% yield (VPC). On the basis of this and unpublished results it appears that satisfactory yields of ketones are obtained by addition of aroyl chlorides if the organolithium reagent has an electron-attracting group in the ortho position. It may well be that such organolithium reagents are less nucleophilic and hence more selective in their reaction. Factors which may also influence the keto acid (**5**) yield may be the stability of the complex (**3**) or the ease of formation of the salt (**4**) of the pseudoacid.

The classical approaches to the synthesis of o-benzoylbenzoic acids have involved the reaction of phthalic anhydrides with arenes (the Friedel–Crafts reaction)[8] or with the Grignard[9] or other organometallic reagents.[10,11] Of these two[12] general methods the second is certainly more versatile, but even when the desired organometallic reagent is available, its addition to an unsymmetrically substituted phthalic anhydride may not occur at the desired carbonyl group. For example, Melby et al.[13] found that the addition of phenylmagnesium bromide to 4-

Scheme I



Scheme II



methoxyphthalic anhydride (**6**) gave chiefly (5:1) 2-benzoyl-4-methoxybenzoic acid (**7**), while the 2-benzoyl-5-methoxybenzoic acid (**8a**) obtained as a byproduct proved very difficult to purify (Scheme I). The best procedure that had been developed to date for the synthesis of (**8a**) had been the oxidation of 2-methyl-4-methoxybenzophenone (**9**) in 10% yield.[14]

A much more satisfactory route (51% yield) to 2-benzoyl-5-methoxybenzoic acid (**8a**) is afforded by addition of 2 mol of butyllithium to 2-bromo-5-methoxybenzoic acid (**10**) at −100 °C followed by addition of benzoyl chloride to the resulting organolithium reagent (**11**). By use of m-methoxybenzoyl chloride with **11** we were able to obtain for the first time a pure sample of 2-(3-methoxybenzoyl)-5-methoxybenzoic acid (**8b**, 72% yield) vainly sought by Melby et al.[13]

Alizarin (**12a**) was at one time a dye of great commercial importance,[15] and its synthesis has been regarded as a milestone in the early development of the organic chemical industry.[15-17] The commercial syntheses had in common

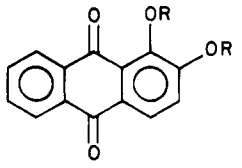
(7) Parham, W. E.; Jones, L. D. *J. Org. Chem.* **1976**, *41*, 1187.
(8) (a) Friedel, C.; Crafts, J. M. *Ann. Chim. (Paris)* **1888**, *14*, 433. (b) Review: Perkins, M. A. In "The Chemistry of Dyes and Pigments"; Lubs, H. A., Ed.; Reinhold: New York, 1955; Chapter 7.
(9) (a) Pickles, S. S.; Weizmann, C. *Chem. News* **1904**, *90*, 276; *Proc. Chem. Soc.* **1904**, *20*, 201. (b) Weizmann, C.; Bergmann, E.; Bergmann, F. *J. Chem. Soc.* **1935**, 1367. (c) Weizmann, C.; Bergmann, E. *J. Chem. Soc.* **1936**, 567. (d) Scholl, R.; Donat, J. *Chem. Ber.* **1931**, *64B*, 318.
(10) Organocadmium: (a) deBenneville, P. L. *J. Org. Chem.*, **1941**, *6*, 462; (b) Tiouflet, J. *Bull. Soc. Sci. Bretagne* **1951**, 69, Spec. No. 26; *Chem. Abstr.* **1953**, *47*, 8692*g*.
(11) Organolithium: Parham, W. E.; Piccirilli, R. M. *J. Org. Chem.* **1976**, *41*, 1268.
(12) Another route to o-benzoylbenzoic acids involves addition of lithium o-lithiobenzoate to aryl esters. While it was initially thought[6] that aryl esters were usually superior to aryl acid chlorides, it now appears that that conclusion was premature.
(13) Melby, R.; Crawford, R.; McGreer, D.; Sandin, R. B. *J. Am. Chem. Soc.* **1956**, *78*, 3816.
(14) Weeks, D. P.; Cella, J.; Chen, L. T. *J. Org. Chem.* **1973**, *38*, 3383.
(15) Fieser, L. F. *J. Chem. Edu.* **1940**, *7*, 2609.

Table I. Reaction of Lithium o-Lithiobenzoate with Acid Chlorides at −100 °C

acid	R	reaction time, h	yield, %	mp, °C	^{1}H NMR, δ[a]
5a	H	1[b]	62	125.5-127[c]	
5b	p-OCH_3	0.25	63	144.5-146.5[d]	3.86 (s, OCH_3)
5c	m-OCH_3	2[e]	65	149-152[f]	3.87 (s, OCH_3)
5d	o-OCH_3	2	40	144-145[g]	3.60 (s, OCH_3)[h]

[a] In $CDCl_3$, resonances of aromatic and carboxylic protons omitted. [b] The temperature was maintained at −78 °C for 1 h followed by warming to 25 °C over 2 h. [c] Lit.[32] mp 128-129 °C. [d] Lit.[33] mp 144.4-146.4 °C. [e] Then allowed to warm to 25 °C over 4 h. [f] Once more recrystallized, mp 155.5-157 °C (lit.[33] mp 154.5-155.4 °C). [g] Lit.[34] mp 144-145 °C. [h] Solvent $CDCl_3/(CD_3)_2SO$.

that one or more of the oxygen functions were introduced by substitution reactions carried out on an anthraquinone or anthracene derivative. The only synthesis of alizarin dimethyl ether[18] (**12b**) by cyclization of a dimethoxy de-



12a, R = H
b, R = Me

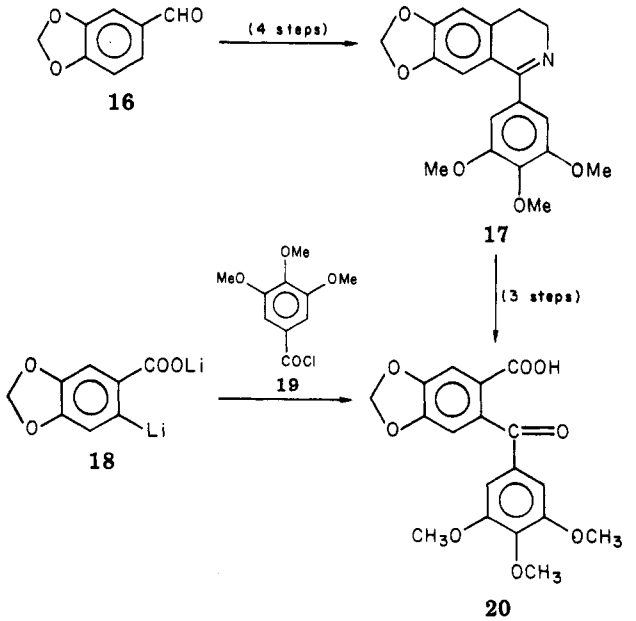
rivative of o-benzoylbenzoic acid was reported by Weizmann and Bergmann.[9] They prepared 2-benzoyl-3,4-dimethoxybenzoic acid (**13**)[19] in unspecified yield by the addition of phenylmagnesium bromide to hemipinic anhydride. Treatment of the acid (**13**) for 24 h with sulfuric acid was stated[9c] to afford an unspecified yield of alizarin dimethyl ether (**12b**) together with an unidentified byproduct (Scheme II).

A more promising route to alizarin dimethyl ether appeared to be via the previously unknown 2-(2,3-dimethoxybenzoyl)benzoic acid (**15**), since acid-catalyzed cyclization would be facilitated by a methoxyl group para to the position of cyclization. The new acid (**15**) was prepared in 57% yield by the addition at −100 °C of 2,3-dimethoxybenzoyl chloride[20] (**14**) to lithium o-lithiobenzoate (**1**). The acid **15** was a liquid which was obtained pure by chromatography on silica gel. In the ^{1}H NMR spectrum the methoxyl methyl signal at δ 3.86 was sharp while that at δ 3.52 was broadened, explicable if the methoxyl methyl group at position 2 were sterically compressed between the methoxyl at position 3 and the carbonyl. In keeping with this hypothesis, repetition of the NMR spectrum at higher temperatures sharpened the signal until at 100 °C the signals were of equal acuity. In concentrated sulfuric acid at room temperature for 4 h, a sample of the new acid cyclized to yield a product which, on recrystallization from acetone–ethanol, afforded alizarin dimethyl ether in 54% yield.

While it might seem that an equally useful route to (2,3-dimethoxybenzoyl)benzoic acid might be via the addition of (2,3-dimethoxyphenyl)magnesium iodide (or bromide) to phthalic anhydride, it has been reported[21] that the needed Grignard reagent cannot be prepared.

6-(3,4,5-Trimethoxybenzoyl)piperonylic acid (**20**) was first obtained as a degradation product of podophyllotoxin,[22] and its structure became certain when a small quantity was obtained by oxidation of an appropriately substituted dihydronaphthalene.[23] Following the discovery[24] that podophyllotoxin had tumor-inhibiting properties, there was increased interest in finding a convenient route[25-28] to **20**, proposed[26,28] as an intermediate in the synthesis of podophyllotoxin.

It is a commentary on the lack of convenient general methods for the synthesis of o-benzoylbenzoic acids that for **20** the synthetic method of choice required seven steps,



starting from piperonaldehyde and involved along the way the synthesis of 1-(3,4,5-trimethoxyphenyl)-6,7-(methylenedioxy)-3,4-dihydroisoquinoline (**17**) followed by quaternization, ring opening, and oxidation.[29]

Lithiation of 6-bromopiperonylic acid[30] at −100 °C with 2 mol of butyllithium afforded lithium 6-lithiopiperonylate (**18**) to which 3,4,5-trimethoxybenzoyl chloride was added at −100 °C; after workup, including recrystallization, 6-(3,4,5-trimethoxybenzoyl)piperonylic acid (**20**) was obtained in 67% yield.

The new method provides a simple and convenient route to many other o-benzoylbenzoic acids difficult or impos-

(16) Wahl, A. *Bull. Soc. Chim. Fr.* **1927**, *41*, 1417.
(17) Leprieur, F. *Recherche* **1979**, 732.
(18) While Lagodzinski earlier (*Chem. Ber.* **1895**, *28*, 1427) reported the synthesis of alizarin monomethyl ether by the cyclization of a methoxyhydroxy-o-benzoylbenzoic acid of unknown structure, the melting point (201 °C) does not agree with that of either the known 1-methyl or 2-methyl ether of alizarin.
(19) This same acid had been prepared earlier by Faltis (*Monatsh. Chem.* **1910**, *31*, 563) by oxidation of phenyldihydroberberine.
(20) Mauthner, F. *J. Prakt. Chem.* **1926** [2], *112*, 60.
(21) Newman, M. G.; Mosby, W. L. *J. Am. Chem. Soc.* **1951**, *73*, 3738.
(22) Späth, E.; Wessely, F.; Nadler, E. *Chem. Ber.* **1933**, *66*, 125.
(23) Haworth, R. D.; Richardson, T. *J. Chem. Soc.* **1936**, 348.
(24) Leiter, J.; Downing, V.; Hartwell, J. L.; Shear, M. J. *J. Natl. Cancer Inst.* **1950**, *10*, 1273.
(25) Reeve, W.; Sterling, J. D., Jr. *J. Am. Chem. Soc.* **1949**, *71*, 3657.
(26) Gensler, W. J.; Samour, C. M. *J. Am. Chem. Soc.* **1950**, *72*, 3318.
(27) Reeve, W.; Eareckson, W. M. *J. Am. Chem. Soc.* **1950**, *72*, 5195.
(28) Gensler, W. J.; Samour, C. M. *J. Am. Chem. Soc.* **1951**, *73*, 5555.
(29) For evidence that the dihydroisoquinoline route to o-benzoylbenzoic acids is still in use see: Shirwalker, A. S.; Kulkarm, A. B. *Indian J. Chem.* **1979**, *17*, 198.
(30) Dallacker, F. *Justus Liebigs Ann. Chem.* **1960**, *C33*, 14.

sible to make by methods used previously.

Experimental Section

Solvents for use with butyllithium were distilled over lithium aluminum hydride or calcium hydride and stored over 4-Å molecular sieves. "Concentrated" refers to evaporation under reduced pressure in a rotary evaporator. Unless otherwise specified the agent used for drying solutions containing organic residues was magnesium sulfate.

Elemental analyses were performed by MHW Laboratories, Phoenix, AZ. Gas chromatography (VPC) was carried out in steel columns, using a thermal-conductivity detector, and VPC yields were determined by triangulation or by cut-and-weigh techniques.[31] Melting points were observed in capillaries and are uncorrected.

Reaction of Lithium *o*-Lithiobenzoate (1) with Acid Chlorides (2). Lithium *o*-lithiobenzoate (1) was prepared from 5.0 g (25 mmol) of *o*-bromobenzoic acid as described previously,[35] the temperature not being allowed to rise above −100 °C. The acid chloride in 5–25 mL of dry tetrahydrofuran was added dropwise at such a rate that the temperature could be kept below −90 °C. After an appropriate period (Table I) the reaction mixture was poured into 100 mL of 5% hydrochloric acid and stirred vigorously for 30 min. The layers were separated and the aqueous layer was extrated with ether (3 × 75 mL). The organic layers were combined, washed with water (100 mL), and extracted with 10% sodium hydroxide solution (3 × 75 mL). The organic layer was dried, filtered, and concentrated to afford the nonacidic fraction. The alkaline extracts were acidified and the acids extracted with ether (3 × 75 mL). The ether extracts were dried and concentrated. The residue was usually purified by recrystallization from benzene–petroleum ether or chloroform–ligroin.

Reaction of Phenyllithium at −100 °C with Benzoyl Chloride. Bromobenzene (3.92 g, 25 mmol) was subjected to halogen–metal exchange with butyllithium for 35 min and subsequently benzoyl chloride was added at −100 °C, all as in the general procedure. The resulting clear yellow solution was stirred for 10 min at −100 °C, then quenched, and worked up as usual. The nonacidic product was a pale yellow slush which was triturated with hexane and filtered to afford triphenylcarbinol (2.35 g, 9.03 mmol) in 72% yield: mp 152–157.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.76 (br. s, 1, OH), 7.05 (s, 15, Ar H). The filtrate was examined by ^{1}H NMR ($CDCl_3$) and found to consist almost entirely of butylbenzene: NMR δ 0.80 (t, 3, CH_3), 1.02–1.50 (m, 4, $CH_2CH_2CH_3$), 2.15 (t, 2, Ar CH_2), 6.79–7.21 (m, 5, Ar H). A recrystallized sample of the triphenylcarbinol, mp 160–161.5 °C (lit.[36] mp 162.5 °C), had the correct elemental analysis.

Reaction of *o*-Tolyllithium at −100 °C with Benzoyl Chloride. To a solution of *o*-tolyllithium prepared at −100 °C from 4.28 g (25 mmol) of *o*-bromotoluene was added benzoyl chloride at −100 °C as described in the general procedure and stirring was continued at the same temperature for 1 h before warming to 25 °C. The pale yellow oil obtained after the usual workup was purified first by column chromatography on silica gel (hexane containing increasing amounts of chloroform) followed by bulb-to-bulb distillation of this fraction. 2-Methylbenzophenone (0.48 g, 2.44 mmol, 10% yield): bp 90–100 °C (0.10 mm) [lit.[37] bp 312–315 °C (735mm)]; ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3, Ar CH_3), 7.10–7.60 (m, 7, Ar H), 7.68–7.90 (br d, J = 7 Hz, 2, *o*-C_7H_7COArH); IR (neat) 1660 cm^{-1} (C=O). Bis(2-methylphenyl)phenylmethanol (2.65 g, 9.19 mmol, 78%): bp 100–110 °C (0.10 mm) [lit.[38] bp 210–213 °C (16 mm)] from hexane as colorless crystals; mp 78–80 °C (lit.[39] mp 82–83 °C); ^{1}H NMR ($CDCl_3$) δ 2.26 (s, 6, CH_3), 2.96 (br s, 1, OH), 6.60–7.36 (m, 13, Ar H); IR (neat) 3540 cm^{-1} (OH).

Reaction of 2-Lithiobenzonitrile with Benzoyl Chloride. *o*-Bromobenzonitrile (4.55 g, 25 mmol) was subjected to halogen–metal excange[7] at −100 °C for 20 min and then benzoyl chloride was added at −100 °C, following the usual procedure. The resulting pale orange solution was stirred for 30 min at −100 °C and worked up as usual, affording 4.77 g of a neutral oil. Vacuum distillation of a portion of this oil was accompanied by extensive decomposition but did provide pure samples of two of the components. The first fraction was valerophenone: bp 60–65 °C (0.05 mm) [lit.[40] bp 135–140 °C (25 mm)]; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J = 9 Hz, 3, CH_3), 1.15–2.05 (m, 4, $CH_2CH_2CH_3$), 2.98 (t, J = 13, 3 Hz, 2, $COCH_2$), 7.23–7.62 (m, 3, Ar H), 7.80–8.17 (m, 2, *o*-RCOArH).[41] The second fraction, bp 80–83 °C (0.05 mm), may have contained 2-butylbenzonitrile while the third fraction definitely contained 2-cyanobenzophenone: bp 125–133 °C (0.05 mm) [lit.[42] bp 215–225 °C (20 mm)]; mp 82.5–84 °C (lit.[42] mp 83.5 °C); ^{1}H NMR ($CDCl_3$) δ 7.34–7.86 (m, Ar H); IR (Nujol mull) 2230 cm^{-1} (C≡N), 1665 (C=O).

Anal. Calcd for $C_{14}H_9NO$: C, 81.14; H, 4.38; N, 6.76. Found: C, 81.17; H, 4.49; N, 6.64.

The crude product was analyzed by vapor-phase chromatography (10% OV-17 on 50/60 Chromsorb W, AW, DMCS, 6 ft × 0.25 in., 215 °C, 60 mL of He/min), using as standards samples obtained by distillation: valerophenone, t_R 0.55 min, 11%; unidentified product (possibly 2-butylbenzonitrile) t_R 0.75 min, ~10%; 2-benzoylbenzonitrile, t_R 3.70 min, 79%.

2-Benzoyl-5-methoxybenzoic Acid (8a). 2-Bromo-5-methoxybenzoic acid[43] (5.78 g, 25 mmol) was converted to the organolithium reagent (11) as described for the preparation of lithium *o*-lithiobenzoate (1), 1 h at −100 °C being allowed for the halogen–metal exchange. Benzoyl chloride was then added as in the general procedure and stirred for 1 h at −78 °C before allowing the temperature to rise to that of the room. Workup gave 6.00 g of acids as a pale yellow solid; ^{1}H NMR of this product showed only a single methyl signal at δ 3.90. Recrystallization from benzene gave 3.27 g (12.8 mmol, 51%) of a colorless powder: mp 152–154 °C [analytical sample, mp 154.5–156 °C (lit.[13] mp 155–156 °C)]; ^{1}H NMR (CD_3COCD_3) δ 3.90 (s, 3, OCH_3), 4.43 (br s, 1, COOH), 7.09–7.73 (m, 8, Ar H); ^{13}C NMR (CD_3COCD_3) δ 56.12, 115.88, 118.36, 129.30, 130.01, 130.66, 132.09, 133.40, 135.29, 139.19, 161.72, 167.58, 195.31.

Anal. Calcd for $C_{15}H_{12}O_4$: C, 70.31; H, 4.72. Found: C, 70.52; H, 4.52.

2-(3-Methoxybenzoyl)-5-methoxybenzoic Acid (8b). The procedure followed in the preparation of **8a** was followed except that *m*-methoxybenzoyl chloride was substituted for benzoyl chloride. After the mixture was stirred at −100 °C for 30 min, it was allowed to warm up to 25 °C over 2 h. Workup, including charcoal treatment, afforded in 78% yield the desired acid (**8b**) as an off-white solid, mp 135–140 °C, which was recrystallized from benzene to afford the analytical sample: mp 144.5–145 °C; ^{1}H NMR (CD_3COCD_3) δ 3.84 (s, 3, $ArCOArOCH_3$), 3.96 (s, 3, $CH_3OArCOOH$), 5.13 (br s, 1, COOH), 7.04–7.58 (m, 7, Ar H); ^{13}C NMR (CD_3COCD_3) δ 55.79, 56.18, 114.45, 115.95, 118.42, 119.46, 122.85, 130.08, 130.47, 130.73, 140.69, 161.00, 161.85, 167.64, 194.72.

Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.13; H, 4.93. Found: C, 66.86, H, 4.91.

2-(2,3-Dimethoxybenzoyl)benzoic Acid (15). To a solution of lithium *o*-lithiobenzoate (1, 25 mmol) prepared in the usual way was added 2,3-dimethoxybenzoyl chloride, following the usual procedure, and the orange solution was stirred for 1 h at −100 °C and then allowed to warm up to 25 °C (2 h). Workup in the usual way furnished 6.71 g of an orange oil of which 3.75 g was subjected to column chromatography on silica gel, using hexane with increasing proportions of ether as an eluant. The first fraction eluted was benzoic acid (360 mg, 2.95 mmol, 21%), identified by melting point and ^{1}H NMR. The second fraction was 2,3-dimethoxy-

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benzoic acid (170 mg, 0.93 mmol, 7%), identified in the same way. The third fraction was a pale yellow syrup that did not crystallize but was analytically pure (2.30 g, 8.03 mmol, 57%): ^{1}H NMR ($CDCl_3$) δ 3.53 (br s, 3, 2-OCH_3), 3.86 (s, 3, 3-OCH_3), 6.93-7.71 (m, 6, Ar H). When the NMR probe was heated to 100 °C the resonance at δ 3.53 became a sharp singlet.

Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.13; H, 4.93. Found: C, 66.99; H, 4.82.

Alizarin Dimethyl Ether (12b). A sample of **15** (0.63 g, 2.2 mmol) was cooled in ice while 6 mL of concentrated sulfuric acid was added slowly with stirring. The resulting orange-brown solution was allowed to stand without further cooling for 4 h before pouring it on ice. The resulting yellow solid was recrystallized from acetone–ethanol as yellow needles (mp 207.5–208.5 °C, 0.32 g, 54%) which was again crystallized from ethanol: mp 210.5–211.5 °C (lit.[44] mp 210–211 °C); ^{1}H NMR (CF_3COOH) δ 4.23 (s, 3, OCH_3), 4.26 (s, 3, OCH_3), 7.64 (d, 1, Ar H), 8.03 (m, 2, Ar H), 8.43 (m, 3, Ar H); ^{1}H NMR ($CDCl_3$)[45] δ 4.00 (s, 6, OCH_3), 7.22 (d, 1, J = 8 Hz, Ar H), 7.60-7.80 (m, 2, Ar H), 8.02-8.30 (m, 3, Ar H).

Anal. Calcd for $C_{16}H_{12}O_4$: C, 71.63; H, 4.51. Found: C, 71.55; H, 4.30.

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2-(3,4,5-Trimethoxybenzoyl)-4,5-(methylenedioxy)benzoic Acid (20). 6-Bromopiperonylic acid[30] (25 mmol) was subjected to halogen–metal exchange with butyllithium for 2 h at −100 °C, following the general procedure. 3,4,5-Trimethoxybenzoyl chloride (25 mmol) was added, following the usual procedure. The yellow suspension was stirred for 30 min at −100 °C and then allowed to rise to 25 °C and stirring was continued for an additional 17 h. The solution was worked up in the usual way; the product, which precipitated on acidification of the bicarbonate solution, was purified by crystallization from ethanol, affording 3.84 g (67% yield) of fluffy colorless needles: mp 211–214.5 °C; ^{1}H NMR (CD_3SOCD_3) δ 3.67 (br s, 9, OCH_3), 6.06 (s, 2, OCH_2O), 6.67–6.84 (m, 3, Ar H), 7.18 (br s, 1, *o*-HOOCAr**H**); ^{13}C NMR (CD_3SOCD_3) δ 55.88, 60.16, 102.72, 106.30, 107.53, 108.70, 124.29, 132.61, 148.33, 150.74, 152.82, 166.53, 194.14. One more recrystallization from ethanol afforded an analytical sample, mp 214–215.5 °C (lit.[28] mp 215.5 °C).

Anal. Calcd for $C_{18}H_{16}O_8$: C, 60.00; H, 4.48. Found: C, 59.91; H, 4.40.

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Registry No. 1, 57901-57-2; **2a**, 98-88-4; **2b**, 100-07-2; **2c**, 1711-05-3; **2d**, 21615-34-9; **5a**, 85-52-9; **5b**, 1151-15-1; **5c**, 2159-36-6; **5d**, 1151-04-8; **8a**, 2159-48-0; **8b**, 76250-90-3; **10**, 22921-68-2; 11, 76250-91-4; **12b**, 6003-12-9; **14**, 7169-06-4; **15**, 76250-92-5; **19**, 4521-61-3; **20**, 7470-99-7; bromobenzene, 108-86-1; triphenylcarbinol, 76-84-6; butylbenzene, 104-51-8; *o*-bromotoluene, 95-46-5; 2-methylbenzophenone, 131-58-8; bis(2-methylphenyl)phenylmethanol, 6324-60-3; *o*-bromobenzonitrile, 2042-37-7; valerophenone, 1009-14-9; 2-cyanobenzophenone, 37774-78-0; 6-bromopiperonylic acid, 60546-62-5.

Palladium-Catalyzed Three Carbon Chain Extension Reactions with Acrolein Acetals. A Convenient Synthesis of Conjugated Dienals

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A variety of vinylic halides has been found to react with acrolein or methacrolein acetals and amines with palladium catalysts to form 5-amino 3-enal acetals and/or dienal acetals. The reaction products yield 2,4-dienals on treatment with aqueous acids, in moderate to good yields. Crotonaldehyde dimethyl acetal also undergoes the reaction, but only in low yields. 3-Buten-2-one ethylene ketal reacted well under the same conditions, however, and Hofmann elimination and hydrolysis of the product amine gave (*E*,*E*)-3,5-heptadien-2-one in 90% yield.

The palladium-catalyzed reaction of vinylic halides with various olefinic compounds to form dienes and/or allylic amines[1,2] is a synthetically useful reaction. Recently we have reported three carbon chain extensions of aryl and vinylic halides forming unsaturated carboxylic acid derivatives using acrylic acid derivatives in the reaction.[2] It would be of synthetic value to be able to add to other three carbon functionalized moieties in a similar manner. In this report we describe the synthesis of aliphatic, diunsaturated aldehydes and ketones by this method.

Results and Discussion

As noted previously with aryl halide reactions,[3] unprotected α,β-unsaturated aldehydes and ketones do not usually react well with organic halides because of competing polymerization, aldol condensation, and 1,4-addition reactions. Accordingly, as before, we have used the protected acetals or ketals. Also, as would have been expected from earlier results, the reaction with unsaturated acetals and ketals proceeded much faster and more cleanly with nucleophilic secondary amines as bases than with triethylamine, in the absence of an activating ester substituent.[2] With secondary amines, the major products are usually amino acetals or ketals, sometimes along with minor amounts of dienal acetals or dienone ketals. The hydrogens α to the acetal or ketal groups in the intermediate palladium complexes, apparently, are not reactive enough for the elimination to conjugated dienes to occur easily. It is interesting and of synthetic advantage that the competing formation of esters by way of intermediate ketene acetals observed in the related aromatic halide reactions[3] is generally much less important and often insignificant in the reactions with vinylic halides and nucleophilic secondary amines. The following major reaction

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