Table I
Conversion of Acyl Cyanides to 2-Substituted 3,3-Dichloroacrylonitriles

RCOCN, R	$Cl_2C{=}CRCN$, % yield: CCl_4[a] method	CCl_3Br[b]
Ia, CH_3	61	90
Ib, CH_3CH_2	45[c]	82
Ic, $(CH_3)_2CH$	40[c]	87
Id, $(CH_3)_3C$	48	91
Ie, p-ClC_6H_4	20	43
If, p-$CH_3OC_6H_4$	60	85

[a] The CCl_4, triphenylphosphine procedure is reported in ref 4 and 5. [b] Yield based on pure distilled or recrystallized product. [c] Yield based on VPC analysis of crude distillate.

ucts and lower yields result whenever more sensitive carbonyl components are added.[4,5]

We now wish to report on an improved method for the preparation of II and some reactions of II with acyl and aroyl cyanides. It has been found that the substitution of bromotrichloromethane for carbon tetrachloride allows the Wittig reagent II to be formed much faster and the concurrent reaction with the carbonyl component is significantly improved with higher yields and virtually no by-product formation. Gas chromatographic analysis of the crude reaction mixture does not show any of the bromochloroethylene derivative.

Although this procedure should be applicable toward the conversion of other carbonyl containing compounds to the dichlorovinyl group ($=CCl_2$) we have studied the carbonyl of acyl cyanides so that yields may be directly compared with our previous work.

$$2Ph_3P + Cl_3CBr \rightarrow Ph_3P{=}CCl_2 + Ph_3PBrCl$$

$$RCOCN + Ph_3P{=}CCl_2 \rightarrow Ph_3PO + Cl_2C{=}CRCN$$

In a typical reaction, excess dry bromotrichloromethane was added to 1.0 equiv of triphenylphosphine in sufficient dry benzene to produce a convenient volume. The mixture was stirred under a dry nitrogen atmosphere at 0° for 15–30 min, then 0.5 equiv of the acyl cyanide, Ia–f, was added and the mixture stirred at 0° for 2–4 hr. An immediate shift of the nitrile band as well as appearance of a strong $=CCl_2$ band in the 920–940-cm^{-1} region was observed[7]. After approximately 30 min, large quantities of triphenylphosphine oxide began to precipitate from the reaction mixture. After 1–2 hr, the carbonyl stretching band was almost totally gone. Stirring the mixture for a longer period of time had little effect on the yield. In cases using aliphatic acyl cyanides, the reaction mixture was rapidly warmed and benzene, excess bromotrichloromethane, and liquid products were removed under vacuum. Unlike our previous report,[4] the 2-alkyl-3,3-dichloroacrylonitriles were virtually free of impurities and easily purified by simple distillation to give yields of 82–91% (Table I). With aroyl cyanides, the benzene and excess bromotrichloromethane was stripped from the reaction mixture and crude products extracted with boiling ligroin and the crude products recrystallized from anhydrous methanol to give yields of 43–85%.

Experimental Section

All reactions were carried out under a dry nitrogen atmosphere. Boiling points and melting points are uncorrected. Infrared spectra were performed on a Beckman IR-8 and calibrated at 1601.0 cm^{-1} with polystyrene film. Commercial triphenylphosphine was used without purification. The bromotrichloromethane and benzene were purified by atmospheric distillation, using only the center cuts.

Acyl Cyanides. The acyl cyanides used in this study were prepared according to procedures reported previously.[4,5]

Reaction of II with Aliphatic Acyl Cyanides. General Procedure. A mixture of triphenylphosphine (0.15 mol) and 80 ml of dry benzene was cooled in an ice bath and then 40 g of bromotrichloromethane was added. The mixture was stirred at 0° for 30 min and then 0.075 mol of the aliphatic acyl cyanide (Ia–d) was added rapidly. After maintaining the reaction at 0° for approximately 3 hr it was heated under vacuum (25–30 mm) to yield benzene, the excess bromotrichloromethane, and crude product. A second distillation of the crude product gave pure 2-alkyl-3,3-dichloroacrylonitriles with physical properties and ir spectra identical with those reported previously.[5]

Reaction of II with Aryl Acyl Cyanides. General Procedure. In a manner similar to that described above, the aryl acyl cyanide (Ie,f) was added rapidly to a mixture of benzene, triphenylphosphine, and bromotrichloromethane at 0°. After 3 hr, the mixture was vacuum stripped to remove the benzene and excess bromotrichloromethane. The solid residue was extracted three times with 100-ml portions of boiling ligroin. The combined extracts were cooled to remove most of the triphenylphosphine oxide. Concentration and cooling the extracts gave a crude product which was recrystallized twice from anhydrous methanol. The pure 2-aryl-3,3-dichloroacrylonitriles displayed physical properties and ir spectra identical with those reported previously.[4]

Acknowledgment. The support of this research by the Robert A. Welch Foundation is gratefully acknowledged.

Registry No.—Ia, 631-57-2; Ib, 4390-78-7; Ic, 42867-39-0; Id, 42867-40-3; Ie, 13014-48-7; If, 14271-83-1; II, 6779-08-4; triphenylphosphine, 603-35-0; bromotrichloromethane, 75-62-7; 2-methyl-3,3-dichloroacrylonitrile, 31413-58-8; 2-ethyl-3,3-dichloroacrylonitrile, 42791-06-0; 2-isopropyl-3,3-dichloroacrylonitrile, 42867-43-6; 2-*tert*-butyl-3,3-dichloroacrylonitrile, 42867-44-7; 2-(p-chlorophenyl)-3,3-dichloroacrylonitrile, 37447-52-2; 2-(p-methoxyphenyl)-3,3-dichloroacrylonitrile, 37447-53-3.

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Synthesis of Some New Hindered Biaryls

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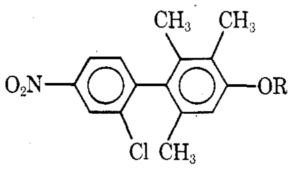
Our studies of the effects of chemical structure on molecular orbital energy levels and electron distributions[1-5] and associated electrical properties[6] have concerned themselves primarily with planar aromatic systems. Some such systems are subject to steric effects or nonbonded interactions which can lead to deviations from coplanarity and hence deviations from anticipated behavior. The biphenyl system is one whose susceptibility to these effects is well known.[7] The target structures **1–5** were designed with a view toward providing (1) a high rotational barrier about the biphenyl bond and (2) systems with an electron-rich ring and an electron-poor ring as well as ones with both rings electron poor or rich.



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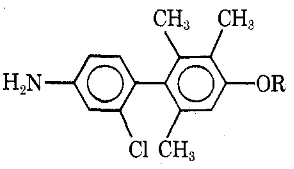

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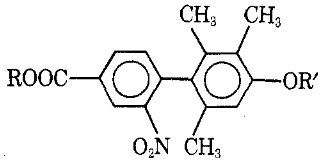

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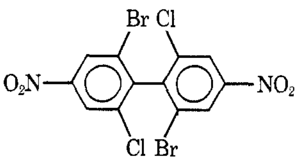

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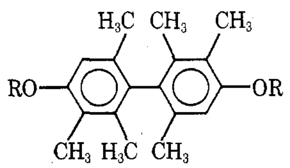

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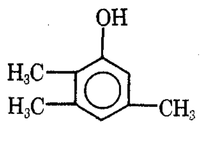
Discussion

A. Series 1. The prime starting material in the synthesis of system 1 was 2,3,5-trimethylphenol (isopseudocumenol, 6), which was converted to the known[8] 7 in 99% yield. Formation of the previously unreported benzyl ether 8 (85% yield) was accomplished by treatment of 7 with benzyl chloride in alkaline solution. Attempts to benzylate 7 without isolation from the reaction mixture were less efficient. Similarly the new *n*-octyl ether 9 was prepared in 97% yield using *n*-octyl iodide and 7. A Sandmeyer reaction of diazotized 10 afforded a 71% yield of the desired 2-chloro-4-nitroiodobenzene (11).[9]



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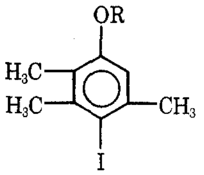
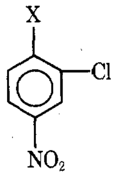


7, R = H

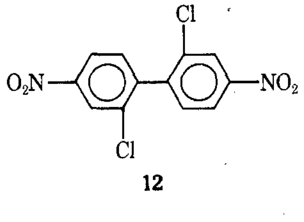
8, R = $CH_2C_6H_5$

9, R = n-C_8H_{17}



10, X = NH_2

11, X = I



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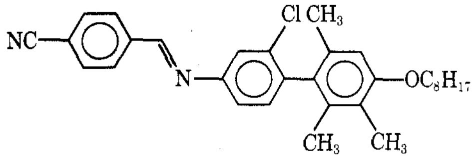
An Ullmann reaction of equimolar amounts of 8 and 11 led to the isolation of the desired 4-benzyloxy-2′-chloro-4′-nitro-2,3,6-trimethylbiphenyl (1, R = $CH_2C_6H_5$) in 36% yield (17% conversion) by means of column chromatography. Accompanying 1, R = $CH_2C_6H_5$, was 2,2′-dichloro-4,4′-dinitrobiphenyl (12).[9] The desired 1, R = H, was obtained in 88% yield by refluxing 1, R = $CH_2C_6H_5$, with a 30% solution of HBr in acetic acid. Formation of octyl ether 1, R = n-C_8H_{17}, was accomplished (89%) by treatment of 1, R = H, with octyl iodide in alkaline medium. 1, R = n-C_8H_{17}, can be obtained in a more direct manner via an Ullmann reaction of 9 and 11. This transformation proceeded in 53% yield (17% conversion).

B. Series 2. The nitro group of 1, R = n-C_8H_{17}, was reduced chemically with stannous chloride, affording a 97% yield of amine 2, R = n-C_8H_{17}. Since 2, R = n-C_8H_{17}, is an oil which could not be purified so as to afford satisfactory carbon analysis, it was derivatized. Condensation of 2, R = n-C_8H_{17}, with *p*-cyanobenzaldehyde afforded anil 13 in 99% yield.



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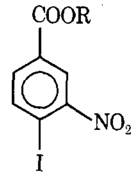

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C. System 3. The approach to series 3 involves utilization of one of the starting materials used for series 1, namely the benzyl ether 8. The other starting material is of structure 14, a 3 nitro-4-iodobenzoate ester. Nitration of ethyl *p*-iodobenzoate gives 14, R = C_2H_5.[10] 9 and 14, R = C_2H_5, were subjected to the conditions of the Ullmann reaction; by column chromatography 3, R = C_2H_5, R′ = n-C_8H_{17}, was isolated in 8% yield. The ester was hydrolyzed to the desired acid 3, R = H, R′ = n-C_8H_{17}, in 90% yield.

D. Series 4. Treatment of 12 with bromine in the presence of silver sulfate and sulfuric acid[11] led to the isolation of only dibromo derivative 4 in quantitative yield. Attempted brominations using organothallium intermediates were fruitless; apparently the aromatic rings of 12 are too deactivated for reaction with these species.

E. Series 5. Subjection of 8 to conditions of the Ullmann reaction for normal reaction times led primarily to recovery of starting material. Extended reaction times (60 hr) caused charring—no identifiable products were isolated. The procedure was that of previous workers who had succeeded in coupling 2,6-dimethyliodobenzene to form 2,2′,6,6′-tetramethylbiphenyl.[12] The present result is somewhat surprising, but can be explained by the presence of the deactivating benzyloxy group and increased steric hindrance at the 1-(iodo) position owing to the buttressing effect of the 3-methyl substituent.

As an alternative to the Ullmann synthesis of 5, R = $CH_2C_6H_5$, a method previously employed for the synthesis of bimesityl[13] was utilized. The Grignard reagent derived from 8 was treated with cupric chloride in anhydrous ether. The hydrolysis product, 3-benzyloxy-1,2,5-trimethylbenzene, which was also synthesized from isopseudocumenol (6), was isolated in 80% yield. This result in light of the synthesis of bimesityl is surprising; it can be rationalized only in terms of the buttressing effect of the 3 and 4 substituents of the Grignard reagent prepared from 4-benzyloxy-2,3,6-trimethyliodobenzene. This apparently makes the 1 position very sterically hindered, even to a greater extent than in that derived from iodomesitylene (2,4,6-trimethyliodobenzene), so that the Grignard reagent does not couple. Thus, attempted syntheses of 5, R = $CH_2C_6H_5$, were unsuccessful.

Experimental Section

General. Melting points were taken in capillaries on a Thomas-Hoover apparatus and are corrected. Infrared (ir) spectra were recorded on a Perkin-Elmer Model 137; nuclear magnetic resonance (NMR) spectra were recorded on a Joelco C-60H unit and all shifts are relative to internal tetramethylsilane. Elemental analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich.

4-Iodo-2,3,5-trimethylphenol (7). This compound, mp 110.0–110.5°, was prepared from 2,3,5-trimethylphenol (6) by the method of Cressman and Thirtle[8] using hydrogen peroxide–iodine in 98% yield: reported[8] mp 112–113°; yield 88%; NMR (CD_3COOD) s, δ 2.20 (3 H, 2-CH_3); s, 2.34 (3 H, 3-CH_3); s, 2.42 (3 H, 5-CH_3); s, 6.70 (1 H, 6-H); s, 11.1 (1 H, OH); ir (KBr) 3300 cm^{-1} (OH).

4-Benzyloxy-2,3,6-trimethyliodobenzene (8). A solution of

63.4 g (0.243 mol) of phenol **7**, 19.5 g (0.348 mol) of 87% potassium hydroxide, 670 ml of ethanol, and 31.4 g (0.248 mol) of benzyl chloride was refluxed overnight, concentrated by distillation of 400 ml of ethanol, and then poured into 1200 g of ice. After filtration the solid was washed with 5 *M* sodium hydroxide and water, then dried and recrystallized from ethanol to give 62.8 g (73%) of material, mp 69–74°. Two more recrystallizations gave colorless crystals, mp 74.0–76.0°. Anal. Calcd for $C_{16}H_{17}IO$: C, 54.56; H, 4.87. Found: C, 54.67; H, 4.89. NMR ($CDCl_3$) s, δ 2.26 (3 H, 3-CH_3); s, 2.44 (3 H, 2-CH_3); s, 2.46 (3 H, 6-CH_3); s, 4.95 (2 H, OCH_2); s, 6.69 (1 H, 5-H); s, 7.30 (5 H, aromatic); ir (KBr) 1110, 1230, 1260 cm^{-1} ($ArOCH_2$–), no OH.

4-Octyloxy-2,3,6-trimethyliodobenzene (9). A solution of 21.0 g (0.0800 mol) of phenol **7**, 19.2 g (0.0800 mol) of *n*-octyl iodide, 5.87 g (0.0900 mol) of 87% potassium hydroxide, 225 ml of ethanol, and 100 ml of dioxane was refluxed for 18 hr. Then most of the ethanol was removed and the resultant mixture was poured into ice–water. The hexane extract was dried and reduced in volume, whereupon 10.9 g (36%) of solid, mp 29–30°, precipitated. The filtrate was eluted through a column of neutral alumina and yielded 11.2 g (37%) more of the same material. Two recrystallizations from methanol–hexane yielded colorless crystals, mp 30.0–31.0°. Anal. Calcd for $C_{17}H_{27}IO$: C, 54.55; H, 7.27; I, 33.91. Found: C, 54.72; H, 7.18; I, 34.03. NMR ($CDCl_3$) m, δ 0.7–2.18 (15 H, OC–C_7H_{15}); s, 2.21 (3 H, 3-CH_3); s, 2.45 (6 H, 2-CH_3, 6-CH_3); t (J = 6 Hz), 3.88 (2 H, OCH_2C); s, 6.63 (1 H, 5-H); ir (KBr) 1050, 1230, 1270 cm^{-1} ($ArOCH_2$), no OH.

Activated Copper Powder. Copper powder was prepared by reduction of copper sulfate with zinc[14] and stored under water. To "activate" it, 114 g of wet copper powder was stirred in a solution of 30 g of iodine in 200 ml of acetone. After washing with acetone it was dried in a vacuum oven to give 67.7 g of catalyst. This "activation" process was carried out just prior to each Ullmann reaction.

4-Benzyloxy-2′-chloro-4′-nitro-2,3,6-trimethylbiphenyl (1, R = $CH_2C_6H_5$). An intimately ground mixture of 40.5 g (0.115 mol) of 4-benzyloxy-2,3,6-trimethyliodiobenzene (**8**) and 32.5 (0.115 mol) of 2-chloro-4-nitroiodobenzene (**11**)[9] was charged to a 400-ml stainless steel beaker containing 1 g of activated copper powder and 2 ml of pyridine and heated with stirring in an oil bath to 220° and a total of 66.7 g of activated copper was added at a rate of approximately 5 g/min. After heating for 1.5 hr, the mixture was cooled and exhaustively extracted with benzene. Concentration of the extract gave 37.8 g of a dark brown oil. This was chromatographed on neutral alumina with 1:1 benzene–hexane to yield 12.4 g of recovered **8** and 7.3 g of desired biphenyl **1**, R = $CH_2C_6H_5$, mp 155–160°. Elution with 3:1 benzene–methanol gave 7.54 g of **12** (see below). Based on unrecovered starting material **11**, the yield and conversion for **1**, R = $CH_2C_6H_5$, are 36 and 54% and for **12**, 17 and 54%. After three recrystallizations from ethanol–acetone the pale yellow crystals of **1**, R = $CH_2C_6H_5$, had mp 165.0–166.0°. Anal. Calcd for $C_{22}H_{20}ClNO_3$: C, 69.20; H, 5.28; N, 3.67; Cl, 9.29. Found: C, 69.74; H, 5.36; N, 3.72; Cl, 9.36. NMR ($CDCl_3$) s, δ 1.97 (3 H, 3-CH_3); s, 2.01 (3 H, 2-CH_3); 2.31 (3 H, 6-CH_3); s, 5.13 (2 H, OCH_2); s, 6.86 (1 H, 5-H); m, 7.5 (6 H, 6′-H, $CH_2C_6H_5$); m, 8.4 (2 H, 3′,5′-H); ir (KBr) 1520, 875 (NO_2); 1130, 1230, 1260 cm^{-1} ($ArOCH_2$–).

2,2′-Dichloro-4,4′-dinitrobiphenyl (12). The crude product (above) after recrystallizations from benzene had mp 107.0–108.5° (reported[9] mp 107°), yield 44% from **11**. Using the same procedure as for the preparation of **1**, R = $CH_2C_6H_5$, 25.0 g (0.0877 mol) of **11** and 18 g of activated copper and column chromatography on neutral alumina in benzene, 2.0 g (15%) of authentic **12** was isolated.

2′-Chloro-4-hydroxy-4′-nitro-2,3,6-trimethylbiphenyl (1, R = H). A solution of 4.04 g (0.0103 mol) of benzyl ether **1**, R = $CH_2C_6H_5$, and 40 ml of 30–32% HBr in acetic acid was refluxed for 2.5 hr and then poured over 125 g of ice. The methylene chloride extract yielded 4.37 g of brown oil. Chromatography of a benzene solution by elution with hexane yielded 0.22 g (100%) of benzyl bromide; elution with 1:1 benzene–methanol gave 2.65 g (88%) of crude product. Recrystallization from ethyl acetate–hexane three times gave tan crystals, mp 140.5–142.0°. Anal. Calcd for $C_{15}H_{14}ClNO_3$: C, 61.75; H, 4.84; N, 4.80. Found: C, 61.62; H, 4.91; N, 4.56. NMR ($CDCl_3$) s, δ 1.90 (6 H, 2,3-CH_3); s, 2.22 (3 H, 6-CH_3); s, 5.15 (1 H, OH); s, 6.63 (1 H, 5-H); d (J = 10 Hz), 7.29 (1 H, 6′-H); q (J = 2, 10 Hz), 8.17 (1 H, 5′-H); d (J = 2 Hz), 8.37 (1 H, 3′-H); ir (KBr) 3550 (OH); 1350, 1520 cm^{-1} (NO_2).

2′-Chloro-4′-nitro-4-octyloxy-2,3,6-trimethylbiphenyl (1, R = *n*-C_8H_{17}). Method A. Iodo compound **9** (4.47 g, 0.0119 mol), 3.38 g (0.0119 mol) of 2-chloro-4-nitroiodobenzene (**11**),[9] and 11.9 g of "activated" copper were allowed to react by the procedure given above for the preparation of **1**, R = $CH_2C_6H_5$. Elution of the crude product from neutral alumina with 1:1 benzene–hexane gave 2.22 g of recovered **9** and 0.83 g of **1**, R = *n*-C_8H_{17}. Elution with 2% methanol–benzene gave 0.96 g of symmetrical biphenyl **12**. Based on unrecovered starting material the yield of **1**, R = *n*-C_8H_{17}, was 53% and that of **12** 67%. The conversion of **9** and **11** to **1**, R = *n*-C_8H_{17}, was 17%. Upon standing **1**, R = *n*-C_8H_{17}, crystallized. Several recrystallizations from chloroform–methanol by use of seed crystals led to off-white crystals, mp 59.5–60.5°. Anal. Calcd for $C_{23}H_{30}ClNO_3$: C, 68.39; H, 7.49; Cl, 8.78; N, 3.47. Found: C, 67.93; H, 7.26; Cl, 9.07; N, 3.57. NMR ($CDCl_3$) m, δ 0.6–2.24 [24 H, $OC(CH_2)_6$ CH_3 and CH_3's including s, 1.77 (3-CH_3), s, 1.83 (2-CH_3), s, 2.05 (6-CH_3)]; t (J = 6 Hz), 3.73 (2 H, OCH_2); s, 6.24 (1 H, 5-H); d (J = 8 Hz), 6.84 (1 H, 6′-H); q (J = 2, 8 Hz), 7.67 (1 H, 5′-H); d (J = 2 Hz), 7.85 (1 H, 3′-H); ir (neat) 1070, 1240, 1260, 1290 ($ArOCH_2$); 1360, 1560 cm^{-1} (NO_2).

Method B. A solution of 5.00 g (0.0171 mol) of phenol **1**, R = H, 4.12 g (0.0171 mol) of *n*-octyl iodide, 1.26 g (0.0193 mol) of 87% potassium hydroxide, 30 ml of ethanol, and 20 ml of dioxane was refluxed for 22 hr, concentrated to ~one-half volume, and diluted with water. The ether extract was washed with 10% sodium hydroxide, water, saturated salt solution, and water and dried over sodium sulfate. Evaporation gave 6.18 g (89%) of crude **1**, R = *n*-C_8H_{17}.

4′-Amino-2′-chloro-4-octyloxy-2,3,6-trimethylbiphenyl (2, R = *n*-C_8H_{17}). A mixture of 4.80 g (0.0119 mol) of nitro compound **1**, R = *n*-C_8H_{17}, 10.7 g (0.0475 mol) of stannous chloride dihydrate, 30 ml of concentrated hydrochloric acid, and 90 ml of ethanol was refluxed for 18.5 hr, cooled, and poured into excess cold sodium hydroxide solution. The methylene chloride extract was washed with water, dried (sodium sulfate), and evaporated to afford 4.33 g (97%) of yellow oil. The oil was chromatographed on neutral alumina by elution with hexane and benzene–hexane mixtures. None of the fractions could be induced to crystallize. Anal. Calcd for $C_{23}H_{32}ClNO$: C, 73.87; H, 8.63; Cl, 9.48; N, 3.74. Found: C, 72.82; H, 8.30; Cl, 8.72; N, 3.57. NMR ($CDCl_3$) m, δ 0.4–2.14 [(24 H, $OC(CH_2)_6CH_3$ and s, 1.80 (3-CH_3), s, 1.84 (2-CH_3), s, 2.02 (6-CH_3)]; broad s, 3.37 (2 H, NH_2); t (J = 6 Hz), 3.70 (2 H, OCH_2-CH_2–); m, 6.05–6.87 (4 H, aromatic H); ir (neat) 1070, 1240, 1270, 1290 ($ArOCH_2$); 3390, 3480 cm^{-1} (NH_2).

4′-(*p*-Cyanobenzylideneamino)-2′-chloro-4-octyloxy-2,3,6-trimethylbiphenyl (13). The amine **2**, R = *n*-C_8H_{17}, and an equimolar amount of *p*-cyanobenzaldehyde were heated in absolute ethanol in the presence of a drop of acetic acid for 4 hr while the ethanol was allowed to boil off. The residue was purified by recrystallization from hexane as pale yellow crystals, mp 96.5–98.5°. Anal. Calcd for $C_{31}H_{35}ClN_2O$: C, 76.44; H, 7.24; N, 5.75. Found: C, 76.13; H, 7.18; N, 5.63. Ir (KBr) 2250 cm^{-1} (CN); 1010, 1030, 1040, 1060, 1240, 1270 cm^{-1} ($ArOCH_2$); no C=O or NH.

Ethyl 4-Iodo-3-nitrobenzoate (14, R = C_2H_5). Nitration of ethyl *p*-iodobenzoate[10] with nitric acid–sulfuric acid[10] afforded the desired compound, mp 78–81° (methanol), as orange crystals in 29% yield (reported[10] mp 88–89.5°, yield 85%): NMR ($CDCl_3$) t (J = 7 Hz), δ 1.44 (3 H, CH_3); q, 4.45 (2 H, CH_2); q (J = 2, 8 Hz), 7.86 (1 H, 6-H); d (J = 8 Hz), 8.17 (1 H, 5-H); d (J = 2 Hz), 8.41 (1 H, 2-H).

4′-Carbethoxy-2′-nitro-4-octyloxy-2,3,6-trimethylbiphenyl (3, R = C_2H_5; R′ = *n*-C_8H_{17}). An Ullmann reaction of 10.9 g (0.0291 mol) of **9**, 3.2 g (0.0100 mol) of **14**, R = C_2H_5, and 5.52 g of activated copper by the method described above for the preparation of **1**, R = $CH_2C_6H_5$, and column chromatography on acidic alumina gave 0.33 g (7.5%) of crude **3**, R = C_2H_5; R′ = *n*-C_8H_{17} (1:1 benzene–hexane elution). This oil could not be crystallized: NMR ($CDCl_3$) m, δ 0.5–2.14 [24 H, $OC(CH_2)_6CH_3$ and s, 1.75 (3-CH_3), s, 1.80 (2-CH_3), s, 2.00 (6-CH_3)]; t (J = 5 Hz), 3.67 (2 H, OCH_2CH_2); s, 6.19 (1 H, 5-H); d (J = 8 Hz), 6.91 (1 H, 5′-H); q (J = 2, 8 Hz), 7.87 (1 H, 6′-H); d (J = 2 Hz), 8.14 (1 H, 3′-H); broad s, 9.59 (–COOH); ir (neat) 1370, 1530 (NO_2); 1030, 1250, 1290, 1310 ($ArOCH_2$); 1750 cm^{-1} (C=O).

4′-Carboxy-2′-nitro-4-octyloxy-2,3,6-trimethylbiphenyl (3, R = H; R′ = *n*-C_8H_{17}). A solution of 0.33 g (0.749 mmol) of the ester **3**, R = C_2H_5; R′ = *n*-C_8H_{17}, 0.15 g of sodium hydroxide, 5 ml of dioxane, and 2 ml of water was refluxed for 2 hr and poured into cold dilute hydrochloric acid. The ether extract was washed with water, dried (sodium sulfate), and evaporated, leaving 0.28 g (90%) of crude product. Three recrystallizations from ethyl acetate–hexane gave yellow crystals, mp 175.6–176.1°. Anal. Calcd for $C_{24}H_{31}NO_5$: C, 69.71; H, 7.56; N, 3.39. Found: C, 69.95; H, 7.48; N, 3.38. Ir (KBr) 1030, 1090, 1260, 1295 ($ArOCH_2$); 1360, 1520 (NO_2); 1700 (C=O); 3000–2500 cm^{-1} (OH).

2,2′-Dibromo-6,6′-dichloro-4,4′-dinitrobiphenyl (4). Bromination of **12** by the method used by Harris and Mitchell[11] led to a quantitative yield of **4** as light orange plates, mp 157.8–160.0° (ethanol). Anal. Calcd for $C_{12}H_{14}Br_2Cl_2N_2O_4$: C, 30.61; H, 0.86; Br, 33.94. Found: C, 30.30; H, 0.91; Br, 34.70. Ir (KBr) 1360, 1530 cm^{-1} (NO_2).

Attempted Self-Coupling of 4-Benzyloxy-2,3,6-trimethyliodobenzene (8) via the Grignard Reagent. The reported procedure for preparation of bimesityl[13] was applied to **8**; the only product, formed in about 80% yield, was 3-benzyloxy-1,2,5-trimethylbenzene (see below).

3-Benzyloxy-1,2,5-trimethylbenzene. Benzylation of the phenol **6** by the procedure described above for the preparation of **8** led to a 75% yield of the ether as an oil. Elution through neutral alumina and distillation gave a colorless oil, bp 165° (2.7 mm), which crystallized (mp 34.5–37.5°). Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 85.44; H, 7.97. NMR ($CDCl_3$) s, δ 2.13 (6 H, 1,2-CH_3); s, 2.20 (3 H, 5-CH_3); s, 5.14 (2 H, OCH_2); broad s, 6.50 (2 H, 4,6-H); m, 7.2 (5 H, C_6H_5); ir (neat) 1120, 1225, 1250, 1290 cm^{-1} ($ArOCH_2$–); no OH.

Registry No.—**1** (R = $CH_2C_6H_5$), 57362-66-0; **1** (R = H), 57362-67-1; **1** (R = n-C_8H_{17}), 57362-68-2; **2** (R = n-C_8H_{17}), 57362-69-3; **3** (R = C_2H_5; R′ = n-C_8H_{17}), 57362-70-6; **3** (R = H; R′ = n-C_8H_{17}), 57362-71-7; **4**, 57362-72-8; **6**, 697-82-5; **7**, 7282-02-2; **8**, 57362-73-9; **9**, 57362-74-0; **11**, 41252-96-4; **12**, 57362-75-1; **13**, 57362-76-2; 14 (R = C_2H_5), 57362-77-3; benzyl chloride, 100-44-7; n-octyl chloride, 629-27-6; p-cyanobenzaldehyde, 105-07-7; ethyl p-iodobenzoate, 51934-41-9; 3-benzyloxy-1,2,5-trimethylbenzene, 57362-78-4.

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A New γ-Keto Aldehyde Synthesis

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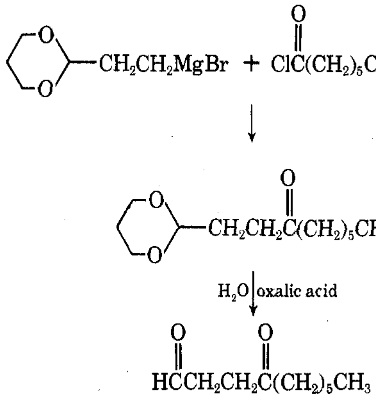
γ-Keto aldehydes are an important class of compounds especially as intermediates for the preparation of cyclopentenones.[1] 1,4-Diketones have found wide application in the Paal–Knorr synthesis of pyrroles, furans, and thiophenes,[2] as well as in pyridazine synthesis,[3] which suggests that γ-keto aldehydes may be useful in the synthesis of these heterocycles as well. The available routes to γ-keto aldehydes include ring opening of substituted furans,[4] radical addition of an aldehyde to acrolein diethyl acetal,[5] oxidative cleavage of olefins,[6] alkylation of 2,4,4,6-tetramethyldihydrooxazine with 2-iodomethyl-1,3-dioxolane,[7] and alkylation of 2-ethoxyallyl vinyl sulfide followed by thio-Claisen rearrangement.[8] Recently a route using condensation of the dianion of γ-oxosulfone acetals with esters followed by removal of activating and protecting groups,[9] and another based on ring opening of cyclopropyl ketones followed by oxidation, were reported.[10] Most of these routes are either lengthy, require multistep preparation of a special reagent, or give low overall yields.

We have found a short route which begins with readily available materials, and gives high yields of γ-keto aldehyde, as outlined in Scheme I. Grignard reagents have found occasional use for preparation of ketones from acid chlorides but the yields are usually low owing to reaction with the ketone, leading to tertiary alcohols.[11-13] Even at dry ice temperature and using inverse addition, the yields are not improved.[14] We have found that the Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxane is exceptional; it affords ketone in high yield with no more than a trace of tertiary alcohol at dry ice temperature.

Scheme I



Grignard reagents derived from β-halo ketals and acetals are known to be unstable[15] owing to their tendency to undergo intramolecular attack leading initially to cyclopropyl ethers. Büchi[16] and others[17] have used the reagent derived from 2-(2-bromoethyl)-1,3-dioxolane by preparing it at 30–35°. This reagent is destroyed if the solvent tetrahydrofuran (THF) is allowed to reflux. We chose to use the six-membered ring acetal and found that its greater stability allowed quick, high-yield preparation of the Grignard reagent at reflux in THF. This then gave 2-(3-oxononyl)-1,3-dioxane in 92% yield based on the bromo compound or the acid chloride.

The six-membered-ring acetal apparently has greater equilibrium stability than the five-membered ring, since boiling the intermediate in aqueous acid gives only partial hydrolysis to the keto aldehyde. However, the equilibrium is easily displaced toward hydrolysis with removal of the product by continuous steam distillation as it is formed. This gave γ-ketodecanal in 89% yield. This particular product is an intermediate in a synthesis of dihydrojasmone.[8] The Grignard reagent derived from 2-(2-bromoethyl)-4,4,6-trimethyl-1,3-dioxane also gives ketones in better than 90% yields but the acetal is more stable and therefore less readily removed with aqueous acid.

The usual technique for preventing overreaction is to first convert the Grignard to the zinc or cadmium reagent, which then affords ketones in better yields.[13,18] In our earlier efforts, we prepared the zinc reagent directly from 2-(2-iodoethyl)dioxolane at 51° in dimethylformamide (DMF);[19] however, we were unable to isolate any ketone products from reaction with acid chlorides. The formation of the organozinc iodide compounds could be followed in the NMR,[20] e.g., that from the iodoacetal gave a high-field triplet at δ 0.13 ppm, comparable with a quartet at δ 0.01 obtained from ethyl iodide and Zn in DMF. The Grignard