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Synthesis of 4-Cyano-4'-halobiphenyls

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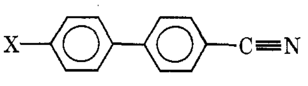
As part of a study of intermolecular halogen–cyanide interactions in the solid state it was desired to prepare very pure samples of the 4-cyano-4'-halobiphenyls. Pummerer and Seligsberger[1] have previously reported the synthesis of Ia and Niwa[2] has reported the synthesis of Ib and Ic. We wish to report the synthesis of these compounds by a different and very simple route involving the displacement of halogen with CuCN in refluxing dimethylformamide[3] (for the iodide and bromide) and *N*-methylpyrrolidone[4] (for the chloride).



Ia, X = I
b, X = Br
c, X = Cl

For the synthesis of Ia and Ib the reaction was run with 1 equiv of CuCN per mole of the dihalogenated biphenyl. The reaction mixture was very conveniently separated by preparative thin layer chromatography. In a few runs the main components of the reaction mixture were isolated and were approximately those expected for a statistical reaction. An attempt was made to run the displacement reaction on 4,4'-dichlorobiphenyl in refluxing dimethylformamide but even at long reaction times no product could be detected. Use of the higher boiling solvent *N*-methylpyrrolidone, an excess of CuCN, and long reflux times were necessary for a successful synthesis of Ic.

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Laser Raman spectra were obtained with a Jeol Model JRS-S1 spectrometer equipped with an argon ion laser. Preparative thin layer chromatography was done on silica gel G PF-254 (E. Merck) using benzene as developer. Compounds were detected using an ultraviolet lamp and products extracted with methanol–chloroform (1:19). Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

4-Cyano-4'-iodobiphenyl (Ia). 4,4'-Diiodobiphenyl (0.50 g, 1.2 mmol), cuprous cyanide (0.11 g, 1.2 mmol), and 15 ml of dimethylformamide were placed in a 50-ml round-bottomed flask and refluxed for 2.5 hr. After cooling, 35 ml of ferric chloride solution (200 g of hydrated $FeCl_3$ and 50 ml of concentrated HCl in 300 ml of water) was added to the reaction vessel. The resulting mixture was heated at 60–70 °C for 20 min. The dimethylformamide–ferric chloride mixture was extracted three times with approximately 20 ml of toluene. The reddish toluene layer was then extracted with 50 ml of 10% HCl, 20 ml of water, and 50 ml of 5% NaOH. The toluene layer was dried over $MgSO_4$ and filtered. The toluene was evaporated at reduced pressure and the residue fractionated by preparative thin layer chromatography. The desired product has R_f 0.51 in benzene. The crude product was sublimed at 135 °C (1 mm), affording 4-cyano-4'-iodobiphenyl (160 mg, 42%). An analytical sample recrystallized from absolute ethanol melted at 179.5–181.5 °C (lit.[1] 166 °C), laser Raman (crystal) 2225 cm^{-1} ($-C\equiv N$).

Anal. Calcd for $C_{13}H_8NI$: C, 51.17; H, 2.64; N, 4.59; I, 41.59. Found: C, 51.05; H, 2.59; N, 4.58; I, 41.65.

4-Bromo-4'-cyanobiphenyl (Ib). The procedure was identical with one used for the iodo compound, except that 4,4'-dibromobiphenyl (0.50 g, 1.6 mmol) and cuprous cyanide (0.14 g, 1.6 mmol) were refluxed in dimethylformamide for 4.0 h. The R_f of 4-bromo-4'-cyanobiphenyl is 0.50 in benzene. The crude product was sublimed at approximately 120 °C (1 mm), producing 4-bromo-4'-cyanobiphenyl (210 mg, 50%). A sample recrystallized from absolute ethanol had mp 153.5–155 °C (lit.[2] 144 °C), laser Raman (crystal) 2225 cm^{-1} ($-C\equiv N$). An analysis of this compound was not performed. Its identity has been confirmed unambiguously by a complete x-ray analysis.[5]

4-Chloro-4'-cyanobiphenyl (Ic). The procedure used was similar to the one used for the iodo compound, except that 4,4'-dichlorobiphenyl (0.50 g, 2.2 mmol) and cuprous cyanide (0.40 g, 4.46 mmol) were refluxed for 93.0 h in *N*-methylpyrrolidone. The R_f of the product is 0.48 in benzene. The crude product was sublimed at about 105 °C (1 mm), affording 4-chloro-4'-cyanobiphenyl (110 mg, 23%). An analytical sample recrystallized from absolute ethanol melted at 133–133.5 °C (lit.[2] 129–130°C), laser Raman (crystal) 2225 cm^{-1} ($-C\equiv N$).

Anal. Calcd for $C_{13}H_8NCl$: C, 73.07; H, 3.77; N, 6.56; Cl, 16.60. Found: C, 73.24; H, 3.78; N, 6.45; Cl, 16.40.

Acknowledgment. We thank Professor Stuart Fenton for the laser Raman spectra and Professor Doyle Britton for his continued interest in this work.

Registry No.—Ia, 57774-34-2; Ib, 57774-35-3; Ic, 57774-36-4; cuprous cyanide, 544-92-3; 4,4'-diiodobiphenyl, 3001-15-8; ; 4,4'-dibromobiphenyl, 92-86-4; 4,4'-dichlorobiphenyl, 2050-68-2.

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† NSF Undergraduate Research Participant, summer 1975.

A Convenient Synthesis of Labile Optically Active Secondary Alkyl Bromides from Chiral Alcohols

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Recent interest and reports[1-3] concerning the synthesis of optically active secondary alkyl halides prompts this disclosure of our experience in the area and of a convenient preparative procedure for active bromides, including those which are prone toward racemization.

Conceivably, one of the simplest approaches to the preparation of active halides involves treatment of the corresponding chiral alcohol with a phosphorus trihalide as in eq 1–4. Unfortunately, in practice this method has met with considerable difficulty primarily because the reactions represented by eq 3 and 4 are slow and have afforded halides of much lower optical purity.[1,4-6] To alleviate this problem, HX is commonly swept out (CO_2 or N_2) which essentially eliminates the last two steps (eq 3 and 4).

This produces product of high optical purity but the resulting low yields (i.e., 23% 2-bromooctane from 2-octanol)[1,7] severely limit the usefulness of the procedure, espe-

Table I. Preparation of Secondary Bromo Compounds from Chiral Alcohols with Phosphorus Tribromide

Alcohol	α^{25}D obsd, deg (optical purity, %)	Unreacted phosphite esters	Treatment with HBr	Product	Yield, %	α^{25}D obsd, deg (optical purity, %)[a]
1-Phenylethanol	−44.2 (100)[12]	Absent		α-Phenylethyl bromide	70–75	+160.8 (94)[12]
	+44.2 (100)[12]	Present	No	α-Phenylethyl bromide	35.1	−85.7 (49)[12]
	+42 (95)[12]	Present	Yes	α-Phenylethyl bromide	71	−143 (88%)[12]
2-Octanol	−7.39 (90.7)[2]	Absent		2-Octyl bromide	67	+39.3 (97)[1]
	−7.39 (90.7)[2]	Present	Yes	2-Octyl bromide	62	+37.8 (94)[1]
2-Pentanol	+9.97 (88.5)[15]	Absent		2-Pentyl bromide	~60	−42.7 (89)[1]
	+9.97 (88.5)[15]	Present	Yes	2-Pentyl bromide	62	−40.5 (84)[1]

[a] The values are corrected for the optical purity of the starting material and are for neat liquids.

$$\begin{tikzcd}
\text{HX} + (\text{RO})_3\text{P} & \text{ROH} + \text{PX}_3 \arrow[r] & \text{ROPX}_2 + \text{HX} \arrow[d, "\text{ROH}"] \\
& & (\text{RO})_2\text{PX} + \text{HX} \arrow[ull, "\text{ROH}"']
\end{tikzcd}$$

(1)

$$(\text{RO})_3\text{P} + \text{HX} \xrightarrow{\text{fast}} (\text{RO})_2\text{PHO} + \text{RX} \qquad (2)$$

$$(\text{RO})_2\text{PHO} + \text{HX}\cdot \xrightarrow{\text{slow}} \text{ROPH(OH)O} + \text{RX} \qquad (3)$$

$$(\text{ROPH(OH)O}) + \text{HX} \xrightarrow{\text{slow}} \text{H}_3\text{PO}_3 + \text{RX} \qquad (4)$$

cially for bromides. Our studies suggest that this loss of optical activity is due primarily to racemization of the product and not to inherent racemization in steps 3 and 4. Thus, if care is taken to maintain the reaction and isolation temperatures relatively mild (5 °C to room temperature or below), good yields of bromides of high optical purity are obtained. The general procedure involves treatment of a solution of the chiral alcohol and twofold molar excess of pyridine[8] in ether at −25 °C with phosphorus tribromide over a 1-h period followed by stirring for 1–2 days at 4 °C to complete cleavage of the intermediate phosphite ester.[9] This latter step is crucial since we observed that attempts to distill the product bromoalkanes in the presence of partially converted phosphite esters results in poor yields and a considerable loss in optical purity, presumably because the higher temperatures required to distill the halide leads to extensive racemization. For example, 1-phenylethyl bromide distills smoothly at room temperature at 0.01–0.02 mm in the absence of phosphite esters to give 70–75% yields and an optical purity of 94% (from 100% optically pure 1-phenylethanol). However, in the presence of phosphite esters, the distillation bath temperature (>70 °C) required to obtain product is detrimental to both yield (35%) and optical purity (49%).[10] However, treatment of the phosphite-containing mixture with HBr prior to work-up improves the yield to 71% and the optical purity to 84%. These observations along with results for other chiral alcohols are summarized in Table I. Thus, as long as reaction and isolation temperatures are kept low and complete conversion of intermediate phosphite esters is accomplished, the reaction of chiral alcohols with PBr_3 to afford the corresponding bromides appears to offer an efficient synthetic method for these useful intermediates.[11]

Experimental Section

Materials. The (+) and (−) isomers of 1-phenylethanol were resolved by the method of Kenyon.[14] Optically active 2-octanol and 2-pentanol were obtained from Norse Chemical Co. A 0.06 M solution of sodium methylsulfide in HMPT was prepared by passing methanethiol (Matheson) through a suspension of an appropriate amount of sodium hydride in 100 ml of dry HMPT at 0 °C until the solution became clear, followed by warming to room temperature to evaporate excess methanethiol.

General Procedure for Making Chiral Secondary Bromo Compounds. The following representative procedure for 1-phenylethyl bromide is presented. Optically pure 1-phenylethanol (9.5 g, 0.078 mol, α^{25}D −44.2°) and dry pyridine (14 g, 0.177 mol) were dissolved in 50 ml of anhydrous ether contained in a 300-ml flask fitted with a mechanical stirrer, pressure-equalizing funnel, and alcohol thermometer. The solution was cooled to −25 to −15 °C using a dry ice–acetone bath. A solution of PBr_3 (24 g, 0.088 mol) in 75 ml of dry ether was added over a period of 1 h, during which time the temperature was kept between −15 and −25 °C. The reaction mixture was then stirred at −10 °C for another 1 h and finally at 5° for 1–2 days in a cold room. The excess PBr_3 was destroyed with ice–water, and the ether layer was separated, washed successively with equal volumes of ice–water, 85% orthophosphoric acid, and cold saturated $NaHCO_3$ solution and twice with ice–water, and dried ($MgSO_4$). A 5-ml portion of the ether solution was withdrawn and evaporated. The infrared spectrum of the residue was examined for peaks at 1250, 950–1000, and 2400 cm^{-1} characteristic of partially converted phosphite esters. If the above peaks were present, the ether solution of the reaction mixture was stirred magnetically in a three-neck 300-ml flask protected by a drying tube. Dry HBr gas was bubbled through the ether solution at a slow rate for about 15 min. The temperature was maintained at ca. 25 °C. When monitoring by ir demonstrated the complete conversion of the phosphite ester, the ether solution was carefully washed with ice–water, saturated $NaHCO_3$ solution, and ice–water and dried ($MgSO_4$). Concentration on a rotary evaporator at room temperature followed by distillation at 0.01–0.02 mm pressure at room temperature gave 10.5 g (73%) of 1-phenylethyl bromide. The observed specific rotation (α^{25}D +160.8°) corresponds to 94% optical purity.[1]

(+)-(*R*)-Methyl 1-Methylbenzyl Sulfide. (−)-(*S*)-1-Phenylethyl bromide (0.5 g, 2.7 mmol, α^{25}D −85.71°) was weighed in a 50-ml flask provided with a nitrogen seal and a magnetic stirrer. A 0.6 M solution of $NaSCH_3$ in HMPT (10 ml) was transferred into the flask with a syringe through a rubber septum. The mixture was stirred for 10 min, poured into a solution of NaCl in water, and acidified with 1 M HCl until the solution was acidic to methyl orange. The mixture was extracted twice with pentane, and the pentane extract was washed with saturated $NaHCO_3$ and water and dried ($MgSO_4$). Concentration and distillation afforded 0.315 g of (+)-(*R*)-methyl 1-methylbenzyl sulfide, bp 58–60 °C (1 mm), n^{25}D 1.5450 [lit.[12] bp 58–59 °C (1 mm), n^{25}D 1.5491]. The observed specific rotation (α^{25}D +95.71°) corresponds to 48.8% optical purity (based on the value of 196° maximum).[12]

Registry No.—(−)-1-Phenylethanol, 1445-91-6; (+)-1-phenylethanol, 1517-69-7; (−)-2-octanol, 6169-06-8; (+)-2-pentanol, 31087-44-2; (+)-α-phenylethyl bromide, 1459-14-9; (−)-α-phenylethyl bromide, 3756-40-9; (+)-2-octyl bromide, 1191-24-8; (−)-2-pentyl bromide, 29117-44-0; (+)-*R*-methyl 1-methylbenzyl sulfide, 57793-28-9; phosphorus tribromide, 7789-61-9.

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(8) The pyridine is utilized to trap the liberated HBr to ensure its presence for the slow cleavage reactions represented by eq 3 and 4.
(9) The conversion of the phosphite ester to bromide may not be complete even after 2 days. This can be readily checked in the crude product by infrared spectroscopy. Incomplete conversion of the ester will result in

strong bands at 1250, 950–1000, and 2400 cm^{-1}, characteristic of P–O, P–O–C, and P–H absorptions, respectively. In the event that cleavage is incomplete, the ether solution is treated with dry HBr at room temperature until the monitored bands above disappear (usually 15 min). The loss of optical purity in this operation is ca. 5% (Table I).

(10) As noted by others,[12] 1-phenylethyl bromide is readily prone toward racemization. For instance, at 27 °C in a 1:1 mixture of HMPT and pentane the optical half-life is only ca. 8 h. When pure, the neat bromide has an optical half-life of about 125 days but racemization seems to be catalyzed by impurities.

(11) In the event that the chiral bromo derivative is part of the synthetic sequence, it is often profitable to use it without purification in order to minimize racemization. If necessary, the optical purity of the produced bromo compound may be obtained by conversion to the corresponding methylsulfide (with inversion) via treatment with sodium methylsulfide–HMPT (see Experimental Section). The methylsulfide derivatives are formed in nearly quantitative yields and can be purified by distillation without fear of racemization. The maximum rotations for a number of such methylsulfides are available[1,12,13a] for evaluation of the optical purities of the bromides.

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Role of Protic and Dipolar Aprotic Solvents in Cycloaddition Reactions Involving Anionic 1,3-Dipoles. Action of Inorganic Azides on Imidoyl Chlorides[1]

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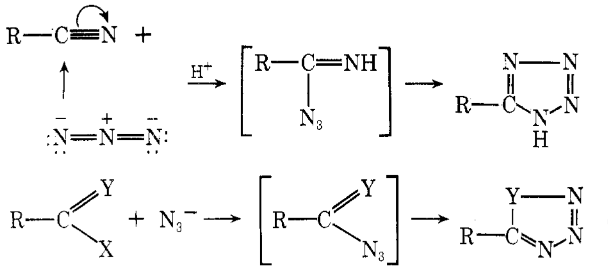
While conventional 1,3-cycloaddition reactions involve the participation of 1,3 dipoles that are polar molecules, cycloadditions of anionic dipoles constitute reactions of an anionic 1,3-dipolar system, such as an azide ion, with a multiple bond.[2] The anionic dipole can undergo either a "direct" or "indirect" cycloaddition. The reaction of the azide ion with nitriles[3] provides an example of "direct" addition (eq 1). The action of inorganic azides on imidoyl chlorides and related compounds[3] may be considered to be an example of "indirect" addition (eq 2).



(1)

(2)

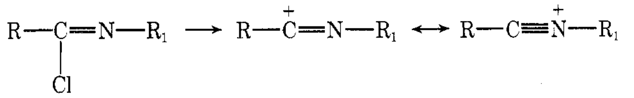
X = halogen, alkoxyl, or other displaceable group and Y = a C unit or a substituted or unsubstituted heteroatom which may or may not, together with R, be part of a cyclic system. Imidoyl chlorides, X = Cl and Y = N–R′

Although reactions of the azide ion with multiple bonds are very useful in heterocyclic synthesis,[3–5] no kinetic or other mechanistic studies exist on many of these reactions. Azide addition may be conceived to occur in a single step following a 1,3-cycloaddition pathway or in a two-step reaction via an azido intermediate. In the reaction of hydrazoic acid with alkynes leading to triazoles, a synchronous 1,3-cycloaddition mechanism is considered more probable.[6] Kinetic data for the addition of azide ion to aromatic diazonium chlorides indicate that the reaction follows a concerted course.[7] Few anionic 1,3 cycloadditions have been proven to proceed in a stepwise manner;[8] in fact, the addition of 2-(*N*,*N*-diisopropylcarbamoyl)allyllithium to the –N=N– bond appears to be the first instance where experimental evidence exists for an anionic 1,3 cycloaddition occurring in a nonconcerted manner.[8]

No kinetic studies are available for the reaction of the azide ion with nitriles (eq 1) or with imidoyl chlorides (eq 2). In the azide–nitrile reaction, an azocarbonium ion appears to be formed first, followed by azide addition.[9] The

$$R{-}C{\equiv}N + H^+ \longrightarrow R{-}C{\equiv}\overset{+}{N}H \longleftrightarrow R{-}\overset{+}{C}{=}NH$$

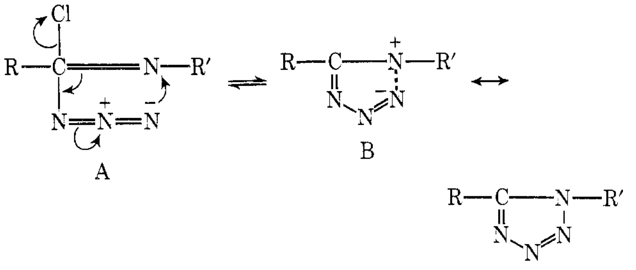
facts, that the reaction is subject to general acid catalysis and that electronegative substituents on the nitrile facilitate addition, are in support of this mechanism.[9]



$$R{-}C(Cl){=}N{-}R_1 \longrightarrow R{-}\overset{+}{C}{=}N{-}R_1 \longleftrightarrow R{-}C{\equiv}\overset{+}{N}{-}R_1$$

A very similar mechanism could be conceived for the azide–imidoyl chloride reactions as well. Very recent studies on the rates of solvolysis of substituted imidoyl chlorides indicate that a unimolecular mechanism involving the formation of an azocarbonium ion intermediate is in operation.[10] However, the possibility of an addition–elimination mechanism for chloride displacement should not be ignored. Such a mechanism is known to be involved in the reaction of azide ion with a number of alkyl- and aryl-substituted β-chlorovinyl ketones[11] [eq 2, X = Cl and Y = C–C(=O)–R$_1$]. Also, there is evidence that anionic nucleophiles, such as the azide ion, react with acyl halides (eq 2, X = Cl and Y = O) via an addition–elimination reaction.[12] Kinetic studies on chloride substitution with amines in diarylimidoyl chlorides have indicated that an addition–elimination mechanism, where bond forming is important, predominates when $\sigma_{\text{N-Ph-substituent}} > 0.3$, while an azocarbonium ion mechanism, where bond breaking is important, prevails when $\sigma_{\text{N-Ph-substituent}} < 0.3$.[13]

Azide addition to the imidoyl chloride (in the addition–elimination mechanism), may be conceived to proceed in a two-step reaction via an azidoazomethine (imidoyl azide) intermediate, or in a single step concerted cycloaddition.[14] The linear azido group must adopt a "bent" configuration[15,16] for cyclization, and as it bends, the resonance form B becomes increasingly important, until cyclization occurs, when the terminal azide nitrogen comes within bonding distance of the azomethine nitrogen.[17] A concerted 1,3-anionic addition is quite likely when a bent transition state similar to B becomes energetically favorable.



In view of the important role of solvents in determining chemical reactivity,[18] recently a program was initiated in our laboratories to understand the true role of protic and dipolar aprotic solvents in 1,3-cycloaddition reactions and how it could be utilized to advantage in heterocyclic synthesis.[19] In the normal 1,3 cycloadditions where no discrete ions are involved, solvent effects, although definite, have been found to be of a small order and to arise mainly from