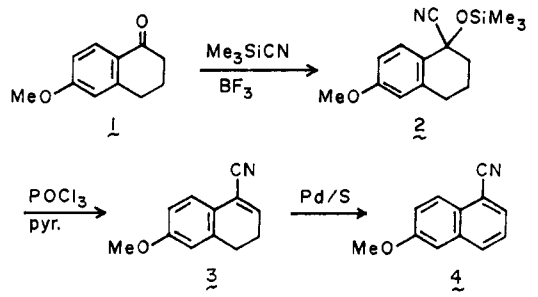
Scheme I



treatment with $POCl_3$ in pyridine undergoes elimination of trimethylsilanol to afford **3**. Dehydrogenation of **3** was most efficiently accomplished by heating with sulfur and a 10% palladium–charcoal catalyst in refluxing triglyme. This reagent combination was more effective than palladium in the absence of sulfur or chemical oxidants such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone or *o*-chloranil, which furnished substantial amounts of secondary products. The utility of the combination of sulfur and palladium for dehydrogenation has been documented previously.[7,8]

While no attempt has been made to extend this synthetic approach to other conjugated nitriles, the method appears potentially quite general.[9]

Experimental Section

3,4-Dihydro-6-methoxynaphthalene-1-carbonitrile (3). 6-Methoxy-1-tetralone[10] (17.6 g, 100 mmol) is placed in a 250-mL Erlenmeyer flask, and cyanotrimethylsilane (10.9 g, 110 mmol) is added with stirring, followed by 2 or 3 drops of BF_3 etherate. The mixture is warmed on a hotplate at 60 °C for 2 h, the temperature is raised to 100 °C to prevent solidification, and heating is continued for an additional 2 h.[11] Then pyridine[12] (75 mL) and $POCl_3$ (15 mL) are added along with a few carborundum boiling chips. A simple distillation head is attached, and the solution is gently boiled for 2 h while a mixture of chlorotrimethylsilane and pyridine distills over. The reaction mixture is then poured into 500 mL of crushed ice, and the product is extracted into ether. The ether layer is washed with water, dilute hydrochloric acid, and water and evaporated to dryness under vacuum. The gummy product is dissolved in a small volume of benzene (25–30 mL), diluted with three times the same volume of hexane, and decolorized by passage through a short column (20 g) of neutral alumina. Concentration of the solution to approximately half volume by partial evaporation of the solvent with a stream of nitrogen followed by cooling precipitates 14.7 g (79%) of **3** as a pale tan, somewhat sticky solid, which was twice recrystallized from methanol: mp 50–51.5 °C (lit.[5] mp 50.5–51.5 °C); NMR ($CDCl_3$) δ 2.3–3.1 (m, 4, CH_2), 3.8 (s, 3 CH_3), 6.6–7.5 (m, 4, vinylic and aromatic). Compound **3** may be dehydrogenated directly without recrystallization or further purification.

6-Methoxynaphthalene-1-carbonitrile (4). Since H_2S is generated as a side product, it is advisable to conduct this reaction in a hood. The unrecrystallized nitrile **3** (30 g, 162 mmol) is combined with 6 g of sulfur, 1.5 g of 10% Pd on charcoal, and 200 mL of triglyme in a 500-mL flask fitted with an air-cooled condenser. The stirred mixture is heated at reflux for 2 h, cooled, and filtered, and the residue is rinsed with ether (100 mL). The ether washings and filtrate are combined in a 2-L separatory funnel. Additional ether (500 mL) is added, and the ether solution is washed with water (500 mL), 10% aqueous NaOH (2 × 100 mL), and water (2 × 100 mL) and dried (Na_2SO_4). The solvent was removed in vacuo to give a viscous oil, which was induced to crystallize by chilling in a dry ice bath. Recrystallization of the crude product from methanol gives 25 g (84%) of **4** [mp 77–78 °C (lit.[1,3] mp 79, 78–79 °C)] and a second crop of 2.7 g (mp 76–78 °C), giving a total yield of the nitrile of 27.7 g (93%).

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Registry No. 1, 1078-19-9; 2, 80859-07-0; 3, 6398-50-1; 4, 77029-01-7.

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(11) If it is desired to isolate the cyanohydrin trimethylsilyl ether intermediate, triethylamine may be added at this point to neutralize the BF_3, and the cyanohydrin derivative may be obtained by vacuum distillation, employing an air condenser to avoid solidification.
(12) Purification of the pyridine by distillation from *p*-toluenesulfonyl chloride is advisable to prevent tar formation.

A Convenient Synthesis of 4-Ethynylphthalic Anhydride via 2-Methyl-3-butyn-2-ol

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Arylacetylenes are important in organic syntheses, judging by the increasing number of publication appearing in recent years.[1–6] Important classical methods for their synthesis include halogenation/dehydrohalogenation of ketones,[7] or olefinic derivatives,[8] displacement of halogens with cupric acetylides,[9,10] and the use of Vilsmeier reagent ($DMF–POCl_3$) with acetophenones.[11,12] While the yields vary from fair to excellent, the procedures are often unreliable, they require isolation and/or purification of intermediates, and are either cumbersome, costly, or unsafe to perform on a preparative scale. Some catalytic method, therefore, is needed for the preparation of arylacetylenes in a cost-effective manner.

In 1975, three papers appeared in the literature describing the palladium-catalyzed reaction of aryl and vinyl halides with acetylenes.[13–15] The order of reactivity for halogens followed the sequence I > Br > Cl.[14–16] Attempts

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Table I. Effect of Triphenylphosphine[a]

catalyst	mmol	PPh_3, mmol	total P/Pd, molar ratio	time, h $T_{1/2}$	time, h total	conv,[d] %	selectivity,[b,d] %
$PdCl_2$	0.07	0	0		22	2	0
$PdCl_2(PPh_3)_2$	0.07	0	2	0.1	3	100[c]	85
$PdCl_2(PPh_3)_2$	0.07	0.95	15.6	0.2	1	100	98
$PdCl_2$	0.07	1.90	27.1	0.8	2.5	100	96
$PdCl_2(PPh_3)_2$	0.07	1.90	29.1	0.9	2.5	100	95
$PdCl_2(PPh_3)_2$	0.07	3.80	56.3	2.6	6	100	90
$PdCl_2(PPh_3)_2$	0.07	7.60	110.6	5	100	91	

[a] Conditions: 0.26 mmol of CuI, 0.1 mol of *m*-bromonitrobenzene, 0.12 mol of 2-methyl-3-butyn-2-ol in refluxing Et_3N (60 mL). [b] 2-Methyl-4-(*m*-nitrophenyl)-3-butyn-2-ol. [c] Frequently complete conversion is not attained without excess PPh_3. [d] mol of *m*-bromonitrobenzene reacted/mol of *m*-bromonitrobenzene charged × 100. [e] mol of 2-methyl-4-(*m*-nitrophenyl)-3-butyn-2-ol formed/mol of *m*-bromonitrobenzene reacted × 100.

to arylate acetylene resulted in a mixture of mono- and disubstituted acetylenes or disubstituted acetylene exclusively.[14,15] The catalyst turnover numbers (mol RX converted/mol catalyst) were too low to be commercially attractive; i.e., ~20,[14] ~75,[13] and ~200,[15] respectively. This work led us to develop a catalytic procedure for displacement of acetylenic hydrogen in 2-methyl-3-butyn-2-ol with *m*-bromonitrobenzene.[17-19] Most recently, an elegant variation of the method was reported in which aryl halides were reacted with ethynyltrimethylsilane in the presence of palladium(0) complexes to prepare arylacetylenes containing base-sensitive functional groups,[20] as well as to synthesize a number of aryl, biphenyl, and naphthyl acetylenes.[21] Because of the prohibitively high cost of the silyl acetylene, this route for all practical purposes will be limited to laboratory procedures.

In this communication, we employ 2-methyl-3-butyn-2-ol methodology in the synthesis of 4-ethynylphthalic acid and anhydride.

Results

In 1978, we reported an efficient palladium-catalyzed reaction of 2-methyl-3-butyn-2-ol with *m*-bromonitrobenzene to give 2-methyl-4-(*m*-nitrophenyl)-3-butyn-2-ol, which, after hydrogenation and/or cleavage with caustic, was used to prepare (*m*-nitrophenyl)- and (*m*-aminophenyl)acetylene in excellenet yield.[17-19] In the present study, we were interested in applying this methodology to the synthesis of 4-ethynylphthalic acid (anhydride) for use in polyimide resins. The procedure chosen is shown in Scheme I.

The reaction of dimethyl 4-bromophthalate with the methylbutynol gave a greater than 95% yield of the arylated methylbutynol (I), which without purification was then simultaneously cleaved and saponified with aqueous caustic to produce 4-ethynylphthalic acid (II) in 98% yield. The starting dimethyl 4-bromophthalate was prepared by the bromination of the disodium salt of phthalic acid in aqueous medium,[22] followed by conventional esterification with methanol. During bromination, no appreciable quantity of isomeric 3-bromophthalic acid was formed. This in itself is surprising as during the corresponding nitration of phthalic acid (or anhydride) a 50:50 mixture of 3-nitro- and 4-nitrophthalic acids was formed.[23,24]

Dehydration of II was carried out by heating in refluxing *o*-xylene while continuously removing water of the reaction to produce 4-ethynylphthalic anhydride (III), a new compound (82%).

Scheme I

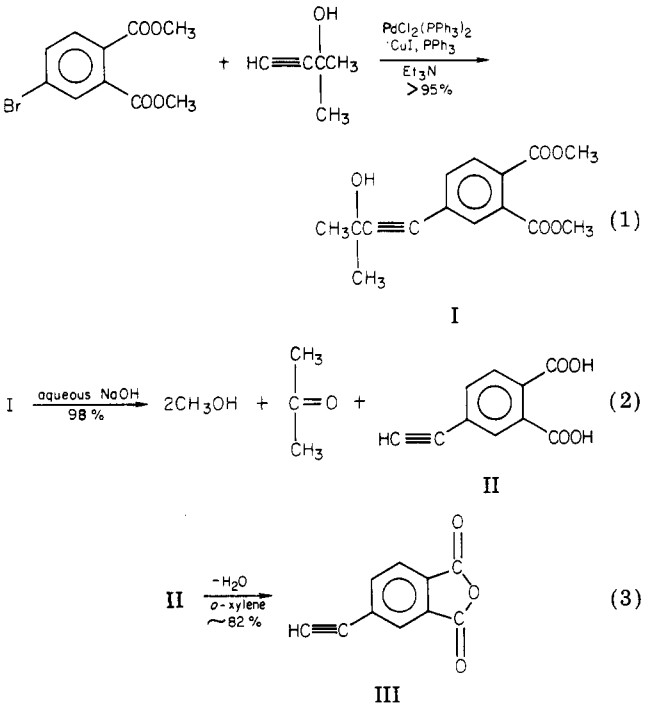

Table II. Effect of Cuprous Iodide[a]

mmol CuI	time, h $T_{1/2}$	time, h total	convn,[c] %	selectivity,[b,e] %
0	9.0	20.5	82	80
0.26	0.9	2.5	100	95
1.04	0.4	1.0	100	93

[a] Conditions: 0.12 mol of *m*-bromonitrobenzene, 0.07 mmol of $PdCl_2(PPh_3)_2$, 1.9 mmol of PPh_3 in refluxing Et_3N (60 mL). [b] 2-Methyl-4-(*m*-nitrophenyl)-3-butyn-2-ol (GLC); minor products included 2,7-dimethylocta-3,5-diyne-2,7-diol, *m,m'*-dibromoazobenzene, and azo derivative of 2-methyl-4-(*m*-nitrophenyl)-3-butyn-2-ol. [c] mol of *m*-bromonitrobenzene reacted/mol of *m*-bromonitrobenzene charged × 100. [d] mol of 2-methyl-4-(*m*-nitrophenyl)-3-butyn-2-ol formed/mol of *m*-bromonitrobenzene reacted × 100.

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Discussion

Catalyst screening investigation showed that dichlorobis(triphenylphosphine)palladium(II) appeared to have the greatest activity for coupling of *m*-bromonitrobenzene with 2-methyl-3-butyn-2-ol. Cuprous iodide and triphenylphosphine both greatly enhanced the rate of reaction (Tables I and II). In the absence of added triphenylphosphine, the reaction often could not be taken to complete conversion; if too much triphenylphosphine was added, the reaction slowed down considerably, requiring higher overall reaction time and a loss in selectivity. Consequently, all three catalyst components in our work were generally added to maintain a balance between reaction rate, catalyst activity, and selectivity. Under optimum Pd/P/Cu ratios, selectivities of over 95% to desired arylacetylene and catalyst turnover in excess of 5000 were routinely obtained. The reaction was carried out in an aliphatic amine solvent, which also served as a means of neutralizing the hydrogen bromide being produced. Solvents such as diethylamine, di-*n*-propylamine, diisopropylamine, and tri-*n*-butylamine proved to be effective, but not pyridine. Triethylamine was the solvent of choice because of reasonable rates at the reflux temperature and because it is still easily separated from the product. The use of a dimethylcarbinol protecting group was deemed necessary to prevent saturation of the triple bond during hydrogenation of the nitro group to an amine and to achieve monoarylation.

It turns out that the use of the methylbutynol has a wide applicability as a general method of synthesis of arylacetylenes. This general methodology was recently used by Ames et al.[25] to prepare ethynyl-*N*-heteroarenes. The arenes that reacted with the methylbutynol included bromo derivatives of quinoline, isoquinoline, cinnoline, and 3-bromo-4-phenoxycinnoline. The catalyst system employed by Ames above was that of Sonogashira et al.[15] with our cleavage conditions.[17-19] The reaction times were unusually long, and the catalyst turnover was low. The use of a higher boiling solvent such as triethylamine instead of diethylamine to enhance the reaction rate was not readily apparent. Dieck and Heck, for example, reported that only the more reactive halides (usually iodides) will add to alkylacetylenes in triethylamine. For most cases, the more basic secondary amines were generally required to apparently effect the removal of acetylenic hydrogen from the less reactive alkylacetylenes.[13] In a related area, Austin et al.[20] found the source and the purity of triethylamine to be extremely important in the reaction of ethynyltrimethylsilane with aromatic halides in the presence of palladium(0) complexes.

In the present study, we take advantage of the sensitivity of the ester linkages toward caustic by carrying out cleavage of the dimethylcarbinol group and saponification of ester I simultaneously in aqueous medium to prepare 4-ethynylphthalic acid (II) in high yield. Dehydration of II was carried out by refluxing in *o*-xylene, a technique earlier developed for nitrophthalic acids.[26]

Experimental Section

All reactions were carried out in standard laboratory glassware, except for esterification experiments, which were performed in a 1-L, 316 stainless steel, magnetically stirred autoclave (The Autoclave Engineers, Inc.). Chromatographic analyses were performed on a Hewlett-Packard 5701A or 5880A chromatograph. The columns employed included a 10-m, 2% OV-101, fused silica capillary column, programmed from 50 to 280 °C at 8°/min, or a 3 m × 0.05 cm column packed with 10% UC 980 on Chromosorb W, programmed from 80 to 200 °C at 30°/min. Phthalic acids were analyzed as their trimethylsilyl derivatives. The ^{1}H NMR spectra were recorded on a Varian T-60 spectrometer, usually in carbon tetrachloride or acetone-d_6. The chemical shifts are given in δ units (ppm) relative to tetramethylsilane (s = singlet, d = doublet, t = triplet, q = quartet). The IR spectra were recorded on a Perkin-Elmer Infracord or a Model 237B spectrometer.

Bromination of Phthalic Acid. To sodium hydroxide (48 g, 1.2 mol) dissolved in water (450 g) was added phthalic acid (100 g, 0.6 mol). When complete solution was obtained, bromine (100 g, 0.63 mol) was incrementally added, while stirring, over 1 h. The reaction mixture was heated to 90 °C and allowed to react under reflux for 6 h. After standing for 10 h, the white solids that crystallized out of solution were filtered, washed with cold water, and analyzed as monosodium 4-bromophthalic acid salt. The total product was dissolved in hot water, and the pH was adjusted to about 1.5 by addition of concentrated hydrochloric acid. The resulting solution was evaporated to dryness on a rotary evaporator and extracted with acetone to give 4-bromophthalic acid (133 g, 90%): NMR (acetone-d_6) δ 8.7 (br s, COOH, exchanges with D_2O, AB pattern, 8.02 (d, 1 H, $J \sim 8$ Hz, ring), 7.85 (d, 1 H, $J \sim 8$ Hz, ring), 7.8 (s, 1 H, ring); neutralization equivalent 122 (theoretical neutralization equivalent 122.5); GLC (trimethylsilyl derivative) 98.6% purity.

Esterification of 4-Bromophthalic Acid. A mixture of 4-bromophthalic acid (100 g, 0.4 mol) and *p*-toluenesulfonic acid (2 g, 0.01 mol) in methanol (450 mL) was heated in a 1-L autoclave for 2 h at 135 °C, developing a final pressure of 180 psi. The product was concentrated in a rotary evaporator, taken up in ether, and washed with water. When analysis by GLC showed some unconverted phthalic acid derivative present, the ether solution was extracted with sodium bicarbonate solution, which left behind the crude dimethyl ester of 4-bromophthalic acid (101 g, 90.7%). Distillation using a 6-in. Vigreaux column gave 83.5 g of product, bp 118–121 °C (1 mmHg). On standing, the ester solidified to a pale yellow product, mp 33–35 °C; NMR (CCl_4) δ 3.8 (s, 6 H, CH_3), 7.55–7.85 (m, 3 H, ring).

Displacement and Cleavage Reaction of 2-Methyl-3-butyn-2-ol with Dimethyl 4-Bromophthalate. A mixture of dimethyl 4-bromophthalate (83 g, 0.3 mol) and 2-methyl-3-butyn-2-ol (30 g, 0.36 mol) was reacted in triethylamine (300 mL) under reflux in the presence of $Pd(Ph_3P)_2Cl_2$ (0.1 g), Cu_2I_2 (0.1 g), and Ph_3P (0.2 g) for 4 h until the displacement reaction was complete. The reaction mixture was cooled, filtered, and stripped of solvent. After the residue was washed with water, the crude product (79.9 g, 95%) was transferred to a flask containing water (600 g) and sodium hydroxide (26 g, 0.65 mol). The cleavage reaction was performed by heating at reflux until the Dean–Stark trap contained no methanol and acetone (18 h). The solution was filtered hot over Celite, and the filtrate was acidified with hydrochloric acid and then taken to dryness in a rotary evaporator. After extraction with acetone, 4-ethynylphthalic acid (53.8 g, 98%; neutralization equivalent 94.6) was isolated; GLC (trimethylsilyl derivative) one major peak (99.3%).

Dehydration of 4-Ethynylphthalic Acid. The crude product prepared above was charged into a flask containing 500 mL of *o*-xylene and 5 g of charcoal, and the reaction mixture was refluxed for 6 h until no more water was being collected in the Dean–Stark trap. The reaction mixture was filtered hot over Celite and concentrated in a rotary evaporator. Filtration afforded 40 g (82%) of a light yellow solid: mp 120–122 °C. NMR δ 4.05 (s, 1 H, C≡CH), 8.0 (s, 3 H, ring); neutralization equivalent 85; IR (Nujol) 3400, (C≡CH), 2160 (C≡C), 1876, 1795 cm^{-1} (anhydride). Anal. Calcd for $C_{10}H_4O_3$: C, 69.77; H, 2.34. Found: C, 70.01; H, 2.31.

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Registry No. I, 87655-09-2; II, 87639-56-3; III, 73819-76-8; $PdCl_2$, 7647-10-1; $PdCl_2(PPh_3)_2$, 13965-03-2; 4-bromophthalic acid, 6968-28-1; dimethyl 4-bromophthalate, 87639-57-4; 2-methyl-3-butyn-2-ol, 115-19-5; cuprous iodide, 7681-65-4; triphenylphosphine, 603-35-0.

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