Table I. Alumina-Assisted Aryl Cyanation[a]

function of alumina	reactant	product	temp, °C	time, h	yield, %[b]
cocatalyst	chlorobenzene	benzonitrile	110	16	0.2 (0)
support	chlorobenzene	benzonitrile	80	16	0
cocatalyst	3-(chloromethyl)benzoate	3-(cyanomethyl)benzoate	100	20	5 (1)
cocatalyst	bromobenzene	benzonitrile	80	24	98 (20)
cocatalyst[c]	bromobenzene	benzonitrile	80	24	46
cocatalyst[d]	bromobenzene	benzonitrile	80	22	11
support	bromobenzene	benzonitrile	80	19	3
support[e]	bromobenzene	benzonitrile	80	19	99
catalyst	1-bromonaphthalene	1-cyanonaphthalene	100	40	90 (13)
support	iodobenzene	benzonitrile	80	2	98 (5)
support	iodobenzene	benzonitrile	80	2	75[f]
cocatalyst	iodobenzene	benzonitrile	80	2	20
cocatalyst[g]	iodobenzene	benzonitrile	80	2	16
support	3-iodotoluene	3-cyanotoluene	80	3	95 (2)
support	3-iodotoluene	3-cyanotoluene	80	3	62[f]

[a] Unless noted otherwise, procedures used were similar to those described in the Experimental Section. [b] Yields were determined by GLC using internal standard techniques. Material balance was >95% in all cases. Numbers in parentheses refer to control experiments carried out in the absence of alumina. [c] Alumina used was 0.1 g. [d] KCN used. [e] A 20 mol % of 1 was used. [f] Isolated yield. [g] Alumina used was 0.5 g.

marized in Table I, it is recommended that alumina be used as a support for cyanation of aryl iodides and as a co-catalyst for aryl bromides.

The use of bis(triphenylphosphine)phenylpalladium(II) iodide as catalyst or potassium cyanide as the source of cyanide ion failed to improve yields. Aryl chlorides gave poor conversions under all conditions employed. Experimental details are described below.

Experimental Section

General Methods. Unless stated otherwise, all reagents and chemicals were obtained commercially and used without purification. Chlorobenzene, bromobenzene, iodobenzene, 1-bromonaphthalene, and 3-iodotoluene were purchased from Aldrich Chemical Co. The 3-chloromethyl benzoate was prepared from 3-chlorobenzoic acid (Aldrich Chemical Co.) by esterification with CH_3OH–concentrated H_2SO_4. Tetrakis(triphenylphosphine)palladium(0) was prepared using established procedures.[9] The palladium complex was handled in air but stored under nitrogen. Toluene was dried by distillation from sodium and benzophenone under a nitrogen atmosphere. Neutral alumina was purchased from Bio-Rad Laboratories (AG-7, 100–200 mesh) and used as obtained. All ^1H, ^{13}C, and IR spectra were recorded using Varian A-60, JOEL FX 60 QD, and Beckman Acculab 7 spectrometers, respectively. Product mixtures were analyzed by GLC on a Hewlett-Packard Model 5830 A flame ionization instrument using internal standards. Culture tubes were used as reaction vessels (25 × 150 mm Corning No. 9826 tubes) and were equipped with a No-Air stopper and a Teflon-coated stirring bar.

Impregnation of NaCN on Alumina. A $NaCN/Al_2O_3$ reagent was prepared using 5 mmol of NaCN per gram of alumina based on procedures similar to those previously described.[3,10]

General Procedure for Small-Scale Reactions. Procedures similar to that described for the conversion of bromobenzene to benzonitrile were followed for all of the small-scale reactions described in Table I. Into an oven-dried 50-mL culture tube equipped with a stirring bar and a No-Air stopper was placed 0.045 g (0.04 mmol) of tetrakis(triphenylphosphine)palladium(0) along with 0.1 g (2.0 mmol) of sodium cyanide crushed together with 0.05 g of alumina (mortar and pestle). The tube was degassed under a stream of nitrogen and 4 mL of a degassed solution of bromobenzene in toluene (0.1 M, 0.4 mmol) containing 0.4 mmol of tridecane (internal standard) was added via syringe. The mixture was heated to 80 °C for 24 h with vigorous stirring. Analysis of the product mixture (GLC) indicated complete conversion to the nitrile. Mass balance was 100%.

For reactions employing impregnated cyanide, 0.5 g of the $NaCN/Al_2O_3$ reagent was used.

Conversion of 3-Iodotoluene to 3-Cyanotoluene. A mixture of 30 g of $NaCN/Al_2O_3$, 5.5 g (25.0 mmol) of 3-iodotoluene, 2.9 g (2.5 mmol) of tetrakis(triphenylphosphene)palladium(0), and 100 mL of toluene was stirred for 3 h at 80 °C in a 250-mL round-bottom flask under a nitrogen atmosphere. Analysis of the product mixture by GLC indicated complete conversion to the nitrile. The mixture was filtered and the alumina was washed with ether. Solvent was then removed under reduced pressure yielding a yellow oil plus a precipitate. Petroleum ether was added to triturate the remaining palladium residue, and upon filtration and distillation 1.81 g (62%) of 3-cyanotoluene [bp 79–81 °C (6 mm)] was obtained having an IR and ^{13}C NMR spectrum identical with an authentic sample.

Registry No. Chlorobenzene, 108-90-7; 3-(chloromethyl)benzoate, 31719-77-4; bromobenzene, 108-86-1; 1-bromonaphthalene, 90-11-9; iodobenzene, 591-50-4; 3-iodotoluene, 625-95-6; benzonitrile, 100-47-0; 3-(cyanomethyl)benzoate, 5689-33-8; 1-cyanonaphthalene, 86-53-3; 3-cyanotoluene, 620-22-4; alumina, 1344-28-1; sodium cyanide, 143-33-9.

(9) Coulson, D. R. *Inorg. Synth.* **1972**, *13*, 121.

(10) It has been found that for cyanide ion displacement on 1-bromooctane, a loading of 5 mmol of NaCN per gram of alumina produces the maximum amount of reactive cyanide: Quici, S., Regen, S. L., unpublished results. Interestingly, if one assumes a closely packed array of sodium and cyanide ions on the alumina surface (surface area equals 240 $m^2 g^{-1}$), this amount of salt corresponds approximately to that required for monolayer coverage.

Selective O-Demethylation of Catechol Ethers. Comparison of Boron Tribromide and Iodotrimethylsilane

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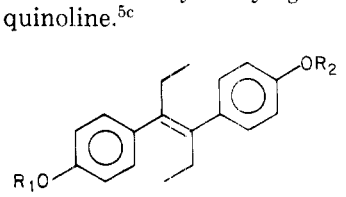
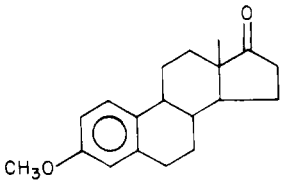
A variety of reagents are available for demethylation of mono- and polymethyl aryl ethers.[1a-e] We sought a demethylating agent which would provide the maximum yield of **1b** rather than the 1:3:2 ratio of **1a**, **1b**, and **1c** obtained with 1.1 equiv of BBr_3 or heating in the presence

(1) (a) C. A. Buehler and D. E. Pearson, "Survey of Organic Synthesis", Vol. 1, Wiley, New York, 1970, p 253; (b) *ibid.*, Vol. 2, 1977, p 275; (c) I. T. Harrison and S. Harrison, "Compendium of Organic Synthetic Methods", Vol. 1, Wiley, New York, 1971, p 92; (d) *ibid.*, Vol. 2, 1974, p 34; (e) *ibid.*, Vol. 3, 1977, p 56; (f) A. L. Wilds and W. B. Mc Cormack, *J. Am. Chem. Soc.*, **70**, 4127 (1948).

0022-3263/79/1944-4444$01.00/0

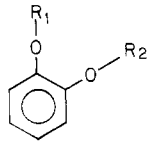
of methylmagnesium iodide.[1f] Recent studies[2] suggested iodotrimethylsilane (Me_3SiI, trimethylsilyl iodide, would serve). Application of Jung's ether cleavage procedure[2b] to **1a** gave, through HPLC studies, **1a**/**1b**/**1c** (2:3:1) with essentially complete accountability of materials.[3] Application of Me_3SiI to **2** was also disappointing since the yield of estrone, in duplicated runs, was only 70% and extra peaks were observed in the HPLC. These extra products may result, in part, from iodination α to the carbonyl group.[4] In comparison BBr_3[5a] or pyridine hydrochloride[5b] react faster. We found the O-demethylation of **2** essentially quantitative with BBr_3 and to be a clean reaction. The reactivity of Me_3SiI has been reported to be enhanced by carrying out O-demethylation in hot quinoline.[5c]





1a, $R_1 = R_2 = CH_3$
b, $R_1 = H$; $R_2 = CH_3$
c, $R_1 = R_2 = H$

2



3a, $R_1 = R_2 = CH_3$
b, $R_1 = H$; $R_2 = CH_3$
c, $R_1 = R_2 = H$

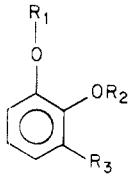
Our demethylation experiences with BBr_3 and Me_3SiI prompted model compound studies of the cleavage of simple methyl aryl ethers with these reagents. The demethylation time for all of the ethers studied is longer with Me_3SiI than with BBr_3. Me_3SiI is less reactive in most cases than BBr_3, i.e., treatment of 2-methoxyphenol (**3b**) with 1.1 equiv of BBr_3 caused complete conversion to catechol (**3c**), whereas with 1.1 equiv of Me_3SiI 33% of **3b** remained unreacted.

We were also curious about the effectiveness of Me_3SiI in attacking hindered methoxyl groups and learned that it is an excellent reagent for regiospecific[6] mono O-demethylation of the apparently less accessible methoxyl group of **4a** and **4e** (Table I). With 1.1 equiv of Me_3SiI there was 94% conversion of **4a** to **4c**. Boron tribromide is less selective in this case, with 40% unreacted **4a**. However, cleavage of the seemingly less hindered methoxyl group does not take place. Changing the alkyl group of **4a** to the bulkier isopropyl in **4e** does not materially alter the result. The regiospecificity observed in the demethylation of **4a** and **4e** with both reagents is no longer observed when the cleavage reaction is applied to **5a** and related diethers. An approximately statistical product distribution resulted. The data for cleavage of **5a** are given in Table I. The product ratios for **4a** and **4e** (Table I) indicate BBr_3 also is a regiospecific demethylating reagent but it is considerably less effective in that starting material was recovered and a catechol was formed.

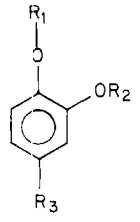
Table I. Product Distribution in the Demethylation of Catechol Methyl Ethers

starting material	Me_3SiI, equiv	BBr_3, equiv	product ratios[a]			
3a	1.1		21	64	15	
3a		1.1	18	60	22	
3a	3.3		0	0	100	
3a		3.3	0	0	100	
3b	1.1		0	33	67	
3b		1.1	0	0	100	
			4a	**4b**	**4c**	**4d**
4a	1.1		6	0	94	0
4a		1.1	40	0	42	18
4a	3.3		0	0	30	70
4a		3.3	0	0	0	100
			4e	**4f**	**4g**	**4h**
4e	1.1		0	0	96	4
4e		1.1	30	0	24	46
4e	3.3		0	0	47	53
4e		3.3	0	0	0	100
			5a	**5b**	**5c**	**5d**
5a	1.1		28	26	33	13
5a		1.1	31	21	26	22
5a	3.3		0	0	0	100
5a		3.3	0	0	0	100

[a] Determined through use of LC.[7]



4a, $R_1 = R_2 = R_3 = CH_3$
b, $R_1 = H$; $R_2 = R_3 = CH_3$
c, $R_1 = R_3 = CH_3$; $R_2 = H$
d, $R_1 = R_2 = H$; $R_3 = CH_3$
e, $R_1 = R_2 = CH_3$; $R_3 = CH(CH_3)_2$
f, $R_1 = H$; $R_2 = CH_3$; $R_3 = CH(CH_3)_2$
g, $R_1 = CH_3$; $R_2 = H$; $R_3 = CH(CH_3)_2$
h, $R_1 = R_2 = H$; $R_3 = CH(CH_3)_2$



5a, $R_1 = R_2 = R_3 = CH_3$
b, $R_1 = H$; $R_2 = R_3 = CH_3$
c, $R_1 = R_3 = CH_3$; $R_2 = H$
d, $R_1 = R_2 = H$; $R_3 = CH_3$

A selective O-demethylation of vicinal polymethoxylated alkaloids in hot mineral acid has been reported.[5d] The similarity in the O-demethylation regiospecificity[6] in our

(2) (a) M. E. Jung, M. A. Mazurek, and R. M. Lim, *Synthesis*, 588 (1978); (b) M. E. Jung and M. A. Lyster, *J. Org. Chem.*, **42**, 3761 (1977); (c) M. G. Voronkov, K. I. Dubinskaya, S. F. Pavlov, and V. G. Gorokhova. *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2355 (1975); *Chem. Abstr.*, **86**, 121414x (1977); (d) T.-L. Ho and G. A. Olah, *Angew. Chem.*, **88**, 847 (1976).

(3) The BBr_3 and Me_3SiI cleavage products of **1a** were identified and the ratios were determined using authentic **1a**, **1b**, and **1c** as standards for HPLC analysis using a C_{18} μ-Bondapack column and acetonitrile/water (4:1). It is of interest that both BBr_3 and Me_3SiI cause formation of side products, presumably double-bond isomerization, which appear as shoulders on the peaks representing **1a** and **1c**, respectively.

(4) M. J. Green, Schering Corp., U.S. Patent 3 980 680, Sept. 14, 1976.

(5) (a) K. Ponsold and H. Wagner, *Z. Chem.*, **17**, 61 (1977); *Chem. Abstr.*, **87**, 6248e (1977); (b) J. C. Sheehan, W. F. Erman, and P. A. Cruickshank, *J. Am. Chem. Soc.*, **79**, 147 (1957); (c) J. Minamikawa and A. Brossi, *Tetrahedron Lett.*, 3085 (1978); (d) S. Teitel and A. Brossi, *Heterocycles*, **1**, 73 (1973). We thank a referee for calling the latter two references to our attention.

(6) A. Hassner, *J. Org. Chem.*, **33**, 2684 (1968).

Table II. ^{1}H NMR Spectral Data and Physical Properties of Phenols and Methyl Ethers[a]

compd	chemical shifts[b] ArH	ArOH	$ArOCH_3$	$ArCH(CH_3)_3$	$ArCH_3$	$ArCH(CH_3)_2$	bp,[a] mp,[c] °C
3a	6.78		3.70				bp 206 (lit.[d] 207)
4a	6.58-6.96		3.74, 3.70		2.22		bp 45-47 (0.3 mm) [lit.[e] 200-202 (76 mm)]
4c	6.43-6.85	6.14	3.60		2.23		mp 39-41 (lit.[f] 42)
4e	6.52-7.10		3.78, 3.73	3.16-3.54		1.19	bp 56-57 (0.33 mm) [lit.[g] 119-121 (24 mm)]
4f	6.54-7.08	5.96	3.74	3.10-3.44		1.20	bp 61-63 (0.25 mm)
4g	6.50-6.90	5.84	3.70	3.10-3.68		1.23	bp 53-54 (0.3 mm) [lit.[h] 122 (25 mm)]
5a	6.60		3.65		2.20		bp 220-222 (lit.[d] 219-222)
5b	6.50-6.88	5.92	3.66		2.21		bp 38-39 (0.2 mm) (lit.[i] 219-222)
5c	6.48-6.80	5.75	3.76		2.22		mp 34-35 (lit.[j] 35-36)
5d	6.48-6.84	5.42			2.20		mp 59-63 (lit.[k] 65)

[a] At 100 MHz in $CDCl_3$. [b] Chemical shifts in δ units. [c] Temperatures are not corrected. [d] Reference 8a. [e] Reference 8b. [f] Reference 9. [g] Reference 10. [h] Reference 11. [i] Reference 12. [j] Reference 13. [k] Reference 14.

examples and those of the earlier report[5d] is striking.

The ratios of products and starting material were determined using HPLC[7] and ^{1}H NMR studies. In each case, standard samples of cleavage products were prepared (procedures I, II, and III) for use in unequivocal product identification and ratio determination.

The physical properties and the ^{1}H NMR spectral data used in identifying compounds studied are presented in Table II.

Experimental Section

The compounds used in the ether cleavage studies were either purchased or prepared by one of the following three procedures. Their purity and identity were established through NMR, GC, and LC studies.

Procedure I—Diethers through Exhaustive Methylation of the Corresponding Catechol.[8a] Dimethyl sulfate and 10% sodium hydroxide were used to prepare **3a** and **5a** from **3c** and **5d** in 82 and 93% yields, respectively.

Procedure II—Limited Methylation of the Corresponding Catechol. Treatment of catechols **4d** and **4h** with 1.1 equiv of dimethyl sulfate in the presence of 2.5 equiv of 10% NaOH afforded monophenols **4b**, **4f**, and **4g** as products soluble in 2% NaOH, whereas **4c** required 10% NaOH for extraction from ether. This preferential solubility procedure also afforded the diethers **4a** and **4e** as neutral products. The yields of **4a**, **4c**, **4e**, and **4g** were 28, 17, 30, and 11%, respectively.

2-Methoxy-3-(1-methylethyl)phenol (4f) (procedure II, 3%): bp 61–63 °C (0.25 mm); IR (thin film) 3400, 2950, 1460, 1270, 1195, 995, 955, 783, 733 cm^{-1}; MS (70 eV) *m/z* (rel intensity) M^+ 166 (53), 153 (16), 152 (100), 137 (8), 95 (9), 91 (19). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.09; H, 8.54.

Both **4f** and **4g** are soluble in 2% NaOH, but separation was achieved with 0.5% NaOH, the latter being insoluble in alkali at this concentration.

Procedure III—Hydrogenolysis of Aromatic Aldehydes to Substituted Toluenes.[15b] 3-Hydroxy-4-methoxybenzaldehyde (isovanillin), 4-hydroxy-3-methoxybenzaldehyde (vanillin), and 3,4-dihydroxybenzaldehyde were readily hydrogenolyzed to **5b**, **5c**, and **5d** in the presence of 5% Pd/C (10:1, substrate/catalyst) in acetic acid at 55 °C and 50 psig in 86, 76, and 72% yields, respectively.

Iodotrimethylsilane Cleavage: General Procedure.[3b] To a 10-mL flask fitted with septum and magnetic stirring bar were added reactant (2 mmol) and 1 mL of chloroform. An inert atmosphere was established and maintained. Iodotrimethylsilane (0.32 mL, 2.2 mmol or 0.96 mL, 6.6 mmol) was added through the septum with a 1-mL syringe. This mixture was magnetically stirred at room temperature for 48 h, diluted with 10 mL of methanol, 20 mL of salt water was added, and this was extracted (2×) with 20 mL of ether. The extract was washed with sodium bisulfite and salt water, dried (Na_2SO_4), and concentrated. This procedure was used for the cleavage of **1a**, **3a**, **3b**, **4a**, **4e**, and **5a**. The product distribution and yields are listed in Table I.

Boron Tribromide Cleavage: General Procedure.[16] To a 10-mL flask were added reactant (3.6 mmol) and 5 mL of dichloromethane. An inert atmosphere was established and maintained. This mixture was cooled in a dry ice/2-propanol bath and boron tribromide (0.13 mL, 1.32 mmol or 0.38 mL, 4.0 mmol) was added through a septum with use of a syringe. The cold bath was removed and the mixture was stirred for 30 min, poured into ice water, stirred for 30 min, saturated with salt, and extracted with dichloromethane. The extract was dried ($MgSO_4$) and concentrated. This procedure was used for the cleavage of **1a**, **3a**, **3b**, **4a**, **4e**, and **5a**. The yields and product distribution are shown in Table I.

Acknowledgment. We thank the Contraceptive Development Branch, Center for Population Research, National Institute of Child Health and Human Development, NIH, for support in the early part of the work through contract no. N01-HD-4-2846. We also thank the National Science Foundation for grants GP 17641 and CHE 76-5571, which enabled purchase of the OSU NMR instrument and FT accessory. We thank Dr. T. S. Chou, Eli Lilly and Company, for a generous sample of diethylstilbestrol used in this study.

Registry No. **1a**, 7773-34-4; **1b**, 7773-60-6; **1c**, 6898-97-1; **3a**, 91-16-7; **3b**, 90-05-1; **3c**, 120-80-9; **4a**, 4463-33-6; **4b**, 18102-31-3; **4c**, 2896-67-5; **4d**, 488-17-5; **4e**, 71720-27-9; **4f**, 71720-28-0; **4g**, 21022-74-2; **4h**, 2138-48-9; **5a**, 494-99-5; **5b**, 93-51-6; **5c**, 1195-09-1; **5d**, 452-86-8; dimethyl sulfate, 77-78-1; 3-hydroxy-4-methoxybenzaldehyde, 621-59-0; 4-hydroxy-3-methoxybenzaldehyde, 121-33-5; 3,4-dihydroxybenzaldehyde, 139-85-5; iodotrimethylsilane, 16029-98-4; boron tribromide, 10294-33-4.

(7) (a) High-pressure liquid chromatography. (b) Analytical HPLC separations were performed on a Waters Associates Model 6000A system using both index of refraction and UV absorbance detectors with a Waters 3.9 mm i.d. × 30-cm μ-Bondapack C_{18} reverse phase column.

(8) (a) M. Windholz, Ed., "The Merck Index", 9th Ed., Merck and Company, Inc., Rahway, N.J., 1976, entry 9610, p 9609; (b) A. P. Kurtz and C. R. Dawson, *J. Med. Chem.*, **14**, 729 (1971).

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(12) R. Schwarz and J. Hering, "Organic Syntheses", Collect. Vol. 4, Wiley, New York, 1963, p 203.

(13) R. F. Graesser-Thomas, J. M. Gulland, and R. Robinson, *J. Chem. Soc.*, 1971 (1926).

(14) L. Anschutz and F. Wenger, *Justus Liebigs Ann. Chem.*, **482**, 25 (1930).

(15) (a) G. S. Hiers and F. D. Hager, "Organic Syntheses", Collect. Vol. 1, Wiley, New York, 1941, p 58; (b) J. W. Burnham and E. J. Eisenbraun, *J. Org. Chem.*, **36**, 737 (1971).

(16) J. F. W. McOmie, M. L. Watts, and D. E. West, *Tetrahedron*, **24**, 2289 (1968).