

propargyl alcohol **42b** (255 mg, 1.17 mmol), 4-(*N,N*-dimethylamino)pyridine (171 mg, 1.40 mmol), ether (10 mL), and chlorodiphenylphosphine (252 μ L, 1.40 mmol) yielded after workup and purification 315 mg (70%) of allenyl phosphine oxide **43b** as a clear viscous oil which was homogeneous by HPLC (10% isopropyl alcohol/hexanes; 4 mL/min; Rainin Dynamax 60A) but contaminated by minor impurities which were apparent in the ^1H NMR and mass spectra. This material was of adequate purity for conversion (including kinetic studies) to the Diels-Alder product as described separately.

(*8R^*,10S^**)-2-(Diphenylphosphinoyl)tricyclo[8.3.0.0^{3,8}]-trideca-1,3-diene (**44a**). A solution of allenylphosphine oxide **43a** (1.11 g, 2.96 mmol) in 20 mL of benzene (freshly distilled from Na/benzophenone) was placed in an ampoule with a screw-cap seal. The sealed, argon-flushed ampoule was placed in an oil bath and heated at 120 $^\circ\text{C}$ for 17 h. After cooling the ampoule, the product was rinsed into a round-bottom flask with ether, and then the ether solution was concentrated. The resulting residue was chromatographed (silica gel, 5 \times 16 cm, 1:1 ethyl acetate/hexanes) to afford after vacuum drying, 987 mg (89%) of phosphine oxide **44a** as a white solid (mp 196-198 $^\circ\text{C}$) which was spectrally homogeneous.

For the kinetic studies, a solution of allenylphosphine oxide **43a** (20 mg, 0.05 mmol) in C_6D_6 (1 mL) was placed in a 7-in. 5-mm NMR tube and put through three freeze-thaw cycles under vacuum. The tube was then sealed under vacuum and placed in a thermostated constant temperature bath set at 98.5 $^\circ\text{C}$. At regular intervals the tube was removed from the bath and cooled and the ^1H NMR spectrum was taken. The spectra typically revealed the presence of both allene **43a** and cyclized product **44a**. The rate of reaction was monitored by following the disappearance

of the δ 6.6 signal (H_2) of allene **43a** versus the appearance of the δ 5.8 signal (H_4) of cyclized product **44a**.

(*8R^*,10S^**)-2-(Diphenylphosphinoyl)-5,5-dimethyltricyclo[8.3.0.0^{3,8}]-trideca-1,3-diene (**44b**). As for the preparation of **44a**, allenylphosphine oxide **43b** (287 mg, 0.71 mmol) in dry benzene (50 mL) was heated at 125 $^\circ\text{C}$ for 12 h. Workup and purification as above afforded 162 mg (56%) of phosphine oxide **44b** as a white solid, which was spectrally homogeneous. Recrystallization with ethyl acetate gave white needles (mp 145-147 $^\circ\text{C}$).

For the kinetic studies, a solution of allenylphosphine oxide **43b** (19 mg, 0.05 mmol) in CDCl_3 (1 mL; freshly passed through a short column of alumina), prepared as described above for the solution of **43a**, was placed in a thermostated constant temperature bath set at 98.5 $^\circ\text{C}$. As above, the rate of reaction was monitored by following the disappearance of the δ 6.0 signal (H_2) of allene **43b** versus the appearance of the δ 5.02 signal (H_4) of cyclized product **44b**. An identical procedure was followed to measure the irreversible first-order rate constant in C_6D_6 . In this case the disappearance of the δ 6.6 signal (H_2) of allene **43b** was monitored versus the disappearance of the δ 5.4 signal (H_4) of cyclized product **44b**.

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Supplementary Material Available: Spectral data for all new compounds and general experimental details (59 pages). Ordering information is given on any current masthead page.

An Efficient and Selective Method for the Preparation of Iodophenols

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Direct iodination of a wide range of phenols may be achieved with unprecedented selectivity in aqueous alcohol solvents by the action of a reagent prepared in situ from sodium hypochlorite and sodium iodide. Para-substituted phenols (or ortho-substituted, when the para-position is already occupied) are obtained in fair to excellent yields by simple isolation techniques. The extent of iodination is easily controlled by stoichiometry. The technique is also useful with some anilines.

In recent years, iodophenols have assumed increasing importance in chemistry and pharmacology. This renewed interest can be ascribed to two developments. First, the weak carbon-iodine bond facilitates the oxidative addition of aryl iodides to low-valent transition metals (for instance, Pd and Rh). The chemistry of the resulting Ar-M-I intermediates has been a popular and fruitful area of investigation,¹ leading to valuable new syntheses of arene-carboxylic acids and esters, aryl olefins, and other useful classes of compounds. While aryl bromides (and occasionally aryl chlorides) often can also be used in these reactions, there are many published cases in which use of the reactive aryl iodides has special value,^{2a} and this is

particularly true in the case of aryl halides substituted by electron-donating groups such as hydroxyl.^{2b}

Secondly, polyiodinated phenols have been used as imaging agents in noninvasive medical diagnostic techniques.³ The ability to iodinate selectively and efficiently will become increasingly important as more specific imaging agents are developed.⁴ In addition, the ability to gain rapid access to specific radioiodinated species is of importance to their use as therapeutic and diagnostic agents.⁵

Despite the importance of iodophenols, and the long history of electrophilic aromatic halogenation, there are

(1) For example, ArPd: Stille, J. K.; Wong, P. K. *J. Org. Chem.* 1975, 40, 532. Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* 1988, 53, 918. Takagi, K.; Iwachido, T.; Hayama, N. *Chem. Lett.* 1987, 839. Heck, R. F. *Acc. Chem. Res.* 1979, 12, 146. Steinmetz, G. R.; Edgar, K. J.; Falling, S. N. U.S. Patent 4,885,384. ArNi: Takagi, K.; Hayama, N.; Okamoto, T. *Chem. Lett.* 1978, 191. Bozell, J. J.; Vogt, C. E. *J. Am. Chem. Soc.* 1988, 110, 2655. Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* 1977, 42, 1823. ArCu: Osuka, A.; Kobayashi, T.; Suzuki, H. *Synthesis* 1983, 67, 69.

(2) (a) Solberg, J.; Undheim, K. *Acta Chem. Scand.* 1987, 41B, 712. Wada, A.; Yasuda, H.; Kanatomo, S. *Synthesis* 1988, 771. Bozell, J. J.; Vogt, C. E. *J. Am. Chem. Soc.* 1988, 110, 2655. (b) Ziegler, C. B.; Heck, R. F. *J. Org. Chem.* 1978, 43, 2941. Garst, M. E.; McBride, B. J. *J. Org. Chem.* 1989, 54, 249.

(3) Papa, D.; Schwenk, E.; Breiger, H.; Peterson, V. *J. Am. Chem. Soc.* 1950, 72, 2619.

(4) Weichert, J. P.; Groziak, M. P.; Longino, M. A.; Schwendner, S. W.; Counsell, R. E. *J. Med. Chem.* 1986, 29, 2457.

(5) Seevers, R. H.; Counsell, R. E. *Chem. Rev.* 1982, 82, 575. Kabalka, G. W.; Varma, R. S.; Gai, Y.-Z.; Baldwin, R. M. *Tetrahedron Lett.* 1986, 27, 3843.

Table I. Scope of the Iodination Method

	substrate (1)	product (2)	% yield ^a		substrate (1)	product (2)	% yield ^a
a			80	a		2d	74 ^b
b			80	a			90
c			74			2j	
d			78	k			87 ^b
e			84 ^c	l			48 ^b
f			72	m			75 ^b
g			75 ^b	n			84
h			66	o			68
i			86	p			11 ^b

^a With the exceptions noted, yields were determined by capillary VPC of the crude product vs naphthalene internal standard. ^b Isolated, pure product. ^c By capillary VPC of the crude product, area percent.

few good methods in the literature for iodination of phenols.⁶⁻¹⁶ With most aromatic substrates, a more powerful iodinating species than I₂ is required. This is usually accomplished by adding an oxidizing reagent in addition to the iodine source. Such methods are not necessary with phenols. Lack of chemoselectivity and/or positional selectivity are more typical problems with the highly reactive phenols. Most phenol iodination methods in the literature are selective only when another ring substituent is present, serving as an additional control element. Clean monoiodination of phenol itself in the para position has been an elusive goal.

Results and Discussion

We have discovered a highly selective method for iodination of phenols, affording para substitution where

possible, in fair to excellent yields.¹⁷ Our method is based on the in situ oxidation of sodium iodide using common bleach, with aqueous alcohols as solvents. Simply by adding aqueous sodium hypochlorite to an alcoholic solution of the phenol and sodium iodide, rapid iodination is achieved at ice bath temperature. The products can be separated by acidification of the reaction mixture. In some instances, the products crystallize and may be isolated by filtration. In other cases extractive workup followed by flash column chromatography easily separates the pure products from small amounts of other isomers and/or polyiodinated products.

The method has been applied successfully to a variety of phenols (Table I). In general, we find that electron-withdrawing substituents such as halogen, carboxyl, and nitro have no deleterious effects on the reaction. Mildly electron donating groups such as alkyl are also well tolerated. In contrast, strongly electron donating substituents such as methoxyl do cause problems, giving a mixture of substitution and oxidation products.

It is a simple matter to control the extent of iodination by stoichiometry. Adding 2 or 3 equiv each of NaI and NaOCl to phenol affords 2,4-diiodophenol or 2,4,6-triiodophenol, respectively, in good to excellent yields. We also find that the reaction can be applied with some success to electron-poor heterocycles. Moderate yields are obtained using either 2-hydroxypyridine or 3-hydroxypyridine as starting material. Even aniline is a useful substrate, affording 4-iodoaniline in moderate yield. It

(6) (a) An excellent review of methods for iodination of aromatic compounds has recently appeared: Merkushev, E. B.; *Synthesis* **1988**, 923. (b) ICl: Block, P.; Powell, G. *J. Am. Chem. Soc.* **1942**, *64*, 1070. Papesch, V.; Burtner, R. R. *J. Am. Chem. Soc.* **1936**, *58*, 1314.

(7) I₂ in P(OCH₃)₃: Pearson, D. E.; Frazer, M. G.; Frazer, V. S.; Washburn, L. C. *Synthesis* **1976**, 621.

(8) I₂/I₃⁻: (a) Suter, C. M.; Shuetz, R. D. *J. Org. Chem.* **1951**, *16*, 1117. (b) Potts, K. T. *J. Chem. Soc.* **1953**, 3711.

(9) I₂/OH⁻: Caldwell, W. T.; Tyson, F. T.; Lauer, L. *J. Am. Chem. Soc.* **1944**, *66*, 1479.

(10) Diiododimethylhydantoin: Orazi, O. O.; Corral, R. A.; Bertorello, H. E. *J. Org. Chem.* **1965**, *30*, 1101.

(11) I₂/morpholine: Giza, C. A.; Hinman, R. L. *J. Org. Chem.* **1964**, *29*, 1453.

(12) NaI/Chloramine T: Komatani, T.; Watt, D. S.; Ji, T. *Tetrahedron Lett.* **1985**, *26*, 2043. Schweiz, P. *Chem. Zentr.* **1952**, 769.

(13) NaI/*t*-BuOCl: Komatani, T.; Watt, D. S.; Ji, T.; Fitz, T. *J. Org. Chem.* **1985**, *50*, 5384.

(14) PhCH₂(CH₂)₃N⁺Cl₂I⁻: Kajigaeshi, S.; Kakinami, T.; Yamasaki, H.; Fujisaki, S.; Kondo, M.; Okamoto, T. *Chem. Lett.* **1987**, 2109.

(15) ICl₂/dioxane: Terentyev, A. P.; Belenky, L. I.; Yanovskaya, L. A. *Zh. Obshch. Khim.* **1954**, *24*, 1251.

(16) I₂/TIOAc: Cambie, R. C.; Rutledge, P. S.; Smith-Palmer, T.; Woodgate, P. D. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1161.

(17) There is one example in the literature in which a KI/KOCl combination was used to iodinate 8-hydroxy-5-sulfoquinoline to the corresponding 7-iodo compound: Claus, A. *Arch. Pharm.* **1893**, *231*, 704. Biochemists have used the combination of bleach and sodium iodide to achieve polyiodination of aromatic amino acids in proteins, but have not investigated the selectivity of the reaction: Redshaw, M. R.; Lynch, S. *S. J. Endocrinology* **1974**, *60*, 527.

Table II. Effect of Solvent

entry ^c	solvent	product yields, ^{a,b} %				para/ortho ratio
		phenol	2IP	4IP	2,4DIP	
1	H ₂ O	8	25	45	18	1.8
2	CH ₃ OH	8	12	64	8	5.4
3	CH ₃ CH ₂ OH	6	10	70	5	6.9
4	(CH ₃) ₂ CHOH	3	10	71	8	7.4
5	(CH ₃) ₃ COH	4	8	66	10	7.8
6	CH ₃ OH ^d	5	10	80	4	8.0

^a All yields determined by capillary VPC of the product vs naphthalene internal standard. ^b Abbreviations: 2IP = 2-iodophenol. 4IP = 4-iodophenol. 2,4DIP = 2,4-diiodophenol. ^c All runs used 2.0 g of phenol in 50 mL of solvent containing 1.0 equiv of NaI (no added NaOH). To each was added 1.0 equiv of NaOCl in 3–5% aqueous solution at 0 °C, except that in entry 5 the temperature was 20 °C to avoid freezing of the solvent. ^d One equivalent of NaOH was added to this run.

Table III. Comparison with Some Other Iodination Methods

entry ^b	reagent	solvent	product yields, ^{c,d} %				
			phenol	2IP	4IP	2,4DIP	2,4,6TIP
1	NaI, NaOCl ^e	CH ₃ OH	5	10	80	4	0
2	(CH ₃) ₃ COI	<i>t</i> -BuOH, THF	28	27	22	2	0
3	ICl ^e	CH ₃ OH	10	2	54	39	13
4	ICl ^e	CH ₃ CN	21	3	41	37	19
5	(CH ₃) ₃ COCl, NaI	CH ₃ CN, H ₂ O	24	2	38	32	25
6	Cl-T, 1.2 equiv	DMF	1	5	67	17 ^e	3
7	Cl-T, 1.0 equiv	DMF	7	9	64	13 ^e	0
8	I ₂ ^a	CH ₃ OH, H ₂ O	11	7	54	17	12

^a One equivalent of base (NaOH or Na₂CO₃) added. ^b All runs made at 0 °C. ^c Yields determined by capillary VPC vs naphthalene internal standard. ^d Abbreviations: Cl-T: Chloramine-T (sodium *N*-chloro-*p*-toluenesulfonamide). 2,4,6TIP: 2,4,6-triiodophenol. ^e Yield of isolated product, because of coelution with *p*-toluenesulfonamide on vapor chromatogram.

seems clear that the positive iodine reagent which is generated will react only with anions (such as phenolates) and highly reactive neutral species (such as *N,N*-dimethylaniline, which affords the 4-iodo compound) under these conditions. Both anisole and acetanilide were recovered unchanged from reaction with the NaI/NaOCl reagent.

We examined the iodination of phenol itself in some depth (Table II). Solvent effects were observed and attributed to the steric bulk of the alcohol used. As the bulk of the R group in ROH increased, the ratio of para to ortho substitution also increased, as did the yield of 4-iodophenol (except that the yield decreased slightly in the case of R = *tert*-butyl). This effect might be attributable either to an alkyl hypoiodite (ROI) iodinating species¹⁸ or to solvation effects.¹⁹ In the first instance, the alcohol contributes the alkyl group of the alkyl hypoiodite, so the reagent will have increasing steric demand as the bulk of R increases. In the second case, solvation of the phenolate or the iodinating species by bulky ROH will tend to favor para substitution as well. We also noted that both yield and selectivity were improved if 1 equiv of NaOH was added to the initial reaction mixture (entry 6, Table II). This can easily be explained if one notes that the product, 4-iodophenol, is a stronger acid than the starting material.

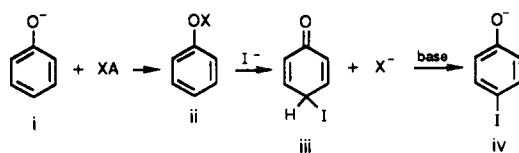
Thus, as the reaction proceeds, the product rather than the starting material will be preferentially deprotonated, resulting in a loss of chemoselectivity. The extra equivalent of hydroxide (1 equiv is generated during the reaction) restores chemoselectivity by deprotonating all of the phenols present.

We have compared our method with other reported methods of phenol iodination, using phenol itself as the common substrate (Table III). The results are from our laboratories. We found that the NaOCl/NaI reagent gave superior yield and selectivity to all other methods examined. As seen in entry 2, *tert*-butyl hypoiodite (generated by the method of Glover and Goosen²⁰) is relatively unreactive and actually has a slight prejudice toward ortho substitution. These results contrast sharply with the high para selectivity and good yield obtained with NaOCl/NaI in aqueous *tert*-butyl alcohol (entry 5, Table II). Iodine monochloride⁶ (entries 3 and 4), on the other hand, is a highly reactive iodinating species with poor selectivity toward monoiodination (even its apparent high para selectivity may be illusory, since further iodination of the initially formed monoiodophenols would be expected to deplete selectively the 2-iodo isomer to form the observed di- and triiodophenols).²¹

We also tested two systems recently developed by Watt and co-workers for the iodination of phenols. The combination of sodium iodide and *tert*-butyl hypochlorite¹³ (entry 5) afforded a highly reactive reagent, which gave considerable overiodination. Comparison with entry 4 (run under identical conditions except for replacement of NaI/*t*-BuOCl with ICl) shows remarkable similarity, and suggests that Watt's active reagent in this case may be ICl. Watt also recently has described the combination of sodium iodide with the oxidant Chloramine T (sodium *N*-chloro-*p*-toluenesulfonamide).^{12,13} Although we found this

(18) The use of alkyl hypoiodites in aromatic iodination has been described: Glover, S. A.; Goosen, A.; Laue, H. A. H. *J. S. Afr. Chem. Inst.* 1973, 26, 77.

(19) A referee has suggested the following mechanism for the iodination of phenols with NaI/NaOCl:



where XA could be: ICl, I₂, ClOH, etc. While we find the mechanism intriguing and are grateful to the referee for suggesting it, we do not feel that it explains adequately the variation in para/ortho ratio with the bulk of the R group in ROH solvent. The position of attack (ortho or para) of iodine ion on ii should be relatively independent of the bulk of R.

(20) Glover, S. A.; Goosen, A. *Tetrahedron Lett.* 1980, 21, 2005.

(21) deRossi and Veglia²² have shown that 2-iodophenol reacts with I₂ in aqueous solution under pseudo-first-order conditions at a rate approximately 9.5 times that of 4-iodophenol.

(22) deRossi, R. H.; Veglia, A. V. *Tetrahedron Lett.* 1986, 27, 5963.

system to be relatively selective with respect to both moniodination and para substitution (entries 6 and 7), we observed several byproducts and could not duplicate the reported high yield of 4-iodophenol (97%). Eliminating the excess of Chloramine T and sodium iodide used by Watt (entry 7) decreased the extent of polyiodination but did not improve the yield of 4-iodophenol. This method, as noted by the original authors, requires chromatographic purification to remove the *p*-toluenesulfonamide byproduct.

We have described a method for the iodination of phenols which affords high selectivity and yields, employs inexpensive reagents and relatively mild conditions, and lends itself to simple product isolation. Control over the extent of iodination is excellent. In addition, iodine is used efficiently, with no lost iodide byproduct. More detailed studies on the mechanism are in progress and will be reported in due course.

Experimental Section

General. Melting points were obtained on a Thomas-Hoover apparatus in open capillary tubes and are uncorrected. Flash chromatography was performed using the method of Still,²³ with Merck EM silica gel 60 (230–400 mesh). Elemental analyses were performed by personnel of the Physical and Analytical Division of the ECC Research Laboratories. All reactions were carried out under a positive pressure of nitrogen. All reagents were used as received. "Dried" refers to drying over anhydrous magnesium sulfate, followed by gravity filtration to remove the drying agent.

Vapor-phase chromatography (VPC) was performed on DB-5 glass capillary columns. The phenolic products were derivatized with *N,O*-bis(trimethylsilyl)acetamide in pyridine and then analyzed by VPC against naphthalene internal standard. Analytically pure standards of the products, usually prepared by the iodination technique, which is the subject of this paper, followed by flash chromatographic purification, were used to determine the response factors used in the VPC analysis. Proton and carbon NMR spectra were acquired on JEOL 270 and 400 MHz, and Varian Gemini 300 MHz spectrometers.

General Iodination Procedure. 4-Iodo-2-methylphenol (2b). 2-Methylphenol (2.00 g) was dissolved in 50 mL of methanol. One equivalent each of sodium iodide (2.77 g) and sodium hydroxide (0.74 g) was added, and the solution was cooled to 0 °C. Aqueous sodium hypochlorite (34.50 g, 4.0% NaOCl) was added dropwise over 75 min at 0–3 °C. As each drop hit the solution, a red color appeared and faded almost instantly. The resulting colorless slurry was stirred for 1 h at 0–2 °C and then was treated with 20 mL of 10% aqueous sodium thiosulfate. The mixture was adjusted to pH 7 using 5% aqueous HCl. In many cases, the product crystallized at this point and could be filtered off. In this case ether (75 mL) was added, and the layers were separated. The organic layer was washed with brine (70 mL) and then dried over MgSO₄. Filtration and rotary evaporation at 40 °C afforded 3.83 g of an orange oil, which quickly crystallized. Analysis of the product by capillary VPC showed that it contained 90.4 wt % 4-iodo-2-methylphenol (80.0% yield) and 3.8 wt % 2-methylphenol, as well as 4.4 area % of a monoiodo isomer (by GC/MS, presumed to be 6-iodo-2-methylphenol), and 1.8 area % of a diiodocresol (by GC/MS, presumed to be 4,6-diiodo-2-methylphenol). A small amount of the product was recrystallized from heptane to afford small white prisms: mp 68.5–69.0 °C (lit.²⁴ mp 64–65 °C); ¹H NMR (acetone-*d*₆) δ 7.42 (d, 1 H, *J* = 2 Hz, 3-H), 7.32 (dd, 1 H, *J*₁ = 8 Hz, *J*₂ = 2 Hz, 5-H), 6.67 (d, 1 H, *J* = 8 Hz, 6-H), 2.17 (s, 3 H, CH₃); ¹³C NMR (acetone-*d*₆) δ 155.1, 138.7, 135.1, 127.3, 116.9, 80.1, 14.8.

2-Chloro-4-iodophenol (2c): mp 54.5–55.5 °C (lit.²⁵ mp 54 °C); ¹H NMR (CDCl₃) δ 7.63 (d, 1 H, *J* = 9 Hz, 3-H), 7.47 (dd, 1 H, *J*₁ = 9 Hz, *J*₂ = 2 Hz, 5-H), 6.78 (d, 1 H, *J* = 9 Hz, 6-H); ¹³C NMR (CDCl₃) δ 154.1, 138.6, 137.8, 122.7, 119.7, 80.8.

2,4-Diiodophenol (2d): mp 73.5–74.0 °C (lit.²⁶ mp 74 °C); ¹H NMR (CDCl₃) δ 7.94 (d, 1 H, *J* = 1 Hz, 3-H), 7.51 (dd, 1 H, *J*₁ = 6 Hz, *J*₂ = 1 Hz, 5-H), 6.77 (d, 1 H, *J* = 6 Hz, 6-H); ¹³C NMR (CDCl₃) δ 155.4, 145.9, 139.5, 117.5, 87.2, 83.1.

4-Iodo-2-phenylphenol (2e): oil (from column chromatography followed by Kugelrohr distillation); bp 125–135 °C (0.5 mm) (lit.²⁷ bp 200–205 °C (15 mm), mp 35.2 °C); ¹H NMR (CDCl₃) δ 7.45 (m, 7 H), 6.71 (d, 1 H, *J* = 8 Hz, 6-H), 5.29 (s, 1 H, OH); ¹³C NMR (CDCl₃) δ 152.8, 139.0, 138.2, 136.0, 131.1, 129.8, 129.6, 129.3, 128.7, 118.5, 83.0; exact mass calcd for C₁₂H₉IO 295.9698, found 295.9691. Anal. Calcd for C₁₂H₉IO: C, 48.67; H, 3.06. Found: C, 48.60; H, 3.21.

4-Chloro-2-iodophenol (2f): mp 75.5–76.5 °C (lit.²⁸ mp 78 °C); ¹H NMR (acetone-*d*₆) δ 7.72 (d, 1 H, *J* = 2 Hz, 3-H), 7.26 (dd, 1 H, *J*₁ = 8 Hz, *J*₂ = 2 Hz, 5-H), 6.96 (d, 1 H, *J* = 8 Hz, 6-H); ¹³C NMR (acetone-*d*₆) δ 156.8, 138.9, 130.2, 125.3, 116.7, 84.6.

2-Iodo-4-nitrophenol (2g): mp 90.0–91.5 °C (lit.²⁹ mp 86–87 °C); ¹H NMR (acetone-*d*₆) δ 8.60 (d, 1 H, *J* = 2 Hz, 3-H), 8.09 (dd, 1 H, *J*₁ = 7 Hz, *J*₂ = 2 Hz, 5-H), 7.08 (d, 1 H, *J* = 7 Hz, 6-H); ¹³C NMR (acetone-*d*₆) δ 163.3, 143.2, 135.9, 126.5, 115.2, 83.3.

4-Hydroxy-3-iodobenzoic acid (2h): mp 175.0–176.0 °C (lit.³⁰ mp 173.5–174.5 °C); ¹H NMR (acetone-*d*₆) δ 8.38 (d, 1 H, *J* = 1 Hz, 2-H), 7.89 (dd, 1 H, *J*₁ = 6 Hz, *J*₂ = 1 Hz, 6-H), 7.03 (d, 1 H, *J* = 6 Hz, 5-H); ¹³C NMR (acetone-*d*₆) δ 166.1, 161.6, 142.1, 132.4, 124.8, 115.3, 83.7.

2-Iodo-4-phenylphenol (2i): mp 116.5–117.0 °C (lit.³¹ mp 115–116 °C); ¹H NMR (acetone-*d*₆) δ 7.99 (d, 1 H, *J* = 2 Hz, 3-H), 7.58 (d, 2 H, *J* = 7.2 Hz, 2'-H), 7.53 (dd, 1 H, *J*₁ = 8 Hz, *J*₂ = 2 Hz, 5-H), 7.42 (t, 2 H, *J* = 7 Hz, 3'-H), 7.31 (t, 1 H, *J* = 7 Hz, 4'-H), 7.03 (d, 1 H, *J* = 8 Hz, 6-H); ¹³C NMR (acetone-*d*₆) δ 157.1, 140.2, 138.3, 135.6, 129.7, 129.1, 127.8, 127.2, 116.1, 85.0.

2,4,6-Triiodophenol (2j): mp 158.5–159.5 °C (lit.¹⁴ mp 159–160 °C); ¹H NMR (CDCl₃) δ 7.94 (s, 2 H, ArH), 5.76 (s, 1 H, OH); ¹³C NMR (acetone-*d*₆) δ 156.6, 147.5, 85.8, 83.7.

2,6-Dimethyl-4-iodophenol (2k): mp 101.5–102.5 °C (lit.³² mp 102.0–102.5 °C); ¹H NMR (CDCl₃) δ 7.30 (s, 2 H, ArH), 4.67 (s, 1 H, OH), 2.23 (s, 6 H, CH₃); ¹³C NMR (CDCl₃) δ 153.0, 137.7, 126.3, 82.7, 15.7.

2-Hydroxy-5-iodopyridine (2l): mp 190.0–191.0 °C (lit.³³ mp 190–191 °C); ¹H NMR (DMSO-*d*₆) δ 7.72 (d, 1 H, *J* = 2 Hz, 6-H), 7.59 (dd, 1 H, *J*₁ = 11 Hz, *J*₂ = 2 Hz, 4-H), 6.33 (d, 1 H, *J* = 11 Hz, 3-H); ¹³C NMR (DMSO-*d*₆) δ 161.7, 148.2, 142.3, 121.8, 66.4.

5-Hydroxy-2-iodopyridine (2m): mp 188–189 °C dec (lit.³³ mp 191.5–192.5 °C); ¹H NMR (CDCl₃) δ 7.99 (dd, 1 H, *J*₁ = 5 Hz, *J*₂ = 1 Hz, 6-H), 7.22 (dd, 1 H, *J*₁ = 8 Hz, *J*₂ = 1 Hz, 3-H), 7.16 (dd, 1 H, *J*₁ = 8 Hz, *J*₂ = 5 Hz, 4-H); ¹³C NMR (acetone-*d*₆) δ 154.7, 142.8, 124.8, 121.9, 110.5.

1-Iodo-2-naphthol (2n): mp 91.0–92.0 °C (lit.³⁴ mp 92 °C); ¹H NMR (CDCl₃) δ 7.92 (d, 1 H, *J* = 9 Hz, 8-H), 7.73 (overlapping doublets, 2 H, 4-H and 5-H), 7.54 (t, 1 H, *J* = 8 Hz, 7-H), 7.38 (t, 1 H, *J* = 8 Hz, 6-H), 7.26 (d, 1 H, *J* = 8 Hz, 3-H); ¹³C NMR (CDCl₃) δ 154.5, 135.5, 131.2, 130.8, 130.3, 126.92, 126.89, 124.8, 117.0, 86.7.

4-Iodoaniline (2o): mp 63.5–64.0 °C (lit.³⁴ mp 63 °C); ¹H NMR (CDCl₃) δ 7.41 (d, 2 H, *J* = 8 Hz, 3-H and 5-H), 6.46 (d, 2 H, *J* = 8 Hz, 2-H and 6-H), 3.68 (br s, 1 H, NH₂); ¹³C NMR (CDCl₃) δ 146.8, 138.6, 117.9, 79.8.

N,N-Dimethyl-4-iodoaniline (2p). *N,N*-Dimethylaniline (6.06 g) and sodium iodide (8.25 g) were dissolved in 120 mL of methanol, and the solution was cooled to 15 °C. Aqueous sodium hypochlorite (53.3 g, 8.4% NaOCl) was added dropwise over 2 h at 10–15 °C. After holding for 3.5 h at 10–15 °C, the mixture was stirred at room temperature overnight. To the thin slurry was added 50 mL of water, and the mixture was extracted with

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CH_2Cl_2 (3 \times 40 mL). The combined organic layer was washed with brine (40 mL) and then dried over MgSO_4 . Filtration and rotary evaporation gave 7.52 g of a dark oil. Unreacted starting material was removed by Kugelrohr vacuum distillation at room temperature (0.1 mm), and then the iodoaniline was distilled at 62–70 °C (0.1 mm). The yellow, air-sensitive product (3.21 g) was crystallized from methanol to yield white plates (1.38 g, 11.2%): mp 76.5–78.5 °C (lit.¹⁶ mp 77 °C); ^1H NMR (CD_2Cl_2) δ 7.44 (d, 2 H, $J = 9$ Hz, 3-H and 5-H), 6.48 (d, 2 H, $J = 9$ Hz, 2-H and 6-H), 2.89 (s, 6 H, CH_3); ^{13}C NMR (CD_2Cl_2) δ 151.0, 138.3, 115.4, 77.5, 40.6.

Comparative Iodination Processes as Applied to Phenol. In all of the following cases the products were analyzed by capillary VPC vs naphthalene internal standard, with results as summarized in Table III.

NaI/Chloramine T Method. A solution of phenol (1.00 g) and sodium iodide (1.91 g) in *N,N*-dimethylformamide (32 mL) was treated with Chloramine T trihydrate (3.59 g) all at once, at 22 °C. The solution turned red and warmed to 24 °C. The mixture was stirred for 1 h at 21–24 °C, by which time the color had faded to pale yellow. The mixture was poured into water (100 mL), and the solution was acidified to pH 1 using 5% HCl. The solution was extracted with ethyl acetate (2 \times 75 mL). The organic extracts were washed with 10% aqueous sodium thiosulfate (50 mL) and then brine (50 mL). The ethyl acetate solution was dried, and then the solvent was evaporated to afford 5.06 g damp, tan solid. The product was analyzed by VPC, which gave all of the yield data (Table III) except that for 2,4-diiiodophenol. Since it coeluted with the *p*-toluenesulfonamide byproduct on VPC, 2,4-diiiodophenol was isolated by flash chromatography (eluant 1:1 heptane– CH_2Cl_2), and this isolated yield is listed in Table III.

tert-Butyl Hypoiodite Method. A solution of ICl (1.72 g) in THF (3 mL) was added dropwise over 5 min at 20–22 °C to a solution of potassium *tert*-butoxide (2.50 g) in *tert*-butyl alcohol (20 mL). The yellow slurry was cooled to 7 °C. A solution of phenol (1.00 g) in THF (2 mL) and *tert*-butyl alcohol (5 mL) was added dropwise over 15 min at 3–7 °C. The yellow slurry was stirred for 1 h at 0–5 °C and then for 1 h at ambient temperature. The mixture was poured into 59 mL of 10% sodium thiosulfate solution and acidified to pH 3 using 5% aqueous HCl. Ether (60 mL) was added, and the layers were separated. The organic layer was washed with brine (50 mL), dried, and filtered. Removal of the solvent in vacuo gave 2.06 g of an orange oil.

I₂/Methanol Method. Iodine (5.39 g) was added in portions over 1 h at –2 to 1 °C to a solution of phenol and sodium hydroxide (1.70 g) in methanol (50 mL). The colorless solution was stirred 20 min at 0 °C and then was acidified to pH 2 (5% HCl). The product was extracted into ether (75 mL). The ether layer was washed sequentially with 10% aqueous sodium thiosulfate (50 mL) and brine (50 mL). The ether layer was dried, then the solvent was removed in vacuo to give 4.05 g of a yellow oil.

ICl/Methanol Method. A solution of phenol (2.00 g) in methanol (50 mL) was treated with sodium carbonate (10.60 g). Iodine monochloride (3.45 g, 1.00 equiv) was added dropwise over 40 min at –1 to 4 °C. The colorless slurry was stirred for 1 h at 0 °C. The slurry was filtered, and the salt was washed with methanol (50 mL). The filtrate was treated with 10% sodium thiosulfate solution (25 mL) and then was adjusted to pH 7 using 3 N H_2SO_4 . This mixture was extracted with ether (3 \times 60 mL). The combined ether extracts were dried and filtered, and then the solvent was removed in vacuo to afford 4.65 g of a pale brown oil.

ICl/Acetonitrile Method. A solution of phenol (2.00 g) and sodium hydroxide (0.85 g, 1.00 equiv) in acetonitrile (50 mL), water (10 mL), and *tert*-butyl alcohol (1.73 g, 1.10 equiv) was treated with ICl (3.45 g, 1.00 equiv) dropwise over 35 min at –2 to 1 °C. The red reaction mixture was stirred for 2 h at 0–5 °C and then for 2 h at 20 °C. The mixture was treated with 10% sodium thiosulfate solution (75 mL) and then was acidified to pH 3 using 5% HCl. The mixture was extracted with ether (2 \times 60 mL). The combined ether extracts were washed with saturated brine (50 mL) and then dried. The ether solution was filtered and concentrated in vacuo to give 4.05 g of an orange oil.

tert-Butyl Hypochlorite/NaI Method. A solution of phenol (2.00 g) and sodium iodide (3.50 g, 1.10 equiv) in acetonitrile (50 mL) and water (10 mL) was treated with *tert*-butyl hypochlorite (2.54 g, 1.10 equiv) dropwise over 13 min at –2 to 2 °C. The red solution was stirred for 17 min at 0 °C and then was treated with 10% sodium thiosulfate solution (100 mL). The product was extracted into 150 mL of ether. The ether solution was washed with saturated brine (50 mL) and dried. The mixture was filtered and concentrated in vacuo to afford 4.52 g of a white semisolid.

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Notes

An Efficient Synthesis of Florfenicol

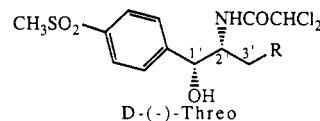
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Florfenicol (1),¹ the 3'-fluoro derivative of the antibiotic thiamphenicol (2), is a broad spectrum antibiotic possessing activity against many Gram negative, Gram positive, and thiamphenicol-resistant microorganisms. Flor-

fenicol is of interest as a veterinary product for use against diseases such as bovine mastitis and bovine shipping fever and for use in aqua culture.



- 1 R = F Florfenicol
2 R = OH Thiamphenicol

A highly efficient synthesis was required to produce large quantities for the competitive animal health market. Initially, florfenicol was synthesized from thiamphenicol.¹ The major drawback of this synthesis was a poor fluorination step. The fluorodehydroxylation of *D-threo*-1-(4-(methylsulfonyl)phenyl)-2-phthalimido-1,3-propanediol was accomplished with DAST, which gave a mixture of all three possible fluorinated products. Also, the hazards and

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