Chemistry in Hydrogen Fluoride. 7. A Novel Synthesis of Aryl Trifluoromethyl Ethers

Andrew E. Feiring

Contribution No. 2656, Central Research and Development Department, Experimental Station, E. I. du Pont de Nemours and Co., Inc., Wilmington, Delaware 19898

Received March 20, 1979

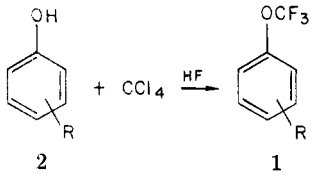
Aryl trifluoromethyl ethers can be prepared by reacting selected phenols with carbon tetrachloride and hydrogen fluoride. Under certain conditions, substantial yields of the corresponding aryl chlorodifluoromethyl ethers can also be obtained. Mild catalysis of the reactions with BF_3 or SbF_3 was observed. 4-Chloro-1-(trifluoromethoxy)benzene is cleanly converted to (trifluoromethoxy)benzene by hydrogenolysis.

The development of new, relatively inexpensive methods for the selective introduction of fluorine into organic molecules remains a key goal of organofluorine research. New methods, based on relatively inexpensive and available hydrogen fluoride, are especially desirable. In previous papers in this series,[1] several new methods for preparing fluorinated compounds based on HF have been described. In this paper, a novel one-step synthesis of potentially useful[2] aryl trifluoromethyl ethers from selected phenols, carbon tetrachloride, and HF is described.

Aryl trifluoromethyl ethers have been prepared by the reaction of hydrogen fluoride or antimony fluorides with aryl trichloromethyl ethers.[3] This method is limited by the availability of the trichloro derivatives.[4] Aryl trifluoromethyl ethers have also been prepared by reaction of phenols with carbonyl fluoride to give aryl fluoroformates followed by treatment with sulfur tetrafluoride[2a] or by conversion of phenols to the chlorothioformates which are reacted with molybdenum hexafluoride.[5] These latter methods are limited by the cost of the fluorinating reagent.[6]

Results

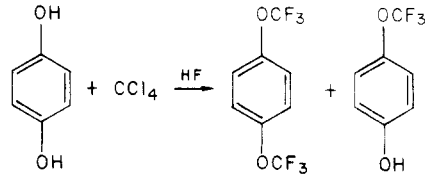
Aryl trifluoromethyl ethers[2a] (**1a–o**) were obtained by



2 1

a, R = *p*-NO_2	f, R = *m*-NH_2	k, R = 4-Cl, 2-Me
b, R = *m*-NO_2	g, R = 2,4-Cl_2	l, R = 4-Me, 3-NO_2
c, R = *p*-Cl	h, R = 2-F	m, R = 4-CN
d, R = *m*-CF_3	i, R = 4-Cl, 3-Me	n, R = 4-Me
e, R = *p*-NH_2	j, R = 3-Me, 4-NO_2	o, R = H

reaction of the corresponding phenols (**2a–o**) with excess carbon tetrachloride and HF in a closed pressure vessel at 100–150 °C under autogeneous pressure. Hydroquinone gave a mixture of the mono and bis OCF_3 derivatives. The results are contained in Table I. In all cases, the yields

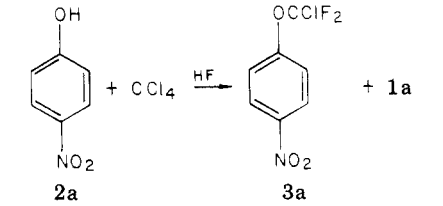


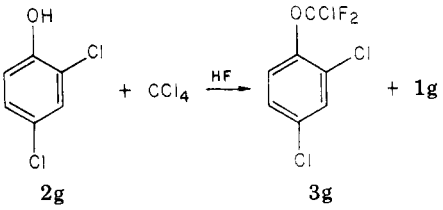
1p 1q

which have not been optimized represent isolated, distilled product. In many cases, unreacted phenol can be recovered. So far, phenols having ortho substituents which can hydrogen bond to the OH group (e.g., –OH, $-NH_2$, or $-NO_2$) have failed to yield trifluoromethoxy derivatives by this procedure. Fluorotrichloromethane (entry 6) and bromotrichloromethane (entry 3) used in place of carbon tetrachloride for the synthesis of **1c** and **1a**, respectively, gave the product in somewhat reduced yield.

From a limited study of conditions, use of excess CCl_4 appears desirable. For example, treatment of **2c** with only 1 equiv of CCl_4, instead of three, reduced the yield from 67 to 43%. Efficient agitation is also necessary; reaction of **2a** in an unstirred vessel under the conditions of Table I decreased the yield to ca. 20%.

Reaction of **2a** or **2g** under milder conditions (lower





1g → 2g

temperature or shorter time) afforded substantial amounts of the corresponding chlorodifluoromethoxy derivatives,[7] **3a** or **3g**, in addition to the expected trifluoromethoxy

(1) A. E. Feiring, *J. Fluorine Chem.* **10**, 375 (1977); **12**, 471 (1978); **13**, 7 (1979); *J. Org. Chem.*, **44**, 1252 (1979).

(2) (a) W. A. Sheppard, *J. Org. Chem.*, **29**, 1 (1964); (b) L. M. Yagupolsky and M. S. Marenets, *J. Gen. Chem. USSR (Engl. Transl.)*, **27**, 1479 (1957); (c) L. M. Yagupolsky and V. I. Troitskaya, *ibid.*, **30**, 3102 (1960); (d) French Patent 1 245 552 (1960); (e) U. S. Patent 3 021 368 (1962); (f) F. E. Herkes, *J. Fluorine Chem.*, **9**, 113 (1977).

(3) N. N. Yarovenko and A. S. Vasil'eva, *J. Gen. Chem. USSR (Engl. Transl.)*, **28**, 2537 (1958); L. M. Yagupolsky, *Dokl. Akad. Nauk SSSR*, **105**, 100 (1955) (*Chem. Abstr.* **50**, 11270 (1956)); British Patent 765 527 (1957).

(4) R. Louw and P. W. Franken, *Chem. Ind. (London)*, 127 (1977).

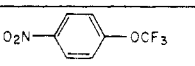
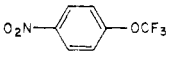
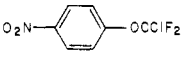
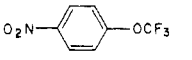
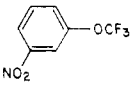
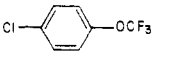
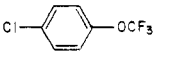
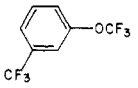
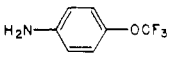
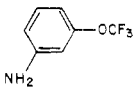
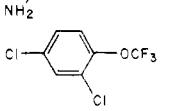
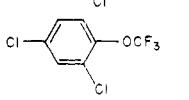
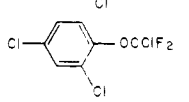
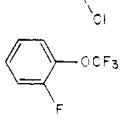
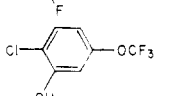
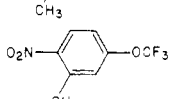
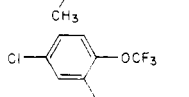
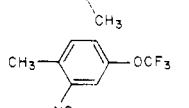
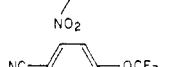
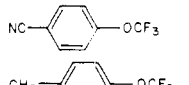
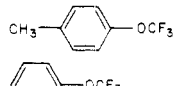
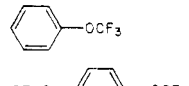
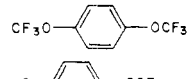
(5) F. Mathey and J. Bensoam, French Patent 2 214 674 (1974); *Tetrahedron Lett.*, 2253 (1973).

(6) Formation of (trifluoromethoxy)benzene from reaction of phenol, carbon tetrachloride, and silver fluoride in HF solution has been observed. W. T. Miller, *U.S. Gov. Res. Dev. Rep.*, **70** (19), 65 (1970). W. T. Miller, R. A. Haggard, D. T. Meshre, and P. C. Warren, Fourth Winter Fluorine Conference, Daytona Beach, Fla., January 1979.

(7) British Patent 765 527 (1957) (*Chem. Abstr.* **51**, 14803); German Patent 2 133 871 (1972) (*Chem. Abstr.* **78**, 97359 (1973)); German Patent 2 117 662 (1972) (*Chem. Abstr.* **78**, 58106r (1973)).

0022-3263/79/1944-2907$01.00/0

Table I. Synthesis of $ArOCF_3$ and $ArOCClF_2$ Compounds

entry	phenol (g, mol)	carbon tetrahalide (g, mol)	g of HF	conditions	product	yield, %[a]
1	4-nitrophenol (7.0, 0.05)	CCl_4 (23, 0.15)	40	150 °C/8 h		56
2	4-nitrophenol (8.4, 0.06)	CCl_4 (28, 0.18)	40	100 °C/8 h		3
						45
3	4-nitrophenol (7.0, 0.05)	$CBrCl_3$ (30, 0.15)	50	150 °C/8 h		10
4	3-nitrophenol (50, 0.36)	CCl_4 (165, 1.07)	300	150 °C/8 h		69
5	4-chlorophenol (77.1, 0.6)	CCl_4 (277, 1.8)	400	150 °C/8 h		70
6	4-chlorophenol (6.43, 0.05)	$FCCl_3$ (20.7, 0.15)	40	150 °C/8 h		31
7	3-(trifluoromethyl)phenol (8.1, 0.05)	CCl_4 (23, 0.15)	40	150 °C/8 h		60
8	4-aminophenol (65.4, 0.6)	CCl_4 (277, 1.8)	400	150 °C/8 h		42
9	3-aminophenol (65.4, 0.6)	CCl_4 (277, 1.8)	400	140 °C/8 h		26
10	2,4-dichlorophenol (8.2, 0.05)	CCl_4 (23, 0.15)	40	150 °C/8 h		73
11	2,4-dichlorophenol (8.2, 0.05)	CCl_4 (23, 0.15)	40	175 °C/1 h		37
						16
12	2-fluorophenol (7.84, 0.07)	CCl_4 (32, 0.21)	40	150 °C/8 h		35
13	4-chloro-3-methylphenol (8.6, 0.06)	CCl_4 (28, 0.18)	40	140 °C/8 h		27
14	3-methyl-4-nitrophenol (9.2, 0.06)	CCl_4 (28, 0.18)	50	150 °C/8 h		17
15	4-chloro-2-methylphenol (8.6, 0.06)	CCl_4 (28, 0.18)	40	140 °C/8 h		9
16	4-methyl-3-nitrophenol (9.2, 0.06)	CCl_4 (28, 0.18)	50	150 °C/8 h		19
17	4-cyanophenol (6.0, 0.05)	CCl_4 (23, 0.15)	40	150 °C/8 h		4
18	4-methylphenol (5.4, 0.05)	CCl_4 (19, 0.12)	30	100 °C/2 h 150 °C/2 h		20
19	phenol (4.7, 0.05)	CCl_4 (23, 0.15)	30	100 °C/2 h 150 °C/4 h		10
20	hydroquinone (5.5, 0.05)	CCl_4 (31, 0.20)	30	150 °C/8 h		36
						20

[a] Isolated yield of distilled product.

compounds (Table I, entries 2 and 11).

Treatment of **3g** with HF at 150 °C gave 80% of the expected trifluoromethoxy compound **1g**. However, 20% of 2,4-dichlorophenol was also isolated.

A brief search for possible catalysts for the reaction of **2a** with CCl_4 and HF gave the results shown in Table II. The use of boron trifluoride or antimony trifluoride resulted in a modest increase in the yield of the desired

Table II. Synthesis of 4-$NO_2C_6H_4OCF_3$ and 4-$NO_2C_6H_4OCClF_2$[a]

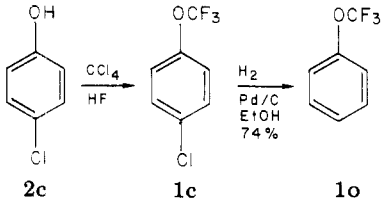
entry no.	catalyst (g)	% of recovered phenol	% of 4-NO-$C_6H_4OCF_3$	% of 4-NO_2-$C_6H_4OCClF_2$
1	none	47	3	45
2	SbF_3 (3)	36	13	40
3	SbF_3 (5) Cl_2 (2)	18	5	25
4	SbF_5/C[b] (3)	62	trace	5
5	BF_3 (2)	18	23	40
6	KF (5)	71	trace	6

[a] 4-Nitrophenol (8.4 g, 0.06 mol), carbon tetrachloride (28 g, 0.18 mol), and HF (40 g, 2.0 mol) at 100 °C for 8 h. [b] 50% antimony pentafluoride/graphite intercalation complex.

trifluoromethoxy derivative. Potassium fluoride inhibited the reaction. Pentavalent antimony (produced in situ from SbF_3 and Cl_2) gave substantial quantities of tar. A preparative scale synthesis (Expermental Section) of **1a** using BF_3 catalysis at 130 °C afforded the desired product in 76% yield.

An experiment was performed to determine the fate of the excess carbon tetrachloride used in these reactions. A 10-mL pressure vessel, charged with 10 mmol of phenol, 14 mmol of carbon tetrachloride, and 200 mmol of HF, was heated at 150 °C for 3 h. The vessel was attached to a metal trap containing sodium fluoride pellets followed by a glass trap cooled in dry ice/acetone. The pressure vessel was vented through the evacuated trap system. The colorless liquid which collected in the glass trap was analyzed by GLC as a mixture of 33% (trifluoromethoxy)benzene, 2% carbon tetrachloride, and 65% fluorotrichloromethane. A control experiment in which carbon tetrachloride and HF were heated in the absence of phenol gave no fluorotrichloromethane.

Although the direct synthesis of (trifluoromethoxy)benzene (**1o**) from phenol, carbon tetrachloride, and HF gave the product in only 10% yield, a two-step procedure has been found which affords synthetically useful yields of the parent compound. As indicated in Table I, the 4-chloro derivative **1c** can be prepared from 4-chlorophenol



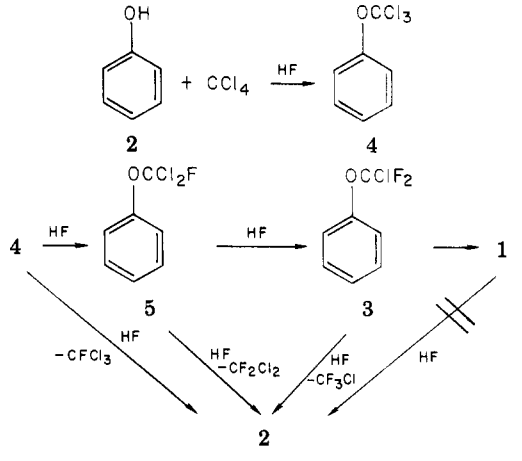
2c **1c** **1o**

in 70% yield. Catalytic hydrogenolysis of **1c** selectively removed the chloro substituent, giving **1o** in 74% yield.

Discussion

From the data presented in Table I, several conclusions regarding the synthetic utility of this process can be drawn. The best yields are obtained using phenols substituted by stable electron-withdrawing substituents such as nitro, chloro, or trifluoromethyl. In these cases, conversions are quite high, and in addition most of the unreacted phenol can be recovered unchanged. It is believed that the electron-withdrawing substituent protects the aromatic nucleus from attack by intermediates generated in the reaction. The amino group is protonated in the medium and acts as a protecting group in the same manner. Phenol and *p*-cresol give OCF_3 derivatives in 10–20% yield. Little or no unreacted phenol can be recovered. The cyano group, although electron withdrawing, appears to undergo side reactions so that only low (~5%) yields have been achieved. Other substituents which might be expected to function poorly because of side reactions include methoxy, acetoxy, and olefinic groups. However, the substituents which give the best results are among the most useful for further synthetic transformation, and the parent compound is readily available in two steps from 4-chlorophenol by this chemistry. The trifluoromethoxy substituent is quite stable under a wide variety of conditions.[2a]

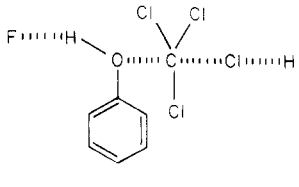
Little mechanistic work has been done as yet on this reaction, but some speculations seem worthwhile. If the corresponding trichloromethoxy compound **4** is formed



from the reaction of a phenol, carbon tetrachloride, and HF, its stepwise conversion to the trifluoromethoxy compound would be expected under the reaction conditions.[3]

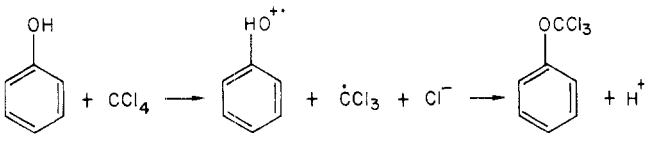
The chlorodifluoromethoxy intermediate **3** has, of course, actually been isolated from the reaction with **2a** and **2g**, and in the latter case it has been shown to give **1g** under the reaction conditions. Neither **4** nor **5** has been detected. Interestingly, **3g** is in part cleaved to the phenol and presumably CF_3Cl. Isolation of $CFCl_3$ from reaction of phenol with carbon tetrachloride is evidence that **4** is also partially transformed back to phenol. The trifluoro derivative is stable under these conditions. Although $CFCl_3$ can reenter the reaction sequence, it is less reactive and CF_2Cl_2 has been independently shown to be inert. The cleavage reaction thus accounts for at least part of the need for excess carbon tetrachloride.

Clearly, the most intriguing step in this sequence is the first, the interaction between phenol, carbon tetrachloride, and HF. No pair in this trio of reagents gives any reaction in the absence of the third at 150 °C. One possible pathway is an acid-catalyzed nucleophilic attack on carbon tetrachloride where a proton assists the departure of Cl^-.



The nucleophilicity of the phenol might also be enhanced by hydrogen bonding to fluoride. The modest enhancement in conversion with BF_3 could result from the increased acidity of the medium.[8] Conversely, potassium fluoride decreases the acidity of the medium, resulting in lower conversion.

An alternative possibility which cannot be eliminated at present is an electron-transfer pathway, which might



be facilitated by the highly polar nature of the hydrogen fluoride solvent.[8] Further experiments will be necessary to discriminate between these possibilities.

Experimental Section

Reagents. Anhydrous hydrogen fluoride was used as received from Air Products. Phenols were reagent grade commerical products used as received.

General Procedure for Synthesis of Aryl Trifluoromethyl Ethers. Caution! HF is extremely corrosive to human tissue. All work with HF should be conducted in an efficient hood with full face shield and protective clothing. Appropriate barricades should be employed for work with pressure vessels.

Reactions were conducted in Hastelloy C pressure vessels of appropriate size. In general, the phenol and carbon tetrachloride were charged to the vessel which was then closed, cooled in dry ice/acetone, evacuated, and charged with HF from a commercial cylinder. The mixture was heated to the reaction temperature and vigorously agitated. After appropriate processing as illustrated below, the products weere isolated by distillation. Conditions and results are contained in Table I.

Preparation of 4-Nitro-1-(trifluoromethoxy)benzene Using BF_3 Catalysis. A 1-L stirred Hastelloy autoclave was swept with N_2 and charged with 83.4 g (0.6 mol) of 4-nitrophenol and 277 g (1.8 mol) of carbon tetrachloride. The autoclave was closed, cooled with dry ice/acetone, evacuated, and charged with 400 g of HF, followed by 10 g of BF_3. The resulting mixture was stirred vigorously, and the contents were heated to 130 °C. After 8 h, the mixture was cooled to room temperature. The HF was removed by aspirator. The residue was dissolved in 600 mL of methylene chloride. Sodium fluoride (0.25 lb) was added to remove residual HF. The mixture was filtered. The filtrate was concentrated on a rotary evaporator. The residue was diluted to 1 L with 5% aqueous KOH and steam distilled. The product separated as a lower yellow layer in the first 300 mL of distillate. After it was dried over $MgSO_4$, distillation gave 95 g (76%) of 4-nitro-1-(trifluoromethoxy)benzene: bp 40-42 °C (0.4 mm); NMR ($CDCl_3$) δ 7.84 (aromatic quartet); fluorine NMR ($CDCl_3$) δ -58.41 (S).

Preparation of 4-Chloro-1-(trifluoromethoxy)benzene. A 1.2-L Hastelloy bomb tube was charged with 77.1 g (0.6 mol) of 4-chlorophenol and 277.2 g (1.8 mol) of carbon tetrachloride. The autoclave was closed, cooled with dry ice/acetone, evacuated, and charged with 400 g of HF. The mixture was agitated for 8 h at 150 °C and cooled to room temperature. Water (300 mL) was injected into the closed vessel. After being cooled again to room temperature, the solution was poured into a plastic bottle. The autoclave was rinsed with 700 mL of ether which was added to the aqueous mixture. After the mixture was stirred for 0.5 h, the layers were separated in a polyethylene separatory funnel. The ether solution was extracted with 100-mL portions of cold 5% KOH in H_2O, until an extract remained alkaline. The ether solution was dried over $MgSO_4$ and filtered. The ether was removed by distillation at atmospheric pressure. The residue was distilled, giving 79.1 g (67%) of 4-chloro-1-(trifluoromethoxy)-benzene: bp 142-145 °C; NMR ($CDCl_3$) δ 7.20 (aromatic quartet); fluorine NMR ($CDCl_3$) δ -58.76 (singlet).

Preparation of 4-(Trifluoromethoxy)aniline. A 1-L stirred Hastelloy autoclave was charged as above with 65.4 g of 4-aminophenol, 277 g of carbon tetrachloride, and 400 g of HF. After 8 h of reaction at 150 °C, the mixture was cooled to room temperature. The HF was removed by aspirator. The residue was rinsed from the autoclave with 600 mL of H_2O. The aqueous solution was added to 1 L of 20% KOH solution under N_2 and steam distilled. The product was collected as an oily lower layer in the first 400 mL of distillate. It was separated, dried over $MgSO_4$, and filtered. Distillation gave 44 g (42%) of colorless 4-(trifluoromethoxy)aniline: bp 82–83 °C (20 mm); ^1H NMR ($CDCl_3$) δ 3.63 (bs, 2 H), 6.76 (q, 4 H); fluorine NMR δ -58.98 (s).

Preparation of 2,4-Dichloro-1-(trifluoromethoxy)benzene and 2,4-Dichloro-1-(chlorodifluoromethoxy)benzene. A 200-mL Hastelloy pressure vessel was charged with 8.2 g (0.05 mol) of 2,4-dichlorophenol and 23 g (0.15 mol) of carbon tetrachloride. The tube was closed, cooled in dry ice/acetone, evacuated, and charged with 40 g of HF. The mixture was heated at 175 °C for 1 h with vigorous agitation. After the mixture had cooled to room temperature, the HF was removed by aspiration. The residue was dissolved in 300 mL of methylene chloride and washed with 100 mL of 5% aqueous KOH. The methylene chloride solution was dried over $MgSO_4$, filtered, and concentrated in vacuo to 7.9 g of liquid. Distillation afforded 4.3 g (37%) of 2,4-dichloro-1-(trifluoromethoxy)benzene [bp 43–45 °C (1.5 mm); NMR ($CDCl_3$) δ 7.25 (2 H), 7.45 (1 H); fluorine NMR ($CDCl_3$) δ -26.44]. 2.0 g (16%) of 2,4-dichloro-1-(chlorodifluoromethoxy)benzene [bp 53–55 °C (1.5 mm); NMR ($CDCl_3$) δ 7.25 (2 H) 7.45 (1 H); fluorine NMR ($CDCl_3$) δ -26.44].

Hydrogenation of 4-Chloro-1-(trifluoromethoxy)benzene. A 500-mL pressure bottle was charged with 1.0 g of 10% Pd on C, a solution of 8.0 g (0.2 mol) of sodium hydroxide in 200 mL of ethanol, and 29 g (0.15 mol) of 4-chloro-1-(trifluoromethoxy)benzene. The mixture was hydrogenated at 40 psi for 5.5 h. The ethanol solution was filtered into a separatory funnel containing 500 mL of H_2O. The lower organic layer was separated. The aqueous solution was extracted with 50 mL of $CFCl_3$. The combined organic phases were washed with water, dried over $CaCl_2$, and filtered. The filtrate was distilled through a 6-in. column. After the $CFCl_3$ and a small amount of benzene were removed, (trifluoromethoxy)benzene (18 g, 74%, bp 105–107 °C) was collected.

Registry No. **1a**, 713-65-5; **1b**, 2995-45-1; **1c**, 461-81-4; **1d**, 42908-82-7; **1e**, 461-82-5; **1f**, 1535-73-5; **1g**, 451-85-4; **1h**, 2106-18-5; **1i**, 70692-42-1; **1j**, 70692-43-2; **1k**, 70692-44-3; **1l**, 70692-45-4; **1m**, 332-25-2; **1n**, 706-27-4; **1o**, 456-55-3; **1p**, 660-36-6; **1q**, 828-27-3; **2a**, 100-02-7; **2b**, 554-84-7; **2c**, 106-48-9; **2d**, 98-17-9; **2e**, 123-30-8; **2f**, 591-27-5; **2g**, 120-83-2; **2h**, 367-12-4; **2i**, 59-50-7; **2j**, 2581-34-2; **2k**, 1570-64-5; **2l**, 2042-14-0; **2m**, 767-00-0; **2n**, 106-44-5; **2o**, 108-95-2; **3a**, 40750-71-8; **3g**, 451-84-3; hydroquinone, 123-31-9; CCl_4, 56-23-5; $CBrCl_3$, 75-62-7; $FCCl_3$, 75-69-4; HF, 7664-39-3.

(8) M. Kilpatrick and J. G. Jones in "The Chemistry of Non-Aqueous Solvents", Vol. II, J. J. Lagowski, Ed., Academic Press, New York, 1967.