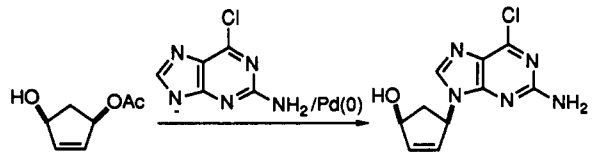
Scheme III



6 Optically pure 1

urated sodium chloride solution and dried over anhydrous magnesium sulfate. Evaporation of the solvent, followed by purification by silica gel chromatography using (i) 1:1 hexanes–ethyl acetate and (ii) ethyl acetate as eluent gave recovered *cis*-(+/−)-2-amino-6-chloro-9-[4-(nitromethyl)-2-cyclopenten-1-yl]-9*H*-purine (0.023 g, 27%) followed by the title compound (0.024 g, 33%): ^{1}H NMR δ 7.89 (s, 1 H), 6.14 (dt, J_1 = 5.5 Hz, J_2 = 2 Hz), 5.79 (dt, J_1 = 5.5 Hz, J_2 = 2 Hz), 5.51 (m, 1 H), 5.18 (br s, 2 H), 3.84 (dd, J_1 = 10.5 Hz, J_2 = 4 Hz, 1 H), 3.73 (dd, J_1 = 10.5 Hz, J_2 = 4 Hz, 1 H). 3.09 (m, 1 H), 2.79 (dt, J_1 = 14.5 Hz, J_2 = 9 Hz, 1 H), 1.97 (dt, J_1 = 14.5 Hz, J_2 = 5.5 Hz, 1 H). The data were identical with an authentic sample.

(1*S*,4*R*)-4-(2-Amino-6-chloro-9*H*-purin-9-yl)-2-cyclopenten-1-ol (1). To a stirred solution of 2-amino-6-chloropurine (0.2 g, 1.18 mmol) in dry DMSO (2 mL) at room temperature under N_2 was added potassium *tert*-butoxide (135 mg, 1.2 mmol), and the mixture was stirred for 20 min. Tetrakis(triphenylphosphine)palladium(0) (50 mg, 0.04 mmol) was added, and the mixture was cooled to 0 °C. To this mixture was added a solution of (1*R*,3*S*)-4-cyclopentene-1,3-diol, 1-acetate (0.17 g, 1.19 mmol) in dry tetrahydrofuran (2 mL) over 10 min, and the resulting mixture was stirred at room temperature for 18 h. The solvents were removed by evaporation at reduced pressure, and the residue was slurried in dichloromethane (approximately 25 mL) and filtered. The filtrate was evaporated, and the residue was purified by chromatography on silica gel using (i) EtOAc followed by (ii) 10:1 EtOAc–MeOH as eluent to give (1*S*,4*R*)-(2-amino-6-chloro-9*H*-purin-9-yl)-2-cyclopenten-1-ol (174 mg, 58%): $[\alpha]_D$ +24° (*c* = 2.5, MeOH); mp 157–159 °C; ^{1}H NMR δ 7.81 (s, 1 H), 6.31 (d, J = 5.5 Hz, 1 H), 5.82 (dd, J_1 = 5.5 Hz, J_2 = 2 Hz, 1 H), 5.23 (dd, J_1 = 9 Hz, J_2 = 2 Hz, 1 H), 5.08 (br s, 2 H), 4.81 (br d, J = 9 Hz, 1 H), 2.95 (ddd, J_1 = 15 Hz, J_2 = 9 Hz, J_3 = 7 Hz, 1 H), 2.10 (br d, J = 15 Hz, 1 H); high-resolution FAB-MS calcd for $C_{10}H_{10}N_5OCl$ 252.0649 (MH^+), found 252.0646. Anal. Calcd, for $C_{10}H_{10}N_5OCl$: C, 47.72; H, 4.00; N, 27.83. Found: C, 47.81; H, 4.05; N, 27.73.

Nitroacetic Acid, 2-(Trimethylsilyl)ethyl Ester. To a stirred solution of ethyl nitroacetate (5.0 g, 37.6 mmol) and 2-(trimethylsilyl)ethanol (6.0 mL, 4.95 g, 42 mmol) in dry benzene (100 mL) was added titanium tetraisopropoxide (1.0 mL, 0.95 g, 3.4 mmol), and the mixture was heated at reflux with collection of the distillate. After 1 h, approximately 25 mL of distillate had been collected and the mixture was allowed to cool to 40 °C. Water (2 mL) was added, and the mixture was stirred at room temperature for 15 min. The solvents were evaporated under reduced pressure, and the residue was taken up in CH_2Cl_2 (100 mL). The solution was dried over $MgSO_4$ and filtered through a small pad of Celite, and the solvent was evaporated. The residue was purified by bulb-to-bulb distillation to give the title compound as a colorless liquid, (6.10 g, 79%): bp 90–95 °C (0.3 mm Hg; ^{1}H NMR δ 5.12 (s, 2 H), 4.33 (m, 2 H), 1.04 (m, 2 H), 0.02 (s, 9 H); EI-MS m/z 178 ($MH^+ - C_2H_4$). Anal. Calcd for $C_7H_{15}NO_4Si$: C, 40.95; H, 7.36; N, 6.82. Found: C, 41.04; H, 7.37; N, 6.85.

Registry No. (±)-1, 134628-01-6; (+)-1, 134679-77-9; 2, 134628-02-7; 3a (isomer 1), 134628-03-8; 3a (isomer 2), 134679-75-7; 3b (isomer 1), 134628-05-0; 3b (isomer 2), 134679-76-8; 4, 134628-04-9; 5, 118237-87-9; 6, 60410-16-4; $CH_2(NO_2)CO_2Et$, 626-35-7; $CH_2(NO_2)CO_2(CH_2)_2TMS$, 134628-06-1; 2-amino-6-chloropurine, 10310-21-1; (±)-cyclopentadiene monoepoxide, 54460-11-6; (−)-carbovir, 120443-30-3; (±)-carbovir, 118353-05-2.

Supplementary Material Available: Proton NMR spectra of racemic 1 and 4 (2 pages). Ordering information is given on any current masthead page.

Aromatic Fluorination by Silver-Ion Promoted Decomposition of Aryl Diazo Sulfides: Efficient Utilization of Substoichiometric Levels of Fluoride Ion

Serkos A. Haroutounian,† James P. DiZio,‡ and John A. Katzenellenbogen*,‡

Department of Chemistry, Agricultural University of Athens, Votanicos, Athens 301, Greece, and Department of Chemistry, University of Illinois, 1209 West California Street, Urbana, Illinois 61801

Received February 1, 1991 (Revised Manuscript Received May 3, 1991)

Introduction

The thermal decomposition of aryl diazonium tetrafluoroborates or hexafluorophosphates (the Baltz–Schiemann reaction and variants, Scheme I) is widely used as a method for preparing aromatic fluoro compounds.[1] Within certain structural and functional constraints, yields vary from moderate to good.[1b] The Baltz–Schiemann reaction, however, is not well suited for fluorination with the short-lived, positron-emitting radionuclide fluorine-18 ($t_{1/2}$ = 110 min).[2] The reaction is inefficient since, at most, only one-quarter (with BF_4^-) or one-sixth (with PF_6^-) of the total added activity can be incorporated; even more serious is the fact that products with very high specific activity cannot be produced, as exchange of the radiofluorine with the stable fluorine of the counterions (BF_4^- and PF_6^-) results in extensive dilution of activity.[2,3] This situation has stimulated a search for alternative approaches to aromatic fluorination that would be better suited for the efficient preparation of high specific activity fluorine-18 labeled products.[2,4-6] While nucleophilic aromatic substitution has proved to be effective in achieving high specific activity radiofluorination of arene systems with electron-withdrawing groups,[5,6] this approach is not well suited for the direct synthesis of electron-rich arenes. Here, the use of diazonium ions or various precursors appears to be the only alternative, and in this regard, aryl dialkyltriazenes, first used in aromatic fluorination by Wallach in the late 1880's,[7] have been reinvestigated, but have, in general, been found to be unsatisfactory for fluorine radiolabeling.[4]

In this report we present an alternative approach utilizing aryl diazo sulfides—we describe the preparation of several model aryl diazo sulfides[8] and their fluorination with excess, stoichiometric, and substoichiometric levels of fluoride ion. The most satisfactory results come from the use of silver ion to generate the diazonium ion from the diazo sulfide. This reaction appears to be well suited for aromatic fluorination at the tracer level (Scheme II).

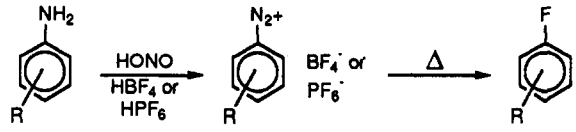
Results and Discussion

The aryl diazo sulfides **3a–e** were prepared in nearly quantitative yield by thiophenol quenching of the aryl diazonium salt **2a–e** (prepared by treatment of the corresponding aniline **1a–e** with nitrous acid; Scheme III).[8] The aryl diazo sulfides are orange to red liquids that are moderately stable (electron poor) to unstable (electron rich) at room temperature, but can be stored indefinitely at −20 °C. For purposes of comparison, some of the corresponding triazene systems were also prepared (**10a–c**). The diazo sulfide systems were selected to represent an

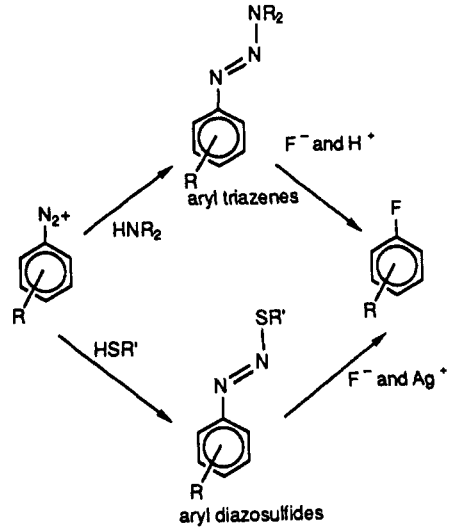
† Agricultural University of Athens.
‡ University of Illinois.

0022-3263/91/1956-4993$02.50/0

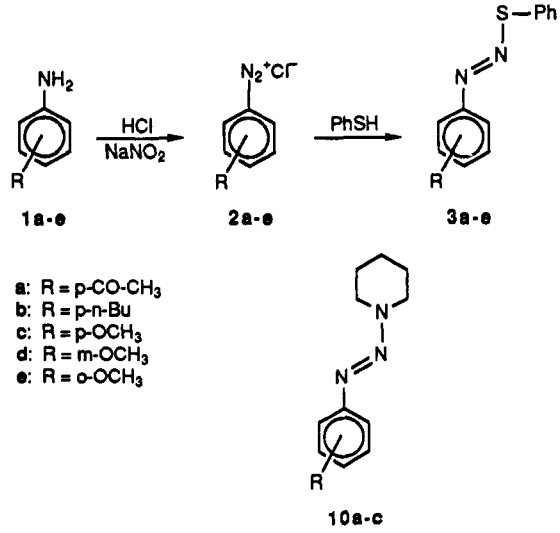
Scheme I



Scheme II



Scheme III



aryl group with an electron-withdrawing substituent **3a**, an alkyl substituent **3b**, and a series with strongly electron-donating substituents **3c–e**, which included an *o*-methoxy-substituted member **3e**, on which fluorination by the Baltz–Schiemann or triazene decomposition method does not work at all.[1,4a]

Scheme IV

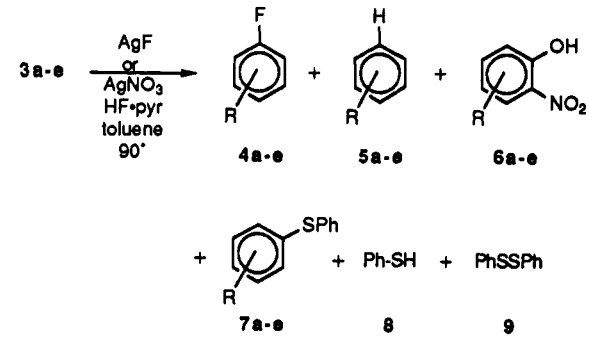


Table I. Yields of Fluorination and Reduction Products from the Silver Ion Promoted Decomposition of Aryl Diazo Sulfides[a]

	% yield of fluorination (4a–c) or reduction (5a–c) from diazo sulfide (3a–c)					
	3a (*p*-Ac)		3b (*p*-*n*-Bu)		3c (*p*-OMe)	
stoichiometry F⁻/diazo sulfide	4a F	5a H	4b F	5b H	4c F	5c H
20:1	71	4	39	54	14	
5:1	44	10	38	42	11	9
1:1	29	22	17	29	9	8
0.5:1	43[b]	22	25[b]	27	12[b]	7
0.1:1	52[b]	25	32[b]	24	21[b]	8

[a] Diazo sulfide and silver nitrate (6 equiv) were warmed with HF–pyridine in toluene for 30 min at 90 °C. Products were quantitated by capillary GLPC with *n*-dodecane as internal standard. For details, see Experimental Section. [b] Yield based on fluoride ion.

Only low yields (<5%) of fluorination products **4a** and **4b** were obtained when the diazo sulfides **3a** and **3b** were warmed with HF–pyridine under conditions suitable for the decomposition of the aryltriazenes.[4,6] Treatment of **3a** and **3b** with "Br–F" generated in situ from HF–pyridine and 1,3-dibromo-5,5-dimethylhydantoin in dichloromethane[9] also failed to give any fluorination product, either at −78 or 25 °C. In all cases, considerable quantities of the corresponding reduced products **5a** and **5b** were formed,

(1) (a) Balz, G.; Schiemann, G. *Chem. Ber.* **1927**, *60*, 1186. (b) Hudlicky, M. *Chemistry of Organic Fluorine Compounds*, 2nd ed.; Ellis Horwood Ltd.: England, 1976.

(2) (a) Welch, M. J. *Radiopharmaceuticals and Other Compounds Labeled with Short Lived Radionuclides*; Pergamon: Oxford, 1977. (b) Fowler, J. S.; Wolf, A. P. *The Synthesis of Carbon-11, Fluorine-18, and Nitrogen-13 Labeled Radiotracers for Biomedical Applications*; National Technical Information Service: Springfield, VA, 1982; (c) Berridge, M. S.; Tewson, T. J. *Appl. Rad. Isotop.* **1986**, *37*, 685. (d) Nickiels, R. J.; Gatley, S. J.; Votaw, J. R.; Kornguth, M. L. *Appl. Radiat. Isot.* **1986**, *37*, 649. (e) Kilbourn, M. R. *Fluorine-18 Labeling of Radiopharmaceuticals*; National Academy Press: Washington, DC, 1990; NAS-NS-3203.

(3) (a) De Kleijn, J. P. *J. Fluorine Chem.* **1977**, *10*, 341. (b) Palmer, A. J.; Eakins, M. N.; Walters, S. L. *Int. J. Appl. Radiat. Isot.* **1977**, *30*, 695.

(4) (a) Ng, J. S.; Katzenellenbogen, J. A.; and Kilbourn, M. R. *J. Org. Chem.* **1981**, *46*, 2520. (b) Widdowson, D. A.; Rosenfeld, M. N. *J. Chem. Soc., Chem. Commun.* **1979**, 914. (c) Tewson, T. J.; Welch, M. *Ibid.* **1979**, 1149. (d) Barrio, J. R.; Satyamurthy, N.; Ku, H.; Phelps, M. *J. Chem. Soc., Chem. Commun.* **1983**, 443. (e) Satyamurthy, N.; Barrio, J. R.; Schmidt, D. G.; Kammerer, C.; Bida, G. T.; Phelps, M. E. *J. Org. Chem.* **1990**, *55*, 4560.

(5) (a) Berridge, M. S.; Crouzel, C.; Cowar, D. *J. Labelled Compds. Radiopharm.* **1985**, *22(7)*, 687. (b) Kilbourn, M. R.; Welch, M. J.; Deuce, C. S.; Tewson, T. J.; Saji, H.; Maeda, M. *Int. J. Appl. Radiat. Isot.* **1989**, *35(7)*, 591. (c) Farrokhzad, S.; Diksic, M. *J. Labelled Compds. Radiopharm.* **1985**, *22(7)*, 721. (d) Shiue, C. Y.; Fowler, J. S.; Wolf, A. P.; McPherson, D. W.; Arnett, C. D.; Zecca, L. *J. Nucl. Med.* **1986**, *27*, 226. (e) Attina, M.; Cacace, F.; Wolf, A. P. *J. Chem. Soc., Chem. Commun.* **1983**, *108*; *J. Labelled Compds. Radiopharm.* **1983**, *10*, 501. (f) Shiue, C.-Y.; Watanabe, M.; Wolf, A. P.; Fowler, J. S.; Savadori, P. *J. Labelled Compds. Radiopharm.* **1984**, *6*, 533. (g) Ding, Y. S.; Shiue, C. Y.; Fowler, J. S.; Wolf, A. P.; Plenevaux, A. *J. Fluorine Chem.* **1990**, *48(2)*, 189.

(6) (a) Maeda, M.; Fukumura, T.; Kojima, M. *Chem. Pharm. Bull.* **1985**, *33*, 1301. (b) Maeda, M.; Fukumura, T.; Kojima, M. *Appl. Radiat. Isot.* **1987**, *38(4)*, 307.

(7) Wallach, O. *Liebigs Ann. Chem.* **1888**, 235, 242, 255.

(8) Aryl diazo sulfides have been used as precursors for aryl diazonium ions, for aromatic substitutions other than fluorination: (a) Brokken-Zup, J.; Bogaert, H. V. D. *Tetrahedron* **1973**, *29*, 4169. (b) VanBaek, L. K.; VanBeek, J. R.; Boven, J.; Schoot, C. J. *J. Org. Chem.* **1971**, *36(5)*, 2194. (c) Smith, P. A. S. *Derivatives of Hydrazine and Other Hydronitrogens Having N–N Bonds*; Benjamin/Cummings: Reading, MA, 1983; pp 150 and 164–5.

(9) (a) Olah, G. A.; Welch, J. T.; Vankar, Y. D.; Nojima, M.; Kerekes, I.; Olah, J. A. *J. Org. Chem.* **1979**, *44*, 3874. (b) Sondej, S. C.; Katzenellenbogen, J. A. *J. Org. Chem.* **1986**, *51*, 3508.

presumably via a homolytic decomposition pathway.[10]

Diazo sulfide **3a** gave a significant yield of aryl fluoride **4a** when allowed to react with silver fluoride in toluene in a two-phase reaction at 90 °C for 30 min (Scheme IV). The yield of fluoro product **4a** with differing AgF to **3a** ratios was as follows: 5:1, 22%; 1:1, 13%; 0.5:1, 5%; and 0.1:1, 1% (with stoichiometries below 1:1, the yield of **4a** was based on the limiting reagent, AgF). Under the same conditions, yields of **4a** from **3a** were much lower with CuOHF and CuF_2. Attempts to conduct the reaction with silver fluoride under more homogeneous conditions, using DMSO, acetonitrile, or *o*-dichlorobenzene as solvent, led mainly to the reduction product **5a**, with only very low yields of aryl fluoride **4a**.

Although the best fluorination yields were obtained with silver fluoride, the reaction did not work well with substoichiometric quantities of AgF, presumably because there was insufficient silver ion to decompose the aryl diazo sulfide via an ionic process.[10] The best results were obtained when the diazo sulfides **3a–e** were treated with a large excess of silver ion (5–10 equiv, as silver nitrate) and varying ratios of fluoride ion (20, 5, 1, 0.5, 0.1 equiv, as pyridinium poly(hydrogen fluoride)) in toluene at 90 °C. The yields of aryl fluoride **4a–c** and the reduction products **5a–c** are presented in Table I.

The best yields of the fluorination product were obtained with the *p*-acetyl-substituted aryl diazo sulfide **3a**. With a large excess of fluoride ion, as is typically used in aryl fluorination reactions, the yield is very high (71%), yet good yields persist when the amount of fluoride ion is decreased, even down to 0.1 equiv.[2-6] Yields for the aryl fluorides **4b** and **c**, derived from the *p*-*n*-Bu- and *p*-OMe-substituted systems **3b** and **c**, though somewhat lower, are still acceptable.

Many mechanisms have been formulated for the reaction of aryl diazonium ions with nucleophiles.[10] Since the yield of fluoro product is highest with diazo sulfide having electron-withdrawing groups or weakly electron-supplying groups (*p*-$COCH_3$ or *n*-Bu), we suggest that a fluoride ion addition–nitrogen elimination mechanism may be operating. A homolytic decomposition to produce the reduced product competes with this mechanism. The yield of the reduction products **4a–c** are highest with the *p*-*n*-Bu-substituted diazo sulfide **3b** and lowest for the *p*-OMe substituted system **3c**.

The yields of fluoro product were not improved when mercuric nitrate or silver acetate were used under the same conditions or when a phase-transfer catalyst such as tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) was employed; in the latter case, reaction was very fast but led mainly to the reduced products. Use of polar solvents such as tetrahydrofuran, acetonitrile, or dimethylformamide resulted in rapid decomposition of the diazo sulfides,[8a,b] but gave low fluorination yields. In contrast, fluorination yields were highest using nonpolar solvents such as toluene, hexane, benzene, and carbon tetrachloride. Toluene was chosen because it allows the reactions to be run at high temperature. Less than 2% yields of aryl fluorides were obtained from diazo sulfides **3d** and **3e**; so, these are omitted from Table I. We have also identified by GC–MS several byproducts **7–9**, which are well-documented as decomposition products of aryl diazo sulfides (Scheme IV).[8]

For comparison purposes we conducted a similar study of aromatic fluorination using decomposition of the corresponding aryltriazenes **10a–c** (Scheme III) with methanesulfonic acid and HF–pyridine in toluene at 90 °C for 20 min. For the *p*-*n*-Bu- and *p*-$COCH_3$-substituted triazene systems **10b** and **10a**, using a variety of triazene/HF–pyridine ratios, we obtained fluorination product yields (ranging from 0–46%) that were, in each case, lower than those obtained with the diazo sulfide method (data not shown). The *p*-OCH_3-substituted system **10a** failed to undergo fluorination. The triazene method also gives higher yields of the reduction (protio) product (1–5 times greater than the fluorination product, depending on the triazene/HF–pyridine ratio).

In conclusion, we have found that aromatic fluorination via silver ion promoted decomposition of aryl diazo sulfides produces moderate to good yields of the fluoroaromatic product in three model systems. The yields of fluorination products are greater than those in the decomposition of the corresponding aryltriazenes, and the generation of the reduction products is lower. Of particular note is the fact that reasonable yields are maintained as the relative amount of fluoride ion is decreased, even to substoichiometric levels, which suggests that this reaction may be useful for the preparation of aromatic compounds labeled with fluorine-18 at high specific activity.

Experimental Section

General. All starting anilines, thiophenol, and pyridinium poly(hydrogen fluoride), as well as all the authentic compounds of fluorine and reduction products, were obtained from Aldrich, except 4-*n*-butylfluorobenzene (**4b**), which was prepared by the described method in a large-scale reaction and was purified by flash column chromatography.[11] The 1-aryl-3,3-dimethyltriazines were prepared according to known procedures[4] and were characterized by elemental and spectroscopic analysis. All solvents were of analytical reagent grade except those used in fluorinations, which were further purified by distillation.

Caution: Pyridinium poly(hydrogen fluoride), while more convenient to use than anhydrous hydrogen fluoride, requires similar safety precautions. It is extremely corrosive to human tissue, and contact with the skin, even in dilute concentrations, can result in painful, slow-healing burns that may not be visible for several hours.[12] *This reagent should only be used in a well-ventilated hood with the user wearing protective clothing (lab coat, rubber gloves, etc.) and a full-face shield. Information dealing on proper safety precautions*[13] *as well as treatments for hydrogen fluoride burns*[12] *is available.*

The reaction products were analyzed by capillary GLPC using a Hewlett-Packard Ultra 1 column. Products were identified by coinjection of authentic standards and further confirmed by GC–MS using a similar column. Products were quantitated relative to an internal standard, *n*-dodecane. Proton magnetic resonance (NMR) spectra were recorded at 300 MHz in $CDCl_3$ as solvent. Melting points are uncorrected. Mass spectra were obtained by electron impact.

General Procedure for Aryl Diazo Sulfide Preparation. Compounds **3a–e** were synthesized by allowing the diazotized arylamines to couple with thiophenol at 2 °C, as described in the literature.[14] The reaction gave orange to red oils that were carefully handled so that exposure to heat and light was minimized. Flash chromatography on silica (1/10 EtOAc/Hex) provided analytically pure products in 40–70% yield (starting from the aniline).

(4-Acetylphenyl)diazo Phenyl Sulfide (3a). Upon refrigeration, the orange oil solidified to a bright yellow-orange solid: mp 31–33 °C; ^1H NMR δ 8.02 (2 H, d, J = 9 Hz), 7.69 (2 H, dd,

(10) (a) Swain, C. G.; Sheats, J. E.; Harbison, K. G. *J. Am. Chem. Soc.* **1975**, *97*(4), 783. (b) Zollinger, H. *Acc. Chem. Res.* **1973**, *6*, 335.

(11) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(12) Trevino, M. A. Herman, G. H.; Sprout, W. L. *J. Occup. Med.* **1983**, *25*, 861.

(13) (a) Pieters, H. A. *Safety in the Chemical Laboratory*; Butterworths Scientific Publications: London, 1951; p 56. (b) Reinehardt, C. F.; Hume, W. G.; Linch, A. L.; Wetherhold, J. M. *Am. Ind. Hyg. Assoc. J.* **1966**, *27*, 166.

(14) Sakla, A. B.; Masoud, N. K.; Sawiris, Z.; Ebaid, W. S. *Helv. Chim. Acta* **1974**, *57*, 481.

J = 8, 1.4 Hz), 7.63 (2 H, d, J = 9 Hz), 7.45–7.55 (3 H, m), 2.62 (3 H, s); IR (KBr) ν_{max} 3080 (w), 2960 (w), 2940 (w), 2820 (w), 1680 (s), 1590 (s), 1570 (s), 1480 (s), 1440 (s), 1285 (m), 1250 (s), 1235 (m), 1045 (s), 1020 (m), 860 (m), 780 (m), 750 (s) cm^{-1}; mass spectrum m/z 230 (M^+ + 2 - 28, 1), 229 (M^+ + 1 - 28, 4), 228 (M^+ - 28, 23), 220 (11), 219 (16), 218 (100), 213 (30), 185 (22), 154 (27), 147 (15), 119 (30), 109 (67), 91 (20), 77 (14), 65 (12). Anal. Calcd for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93; S, 12.51. Found: C, 65.80; H, 4.88; N, 10.94; S, 12.57.

(4-*n*-Butylphenyl)diazo phenyl sulfide (3b): ^1H NMR δ 7.66 (2 H, d, J = 7 Hz), 7.49 (2 H, d, J = Hz), 7.37–7.45 (3 H, m), 7.19 (2 H, d, J = 8 Hz), 2.59 (2 H, t, J = 8 Hz), 1.57 (2 H, m), 1.32 (2 H, m), 0.90 (3 H, t, J = 7 Hz); IR (neat) ν_{max} 3030 (w), 2955 (m), 2920 (m), 2850 (w), 1580 (m), 1475 (s), 1440 (m), 1020 (m), 830 (w), 740 (m) cm^{-1}; mass spectrum m/z 244 (M^+ + 2 - 28, 4), 243 (M^+ + 1 - 28, 11), 242 (M^+ - 28, 56), 220 (10), 219 (15), 218 (100), 199 (83), 185 (16), 154 (24), 109 (69), 91 (22), 65 (8). Anal. Calcd for $C_{16}H_{18}N_2S$: C, 71.07; H, 6.71; S, 11.86. Found: C, 71.17; H, 6.51; S, 12.20.

(4-Methoxyphenyl)diazo phenyl sulfide (3c): ^1H NMR δ 7.65 (2 H, d, J = 7 Hz), 7.55 (2 H, d, J = 9 Hz), 7.35–7.45 (3 H, m), 6.88 (2 H, d, J = 9 Hz), 3.76 (3 H, s); IR (neat) ν_{max} 3060 (m), 3010 (m), 2970 (w), 2930 (w), 2830 (w), 1590 (m), 1580 (s), 1490 (s), 1475 (s), 1440 (s), 1250 (s), 1170 (m), 1020 (m), 830 (m), 800 (w) cm^{-1}. Anal. Calcd for $C_{13}H_{12}N_2OS$: C, 63.91; H, 4.95; N, 11.47; S, 13.12. Found: C, 64.12; H, 5.08; N, 11.25; S, 13.16.

(3-Methoxyphenyl)diazo phenyl sulfide (3d): ^1H NMR δ 7.44 (2 H, d, J = 8.9 Hz), 7.34 (1 H, d, J = 8.2 Hz), 6.92–7.30 (5 H, m), 6.71 (1 H, dd, J = 8.4, 1.7 Hz), 3.63 (3 H, s); IR (neat) ν_{max} 3080 (w), 3000 (w), 1960 (w), 2940 (w), 2830 (w), 1590 (s), 1575 (s), 1480 (s), 1440 (s), 1285 (m), 1250 (s), 1045 (s), 860 (m), 780 (m), 750 (s), 710 (w) cm^{-1}. Anal. Calcd for $C_{13}H_{12}ON_2S$: C, 63.91; H, 4.95; N, 11.47; S, 13.12. Found: C, 63.85; H, 4.96; N, 11.42; S, 13.17.

(2-Methoxyphenyl)diazo Phenyl Sulfide (3e). After purification, the orange oil was taken up in ether/petroleum ether, and then the solvent was evaporated. Upon refrigeration the orange oil solidified to a light orange solid: mp 31–33 °C; ^1H NMR δ 7.49 (2 H, d, J = 8.9 Hz), 7.31 (1 H, dd, J = 8.3, 2.4 Hz), 7.07–7.24 (5 H, m), 6.78 (1 H, dd, J = 8.3, 2.5 Hz), 3.71 (3 H, s); IR (neat) ν_{max} 3060 (w), 3010 (w), 2960 (w), 2930 (w), 2830 (w), 1580 (m), 1480 (s), 1440 (m), 1250 (s), 1170 (m), 1025 (s), 750 (s), 705 (m) cm^{-1}. Anal. Calcd for $C_{13}H_{12}ON_2S$: C, 63.91; H, 4.95; N, 11.47; S, 13.12. Found: C, 64.28; H, 5.14; N, 11.16; S, 12.88.

General Procedure for Fluorination Reaction. A portion (100 μmol) of diazo sulfide and a precise amount of *n*-dodecane (internal standard) was weighed in a polyethylene vial. Toluene was added (0.75 mL), and the solution was cooled in an ice bath. Stirring was initiated, and HF–pyridine then was added. When a 20- or 5-fold excess of HF was used, it was added as neat pyridinium poly(hydrogen fluoride); for lower stoichiometries, a freshly prepared 0.5 or 0.2 M solution in THF was used. Immediately thereafter, 6–10 equiv of $AgNO_3$ was added, and the vial was sealed with a Teflon-lined screw cap and gradually warmed to 90 °C for 30 min with continued stirring. The reaction mixture was then cooled and filtered through a small silica gel column, eluting with acetone.

Product yields were determined through GC analysis of the eluate. This was achieved with the aid of a calibration curve which related the response factors of the product with the response factors of the internal standard, *n*-dodecane. The fluorinated products were identified by GC–MS and by coinjection on the GC with authentic samples. Byproducts were determined either by GC–MS and coinjection or by ^1H NMR and mass spectra analysis.

Acknowledgment. We are grateful for support of this work by a grant from the National Institutes of Health (PHS 5RO1 CA25836). The assistance of D. O. Kiesewetter in preliminary studies is acknowledged, as is the help of R. Srinivasan. Mass spectroscopic analysis was performed on instruments supported by the National Institutes of Health (GM27029).

Registry No. **1a**, 99-92-3; **1b**, 104-13-2; **1c**, 104-94-9; **1d**, 536-90-3; **1e**, 90-04-0; **3a**, 111278-45-6; **3b**, 134705-05-8; **3c**, 114650-58-7; **3d**, 114650-57-6; **3e**, 107046-27-5; **4a**, 403-42-9; **4b**, 20651-65-4; **4c**, 459-60-9; **5a**, 98-86-2; **5b**, 104-51-8; **5c**, 100-66-3; **8**, 108-98-5; **10a**, 87261-60-7; **10b**, 77153-60-7; **10c**, 74148-29-1; silver ion, 14701-21-4.

A Facile Synthesis of α,ω-Dicarboxylic Acids Containing Perfluoroalkylene Groups

Hisao Urata, Yoshihiro Kinoshita, Tatsuya Asanuma, Osamu Kosukegawa, and Takamasa Fuchikami*

Sagami Chemical Research Center, 4-4-1, Nishi-Ohnuma, Sagamihara, Kanagawa 229, Japan

Received December 18, 1990

Introduction

A variety of fluorine-containing polymers have been used as gas-permeable membranes, contact lenses, optical fiber sheathing materials, photoresistors, or biomedical materials.[1] They display the characteristic virtues of water and oil repellency, low surface energy, high affinity for oxygen, high chemical and light resistance, and bioinactivity. Fluorinated difunctional monomers like polyfluorinated α,ω-dicarboxylic acids and α,ω-diisocyanates are among the most promising starting materials for the synthesis of a new class of such polymers via condensation polymerization and addition polymerization. Two types of these fluorinated monomers have been described: type A diacids of the formula $HO_2CCH_2(CF_2)_nCH_2CO_2H$ (n = 2, 4, 6)[2,3] and type B diacids of the formula $HO_2CCH_2CH_2(CF_2)_nCH_2CH_2CO_2H$ (n = 3, 4).[4,5] In type A diacids, the α-hydrogen atoms are strongly acidic, and elimination of HF takes place easily under basic conditions. In type B acids, the α-hydrogen atoms are less acidic, which should make the chemical stability of polymers derived from such acids superior to that of polymers derived from type A diacids. However, the known methods for the synthesis of type B diacids are not straightforward. Obviously, an industrially feasible synthesis of such compounds is highly desirable. We recently described the perfluoroalkylation of carbon–carbon multiple bonds[6] and of aromatic rings,[7] and the carbonylation[8] of perfluoroalkyl-substituted organic compounds, both catalyzed by transition-metal complexes. The polyfluorinated organic compounds so obtained are expected to be versatile building blocks for

(1) Kato, M.; Takakura, T.; Yamabe, M.; Okano, T.; Kataoka, K.; Sakurai, Y.; Imachi, K.; Atsumi, K. *Prog. Artif. Organs* **1983**, *2*, 858.
(2) Drysdale, J. J. U.S. Pat. 2871260, 1959; *Chem. Abstr.* **1959**, *53*, P12186cd.
(3) Takakura, T.; Yamabe, M.; Kato, M. *J. Fluorine Chem.* **1988**, *41*, 173.
(4) (a) Brace, N. O. *J. Org. Chem.* **1962**, *27*, 3033. (b) Moore, L. D. *J. Chem. Eng. Data* **1964**, *9*, 251.
(5) Bloechl, W. Fr. Pat. 1404744, 1965; *Chem. Abstr.* **1965**, *63*, 11367g.
(6) (a) Fuchikami, T.; Ojima, I. *Tetrahedron Lett.* **1984**, *25*, 303. (b) Idem., *Ibid.* **1984**, *25*, 307. (c) Fuchikami, T.; Shibata, Y.; Urata, H. *Chem. Lett.* **1987**, 521.
(7) Fuchikami, T.; Ojima, I. *J. Fluorine Chem.* **1983**, *22*, 541. (b) Urata, H.; Fuchikami, T. *Tetrahedron Lett.* **1991**, *32*, 91.
(8) (a) Fuchikami, T.; Ojima, I. *J. Am. Chem. Soc.* **1982**, *104*, 3257. (b) Fuchikami, T.; Ohishi, K.; Ojima, I. *J. Org. Chem.* **1983**, *48*, 3803. (c) Ojima, I.; Hirai, K.; Fujita, M.; Fuchikami, T. *J. Organomet. Chem.* **1984**, *279*, 203. (d) Ojima, I.; Kato, K.; Okabe, M.; Fuchikami, T. *J. Am. Chem. Soc.* **1987**, *109*, 7714. (e) Urata, H.; Yugari, H.; Fuchikami, T. *Chem. Lett.* **1987**, 833. (f) Urata, H.; Kosukegawa, O.; Ishii, Y.; Yugari, H.; Fuchikami, T. *Tetrahedron Lett.* **1989**, *30*, 4403. (g) Urata, H.; Ishii, Y.; Fuchikami, T. *Tetrahedron Lett.* **1989**, *30*, 4407.

0022-3263/91/1956-4996$02.50/0