p-**Chlorophenyl Cyclohexylidenemethyl Sulfone (VII).**—The solution of diethyl (*p*-chlorophenylsulfono)methylphosphonate anion was stirred at −78° for 2 hr before addition of cyclohexanone. Work-up involved stirring at 50° for 4 hr. The crude product (2.865 g of yellow oil) was purified by column chromatography over 100 g of Florisil with benzene eluent, to give 1.953 g (72% of VII, mp 70–71.5°) upon evaporation. Recrystallization from ethanol gave 1.782 g of white needles: mp 71–72.5°; nmr δ 1.6 (broad s, 6 H, cyclohexyl protons β and γ to double bond), 2.2 (broad s, 2 H, cyclohexyl protons α to double bond), 2.79 (broad s, 2 H, cyclohexyl protons α to double bond), 6.20 (s, 1 H, vinyl proton), 7.55 (d, 2 H, J = 9 Hz, aromatic protons), and 7.92 (d, 2 H, J = 9 Hz, aromatic protons); ir 2925, 2845 (CH), 1620, 1580 (C=C), 1140, 1083 cm^{-1} (SO_2).

Anal. Calcd for $C_{13}H_{15}SO_2Cl$: C, 57.66; H, 5.58; S, 11.84; Cl, 13.09. Found: C, 57.79; H, 5.67; S, 11.98; Cl, 12.92.

Registry No.—II, 35324-47-1; III, 35378-30-4; IV, 35378-31-5; V, 7854-83-7; VI, 35324-49-3; VII, 35324-50-6.

Synthesis of Sulfonyl Fluorides by Use of a Fluoride Ion Exchange Resin

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We wish to report an extremely rapid and efficient method for the synthesis of small quantities of sulfonyl fluorides from the corresponding sulfonyl chlorides by ion exchange chromatography. The technique is characterized by high yields (82–94%, starting with 1 g of aromatic sulfonyl chloride) and pure products which are easily isolated by evaporation of the solvent and need no recrystallization.

Experimental Section

General.—Melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were measured on a Perkin-Elmer Model 700 spectrophotometer. Solvents were evaporated on a Buchler flash evaporator. Elemental analyses were determined by Galbraith Laboratories, Knoxville, Tenn.

Starting Materials.—2,4-Dinitrobenzenesulfonyl chloride, *p*-chlorobenzenesulfonyl chloride, *p*-bromobenzenesulfonyl chloride, and *p*-fluorosulfonylbenzenesulfonyl chloride were purchased from Aldrich Chemical Co. *p*-Nitrobenzenesulfonyl chloride and *m*-nitrobenzenesulfonyl chloride were purchased from Matheson Coleman and Bell. *p*-Toluenesulfonyl chloride was obtained from Eastman Organic Chemicals, and methanesulfonyl chloride was a product of the J. T. Baker Co. For the purposes of comparison, authentic samples of *p*-nitrobenzenesulfonyl fluoride, *m*-nitrobenzenesulfonyl fluoride, *p*-chlorobenzenesulfonyl fluoride, and *p*-bromobenzenesulfonyl fluoride were synthesized by the method of Davies and Dick.[2]

Preparation of the Fluoride Anion Exchange Resin.—The strongly basic quaternary amine anion exchange resin, AG1-X10 (200–400 mesh), was purchased from Bio-Rad Laboratories in the chloride form. Oven-dried resin (80 ml, 40 g) was suspended in water and transferred to a burette. The resin was eluted with 5.0 *M* aqueous potassium fluoride, at a rate of 150 ml per hour, until a spot test of the eluate with aqueous $AgNO_3$ indicated the absence of chloride. Approximately 3 l. of 5.0 *M* KF solution was needed to elute the chloride from the resin.[3] The fluoride form resin was washed with three 100-ml portions of distilled water, dried in an oven at 115° for 2 hr, and stored in a desiccator. This preparation yielded 38.7 g of dried resin.

Synthesis of Sulfonyl Fluorides.—The oven-dried fluoride form resin (5 ml) was transferred to a 10-ml B-D disposable syringe and washed with 20 ml of acetonitrile. The appropriate sulfonyl chloride (1.000 g) was dissolved in 10 ml of acetonitrile and passed through the resin at a rate of approximately 1 ml/min.[4] The resin was then washed with two 5-ml portions of acetonitrile, and the combined eluent and washings were evaporated to near dryness on a rotary evaporator. On cooling in an ice bath for several minutes, the solid products crystallized. For the synthesis of methanesulfonyl fluoride (**8**), the quantities were increased by a factor of 3, and the final product was purified by microdistillation.

Results and Discussion

The results of the synthesis of eight different sulfonyl fluorides from the corresponding sulfonyl chlorides by the ion exchange method are indicated in Table I.

TABLE I
SYNTHESIS OF SULFONYL FLUORIDES BY USE OF A FLUORIDE ION EXCHANGE RESIN[a]

Compd	No.	Mp (bp), °C	Lit. mp (bp), °C	Yield, %
4-Bromobenzenesulfonyl fluoride	1	64–65	65–66[b]	92
4-Chlorobenzenesulfonyl fluoride	2	47–48	47–48[c]	82
p-Toluenesulfonyl fluoride	3	39–41	41–42[c]	86
3-Nitrobenzenesulfonyl fluoride	4	45–46	46–47[b]	86
4-Nitrobenzenesulfonyl fluoride	5	76–77	75–78[b]	89
2,4-Dinitrobenzenesulfonyl fluoride	6	97.5–98.5	*d*	91
1,4-Benzenedisulfonyl fluoride	7	155–156	*e*	94
Methanesulfonyl fluoride	8	(120–122)	(124)[f]	71

[a] Acetonitrile used as solvent. [b] See M. E. Aberlin and C. A. Bunton, *J. Org. Chem.*, **35**, 1825 (1970). [c] See ref 2. [d] Not reported in literature. Recrystallized from absolute ethanol. *Anal.* Calcd for $C_6H_3FN_2O_6S$: C, 28.45; H, 1.44. Found: C, 28.56; H, 1.50. [e] Not reported in literature. Recrystallized from ethanol–water. *Anal.* Calcd for $C_8H_4F_2O_4S_2$: C, 29.75; H, 1.66. Found: C, 29.55; H, 1.54. [f] See W. Davies and J. H. Dick, *J. Chem. Soc.*, 483 (1932).

These results were obtained using acetonitrile as solvent. They indicate high purity, as determined by the comparison of melting points to literature values for reported compounds, and by comparison of infrared spectra to those of the authentic materials for compounds **1–4**.

Infrared spectra were a useful tool in determining the extent of conversion of the sulfonyl chlorides to sulfonyl fluorides. The strong asymmetric and symmetric sulfur–oxygen stretching frequencies of aromatic sulfonyl chlorides occur at 1385–1340 and 1185–1160 cm^{-1}, respectively.[5] On conversion to the sulfonyl

(1) (a) Taken in part from the Senior Independent Study Thesis of D. L. MacDonell, The College of Wooster, 1972. (b) NSF undergraduate research participant, summer, 1971.

(2) W. Davies and J. H. Dick, *J. Chem. Soc.*, 2104 (1931).

(3) Subsequent regeneration steps required approximately 2 l. of 5.0 *M* aqueous KF.

(4) When the sulfonyl chloride was dissolved in 50 ml of acetonitrile and passed through the resin, a low yield of impure product was obtained.

(5) R. T. Conley, "Infrared Spectroscopy," Allyn and Bacon, Boston, Mass., 1966, p 181.

fluorides, these stretching frequencies are shifted to 1420–1395 and 1235–1200 cm^{-1}. In addition a very strong peak, due to the vibrational stretching of the sulfur–fluorine bond, appears at 800–750 cm^{-1}.[6]

Several encouraging aspects of this work include the high yields obtainable with small quantities of starting material (Table I), and the applicability of this technique to the synthesis of aliphatic sulfonyl fluorides. This type of compound is more difficult to synthesize than analogous aromatic sulfonyl fluorides. It is reported by Davies and Dick to require longer reaction times at higher temperatures, and produces lower yields of product.[7] When methanesulfonyl chloride was passed through the fluoride resin in this work, under the identical conditions used for aromatic analogs, methanesulfonyl fluoride (**8**) was produced in 71% yield.

The choice of solvents for the described technique was fairly critical. Since at least some of the reacting species were ionic, the dielectric constant of the solvent was a determining factor. An added consideration was that the solvent should not undergo reaction with the starting material or product. Acetonitrile was the obvious choice, and proved to give excellent results. Methanol was also tried, but infrared analysis of the products obtained using methanol as solvent and eluent indicated that only a portion of the starting material had been converted to the sulfonyl fluoride, while the major portion of the product was undoubtedly the methyl sulfonate.

Strongly basic quaternary amine type anion exchange resins have a low affinity for fluoride ion.[8] In fact, fluoride has the lowest affinity for Bio-Rad AG1 resins of some 16 monovalent anions reported in the commercial literature of this compound.[9] Sulfonyl fluorides are also much less reactive than the corresponding sulfonyl chlorides.[2,10] Thus, when fluoride exchanges with the chloride in the sulfonyl chlorides, the chloride generated binds tightly to the resin and the resulting more stable sulfonyl fluoride is easily isolated in the eluent from the resin. Another advantage of using the resin technique is that any sulfonic acids resulting from hydrolysis of the sulfonyl halides would have a very strong affinity for the resin,[8] and would thus be separated from the sulfonyl fluoride.

The large amount of fluoride necessary to convert a small amount of the resin from the chloride to the fluoride form bear out the observations of Gregor, *et al.*[8] This large amount of fluoride is rather prohibitive if one were to attempt to use this technique to synthesize sulfonyl fluorides in large quantities. Still, we feel that it is a very valuable method where small quantities or difficult-to-obtain starting materials are involved.

We are pursuing the use of the fluoride ion exchange resin described here in the synthesis of other fluorine-containing compounds.

Registry No.—2,4-Dinitrobenzenesulfonyl fluoride, 35426-71-2; 1,4-benzenedisulfonyl fluoride, 35426-72-3.

(6) C. J. Pouchert, "The Aldrich Library of Infrared Spectra," Aldrich Chemical Co., Inc., 1970, p 839.
(7) W. Davies and J. H. Dick, *J. Chem. Soc.*, 483 (1932).
(8) H. P. Gregor, J. Belle, and R. A. Marcus, *J. Amer. Chem. Soc.*, **77**, 2713 (1955).
(9) Price List W, Bio-Rad Laboratories, June 1971, p 12.
(10) C. G. Swain and C. B. Scott, *J. Amer. Chem. Soc.*, **75**, 246 (1953).

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The Stepwise Removal of the *S*-*p*-Nitrobenzyl Protecting Group

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In the course of our work on 4-thio-substituted β-lactams[1] the need for a sulfhydryl protecting group which can be removed without destroying the β-lactam ring arose. It was initially considered that the *p*-nitrobenzyl group, proposed by Berse and coworkers[2] as a sulfur protecting group, can fulfill this requisite. According to these authors the *p*-nitrobenzyl group is removable from *S*-*p*-nitrobenzyl-L-cysteine by catalytic hydrogenation in the presence of palladium/charcoal. A similar reductive cleavage was postulated by Baker and Kozma[3] who reported that catalytic hydrogenation of 2- and 8-*p*-nitrobenzylthiohypoxanthine afforded the respective 2- and 8-mercaptohypoxanthine and *p*-toluidine; unfortunately no quantitative figures were given. Although it could have been expected that a protective group having this quality would be widely used in peptide syntheses, the removal of the *S*-*p*-nitrobenzyl group from peptide derivatives has not yet been described.[4] This protecting group was applied by Katsoyannis[5] for the protection of cysteine in the synthesis of some peptides related to insulin, but no experiments describing its removal were reported. Ondetti and Bodanszky[6] reported that *N*-benzyloxycarbonyl-*S*-*p*-nitrobenzyl-L-cysteinylglycine was catalytically hydrogenated to *N*-benzyloxycarbonyl-*S*-*p*-aminobenzyl-L-cysteinylglycine, and *S*-*p*-nitrobenzyl-L-cysteine was reduced to *S*-*p*-aminobenzyl-L-cysteine (only R_f values are given for the last compound). Similarly Hiskey and Tucker[7] observed the absorption of the required amount of hydrogen for the catalytic hydrogenation of ethyl *N*-benzyloxycarbonyl-*S*-*p*-nitrobenzylcysteinate but could not isolate any thiol. The stepwise removal of the sulfur protecting group from *S*-*p*-nitrobenzyl-L-cysteine which is described in the present paper might offer an explanation for the discrepancy between the reported[2,6,7] results.

Hydrogenation of *S*-*p*-nitrobenzyl-L-cysteine in the presence of 10% palladium/charcoal, under the condi-

(1) M. D. Bachi and O. Goldberg, *J. Chem. Soc., Chem. Commun.*, 319 (1972).
(2) C. Berse, R. Boucher, and L. Piche, *J. Org. Chem.*, **22**, 805 (1957).
(3) B. R. Baker, and J. Kozma, *J. Med. Chem.*, **10**, 682 (1967).
(4) For examples and references to the use of sulfhydryl protecting groups in peptide synthesis, see E. Schröder and K. Lübke (transl. E. Gross) in "The Peptides," Academic Press, New York and London, Vol. 1, 1965; M. Bodanszky and M. A. Ondetti, "Peptides Synthesis," Interscience, New York, N. Y., 1966; J. H. Jones in "Amino Acids, Peptides, and Proteins," Vol. I, The Chemical Society Specialist Periodical Reports, London, 1969, Chapter 3, and Vol. II, 1970, Chapter 3.
(5) P. Katsoyannis, *J. Amer. Chem. Soc.*, **83**, 4053 (1961).
(6) M. A. Ondetti and M. Bodanszky, *Chem. Ind. (London)*, 697 (1962).
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