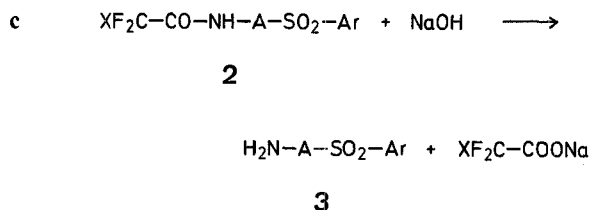
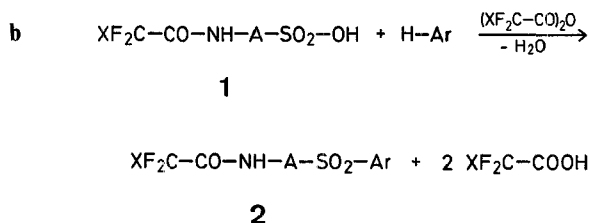
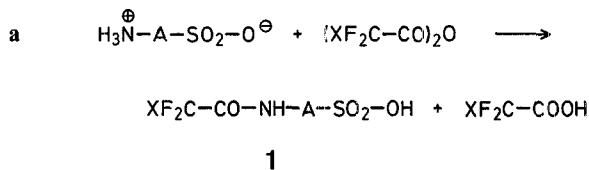


Several attempts on our part to extend this approach to the preparation of aminoaryl sulfones gave none of the desired product, and the method was concluded to be inapplicable. It is not surprising that the aminosulfonic acids, which exist as zwitterions (cf. Reaction a), should differ in their ability to form sulfones from sulfonic acids not containing a basic group.

We have found that heating an aminosulfonic acid with trifluoroacetic (or chlorodifluoroacetic) anhydride and an aromatic compound yields trifluoroacetaminoaryl sulfones (or the chlorodifluoroacetyl analogues) (2), via Reactions a and b; hydrolysis (Reaction c) yields the free bases (3):



A = arylene

X = F, Cl

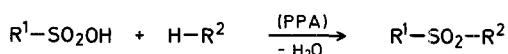
Aminoaryl Sulfones; A New Preparative Procedure

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Known procedures for preparing aminoaryl sulfones are limited in scope and/or involve several steps. One method involves reaction of 2- or 4-chloronitrobenzene with an aromatic thiol, followed by oxidation of the sulfide to the sulfone and reduction of the nitro group to amino^{1,2}. Another approach² comprises reaction of 4-acetaminobenzenesulfonyl chloride with an aromatic compound in the presence of aluminum chloride, followed by hydrolytic removal of the acetyl group.

A widely applicable procedure for preparing sulfones, first observed by Proctor and Thomson³ and later studied in detail by Graybill⁴, involves reaction of a sulfonic acid with an aromatic hydrocarbon in the presence of polyphosphoric acid (PPA):



This general procedure was used to prepare the aminoaryl sulfones listed in Tables 1 and 2. It will be noted that the amino group can be located *ortho*, *meta*, or *para* to the sulfone group, and that the aminosulfonic acid can also contain alkyl or halogen groups, or be derived from benzene or naphthalene. The aromatic compound reacted with the sulfonic acid can be benzenoid or naphthalene, or substituted by mono- or polyalkyl, aryl, aryloxy, arylthio, or halogen.

It has been shown⁹ that trifluoroacetic anhydride induced sulfone formation between *p*-toluenesulfonic acid and anisole or mesitylene; however, aminosulfonic acids were not considered in this study.

Discussion of Process Variables

Our usual procedure involves refluxing a mixture of the aminosulfonic acid, the aromatic substrate to be converted to the sulfone, trifluoroacetic acid, and trifluoroacetic anhydride. Use of the trifluoroacetic acid is optional, since equivalent results are obtained without it, although a longer reaction time is required. This is presumed to result from the higher reaction temperature attained by adding the acid (b. p. 72°) to the anhydride (b. p. 39°).

Table 1. Amino Sulfones Derived from Sulfanilic Acid

Substrate	Reaction time hr	Trifluoroacetyl Derivative ^a				Free Base			
		m. p.	Analysis	Spectra ^b I. R. N. M. R.		m. p.	Analysis	Spectra I. R. N. M. R.	
Benzene	72	182–184°	calc. C 51.2 H 3.0 found 51.4 3.3	×	×	173–175° ^c	calc. C 62.0 H 4.3 found 62.3 4.3	×	×
Toluene	6	186–189°	calc. C 52.5 H 3.5 found 52.4 3.6			180–182° ^d	calc. C 63.1 H 5.3 found 63.2 5.3	×	
<i>p</i> -Xylene	8	175–177°	calc. C 53.9 H 3.9 found 54.2 3.8	×	×	157–159° ^e	calc. C 64.5 H 5.8 found 64.4 5.9	×	×
Mesitylene	8	192–194°	calc. C 55.0 H 4.3 found 55.0 4.1			193–195° ^e	calc. C 65.5 H 6.2 found 65.3 6.0		
Naphthalene	24	160–163°	calc. C 57.0 H 3.2 found 56.9 3.3			203–205° ^f	calc. C 67.8 H 4.6 found 67.6 4.5		
Biphenyl	6	231–233°	calc. C 59.9 H 3.5 found 59.7 3.7			242–244° ^e	calc. C 70.0 H 4.9 found 69.9 5.0	×	
Chlorobenzene	96	174–176°	calc. C 46.3 H 2.1 found 46.6 1.9	×	×	182–186° ^g	calc. C 53.9 H 3.8 found 53.9 4.1	×	×
Diphenyl sulfide	6	149–151°	calc. C 55.0 H 3.2 found 55.0 3.0	×	×	174–176° ^h	calc. C 63.4 H 4.4 found 63.5 4.3	×	×
Diphenyl oxide	6	210–213°	calc. C 57.1 H 3.3 found 57.2 3.6	×	×	175–177° ⁱ	calc. C 66.5 H 4.6 found 66.7 4.6		
Mesitylene ^j	3.5	173–175°	calc. C 52.6 H 4.1 found 52.8 3.8			j			

^a All of the compounds in this column are new.^b "×" indicates that the spectrum agreed with the assigned structure; compounds not so designated were not studied.^c Ref.¹, m. p. 175–176°.^d Ref.⁵, m. p. 181–185°.^e New compound.^f Ref.³, m. p. 202°.^g Ref.⁶, m. p. 183–187°.^h Supposedly cited in Ref.⁸; this compound could not be positively identified therein.ⁱ Ref.⁷, m. p. 176°.^j This sulfone was prepared using chlorodifluoroacetic anhydride, (ClF₂C—CO)₂O; the free base had the same m. p. and mixture m. p., and I. R. spectrum as that prepared from trifluoroacetic anhydride, (F₃C—CO)₂O.Table 2. Miscellaneous Amino Aryl Sulfones^a

Sulfonic acid	Hydrocarbon	Reaction time hr	Trifluoroacetyl Derivative		Free Base	
			m. p.	Analysis	m. p.	Analysis
		24	143–145°	calc. C 53.8 H 3.9 found 53.9 4.0	125–127°	calc. C 64.5 H 5.8 found 64.4 5.5
		24	161–163°	calc. C 55.0 H 4.3 found 55.2 4.5	147–149°	calc. C 65.5 H 6.2 found 65.4 6.3
		96	207–210°	calc. C 59.1 H 4.1 found 59.4 4.1	206–208°	calc. C 69.5 H 5.5 found 69.4 5.6
		8	150–156°	calc. C 50.3 H 3.7 found 50.4 3.8	206–208°	calc. C 58.0 H 5.2 found 58.2 5.4

^a All compounds in this table are new.

The aminosulfonic acid is initially insoluble in the warm reaction mixture, but gradually dissolves over a period of time (apparently determined by the temperature), forming a clear solution. This corresponds to acylation by Reaction a, as was proven by conducting the reaction in the absence of a sulfone-forming aromatic compound. A species of structure 1 was isolated and identified as the aniline salt. Direct acylation of aminosulfonic acids is apparently previously unknown, although acetylation of the alkali metal salts is easily effected. Efforts on our part to employ acetic anhydride, or the higher-boiling isobutyric anhydride, in Reaction a were unsuccessful. On the other hand, much more rapid acylation was achieved by using a mixture of chlorodifluoroacetic anhydride (b.p. 94°) and chlorodifluoroacetic acid (b.p. 122°), with a correspondingly higher reflux temperature.

The usual procedure involves mixing all the reagents followed by heating—i.e. conducting Reaction a and b simultaneously. Equally satisfactory results were obtained by heating the mixture without the sulfone-forming aromatic compound until a clear solution was obtained by Reaction a, followed by adding the aromatic compound and further heating to effect Reaction b. No advantage is seen from using the stepwise procedure, however.

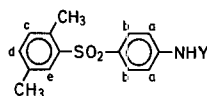
Melting points were taken in capillary tubes on a Mel-Temp apparatus and are uncorrected. Trifluoroacetic anhydride and acid were obtained from Specialty Chemicals Division, Allied Chemical Corporation, Morristown, N.J. The proton N.M.R. spectra were obtained on a Varian Associates Model A-60 Spectrometer in deuteroacetone solution with tetramethylsilane as internal reference. I.R. spectra were taken on a Perkin-Elmer Model 521 Spectrophotometer.

The following procedure is typical.

4-Amino-2',5'-dimethyldiphenyl Sulfone:

2',5'-Dimethyl-4-trifluoroacetaminodiphenyl Sulfone: Sulfanilic acid monohydrate (5.0 g, 0.26 mmol), *p*-xylene (3.0 g, 28 mmol), trifluoroacetic acid (20 g), and trifluoroacetic acid anhydride (21 g, 0.1 mol) were mixed and refluxed with magnetic stirring in an Erlenmeyer flask for 8 hr. The sulfanilic acid gradually dissolved over a period of ~6 hr, yielding a clear solution. After the 8 hr heating period, the solution was evaporated to dryness; yield: 9.5 g 2',5'-dimethyl-4-trifluoroacetaminodiphenyl sulfone as hard, colorless solid (theoretical yield is 8.9 g). Recrystallization from butanol gave the sulfone in pure form; m.p. 175–177° (for analytical data, see Table 1).

I.R. (KBr): 3320 and 3180 cm^{-1} (NH), 3100 and 3500 (aromatic CH), 2940, 2910, and 2850 (aliphatic CH), 1715 (amide I), 1590 and 1580 (phenyl mode), 1530 (amide II), 1280 and 1270 (asymmetric SO_2), 1235 and 1185 (CF stretch), 1130 (symmetric SO_2), and 1075 and 1045 ($\text{C}_6\text{H}_5\text{—S}$).



N.M.R. (acetone- d_6) for $\text{Y} = \text{F}_3\text{C—CO—}$: $\delta = 2.40$ (s, 6H, CH_3), 7.25 (d, 1H, H^c , $J_{cd} = 8$ Hz), 7.40 (d, 1H, H^d , $J_{cd} = 8$ Hz), 8.00 (s, 4H, H^a , H^b), 8.07 (s, 1H, H^c); —NH— not observed.

4-Amino-2',5'-dimethyldiphenyl Sulfone: Hydrolysis of the trifluoroacetamino sulfone to the free base was effected as follows.

The sulfone was mixed with 10% sodium hydroxide at room temperature, yielding a clear solution. Upon warming, the free base began to precipitate immediately. After heating at 100° for 5 min, the amino sulfone was filtered, washed and air-dried; yield: quantitative; m.p. 157–159° (for analytical data, see Table 1).

I.R. (KBr): 3440 and 3360 cm^{-1} (NH stretch), 1625 (NH deformation), 1580 (phenyl mode), 1255 and 1130 (asymmetric and symmetric SO_2), 1080 ($\text{C}_6\text{H}_5\text{—S}$), other bands at 810, 700, 655, 580, and 510.

N.M.R. (acetone- d_6) for $\text{Y} = \text{H}$: $\delta = 2.32$ (s, 3H, $m\text{—CH}_3$), 2.40 (s, 3H, $o\text{—CH}_3$), 5.52 (s, 2H, NH_2), 6.80 (d, 2H, H^a , $J_{ab} = 9$ Hz), 7.15 (d, 1H, H^c , $J_{cd} = 8$ Hz), 7.32 (d, 1H, H^d , $J_{cd} = 8$ Hz), 7.62 (d, 2H, H^b , $J_{ab} = 9$ Hz), 7.99 (s, 1H, H^e).

The other sulfones in Tables 1 and 2 were prepared similarly, except for the indicated variations in reaction times. Yields in all cases were nearly theoretical.

4-Trifluoroacetaminobenzenesulfonic Acid:

Sulfanilic acid monohydrate, trifluoroacetic acid, and trifluoroacetic anhydride were mixed in the proportions given above and refluxed with stirring until a clear solution was obtained (~6 hr). The solution was evaporated to dryness; yield: 7.0 g solid (theoretical yield is 6.8 g). Recrystallized from concentrated hydrochloric acid, the sulfonic acid softened at ~180°, and blackened without melting upon heating to 350°. The crude sulfonic acid (2.7 g–10 mmol) was dissolved in water (10 ml), aniline (1 g–11 mmol) was added, and the mixture was heated to boiling. The clear solution was cooled and the aniline salt was crystallized, filtered, and dried. It was recrystallized from hot water, m.p. 280–300°.

$\text{C}_{14}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_4\text{S}$	calc.	C 46.5	H 3.6
	found	46.8	3.4

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