Synthesis of Arylsulfamic Acid Esters using Phase-Transfer and Triethylamine-Mediated Methods

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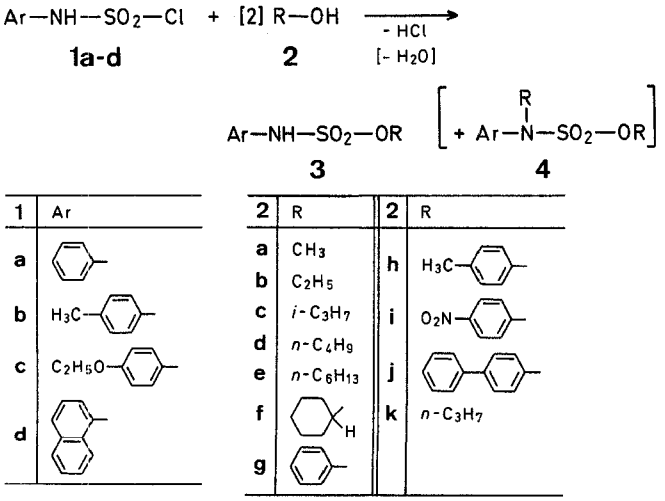
There are only a few examples in the literature of the synthesis of esters of arylsulfamic acids[1-5]. Methyl phenylsulfamate **(3aa)** has been prepared in 23% yield by photolysis of benzenesulfonyl azide in methanol and both **3aa** and ethyl phenylsulfamate **(3ab)** have been obtained in ~65% yield by reaction of the triethylammonium salt of *N*-(4-nitrophenylsulfonyloxy)-benzenesulfonamide with methanol or ethanol, respectively, over a few days at room temperature[1]. Reaction of appropriate arylaminosulfonyl azides[2] or azide salts[3] with methanol or isopropanol gave methyl *N*-(4-acetylaminophenyl)-sulfamate or isopropyl *N*-(4-methylphenyl)-sulfamate, respectively, in ~75% yields. Compound **3ab** may have been formed in the reaction of phenylimidosulfuric difluoride with sodium ethoxide[4]. A series of 2-hydroxyphenyl alkyl(aryl, cycloalkyl)sulfamates have been prepared by reaction of *o*-phenylene sulfate (catechol sulfate) with the appropriate amines[5]. The latter method worked well but it is restricted in that all the esters contain the 2-hydroxyphenyl moiety. A few sulfamic esters of steroid alcohols have been prepared from arylsulfamic chlorides and the hydroxysteroids under phase-transfer conditions (liquid/liquid, using quaternary ammonium salts)[6].

It was our objective to find a general, convenient, high-yield procedure for the synthesis of arylsulfamic esters. This we



1	Ar
a	
b	H_3C
c	C_2H_5O
d	

2	R
a	CH_3
b	C_2H_5
c	i-C_3H_7
d	n-C_4H_9
e	n-C_6H_{13}
f	
g	

2	R
h	H_3C
i	O_2N
j	
k	n-C_3H_7

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Table 1. *N*-Arylsulfamic Esters (3) prepared

Product[a]	Yield [%][b] Method A	Method B	Molecular formula[c]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int})[d] δ [ppm]	^{13}C-N.M.R. ($CDCl_3$ or DMSO-d_6/TMS_{int})[e] δ [ppm]
3aa	82 (65)[1] (23)[1] 43[f]	64	$C_7H_9NO_3S$ (187.2)	3.85 (s, 3 H); 7.2 (m, 5 H)	57.3, 119.61, 124.88, 125.0, 136.31
3ab	80 (65)[1]	63	$C_8H_{11}NO_3S$ (201.2)	1.3 (t, 3 H); 4.2 (q, 2 H); 7.2 (m, 5 H)	14.52, 68.35, 119.68, 124.88, 129.55, 136.44
3ac	—	48	$C_9H_{13}NO_3S$ (215.2)		22.24, 79.94, 118.53, 123.21, 128.8, 137.63
3ad	—	54	$C_{10}H_{15}NO_3S$ (229.25)		12.75, 17.95, 29.91, 68.06, 118.4, 123.1, 128.55, 136.98
3ae	28[g]	18	$C_{12}H_{19}NO_3S$ (257.3)		14.03, 22.61, 25.21, 28.72, 31.19, 67.70, 119.8, 124.88, 129.56, 136.58
	15[f] 35[h]				
3af	—	48	$C_{12}H_{17}NO_3S$ (255.3)		23.52, 25.21, 33.00, 76.05, 119.42, 124.36, 129.3, 137.0
3ag	88	—	$C_{12}H_{11}NO_3S \cdot 1/3\,H_2O$ (255.2)		115.35, 119.77, 122.37, 125.1, 127.31, 129.65, 136.02, 149.92
3ah	75	—	$C_{13}H_{13}NO_3S$ (263.3)	2.3 (s, 3 H); 7.2 (m, 9 H)	20.92, 119.68, 121.76, 125.01, 126.7, 129.56, 130.2, 137.2, 147.9
3ai	20	—	$C_{12}H_{10}N_2O_5S \cdot H_2O$ (312.25)		115.78, 120.72, 122.9, 125.66, 126.31, 129.94, 135.53, 154.5
3aj	10	—	$C_{18}H_{15}NO_3S$ (325.3)		119.83, 122.43, 125.22, 126.72, 127.1, 127.75, 128.53, 129.71, 136.2, 140.1, 140.49, 149.33
3ba	69	—	$C_8H_{11}NO_3S$ (201.2)		20.04, 56.49, 116.88, 131.37, 132.4, 138.71
3bg	70	—	$C_{13}H_{13}NO_3S$ (263.3)		20.04, 116.88, 121.78, 124.37, 129.47, 131.37, 132.4, 138.71, 149.97
3cb	63[i]	—	$C_{10}H_{15}NO_3S$ (229.2)		14.68, 14.68, 63.80, 67.96, 115.26, 123.84, 128.65, 157.1
3ch	85	—	$C_{15}H_{17}NO_3S$ (291.3)	1.4 (t, 3 H); 2.2 (s, 3 H); 4.2 (q, 2 H); 7.0 (m, 8 H)	14.69, 20.79, 63.81, 115.41, 121.76, 123.30, 129.52, 129.65, 130.22, 149.68, 156.85
3da	80	—	$C_{11}H_{11}NO_3S$ (237.2)		57.3, 120.59, 122.54, 125.14, 125.66, 125.68, 125.92, 127.61, 132.42, 133.58
3db	76	—	$C_{12}H_{13}NO_3S$ (251.25)		14.42, 67.05, 119.35, 121.95, 122.86, 125.59, 126.30, 126.89, 128.38, 132.42, 133.97
3dg	70	—	$C_{16}H_{13}NO_3S$ (299.3)		120.39, 122.21, 122.95, 123.49, 125.55, 125.59, 125.92, 127.09, 127.81, 129.04, 132.42, 133.59, 153.07

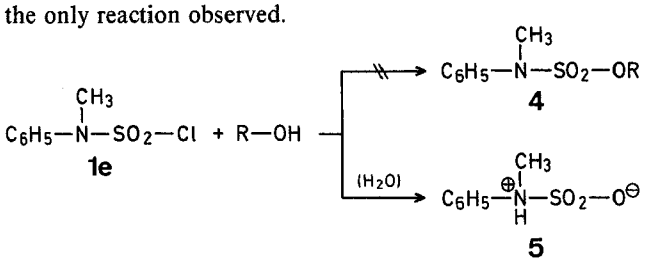
[a] The first letter in the product number refers to the group Ar of **1** and the second letter to the group R of **2**.
[b] Literature yields in parentheses.
[c] The microanalyses of the following compounds were in acceptable agreement with the calculated values: **3ab, 3ag, 3ah, 3aj, 3ba, 3bg, 3ch, 3da, 3dg**; maximum deviations from the calculated values: C, ±0.36; H, ±0.19; N, ±0.42. In the other cases, higher limits of error were obtained; hydration of sulfamic esters is a common problem[14].
[d] Recorded on a JEOL JNM-100 spectrometer.
[e] Recorded on a JEOL FX-60 spectrometer.
[f] Without the catalyst.
[g] A 33% yield was obtained using tetrabutyl- or tetraoctylammonium bromide and a 44% yield was obtained using 18-crown-6.
[h] Using dichloromethane as solvent.
[i] m.p. 78 °C.
[j] m.p. 78–79 °C.
[k] m.p. 90–91 °C.
[l] m.p. 118–120 °C.

have been able to do using the mentioned reaction of arylsulfamic chlorides **(1)** with alcohols **(2)** both under phase-transfer conditions (Method A, cf. Ref.[6]) and non-phase transfer conditions (Method B). Using equimolecular amounts of compounds **1** and **2**, esterification of **1** is achieved exclusively to give the alkyl or aryl arylsulfamates **3**. Using chlorides **1** and alcohols **2** in a 1:2 ratio, alkyl *N*-alkyl-*N*-arylsulfamates **(4)** are obtained together with considerable amounts of esters **3**. The preferential or exclusive formation of esters **4aa** and **4ab** can be achieved by employing longer reaction times.

As regards the preparation of esters **3**, some points from Table 1 are worthy of note:

- where comparison is possible the yields by Method A are superior to those reported and also involve a shorter reaction time (5 h) and lower temperature (0 °C);
- even in the absence of a phase-transfer catalyst, appreciable reaction sometimes occurs;
- "better" catalysts or change of solvent do not improve significantly the yields in a "poor" reaction;
- Method A (5 h, 0 °C) gives better yields than Method B (8 h 0 °C);
- almost all the esters are liquids (the naphthol esters are solids) but they could not be distilled because of decomposition; they were purified by column chromatography.

Esters **4aa** and **4ab** have been obtained by alkylation of esters **3aa** and **3ab** with methyl iodide or ethyl bromide, respectively. Our method offers a direct, one-pot synthesis from the sulfamic chloride **1a**. An anticipated advantage of the method of Ref.[1] namely that esters **4** containing two different groups R might be obtainable by, for example, ethylation of **3aa** cannot in fact be realised since due to competition by the esters as alkylating agents an inseparable mixture of diester products was obtained[1]. Another attempted approach to esters **4** failed; using *N*-methyl-*N*-phenylsulfamic chloride **(1e)** we hoped to obtain esters **4** by reaction with methanol or ethanol. However, chloride **1e** is extremely unreactive (see Table 2) and even under forcing conditions hydrolysis (presumably by small amounts of water present) to the zwitterionic parent acid was the only reaction observed.



The ease with which the conversion **1**→**3** occurs is of the following order (*N*-substituents of **1**): cycloalkyl[7], aryl > alkyl > aryl + alkyl.

The present methods offer a useful and general route to arylsulfamic esters **(3)** which are of interest as potential sweetening[8] and alkylating agents[1]. Esters of the type **4** (including those having different groups R) are accessible by reaction of *N*-alkylanilines with alkyl chlorosulfates but the yields are low[9].

The arylsulfamic chlorides **1** are prepared by the method of Ref.[10]. The reactions are carried out under a dry nitrogen atmosphere.

N-Phenylsulfamic Chloride **(1a)**; reaction time: 21 h. The crude product **1a** is distilled (b.p. 130 °C/2.5–3 torr) to give a yellow oil which crystallises on standing; yield: 60%; m.p. 69–70 °C (Ref.[10], m.p. 69–70 °C).

As mentioned in Ref.[10], a large amount of **1a** decomposes during distillation. In view of this decomposition, the other chlorides were used as obtained since their I.R. spectra showed the typical sulfamic chloride frequencies and their microanalyses were reasonable.

N-(4-Methylphenyl)-sulfamic Chloride **(1b)**; reaction time: 21 h; yield: 57%.

$C_7H_8ClNO_2S$	calc.	C 40.88	H 3.92	N 6.81
(205.7)	found	37.0	3.80	6.03

N-(4-Ethoxyphenyl)-sulfamic Chloride **(1c)**; reaction time: 6 h; yield: 87%.

$C_8H_{10}ClNO_3S$	calc.	C 40.77	H 4.28	N 5.94
(235.7)	found	39.7	3.80	5.03

N-(1-Naphthyl)-sulfamic Chloride **(1d)**; reaction time: 6 h; yield: 70%.

$C_{10}H_8ClNO_2S$	calc.	C 49.69	H 3.31	N 5.80
(241.65)	found	50.1	3.80	5.40

N-Methyl-N-phenylsulfamic Chloride **(1e)**; reaction time: 12 h; yield: 43%.

$C_7H_8ClNO_2S$	calc.	C 40.88	H 3.92	N 6.81
(205.7)	found	40.9	3.90	6.50

I.R. (neat) of compounds **1a–e**: ν = 880–930 (N—S); 1150–1190, 1360–1390 (SO_2); 1600–1610 (aryl); 3240–3300 cm^{-1} (N—H, absent for **1e**).

Arylsulfamic Esters (3); General Procedures:

The alcohols **2**, benzene, and dichloromethane are dried before use. The quaternary salts and crown ethers are commercially available.

Method A[7,12]: A solution of the alcohol (0.005 mol) or phenol (0.01 mol) in dry benzene (or dichloromethane, see Table 1; 5 ml) in a suitable reaction flask is chilled in an ice/water bath. Anhydrous sodium carbonate (3 g), benzyltriethylammonium chloride (or other catalyst, see Tables 1; 0.001 mol), and the sulfamic chloride (**1**; 0.005 mol) in dry benzene (or dichloromethane) (2.5 ml) are added. The mixture is vigorously stirred for 5 h (or as stated in Table 1). The solids are filtered off and washed with dry benzene. The filtrate and washings are concentrated under reduced pressure to yield the oily or solid crude ester.

Method B: The sulfamic chloride (**1**; 0.1 mol) is added to dichloromethane (10 ml) and the solution is cooled to 0 °C with an acetone/ice mixture. A solution of triethylamine (0.1 mol) and alcohol (**2**; 0.1 mol) in dry dichloromethane (10 ml) is added dropwise to the solution of chloride **1** while the temperature of the reaction is maintained at 0 °C.

Table 2. Synthesis or Attempted Synthesis of Alkyl *N*-Methyl-*N*-phenylsulfamates **(4)**

Substrate	Alcohol	Products	Yield [%][a]		Molecular formula[b]	I.R. (neat)[c] ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int})[d] δ [ppm]
			Method A[e]	Method B			
1a	**2a**	**4aa**	68 (30)[1]	—	$C_8H_{11}NO_3S$	1185, 1378	3.35 (s, 3H); 3.85 (s, 3H); 7.3 (m, 5H)
		3aa	16	—	(201.2)	—[e]	
1a	**2b**	**4ab**	62[f] (60)[1]	—	$C_{10}H_{15}NO_3S$ (229.2)	920, 1175, 1360, 1605	1.0, 1.3 (d, 6H); 3.67 (s, 2H); 4.15 (s, 2H); 7.35 (m, 5H)
		3ab	18	—		—[e]	
1a	**2k**	**3ak**	24	—	$C_9H_{13}NO_3S$ (215.2)		[17.90, 29.91, 68.06, 118.4, 123.08, 128.53, 136.96][g]
1e	**2a** or **2b**	—	—	0			
1e	**2a** or **2b**	**5**[h]	44	—	$C_7H_9NO_3S$ (187.2)	—[i]	—

[a] Literature yields in parentheses. In Method A, a 2:1 molar ratio of alcohol **2** to sulfamic chloride **1** (0.005 mol) was used.
[b] The microanalyses were in satisfactory agreement with calculated values: C, ±0.18; H, ±0.27; N, ±0.38.
[c] Measured with a Perkin-Elmer 334 spectrophotometer.
[d] Recorded on a JEOL JNM-100 spectrometer.
[e] See Table 1.
[f] After 1 h, 45% of **4ab** and 40% of **3ab** were formed.
[g] ^{13}C-N.M.R. chemical shifts: conditions as in Table 1.
[h] Reaction for 5 h (at 0 °C, 20 °C or 50 °C) gave no product. After reflux at 80 °C, the betaine **5** shown was isolated.
[i] m.p. 240 °C (the m.p. of *N*-methylaniline sulfate is 140 °C). On addition of barium chloride solution to an aqueous solution of the material isolated no precipitate formed, however on boiling in 50% aqueous sodium hydroxide 98% of the theoretical barium sulfate was formed.

The reaction mixture is stirred vigorously for 8 h. The solution is extracted with water (2 × 20 ml) to remove the amine hydrochloride and then extracted with 5% sodium hydrogen carbonate solution (20 ml). After acidifying the hydrogen carbonate solution to pH 4 with potassium hydrogen sulfate it is extracted with ether (2 × 10 ml). The ether extracts are dried and concentrated under reduced pressure to yield crude product.

Purification of Products **3:** Almost all the esters **3** prepared are liquids which can only in a few cases be brought to crystallisation. In accord with Ref.[1], methyl and phenyl sulfamate **(3aa, 3ab)** and also the other esters **3** are not distillable even under reduced pressure due to decomposition and are therefore purified by column chromatography (silica gel, activated at 200 °C overnight) by elution with benzene (5 × 10 ml), chloroform (5 × 10 ml), and ether (5 × 10 ml).

I.R. (neat) of compounds **3aa-3aj:** ν = 1170-1175, 1360-1385 (SO_2); 1600-1605 (aryl); 3250-3295 cm^{-1} (N—H).

I.R. (neat) of compounds **3ba-3dg:** ν = 1160-1180, 1350-1175 (SO_2); 1590-1610 (aryl); 3270-3285 cm^{-1} (N—H).

The above I.R. frequencies agree with those previously reported for arylsulfamic esters[1,2,7,13].

Methyl- and Ethyl *N*-Methyl-*N*-phenylsulfamate (4aa or **4ab,** respectively**):**
The reaction is carried out according to Method A with the modification that a 2:1 ratio of alcohols **(2)** to sulfamic chloride **(1)** is used.

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