Preparation of Sulfonamides from Sodium Sulfonates: $Ph_3P•Br_2$ and $Ph_3P•Cl_2$ as a Mild Halogenating Reagent for Sulfonyl Bromides and Sulfonyl Chlorides

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Abstract: Arene- and alkanesulfonamides were prepared by treatment of the corresponding sodium sulfonates with triphenylphosphine dibromide or dichloride followed by amines in the presence of triethylamine via sulfonyl halides. Reactions of sodium aminosulfonates gave cyclized products. Amidation of *p*-toluenesulfonic acid with triphenylphosphine dichloride was also examined to give *N*-benzyl-*p*-toluenesulfonamide. Methyl *p*-toluenesulfonate was obtained by esterification of sodium *p*-toluenesulfonate via *p*-toluenesulfonyl chloride.

Key words: triphenylphosphine dihalide, halogenation, sodium sulfonate, sulfon amide, sultam

The sulfamoyl group is a key unit of a number of biologically active molecules, and plays an important role to bring about the activity of sweeteners and drugs such as diuretics, uricosuric, hypoglycemic, antimicrobial reagents and so on as well as herbicides in the field of agriculture.[1] A wide variety of methods have been reported for the preparation of sulfonamides.[2] The most common synthetic method involves the preparation of a sulfonyl chloride,[3] which is usually obtained from a sulfonic acid or its sodium salt with phosphorus pentachloride, phosphoryl chloride or thionyl chloride. However, these processes are exothermic and often need high temperature to complete the reaction and are often inconvenient for other existing functional groups. In addition, there is the disadvantage that the stoichiometric amount of phosphoryl chloride or sulfur dioxide are formed as a byproduct, which are highly toxic and corrosive, when phosphorus pentachloride or thionyl chloride are used as a chlorinating reagent. This prompted us to investigate a mild method to convert sodium sulfonates into sulfonyl halides under neutral conditions. Triphenylphosphine dibromide **1** and dichloride **2** are well-known reagents for C–O bond cleavage in alcohols, phenols,[4] and ethers[5] to give the corresponding C–Br or C–Cl bonds owing to the strong oxygen affinity of phosphorus. Fujimori and co-workers reported that triphenylphosphine/iodine reduced arenesulfonic acids and their derivatives into thiols[6] and the following paper described conversion of aliphatic sulfonic acid derivatives into the corresponding alkyl iodides by the combination of triphenylphosphine and iodine.[7] The driving force of this reduction is both the strong oxygen affinity of a phosphorus and the relatively strong reducing power of an iodide anion. We considered that treatment of sodium sulfonates with triphenylphosphine dibromide or dichloride would provide sulfonyl bromides and chlorides, respectively, because bromide and chloride ions are less reductive than an iodide ion (equation 1). In addition, triphenylphosphine dihalides possess the advantage with regard to formation of neutral triphenylphosphine oxide instead of phosphoryl chloride or sulfur dioxide. In this paper we describe conversion of sodium sulfonates and a sulfonic acid to sulfonamides and a sulfonic acid ester by treatment with $Ph_3P•Br_2$ and $Ph_3P•Cl_2$ via sulfonyl halides. $Ph_3P•Cl_2$ (**2**) is commercially available and $Ph_3P•Br_2$ (**1**) is readily generated in situ by reaction of triphenylphosphine with bromine in acetonitrile.[8] First, we examined bromination of sodium sulfonates **3** with $Ph_3P•Br_2$ (**1**) followed by amidation with amines **4** (Scheme 1, Table 1). Both arene- and alkanesulfonates, except for the naphthalene derivatives, were smoothly converted to the corresponding sulfonyl bromides at room temperature after 1–3 hours to give sulfonamides **5** in good yields after treatment with an amine in the presence of triethylamine. Bromination proceeded even at 0°C after 7–10 hours. β-Hetero substituted sulfonamides **5k** and **5l** were obtained from corresponding sodium sulfonates in moderate yields (entries 15 and 16). The low yield especially for **5l** is probably due to nucleophilic participation of a heteroatom with liberation of sulfur dioxide to form an epionium ion.[9] Bulky sodium 10-camphorsulfonate also converted to the corresponding sulfonamide **5m** in good yield (entry 17).

$$RSO_3Na \xrightarrow[\textbf{1}: X=Br;\ \textbf{2}: X=Cl]{Ph_3P•X_2} RSO_2X \quad (1)$$

Scheme 1

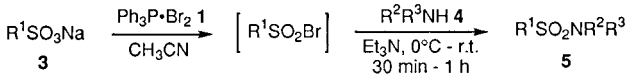


Table 1. Preparation of Sulfonamides from Sodium Sulfonates and $PPh_3•Br_2$ **1**

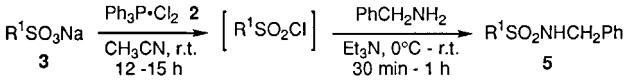
Entry	R^1	R^2	R^3	Temp (°C)	Time (h)	Product	Yield (%)
1	Ph	$PhCH_2$	H	r.t.	1	**5a**	83
2	Ph	$PhCH_2$	H	0	7	**5a**	84
3	Ph	Et	Et	r.t.	1	**5b**	82
4	Ph	H	H	r.t.	1	**5c**	79
5	*p*-Tol	$PhCH_2$	H	r.t.	1	**5d**	86
6	*p*-Tol	$PhCH_2$	H	0	7	**5d**	86
7	1-naphthyl	$PhCH_2$	H	r.t.	5	**5e**	43
8	2-naphthyl	$PhCH_2$	H	r.t.	20	**5f**	65
9	Me	H	H	r.t.	3	**5g**	68
10	Pr	$PhCH_2$	H	r.t.	3	**5h**	72
11	Pr	$PhCH_2$	H	0	10	**5h**	81
12	Bu	$PhCH_2$	H	r.t.	1	**5i**	67
13	Bu	$PhCH_2$	H	0	9	**5i**	84
14	*i*-Bu	$PhCH_2$	H	r.t.	3	**5j**	83
15	$PhOCH_2CH_2$	$PhCH_2$	H	r.t.	3	**5k**	67
16	$PhSCH_2CH_2$	$PhCH_2$	H	r.t.	3	**5l**	45
17	10-camphor	$PhCH_2$	H	r.t.	2.5	**5m**	78

Table 2. Spectroscopic Data of New Sulfanomides **5**[a]

Product[b]	mp (°C)	IR (KBr) ν (cm^{-1})	^1H NMR ($CDCl_3$) δ, J (Hz)	MS (EI, 70 eV) *m/z* (%)
5h	51–53	3295 (NH), 1320, 1140 (SO_2)	0.95 (t, 3 H, J = 7, CH_3), 1.70–1.81 (sextet, 2 H, CH_2), 2.85 (t, 2 H, J = 7, SO_2CH_2), 4.26 (d, 2 H, J = 6, NCH_2), 5.04 (br s, 1 H, NH), 7.26–7.34 (m, 5 H, ArH)	213 (M^+, 2), 106 (100), 91 (22), 79 (11)
5i	56–57	3290 (NH), 1320, 1145 (SO_2)	0.84 (t, 3 H, J =7.3, CH_3), 1.28 (sextet, 2 H, J = 7.3, CH_2), 1.64 (quintet, 2 H, J = 7.3, CH_2), 2.81 (t, 2 H, J = 7.3, SO_2CH_2), 4.23 (d, 2 H, J = 5.9, NCH_2), 5.46 (br s, 1 H, NH), 7.27–7.32 (m, 5 H, ArH)	227 (M^+, 2), 106 (100), 91 (18)
5j	56–56.5	3250 (NH), 1310, 1140 (SO_2)	1.05 (d, 6 H, J = 6.6, CH_3 × 2), 2.00–2.44 (m, 1 H, CH), 2.84 (d, 2 H, J = 6.4, SO_2CH_2), 4.30 (d, 2 H, J = 5, NCH_2), 4.46 (br s, 1 H, NH), 7.35 (s, 5 H, ArH)	227 (M^+, 1), 107 (11), 106 (100), 91 (22), 79 (12)
5k	84–86	3300 (NH), 1315, 1140 (SO_2)	3.41 (t, 2 H, J = 6, SO_2CH_2), 4.29 (d, 1 H, J = 6, NCH_2), 4.33 (t, 2 H, J = 6, OCH_2), 4.91 (br t, 1 H, J = 6, NH), 6.83 (d, 2 H, J = 7.8, ArH), 6.97 (t, 1 H, J = 7.3, ArH), 7.24–7.34 (m, 7 H, ArH)	291 (M^+, 22), 120 (19), 106 (91), 93 (44), 91 (100), 77 (25), 65 (18)
5l	98–100	3300 (NH), 1320, 1150 (SO_2)	3.15–3.25 (m, 4 H, CH_2CH_2), 4.43 (d, 2 H, J = 6.4, NCH_2), 4.59 (br s, 1 H, NH), 7.24–7.37 (m, 10 H, ArH)	307 (M^+, 18), 137 (49), 136 (100), 135 (46), 108 (57), 106 (86), 91 (39)

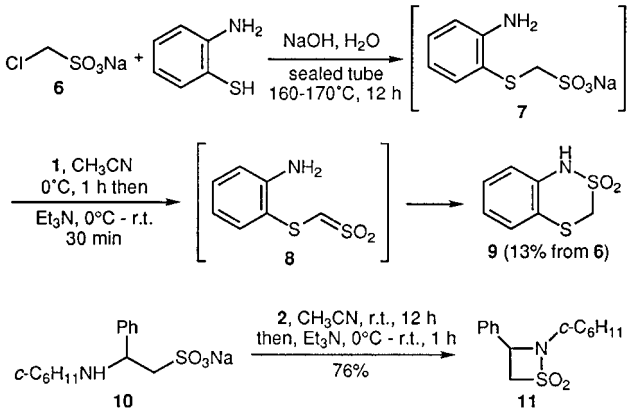
[a] References for spectroscopic or physical data of known compounds: **5a**,[11] **5b**,[12] **5d**,[13] ,**5m**.[11] Compounds **5c** and **5g** were compared with authentic samples which are commercially available from Aldrich Chemical Co., Inc. Known sulfonamides **5e** and **5f** gave satisfactory spectroscopic and elemental analyses data.[15]
[b] Satisfactory elemental analyses obtained: C ± 0.25, H ± 0.23, N ± 0.17.

Next, sulfonamidation of some sodium sulfonates **3** was investigated by use of $Ph_3P{\bullet}Cl_2$ (**2**) via sulfonyl chlorides (Scheme 2). Chlorination with $Ph_3P{\bullet}Cl_2$ was slower than bromination and it took 12–15 hours at room temperature to complete chlorination. In all cases sulfonamides **5** were obtained in good to high yields.



R^1	Ph	*p*-Tol	1-Naphthyl	2-Naphthyl	Pr	Bu	*i*-Bu
Product	**5a**	**5d**	**5e**	**5f**	**5h**	**5i**	**5j**
%Yield	64	85	84	94	93	92	89

Scheme 2



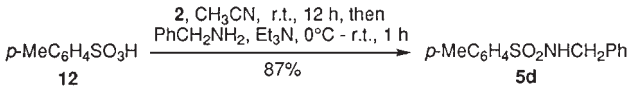
Scheme 3

We intended to apply this halogenation to the construction of heterocyclic rings by intramolecular amidation (Scheme 3). An unknown 2*H*,4*H*-1,3,4-benzodithiazine 3,3-dioxide framework was selected as the first target. Sodium chloromethanesulfonate reacted with *o*-aminobenzenethiol in alkaline solution at 160–170°C for 12 hours in a sealed tube to give sodium aminosulfonate **7**. 2*H*,4*H*-1,3,4-Benzodithiazine 3,3-dioxide **9** was obtained in 13% yield from **6** by treatment of the crude salt **7** with $Ph_3P{\bullet}Br_2$ (**1**) at 0 °C for 1 hour in acetonitrile followed by triethylamine. The low yield of **9** would be due to decomposition of sulfene intermediate **8**[10] to a carbene stabilized by an α-sulfur atom. Next, taurine derivative **10** was treated with $Ph_3P{\bullet}Cl_2$ (**2**) followed by triethylamine to give β-sultam **11** in 76% yield. These results suggest that triphenylphosphine dihalides are effective for substrates possessing an ammo group.

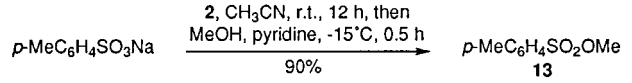
Amidation of *p*-toluenesulfonic acid **12** was also examined (Scheme 4). Treatment of **12** with 1.3 equivalents of $Ph_3P{\bullet}Cl_2$ (**2**) in acetonitrile at room temperature for 12 hours gave *p*-toluenesulfonyl chloride which subsequently reacted with benzylamine and triethylamine to give sulfonamide **5d** in 87% yield. Triphenylphosphine dihalides would be applicable for conversion of sulfonic acids to sulfonyl halides.

Methyl *p*-toluenesulfonate **13** was obtained in high yield from sodium *p*-toluenesulfonate by esterification of an intermediate sulfonyl chloride with 5 equivalents of methanol and 4 equivalents of pyridine at –15 °C for 30 min (Scheme 5).

Mps were obtained with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra of solids (KBr) and liquids (NaCl)



Scheme 4



Scheme 5

were recorded on a JASCO IRA-100 spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL GX-270 (270 MHz) or a JEOL EX-400 (400 MHz) or JEOL EX-90 (90 MHz) spectrometer with TMS as an internal standard. The *J* values are given in Hz. Mass spectra were recorded on a JEOL JMS-D 300 spectrometer with a direct-insertion probe at 70 eV. Elemental analyses of new compounds were performed by a Yanaco CHN Corder MT-5. All chromatographic isolations were accomplished with either Kieselgel 60 (70–230 mesh) for column chromatography or Kieselgel 60 PF_{254} containing gypsum for preparative TLC.

***N*-Benzylbenzenesulfonamide (5a); Typical Procedure with Sodium Sulfonates and $Ph_3P{\bullet}Br_2$ (1):**

To a suspension of Ph_3P (2.62 g, 10 mmol) in MeCN (10 mL) was carefully added dropwise at 0 °C Br_2 (ca. 0.52 mL, 10 mmol) until the color of Br_2 did not disappear. A trace amount of Ph_3P was added to the suspension to consume slightly excess Br_2. Sodium benzenesulfonate (1.80 g, 10 mmol) was added in portions to the mixture at r.t. After 1 h, benzylamine (1.07 g, 10 mmol) and Et_3N (1.4 mL, 10 mmol) were added dropwise successively at 0 °C. After 30 min, water (40 mL) was added to the mixture and the whole was extracted with EtOAc (3 × 40 mL). The extracts were combined, washed with sat. brine (2 × 40 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc 20:1–5:1) to give *N*-benzylsulfonamide **5a**; yield: 2.06 g (83%).

N-Benzylbenzenesulfonamide (5a); Typical Procedure with Sodium Sulfonates and $Ph_3P{\bullet}Cl_2$ (2):

To a suspension of $Ph_3P{\bullet}Cl_2$ **(2)** (323–420 mg, 1–1.3 mmol) in MeCN (2 mL) sodium benzenesulfonate (180 mg, 1 mmol) was added in portions at r.t. The mixture was stirred overnight at r.t. and benzylamine (107 mg, 1 mmol) and Et_3N (0.14 mL, 1 mmol) were successively added dropwise at 0°C. After 30 min, water (10 mL) was added to the mixture and it was extracted with EtOAc (3 × 10 mL). The extracts were combined, washed with sat. brine (2 × 10 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by preparative TLC (silica gel, hexane/EtOAc, 5:1) to give *N*-benzylsulfonamide **5a**; yield: 1.59 g (64%).

2*H*,4*H*-1,3,4-Benzodithiazine 3,3-Dioxide (9):

A mixture of **6** (0.458 g, 3 mmol), *o*-aminobenzenethiol (0.451 g, 3.6 mmol) and NaOH (0.120 g, 3 mmol) in degassed water (12 mL) was heated at 160–170°C under N_2 in a sealed tube for 12 h. The mixture was cooled and evaporated under reduced pressure. The resultant solid was washed well with EtOAc to remove excess *o*-aminobenzenethiol and it's oxidized product, 2,2′-diaminodiphenyl disulfide. The crude sodium salt 7 was added to a suspension of $Ph_3P{\bullet}Br_2$ [**1**, prepared from 0.786 g (3 mmol) of Ph_3P and ca. 0.15 mL (0.3 mmol) of Br_2 as described above] in MeCN (10 mL) in portions at 0 °C. The mixture was stirred at the same temperature for 1 h and Et_3N (0.42 mL, 3 mmol) was added dropwise. After 30 min, water (40 mL) was added to the mixture and it was extracted with EtOAc (3 × 40 mL). The extracts were combined, washed with sat. brine (2 × 40 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by preparative TLC (silica gel, hexane/EtOAc, 3:1) to give 1,3,4-benzodithiazine 3,3-dioxide **9** as colorless leaves (Et_2O/hexane); yield: 81 mg (13%); mp 144–146 °C.

Anal. $C_7H_7NO_2S_2$ (201.3): Calcd C 41.78, H 3.51, N 6.96. Found C 41.76, H 3.46, N 7.03.
MS (EI): *m/z* (%) = 201 (M^+, 29), 149 (9), 137 (9), 136 (100), 109 (12), 86 (9), 84 (14), 69 (7), 49 (18), 44 (11).
IR (KBr): ν = 3250 (N-H), 1310, 1150 cm^{-1} (SO_2).
^{1}H NMR (acetone-d_6): δ = 4.40 (s, 2 H, CH_2), 6.96 (d, 1 H, *J* = 7.8 Hz, ArH), 7.04 (t, 1 H, *J* = 7.8 Hz, ArH), 7.18 (t, 1 H, *J* = 7.8 Hz, ArH), 7.24 (d, 1 H, *J* = 7.8 Hz, ArH), 9.10 (br s, 1 H, NH).
^{13}C NMR (acetone-d_6): δ = 46.1 (t), 118.4 (s), 122.1 (d), 124.8 (d), 128.0 (d), 128.3 (d), 138.4 (s).

2-Cyclohexyl-3-phenyl-1,2-thiazetidine 1,1-Dioxide (11):

To a suspension of $Ph_3P{\bullet}Cl_2$ **(2)** (323 mg, 1 mmol) in MeCN (2 mL) sodium aminosulfonate **10** (305 mg, 1 mmol) was added in portions at r.t. The mixture was stirred overnight at r.t. and Et_3N (0.14 mL, 1 mmol) was added dropwise at 0°C. After 1 h at r.t., water (10 mL) was added to the mixture and it was extracted with EtOAc (3 × 10 mL). The extracts were combined, washed with sat. brine (2 × 10 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by preparative TLC (silica gel, hexane/EtOAc, 5:1) to give *β*-sultam **11** as colorless prisms (EtOAc/hexane); yield: 202 mg (76%); mp 128–129 °C.
Anal. $C_{14}H_{19}NO_2S$ (265.4): Calcd C 63.37, H 7.22, N 5.28. Found C 63.34, H 7.15, N 5.34.
MS (EI): *m/z* (%) = 265 (M^+, 5), 232 (24), 158 (9), 110 (16), 105 (12), 104 (100), 91 (12), 55 (11), 41 (19).
^{1}H NMR ($CDCl_3$) δ = 1.08–1.27 (m, 4 H), 1.42–1.74 (m, 5 H), 2.04 (br d, 1 H, *J* = 13 Hz), 3.20–3.28 (m, 1 H, 1′-H), 3.86 (dd, 1 H, *J* = 8.8 and 15.1 Hz, 4-H), 4.34 (dd, 1 H, *J* = 7.8 and 15.1 Hz, 4-H), 4.35 (dd, 1 H, *J* = 7.8 and 8.8 Hz, 3-H), 7.27–7.43 (m, 3 H, ArH), 7.50–7.53 (m, 2 H, ArH).
^{13}C NMR ($CDCl_3$) δ = 24.0 (t), 24.2 (t), 25.3 (t), 30.2 (t), 31.6 (t), 49.1 (d), 56.8 (d), 65.9 (t), 126.5 (d), 128.8 (d), 129.0 (d), 139.0 (s).
IR (KBr): ν = 1310, 1140 cm^{-1} (SO_2).

***N*-Benzyl-*p*-toluenesulfonamide (5d) by Amidation of *p*-Toluenesulfonic Acid (12):**

To a suspension of $Ph_3P{\bullet}Cl_2$ **(2)** (420 mg, 1.3 mmol) in MeCN (2 mL) *p*-toluenesulfonic acid (172 mg, 1 mmol) was added in portions at r.t. The mixture was stirred overnight at r.t. and benzylamine (107 mg, 1 mmol) and Et_3N (0.14 mL, 1 mmol) were added dropwise at 0 °C. After 1 h at r.t., water (10 mL) was added to the mixture and it was extracted with EtOAc (3 × 10 mL). The extracts were combined, washed with sat. brine (2 × 10 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by preparative TLC (silica gel, hexane/EtOAc, 5:1) to give *N*-benzylsulfonamide **5d;** yield: 228 mg (87%).

Methyl *p*-Toluenesulfonate (13) by Esterification of Sodium *p*-Toluenesulfonate:

To a suspension of $Ph_3P{\bullet}Cl_2$ (**2**) (840 mg, 2.6 mmol) in MeCN (4 mL) sodium *p*-toluenesulfonate (388 mg, 2 mmol) was added in portions at r.t. The mixture was stirred overnight at r.t. and MeOH (0.41 mL, 10 mmol) and pyridine (0.65 mL, 8 mmol) were added dropwise at –15 °C. After 30 min at –15 °C, water (20 mL) was added to the mixture and it was extracted with EtOAc (3 × 20 mL). The extracts were combined, washed with sat. brine (2 × 20 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by preparative TLC (silica gel, hexane/EtOAc, 5:1) to give **13**; yield: 334 mg (90%).

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