A General and Efficient Method for the Preparation of Organic Sulfonic Acids by Insertion of Sulfur Trioxide into the Metal−Carbon Bond of Organolithiums

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Although direct sulfonation of aromatic compounds is the most general method of preparing aromatic sulfonic acids, alternative methods are sometimes required, especially in the case of complex compounds. The most common method for generation of aliphatic sulfonate salts is reaction of aliphatic bromides with sodium sulfite,[1,2] but this reaction is not suitable for vinyl and aryl bromides. Much work has been done on the insertion reaction of sulfur dioxide with organometallic compounds to form sulfinic acids.[3−5] On the other hand, the only reports of similar reactions of sulfur trioxide have been of insertions into the bonds between carbon and other elements of main Group IV[6−9] or mercury.[10] The lack of reports concerning reactions of reactive organometallic reagents with sulfur trioxide and our continuing interest in organolithium chemistry[11−13] prompted us to investigate the reactions of organolithium reagents with sulfur trioxide in order to see if organic sulfonic acids could be produced.

Since sulfur trioxide complexes[14] are much milder and easier to handle, we chose them as starting materials instead of free SO_3. We now report that trimethylamine−sulfur trioxide reacts with organolithiums to give lithium sulfonates. Subsequent treatment with acid affords the corresponding sulfonic acids (Scheme 1).

Our initial investigations involved the reactions of *n*-butyllithium with commercial SO_3 complexes of pyridine and trimethylamine. The reaction of sulfur trioxide−pyridine with *n*-butyllithium, in diethyl ether or tetrahydrofuran (THF) and at −78 °C rising to room temperature, gave a complex mixture of products, including the product of addition of butyllithium to pyridine.[15] Treatment of sulfur trioxide−trimethylamine complex (STTAC) with *n*-butyllithium in diethyl ether also resulted in a complex mixture. However, when THF was used as the solvent the reaction of commercial STTAC with *n*-butyllithium gave a mixture containing the desired butanesulfonate and just one other major component, possibly lithium butanesulfinate.[16,17] Many attempts to vary the conditions failed to inhibit the formation of the byproduct when commercial STTAC was used directly.

Scheme 1

$$\underset{\mathbf{1}}{\text{R-Li}} + \underset{\mathbf{2}}{\text{SO}_3\cdot\text{NMe}_3} \longrightarrow \text{NMe}_3 + \underset{\mathbf{3}}{\text{R-SO}_3\text{Li}} \xrightarrow{[\text{H}^+]} \underset{\mathbf{4}}{\text{R-SO}_3\text{H}}$$

The ^{1}H NMR spectrum of commercial STTAC showed that it contained two major components with signals at δ 3.06 and 2.77. We therefore undertook its purification by recrystallization from cold water.[18,19] A saturated solution of the commercial material was concentrated to one-fourth of its volume in the cold. White crystals were recovered in 50% yield and dried under vacuum. The crystalline material consisted almost entirely of a single component (δ 3.06) according to its ^{1}H NMR spectrum. The reaction of this with butyllithium was therefore studied in more detail. The following procedure was found to be useful.

To a suspension of crystalline STTAC (835 mg, 6 mmol) in dry THF (30 mL) was added a solution of *n*-butyllithium (2.5 M in hexane, 2.4 mL, 6 mmol) dropwise at −78 °C with a syringe over 15 min. The reaction mixture was stirred for another 2 h at −78 °C and then allowed to warm to room temperature over 20 h. After removal of the solvent on a rotary evaporator, hydrochloric acid (6 M, 4 mL, 24 mmol) was added. The mixture was extracted with ethyl acetate (4 × 25 mL), and the combined organic extract was dried ($MgSO_4$) and then evaporated to give a viscous oil. Diethyl ether (20 mL) was added and some white solid precipitated. This was washed with further ether (2 × 15 mL). The ether solution was concentrated to give 1-butanesulfonic acid (**5**) (665 mg, 79%, but 96% pure, so yield 76%).

A similar procedure was applied to the synthesis of a range of sulfonic acids from the corresponding organolithium reagents (Table 1). Compounds **5**−**9** were obtained using commercial solutions of the organolithiums, and compound **10** was obtained using a commercial solution of allylmagnesium bromide. The reagent used for preparation of **11** was obtained by treatment of 4-bromotoluene with 1 equiv of *n*-butyllithium.[20] The reagents used for the syntheses of **12** and **13** were obtained by double lithiation of *N*-pivaloylaniline[11a,21,22] and 2-methyl-3-(pivaloylamino)quinazolin-4(3*H*)-one,[23,24] respectively.

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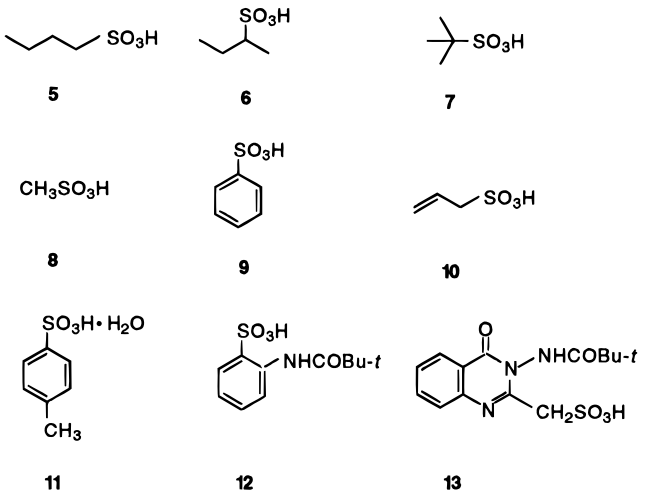
Table 1. Organic Sulfonic Acids Prepared by the Reaction of STTAC with Organometallic Compounds

starting material	product	purity (%)[a]	yield (%)[b]
n-C_4H_9Li	**5**	96	76
s-C_4H_9Li	**6**	98	74
t-C_4H_9Li	**7**	95	69
CH_3Li	**8**	96	60
phenyllithium	**9**	95	78
CH_2=$CHCH_2MgBr$	**10**	97	78
4-bromotoluene	**11**	96	62
N-pivaloylaniline	**12**	99	79
2-methyl-3-(pivaloylamino)-quinazolin-4(3*H*)-one	**13**	98	65

[a] The product was titrated against standard 0.5 M NaOH and the titre compared with the theoretical expectation. [b] Yield of isolated purified product after correction for purity.



The results obtained from the above reactions show that sulfur trioxide−trimethylamine complex is a useful reagent for the formation of organic sulfonic acids from the corresponding organolithium reagents. The complex is stable and easily handled. It is a cheap and convenient commercial product, but the commercial material is not pure enough for direct reaction. Purification by crystallization from cold water provides material which can then be used effectively.

In conclusion, we have achieved insertion of sulfur trioxide into the metal−carbon bond of organolithiums and Grignard reagents to produce organic sulfonic acids in high yield. The reaction is suitable for both aliphatic and aromatic sulfonic acids, and the formation of compounds **12** and **13** demonstrates that it can be used for preparation of relatively complex products. This general and efficient method should therefore be a very useful additional tool for organic chemists.

Experimental Section

All experiments were performed under an atmosphere of dry nitrogen unless indicated otherwise. Organolithiums were estimated prior to use by the method of Watson and Eastham.[25] THF was distilled from sodium benzophenone ketyl. Solvents were purified by standard procedures. ^1H and ^{13}C NMR spectra were recorded at 400 MHz for ^1H and 100 MHz for ^{13}C NMR measurements. Mass spectra were recorded at 70 eV (EI) or by use of ammonia as ionizing gas (CI).

Purification of Commercial Sulfur Trioxide Complex by Recrystallization. STTAC (10 g) suspended in distilled water (800 mL) was stirred for 8 h at room temperature. After filtration, the aqueous solution was concentrated to 200 mL in the cold to give white crystals, which were washed with cold water (15 mL × 6) and dried under vacuum at 80 °C for 6 h to give a dry sample of STTAC (5.0 g, 50%).

1-Butanesulfonic Acid (5). A crystalline sample of STTAC obtained as above (835 mg, 6.0 mmol) in tetrahydrofuran (THF) (30 mL) was cooled in CO_2/acetone. A hexane solution of *n*-BuLi (2.5 M, 2.4 mL, 6.0 mmol) was added dropwise over 15 min. The reaction mixture was stirred for another 2 h at −78 °C and then allowed to warm to room temperature over 20 h. After removal of the solvent, HCl (6 M, 4 mL, 24 mmol) was added. The mixture was extracted with EtOAc (4 × 25 mL), and the combined organic extract was dried ($MgSO_4$) and then evaporated to give a viscous oil. Et_2O (20 mL) was added and some white solid precipitated. This was washed with further Et_2O (2 × 15 mL). The combined Et_2O solution was concentrated to give 1-butanesulfonic acid (665 mg, 76%) as a pale yellow oil. ^1H NMR δ (D_2O): 0.94 (t, J = 7.3 Hz, 3 H), 1.46 (m, 2 H), 1.82 (m, 2 H), 3.07 (t, J = 7.8 Hz, 2 H).

The following were prepared similarly:

2-Butanesulfonic acid (6) in 74% yield; pale yellow oil. ^1H NMR δ (D_2O): 1.02 (t, J = 8.0 Hz, 3 H), 1.31 (d, J = 6.9 Hz, 3 H), 1.48 (m, 1 H), 1.97 (m, 1 H), 2.83 (m, 1 H).

2-Methyl-2-propanesulfonic acid (7) in 69% yield; pale yellow oil. ^1H NMR δ (D_2O): 1.25 (s).

Methanesulfonic Acid (8). As methanesulfonic acid is more soluble in water, the residue from evaporation of the aqueous solution was further extracted to provide additional material. This gave the product in 60% overall yield as a pale yellow oil. ^1H NMR δ (D_2O): 2.96 (s).

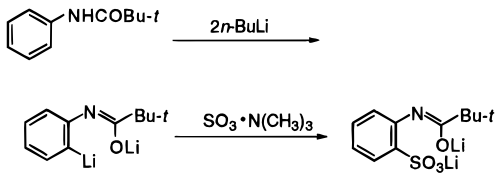
Benzenesulfonic acid (9) in 78% yield; light-brown crystals: mp 63−65 °C (lit.[26a] mp 65−66 °C). ^1H NMR δ ($CDCl_3$): 7.47 (m, 3 H), 7.61 (m, 2 H).

3-Propenesulfonic acid (10) in 78% yield; pale yellow oil. ^1H NMR δ (D_2O): 3.62 (d, J = 9.3 Hz, 2 H), 5.35 (m, 2 H), 5.89 (m, 1 H).

4-Toluenesulfonic Acid (11). To 4-bromotoluene (518 mg, 3.1 mmol) was added *n*-BuLi (2.3 M in hexane, 1.35 mL, 3 mmol) over 10 min with cooling (ice bath). After 6 h, the supernatant solution was used in the next stage.

To a stirred suspension of crystalline STTAC (431 mg, 3.1 mmol) in dry THF (15 mL) at −78 °C was added the preformed hexane solution of *p*-tolyllithium dropwise over 15 min. The reaction mixture was stirred for 2 h at −78 °C and then allowed to warm to room temperature over 18 h. After removal of solvent, H_2O (10 mL) and KOH (3 M, 1 mL, 3 mmol) were added to the mixture, which was then extracted with Et_2O (2 × 15 mL) to remove unreacted 4-bromotoluene. The aqueous solution was evaporated to a white solid. HCl (6 M, 4 mL, 24 mmol) was added. The mixture was extracted with EtOAc (4 × 20 mL), and the combined organic extract was dried ($MgSO_4$) and

(22) The reaction involves the following steps:



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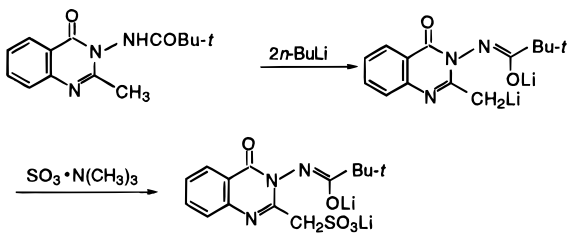
(24) The reaction involves the following steps:



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evaporated to give a moist solid. Et_2O (15 mL) was added and some white solid precipitated. This was washed with further Et_2O (2 × 10 mL). The combined Et_2O extracts were concentrated to give white crystals (383 mg, 62%) of the monohydrate: mp 104−106 °C (lit.[26b] mp 104−105 °C). ^{1}H NMR δ (D_2O): 2.30 (s, 3 H), 7.27 (d, J = 8.5 Hz, 2 H), 7.60 (d, J = 8.5 Hz, 2 H).

2-(Pivaloylamino)benzenesulfonic Acid (12). A solution of *N*-pivaloylaniline (780 mg, 4.4 mmol) in THF (12 mL) was cooled in ice, and *n*-BuLi (2.3 M in hexane, 4.2 mL, 9.6 mmol) was added dropwise. The reaction mixture was stirred for 1 h at 0 °C and 19 h at room temperature. The solution of the dianion was used in the next stage.

With the same procedure as for compound **11**, compound **12** was prepared as white crystals in 79% yield: mp 142−145 °C. ^{1}H NMR δ (D_2O): 1.24 (s, 9 H), 7.28 (m, 1 H), 7.54 (m, 1 H), 7.82 (d, J = 9.5 Hz, 1 H), 7.93 (d, J = 9.0 Hz, 1 H). ^{13}C NMR (D_2O): δ 181.6, 134.5, 13.8, 133.0, 127.9, 126.0, 124.7, 40.2, 27.2. HRMS (EI) m/z: (M^+) calcd for $C_{11}H_{15}NO_4S$ 257.0721, found 257.0720. Because this compound is hygroscopic, it was difficult to obtain an exact microanalysis. Anal. Calcd for $C_{11}H_{15}NO_4S+0.4H_2O$: C, 49.95; H, 6.02; N, 5.30. Found: C, 50.35; H, 6.67; N, 5.22.

Compound 13. To a cooled (−78 °C), stirred solution of 2-methyl-3-(pivaloylamino)quinazolin-4(3*H*)-one (475 mg, 1.83 mmol) in THF (18 mL) under nitrogen was added *n*-BuLi (2.3 M in hexane, 1.7 mL, 3.9 mmol). Formation of the dianion was observed as an orange-red solution. The mixture was stirred at −78 °C for an additional 30 min and used in the next stage.

With the same procedure as compound for **11**, compound **13** was prepared as light-yellow crystals in 65% yield: mp 200−202 °C. ^{1}H NMR δ (D_2O): 1.37 (s, 9 H), 3.16 (s, 2 H), 7.75 (m, 2 H), 8.03 (m, 1 H), 8.26 (d, J = 8.0 Hz, 1 H). MS (ES) m/z: [M − H]$^-$ 338. Because this compound is hygroscopic, it was difficult to obtain an exact microanalysis. Anal. Calcd for $C_{14}H_{17}N_3O_5S+0.75H_2O$: C, 47.61; H, 5.24; N, 11.90. Found: C, 47.86; H, 5.55; N, 11.75.

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