A New Effective Synthesis of Arene Mono and Disulfonyl Chlorides

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Abstract: Arene mono and disulfonyl chlorides have been easily synthesized starting from the corresponding anilines via aqueous oxidative chlorination of *S*-aryl *O*-ethyl dithiocarbonates intermediates, or aryl methyl sulfides, or from arenethiols.

Key words: arenesulfonyl chlorides, disulfonyl chlorides, oxidative chlorination, arenediazonium salts, aryl dithiocarbonates

Recently, we have reported the use of *o*-benzenedisulfonimide (**1**, Figure 1) as a new organocatalyst in some Brønsted acid-catalyzed organic reactions.[1] The key intermediate for the synthesis of **1** is *o*-benzenedisulfonyl chloride (**5f**), which has been prepared from *o*-benzenedisulfonic acid dipotassium salt,[2c,e] *o*-aminobenzenesulfonic acid,[2a-d,g] anthranilic acid,[2f] and *o*-bis(methylthio)benzene.[2h] Nowadays, both disulfonyl chloride **5f** and imide **1** are commercially available, although quite expensive.

1 **5f**

Figure 1

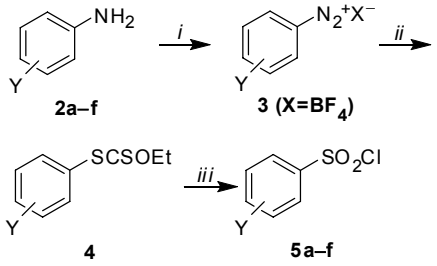
Despite the number of synthetic procedures in the literature, the interest in alternative and more convenient procedures for the synthesis of **1** is high. This is due to the usefulness and versatility of **1** and its interesting chiral analogues[3a,b] as safe, nonvolatile, non corrosive, recoverable and recyclable organocatalyst.[1,3a] In this paper, we wish to report preliminary results concerning a new advantageous synthesis of **5f**, along with a general procedure for a laboratory scale synthesis of arene mono and disulfonyl chlorides.

Retrosynthetic analysis of compound **5f** always requires the presence of two *ortho* sulfur functionalities on the aromatic ring. These have to be converted into the sulfonyl chloride group independently of the sulfur atom oxidation state. Sulfonyl chlorides are useful intermediates for the synthesis of a wide range of organic derivatives. They are usually prepared through the oxidative chlorination of various sulfur compounds (such as thiols, sulfides, disulfides, but also thioacetates and thiocarbamates), by treatment with chlorine in H_2O or in organic solvents (mainly halogenated).[4a] Other less hazardous chlorinating agents have been also proposed.[4b]

In the past, we patented two procedures to prepare alkyl and arylalkyl sulfonyl chlorides by the aqueous oxidative chlorination of *S,S*-dialkyl and *S,S*-diarylalkyl dithiocarbonates,[5a,b] and mono-

and di- alkyl and arylalkyl sulfonyl chlorides from dialkyl or diarylalkyl trithiocarbonates.[5c] With this in mind, we recognized the potential of the *O,S*-diester of dithiocarbonic acid (xanthogenate), as a promising sulfurated functional group. This was more frequently used in the past, but has also occasionally been used in organic synthesis more recently.[6] Xanthogenates have never hitherto been used for oxidative chlorination. In fact, *O*-ethyl *S*-aryl dithiocarbonates were intermediates in the earlier syntheses of *o*-benzenedisulfonyl chloride, in which they were oxidized to the corresponding sulfonic acid by $KMnO_4$ or HNO_3, and converted into the final derivative by treatment with PCl_5.[2a,b]

From a theoretical point of view, a very straightforward synthesis of *o*-benzenedisulfonyl chloride could start from *o*-phenylenediamine via its intermediate dithiocarbonic acid *S,S*-diester. However, as is well-known in the literature,[7] only 1*H*-benzotriazole has been produced in trial reactions by diazotization of the diamine. Therefore, we decided to explore the feasibility of the proposed synthetic procedure by testing anilines **2a-e** first. Arenediazonium tetrafluoroborates **3** were isolated in satisfactory yield and purity by diazotization of the corresponding aromatic amines and then directly reacted. *O*-Ethyl *S*-aryl dithiocarbonates **4** were prepared *via* the Leuckart reaction[8] by careful addition of salts **3** to a solution of the commercially available potassium *O*-ethyl dithiocarbonate (Scheme 1).



i: *i*-$C_5H_{11}ONO$ / HCOOH / HBF_4 54% in Et_2O; 0–15 °C
ii: KSCSOEt / Na_2CO_3 / H_2O; 60 °C
iii: Cl_2 / H_2O; 5–10 °C

Scheme 1. Conversion of anilines **2a-f** into sulfonyl chlorides **5a-f**

GC-MS analyses and ^{1}H NMR spectra of crude reaction mixtures revealed that the expected *O,S*-diesters **4** were present as the major species. There were also traces of *S*-ethyl *S*-aryl dithiocarbonates (isomerization products), and other sulfur derivatives (i.e. disulfides, sulfides, diaryl trithiocarbonates ...). In trial reactions, crude mixtures were reacted under different conditions: chlorinating agent (Cl_2 or NCS), solvent (H_2O / halogenated solvent or H_2O alone), and arenediazonium counter anion (tetrafluoroborate, **3f** or *o*-benzenedisulfonimide,[9] **3g**) (Table 1, entries 1–4). The optimized conditions were then successfully applied to some representative aromatic amines, and the corresponding arenesulfonyl chlorides **5a-e** were isolated in good overall yields, ranging from 84 to 90% in each step (Table 1, entries 5–8).

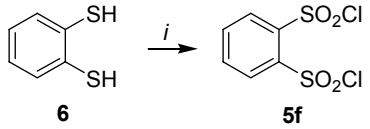
Table 1: Reaction conditions and yields for the conversion of anilines **2a-f** into arenesulfonyl chlorides **5a-f**

Entry	**2**	Y in **2** and **5**	Oxidative chlorination conditions	**5**	**5** Overall yields[1] (%)
1	**2a**	4-Cl	NCS[2] / 2 N HCl / MeCN	**5a**	53

2	**2a**		Cl_2 / H_2O / CH_2Cl_2	**5a**	65
3	**2a**		Cl_2 / H_2O	**5a**	66
4	**2a**		Cl_2 / H_2O	**5a**	64[3]
5	**2b**	4-NO_2	Cl_2 / H_2O	**5b**	59
6	**2c**	2-Cl	Cl_2 / H_2O	**5c**	68
7	**2d**	2-I	Cl_2 / H_2O	**5d**	62
8	**2e**	4-Me	Cl_2 / H_2O	**5e**	72
9	**2f**	2-MeS	Cl_2 / H_2O	**5f**	62
10	**2f**	2-MeS	Cl_2 / H_2O	**5f**	58[3]

[1] Yields refer to pure isolated products
[2] NCS, *N*-chlorosuccinimide.
[3] Counter anion of salt **3** was *o*-benzenedisulfonimide

Then 2-methylsulfanylaniline (**2f**) was tested. In the literature few procedures have been proposed in order to convert an alkyl aryl sulfide into arenesulfonyl chloride, and the oxidation of a sulfide to sulfone is an unavoidable side reaction. Chlorinating agents were chlorine or SO_2Cl_2, in H_2O in the presence of organic solvents and/or acids (HCOOH or MeCOOH). A HCOOH / H_2O mixture was chosen according to the literature data.[10] Salt **3f** was converted into **5f** (62% overall yield) in the presence of 10 equiv of H_2O. Comparable results were obtained starting from the *o*-benzenedisulfonimide salt **3g**[11] (entries 9 and 10).



6 **5f**

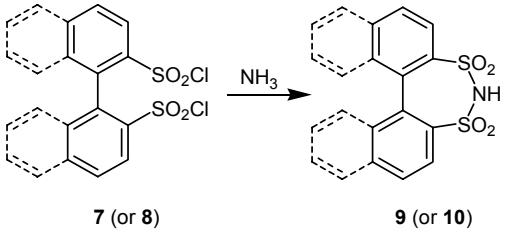
i: NCS (8.0 equiv)/ HCl : MeCN, 1 : 5 / 0–10 °C

Scheme 2. Oxidative chlorination of benzene-1,2-dithiol (**6**) with NCS

Another route to **5f** was attempted with the treatment of benzene-1,2-dithiol **6** with *N*-chlorosuccinimide (NCS, 8.0 equiv) in 2 N HCl / MeCN (1 : 5) at 0–10 °C,[4b] and **5f** was obtained in 80% yield (Scheme 2).

We decided to extend this synthetic strategy to obtain the 2,2'-biphenyl and 2-2'-binaphthyldisulfonyl chlorides **7** and **8**, more interesting synthetic goals, since they can afford the corresponding strong acidic cyclic imides **9**[12] and **10**, simply by treatment with ammonia (Scheme 3). Biphenyl-2,2'-disulfonyl chloride (**7**) was prepared in 1891 by Limpricht with a laborious synthesis which started from 3,3'-dinitrobiphenyl-2,2'-disulfonic acid.[13] Disulfonyl chlorides **7** and **8** were then prepared by Barber and Smiles in 1928[14] via the Ullmann reaction, from sodium *o*-iodobenzenesulfonate or potassium 1-iodobinaphthyl-2-sulfonate, and later by Armarego and Turner from phenyl *o*-iodobenzenesulfonate or 1-iodobinaphthyl-2-sulfonate.[15a,b] Recently, pure

(*R*)-**8**[3b] and a 3,3'-disubstituted derivative[3a] have been prepared in three and four steps, respectively, from (*R*)-BINOL (overall yields 24–39% and 46%). Both syntheses involved a Newman-Kwart rearrangement of *N,N*-dimethylthiocarbamate intermediates, followed by direct oxychlorination with NCS or oxidation to disulfonic acid/chlorination.



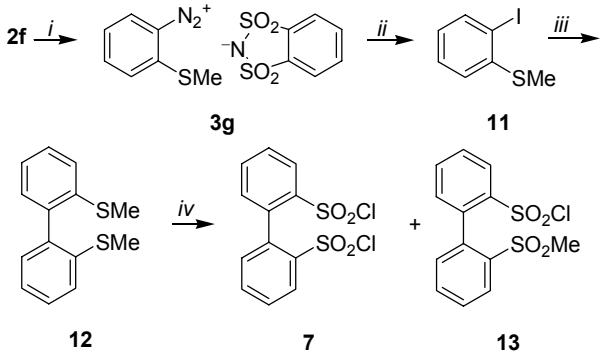
7 (or **8**) **9** (or **10**)

Scheme 3. Conversion of disulfonyl chlorides **7** or **8** to the corresponding cyclic imides **9** or **10**.

To synthesize **7**, we attempted the dixanthate pathway first.

After successful reduction of 2,2'-dinitrobiphenyl[16] and diazotization of the resulting 2,2'-diaminobiphenyl, the Leuckart reaction of the corresponding tetrafluoroborate unfortunately only afforded tar by-products. It was therefore decided to synthesize a biphenyl derivative which bears two sulfur functionalities in 2 and 2' positions, using the Suzuki coupling reaction. Initially, the palladium-catalyzed homocoupling of arenediazonium salt **3f** was tested,[17] but unfortunately only traces of product were detected by GC-MS analyses. Next, Suzuki coupling conditions[18] were applied to 2-methyl-sulfanylbenzenediazonium salt (tetrafluoroborate, **3f** or *o*-benzenedisulfonimide, **3g**) and 2-methylsulfanyl-phenylboronic acid, in anhydrous dioxane at 60 °C, in the presence of $Pd(OAc)_2$ 5–10 mol%: the expected 2,2'-bis(methylsulfanyl)biphenyl (**12**) was isolated in poor yields (10–12 %).

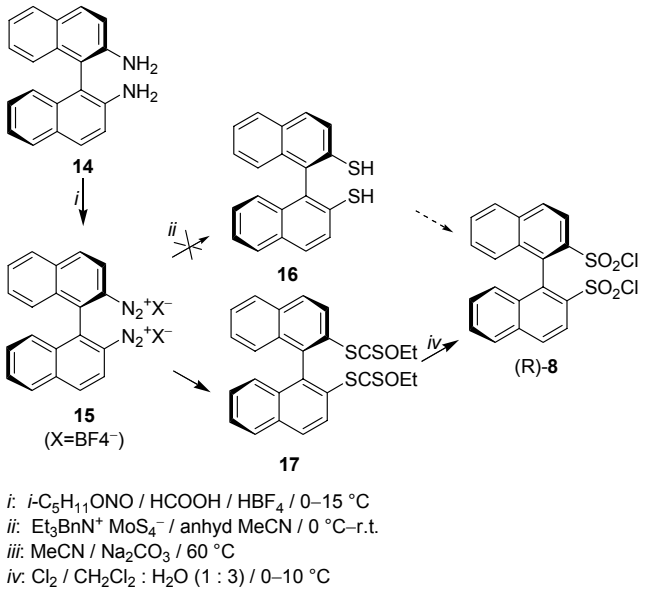
Finally, according to a previously optimized procedure,[19] 2-methylsulfanyl *o*-benzenedisulfonimide (**3g**) was converted into 2-iodophenyl methyl sulfide (**11**, 82% yield). Sulfide **11** was then reacted with 2-methylsulfanyl-phenylboronic acid, in toluene at 60 °C, in the presence of $Pd_2(dba)_3$ 5 mol% to yield 2,2'-bis(methylsulfanyl)biphenyl (**12**) in 88% yield. Then, the biphenyl derivative **12** was tested for oxidative chlorination under different conditions. Chlorination with an excess of gaseous Cl_2 in CH_2Cl_2 / HCOOH / H_2O, afforded disulfonyl chloride **7** in 60% yield (racemic mixture; Scheme 4), along with 2'-methylsulfonylbiphenyl-2-sulfonyl chloride **13** (isolated in 40% yield).



i: *i*-$C_5H_{11}ONO$ / HCOOH / 1 (1.2 equiv) / 0–15 °C
ii: $Bu_4N^+ I^-$ / MeCN / r.t
iii: 2-$MeSC_6H_4B(OH)_2$ / Tol / Na_2CO_3 / 60 °C
iv: Cl_2 / CH_2Cl_2 : HCOOH : H_2O (1 : 1 : 0.1) / 0–10 °C

Scheme 4. Conversion of aniline **2f** into biphenyl-2,2'-disulfonyl chloride (**7**)

As regards to **8**, an initial synthetic strategy was suggested by the literature. It was reported that 2,2'-binaphthyldithiol[21] was isolated in 61% yield by the reaction of 2,2'-binaphthyldiazonium tetrafluoroborate with tetrathiomolibdate.[20] The diazotization, as above, of (*R*)(+)-2,2'-binaphthyldiamine (**14**), the subsequent reaction with ammonium tetrathiomolibdate, and the final aqueous oxidative chlorination as in Scheme 2, were expected to give (*R*)-**8** (Scheme 5). Unfortunately, we were not able to obtain dithiol **16**, and therefore this reaction pathway was abandoned.



Scheme 5 Conversion of aniline **14** into binaphthyl-2,2'-disulfonyl chloride (**8**)

Finally, the xanthate path as attempted (Scheme 5). This approach began with tetrafluoroborate salt **15**, which was reacted with KSCSOEt in MeCN. Crude xanthate **17** was treated with an excess of gaseous chlorine in H_2O / CH_2Cl_2. Enantiomeric pure (*R*)-2,2'-binaphthyldisulfonyl chloride ((*R*)-**8**) was isolated in 27% overall yield. Further optimization is currently under study.

According to a previously optimized procedure,[9b] pure (*R*)-(**8**) was converted into enantiomeric pure (*R*)-2,2'-binaphthyldisulfonimide ((*R*)-**10**) in 90% yield.[3b]

In summary, we have developed a new synthesis of arene mono and disulfonyl chlorides which are key intermediates for the synthesis of strong Brönsted acids, which have recently been reported as promising organocatalysts.

Supporting Information for this article, including new or relevant physical and spectral data for given products, is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

This work was supported by Italian MIUR and by Università degli Studi di Torino.

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(22) **Diazotization of Amines 2: General procedure** To a stirred solution of amines **2** (1.0 mmol) and HBF_4 (54% in Et_2O; 1.2 mmol; 1.90 g) in HCOOH (15 mL), at 5–10 °C, 3-methylbutyl nitrite (1.29 g; 1.1 mmol) was slowly added at such a rate that the temperature did not exceed 10 °C. Then the reaction mixture was stirred for 10 min in an ice bath, and at rt for 5 min. Finally, after cooling at 0–5 °C, anhyd Et_2O was added to precipitate salts **3**, gathered by filtration on a Büchner funnel and washed several times with Et_2O. After drying under vacuum, pure salts **3** were obtained and immediately reacted (physical and ^1H and ^{13}C NMR spectral data identical to literature). **Conversion of crude salts 3 to *O*-ethyl *S*-aryl dithio-carbonates 4 and oxidative chlorination of crudes 4 to arenesulfonyl chlorides 5: General Procedures**
Crude salts **3** (1.0 mmol) were carefully added under stirring to a solution of potassium *O*-ethyl dithiocarbonate (1.0 mmol; 1.60 g) and Na_2CO_3 (1.0 mmol; 1.06 g) in H_2O (40 mL), heated to 35–40 °C.Then the reaction mixture was stirred at 60 °C for 20 min. After cooling at rt, the resultant mixture was poured into Et_2O–H_2O (40 mL; 2:1). The aqueous layer was separated and extracted with Et_2O (2 x 20 mL). The combined organic extracts were washed with H_2O (20 mL), dried over Na_2SO_4, and evaporated. The crude residues were directly reacted to give arenesulfonyl chlorides **5**. A small stream of Cl_2 was bubbled through a well-stirred ice-cooled emulsion of crudes **4** in water (20 mL) or HCOOH/water (40 mL, 9:1; for crude **4f**), at such a rate that the temperature did not rise to 10 °C. The reaction was stopped when Cl_2 was no longer absorbed and TLC analysis (PE– Et_2O, 8:2) showed the presence of only one persistent spot. After removing chlorine excess, the reaction mixture was extracted with CH_2Cl_2 (3 x 20 mL); organic extracts were neutralized with 10% aqueous $NaHCO_3$, dried and evaporated under reduced pressure. Crude residues chromatographed on a short column (PE–Et_2O, 9:1) provided pure arenesulfonylchlorides **5** (comparison with literature data or commercially pure samples).
Benzene-1,2-disulfonyl chloride (5f)[2g] After completion of oxidative chlorination (TLC analysis and appearance of a fine dispersed white solid), chlorine excess was removed under vacuum; crude virtually pure **5f** was filtered on a Büchner funnel and washed with cold water. Mp 143–144 °C (CCl_4; lit. 143–144 °C).[2f] ^1H NMR (200 MHz, $CDCl_3$) δ = 8.04–8.11 (m, 2 H), 8.45–8.53 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 132.6 (2 C), 136.4 (2 C), 141.4 (2 C). MS (EI): *m/z* (%) = 274 (20, M^+).
Biphenyl-2,2'-disulfonyl chloride (7) Mp 143–144 °C. ($CHCl_3$–PE; lit 144–145 °C).[23] Prepared by suspending crude **17** in CH_2Cl_2 / water (10 mL; 10:1) and reacting with excess chlorine at 0–10 °C for 30 min; then HCOOH (10 mL) was added and chlorination was continued until only two persisting spots were present on TLC analysis. By column chromatography (CH_2Cl_2 – MeOH, 99:1), disulfonyl chloride **7** was eluted as first product (R_f 0.8); the second eluted product was **13** (R_f 0.3). Mp 143–144 °C. ($CHCl_3$–PE; lit.[23] 144–145 °C). ^1H NMR (200 MHz, $CDCl_3$) δ = 7.49 (dd, , *J* = 1.8, 7.2 Hz, 1 H), 7.67 (td, *J* = 1.8, 7.6 Hz, 1 H), 7.75 (td, *J* = 1.6, 7.6 Hz, 1 H), 8.20 (dd, *J* = 1.6, 8.0 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 129.0 (2 C), 129.8 (2 C),132.0 (2 C), 134.3 (2 C), 135.7 (2 C), 142.6 (2 C). **(*R*)-Binaphthyl-2,2'-disulfonyl chloride (8)** Colorless needles; mp 241.2-242.2 °C. ($CHCl_3$–PE; lit 244.3 °C).[3b] ^1H NMR (200 MHz, $CDCl_3$) δ = 7.09 (d, *J* = 8.6 Hz, 2 H), 7.38 (ddd, *J* = 1.4, 7.0, 8.6 Hz, 2 H), 7.65 (ddd, *J* = 1.2, 7.0, 8.2 Hz, 2 H), 8.00 (d, *J* = 8.4), 8.20 (d, *J* = 9.0 Hz, 2 H), 8.27 (d, *J* = 9.0 Hz, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 123.2 (2 C), 127.9 (2 C), 128.4 (2 C), 128.5 (2 C), 130.1 (2 C), 131.0 (2 C), 131.8 (2 C), 133.6 (2 C), 135.3 (2 C), 140.7 (2 C).

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