Tetrahedron Letters 51 (2010) 418–421

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A simple and highly effective oxidative chlorination protocol for the preparation of arenesulfonyl chlorides

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ARTICLE INFO

Article history:
Received 30 September 2009
Revised 9 November 2009
Accepted 10 November 2009
Available online 14 November 2009

ABSTRACT

2,4-Dichloro-5,5-dimethylhydantoin (DCDMH) was found to be a mild and efficient reagent for the direct oxidative conversion of sulfur compounds to the corresponding arenesulfonyl chlorides in good to excellent yields through the oxidative chlorination. The method is suitable for many types of sulfur substrates (thiols, disulfides or benzylic sulfides). The overall process is simple, practical, and it provides convenient access to a variety of aryl or heteroarylsulfonyl chlorides. The mild reaction conditions and the broad substrate scope render this method attractive, and complementary to existing syntheses of aryl or heteroarylsulfonyl chlorides.

Aryl and heteroarylsulfonyl chlorides are an important class of compounds primarily used in the preparation of sulfonamides. Sulfonamide motifs are prevalent in a variety of biologically active compounds with a broad range of biological and pharmaceutical activities including inhibition of carbonic anhydrase,[1] novel and selective cholecystokinin-2 receptor antagonists,[2] β_3 receptor agonists,[3] and HCV polymerase inhibitors.[4] During the course of the synthesis of HCV polymerase inhibitors as potential drug candidates for the treatment of Hepatitis C Virus (HCV) infection, it was necessary for us to prepare a number of thienothiadiazine derivatives on scale for in vitro and in vivo biological evaluation as well as the safety profiling of these compounds (Fig. 1).[5]

The key challenge of the synthesis was to develop an efficient and scaleable process for the preparation of highly functionalized thiophene sulfonyl chlorides **2**, en route to these thienothiadiazine analogs.

Traditionally, aryl or heteroarylsulfonyl chlorides can be accessed by a number of synthetic methods. Of these, direct electrophilic substitution of aromatic compounds was for years the most straightforward. While the reaction of sulfur electrophiles such as SO_2 or SO_2Cl_2 with organo-metallic species derived from an aryl halide could give rise to the desired sulfonyl chlorides.[6] However, these methods suffer from significant limitations. In the former case, the scope of the reaction is confined to the use of a relatively activated aromatic compound with pre-established regioselectivity. In the latter case, the aryl halide is limited to the structurally simple one that is compatible with the reaction conditions. In contrast, oxidative chlorination of a sulfur compound occurs under mild reaction conditions, and displays good functional group tolerance. As a result, it offers distinct advantages in the preparation of heteroarylsulfonyl chlorides. Furthermore, many of the aromatic sulfur compounds (thiols, sulfides, and disulfide) are becoming increasingly accessible either by direct nucleophilic substitution or a transition-metal catalyzed cross-coupling reaction of aryl or heteroaryl halide with an appropriate sulfur-source. These developments have prompted us to consider a synthetic strategy toward **3** based on the oxidative chlorination of **1** as a key step (Scheme 1).

Typically, oxidative chlorination protocol employed chlorine gas, which is quite hazardous and requires careful handing.[7] Additionally, the reaction usually generates very high exotherms. These drawbacks make it the less desirable for routine use, especially for the large-scale synthesis. Recently, numerous and more convenient variants for the oxidative chlorination have been reported. These included dual-function agents such as NaOCl,[8] and NCS[9] under

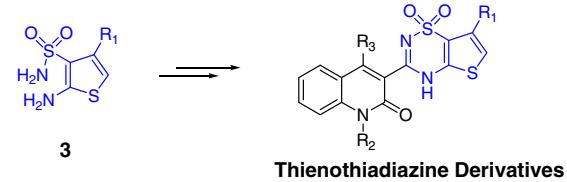
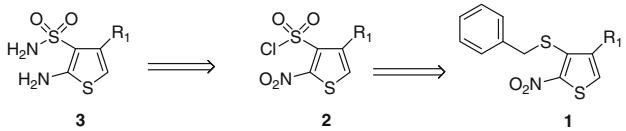


Figure 1. Structures of thienothiadiazine derivatives.



Scheme 1. Retrosynthetic analysis of **3**.

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doi:10.1016/j.tetlet.2009.11.047

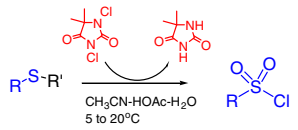
the acidic and aqueous medium. A less common protocol entails starting with the combination of the oxidant-chlorinating agent, such as KNO_3–TMSCl,[10] KNO_3–SO_2Cl_2[11] H_2O_2–$SOCl_2$,[12] Oxone–$SOCl_2$,[13] or Br_2–Cl_3PO.[14]

For our initial investigation of the proposed synthetic route to **3**, we chose **1a** as the test substrate, which was obtained via a multi-step sequence.[5] Having made the requisite **1a**, we then explored the key step in the synthesis. We commenced our research on this transformation with the standard chlorinolysis protocol (Table 1, entry 1). As expected, desired product **2b** was obtained in very good yield. However, this transformation was found indeed to be extremely exothermic. We then focused on other known dual-function agents. A number of the oxidants were examined to achieve oxidative chlorination of **1a**, including the use of SO_2Cl_2, NCS, and NaOCl in CH_2Cl_2–HOAc–H_2O at ~5 °C. The results were shown in the Table 1. Sulfuryl chloride (SO_2Cl_2) was effective in converting **1a** to the corresponding sulfoxide **2a** in high yield with 3.0 equiv of the reagent, but it was ineffective in breaking the C–S bond required for the formation of sulfonyl chloride. Use of an additional 3.0 equiv of this reagent did not have a positive influence on the outcome of the reaction (Table 1, entry 2). Although *N*-chlorosuccinimide (NCS) has been reported to effect a similar transformation, it gave little or no desired product (Table 1, entry 3). The starting material was recovered and found to be unchanged. We observed that sodium hypochlorite solution (NaOCl) afforded 95% of **2a** and 5% of the desired product **2b** with 3.0 equiv of this reagent, but the conversion to the sulfonyl chloride required 6.0 equiv of the reagent (Table 1, entry 4). However, the concentration of commercially available sodium hypochlorite solution is generally not high and varied. For the best results, the solution has to be titrated prior to use.

Unsatisfied with the initial screening results, we began to search for an alternative, effective and easy to use oxidative chlorination agent. 2,4-Dichloro-5,5-dimethyl hydantoin (DCDMH) is an inexpensive and readily available compound. It has been primarily used as a swimming pool-treatment agent. Although it was occasionally reported as chlorination agent[15] or oxidation agent[16], its use as an effective oxidative chlorination agent has been largely unexplored. Remarkably, when **1a** was subjected to the standard reaction conditions with 3.0 equiv of DCDMH, the desired product **2b** was formed in very good yield and purity (Table 1, entry 5), similar to those from chlorine gas.

We then screened several different solvents (toluene, CH_2Cl_2, IPAC, IPA, **CH_3CN**, and DMF) to achieve the optimal reaction condition in combination with acetic acid and water, using **1a** as a substrate. From these studies, the reaction stalled at 10% completion in IPA, presumably due to decomposition of DCDMH. On the other extreme, the starting material was completely consumed and no desired product detected in DMF. The reaction proceeded cleanly to give the desired product **2b** in acetonitrile within 1 h at 5 °C, and was less effective in isopropyl acetate. The reaction is much slower in non-polar solvents, such as CH_2Cl_2 and toluene. Overall, it was found that the oxidative chlorination reaction of **1a** with DCDMH in the aqueous acetonitrile is mild and effective. Under these conditions, both chlorine atoms of DCDMH are consumed during the reaction.

Table 2
Oxidative chlorination of arylbenzyl sulfide **1** with DCDMH[a]



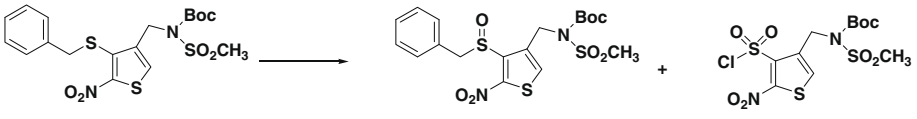
R = Aryl or Heteroaryl
R' = Benzyl, Methyl

Entry	Substrate	% yield[b]
1	**1a**	85
2	C_6H_5–S–CH_2–C_6H_5	90
3	4-CF_3–C_6H_4–S–CH_2–C_6H_5	92
4	3-CF_3–C_6H_4–S–CH_2–C_6H_5	90
5	2-CF_3–C_6H_4–S–CH_2–C_6H_5	88
6	4-CH_3O–C_6H_4–CH_2–S–$CH_2C_6H_5$	86
7	2-Naphthalenyl–S–$CH_2C_6H_5$	86
8	3-Quinolinyl –S–$CH_2C_6H_5$	84
9	4-Br–C_6H_4–S–CH_3	0

[a] Reaction conditions: 4.0 mmol of the benzylsulfide and 2.0 equiv oxidation agent in CH_3CN–HOAc–H_2O (40.0 mL:1.5 mL:1.0 mL) at 5 °C for 2 h.
[b] The assayed yields are the average of two runs.

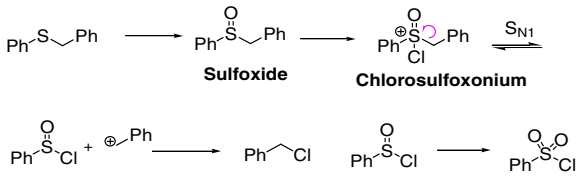
To further demonstrate the effectiveness and scope of oxidative chlorination reactions of DCDMH, we prepared several arylbenzyl sulfides **1**, and carried out the oxidative chlorination on these substrates under the optimized reaction conditions. The results are reported in Table 2. In all cases, the oxidative chlorination proceeded smoothly to afford the desired sulfonyl chlorides in good yields (Table 2, entries 1–8). It is noted that no desired product was formed from *p*-bromophenylmethyl sulfide (Table 2, entry 9). Instead, a mixture of α-chloromethyl, α,α-dichloromethyl and α,α,α-trichloromethyl *p*-bromophenyl sulfoxides was obtained. These results could be rationalized by the reaction mechanism proposed in Scheme 2. The reactions proceed, in general, by the inter-

Table 1
Initial screening on oxidative chlorination agents with **1a**[a]



Entry	Reagent	Conversion[b] (%)	Sulfoxide[b] **2a** (%)	Sulfonyl chloride[b], **2b** (%)
1	Cl_2	100	0	100
2	SO_2Cl_2	100	100	0
		100	100	0[c]
3	NCS	0	0	0
4	NaClO	100	95	5
		100	5	95 [c]
5	DCDMH	100	0	100

[a] Reaction conditions: 4.0 mmol of the benzylsulfide **1a** and 3.0 equiv agent in CH_2Cl_2–AcOH–H_2O (15.0 mL:2.0 mL:4.0 mL) at 5 °C for 20 h.
[b] The product distributions are the average of two runs, and are analyzed by HPLC against a pure and characterized standard.
[c] 6 equiv agent used.



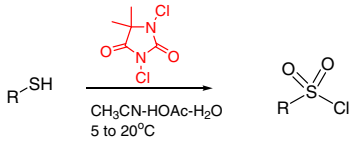
Scheme 2. The plausible mechanism for the oxidative chlorination of benzylic sulfides with DCDMH.

mediacies of sulfoxide and chlorosulfoxonium cation, followed by the cleavage of benzylic C–S bond in the S_N1 fashion. Only these sulfides bearing the cleavable function groups (such as benzyl group) which have the inherent ability to stabilize positive charge at the carbon attached to the sulfur could undergo the oxidative cleavage, giving rise to the corresponding arylsulfonyl chlorides

The proposed mechanism is further supported by the observed reaction by-products. Small amount of *N*-benzylacetamide (~15%) was always present in the reaction mixtures, presumably due to the reaction of benzylic cation with acetonitrile, followed by hydrolysis (Ritter reaction), in addition to the expected benzyl chloride. These reactions are generally fast, and completed in several minutes, suggesting that DCDMH reacts directly with the sulfide, sulfoxide or the other intermediates to furnish arylsulfonyl chlorides rather than in situ generates reactive chlorine gas. In practice, because of the instability of the sulfonyl chlorides, it is unnecessary to remove these benzylic by-products (benzyl chloride and *N*-benzylacetamide) before converting them to more stable sulfonamides.

Extension of this new protocol to other commonly used sulfides such as thiols and disulfides is anticipated. This required only slight modification to the original reaction condition. For example, in the former case, the amount of DCDMH required decreased from 2.0 equiv to 1.5 equiv. When several commercially available arylthiols were subjected to the modified reaction conditions, the corresponding sulfonyl chlorides were formed exclusively and rapidly, usually in less than 1 h at room temperature (Table 3) except entry 7. In this case, the instability of the sulfonyl chloride accounted for this exception due to desulfonylation of the product to 4-chloropyridine during the workup and isolation. Only notable by-product present in reaction mixture is the spent reagent, 5,5-dimethylhydantoin, which was readily removed by a simple and extractive aqueous workup. As a result, the corresponding sulfonyl chlorides were obtained in good to excellent yield and good purity, and could be used directly without further purification. The reactions were generally well tolerated. Aryl or hetero-arylthiol with the electron-donating or withdrawing substitute was converted to the corresponding sulfonyl chloride without any noticeable difference in the reaction rate.

Table 3
Preparation of sulfonyl chlorides from thiols[a]



R = Aryl ,Hetereoaryl

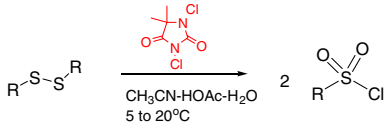
Entry	RSH	% yield[b]
1	C_6H_5	92
2	4-F–C_6H_4	94
3	4-Me–C_6H_4	88
4	3-Cl–C_6H_4	94
5	8-Quinolinyl	100
6	2-Naphthalenyl	88
7	4-Pyridyl	0
8	4-CF_3–C_6H_4	85
9	3-CF_3–C_6H_4	90

[a] Reaction conditions: 8.0 mmol of thiol and 1.5 equiv DCDMH in CH_3CN–AcOH–H_2O was mixed at 0 °C. The reaction mixture was allowed to warm to rt and mixed for 1 h.
[b] The isolated yields are the average of two runs.

As for disulfide substrates, the reaction was found to be best with 2.5 equiv of DCDMH. The substrate scope of the reaction was investigated. Mono, di, and tri-substituted disulfides were effectively transformed into the corresponding sulfonyl chlorides. Also, the disulfides containing either the electron-donating or electron-withdrawing group were converted to the corresponding sulfonyl chlorides. As a result, the products were obtained in good to excellent yield and purity in the expected stoichiometric amounts after the simple extractive workup. These products could be used directly without further purification (Table 4).

Oxidative chlorination of thiol and disulfide is believed to proceed via the intermediates: disulfide (**a**), thiosulfinate (**b**) and thiosulfonate (**c**) as shown in Scheme 3. The proposed mechanism rested on the following evidence: when the reaction progress was closely monitored by HPLC, and LC–MS, the formation of thiosulfinate (**b**) and thiosulfonates (**c**) were detected. Furthermore, when the reaction mixture from entry 3, Table 3 was intercepted,

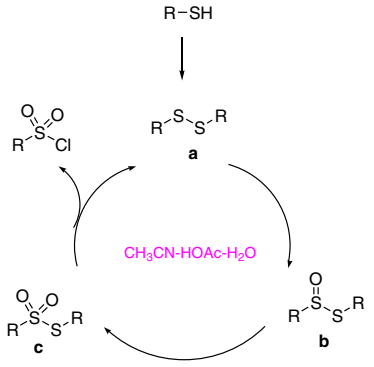
Table 4
Synthesis of sulfonyl chlorides from disulfides[a]



R = Aryl ,Hetereoaryl, and Alkyl

Entry	R–S–S–R	% yield[b]
1	C_6H_5	89
2	4-MeO–C_6H_4	92
3	4-Cl–C_6H_4	90
4	3,5-Di-Cl–C_6H_3	96
5	2,4,5-tri-Cl–C_6H_2	96
6	4-NO_2–C_6H_4	87
7	C_6H_5–CH_2	92
8	2-Pyridyl	78[c]
9	8-Quinolinyl	99

[a] Reaction conditions: A disulfide (4.0 mmol) and DCDMH (10.0 mmol) in CH_3CN–AcOH–H_2O was mixed at 0–5 °C. The mixture was allowed to warm up to rt and mixed at rt for 1 h.
[b] The isolated yields are the average of two runs.
[c] ~20% of 2-chloropyridine was obtained as a desulfonylation by-product.



Scheme 3. The possible mechanism of arylsulfonyl chloride formation from thiol or disulfide

the corresponding thiosulfinate (**b**) and thiosulfonate (**c**) were isolated and identified.

In summary, we have developed a simple & effective oxidative chlorination procedure for the synthesis of aryl or heteroaryl sulfonyl chlorides with DCDMH as a safe and inexpensive equivalent to chlorine gas. Many aromatic sulfur substrates (thiols, disulfides and benzyl sulfides) can be converted to the corresponding arylsulfonyl chlorides in good to excellent yields, making it a superior to those described previously. Further studies into the synthesis of the sulfoxides with DCDMH will be conducted.

Supplementary data

Supplementary data (complete description of experimental details and product characterization) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.047.

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