Tetrahedron Letters 53 (2012) 354–358

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Synthesis of sulfonyl chlorides and thiosulfonates from H_2O_2–$TiCl_4$

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ARTICLE INFO

Article history:
Received 23 September 2011
Revised 28 October 2011
Accepted 11 November 2011
Available online 22 November 2011

Keywords:
Sulfonyl chlorides
Oxidative chlorination
Thiosulfonates
Titanium tetrachloride
Hydrogen peroxide

ABSTRACT

A new method is described for the oxidative chlorination of thiols to sulfonyl chlorides using titanium tetrachloride in combination with the oxidant hydrogen peroxide. Direct conversion of thiols into their corresponding thiosulfonates is also reported. Good to excellent yields, short reaction times, high efficiencies, cost-effectiveness, and, facile isolation of the desired products make the present methodology a practical alternative.

The demand for structural diversification in compound libraries for screening in drug discovery is the driving force behind the development of new methodologies and structural motifs.

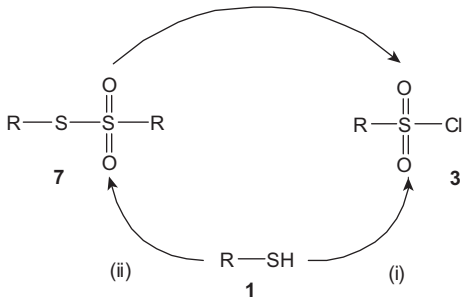
Sulfonyl chlorides are an important class of organic compounds. They are common intermediates for sulfonamides, many of which are medicinal or crop protection agents.[1] Traditionally, aryl or alkylsulfonyl chlorides can be accessed by a number of synthetic methods.[2–7] Of these, the oxidative chlorination of sulfur compounds such as, thiols, sulfides, thioacetates, and thiocarbamates, with aqueous chlorine[2] was for years the most typical method for the preparation of these compounds. However, these methods suffer from significant limitations. For example, many of these reactions involve stepwise oxidation followed by chlorination giving low yields of products and are not convenient and safe due to the use of hazardous and noxious reagents.

Titanium tetrachloride is a valuable reagent promoting various synthetic reactions, both in cases requiring a stoichiometric amount of $TiCl_4$ or catalytic amounts of $TiCl_4$ together with other metal salts.[8]

From an economical and environmental viewpoint, the use of hydrogen peroxide as an oxidant is valuable because it is stable at ambient temperature and readily available, is relatively cheap and water is the only expected side product.[9]

The versatile biological activity of sulfonyl chlorides has prompted us to consider synthetic strategies toward these compounds based on the oxidative chlorination of thiols. Selective conversion of thiols into sulfonyl chlorides and thiols into thiosulfonates with the same reagent system is an important process in synthetic organic chemistry, and to the best of our knowledge, there have been no reports employing related systems for this purpose. As an extension to our reported work in this field,[10] herein, we describe for the first time, H_2O_2–$TiCl_4$ for the direct oxidative chlorination of thiols into the corresponding sulfonyl chlorides and the conversion thiols into thiosulfonates. The route for the synthesis of sulfonyl chlorides and thiosulfonates is shown in Scheme 1.

The choice of the organic solvent is of particular importance. For our initial investigation of the proposed synthetic route, we chose 4-bromothiophenol as the test substrate and its oxidative chlorination was carried out under identical reaction conditions using various organic solvents. Acetonitrile and 1,4-dioxane were found to be suitable, giving rise to a relatively fast reaction rate at room temperature. If the reactions were carried out in less polar solvents



Scheme 1. Reagents and conditions: (i) H_2O_2 (3 equiv), $TiCl_4$ (1 equiv), CH_3CN, 25 °C; (ii) H_2O_2 (3 equiv), $TiCl_4$ (0.25 equiv), CH_3CN, 25 °C.

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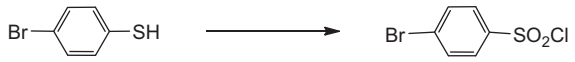
doi:10.1016/j.tetlet.2011.11.052

Table 1
Effect of increasing the amounts of H_2O_2 and $TiCl_4$ on the oxidative chlorination of 4-bromothiophenol[a]



Entry	$TiCl_4$ (mmol)	30% H_2O_2 (mmol)	Yield[b] (%)
1	1	0	5
2	0.8	1	50
3	0.8	2	80
4	1	2	97
5	1	3	95

[a] Reaction conditions: 4-bromothiophenol (1 mmol), 2 min, 25 °C.
[b] Isolated yield.

such as dichloromethane, chloroform, or some ethers, they became sluggish and did not reach completion.

To arrive at an optimum stoichiometry for the synthesis of sulfonyl chlorides, the reaction of 4-bromothiophenol was selected as a model to examine the effects of different amounts of H_2O_2 and $TiCl_4$ in acetonitrile at room temperature. As shown in Table 1, higher amounts of H_2O_2 neither increased the yield nor lowered the reaction time and $TiCl_4$ was effective only in the presence of H_2O_2. The best result (97% yield) was obtained by carrying out the reaction with a 1:3 mol ratio of thiol to H_2O_2 in the presence of 1 mmol of $TiCl_4$ over 2 min.

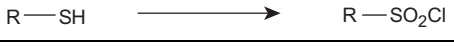
Under these conditions, a wide range of thiols containing aromatic, aliphatic, and, cyclic thiols were converted into the corresponding sulfonyl chlorides in excellent yields and short reaction times with high purity (monitored by NMR). As can be seen from Table 2, both electron-rich and electron-deficient thiols afforded excellent yields of products irrespective of the electronic effects.

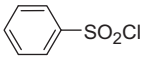
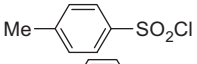
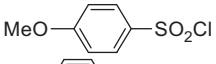
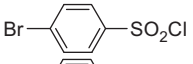
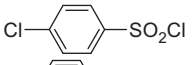
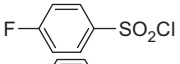
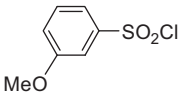
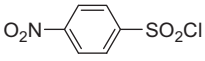
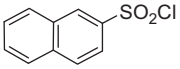
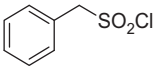
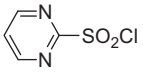
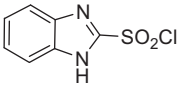
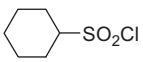
Similarly, aliphatic thiols such as cyclohexanethiol, 1-octanethiol, and, butanethiol afforded the corresponding sulfonyl chlorides in excellent yields (Table 2, entries 13–15). This reaction was also compatible with other functional groups such as halo, nitro, and, ether (Table 2, entries 3–8).

To determine further the scope of the reaction, we studied the oxidative chlorination of thiols in the presence of an alcohol and an oxime (Scheme 2). The results suggest that this method can be applied for the oxidative chlorination of thiols in the presence of the above-mentioned functional groups in multifunctional molecules.

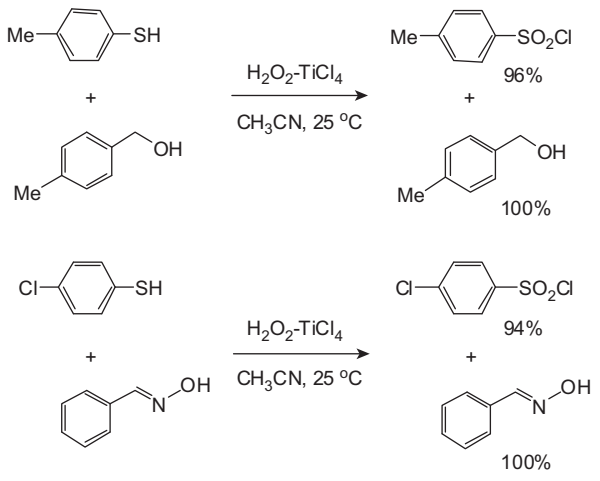
Under similar reaction conditions, this procedure failed to produce clean oxidative chlorination with 2-mercaptopyrimidine and 2-mercaptobenzimidazole. Sulfonyl chlorides of such compounds are unstable at room temperature and produce mixtures of products.[16–18]

Table 2
Synthesis of sulfonyl chlorides from thiols[a]



Entry	Product	Yield[b] (%)	Time (min)	Mp (°C) (Lit mp)	Ref.
1		95	1	Oil (oil)	6
2		97	1	69–70 (70–71)	4
3		90	5	39–40 (39–40)	12
4		97	2	71–72 (75)	13
5		94	2	49–51 (50–52)	4
6		95	2	34 (33–34)	12
7		85	5	Oil (oil)	14
8		90	2	71–73 (72–73)	6
9		92	2	73–75 (74–76)	4
10		95	2	90–93 (91–93)	6
11		0	60	Mixture of products	–
12		0	60	Mixture of products	–
13		92	7	Oil (oil)	6
14	*n*-Octyl–SO_2Cl	92	7	Oil (oil)	15
15	*n*-Butyl–SO_2Cl	90	7	Oil (oil)	15

[a] The products were characterized by comparison of their spectroscopic and physical data with authentic samples synthesized by reported procedures.
[b] Yields refer to pure isolated products.



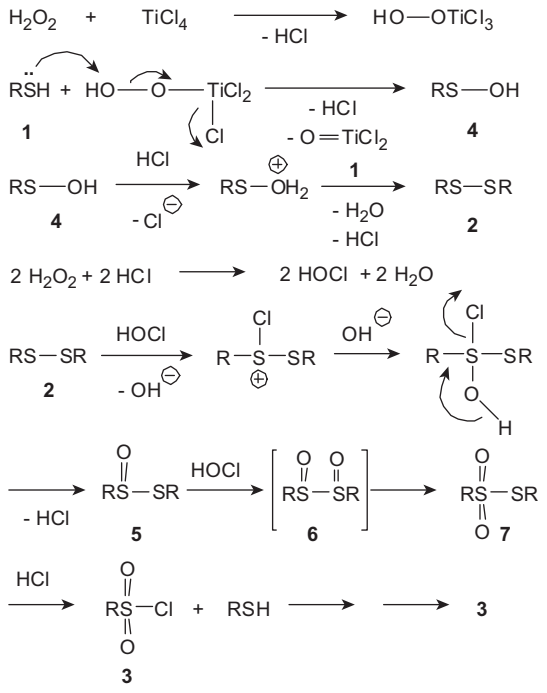
Scheme 2. Reagents and conditions: molar ratio of substrates: H_2O_2:$TiCl_4$ (1:1:3:1), CH_3CN, 25 °C.

These results can be rationalized by the reaction mechanism proposed in Scheme 3. The reactions proceed, in general, via the intermediacy of disulfide **2** and thiosulfonate **7** which furnishes sulfonyl chloride **3**. Conversion of **5** to **7** via **6** has been well documented and recognized.[11]

In order to check the rationalization of the proposed mechanism, we started to study the effect of HCl on the conversion of *S*-phenyl benzenesulfonothioate (Table 3, entry 1) into benzenesulfonyl chloride. The results show that this reaction produces benzenesulfonyl chloride and thiophenol in quantitative yields.

The proposed mechanism is further supported by the observed reaction by-products. A small amount of the corresponding thiosulfonate (10%) was obtained in the reaction of 3-methoxythiophenol (Table 2, entry 7).

Thiosulfonates with strong sulfenylating ability, have found wide industrial applications both in polymer production and in photographic processes.[19] Thus the syntheses of these compounds are of continuing interest. There are various synthetic methods for



Scheme 3. A possible mechanism for the formation of sulfonyl chloride and thiosulfonate from a thiol with the H_2O_2–$TiCl_4$ reagent system.

the preparation of symmetric thiosulfonates.[20–27] However, since many of these transformations are limited by side reactions, unsatisfactory yields, lack of chemoselectivity, difficult to obtain reagents, or harsh conditions, the search for new improved methods based on readily available reagents and operationally simple procedures remains justifiable.

To further verify the mediation of thiosulfonates in the oxidative chlorination of thiols, the reactions were repeated for the preparation of symmetric thiosulfonates (Scheme 1).

This required only slight modification to the original reaction conditions. For example, the amounts of $TiCl_4$ required decrease from 1 equiv to 0.25 equiv. The substrate scope of the reaction was investigated. When several commercially available thiols were subjected to the modified reaction conditions, the corresponding symmetric thiosulfonates were formed in good to excellent yields. Both electron-rich and electron-deficient aryl thiols worked well, mostly leading to excellent yields of products. However, as can be seen from the data in Table 3, the chemoselectivity of this process was similar to that of the synthesis of sulfonyl chlorides. More importantly, acid-sensitive thiols such as 2-(furan-2-yl)methanethiol (Table 2, entry 10) formed the desired thiosulfonate in a 92% yield and the furyl moiety remained unaffected under the oxidative chlorination conditions.

In conclusion, a simple and convenient oxidative chlorination procedure using the H_2O_2–$TiCl_4$ system is described and found to be very useful for the direct conversion of thiols into their corresponding sulfonyl chlorides in good to excellent yields and short reaction times. This reagent system was also found to be an efficient oxidizing agent for the oxidation of thiols into the corresponding symmetric thiosulfonates in good to excellent yields. The reaction is highly selective, simple, and clean in most cases. Further utilization of this procedure is in progress in our laboratory.

General procedure for the oxidative chlorination of thiols into sulfonyl chlorides

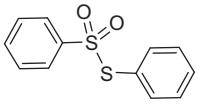
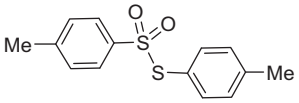
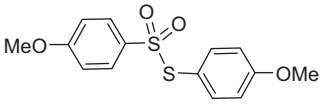
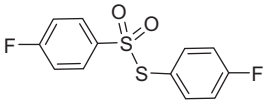
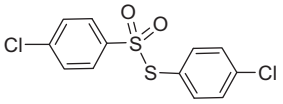
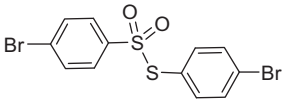
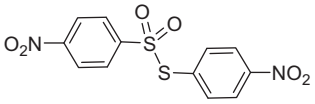
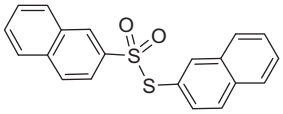
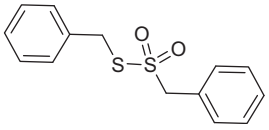
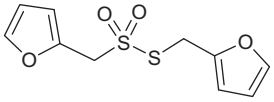
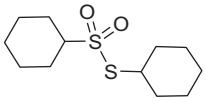
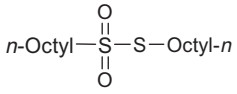
A mixture of thiol (1 mmol), 30% H_2O_2 (3 mmol, 0.3 mL), and $TiCl_4$ (1 mmol, 0.11 mL) was stirred in CH_3CN at 25 °C for the time indicated in Table 1. A white solid, (TiO_2) immediately precipitated. After completion of the reaction as indicated by TLC, the mixture was quenched by adding H_2O (10 mL), extracted with EtOAc (4 × 5 mL), and the extract was dried over anhydrous $MgSO_4$. The filtrate was evaporated under vacuum to afford the analytically pure product or chromatographed by passing through a short column of silica gel, and the products were identified by comparison of their ^1H and ^{13}C NMR spectra, and melting point with authentic samples prepared by known methods.

General procedure for the preparation of thiosulfonates

To a mixture of thiol (2 mmol) and 30% H_2O_2 (6 mmol, 0.6 mL) in CH_3CN (5 mL), $TiCl_4$ (0.5 mmol, 0.06 mL) was added. The mixture was stirred at room temperature for the appropriate period of time (Table 3). A white solid, (TiO_2) immediately precipitated. After complete consumption of the starting material as observed by TLC, the reaction mixture was filtered to give TiO_2. The filtrate was poured into H_2O (15 mL). The aqueous was then extracted with EtOAc (4 × 5 mL), dried over anhydrous magnesium sulfate, and evaporated to afford the corresponding thiosulfonate as the only product. In the case of *S*-4-methoxylphenyl 4-metoxybenzenesulfonothioate (Table 3, entry 3), the crude product after evaporation of the solvent was purified by column chromatography on silica gel using a mixture of cyclohexane and EtOAc as eluent (90:10).

All of the products are known compounds, and were characterized by comparison with authentic samples (^1H and ^{13}C NMR

Table 3
Synthesis of thiosulfonates from thiols[a]

Entry	Product	Yield[b] (%)	Time (min)	Mp (°C) (Lit mp)	Ref.
1		95	2	39–41 (38–39)	28
2		98	1	71 (72–74)	25
3		85	5	89–90 (89–90)	29
4		97	2	70 (69–70)	28
5		90	2	134–136 (135–136)	28
6		90	2	160 (158–159)	28
7		93	2	181–183 (182)	30
8		90	2	104–106 (104.5–106.5)	31
9		98	1	105–107 (107)	32
10		92	4	Oil (—)	—
11		93	7	Oil (oil)	32
12		88	5	Oil (oil)	32

[a] The products were characterized by comparison of their spectroscopic and physical data with authentic samples synthesized by reported procedures.
[b] Yields refer to pure isolated products.

spectra, and melting points). Spectral and analytical data for new compound follow.

S-Furan-2-ylmethyl furan-2-ylmethanesulfonothioate (Table 3, Entry 10)

Mp oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 4.28 (s, 2H, CH_2), 4.43 (s, 2H, CH_2), 6.37–6.45 (m, 4H, ArH), 7.44–7.49 (m, 2H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 33.2, 61.6, 109.8, 111.0, 111.3, 113.4, 142.0, 143.3, 144.4, 148.0. Anal. Calcd for $C_{10}H_{10}O_4S_2$: C, 46.50; H, 3.90; S, 24.83. Found: C, 46.65; H, 3.86; S, 24.62.

Acknowledgment

We are thankful to the Razi University Research Council for partial support of this work.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.11.052.

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