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Metal-free Chlorothiolation of Alkenes using HCl and Sulfoxides

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Abstract

We report a novel method for the chlorothiolation of alkenes using HCl and sulfoxides to achieve the 1,2-difunctionalization of unactivated alkenes. The combination of our new HCl reagent (HCl/DMPU) with sulfoxides forms a unique chlorothiolation system. Both terminal and internal alkenes are suitable substrates. This method works at gram scale and is applicable in further synthetic elaborations.

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This method for the chlorothiolation of alkenes using HCl and sulfoxides is novel. This combination of our new HCl reagent (HCl/DMPU) with sulfoxides forms a unique chlorothiolation system with high regioselectivity and good chemical yields.

Keywords

Chlorothiolation; Alkene; Difunctionalization; Regioselective; Sulfoxides

Carbon-sulfur bond forming reactions are highly desirable because sulfur-containing compounds are commonly found in biologically important natural and synthetic products,^[1] and functionalized materials.^[2] Therefore, there have been increasing efforts to develop carbon-sulfur bond forming reactions.^[3] The difunctionalization of alkenes is a fundamentally important transformation in organic synthesis.^[4] More specifically, 1,2-chlorothiolation of olefins installs both the chloro- and thio-groups simultaneously. The resulting β -chlorothiolated compounds have been shown to possess insecticidal, antibacterial and antifungal properties.^[5] Chlorothiolated compounds are commonly synthesized via electrophilic addition of sulfonylchlorides to olefins.^[5a, 6] Recently, chloromethylsulfide was shown to be the species responsible for the chlorothiolation of alkynes.^[7] However, this

method presents certain challenges: the instability and volatility of lower alkylsulfonyl chlorides require extremely low reaction temperatures.

Dimethylsulfoxide (DMSO), which is an environmentally benign and easy to handle reagent, has been utilized in the past decade as a one-carbon synthon for C-C homologation^[8] and as the source of the thiomethyl moiety^[9] as well as other reactions.^[10] Several DMSO-Lewis acid combinations have been employed with chloride and bromide sources to achieve β -halothiolation.^[11] Pagnoni and co-workers^[11c] reported the transformation of alkenes to their corresponding β -chloromethylthiolated products using dialkylsulfoxide-trimethylchlorosilane [$R_2SO-(CH_3)_3SiCl$]. They subsequently used a dimethylsulfoxide-dimethylsulfide-sulfonyl chloride (DMSO-DMS- SO_2Cl_2) combination to achieve the same transformation (Scheme 1a). The importance of incorporating the thiomethyl moiety within molecules has engrossed research interests lately as demonstrated by the DMSO-mediated thiomethylation of arenes (Scheme 1b).^[3b-d] The above methods suffer from poor atom economy or use of strong oxidants and expensive transition metal catalysts. We reasoned that the reactive chlorosulfonium species can be generated *in situ* directly from a sulfoxide and a Brønsted acid like HCl, which can then react with unactivated alkenes to give β -chlorothiolated compounds in an atom-economical fashion (Scheme 1c).

We began our investigation using allylbenzene (**1a**) as the model substrate (Table 1). Using ethyl acetate as choice solvent^[12], no reaction took place when aqueous concentrated aqueous HCl (37%) was employed (Table 1, entry 1). However, using our newly developed DMPU-HCl reagent,^[13] we succeeded in generating the reactive methylsulfinyl chloride, which then reacted with allylbenzene to give the desired product (Table 1, entry 2). Increasing the amounts of DMSO (Table 1, entries 3–4) gave complete conversion in a shorter reaction time. When the reaction was run in more dilute conditions, the conversion was reduced (Table 1, entry 5). Concentrated aqueous HCl (37%) also resulted in moderate conversion at higher temperatures (Table 1, entry 6). Commercial 5M HCl/isopropanol solution (Table 1, entry 5) also gave good conversion, but suffered from the formation of side products due to further reaction with isopropanol.

The optimized reaction conditions were then tested on a range of alkenes (Table 2). A wide variety of functional groups were well tolerated giving moderate to excellent yields. 5-Hexene-1-ol (**1c**) gave the desired transformation with a simultaneous chloride substitution of the alcohol in 86% yield. Protected alcohols **1d**, **1e**, **1f**, **1i** and **1k** smoothly furnished the corresponding β -chloromethylthiolated products in 82%, 71%, 65%, 62% and 93% respectively. Phthalimides **1g** and **1h** gave the desired conversions in 87% and 59% respectively. Worthy of note is the significant loss in regioselectivity due to the neighboring group participation of carbonyl and ether oxygen in close proximity to the alkene. As a result, the allylic substrates resulted in a mixture of regioisomers (Table 2, 2h and 2i).

Other functionalities like carboxylic acids (**2j**), aldehydes (**2l**) and nitriles (**2n**) were equally tolerated furnishing products in moderate to excellent yields. Internal alkenes (**1q**, **1r**, **1s**, **1t**) also proceeded in 89%, 81%, 80% and 69% yields, respectively. The reaction is highly stereoselective giving exclusively the trans-addition products and single diastereomers. This result is consistent with the trans-addition product expected in the reaction of

methylsulphenylchlorides to alkenes.^[11c, 14] Styrene substrates also worked well, but the labile benzylic chloride was hydrolyzed during work up to form **2s** and **2t** in 74% and 82 % yields respectively. The reactive 4-vinylanisole gave a complex mixture, possibly due to the instability of the product.

Given the prevalence of the arylsulfides in bioactive compounds, we sought to extend this methodology to the synthesis of substituted arylsulfides. Allylbenzene served as the model substrate for the reaction with various arylmethylsulfoxides (Table 3).

Phenylmethylsulfoxide, *p*-tolylmethylsulfoxide, 4-bromophenylmethylsulfoxide and 4-chlorophenylmethylsulfoxide gave the corresponding arylsulfides **3a**, **3b**, **3c** and **3d** in moderate yields.

However, the electron deficient arylmethylsulfoxides **3e** and **3f** gave poor yields. In these cases, the sulfoxides were mostly reduced to the corresponding sulfides. Reactions of dialkylsulfoxides such as dibutylsulfoxide was unsuccessful probably due to the slower formation of the reactive intermediate. The use of butylmethylsulfoxide gave the chloromethylthiolated product as the major adduct.

To further explore the scalability and application of this method, we performed a gram-scale reaction which, upon isolation, was efficiently oxidized to the corresponding sulfone, **4** (Scheme 2a), all in good yields. The process is also amenable to late stage functionalization, as demonstrated by the protected sugar **2v**, the chlorothiolated derivative of which was isolated in 46% yield (Scheme 2b). The rather unexpected result of **2w**, gave us another platform for further elaboration of our method: using *m*-vinylbenzoic acid (**1w**), we were pleased to observe an intramolecular cyclization to form the methylsulfide substituted isobenzofuranone. Using 4-fluorostyrene **1x**, we were able to produce an intermolecular β -carbomethylthiolation to produce **5** in good yields (Scheme 2c). The newly formed β -chloromethylsulfides should also be amenable to other synthetic processes such as the base-promoted elimination of HCl to give the corresponding vinyl thioether,^[15] or transition metal catalyzed cross-coupling reactions with boronic acids.^[16]

The proposed mechanism (Scheme 3) involves the protonation of DMSO, generating sulfonium salt **I**, and subsequent elimination of water to form dimethylsulfonium chloride **II**. The reaction of this highly electrophilic species with another equivalent of HCl leads to another electrophilic sulfur species **III**. **III** is then attacked by the alkene to generate the thiiranium intermediate **IV**, which is then trapped by the nucleophilic chloride to obtain the chlorothiolated product.

Both Kharasch^[17] and Mueller^[14, 18] reported the formation of a thiiranium ion in the addition of sulphenylhalides to olefins.^[14, 19] The opening of the cyclic thiiranium ion **IV** by chloride would follow an S_N1-like pathway: the nucleophile (Cl⁻) preferentially attacks at the more hindered position resulting in the trans-addition product.^[14, 20] Notably, our HCl-DMSO system does not work for alkynes.^[21]

In conclusion, we have achieved the chlorothiolation of alkenes, a transformation that affords biologically and synthetically relevant β -chlorothiolated compounds, using common

and easy to handle starting materials: DMPU-HCl, DMSO and alkenes. The procedure shows good functional group compatibility—both terminal and internal alkenes are suitable substrates—and is suitable for gram scale synthesis.

Experimental Section

The HCl/DMPU was prepared as reported in literature.^[13b, 22]

General procedure for the β -chloromethyl/arylthiolation of alkenes

A glass vial equipped with a screw cap and a stirring bar was charged with alkene **1** (0.5 mmol). Then ethyl acetate was added (0.5 mL) followed by DMSO (1.2 mmol) and HCl/DMPU (102 μ L, 1.2 mmol). The reaction mixture was stirred at 65 °C (or 75 °C for less reactive substrates) and the progress of the reaction was monitored by GC-MS or TLC. Upon completion, the reaction mixture was quenched with water and extracted with DCM. The combined organic layers were then dried over anhydrous Na₂SO₄, filtered and solvent evaporated. The crude product was purified by silica gel column chromatography (hexanes/ethyl acetate).

Synthesis of sulfone, 4—Upon isolation of the gram-scale product **2a** prepared using general procedure, (0.5 mmol, 100 mg) of it was measured into a screw cap vial equipped with a stir bar. Acetic acid (90.5 mL) was added and vial placed into an ice-bath to chill to 0 °C. H₂O₂ (170 μ L, 1.7 mmol) was added dropwise and the reaction mixture let to stir and warm up to rt. The reaction progress was monitored by GCMS and TLC. Upon completion, reaction was quenched with saturated aqueous Na₂S₂O₃ (2 mL), extracted with DCM (2 mL), washed twice with water (2 X 2 mL). The organic phase was dried over Na₂SO₄, filtered off and solvent evaporated. The residue was purified by flash chromatography on silica gel to obtain **4** (1:9 EtOAc:Hex) to yield the desired product. Colorless oil, 113.6 mg, 98 %.

Synthesis of 5—A glass screw cap vial equipped with a stir bar was charged with alkene **1** (0.5 mmol). Ethylacetate was added (0.5 mL). DMSO (1.2 mmol) and HCl/DMPU (102 μ L, 1.2 mmol). The reaction mixture was stirred at 65 °C and the progress of the reaction was monitored by GCMS or ¹H-NMR. Upon completion, the reaction mixture was cooled to rt then excess pyrrole (3.6 mmol, 0.25 mL) added and the reaction stirred for another 1 h. Upon full conversion, reaction mixture was quenched with saturated bicarbonate and extracted with DCM. It was then dried over anhydrous Na₂SO₄, filtered and solvent evaporated. The crude product was purified by silica gel column chromatography (hexanes/ethyl acetate).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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a) TMSCl mediated chloromethylthiolation of alkenes.

b) Directing group assisted metal-catalyzed methylthiolation of arenes

c) HCl mediated chlorothiolation of unactivated alkenes (**this work**).

Scheme 1.

Chlorothiolation of alkenes and arenes.

a) Gram scale reaction and synthetic versatility

b) Late stage functionalisation

c) Utility of styrenes for intra- and intermolecular functionalization

Scheme 2.
Generality and applications of method.

Scheme 3.
Proposed mechanism.

Table 1.

Optimization of reaction conditions.^a

Reaction scheme: 1a $\xrightarrow[\text{EtOAc, 60 } ^\circ\text{C}]{\text{DMSO (X equiv), HCl source (2.4 equiv)}}$ 2a

Entry	X (equiv)	HCl source	Solvent amount/mL	Time/h	Conversion ^b %
1	1.2	36.6–38% HCl (aq)	0.5	24	trace
2	1.2	HCl/DMPU (38–42 % w/w)	0.5	24	71
3	2.4	HCl/DMPU (38–42 % w/w)	0.5	5	100
4	4.8	HCl/DMPU (38–42 % w/w)	0.5	2	100
5	2.4	HCl/DMPU (38–42 % w/w)	1	5	95
6	2.4	36.6–38% HCl(aq)	1	24	54 ^c
7	4.8	HCl/DMPU (38–42 % w/w)	0.5	2	100
8	2.4	5M HCl/isopropanol	0.5	5	90

^aReaction conditions: **1a** (0.5 mmol), HCl/DMPU (1.2 mmol), DMSO (1.2 mmol), EtOAc, 60 °C.^bDetermined by GC-MS with dodecane as the internal standard.^cReaction run at 70 °C

Table 2.

Alkene substrate scope for chlorothiolation.

Table 3.Sulfoxide substrate scope in the β -chloroarylthiolation of alkenesa