Tetrahedron Letters 56 (2015) 6965–6969

Contents lists available at ScienceDirect

Tetrahedron Letters

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

A metal free chlorothiolation strategy for synthesis of vinyl sulfides from internal alkynoates

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ARTICLE INFO

Article history:
Received 12 August 2015
Revised 5 October 2015
Accepted 7 October 2015

Keywords:
Alkynes
Chlorothiolation
Vinyl sulfides
Phenyl iodine di acetate
Vinyl sulfoxides

ABSTRACT

A metal free chlorothiolation approach has been developed for conversion of internal alkynoates to vinyl sulfides and also utilized mild PIDA mediated oxidation to yield the corresponding sulfoxides.

Sulfides and sulfoxides are prevalent in a number of biologically active natural products having antimicrobial, antibiotic, antifungal and antibacterial activities and thus attract a great deal of attention from medicinal and synthetic organic chemists.[1,2] Recently, aryl sulfides have been reported as anti-inflammatory agents and also they find use in the treatment for diseases like Alzheimer's, Parkinson's, asthma, tuberculosis, anthrax diseases, etc. Similarly, sulfoxides can also be used as oxo-transfer agents and ligands for different asymmetric synthesis.[3] Therefore, the development of efficient methods for the stereoselective synthesis of vinyl sulfides and their sulfoxides is highly desirable in organic synthesis. Literature report reveals that the most common and general approaches toward the synthesis of alkenyl sulfides depends on disulfidation or hydrosulfidations of terminal alkynes using transition metal catalysts.[4] In these hydrosulfidation or disulfidation approaches, regio/stereoselectivity depends upon the catalyst or substrate used and they are applicable only on terminal alkynes. Furthermore, it is still very difficult to control the stereoselectivity of addition products. Recently we also reported synthesis of artemisinin derived chlorovinyl sulfides starting from C-10 oxa terminal alkynes in good to excellent yields.[5] Thus, the development of an efficient and metal free method for stereoselective chlorothiolation of internal alkynes is highly necessary.

Literature study showed that the electrophilic addition of sulfenyl chloride to carbon–carbon triple bond can give both the 1:1 adducts with *trans*-stereospecificity.[6] In general, a marked preference for *anti*-orientation is observed.

It is well known that for terminal alkynes, electrophilic addition of sulfenyl chloride to give both the *syn* and *anti* product depends on the substrate and solvent used.[7] Montevecchi and his coworkers reported that both the *cis*- and *trans* products are formed during bromothiolation of internal alkyne.[8] In addition to this, recently Cikotiene and Buksnatiene reported an aryl selenyl chloride promoted addition of propargyl amides to yield *anti*-adducts.[9] In this Letter we wish to report a method that produces only stereoselective vinyl sulfides by the electrophilic addition of sulfenyl chlorides to internal alkynes.

To explore a mild and general access to stereoselective β-chloro alkenyl sulfides, we initially synthesized the internal alkyne **3a** by Sonogashira cross coupling reaction followed by acetylation.[10] Chlorothiolation of **3a** by using 4-bromo benzenethiol in the presence of *N*-chlorosuccinimide (NCS) afforded the addition product **4a**. To our delight chlorothiolation of **3a** occurred very smoothly in dichloromethane to afford β-chloroalkenyl sulfide **4a** with the yield of 78% as shown Scheme 1.

According to previous work, the addition of sulfenyl chloride to alkynes proceeds via a thiirenium ion intermediate where the chloride ion can attack at either ring of carbon resulting in the adducts.[6,11]

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http://dx.doi.org/10.1016/j.tetlet.2015.10.028
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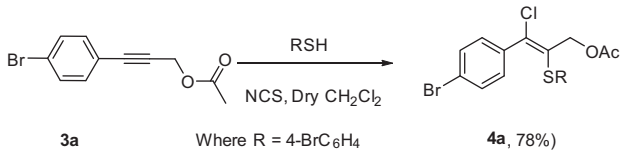


Scheme 1. Chlorothiolation of internal alkyne.

But in our case we obtained **4a** as a sole product. To confirm the exact structure as well as configuration of vinyl sulfide, we transformed **4g** into sulfoxide **5g** using PIDA as mild oxidant. Further chlorovinyl sulfoxide **5g** was treated with 4-methylbenzenethiol in the presence of excess triethylamine resulting the substituted product **6** (Scheme 2).

Similarly, most of synthetic methods selected for oxidation of sulfides to sulfoxides are an intermediate step in the synthesis of sulfones.[12] Hence investigations toward finding mild oxidants which convert sulfides to only sulfoxides is a very interesting area of synthetic organic chemistry as well.

The product **6** was purified by using the column chromatographic technique and the ORTEP diagram of **6** confirms the original structure of product **4g** (Fig. 1).

After confirming the exact structure of **6**, we next studied the solvent effects on this reaction. Initially, the effectiveness of different solvents such as EtOAc, DCE, toluene and CH_3CN were tested and we found that there was no dramatic change in the product in all these solvent systems. *N*-bromosuccinimide also reacted with thiol to produce sulfenyl bromide that underwent addition with alkyne **3a** to produce bromovinyl sulfide with mild regioselectivity. In the absence of a halogen source (NBS, NCS) no reaction took place. Thus, we have found the halogen source (NCS, NBS) is essential for the in situ generation of sulfenyl halide to undergo addition with internal alkyne (**3**) to afford *anti* product as shown in Table 1. With these successful regio/stereoselective chlorothiolation conditions in hand, we next proceeded to examine the generality of these reactions as illustrated in Table 2. Various substituted thiols were treated with internal alkyne **3** as shown in Table 2 (**4b**–**4p)** in good to excellent yields. Under these conditions electron rich thiols underwent chlorothiolation faster as compared to electron deficient thiols like –F, but the thiols containing the NO_2 group do not undergo reaction with the substrate **3a**. Even the alkylated thiols , like cyclohexane thiol underwent chlorothiolation to yield the corresponding chloroalkenyl sulfide (**4h**). Finally, chlorothiolation strategy was also utilized by changing the alkyne containing –Me and –OMe substituent in the place of –Br to produce vinyl sulfides **4o** (60%) and **4p** (77%). However in the case of a substrate bearing an –OMe group, afforded a vinyl sulfide mixture (see Scheme 3).

In recent years, hypervalent iodine reagents are broadly applied as powerful electrophiles and highly selective oxidants due to their low toxicity, mild reactivity, high stability, and easy handling in organic synthesis.[13] Firstly Togo et al. converted diaryl sulfides into corresponding sulfoxides and sulfones by using phenyl iodine di acetate (PIDA) as oxidant.[14] Recently Yu et al. synthesized

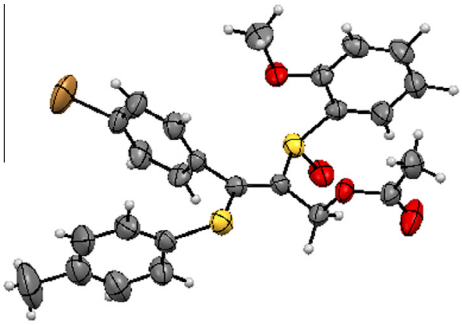


Figure 1. ORTEP diagram of compound **6**.

Table 1
Optimization of chlorothiolation reaction

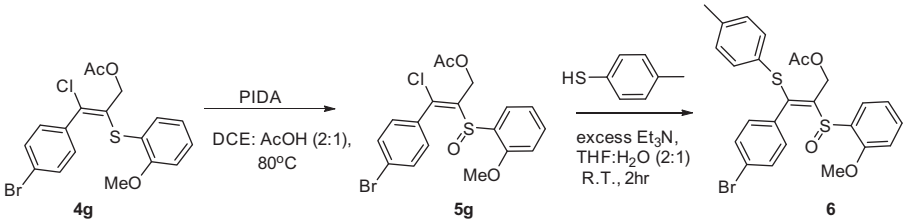
Entry	Solvent[a]	Time (h)	Yield[b] (%)
1	EtOAc	5	65
2	DCE	6	70
3	Toluene	7	68
4	CH_3CN	8	63
5	DCM	3	78

[a] Anhydrous solvents used.
[b] Isolated yields.

sulfoxides and sulfones from sulfides by using in situ generated Koser's reagent in aqueous media.[13g] In addition to this, PIDA is used as a mild oxidant and found in several sulfoxides synthesised from sulfides.[15] Recently Sokolenko et al. explored the utility of perfluroalkyl vinyl sulfoxides by alkylation via Heck reaction.[16] These results prompted us to work on vinyl sulfides followed by sulfoxide synthesis and here we wish to report regio/stereoselective chlorothiolation of alkynoates and PIDA mediated oxidation to sulfoxides.

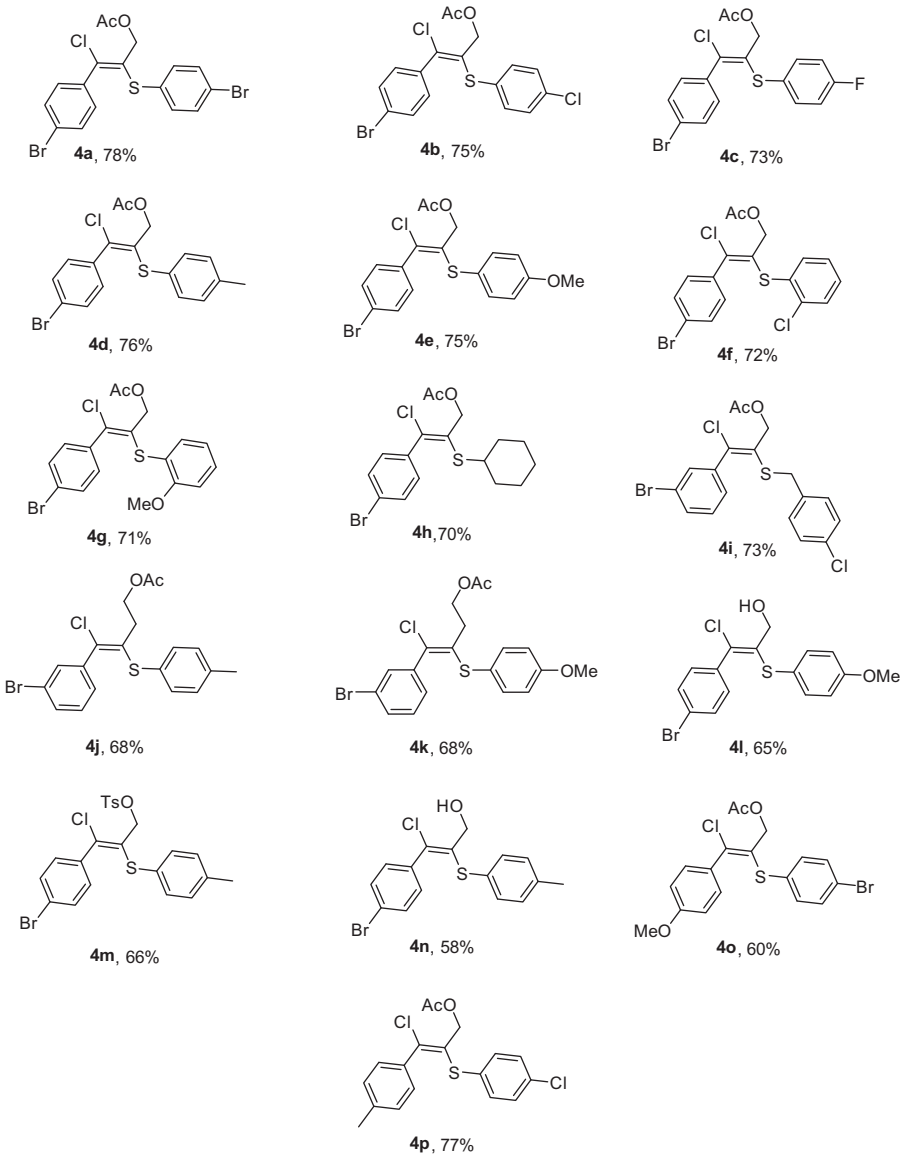
As organo sulfoxides are important intermediates in the synthesis of various biologically important natural products as well as vinyl sulfoxides used as starting materials in Heck coupling reaction also, we decided to convert our synthesized β-chloro alkenyl sulfides to β-chloroalkenyl sulfoxides. In general, oxidation of sulfides involved different hypervalent iodine reagents which are required prior to the preparation of catalyst or synthesis of Koser's reagent as oxidant in the presence of stoichiometric amounts of additives. To the best of our knowledge there is no report on metal free chlorothiolation reaction of internal alkynoates and their subsequent PIDA mediated selective oxidations to corresponding sulfoxides.

Finally, we carried out the oxidation of sulfur by using PIDA as oxidant to convert β-chloroalkenyl sulfides into sulfoxides. We began our investigation on a model substrate **4a**. PIDA mediated oxidation proceeded at room temperature in a solvent system consisting of DCE/AcOH (2:1) and we observed the formation of a trace amount of sulfoxide. To complete the conversion of **4a**, we heated the reaction mixture at 80 °C to afford sulfoxide **5a** with high selectivity. The formation of sulfoxide was confirmed by ^1H NMR, ^{13}C

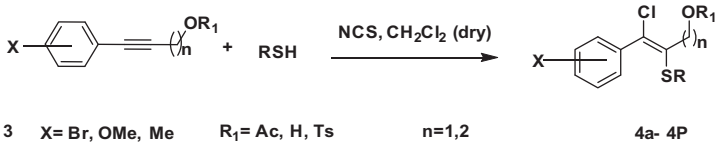


Scheme 2. Synthesis of (*E*)-3-(4-bromophenyl)-2-((2-methoxyphenyl)sulfinyl)-3-(*p*-tolylthio)allyl acetate **6**.

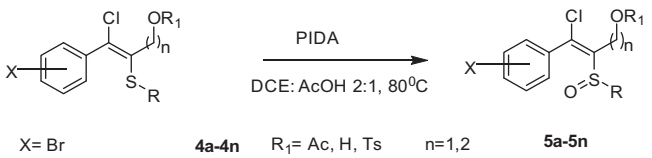
Table 2
Chlorothiolation* adducts of internal alkynoates **4**(**a**–**p**)



* Reaction conditions: internal alkyne (0.5 mmol), thiol (0.65 mmol) and NCS (0.65 mmol) stirred at room temperature. Yields after column chromatography.

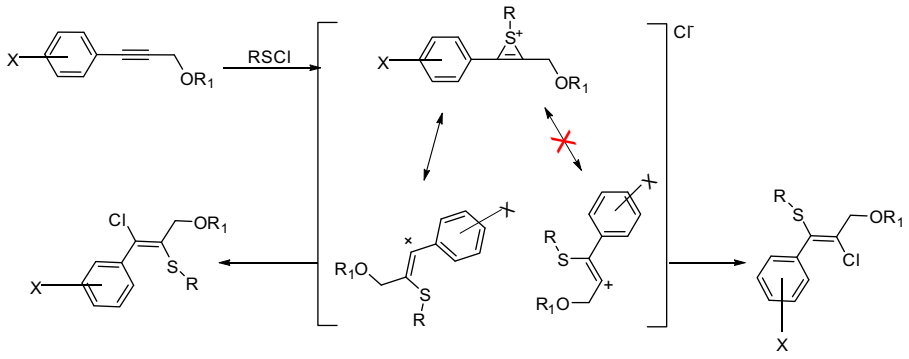


Scheme 3. General reaction of chlorothiolation of internal alkynoates.



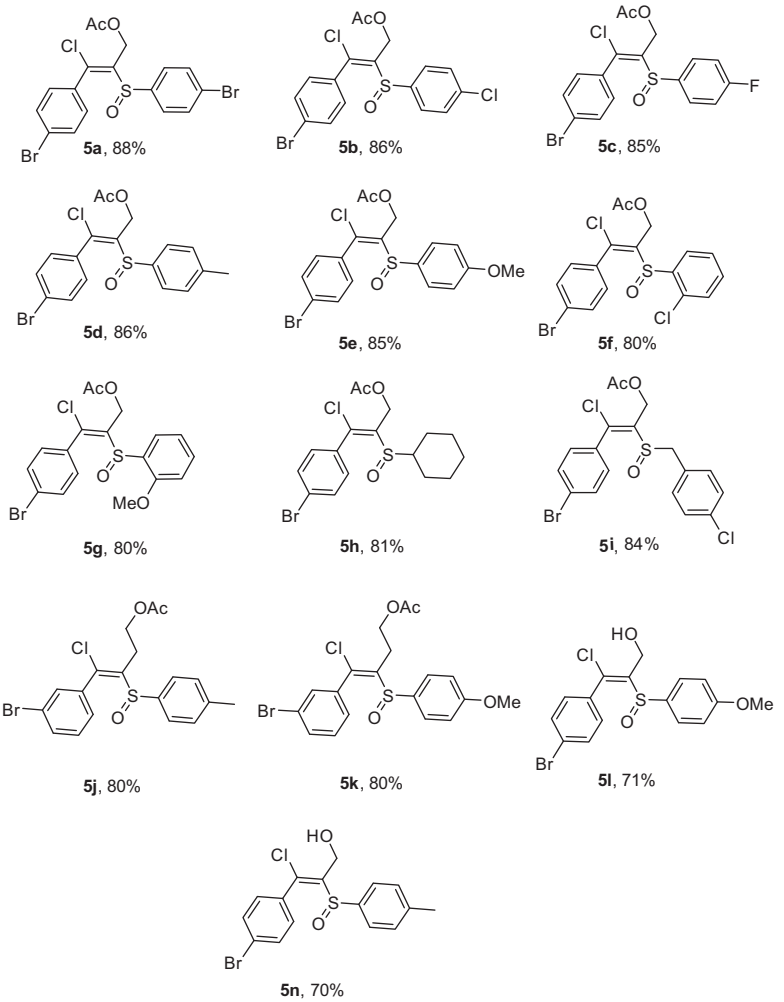
Scheme 4. General reaction of alkenyl sulfides to sulfoxides.

NMR and DEPT spectra (see Scheme 4). However, when solvents viz. AcOH, $(CH_2)_2Cl_2$, CH_2Cl_2, $CHCl_3$ and THF were used in place of DCE/AcOH (2:1), the reaction did not proceed in the desired direction to give sulfoxide **5a**. Therefore, the reaction has been generalized using DCE/AcOH (2:1) through substrates **4b**–**4n** in Table 3 and the yield corresponding sulfoxides **5b**–**5n**. However in the case of sulfide **4n**, along with sulfoxide **5n** a trace amount of sulfone was also formed under this reaction condition (Table 3).



Scheme 5. Plausible mechanism for chlorothiolation of internal alkynoates.

Table 3
Synthesis* of chloroalkenyl sulfoxides from chloroalkenyl sulfides



5a, 88% **5b**, 86% **5c**, 85%

5d, 86% **5e**, 85% **5f**, 80%

5g, 80% **5h**, 81% **5i**, 84%

5j, 80% **5k**, 80% **5l**, 71%

5n, 70%

* Reaction conditions: vinyl sulfide (0.5 mmol), PIDA (0.65 mmol) stirred at 80 °C. Yields were after column chromatography.

Plausible mechanism for the chlorothiolation internal alkynoates

Previous studies indicate that chlorothiolation of alkynes undergoes addition of sulfinyl chlorides to form thiirenium ion intermediate.[6,7,11] Accordingly we predicted that, the chloride ion attacks where the carbon atom adjacent to the phenyl ring which is electron deficient may enhance carbocation stability by + inductive effect of phenyl ring rather than the alkoxy group, to produce regio/stereoselective chlorovinyl sulfides (see Scheme 5).

In conclusion, we have developed an efficient metal free reaction protocol for the synthesis of stereoselective chlorovinyl

sulfides followed by synthesis of chlorovinyl sulfoxides from internal alkynes in good to excellent yields. In this protocol we have also found that β-chloroalkenyl sulfoxide moiety, the chloride group is easily substituted by thiol under much simpler experimental conditions to give an *anti* sulfoxide-sulfur compound **6** with good yield. Detailed mechanistic studies of chlorothiolation strategy are under progress in our laboratory.

Acknowledgments

This work was funded by the in-house project (MLP-3000) of CSIR- NEIST, Jorhat, India. N.S. thanks the UGC – New Delhi, India and P.B. thanks the CSIR – New Delhi, India for the grant of research fellowships.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.10.028.

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