Regioselective Hydrothiolation of Alkynes by Sulfonyl Hydrazides Using Organic Ionic Base—Brønsted Acid

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A practical and novel approach has been developed for the synthesis of vinyl sulfides by the reaction of sulfonyl hydrazides with aryl/ heteroarylacetylenes using a DBU-based ionic liquid. The system offers a new sulfur source for hydrothiolation and is endowed with green credentials.

Regioselective hydrothiolation of terminal alkynes using thiols is an established strategy.¹ The vinyl sulfides, produced as a result of the anti-Markownikoff addition, serve as important synthetic intermediates in total syntheses and as

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precursors to a wide range of functionalized molecules.^{2–5} Many natural products and compounds exhibiting remarkable biological properties contain the vinyl sulfide moiety.⁶ These compounds have also found extensive applications in materials science⁷ and thus are cherished targets of contemporary interest. Although lower compatibility of the sulfur compounds to the metal-catalyzed

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reactions has limited their exploration, some reactions involving thiols have been developed.^{8a-c} In this regard, Markovinkov selective hydrothiolation using styrene and its derivatives with 2-mercaptobenzothiazole is worth mentioning.^{8d} The use of disulfides has also been made to some extent,^{9a,b} although the reactions are often endowed with the formation of bisulfidation products.^{9c-e} Limited exploration in this direction with unpleasant smelling thiols as the prominent source and the use of heavy metals for the accomplishment of the reaction, has set a considerable demand for developing a safer alternative for hydrothiolation under practical reaction conditions.

Sulfonyl hydrazides, being stable solids, have been nicely used as reductants,¹⁰ sulfonyl sources¹¹ through the cleavage of their sulfur–nitrogen bonds, and aryl sources¹² through the cleavage of their carbon–sulfur bonds. However, to the best of our knowledge, there exists no report on the use of sulfonyl hydrazide as a thiol equivalent.

In the existing green chemistry scenario, microwaveassisted organic synthesis (MAOS) has attained the status of a new and fascinating discipline.¹³ Ionic liquids (ILs) have further strengthened the domain owing to their ecosafe properties.¹⁴ 1,8-Diazabicycloundec-7-ene (DBU) is widely used as an organic base, ^{15a-c} and DBU-based ionic liquids, such as [DBU][HOAc], are particularly useful as a non-nucleophilic task-specific organic ionic base.^{15d} According to the current synthetic requirements, relevance of microwave (MW) methodology using ionic liquids is particularly welcome.¹⁶ It is hence imperative to exploit the combination of MW and IL for organic transformations with careful assessment of a pair of distinct organo systems

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in different permutations. In view of the above and as a part of our current research program,¹⁷ it is a highly exigent and timely endeavor to report a rapid and useful alternative for hydrothiolation of alkynes by using a new S-source (Scheme 1).

Scheme 1

Previous Approach:



Our studies were indeed initiated to achieve a green protocol for the preparation of allenes by the reaction of benzaldehyde tosylhydrazone with phenylacetylene in the presence of [DBU][HOAc] following the Bamford–Stevens strategy.¹⁸ To our surprise, the spectral data of the isolated product could not match with the expected allene product. For that reason, we resorted to the use of single-crystal X-ray of the molecule so as to finally prove the structure as vinyl sulfide **3a** (Scheme 2, Figure 1), which was also in full agreement with the spectral data.



Encouraged by this unique observation, and to further simplify this new source of sulfur, we undertook the envisaged reaction employing tosyl hydrazide rather than tosyl hydrazone, which also served the same cause with equal readiness facilitating the formation of vinyl sulfide. But, when tosyl hydrazone/tosyl hydrazide was replaced by tosyl chloride under the same set of conditions, the reaction could not succeed. As an outcome, it appears that the use of organic ionic base reduces the sulfonyl hydrazide and thus could eventually make it serve as an effective sulfur source for hydrothiolation. In order to optimize the reaction conditions for hydrothiolation of terminal

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Figure 1. ORTEP diagram of product 3a.

alkynes, a model reaction between inexpensive and easily available tosyl hydrazide and phenyacetylene was investigated in detail by varying different parameters, and the results are given in Table 1.

Table 1. Optimization of Reaction Conditions^a



1 DBU 60 120 2 Bmim[BF_4] 60 120	8
2 $Bmim[BF_4]$ 60 120	~
2 DimmeDr 41 00 120	Э
3 $Bmim[PF_6]$ 60 120	0
4 Bmim[Br] 60 120	0
5 Bmim[OH] 60 120	15
6 [DBU][HOAc] 60 120	40
7 [DBU][n-Pr] 60 120	35
8 [DBU][n-Bu] 60 120	20
9 [DBU][TFA] 60 120	0
10 [DBU][HOAc] AcOH (1) 60 120	90
11 [DBU][HOAc] AcOH (0.5) 60 120	65
12 [DBU][HOAc] AcOH (2) 60 120	89
13 [DBU][HOAc] AcOH (1) 100 120	90
14 [DBU][HOAc] AcOH (1) 60 120	90^c
15 [DBU][HOAc] AcOH (1) 60 100	78
16 [DBU][HOAc] DABCO (1) 100 120	42
17 [DBU][HOAc] L-proline (1) 100 120	50
$18 [DBU][HOAc] \qquad BF_3 \cdot Et_2O\left(1\right) \qquad 100 \qquad 120$	20

^{*a*} Reaction conditions: **1a** (1 mmol), **2a** (1.2 mmol), [DBU][HOAc] (1 mL), additive (0.5–2.0 equiv), 5 min. ^{*b*} Isolated yield based on **1a**. ^{*c*} Reaction carried out at 120 °C for 10 min.

At the outset, DBU and different ionic liquids such as Bmim[BF₄], Bmim[PF₆], Bmim[Br], Bmim[OH], and [DBU][HOAc] were tested for the reaction (entries 1–6), which afforded the best results with the non-nucleophilic ionic base [DBU][HOAc]. Therefore, the studies were directed to look at the prospective of other DBU based ionic liquids like [DBU][*n*-Pr], [DBU][*n*-Bu], and [DBU][TFA] as well (entries 7–9), but none of them could match the efficacy of [DBU][HOAc]. The role of an efficient additive was also examined to look into the effect of cooperative operation. Different additives namely AcOH, DABCO, L-proline, and $BF_3 \cdot Et_2O$ (entries 10 and 16–18) were assessed with [DBU][HOAc] under the optimized conditions, and to our delight, the conjugate acid of the counterion (1 equiv, entry 10) appeared to be on the top. Increasing or decreasing permutations of the additive AcOH did not improve the product yields (entries 11 and 12). The reaction was further probed by varying MW power, temperature and time (entries 13–15) with the end result of 60 W power output at 120 °C in 5 min to achieve the maximum conversion (entry 10). The same reaction under conventional conditions in a Schlenk tube at 120 °C required over 24 h and ended with much lower yield (52%).



Figure 2. Synthesis of vinyl sulfides 3a-u. Reaction conditions: 1 (1.0 mmol), 2 (1.2 mmol), [DBU][HOAc] (1 mL), AcOH (1.0 equiv), 120 °C, 60 W, 5 min. ^aIsolated yield based on 1. ^bE/Z ratio determined by ¹H NMR analysis.

Intrigued by these observation and with the stipulated conditions in hand, the scope of this method was extended to achieve the reaction of a wide range of diverse substrates including a variety of sulfonyl hydrazides, viz. *p*-tolyl-,

Scheme 3



phenyl-, p-methoxyphenyl-, p-nitrophenyl-, p-tertbutylphenyl-, and benzylsulfonyl hydrazides with terminal alkynes like phenylacetylene, p-methylphenylacetylene, *p-tert*-butylphenylacetylene, 2-ethynylpyridine, and *p*-fluorophenylacetylene to afford a diverse range of vinyl sulfides 3a-u in reasonably good to excellent yields under MW irradiation in 5 min (Figure 2). Sulfonyl hydrazides containing electron-donating groups and alkynes with electron-withdrawing groups showed better conversion. Aliphatic terminal alkynes like 1-octyne as well as internal alkynes failed to register any product formation. This is the first report on the use of tosyl hydrazide as thiol equivalent. While preparing the present manuscript, however, a report by Tian et al. has appeared for the iodine-catalyzed sulfenylation of indoles, albeit using sulfonyl hydrazide as a sulfur electrophile source.¹⁹ The recyclability of the ionic liquid was also checked for the model reaction. Upon completion of the reaction, the product was isolated via standard work up procedure and the aqueous layer containing [DBU][HOAc] was dried under vacuum at 60 °C to remove water and then washed with diethyl ether. The recovered ionic liquid was recycled up to five times without any significant loss in its activity. It is worthwhile to mention that the hydrothiolation is invariably regioselective adopting anti-Markownikoff addition. Although some of the products came up with good stereoselctivity but in many cases different cis-trans ratios were observed as specified in Figure 2.

In order to gain insight of the mechanism, a control experiment with phenylsulfonyl hydrazide, in the absence of the alkyne, was carried out, which led to the formation of the corresponding disulfide under optimized conditions. Further, when the resulting disulfide was separately made to react with phenylacetylene under the established conditions, it gave rise to the final product **3e** although with a diminished yield. On the basis of isolation of products, control experiments and the existing literature,^{19,20} a plausible mechanism is outlined in Scheme 3.

In conclusion, we have developed a novel and efficient MW-assisted synthetic protocol for regioselective hydrothiolation of terminal alkynes using sulfonyl hydrazides as thiol equivalent. Due to high conversion, excellent regioselectivity, short reaction time and use of a recyclable ionic liquid, the process promises to be a practical and greener alternative. The study will open a new window to many other useful transformations in organic synthesis. Further studies on the application of sulfonyl hydrazides are underway in our laboratory.

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Supporting Information Available. Detailed experimental procedure and spectral data of all products along with copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.