Sodium iodide-mediated synthesis of vinyl sulfides and vinyl sulfoxones with solvent-controlled chemical selectivity†

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Vinyl sulfides and vinyl sulfoxones are ubiquitous structures in organic chemistry because of their presence in natural and biologically active compounds and are very frequently encountered structural motifs in organic synthesis. Herein we report an efficient synthesis of vinyl sulfides and vinyl sulfoxones via transition metal-free sodium iodide-mediated selenylation of alcohols and sulfenic acids with solvent-controlled selectivity.

Introduction

Functionalized olefins are valuable intermediates in organic synthesis, because of their ability to serve as convenient substrates in transition metal-catalyzed cross-coupling reactions and their presence in natural and biologically active compounds.1 In this respect, sulfur-containing olefins as important building units or intermediates have been applied in many different fields, such as total synthesis, functional materials science and medicinal chemistry.2 For example, vinyl sulfides are employed as precursors for enol substituents,3 Michael acceptors,4 in cycloaddition reactions,5 in olefin metathesis,6 as reagents in cross-coupling,7 in Heck reactions,8 as equivalents of enolate anions,9 and in aldehyde/ketone formation.10 Vinyl sulfoxides and their derivatives have been reported to be potent inhibitors of enzymes such as sortase,11 protein tyrosine phosphatases,12 and cysteine proteases.13 In view of their significance, developing more practical and efficient synthetic approaches to construct these compounds is of great interest.14 Two common methods are frequently utilized for the synthesis of vinyl sulfides, including the copper-catalyzed S-vinylation of thiol with vinyl halides and the addition of thiols to alkenes.15 Recently, Zhang and co-workers reported a copper-mediated stereospecific C–H oxidative selenylation of terminal alkenes with disulfides.16 For the synthesis of vinyl sulfoxides, Wittig reaction of α-sulfynl phosphonium ylides, β-elimination of halosulfones, condensation of aldehydes with sulfonic-acetic, and the oxidation of the corresponding sulfides are the most common synthesis methods.16 Recently, Zhan’s group reported a copper(II)-catalyzed chemo- and stereosselective synthesis of vinyl sulfoxones via decarboxylative sulfonylation of allylpropionic acids with sulfinic acids.17 In spite of the great success achieved so far in this area, there are still certain limitations, such as difficulties in controlling stereoselectivities and chemoselectivities, expensive substrates, moderate scope and functional group tolerance. Therefore, a new general, flexible, high stereoselective and chemoselective approach for the synthesis of vinyl sulfides and vinyl sulfoxones is still necessary.

Sulfinic acids are readily accessible and have been widely used as sulfur sources in medicinal chemistry.18 Moreover, sulfinic acids can be reduced to disulfides, which are active intermediates that can be used as sulfonylating agents. So we envisioned that sulfinic acids might be served as potential sulfur sources to react with alcohols under certain reaction conditions. To our knowledge, there are no examples describing the reaction of sulfinic acids and alcohols. Herein we report an efficient synthesis of vinyl sulfides and vinyl sulfoxones via transition metal-free sodium iodide-mediated sulfonylation of alcohols with sulfinic acids.

Results and discussion

To obtain the optimized reaction conditions, several acids (10 mol%) were examined in the model reaction of alcohol 1a with benzenesulfinic acid 2a using tetrabutylammonium iodide as an additive in 1,2-dichloroethane at 80 °C (Table 1, entries 1–4). To our delight, TsOH·H2O was identified as the acid of choice, which promoted the formation of vinyl sulfide 3a in 61% yield (Table 1, entry 1). Iodine and several iodides such as NaI, KI were investigated to improve the reaction efficiency (Table 1, entries 5–7). Among the above iodides examined, NaI was found to be the most effective additive to give the target product 3a in 70% yield (Table 1, entry 5). Further solvent screening showed
interesting results: (1) we observed the generation of vinyl sulfone 4a in MeCN (Table 1, entry 8). (2) MeNO₂ was the best solvent for the formation of 4a, and improved the yield to 59% yield (Table 1, entry 9). (3) DCE was the best solvent for the formation of 3a. These results demonstrate that solvent plays an important role in controlling the chemoselectivity of the reaction, which could be explained by the fact that MeNO₂ is beneficial to the production of free radical intermediates. A high yield was obtained when the loading of sodium iodide was increased to 1.5 equivalents (Table 1, entry 15). Further efforts to increase the yield of vinyl sulfide 3a by increasing the loading of TsOH-\(\text{H}_2\text{O}\) to 0.2 equivalent resulted in a higher yield of 90% (Table 1, entry 16). Similarly, the yield of 4a was increased to 86% in the presence of 1.5 equivalents of NaI and 20 mol% TsOH-\(\text{H}_2\text{O}\) in MeNO₂.

Encouraged by our preliminary findings, the substrate scope of alcohols and sulfonic acids for the synthesis of vinyl sulfides was explored, and the results were shown in Table 2. In the presence of 1.5 equivalents of NaI, 20 mol% TsOH-\(\text{H}_2\text{O}\) and DCE as solvent, a broad range of bisbenzyl, monobenzyl and naphthyl alcohols smoothly underwent this kind of transformation, generating structurally diverse vinyl sulfide 3 in moderate to excellent yields with extremely high stereoselectivity (Table 2, entries 1–11). The reactivity of monoaryl alcohols is lower than diaryl alcohol. Notably, this protocol proved useful for the construction of vinyl sulfides containing polycycles such as 3d-f (Table 2, entries 4–6). However, this protocol was not applicable to less reactive alkyl alcohols (Table 2, entry 9) substrate scope is also broad with respect to the sulfonic acids. Various arylsulfonic acids smoothly reacted with alcohol 1a to give the corresponding vinyl sulfides in good to excellent yields (Table 2, entries 12–22). It is noteworthy that both electron-withdrawing and electron-donating groups were introduced into the vinyl sulfides by employing arylsulfonic acid bearing such groups on the aromatic ring. Furthermore, alkylsulfonic acids could also smoothly react with alcohol 1a to give the corresponding vinyl sulfides (Table 2, entries 23–25). But the yield is lower than arylsulfonic acids, this may be due to the low activity of alkylsulfonic acids.

Next, the substrate scope of alcohols and sulfinic acids for the synthesis of vinyl sulfones was explored, and the results were shown in Table 3. In the presence of 1.5 equivalents of NaI, 20 mol% TsOH-\(\text{H}_2\text{O}\) and MeNO₂ as solvent, a broad range of bisbenzyl and monobenzyl alcohols were found to react well with benzenesulfinic acids to yield structurally diverse vinyl sulfones derivatives in good to excellent yields with extremely high stereoselectivity (Table 3, entries 1–7). The results represented in Table 3 show that the scope of sulfinic acids is also very general in the sulfonylation of alcohols. A number of arylsulfinic acids bearing either electron-donating groups or electron-withdrawing groups on the aromatic rings were transformed into their corresponding vinyl sulfones at 80 °C in good to excellent yields (Table 3, entries 8–14). Moreover, alkylsulfinic acids could also smoothly react with alcohol 1a to give the corresponding vinyl sulfones (Table 3, entry 15).

In order to gain further insight into the reaction mechanism, four control experiments were set up under various reaction conditions. Benzenesulfinic acid was reduced to diphenyldisulfane 2a’ in 94% yield in the presence of 1.5 equivalents of NaI, 20 mol% TsOH-\(\text{H}_2\text{O}\) and DCE as solvent (Scheme 1a).

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### Table 1  Optimization of reaction conditions

| Entry | Solvent | Additive (eq.) | Acid (eq.) | Yield\(^a\) (%) 3a | Yield\(^b\) (%) 4a |
|-------|---------|----------------|------------|-------------------|-------------------|
| 1     | DCE     | n-Bu₄NI (1.0)  | TsOH-\(\text{H}_2\text{O}\) (0.1) | 61                | 0                |
| 2     | DCE     | n-Bu₄NI (1.0)  | HCl (0.1)  | 57                | 0                |
| 3     | DCE     | n-Bu₄NI (1.0)  | TFOH (0.1) | 53                | 0                |
| 4     | DCE     | n-Bu₄NI (1.0)  | \(\text{H}_2\text{SO}_4\) (0.1) | 58                | 0                |
| 5     | DCE     | NaI (1.0)      | TsOH-\(\text{H}_2\text{O}\) (0.1) | 70                | 0                |
| 6     | DCE     | KI (1.0)       | TsOH-\(\text{H}_2\text{O}\) (0.1) | 63                | 0                |
| 7     | DCE     | I₂ (1.0)       | TsOH-\(\text{H}_2\text{O}\) (0.1) | 0                 | 0                |
| 8     | MeCN    | NaI (1.0)      | TsOH-\(\text{H}_2\text{O}\) (0.1) | 18                | 44               |
| 9     | MeNO₂   | NaI (1.0)      | TsOH-\(\text{H}_2\text{O}\) (0.1) | Trace             | 59               |
| 10    | Toluene | NaI (1.0)      | TsOH-\(\text{H}_2\text{O}\) (0.1) | 42                | 30               |
| 11    | DMSO    | NaI (1.0)      | TsOH-\(\text{H}_2\text{O}\) (0.1) | 17                | 21               |
| 12    | DMF     | NaI (1.0)      | TsOH-\(\text{H}_2\text{O}\) (0.1) | Trace             | 15               |
| 13    | Dioxane | NaI (1.0)      | TsOH-\(\text{H}_2\text{O}\) (0.1) | 30                | 0                |
| 14    | EtOH    | NaI (1.0)      | TsOH-\(\text{H}_2\text{O}\) (0.1) | Trace             | 39               |
| 15    | DCE     | NaI (1.5)      | TsOH-\(\text{H}_2\text{O}\) (0.1) | 78                | Trace            |
| 16    | DCE     | NaI (1.5)      | TsOH-\(\text{H}_2\text{O}\) (0.2) | 90                | Trace            |
| 17    | MeNO₂   | NaI (1.5)      | TsOH-\(\text{H}_2\text{O}\) (0.2) | Trace             | 86               |

\(^a\) Reaction conditions: alcohol 1a (0.20 mmol), benzenesulfinic acid 2a (0.30 mmol), additive, acid, solvent (1.0 mL), 80 °C, 24 h. \(^b\) Isolated yield.
Under the 1.0 equivalents of iodine, diphenyldisulfane 2a smoothly reacted with alcohol 1a to give the corresponding vinyl sulfide 3ab in 91% yield (Scheme 1b). Under the standard reaction conditions, alcohol 1a and diphenyldisulfane 2a don’t react (Scheme 1c). In the presence of 1.5 equivalents of NaI, 20 mol% TsOH and DCE as solvent, alkene 6a was found to react smoothly with benzenesulfonic acids to give vinyl sulfide 3ab in 93% yields (Scheme 1d).

On the basis of the above experimental results and previous relevant mechanism studies, we proposed the reaction pathway depicted in Scheme 2. Initially, alcohol 1 undergo elimination reaction to form alkene 6 under TsOH and heating conditions. Meanwhile, 1,2-diphenyldisulfane (2a) is generated from sulfonic acid 2 in the presence of NaI and TsOH. Then 2a reacts with I2 to give the sulfenyliodide 5, which is attacked by 6.

### Table 3 Sulfenylation of alcohols with sulfonic acids

| Entry | 1    | 2    | Product | Yield (%) |
|-------|------|------|---------|-----------|
| 1     | 1a   | 2a   | 4aa     | 86        |
| 2     | 1b   | 2a   | 4ba     | 93        |
| 3     | 1c   | 2a   | 4ca     | 88        |
| 4     | 1d   | 2a   | 4da     | 90        |
| 5     | 1f   | 2a   | 4fa     | 81        |
| 6     | 1g   | 2a   | 4ga     | 67        |
| 7     | 1h   | 2a   | 4ha     | 69        |
| 8     | 1i   | 2a   | 4ia     | 65        |
| 9     | 1j   | 2a   | 4ja     | 43        |
| 10    | 1j   | 2a   | 4ja     | 43        |
| 11    | 1k   | 2a   | 4ka     | 56        |
| 12    | 1l   | 2a   | 4la     | 51        |
| 13    | 1m   | 2a   | 4ma     | 51        |
| 14    | 1n   | 2a   | 4na     | 51        |
| 15    | 1o   | 2a   | 4oa     | 51        |
| 16    | 1p   | 2a   | 4pa     | 51        |
| 17    | 1q   | 2a   | 4qa     | 51        |
| 18    | 1r   | 2a   | 4ra     | 51        |
| 19    | 1s   | 2a   | 4sa     | 51        |
| 20    | 1t   | 2a   | 4ta     | 51        |
| 21    | 1u   | 2a   | 4ua     | 51        |
| 22    | 1v   | 2a   | 4va     | 51        |
| 23    | 1w   | 2a   | 4wa     | 51        |
| 24    | 1x   | 2a   | 4xa     | 51        |
| 25    | 1y   | 2a   | 4ya     | 51        |

### Table 2 Sulfonylation of alcohols with sulfonic acids

| Entry | 1    | 2    | Product | Yield (%) |
|-------|------|------|---------|-----------|
| 1     | 1a   | 2a   | 3aa     | 90        |
| 2     | 1b   | 2a   | 3ba     | 83        |
| 3     | 1c   | 2a   | 3ca     | 89        |
| 4     | 1d   | 2a   | 3da     | 91        |
| 5     | 1e   | 2a   | 3ea     | 81        |
| 6     | 1f   | 2a   | 3fa     | 77        |
| 7     | 1g   | 2a   | 3ga     | 65        |
| 8     | 1h   | 2a   | 3ha     | 69        |
| 9     | 1i   | 2a   | 3ia     | 0         |
| 10    | 1j   | 2a   | 3ja     | 43        |
| 11    | 1k   | 2a   | 3ka     | 56        |
| 12    | 1l   | 2a   | 3la     | 51        |
| 13    | 1m   | 2a   | 3ma     | 51        |
| 14    | 1n   | 2a   | 3na     | 76        |
| 15    | 1o   | 2a   | 3oa     | 67        |

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$^a$ Reaction conditions: alcohol 1 (0.20 mmol), sulfonic acid 2 (0.30 mmol), NaI (0.30 mmol), TsOH·H₂O (0.040 mmol), MeNO₂ (1.0 mL), 80 °C, 24 h. $^b$ Isolated yield.

Under the 1.0 equivalents of iodine, diphenyldisulfane 2a smoothly reacted with alcohol 1a to give the corresponding vinyl sulfide 3ab in 91% yield (Scheme 1b). Under the standard reaction conditions, alcohol 1a and diphenyldisulfane 2a don’t react (Scheme 1c). In the presence of 1.5 equivalents of NaI, 20 mol% TsOH and DCE as solvent, alkene 6a was found to react smoothly with benzenesulfonic acids to give vinyl sulfide 3ab in 93% yields (Scheme 1d).

On the basis of the above experimental results and previous relevant mechanism studies, we proposed the reaction pathway depicted in Scheme 2. Initially, alcohol 1 undergo elimination reaction to form alkene 6 under TsOH and heating conditions. Meanwhile, 1,2-diphenyldisulfane (2a) is generated from sulfonic acid 2 in the presence of NaI and TsOH. Then 2a reacts with I₂ to give the sulfenyliodide 5, which is attacked by 6.
to give intermediate 7. Finally, elimination of HI from 7 affords the corresponding vinyl sulfide 3.

We performed a relevant control experiment for vinyl sulfones (Scheme 3). When a stoichiometric amount of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy, a well known radical-capturing species) was added to this reaction mixture, the formation of 4a was completely inhibited in the reaction. Therefore, we reason that a radical process should be involved in this reaction.

On the basis of the preliminary result above and previous relevant mechanism studies, we proposed a plausible mechanism for the generation of vinyl sulfones in Scheme 4. First, alcohol 1 undergoes elimination reaction to form alkene 6 under TsOH and heating conditions. Meanwhile, sulfonyl iodide 8 was generated from benzenesulfonic acid in the presence of NaI under air. Then, 8 experienced homolytic cleavage to produce a sulfonyl radical 9, which interacted with alkene 6 to give intermediate 10. Next, intermediate 10 reacts with an iodine radical to give intermediate 11. Finally, elimination of HI from 11 produces the corresponding vinyl sulfone 4.

Conclusions

In conclusion, we have developed a NaI mediated elimination/coupling reaction of alcohols and sulfonic acids, constructing structurally diverse vinyl sulfides and vinyl sulfones. Solvent is crucial for the chemical selectivity. Solvent-controlled selectivity of the elimination/coupling reaction was realized for divergent synthesis of vinyl sulfides and vinyl sulfones. The described protocol is more convenient for the preparation of vinyl sulfide than vinyl sulfone related skeletons and the starting materials are readily available. Current efforts are directed toward further methodological refinement and synthetic applications.

Experimental

General procedure for the synthesis of vinyl sulﬁdes (Table 2)

To a solution of alcohol 1 (0.20 mmol) in DCE (1.0 mL) under an air atmosphere at room temperature were added sulfonic acid 2 (0.30 mmol), NaI (45.0 mg, 0.30 mmol) and TsOH $\cdot$ H$_2$O (7.6 mg, 0.040 mmol). The mixture was stirred at 80 °C for 24 h, cooled to room temperature, and directly purified by preparative thin layer chromatography on silica gel, developing with petroleum ether/ethyl acetate (100 : 0 to 20 : 1), to give compound 3.

General procedure for the synthesis of vinyl sulfoxones (Table 3)

To a solution of alcohol 1 (0.20 mmol) in MeNO$_2$ (1.0 mL) under an air atmosphere at room temperature were added sulfonic acid 2 (0.30 mmol), NaI (45.0 mg, 0.30 mmol) and TsOH $\cdot$ H$_2$O (7.6 mg, 0.040 mmol). The mixture was stirred at 80 °C for 24 h, cooled to room temperature, and directly purified by preparative thin layer chromatography on silica gel, developing with petroleum ether/ethyl acetate (20 : 1 to 5 : 1), to give compound 4.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

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