SHORT COMMUNICATION

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# A Synthetic Approach to Tetrasubstituted Alkenes: Using β-Carbonyl Benzothiazol-2-yl Sulfones as Electrophiles

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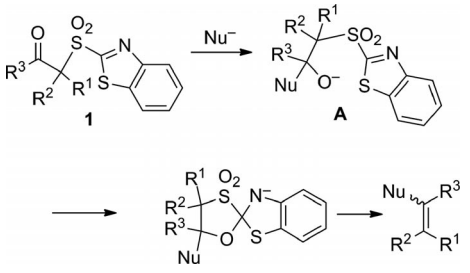
**Keywords:** Olefination / Alkenes / Rearrangement / Sulfur / Lithium

A novel olefination method based on the modified Julia olefination reaction was developed. The reactions of β-carbonyl benzothiazol-2-yl sulfones with a series of alkynyllithiums and TMSCN gave the corresponding β-alkoxy sulfone intermediates, which underwent facile Smiles rearrangement and spontaneous elimination to yield tetrasubstituted enynes and cyanoalkenes, respectively.

## Introduction

The olefin structure is present in many biologically active compounds. Many olefins are also key intermediates as building blocks in the total syntheses of natural products.[1] Over the past several decades, a variety of approaches to the synthesis of olefins have been developed that have attempted to address these stringent demands. The most generally applicable methods involve the direct olefination of carbonyl compounds, such as the Wittig,[2] Wadsworth–Emmons,[3] Peterson,[4] Horner,[5] Johnson,[6] and Julia–Kocienski[7] reactions. In Julia–Kocienski olefination, the reductive elimination of β-acyloxy sulfones is the alkene formation step. This methodology has found pivotal use in the synthesis of many natural products.

Tetrasubstituted olefins have found wide application in the preparation of drugs,[8] biologically active compounds,[9] and materials, and they have additionally been used in catalysis[10] and synthetic chemistry,[11] but the efficient synthesis of tetrasubstituted olefins remains a challenge. In a typical modified Julia olefination reaction, the key β-alkoxy sulfone intermediate is formed by the addition of a nucleophilic metalated sulfone to a carbonyl compound. We conceived that if electron-deficient benzothiazolylsulfones **1** containing a carbonyl group located at the β position were used as electrophiles (Scheme 1), the addition of nucleophiles to the carbonyl group would result in the formation of β-alkoxy sulfones **A**, which have a structure similar to that of the key intermediates in the Julia olefination reaction. These sulfone intermediates could then undergo Smiles rearrangement[7a–7e] and elimination to produce alkenes along the mechanism of the modified Julia olefination reaction. In this case, the key β-alkoxy sulfone intermediate would be formed in a new manner and it should be possible to prepare various alkenes including tetrasubstituted olefins by changing the structures of both the arylsulfones and the nucleophiles. To realize this assumption, we synthesized a series of β-carbonyl benzothiazol-2-yl (BT)-sulfones and investigated their reactions with various nucleophiles. The results are reported in this paper.




Scheme 1. The proposed olefination of β-carbonyl BT-sulfones.

## Results and Discussion

First, we prepared 2-(benzothiazole-2-sulfonyl)-1-phenylethanone (**1a**) from the reaction of 2-mercaptobenzothiazole with α-bromoacetophenone followed by the oxidation of the resulting thioether. Unfortunately, this β-carbonyl sulfone underwent enolization upon the addition of the basic nucleophile, and the enolate thus formed could not react further with the nucleophiles. To avoid the enolization, we designed and synthesized a series of β-carbonyl benzothiazol-2-yl sulfones **1b**–**g** without α-hydrogen, as shown in Table 1.

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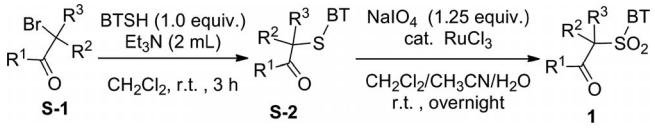
Table 1. Preparation of β-carbonyl BT-sulfones.

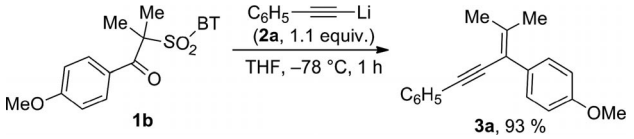



S-1 S-2 1

| Entry | S-1 | $R^1$ | $R^2$ | $R^3$ | 1 | Yield [%][a] |
|---|---|---|---|---|---|---|
| 1 | **S-1a** | $C_6H_5$ | H | H | **1a** | 84 |
| 2 | **S-1b** | *p*-$MeOC_6H_4$ | Me | Me | **1b** | 89 |
| 3 | **S-1c** | *p*-tolyl | Me | Me | **1c** | 92 |
| 4 | **S-1d** | $C_6H_5$ | Me | Me | **1d** | 91 |
| 5 | **S-1e** | 1-naphthyl | Me | Me | **1e** | 87 |
| 6 | **S-1f** | $C_6H_5$ | Me | Et | **1f** | 84 |
| 7 | **S-1g** | $C_6H_5$ | Me | $C_6H_5$ | **1g** | 45 |

[a] Total yield of the isolated product over two steps. BTSH = 2-mercaptobenzothiazole.

Having β-carbonyl BT-sulfones **1b**–**g** in hand, we next examined their reactions with a series of nucleophiles. However, oxygen and nitrogen nucleophiles, such as NaOMe, NaOEt, KO*t*Bu, and amines, failed to afford the olefin products. To our delight, it was found that carbon nucleophiles attacked the β-carbonyl group of these sulfones. Phenylmagnesium bromide reacted with **1b** at room temperature to afford the desired olefin in low yield (<30%) alongside some unidentified side products. Therefore, some carbon nucleophiles were screened and alkynyllithium reagents were found to be a good choice. At –78 °C, phenylethynyllithium reacted with sulfone **1b** readily in THF to yield desired β-alkoxy sulfone **A**, which underwent the tandem Smiles rearrangement and elimination to give desired tetrasubstituted olefin **3a** in 93% yield (Scheme 2).

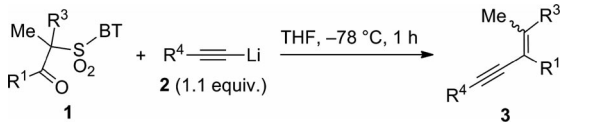



Scheme 2. Reaction of **1b** with phenylethynyllithium.

Optimization of the reaction conditions showed that THF and toluene were the preferred solvents for this reaction. Other solvents such as hexane and ethyl ether were excluded owing to their poor solvency for the substrates. Both typical operation methods, the Barbier procedure[12] and the premetalated procedure,[13] gave almost the same results.

Using the Barbier procedure, we examined the scope of β-carbonyl sulfones **1b**–**g** and alkynyllithium **2**. Both electron-poor and electron-rich alkynyllithiums were evaluated, and the results are summarized in Table 2. This novel olefination procedure tolerated a broad range of functional groups. The reactions of alkynyllithiums bearing aryl, trifluoromethyl, silyl, and alkyl substituents proceeded well to give the corresponding conjugated enynes in good to excellent yields under the optimized reaction conditions. The presence of the COOEt group in the nucleophiles lowered the yield of the enyne as a result of the high reactivity of this group to the alkynyllithium (Table 2, entry 6). However, this deficiency could be overcome by adding 2,2′-bipyridine (1.2 equiv.) as a ligand to stabilize and deactivate the alkynyllithium (Table 2, entries 7, 10, 13, 16, and 20). For different $R^1$ substituents including tolyl, phenyl, and naphthyl, the reaction performed well. In the case of sulfone **1f**, the reaction gave alkenes **3q**–**s** in high yields as mixtures of *E* and *Z* isomers.[14] The reaction did not exhibit significant stereoselectivity (1.27:1–1.92:1), which was attributed to the similar steric and electronic properties of the methyl and ethyl group. Unfortunately, the reaction of β-carbonyl BT-sulfone **1g** was unsuccessful and no desired product was formed because of steric hindrance (Table 2, entry 22).

Table 2. The reaction of β-carbonyl sulfones with alkynyllithium.[a]




1 3

| Entry | 1 | $R^1$ | $R^3$ | $R^4$ | 3 | Yield [%] (*E*/*Z*)[b] |
|---|---|---|---|---|---|---|
| 1 | **1b** | *p*-$MeOC_6H_4$ | Me | $C_6H_5$ | **3a** | 93 |
| 2[c] | **1b** | *p*-$MeOC_6H_4$ | Me | $C_6H_5$ | **3a** | 92 |
| 3 | **1b** | *p*-$MeOC_6H_4$ | Me | $CF_3$ | **3b** | 89 |
| 4 | **1b** | *p*-$MeOC_6H_4$ | Me | $Me_3Si$ | **3c** | 94 |
| 5 | **1b** | *p*-$MeOC_6H_4$ | Me | *n*-$C_4H_9$ | **3d** | 89 |
| 6 | **1b** | *p*-$MeOC_6H_4$ | Me | COOEt | **3e** | 45 |
| 7 | **1b** | *p*-$MeOC_6H_4$ | Me | COOEt | **3e** | 87[d] |
| 8 | **1c** | *p*-$MeC_6H_4$ | Me | $C_6H_5$ | **3f** | 91 |
| 9 | **1c** | *p*-$MeC_6H_4$ | Me | $CF_3$ | **3g** | 88 |
| 10 | **1c** | *p*-$MeC_6H_4$ | Me | COOEt | **3h** | 84[d] |
| 11 | **1d** | $C_6H_5$ | Me | $C_6H_5$ | **3i** | 91 |
| 12 | **1d** | $C_6H_5$ | Me | $CF_3$ | **3j** | 88 |
| 13 | **1d** | $C_6H_5$ | Me | COOEt | **3k** | 82[d] |
| 14 | **1e** | 1-naphthyl | Me | $C_6H_5$ | **3l** | 92 |
| 15 | **1e** | 1-naphthyl | Me | $CF_3$ | **3m** | 89 |
| 16 | **1e** | 1-naphthyl | Me | COOEt | **3n** | 84[d] |
| 17 | **1e** | 1-naphthyl | Me | $Me_3Si$ | **3o** | 93 |
| 18 | **1f** | $C_6H_5$ | Et | $C_6H_5$ | **3p** | 92 (1.75:1)[e] |
| 19 | **1f** | $C_6H_5$ | Et | $CF_3$ | **3q** | 89 (1.50:1)[e] |
| 20 | **1f** | $C_6H_5$ | Et | COOEt | **3r** | 83[d] (1.27:1)[e] |
| 21 | **1f** | $C_6H_5$ | Et | $Me_3Si$ | **3s** | 94 (1.92:1)[e] |
| 22 | **1g** | $C_6H_5$ | $C_6H_5$ | $C_6H_5$ | **3t** | –[f] |

[a] Results are shown for reactions performed by following the Barbier procedure unless otherwise indicated. [b] Yield of isolated product. [c] The premetalated method was used. [d] 2,2′-Bipyridine (1.2 equiv.) was added. [e] The *E*/*Z* ratio was determined by $^1H$ NMR spectroscopy. [f] No desired product.

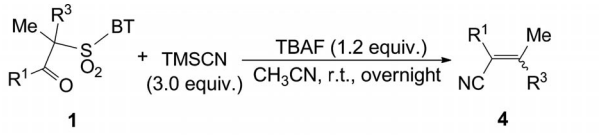
Using this novel protocol, we further investigated the reaction of β-carbonyl BT-sulfones with trimethylsilyl cyanide to develop a mild method to synthesize cyanoalkenes.[15] It was found that the expected cyanoalkenes could be produced under mild conditions. The use of tetrabutylammonium fluoride (TBAF, 1.2 equiv.) as an additive could help to release the cyanide anion and reduce the reaction time. However, inorganic reagents such as KCN and NaCN failed to initiate this transformation. Further examination of solvent effects revealed that $CH_3CN$ was the best solvent for this transformation.

We examined the scope of β-carbonyl BT-sulfones **1b**–**g** with TMSCN (3.0 equiv.) in the presence of TBAF

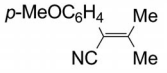
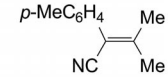
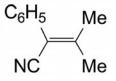
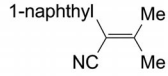
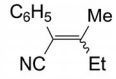
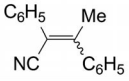
  

(1.2 equiv.) in $CH_3CN$, and the results are shown in Table 3. If $R^3$ was an alkyl group, the reactions worked well and afforded corresponding cyanoalkenes **4a**–**e** in good yields (77–87%; Table 3, entries 1–5). The reaction of β-carbonyl BT-sulfone **1g**, in which $R^3$ = phenyl, failed to produce alkene **4f** under the same reaction conditions (Table 3, entry 6). On the basis of the above experimental results, the new olefination method we proposed in Scheme 1 may have success with some other nucleophiles to afford the corresponding tetrasubstituted alkenes.

Table 3. The reaction of β-carbonyl sulfones with TMSCN.[a]




1 4

| Entry | 1 | 4 | Structure | Yield [%][b] |
|---|---|---|---|---|
| 1 | **1b** | **4a** |  | 87 |
| 2 | **1c** | **4b** |  | 85 |
| 3 | **1d** | **4c** |  | 83 |
| 4 | **1e** | **4d** |  | 77 |
| 5 | **1f** | **4e** |  | 82 (1:1.6)[c] |
| 6 | **1g** | **4f** |  | _[d] |

[a] Reaction conditions: **1** (1.0 mmol), TMSCN (3.0 mmol), and TBAF (1.2 mmol) in $CH_3CN$ (10.0 mL) at room temperature, overnight. [b] Yield of isolated product. [c] The *E*/*Z* ratio was determined by $^1H$ NMR spectroscopy. [d] No desired product.

## Conclusions

In conclusion, we have developed a novel olefination method based on the mechanism of the modified Julia olefination reaction, in which a new route to give access to key β-alkoxy sulfone intermediate **A** was introduced. In comparison with the traditional Julia olefination reaction, this new synthetic approach can add diversity to the olefin products by varying the structures of both the sulfones and the nucleophiles and is especially useful for the synthesis of tetrasubstituted olefins.

## Experimental Section

**Procedure for the Reaction of Alkynyllithiums with β-Carbonyl BT-Sulfones:** To a solution of phenyl ethyne (110 mg, 1.1 mmol) in THF (10 mL) was added *n*BuLi (0.4 mL, 2.5 M in hexane) at –78 °C. The mixture was stirred at –78 °C for 30 min, and then a solution of β-carbonyl sulfone **1b** (375 mg, 1.0 mmol) in THF (2 mL) was added dropwise. The resulting mixture was stirred at –78 °C for 1 h and then warmed to room temperature and quenched with saturated aqueous $NH_4Cl$ solution. The aqueous layer was extracted with ethyl ether (10 mL × 3). The combined organic layer was washed with $H_2O$ (10 mL × 3) and dried with anhydrous $Na_2SO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (petroleum ether) to give **3a** as a colorless oil (243 mg, 93%).

**Procedure for the Reaction of TMSCN with β-Carbonyl BT-Sulfones:** TBAF (296 mg, 1.2 mmol) was added to a solution of β-carbonyl BT-sulfone **1b** (375 mg, 1 mmol) and TMSCN (297 mg, 3.0 mmol) in $CH_3CN$ (10 mL). The mixture was stirred at room temperature overnight. After removal of solvent under reduced pressure, the residue was purified by column chromatography on silica gel (petroleum ether) to give **4a** as a colorless oil (162 mg, 87%).

**Supporting Information** (see footnote on the first page of this article): General information, general procedure for olefination, characterization data, and copies of the $^1H$ NMR and $^{13}C$ NMR spectra.

## Acknowledgments

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[12] Typical Barbier procedure: Lithium diisopropylamide (LDA; 1.1 mL, 1.0 M in THF/hexane = 1:1) was added to a solution of β-carbonyl sulfone **1** (1.0 mmol) and phenyl ethyne (110 mg, 1.1 mmol) in THF (12 mL) at –78 °C. The resulting mixture was stirred at –78 °C for 1 h.

[13] Typical premetalated procedure: *n*BuLi (0.4 mL, 2.5 M in hexane) was added to a solution of phenyl ethyne (110 mg, 1.1 mmol) in THF (10 mL) at –78 °C. The mixture was stirred at –78 °C for 30 min and then a solution of β-carbonyl sulfone **1** (1.0 mmol) in THF (2 mL) was added dropwise. The resulting mixture was stirred at –78 °C for 1 h.

[14] According to the $^1$H NMR spectroscopic data of known substituted alkenes, the chemical shift of the resonance of the alkyl group in a *cis* configuration to the alkynyl (or cyano) group is higher than that of the alkyl group in a *trans* configuration.

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