Transition-Metal-Free Reductive Cross-Coupling Employing Metabisulfite as a Connector: General Construction of Alkyl–Alkyl Sulfones

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A multicomponent reductive cross-coupling of unactivated alkyl halides and alkyl tosylates connected via sodium metabisulfite was established for the general construction of alkyl–alkyl sulfones. Neither a metal catalyst nor a metal reductant is required in this “green” reductive cross-coupling. Inorganic sodium metabisulfite served as both the sulfur dioxide source and the robust connector. Safe formate was used as a highly efficient single-electron reductant. Both intramolecular and intermolecular reductive cross-couplings were achieved with broad substrate scopes. Diverse biologically important molecules were efficiently cross-linked with steroids, saccharides, amino acids, peptides, and pharmaceuticals with sensitive functional groups, affording sulfone-bridged hybrid molecules. Mechanistic studies demonstrated that alkyl radicals were involved in the singly occupied molecular orbital (SOMO) of the metabisulfite salt, initiating the transformation.

Keywords: alkyl sulfone, formate, sodium metabisulfite, reductive cross-coupling, transition-metal-free

Introduction

Sulfone motifs have attracted considerable interest in drug discovery because of their dramatic effects on stability, liposolubility, and metabolism.¹–⁴ The linkage of carbon chains to sulfone motifs always improves drug metabolism. Alkyl–alkyl sulfones are among the most frequently occurring sulfone motifs in pharmaceuticals due to their excellent effects on the balance between water solubility and lipid solubility. Several representative and well-known pharmaceutical inhibitors containing alkyl–alkyl sulfones are shown in Scheme 1a.⁵–¹⁰ Conventionally, sulfones are prepared via the oxidation of sulfides with strong oxidants after thiol-involved couplings,¹¹,¹² resulting in low functional group compatibility. Strategies for sulfone construction via the introduction of hypervalent sulfur in the same oxidation state into organic frameworks are of great

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interest due to the oxidative economy and step economy of such processes. For instance, transition-metal-catalyzed syntheses of aryl–aryl(alkyl) sulfones have been well developed via halides and organometallic reagents. However, a general approach for the introduction of sulfone motifs into C(sp3)−C(sp3) organic frameworks is lacking since the β-hydrogen in alkyl coupling partners is likely to be poorly compatible with transition-metal-catalyzed systems. Although we have achieved the construction of aryl–alkyl sulfone by virtue of the distinction between aryl and alkyl halides, tin is still necessary as a stoichiometric metal reductant. Developing cheap salts for green and safe hydrogen storage and for replacing environmentally unfriendly

Scheme 1 | (a–c) Sulfone-bridged reductive cross-coupling.
metals as reductants in reductive cross-couplings is a long-standing goal.\textsuperscript{31}\textendash 38 In addition, the smaller distinction between two different alkyl coupling partners is a tough challenge compared with the distinction between aryl and alkyl halide coupling partners.\textsuperscript{39} Traditionally, the direct reductive cross-couplings of electrophilic partners are realized via preactivation of alkyl halides by a metal reductant to avoid precast organometallic reagents (Scheme 1b). Previously, we showed that the SO$_2$ motif in inorganic sulfur dioxide salts possesses a sufficiently active hybridized singly occupied molecular orbital (SOMO) to participate in a radical process.\textsuperscript{29,40\textendash 51} Alkyl halides can be used as precursors for alkyl radicals, leading to radical capture with inorganic sulfur dioxide salts for the generation of sulfonyl radicals. Due to the slightly higher electronegativity of sulfur atoms than carbon atoms, sulfonyl radicals were apt to be reduced than alkyl radicals. A release-controlled hydrogen storage salt instead of rapid electron transfer from reductive metal powders is the key factor for the highly selective reduction of sulfonyl radicals. Alkyl tosylates are rather inert during the single-electron transfer (SET) process since the high-lying $\pi^*(C\text{-}O)$ orbital is protected from radical reduction and involved in subsequent nucleophilic substitution. The sequential radical release and coupling limits the undesired homocoupling of the partners (Scheme 1c). Herein, we disclose a transition-metal-free reductive cross-coupling of unactivated alkyl halides, alkyl tosylates, and metabisulfite for the modular construction of alkyl$\text{-}$alkyl sulfonyl-bridged compounds.

## Results and Discussion

We commenced our evaluation of this reductive cross-coupling with unactivated alkyl tosylates 1a, alkyl halides 2a, and sodium metabisulfite in the presence of a base in dimethyl sulfoxide (DMSO). To increase the solubility of inorganic salts, phase-transfer catalyst tetrabutylammonium bromide (TBAB) was added. No desired product 3a was detected in the absence of a reductant in this transformation (Table 1, entry 1). To our delight, bench-stable formic acid and formate reductants could afford the cross-coupled product in moderate yields (Table 1, entries 2\textendash 4). Diverse inorganic sulfur dioxide surrogates possessing different masking groups and unique SET abilities were tested as the connector in the current transformation. Sodium metabisulfite was found to provide the best efficiency (65\% yield, Table 1, entries 5\textendash 7). Further evaluation of bases revealed that the stronger base cesium carbonate delivers 3a in a better yield (Table 1, entries 8\textendash 11). Considering the effect of the solvent, DMSO is the best choice since it is beneficial for the dissolution of inorganic salts (Table 1, entries 12\textendash 14).

| Entry | Reductant | SO$_2$ Source | Base | Solvent | Yields (%)$^b$ |
|-------|-----------|---------------|------|---------|----------------|
| 1     | –         | Na$_2$S$_2$O$_5$ | K$_2$HPO$_4$ | DMSO | NP            |
| 2     | HCO$_2$H  | Na$_2$S$_2$O$_5$ | K$_2$HPO$_4$ | DMSO | 49            |
| 3     | HCO$_2$Na | Na$_2$S$_2$O$_5$ | K$_2$HPO$_4$ | DMSO | 60            |
| 4     | HCO$_2$K  | Na$_2$S$_2$O$_5$ | K$_2$HPO$_4$ | DMSO | 65            |
| 5     | HCO$_2$K  | K$_2$S$_2$O$_5$ | K$_2$HPO$_4$ | DMSO | 40            |
| 6     | HCO$_2$K  | Na$_2$S$_2$O$_4$ | K$_2$HPO$_4$ | DMSO | 41            |
| 7     | HCO$_2$K  | DABSO         | K$_2$HPO$_4$ | DMSO | 44            |
| 8     | HCO$_2$K  | Na$_2$S$_2$O$_5$ | –       | DMSO | 49            |
| 9     | HCO$_2$K  | Na$_2$S$_2$O$_5$ | NaHCO$_3$ | DMSO | 44            |
| 10    | HCO$_2$K  | Na$_2$S$_2$O$_5$ | Et$_3$N  | DMSO | 57            |
| 11    | HCO$_2$K  | Na$_2$S$_2$O$_5$ | Cs$_2$CO$_3$ | DMSO | 77            |
| 12    | HCO$_2$K  | Na$_2$S$_2$O$_5$ | Cs$_2$CO$_3$ | DMA  | 66            |
| 13    | HCO$_2$K  | Na$_2$S$_2$O$_5$ | Cs$_2$CO$_3$ | DMF  | 54            |
| 14    | HCO$_2$K  | Na$_2$S$_2$O$_5$ | Cs$_2$CO$_3$ | Toluene | 22        |

Note: NP, no product; DMA, dimethylacetamide; DMF, dimethylformamide. Bold-italic text represents optimal conditions

$^a$ Conditions: 1a (0.2 mmol), SO$_2$ source (0.4 mmol), 2a (0.5 mmol), base (0.4 mmol), reductant (0.5 mmol), TBAB (0.3 mmol), solvent (2.0 mL), 100 °C, N$_2$, 10 h.

$^b$ Isolated yields.
The scope of the reductive cross-coupling employing sodium metabisulfite as a connector is shown in Scheme 2 (for characterizations see the Supporting Information). Aryl propyl sulfones with a broad range of substituents, including those with different electronic properties, at various positions were efficiently afforded (3a–3f). A series of alkyl coupling partners, even linear hexadecane (C16), were well tolerated in the coupling (3g–3k). Heterocycle-containing alkyl tosylates provided the desired alkyl-alkyl products in excellent yields (3l). Fused-ring anthracene and pyrene derivatives, common motifs in luminescent materials, successfully underwent the current transformation, furnishing the corresponding sulfone products (3m–3n). Furthermore, this reaction was not only restricted to intermolecular variants but also applicable to the intramolecular synthesis of cyclic sulfones (3o–3p). Regrettably, when secondary tosylates were employed, no desired cross-coupling products were detected. Linear alkyl (3q–3s), trifluoropropyl (3t), and alkoxy (3u) derivatives successfully participated in the multicomponent reductive cross-coupling. Various nitrogen-containing structures (3v–3y) and even amino acids (3y) were compatible with this reductive cross-coupling, efficiently providing the desired sulfones. In addition, secondary alkyl halides are also compatible with this transformation, and these substrates were a notable challenge in C(sp3) reductive cross-coupling. Various nitrogen-containing structures (3v–3y) and even amino acids (3y) were compatible with this reductive cross-coupling, efficiently providing the desired sulfones. In addition, secondary alkyl halides are also compatible with this transformation, and these substrates were a notable challenge in C(sp3) reductive cross-couplings. Both linear (3z) and cyclic (3aa–3ae) secondary alkyl halides underwent this transformation. The compatibility with 7- (3ad) and 12-membered (3ae) rings highlighted the high tolerance of this strategy. The structure of 3ab was confirmed via X-ray diffraction analysis.a

To further demonstrate the practical applicability of this cross-linking protocol, we sought to link structurally

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**Scheme 2** | Collective alkyl sulfone construction. Reaction conditions: 1 (0.2 mmol), Na2S2O5 (0.4 mmol), 2 (potassium formate, 0.5 mmol), HCOOK (0.5 mmol), Cs2CO3 (0.4 mmol), TBAB (0.3 mmol), DMSO (2 mL), 100 °C, 10 h, isolated yields.
Complicated, naturally occurring molecules with pharmaceuticals by employing sodium metabisulfite as a connector (Scheme 3). The linkage of dehydroepiandrosterone, estrone, and a derivative of the anti-inflammatory drug isoxepac was smoothly achieved under the standard conditions (3af–3ah). The linkage of natural cholic acid and tetrahydropyran provided the corresponding product in an excellent yield (3ai). The structure of 3ai was confirmed via X-ray diffraction analysis. The reductive cross-couplings between an amino acid (L-tyrosine), a saccharide (glucose), steroids (dehydroepiandrosterone and estrone), and nonsteroidal anti-inflammatory drug oxaprozin were all successful, affording the corresponding sulfone-bridged hybrid molecules in good yields (3aj–3an). Notably, this strategy can efficiently connected long-chain linoleic acids and peptides from the corresponding alkyl precursors (3ao).

To demonstrate the mechanism of this multicomponent reductive cross-coupling reaction, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was first added to the system under the standard conditions, and sulfone production was suppressed (Scheme 4a). Subsequently, a radical clock experiment involving (bromomethyl)cyclopropane (4) and alkyl tosylates 1a was conducted under the standard conditions (Scheme 4b). Cyclopropane-opened product 5 was generated in 14% yield, indicating that an alkyl radical intermediate was formed from the alkyl bromide substrate during the transformation. These results demonstrated that the multicomponent reductive cross-coupling began with the radical reduction of the alkyl halide followed by SOMO interaction with sodium metabisulfite. Cyclic voltammetric analyses showed that the reduction potentials of alkyl tosylate 1a was −2.75 V and alkyl halide 2a was −2.40 V, which indicated that 2a was likely to be preferentially reduced relative to 1a. Two reduction peaks at −1.50 and −2.40 V were observed in Scheme 4c, corresponding to two successive SETs to alkyl halide 2a, which demonstrated that 2a easily underwent a single-electron reduction process. Thus, the proposed

**Scheme 3** | The cross-linking of steroids, saccharides, amino acids, and pharmaceuticals. Reaction conditions: 1 (0.2 mmol), Na$_2$S$_2$O$_5$ (0.4 mmol), 2 (0.5 mmol), HCOOK (0.5 mmol), Cs$_2$CO$_3$ (0.4 mmol), TBAB (0.3 mmol), DMSO (2 mL), 100 °C, 10 h, isolated yields.
reaction pathway is depicted in Scheme 4d. Initially, the homolysis of the alkyl halide generated alkyl radical \( \cdot{}^{9}Bu \) and iodine radical, which was reduced to iodide ion by the slowly released formate. Subsequently, the reaction of alkyl radical \( \cdot{}^{9}Bu \) and metabisulfite furnished sulfonyl radical \( \cdot{}^{10}Bu \), which was reduced by formate radical cation, affording sulfonyl anion \( \cdot{}^{11}Bu \) and sulfinate \( \cdot{}^{11'}Bu \) in equilibrium. Finally, alkyl coupling of alkyl tosylates 1 and intermediate \( \cdot{}^{11}Bu \) delivered the desired sulfone product 3.

**Conclusion**

A transition-metal-free multicomponent reductive cross-coupling of unactivated alkyl halides, alkyl tosylates, and sodium metabisulfite was achieved for the construction of alkyl–alkyl sulfones. Inorganic sodium metabisulfite salt served both as the sulfur dioxide source and a robust connector. No transition-metal catalyst was necessary, and a controlled-release hydrogen storage...
salt instead of metal powder reductant allowed the sequential and highly selective reduction of sulfonyl radicals. The linkage of diverse biologically important molecules, such as steroids, saccharides, amino acids, peptides, and pharmaceuticals, was efficiently achieved and delivered sulfone-bridged hybrid molecules. Mechanistic studies demonstrated that alkyl radicals interacted with the SOMO of metabisulfite, initiating the transformation, and the high-lying $\sigma^*(C=O)$ orbital of the alkyl tosylate participated in the subsequent nucleophilic substitution. Further cross-linking protocols with inorganic sulfur salts are being explored in our laboratory.

**Footnote**
* CCDC 2007887 (3ab) and CCDC 2007888 (3ai) can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

**Supporting Information**
Supplemental Information is available and includes general information, general procedure for the synthesis of sulfones, optimization of reaction conditions, characterization of alkyl-alkyl sulfone products, X-ray crystal structures, and electrochemical measurements.

**Conflict of Interest**
The authors declare no competing financial or nonfinancial interests.

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