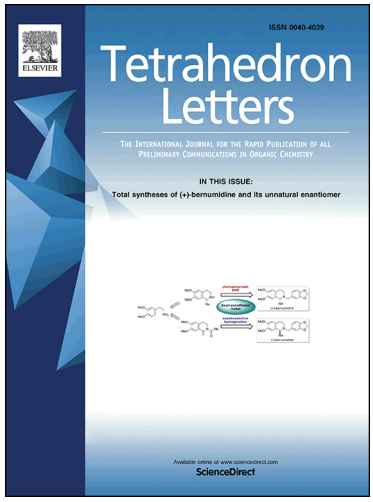

Metal-Free TBAI-Catalyzed Oxidative C*sp* ^{3}-S Bond Formation through C*sp* ^{2}-C*sp* ^{2} Bond and S-N Bond Cleavage: A New Route to β-keto-Sulfones

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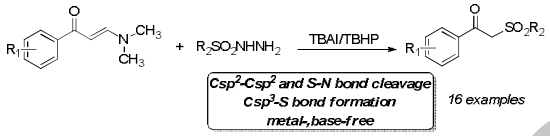

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Metal-Free TBAI-Catalyzed Oxidative Csp^3-S Bond Formation through Csp^2-Csp^2 Bond and S-N Bond Cleavage: A New Route to β-keto-Sulfones

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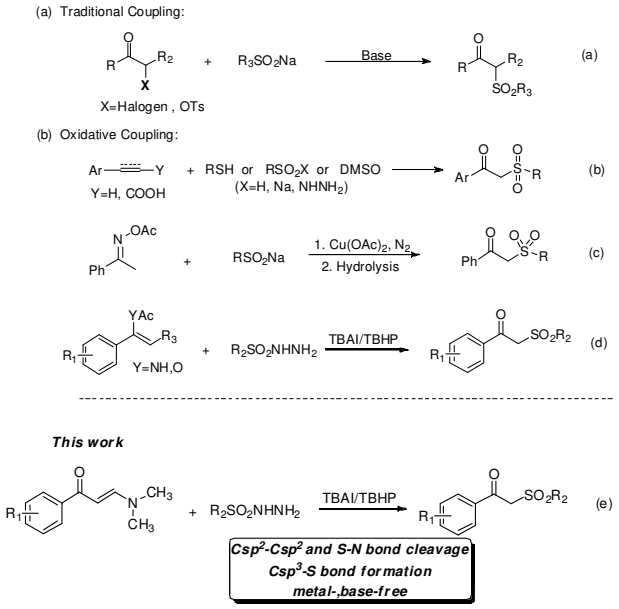
ABSTRACT

A novel TBAI-catalyzed radical sulfonylation of readily available *N,N*-dimethylenaminones with sulfonylhydrazides to afford functionalized β-keto-sulfones has been developed. Various functional groups were tolerated well under the present oxidative conditions and the corresponding β-keto-sulfone compounds were obtained in moderate to good yields. Importantly, this transformation offered the first protocol for Csp^3-S bond formation by oxidative Csp^2-Csp^2 bond cleavage in one step.

1. Introduction

Organosulfur compounds are an attractive component of many biologically active compounds and marketed drugs,[1] and also widely present in natural products, medical chemistry and functional materials science.[2] Thus, great progress has been achieved in the development of new methods for the construction of C-S bond.[3] Among them, the sulfur radical or sulfonyl radical addition to Csp^2-Csp^2 compounds have been developed as a powerful strategy for the construction of C-S bonds.[4] Mechanism studies demonstrated that these Csp^2-H functionalizations undergo either radical addition/elimination or radical addition/oxidation process. To the best of our knowledge, no example of new Csp^3-S bond formation through selective cleavage of Csp^2-Csp^2 bonds has been described. Therefore, the development of a new free-radical-mediated protocol for Csp^3-S bond formation *via* Csp^2-Csp^2 bonds cleavage remains an unsolved challenge.

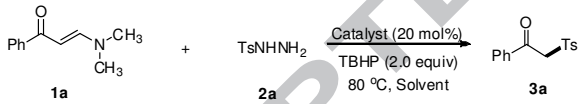
β-keto-sulfones, on the other hand, are a highly useful class of organosulfur compounds, owing to their unique biological properties and synthetic versatile applications in organic synthesis.[5] Thus, many efforts have been put into the development of efficient synthetic approaches to construct these scaffolds. Generally, β-keto-sulfones are prepared by the traditional coupling of sulfinates with phenacyl halides or tosylates, which suffer from some certain disadvantages such as the pre-functionalized materials, relatively complicated or harsh reaction conditions (Scheme 1a).[6] For recent years, an efficient synthesis of β-ketosulfones has been achieved *via* the oxidative coupling of alkynes or alkenes with sulfonylating agents (RSO_2H, RSO_2NHNH_2, RSO_2Na, RSH, *etc.*), which involved sequential Csp/sp^2-H/Csp-C bond breaking followed by C=O and Csp^3-S bond reconstruction (Scheme 1b).[4, 7] In addition, the Jiang group developed a novel copper-catalyzed oxidative coupling of oxime acetates and sodium sulfinates leading to the construction of Csp^3-S bond to afford β-ketosulfones (Scheme 1c),[8] and Li and co-workers also reported the synthesis of β-ketosulfones from enamides or vinyl acetates with sulfonylhydrazides using TBAI/TBHP as catalytic system (Scheme 1d).[9] Some other methods were also be developed to prepare β-ketosulfones.[10] However, to the best of our knowledge, examples of the reconstruction of Csp^3-S bond toward β-ketosulfones through the selective cleavage of the Csp^2-Csp^2 bond have been rarely studied. Herein, we report the first TBAI-catalyzed strategy to construct β-ketosulfones from readily available *N, N*-dimethylenaminones and sulfonylhydrazides through selective oxidative Csp^2-Csp^2 bond cleavage and Csp^3-S bond formation (Scheme 1e).



Scheme 1. Different synthetic approaches to *β*-ketosulfones

Our investigation commenced with the reaction of *N*, *N*-dimethylenaminones (**1a**) and *p*-toluenesulfonylhydrazide (**2a**) in CH_3CN at 80 °C under air atmosphere. To our delight, the desired coupling product **3a** was obtained in 45% yield with 20mol% of TBAI and 2.0 equivalents of TBHP (70 wt% in water) as an external oxidant (Table 1, entry 1). Encouraged by this result, we then screened other catalysts such as KI, NaI and $Cu(OAc)_2$, and result proved that TBAI was most efficient (Table 1, entries 1-4). Further optimization revealed that solvent played an important role in this transformation (Table 1, entries 5-9). The reaction yield was further increased to 68% when 1, 4-dioxane was used as the reaction media (Table 1, entry 6). Upon decreasing the loading of **2a** to 1.5 equivalents, the yield of **3a** decreased to 58% (Table 1, entry 10).

Table 1 Optimization of reaction conditions[a]

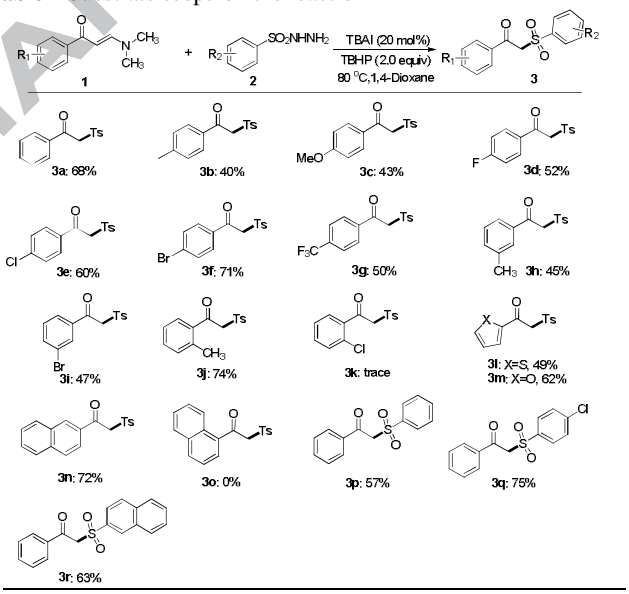


Entry	Catalyst	Solvent	Yield(%)[b]
1	TBAI	MeCN	45
2	KI	MeCN	40
3	NaI	MeCN	37
4	$Cu(OAc)_2$	MeCN	16
5	TBAI	H_2O	44
6	TBAI	**1,4-Dioxane**	68
7	TBAI	THF	53
8	TBAI	DMSO	10
9	TBAI	DMF	34
10	TBAI	1,4-Dioxane	58[c]

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (2.0 eq.), catalyst (20 mol%), TBHP (2.0 eq, 70% aqueous solution) and solvent (2.0 mL) at 80 °C for 8 h. [b] Isolated yield. [c] 1.5 equiv of **2a**

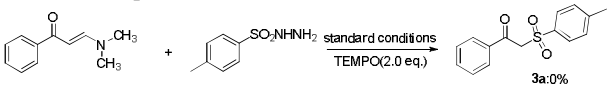
With the optimized reaction conditions in hand, we next investigated the scope of *N*, *N*-dimethylenaminones in this reaction system and results are summarized in Table 2. It was found that various functional groups at the *para*-position were tolerated well under the present oxidative conditions affording the products in moderate to good yields (products **3b**-**3g**). It is worth noting that halogen-substituted substrates (F, Cl, Br) were tolerated in this reaction, which were suitable for potential further structural modifications. The reaction also proceeded smoothly with both electron-donating (Me) and halogen-substituted (Br) substituents at the *meta* position of the aromatic ring under this reaction conditions (products **3h-3i**). Substrates bearing a methyl group in the *ortho*-position of the phenyl ring resulted in slightly lower yield while Cl-substituted substituent gave no corresponding product, this difference might caused by a dehalogenation process (products **3j**-**3k**).[11] In addition, heteroaryl substituted *N*,*N*-dimethylenaminones, such as thiophene and furan, were also compatible substrates and delivered the corresponding *β*-keto-sulfones (**3l** and **3m**) in 49% and 62% yields, respectively. Moreover, 2-naphthyl-derived enaminones could also be used well in this reaction, and the desired product could be isolated in reasonable yield, while 1-naphthy-derived enaminones gave no product (products **3n**-**3o**). Finally, sulfonylhydrazides with different substituents were also investigated to extend the reaction scope. It was found that phenyl, *p*-cholophenyl and 2-naphthalene substituted sulfonylhydrazides were all tolerated in the reaction to give the corresponding *β*-ketosulfones **3p-3r** in good yields.

Table 2 Substrate scope of the reaction[a,b]



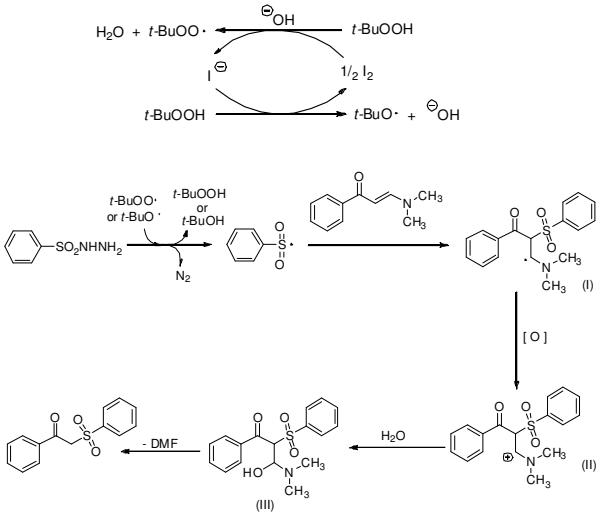
[a] Reaction conditions:**1** (0.25 mmol), **2** (0.5 mmol), TBAI (0.05 mmol), TBHP (0.5 mmol, 70% aqueous solution) in 2.0 mL of 1, 4-dioxane at 80 °C for 8 h. [b] isolated yield.

In order to better understand the mechanism of this transformation, a radical capture experiment was carried out. As shown in Scheme 2, when the reaction of *N*, *N*-dimethylenaminone with $TsNHNH_2$ was performed in the presence of TEMPO (2, 2, 6, 6-tetramethylpiperidine-1-oxyl), a common radical scavenger, the desired coupling product **3a** was extremely inhibited , which indicated that a radical process might involved in the present transformation.



Scheme 2. Control experiment.

Based on the above results and on previous reports,[4a, 9, 12] a possible reaction pathway is proposed as shown in Scheme 3. Initially, TBAI-assisted decomposition of TBHP generated the *tert*-butoxyl radical, which abstracted hydrogen of sulfonyl hydrazide to form sulfonyl radicals. Then, the addition of resulting sulfonyl radicals to *α*-position of *N*,*N*-dimethylenaminones **1** gave carbon radical (**I**). Futher oxidation leads to the corresponding carbocation intermediate (**II**), which following by the nucleophilic attack of H_2O to give intermediate (**III**). Finally, the loss of a molecule of *N*, *N*-dimethylformamide (DMF) from intermediate (**III**) leading to *β*-ketosulfones.



Scheme 3. Proposed preliminary mechanisms

In conclusion, we have reported a novel TBAI-catalyzed radical sulfonylation of readily available *N*,*N*-dimethylenaminones with sulfonylhydrazides to afford functionalized *β*-keto-sulfones.[13] Various functional groups were tolerated well under the present oxidative conditions and the corresponding *β*-keto-sulfone compounds were obtained in moderate to good yields. Importantly, this transformation offered the first protocol for Csp^3-S bond formation by oxidative Csp^2-Csp^2 bond cleavage in one step. Further studies on the scope and application of this reaction are under way in our laboratory.

Acknowledgments

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13. **Typical Procedure for the Synthesis of 3**
To a stirred solution of *N,N*-dimethylenaminone (0.25 mmol), $TsNHNH_2$ (0.5 mmol) and TBAI (0.05 mmol) in 1,4-dioxane (2 mL) was added TBHP (0.5 mmol, 70% aqueous solution) at room temperature. The mixture was heated at 80 ºC for 8 h and cooled down to room temperature. The excess solvent was removed under vacuum, and the residue was directly purified by silica gel column chromatography to afford desired *β*-keto-sulfones.
1-phenyl-2-tosylethanone(**3a**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.2 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.66-7.58 (m, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 4.72 (s, 2H), 2.44 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 188.1, 145.4, 135.8, 135.8, 134.3, 129.8, 129.3, 128.8, 128.6, 63.6, 21.7.

Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

Highlights:

We have developed a novel Csp^3-S bond formation by oxidative Csp^2-Csp^2 bond cleavage in one step.

This protocol provided a new route to various functionalized β-keto-sulfones in moderate to good yields.

The compound was synthesized from readily available *N*,*N*-dimethylenaminones and arylsulfonyl hydrazides.