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Bu_4NI-Catalyzed Cross-Coupling between Sulfonyl Hydrazides and Diazo Compounds To Construct β-Carbonyl Sulfones Using Molecular Oxygen

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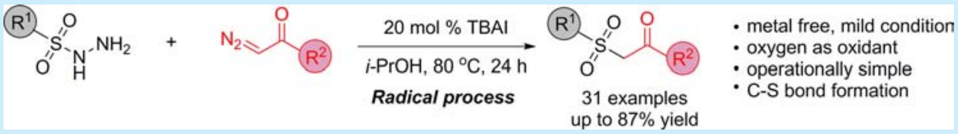
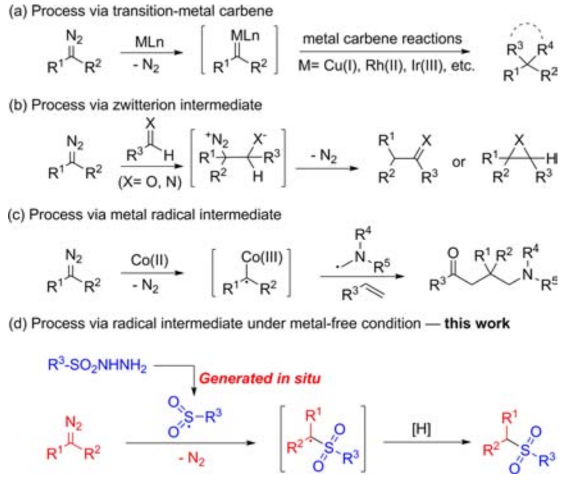
Ⓢ *Supporting Information*



ABSTRACT: A new cross-coupling reaction between sulfonyl hydrazides and diazo compounds has been established, leading to a variety of β-carbonyl sulfones in good yields. This methodology was distinguished by simple manipulation, easily available starting materials, and wide substrate scope. A plausible mechanism involving a radical process was proposed based upon the experimental observations and literature.

Diazo compounds are highly useful and versatile substrates that have been widely applied to various reactions in the past few decades.[1] Generally, there are four patterns in the process of the dinitrogen elimination of diazo compounds, leading to different reactive intermediates involved in organic transformation.[2,3b] In most cases, diazo compounds are used as metal carbene precursors, which have been proven to be highly efficient intermediates in numerous reactions, such as cyclopropanation of alkenes, X−H insertion reactions (X = C, N, O, S, Si, etc.), and ylide reactions (Scheme 1a).[3] In addition, it could also be attacked by some electrophilic reagents, including aldehyde, imine, etc., to form zwitterion intermediates for further transformation (Scheme 1b).[4] In 2015, we reported a tandem reaction for the synthesis of β-ester-γ-amino ketones from diazo compounds, olefins, and tertiary amines via a cross-coupling of a cobalt-based carbene radical and α-aminoalkyl radical (Scheme 1c).[5] Recently, Jiang and co-workers reported a three-component reaction between *N*-hydroxyphthalimide, diazo compounds, and *N*,*N*-dimethylanilines to construct α-aminooxy-β-amino ketones catalyzed by $PhI(OAc)_2$, which involved the addition of α-aminoalkyl radicals to diazo compounds in this transformation.[6] The sulfonyl radical, an excellent segment to introduce sulfonyl groups, has huge synthetic potential in chemical and biomedical fields.[7] In general, a simple and efficient synthetic strategy that merges both diazo compounds and radicals into a one-pot reaction under metal-free conditions is still sparse and highly desirable. Recently, sulfonylation reactions via sulfonyl radicals generated in situ from sulfonyl hydrazides were developed by several groups using external oxidants.[8] Herein, we describe the successful execution of this cross-over reaction between sulfonyl radicals and diazo compounds, which resulted in the efficient formation of β-carbonyl sulfones without employing any metal catalysts (Scheme 1d).

Scheme 1. Various Reactivity of Diazo Compounds



Tosyl hydrazide **1a** and ethyl diazoacetate **2a** were chosen as the reactants to identify this coupling process for the synthesis of ethyl 2-tosylacetate **3a**. Initially, several metal catalysts and oxidants were screened to identify the reaction conditions. Unfortunately, all of these systems were inert and ineffective for this transformation (see Table S1 of the Supporting Information). Notably, a combination of tetrabutylammonium

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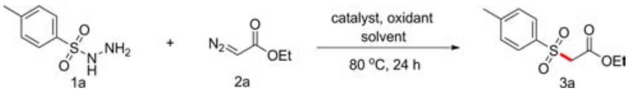
iodide (TBAI) and *tert*-butyl hydroperoxide (TBHP), a well-established system for the in situ generation of sulfonyl radicals,[9] also did not provide the desired product **3a** (Table 1, entry 1).

Table 1. Optimization of the Reaction Conditions[a]



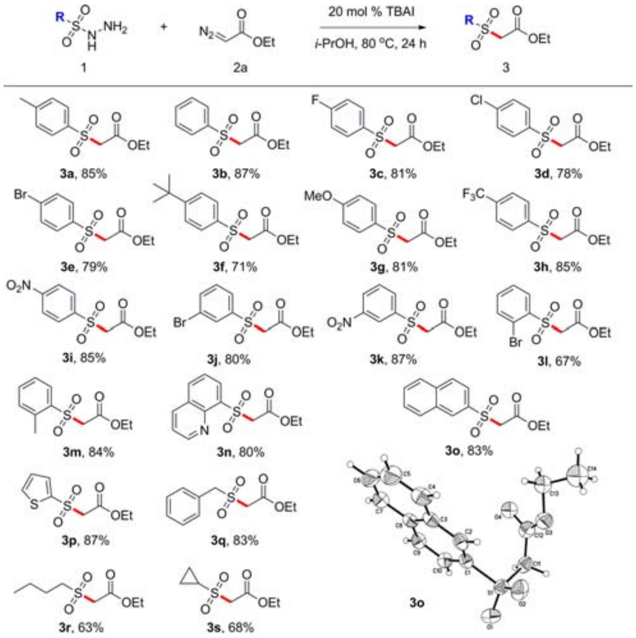
entry	catalyst	oxidant	solvent	yield (%)[b]
1	TBAI	TBHP	CH_3CN	<5
2	TBAI	air	CH_3CN	69
3	TBAI	air	PhH	77
4	TBAI	air	DMSO	74
5	TBAI	air	cyclohexane	68
6	TBAI	air	H_2O	33
7	**TBAI**	**air**	***i*-PrOH**	**85**
8		air	*i*-PrOH	<5
9	I_2	air	*i*-PrOH	69
10	NaI	air	*i*-PrOH	82
11	NH_4I	air	*i*-PrOH	52
12	NIS	air	*i*-PrOH	80
13	PhI(OAc)$_2$	air	*i*-PrOH	<5
14	TBAB	air	*i*-PrOH	65
15	TBAC	air	*i*-PrOH	48
16	18-crown-6	air	*i*-PrOH	<5
17	SDS[c]	air	*i*-PrOH	<5
18	TBAI	O_2	*i*-PrOH	82
19	TBAI	N_2	*i*-PrOH	<5

[a] Reaction conditions: **1a** (0.5 mmol, 1.0 equiv), **2a** (1.0 mmol, 2.0 equiv), catalyst (0.1 mmol, 20 mol %), oxidant (1.5 mmol, 3.0 equiv), and solvent (2 mL) for 24 h under air. [b] Isolated yields. [c] SDS: sodium dodecyl sulfate.

Gratifyingly, when air was used instead of TBHP as the oxidant, the reaction proceeded smoothly and gave the desired ethyl 2-tosylacetate **3a** in moderate yield (Table 1, entry 2). Further screenings of solvents (Table 1, entries 3−7) found that *i*-PrOH was particularly effective for this transformation, resulting in the formation of product **3a** in a high 85% yield (Table 1, entry 7). It is noteworthy that no product **3a** could be obtained in the absence of TBAI (Table 1, entry 8). Continuously, we examined several iodine reagents and phase transfer catalysts and found there were no obvious improvement in yields compared with TBAI (Table 1, entries 9−17). In addition, the results replacing air with O_2 or N_2 showed that molecular oxygen is essential as an oxidant for this transformation (Table 1, entries 18 and 19).

With the optimized reaction conditions in hand, a series of sulfonyl hydrazides were used to assess the scope of the reaction (Scheme 2). Pleasingly, various *ortho*-, *meta*-, and *para*-substituted arylsulfonyl hydrazides underwent smooth sulfonylations and provided the desired products in good to excellent yields (**3a**−**3m**). Notably, both electron-withdrawing and electron-donating groups hardly affected the reactivity of the reaction. Furthermore, the steric effect was inconspicuous, both 4-Me-phenylsulfonyl hydrazide and 2-Me-phenylsulfonyl hydrazide could be converted into the corresponding β-carbonyl sulfones in 85 and 84% yields (**3a** and **3m**), respectively. To our delight, the heteroaryl sulfonyl hydrazides, including quinolone and thiophene, resulted in the formation of corresponding products (**3n** and **3p**) in satisfactory yields. In addition, both benzylsulfonyl hydrazide and alkylsulfonyl hydrazides afforded the corresponding products (**3q**−**3s**) in moderate to high yields.

Scheme 2. Scope of Sulfonyl Hydrazides[a]

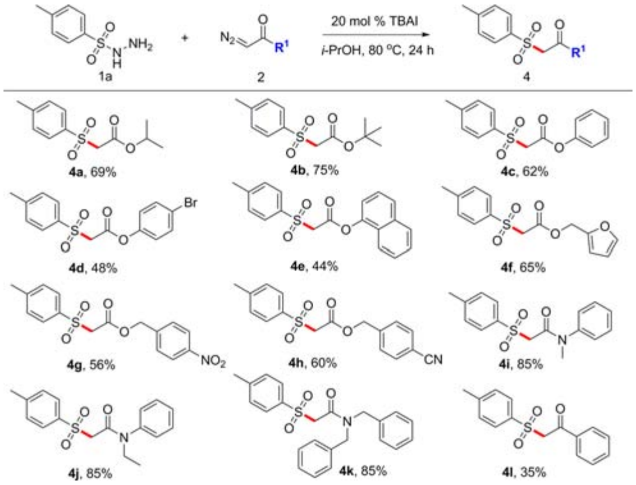


[a] Reaction conditions: **1** (0.5 mmol, 1.0 equiv), **2a** (1.0 mmol, 2.0 equiv), TBAI (0.1 mmol, 20 mol %), and *i*-PrOH (2 mL) for 24 h under air. Isolated products.

The exact structure of representative product **3o** has been conclusively confirmed by the single-crystal X-ray diffraction.

To further explore the diversity of this transformation, a representative selection of diazo compounds was subjected to this process, and the results are presented in Scheme 3. A series of α-diazocarbonyl compounds **2** reacted with $TsNHNH_2$ **1a**, leading to the corresponding products in moderate to high yields (**4a**−**4l**). It is noteworthy that the diazoacetamides were also found to be reactive in this transformation, providing the desired products (**4i**−**4k**) in high yields. Notably, reaction of **1a** and 2-diazo-1-phenylethan-1-one also afforded the desired product 1-phenyl-2-tosylethan-1-one (**4l**), albeit in a low 35% yield.

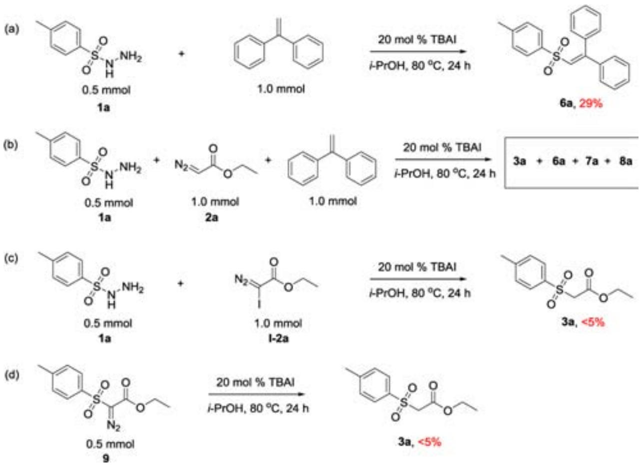
Scheme 3. Scope of Diazo Compounds[a]



[a] Reaction conditions: **1a** (0.5 mmol, 1.0 equiv), **2** (1.0 mmol, 2.0 equiv), TBAI (0.1 mmol, 20 mol %), and *i*-PrOH (2 mL) for 24 h under air. Isolated products.

Several control experiments were designed to understand the mechanism of this process. The addition of the radical inhibitor TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) prohibited the reaction, which implies that a radical process was involved in this transformation. At the same time, the sulfonyl radical intermediate was captured by TEMPO, leading to the radical adduct **5a** (see Scheme S1 in the Supporting Information). Next, we tried to react TsNHNH$_2$ **1a** with 1,1-diphenylethylene instead of ethyl diazoacetate in our conditions. As desired, the product (2-tosylethene-1,1-diyl)dibenzene **6a** was isolated in 29% yield, which indicated that a sulfonyl radical participated in the reaction (Scheme 4a).[7i,10] When ethyl diazoacetate was added to the reaction simultaneously, products **6a**−**8a** could be detected by LC−MS (Scheme 4b). Based upon the above results, we suspected three radical species **6b**−**8b** as key intermediates were involved in this transformation (Figure 1). Notably, the use of ethyl diazoiodoacetate **I-2a**[11] or ethyl 2-diazo-2-tosylacetate **9** as substrates failed to afford the desired product **3a** (Scheme 4c,d), which suggested that both were not the reactive intermediates in this process.

Scheme 4. Probe for the Possible Mechanism



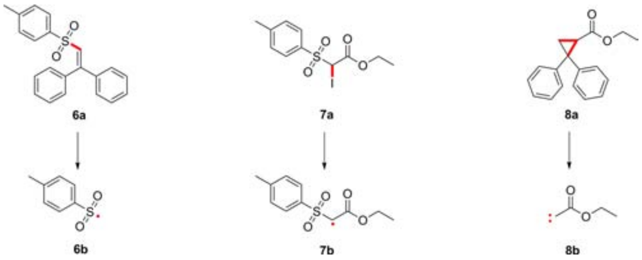
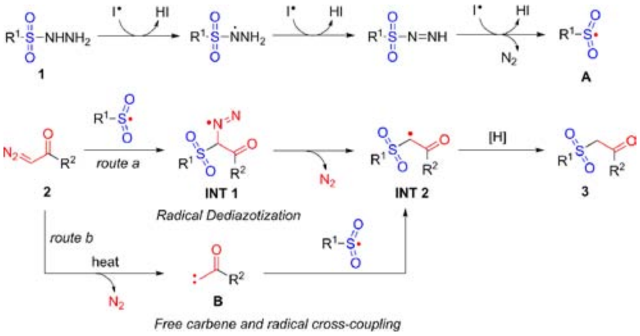


Figure 1. Three radical intermediates.

Based upon the above results and literature, a plausible mechanism was proposed, as shown in Scheme 5. Initially, the iodine anion was oxidized to iodine by air. Next, the iodine radical could be generated from iodine upon heating.[12] The sulfonyl radical **A** was formed in situ from sulfonyl hydrazides **1** through the continuous exchange of an iodine radical.[13] Subsequently, the addition of sulfonyl radicals **A** to diazo compound **2** afforded radical intermediate **INT1**, which underwent radical-triggered dediazotization with the release of N$_2$ to form radical intermediate **INT2**.[6] According to the previous work[14] and our experiment observations (Figure 1, detection of product **8a**), another pathway could be put forward, in which the diazo compound **2** decomposed to generate free carbene **B** under thermal conditions. Its subsequent coupling with sulfonyl radical **A** also afforded radical intermediate **INT2**. Finally, **INT2** underwent H-abstraction and delivered the desired *β*-carbonyl sulfone **3**.

Scheme 5. Proposed Reaction Mechanism



In conclusion, we have successfully developed an efficient approach for the construction of *β*-carbonyl sulfones from the coupling between sulfonyl hydrazides and diazo compounds catalyzed by TBAI. A radical mechanism has been proposed to account for this reaction, which possibly undergoes two routes and proceeds under metal-free conditions. This methodology allows a wide substrate scope, utilizes readily available starting materials, and provides operational simplicity. Efforts to develop other metal-free cross-coupling reactions between radicals and diazo compounds are in progress in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02532.

Experimental procedures and full spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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