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Iodine-catalysed sp^3 C–H sulfonylation to form β-dicarbonyl sulfones with sodium sulfinates†

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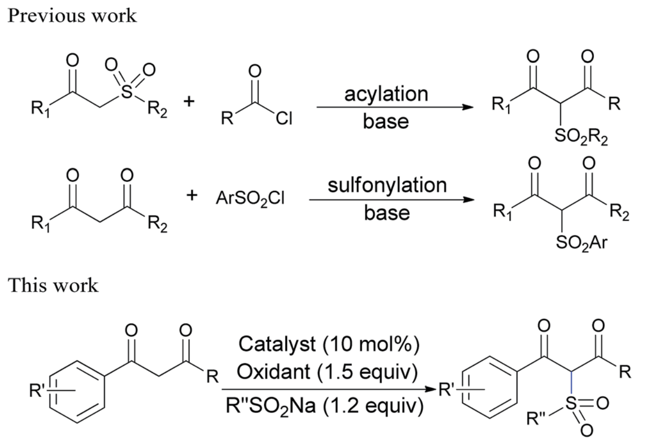
An efficient and easily handled method for β-dicarbonyl sulfones with sodium sulfinates as the sulfonyl source was developed. This transformation was involved in the iodine-catalysed sp^3 C–H sulfonylation of β-dicarbonyl compounds.

Sulfones belong to a known class of organosulfur compounds, which have found diverse applications in organic synthesis, polymer materials, and medicinal chemistry.[1] Among them, β-dicarbonyl sulfones have attracted much attention due to their excellent biological effects, such as antimicrobial,[2a] anticoagulant[2b] and anti-schistosomal activities.[2c] Furthermore, since β-dicarbonyl compounds are commonly used intermediates for heterocycle synthesis,[3] β-dicarbonyl sulfones would provide alternative units to construct sulfonylated heteroaromatic compounds in the design of potential drugs.[4] Surprisingly, only a limited number of procedures was developed for the synthesis of β-dicarbonyl sulfones during last decades. In most cases, β-dicarbonyl sulfones were prepared through either C-acylation of β-keto sulfones with acyl halides or C-sulfonylation of β-dicarbonyl compounds with sulfonyl halides. These methods usually required excess amount of strong bases (NaOMe,[2a,c] NaH,[5] or LDA[6]), which are not suitable for sensitive substrates; the acyl or sulfonyl reagents are much reactive and moisture-sensitive, resulting in side reactions and byproducts, especially in the synthesis of complex molecules. Therefore, it is highly desirable to develop an efficient and easily handled method for β-dicarbonyl sulfones with less reactive sulfonyl sources (Scheme 1).

Recently, iodine or tetrabutylammonium iodide has emerged as a promising alternative to catalyse oxidative sulfonylation due to their high efficiency, mild reaction conditions and metal-free features. Especially, the sulfonylation of heteroaromatic compounds and C–C unsaturated bonds has been well established, and examples include regioselective 2-sulfonylation of indoles with sodium sulfinates,[7] synthesis of sulfonated pyrazoles with sulfonyl hydrazides,[8] sulfonylation of alkenes with sulfonyl hydrazides to form alkenyl sulfones,[9a] allylic sulfones,[9b,c] and sulfonated oxindoles,[9d] and sulfonylation of alkynes with sulfonyl hydrazides to synthesize β-iodovinyl sulfones.[9e] Although these studies achieved much progress, little attention has been paid to investigate the sulfonylation of sp^3 C–H bond. In this regard, we described a novel and efficient method for the synthesis of β-dicarbonyl sulfones by iodine-catalysed sulfonylation of sp^3 C–H bond with sodium sulfinates.

Initially, ethyl benzoyl acetate (**1a**) and sodium benzenesulfinate (**2a**) were selected as model substrates to explore the optimal reaction conditions. It was found that ethyl α-phenylsulfonylbenzoylacetate (**3a**) was obtained in 27% yield by using iodine (10 mol%) and *tert*-butyl hydroperoxide (TBHP, 1.5 equiv.) in CH$_3$CN at 25 °C (Table 1, entry 1). The yield of **3a**



Scheme 1 Different methodologies for the synthesis of β-dicarbonyl sulfones.

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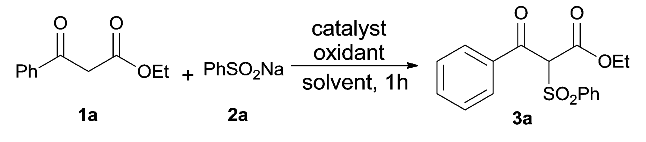
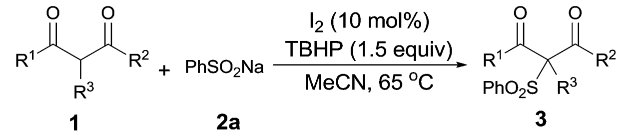
Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	Oxidant	Solvent	T (°C)	Yield[b] (%)
1	I_2	TBHP	CH_3CN	25	27
2	I_2	TBHP	CH_3CN	45	73
3	I_2	TBHP	CH_3CN	65	94
4	I_2	TBHP	CH_3CN	Reflux	94
5[c]	I_2	TBHP	CH_3CN	65	89
6	—	TBHP	CH_3CN	65	0
7[d]	I_2	—	CH_3CN	65	21
8	KI	TBHP	CH_3CN	65	85
9	Bu_4NI	TBHP	CH_3CN	65	66
10	KIO_3	TBHP	CH_3CN	65	0
11	I_2	H_2O_2	CH_3CN	65	49
12	I_2	Oxone	CH_3CN	65	17
13	I_2	TBHP	THF	65	87
14	I_2	TBHP	EtOAc	65	85
15	I_2	TBHP	$CHCl_3$	65	38
16	I_2	TBHP	CH_3COOH	65	Trace

[a] Reaction conditions: 0.5 mmol of **1a**, 0.6 mmol of **2a**, 0.05 mmol of catalyst, 0.75 mmol of oxidant, in 2 mL of solvent for 1 h. [b] Isolated yield. [c] The reaction was run under N_2. [d] The reaction was run with 1.0 equiv. of iodine.

Table 2 The scope of β-dicarbonyl compounds[a]



Entry	β-Dicarbonyl compound	Product	Yield[b] (%)
1	$R^1 = C_6H_5$, $R^2 = OEt$, $R^3 = H$	**3a**	94
2	$R^1 = 4\text{-}BrC_6H_4$, $R^2 = OEt$, $R^3 = H$	**3b**	87
3	$R^1 = 2\text{-}MeC_6H_4$, $R^2 = OEt$, $R^3 = H$	**3c**	71
4	$R^1 = 4\text{-}MeOC_6H_4$, $R^2 = OEt$, $R^3 = H$	**3d**	87
5	R^1 = 2-naphthyl, $R^2 = OEt$, $R^3 = H$	**3e**	93
6	R^1 = 2-furyl, $R^2 = OEt$, $R^3 = H$	**3f**	71
7	R^1 = 2-thienyl, $R^2 = OEt$, $R^3 = H$	**3g**	82
8[c]	$R^1 = C_6H_5$, $R^2 = OEt$, $R^3 = Me$	**3h**	9
9	$R^1 = {}^iPr$, $R^2 = OEt$, $R^3 = H$	**3i**	66
10	$R^1 = {}^tBu$, $R^2 = OEt$, $R^3 = H$	**3j**	51
11	$R^1 = CO_2Me$, $R^2 = CO_2Me$, $R^3 = H$	**3k**	66
12	$R^1 = CO_2Et$, $R^2 = CO_2Et$, $R^3 = H$	**3l**	54
13	$R^1 = CO_2{}^tBu$, $R^2 = CO_2{}^tBu$, $R^3 = H$	**3m**	48
14[d]	$R^1 = C_6H_5$, $R^2 = C_6H_5$, $R^3 = H$	**3n**	81

[a] Reaction conditions: 0.5 mmol of **1**, 0.6 mmol of **2a**, 0.05 mmol of I_2, 0.75 mmol of TBHP (70% in water), in 2 mL of MeCN at 65 °C, for 1–4 h. [b] Isolated yield. [c] Conversion: 38%. [d] Solvent: THF (2 mL).

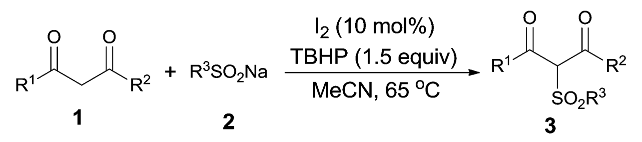
could be increased when the reaction temperature was raised (entries 1–3), and the best result (94% yield of **3a**) was obtained when heating the reaction mixture to 65 °C (entry 3), while a higher temperature could not give a better result (entry 4). **3a** was obtained in slightly lower yields when the reaction was run under N_2 atmosphere (entry 5). Control experiments indicated that the desired product **3a** could not be determined in the absence of iodine catalyst (entry 6), and only 21% yield of **3a** was obtained even using stoichiometric amount of iodine in the absence of TBHP (entry 7). Other catalysts such as KI, Bu_4NI, and KIO_3 were examined but found less effective than iodine: for KI and Bu_4NI, **3a** was just afforded in 85% and 66% yields separately (entries 8 and 9); while no desired product was detected when using potassium iodate as the catalyst (entry 10). Two commonly used oxidants (H_2O_2 and Oxone) were also tested for this transformation, while **3a** was produced in inferior yields (entries 11 and 12). Other different solvents were also attempted for this transformation but they failed to provide a more favorable outcome (entries 13–16). For example, **3a** could be produced in high yield in the solvents like THF and EtOAc (entries 13 and 14), while low yields of **3a** were obtained when using $CHCl_3$ or AcOH as the solvent (entries 15 and 16).

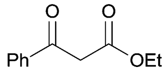
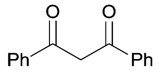
With the optimal reaction conditions in hand (Table 1, entry 3), a series of β-dicarbonyl compounds (**1**) was then investigated to couple with sodium benzenesulfinate (**2a**). It was found that various β-dicarbonyl compounds including β-keto esters, β-diesters and β-diketones were suitable for this transformation (Table 2). Ethyl benzoylacetate derivatives bearing electro-donating or electron-withdrawing group on the phenyl ring gave the corresponding products in good to high yields (**3b–d**). Other aromatic rings such as naphthyl, furyl, and thienyl groups could also be tolerated, and delivered the corresponding products **3e–g** in good to excellent yields. It was noteworthy that the location of a methyl group at the α-position of β-keto esters impeded the reaction process, and the desired product **3h** was only furnished in 9% yield. Furthermore, the aliphatic β-keto esters were also attempted and gave the corresponding products in moderate yields (**3i**, **3j**). As for the different β-diesters, the reaction also proceeded well, and gave the desired products **3k**, **3l** and **3m** in moderate yields. The β-diketone such as dibenzoylmethane was proved to be a good substrate for this transformation, and the product **3n** was obtained in 81% yield.

The different sodium sulfinates were also evaluated for this transformation (Table 3). Arylsulfinic acid sodium salts bearing electro-donating or electro-withdrawing substituents on the phenyl ring could smoothly react with ethyl benzoylacetate to give the corresponding products in high yields (**3o**, **3p**). Furthermore, the aliphatic sulfinic acid sodium salts like sodium methanesulfinate were also suitable for this reaction, and coupled with β-keto esters or β-diketones in moderate yields (**3q**, **3r**). Besides, the reactions of β-diketones with different kinds of aromatic sulfinic acid sodium salts also proceeded smoothly, and provided the β-diketo sulfones in high to excellent yields (**3s–u**).

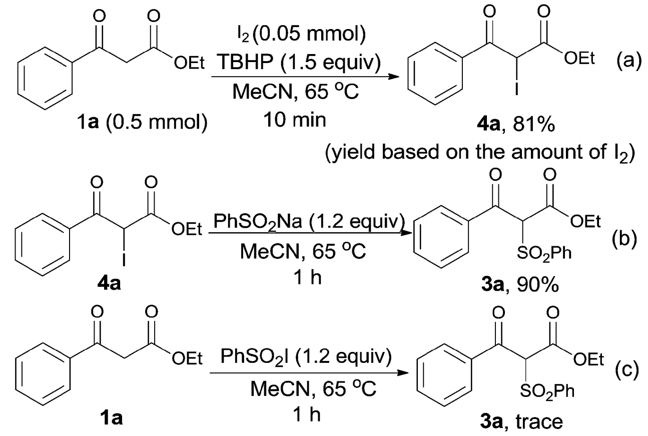
The mechanism of the present transformation is worth discussing. Several control experiments were carried out in order to obtain some insight of the possible mechanism. In the reaction of ethyl benzoylacetate with sodium benzenesulfinate, the α-iodinated ester **4a** was detected at the first few minutes. **4a**

Table 3 The scope of sodium sulfinates[a]



Entry		Sodium sulfinate	Product	Yield[b] (%)
1		$R^3 = 4\text{-OMeC}_6H_4$	**3o**	85
2		$R^3 = 4\text{-BrC}_6H_4$	**3p**	89
3		$R^3 = \text{Me}$	**3q**	43
4[c]		$R^3 = \text{Me}$	**3r**	57
5[c]		$R^3 = 4\text{-FC}_6H_4$	**3s**	82
6[c]		$R^3 = 2\text{-naphthyl}$	**3t**	89
7[c]		$R^3 = 4\text{-MeC}_6H_4$	**3u**	95

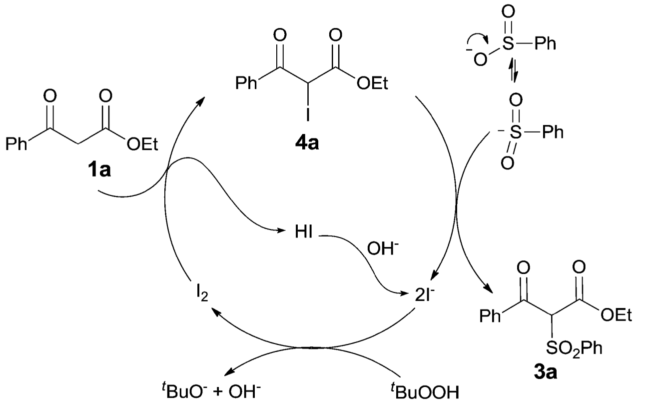
[a] Reaction conditions: 0.5 mmol of **1**, 0.6 mmol of **2**, 0.05 mmol of I_2, 0.75 mmol of TBHP (70% in water), in 2 mL of MeCN at 65 °C, for 1–4 h. [b] Isolated yield. [c] Solvent: THF (2 mL).



Scheme 2 Control experiments for mechanism studies.

could be isolated in 81% yield in the absence of sodium sulfinates under the standard conditions (Scheme 2a). The treatment of **4a** with 1.2 equiv. of $PhSO_2Na$ gave the desired product **3a** in 90% yield (Scheme 2b). Since another iodinated intermediate benesulfonyl iodide was also likely to be involved under the present conditions,[10] the reaction between ethyl benzoylacetate and benesulfonyl iodide was consequently tested, however, only trace amount of **3a** was obtained (Scheme 2c).

Based on the results of control experiments and literature reports,[11] a plausible mechanism is proposed in Scheme 3. The α-iodination of ethyl benzoylacetate proceeds smoothly under the standard conditions to produce the intermediate **4a**. The oxygen-centered anion of sodium benzenesulfinate can be resonated to a sulfonyl anion, of which nucleophilic attraction to the iodinated carbon of **4a** would afford the desired product **3a**. All released iodide ions can be reoxidized to molecular iodine by TBHP.



Scheme 3 The proposed mechanism.

In summary, we have developed a novel method for the synthesis of β-carbonyl sulfones with sodium sulfinate as the sulfonyl source under metal-free conditions. This transformation was catalysed by molecule iodine through the sulfonylation of sp^3 C–H bond, and the α-iodinated β-dicarbonyl compounds were believed as the key intermediates. The ready availability of starting materials, broad substrate scope, high efficiency and operational simplicity make the present method attractive to construct β-dicarbonyl sulfones and the derived biologically active molecules.

Acknowledgements

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