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Direct Iodosulfonylation of Alkylynones with Sulfonylhydrazides and Iodine Pentoxide Leading to Multisubstituted α,β-Enones

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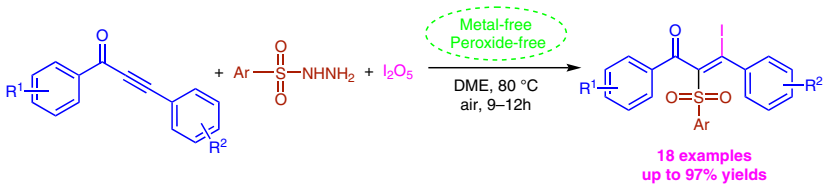

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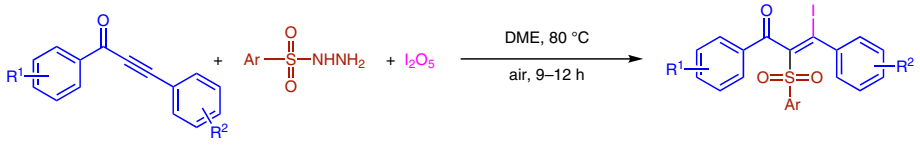
Abstract A facile and efficient method has been developed for the construction of multisubstituted α,β-enones through the direct selective iodosulfonylation of alkylynones with sulfonylhydrazides and iodine pentoxide. The present methodology offers a simple and attractive approach to various multisubstituted α,β-enones in moderate to good yields with excellent stereo- and regioselectivities under the metal- and peroxide-free conditions.

Key words multifunctionalized α,β-enones, iodosulfonylation, alkylynones, sulfonylhydrazides, iodine pentoxide

α,β-Enones represent a common structural motif in many useful reactions.[1] Furthermore, they frequently serve as important bifurcations for the construction of drug-like heterocyclic libraries.[2] In particular, functionalized α,β-enones have drawn particular interest from chemists because of their widespread applications in synthetic and medicinal chemistry. To date, various approaches towards the synthesis of α,β-enones have been developed, such as aldol condensation,[3] dehydration of α-hydroxy carbonyl compounds,[4a] isomerization of propargylic alcohols,[4b] and Horner–Wadsworth–Emmons (HWE) reaction.[5] Nevertheless, most of these methods mainly focus on the synthesis of unfunctionalized α,β-enones. Direct and efficient methods for the preparation of multifunctionalized α,β-enones with defined substitution patterns are relatively rare, and they usually involve harsh reaction conditions and multiple steps.[6]

Sulfone groups are extremely valuable functionalities that are frequently found in various natural products, biologically active compounds, and materials.[7] Thus, the incorporation of sulfone groups into organic frameworks to construct various organic sulfones has attracted increasing attention from chemists.[8] Over the past several years, the halosulfonylations of alkynes have been developed to access β-halovinyl sulfones,[9,10] in which both halogen and sulfone groups could be simultaneously introduced into organic molecules. However, most of these methods are restricted to terminal alkynes, and only a few successful strategies have been developed for the halosulfonylation of internal alkynes in a highly regioselective manner because of steric and electronic issues.[11,12] With our continued interests in the construction of sulfone-containing compounds,[13] herein, we wish to describe a convenient and efficient synthetic method for the construction of multifunctionalized α,β-enones through selective iodosulfonylation of alkylynones with iodine pentoxide and sulfonylhydrazides (Scheme 1). This protocol provides an attractive approach to various multisubstituted α,β-enones in moderate to good yields with excellent stereo- and regioselectivities under the metal- and peroxide-free conditions.



Scheme 1 Iodosulfonylation of alkylynones with sulfonylhydrazides and I_2O_5

In an initial experiment, we started our investigation by choosing 1,3-diphenylprop-2-yn-1-one (**1a**) and benzenesulfono-hydrazide (**2a**) as model substrates to optimize the reaction conditions in the presence of I_2O_5 (1 equiv) (Table 1). When the model reaction was carried out in 1,2-dimethoxyethane (DME) at room temperature, the desired product **4aa** was obtained in only 10% yield (entry 1). To our delight, the efficiency of the reaction clearly improved with an increase in the reaction temperature (entries 2–4), and a good yield (83%) was obtained when the reaction was carried out at 80 °C (entry 3). The structure of **4aa** was further unambiguously confirmed by single-crystal X-ray analysis (Figure 1). Solvent screening studies established that the use of 1,2-dichloroethane (DCE) also resulted in good yield (81%) ((entry 5), and other solvents such as THF, CH_3CN, toluene, MeOH, and H_2O gave low to moderate yields (entries 6–10). No transformation was observed when either DMF or DMSO was used as solvent (entries 11 and 12, respectively). Furthermore, replacing I_2O_5 with other iodine reagents such as I_2, KI, NaI, or TBAI all resulted in low reaction efficiency (entries 13–16), indicating the important role of I_2O_5 in the present reaction system. Either reducing or increasing the amount of I_2O_5 slightly decreased the yields (entries 17 and 18). In addition, the substrate ratio was also examined, and the appropriate proportion of **1a**, benzenesulfono-hydrazide **2a**, and I_2O_5 was 1:3:1 (entries 19 and 20).

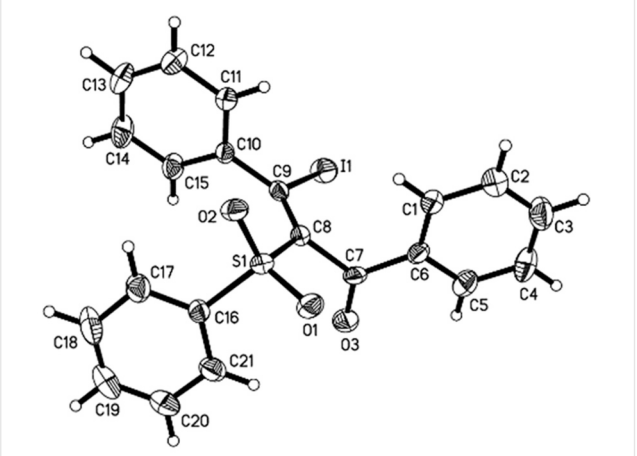
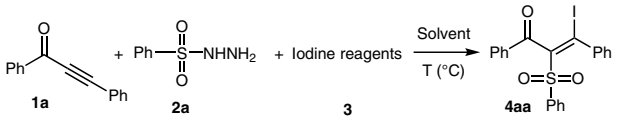


Figure 1 The crystal structure of **4aa**. ORTEP drawing of $C_{21}H_{15}IO_3S$ with 50% probability ellipsoids, showing the atomic numbering scheme.

After establishing the optimal reaction conditions for the iodosulfonylation of alkylynones, the scope of the reaction with various alkylynones and sulfonylhydrazides was examined. Firstly, the impact of substitution variation at the keto terminal of the ynone was investigated. As shown in Scheme 2, aromatic ynones containing either an electron-donating group or an electron-withdrawing group all reacted with sulfonylhydrazide to give the corresponding products **4aa–ga** in good yields.

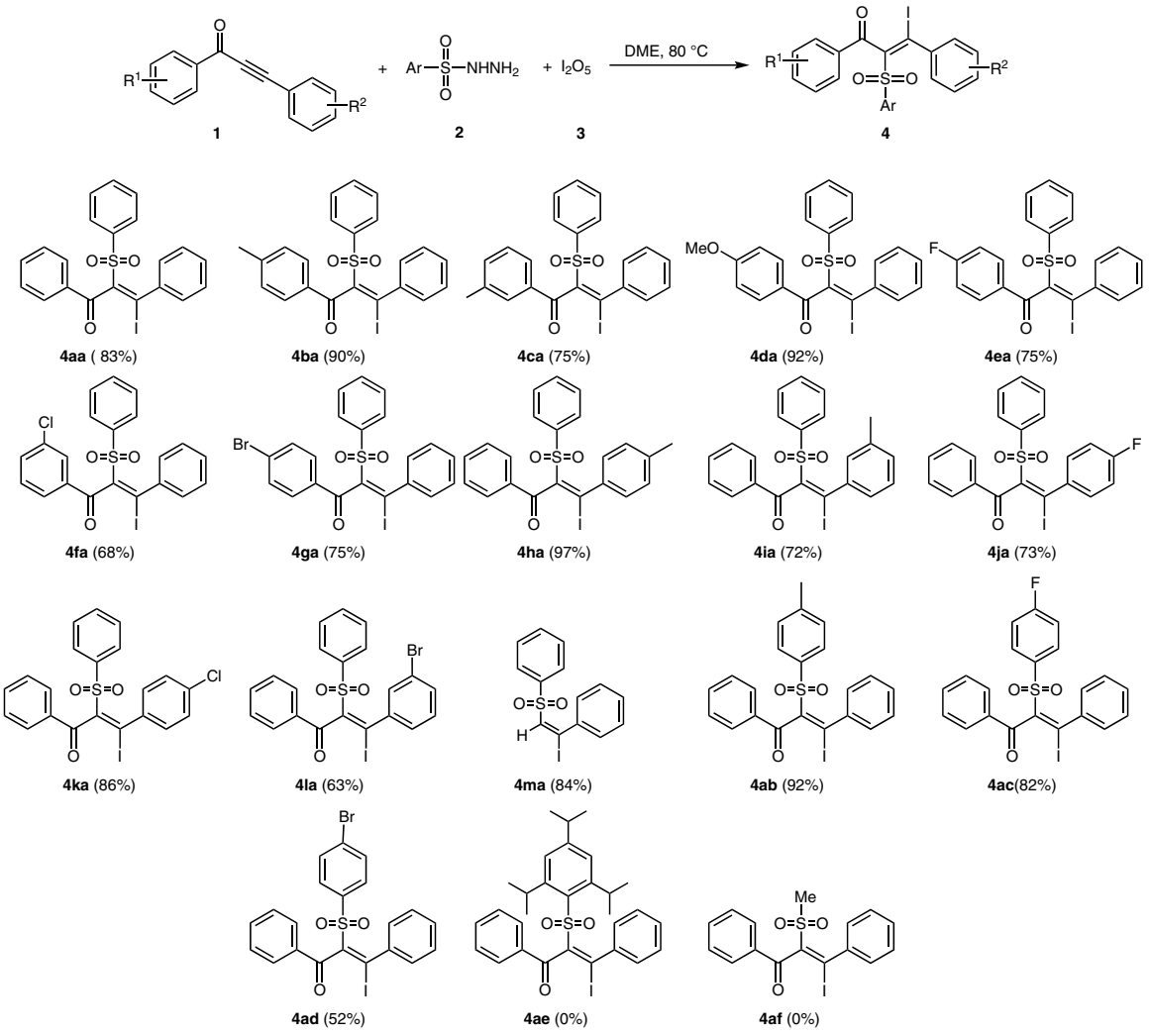
Table 1 Optimization of Reaction Conditions[a]



Entry	Iodine reagents (equiv)	Solvent	Temp. (°C)	Yield (%)[b]
1	I_2O_5 (1)	DME	25	10
2	I_2O_5 (1)	DME	60	77
3	I_2O_5 (1)	DME	80	83
4	I_2O_5 (1)	DME	100	82
5	I_2O_5 (1)	DCE	80	81
6	I_2O_5 (1)	THF	80	62
7	I_2O_5 (1)	CH_3CN	80	40
8	I_2O_5 (1)	toluene	80	27
9	I_2O_5 (1)	MeOH	80	10
10	I_2O_5 (1)	H_2O	80	20
11	I_2O_5 (1)	DMF	80	0
12	I_2O_5 (1)	DMSO	80	0
13	I_2 (1)	DME	80	10
14	KI (1)	DME	80	35
15	NaI (1)	DME	80	24
16	TBAI (1)	DME	80	15
17	I_2O_5 (0.5)	DME	80	49
18	I_2O_5 (1.5)	DME	80	77
19	I_2O_5 (1)	DME	80	30[c]
20	I_2O_5 (1)	DME	80	57[d]

[a] Reaction conditions: **1a** (0.125 mmol), **2a** (0.375 mmol), iodine reagent (0.125 mmol), solvent (2 mL), 25–80 °C, under air, 12 h.
[b] Isolated yield based on **1a**.
[c] **1a** (0.125 mmol), **2a** (0.125 mmol).
[d] **1a** (0.125 mmol), **2a** (0.25 mmol).

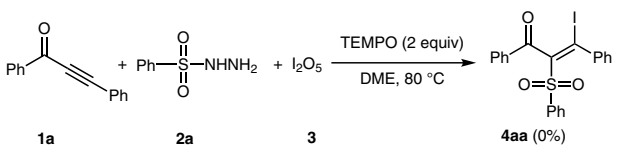
In general, electron-donating group substituted alkylynones (**1b**, **1d**) showed higher activity than those bearing electron-withdrawing groups (**1e–g**). Furthermore, the reaction efficiency was also affected by steric effects; substrates bearing a methyl group in the *meta*-position of the phenyl ring resulted in slightly lower yield than those substituted on the *para*-position of the phenyl ring (**4ab** vs. **4ac**). Moreover, haslide substituents such as F, Cl, and Br groups were compatible with this reaction, leading to the corresponding products **3ea–ga**, which could be used for further structural modifications. Subsequently, the impact of alkyne end substitution on the reaction was studied. Similarly, arylynones including an electron-donating group



Scheme 2 Results for the reactions of iodosulfonylation of alkylynones with sulfonohydrazides and I_2O_5. *Reagents and conditions*: **1** (0.125 mmol), **2** (0.375 mmol), **3** I_2O_5 (0.125 mmol), DME (2 mL), 80 °C, under air, 9–12 h (isolated yields based on **1**).

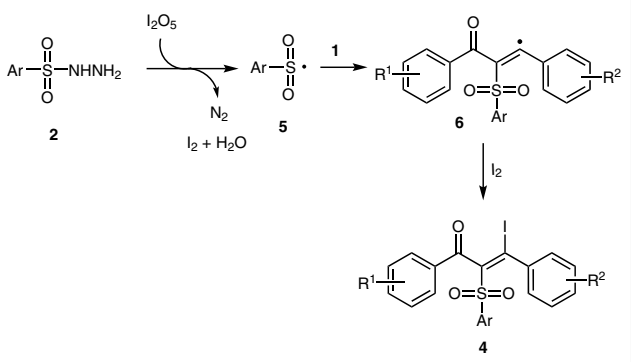
or an electron-withdrawing group were all suitable for this reaction, and the corresponding products **4ha–la** were obtained in good to excellent yield. In addition, compounds with a terminal alkyne such as phenylacetylene was also compatible with this reaction, leading to the corresponding product **4ma** in 84% yield. Finally, with respect to sulfonohydrazides, in addition to benzenesulfonohydrazide **2a**, a series of arylsulfonohydrazides bearing both electron-donating groups (Me) and electron-withdrawing groups (F, Br) could also be smoothly transformed into the corresponding products **4ab–ad**. However, none of desired products were detected when a more sterically hindered sulfonylhydrazide such as 2,4,6-triisopropylbenzenesulfonohydrazide or a alkylsulfonohydrazide such as methanesulfonohydrazide were employed in the present reaction system.

To gain further insight into the mechanism, a radical capture experiment was carried out. As shown in Scheme 3, when 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was added into the reaction system, the model reaction was extremely inhibited and only a trace amount of desired product **4aa** was detected, suggesting that a radical pathway might be involved in this transformation.



Scheme 3 Preliminary mechanistic study

Based on the above results and on previous reports,[9–12,14] a possible reaction pathway is proposed as shown in Scheme 4. Initially, sulfonyl radical **5** and I_2 are generated from the single-electron oxidation of sulfonylhydrazide **2** by I_2O_5.[14] Subsequently, the selective addition of sulfonyl radical **5** to alkylynone **1** gives vinyl radical **6**. Finally, the interaction of radical **6** with molecular iodine would lead to the formation of the desired product **4**.



Scheme 4 Postulated reaction pathway

In summary, a new and efficient iodosulfonylation of alkylynones with iodine pentoxide and sulfonylhydrazides leading to multisubstituted α,β-enones has been developed.[15] The present protocol, which utilizes simple and readily available starting materials, as well as metal- and peroxide-free conditions, provides an attractive approach to various multisubstituted α,β-enones in moderate to good yields with excellent stereo- and regioselectivities. Further studies on the scope and application of this reaction are under way in our laboratory.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1589160.

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(15) **Preparation of (*E*)-3-iodo-1,3-diphenyl-2-(phenylsulfonyl)prop-2-en-1-one (4aa)**: In a 25 mL round-bottomed flack, alkylynone **1a** (0.125 mmol), sulfonylhydrazide **2a** (0.375 mmol), I_2O_5 (**3**; 0.125 mmol), and DME (2 mL) were added. The reaction mixture was stirred at 80 °C for 12 h. After completion the reaction, the solvent was then removed under vacuum. The residue was purified by flash column chromatography using a mixture of petroleum ether and ethyl acetate as eluent to give the desired product **4aa**. Yield: 49 mg (83%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.28 (d, *J* = 7.2 Hz, 2 H), 7.72 (t, *J* = 7.3 Hz, 1 H), 7.62 (t, *J* = 7.8 Hz, 2 H), 7.54 (t, *J* = 7.4 Hz, 1 H), 7.49 (d, *J* = 7.3 Hz, 2 H), 7.36–7.26 (m, 5 H), 7.17 (d, *J* = 6.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 190.6, 149.3, 140.4, 140.0, 134.7, 133.8, 133.7, 130.3, 129.6, 129.3, 129.0, 128.8, 128.3, 128.0, 127.5; HRMS: *m*/*z* $[M + Na]^+$ calcd. for $C_{21}H_{15}IO_3SNa$: 496.9684; found: 496.9689.