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## Iodine–DMSO-promoted divergent reactivities of arylacetylenes†

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An unprecedented set of efficient, economical, atom-economic and exceedingly selective  $I_2$ –DMSO-promoted methods is described for the generation of different structures. The reaction represents the first of its kind, involving the use of different iodine concentrations, temperatures, acids and salt to adjust the selectivity for the synthesis of different alkenes,  $\alpha$ -functionalized ketones and  $\alpha$ -ketomethylthioesters.

DMSO is a well-known polar aprotic organosulfur compound reported for its diverse roles as a solvent, oxidant, ligand, inhibitor of DNA primer, cryoprotectant, etc.<sup>1</sup> Furthermore, the combination of iodine and DMSO has astoundingly altered the view of chemists in seeking prolific oxidative reactions.<sup>2</sup> This unique combination has caught researchers' attention owing to (a) its inexpensive protocols, (b) their stability towards air and moisture, (c) their environmentally benign nature, (d) efficient atom and step economy, (e) no need for pre-functionalization of starting materials, (f) high throughput results and (g) good functional group tolerance.<sup>3</sup> The  $I_2$ –DMSO system with acetylenes, alkenes and acetophenones has been broadly classified to act in two ways: (i)  $I_2$ -catalyzed reactions in DMSO medium and (ii)  $I_2$ –DMSO-mediated oxidative transformations.<sup>4</sup> Previously, in either pathway, this system involved prior iodination of substrates, inclusive of different sp, sp<sup>2</sup> and sp<sup>3</sup> functionalities in the presence of molecular iodine, followed by Kornblum oxidation to 2-oxoaldehydes (OAs). Kornblum oxidation represents the conversion of primary halides into aldehydes by the action of DMSO with the simultaneous production of DMS and it is predominantly accessible at higher temperatures.<sup>5</sup> These reactions of arylacetylenes in  $I_2$ –DMSO to form aldehydes (OAs) mechanistically bear a resemblance to the reactions of alkenes and acetophenones and are well-documented.<sup>6</sup> However, alkynes are recognized to exemplify divergent behaviours because the triple bonds can be functionalized into a myriad of constructions.<sup>7</sup> In this regard, we present a different array of novel  $I_2$ –DMSO-promoted selective reactions that are possible through the use of terminal

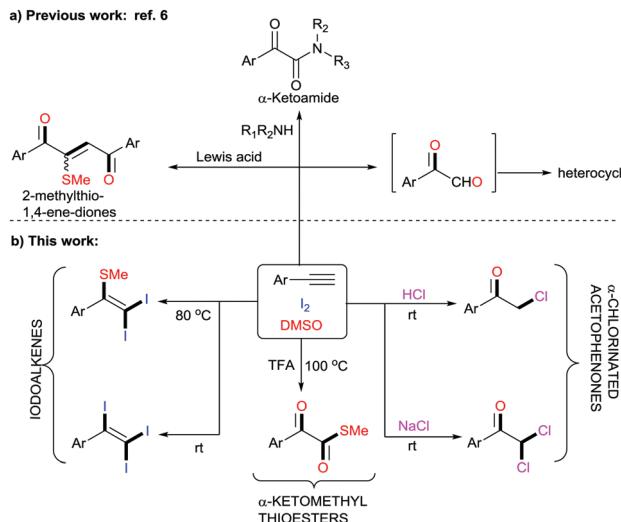
alkynes and justify their divergent behaviour. On the one hand, at room temperature different arylacetylenes were exclusively transformed into tri-iodinated alkenes that were earlier reported to be obtained through the use of multiple expensive reagents/additives.<sup>8</sup> Interestingly, on the other hand, the same reaction under heated conditions engendered unique – SMe-substituted regioselective di-iodinated alkenes. Such compounds are known to exhibit a wide variety of applications as key synthetic precursors and building blocks in organic synthesis.<sup>9</sup> Further, we established direct conversion of alkynes into  $\alpha$ -functionalized ketones such as  $\alpha$ -mono and di-chlorinated ketones at room temperature in a regioselective manner using 2 N HCl and NaCl, respectively. Mono- and bis- $\alpha$ -chloro ketones are established as bis-electrophiles, which accounts for their extensive use, particularly in cyclocondensations to furnish different valuable heterocycles.<sup>10</sup> Consequently, a number of synthetic methods for the construction of mono and bis- $\alpha$ -chloro ketones have been established in the past decades.<sup>11</sup> Nevertheless, most of these procedures require dealing with toxic reagents, challenging waste streams, and corrosivity.<sup>12</sup> Another divergence in the reactivity of arylacetylenes under heated conditions using TFA was illustrated for the generation of different novel  $\alpha$ -ketomethylthioesters, which had not been previously reported (Scheme 1).<sup>13</sup> Here as well, DMSO served as a cheap and efficient source of oxygen and SMe. As is evident, DMSO acted as an alternative for methanethiol gas, which is quite expensive and difficult to handle. In general, all these compounds as such are useful synthons for the generation of different complex organic architectures or can be used *in situ* to generate different structures.

In our initial investigation, we endeavoured to examine the nature of the products obtained on reacting phenylacetylene **1a** and glycine-methylester hydrochloride (Table 1, entry 1). As per our previous work entitled "Divergent Reactivity of Amino Acid Alkyl Ester Hydrochlorides with 2-oxoaldehydes: Role of Selenium Dioxide To Promote Regioselective Synthesis of Imidazoles", we expected methyl-2-(2-benzoyl-5-phenyl-1*H*-imidazol-1-yl)acetate as the major product.<sup>14</sup> However, surprisingly, the reaction produced a mixture of unexpected products **2a**, **3a**, **4a**, **5a**, and **6a** along with phenylglyoxal **7a**. In order to attain better yields and product selectivity, a preliminary

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Scheme 1 Summary of this work.

set of reactions was carried out under different conditions (Table 1, entries 2–15). Primarily, we examined the reaction of phenylacetylene **1a** (1 mmol) with 1.2 mmol of  $I_2$  in DMSO at 80 °C for 2 h (entry 2). We observed that the (2,2-diiodo-1-phenylvinyl)(methyl)sulfane **2a** was produced predominantly in 67% yield. Later, screening of our reaction at different concentrations of  $I_2$  was performed (entries 3–5), wherein we predominantly isolated **2a** in 79% yield. Further, we observed an increase in the yield of triiodinated product **3a** with a decrease in temperature (entries 6–8). However, the best yields were obtained when **1a** (1 mmol) was stirred with  $I_2$  (2.2 mmol) in DMSO at r.t. for 4 h (entry 8). Further, in the reaction of phenylacetylene **1a** and glycine methyl ester hydrochloride (entry 1, Table 1), we noticed

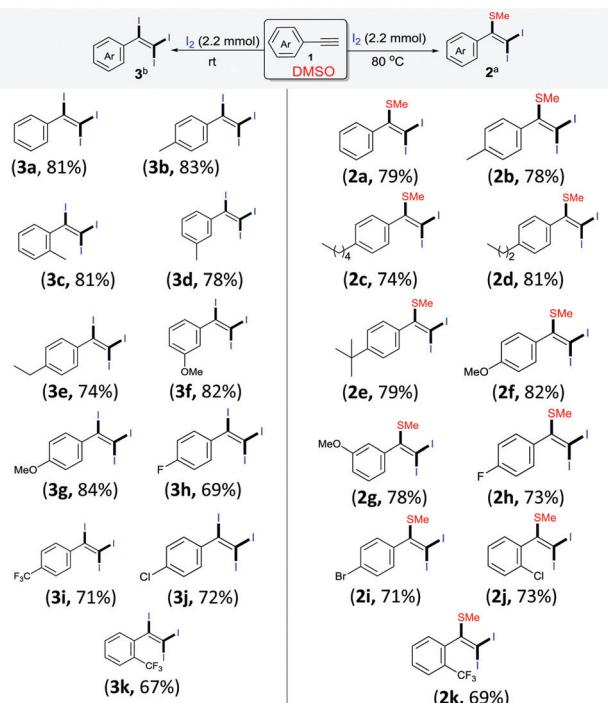
$\alpha$ -functionalized ketones and  $\alpha$ -ketomethylthioester as well. Thereby, we conducted different reactions in the presence of 2 N HCl (entries 9 and 10). Surprisingly, 2-chloro-1-phenylethan-1-one **4a** was isolated in 72% yield when **1a** (1 mmol) was stirred with  $I_2$  (2.2 mmol) and 2 N HCl in DMSO for 16 h at r.t. (entry 9). No further increase in yield was observed when the reaction was carried out with 2.5 mmol of  $I_2$  (entry 10). Later, a reaction was conducted with 1 mmol of NaCl and we noticed predominant conversion of **1a** to 2,2-dichloro-1-phenylethan-1-one **5a** (entry 11). In order to attain the maximum yield of **5a**, reaction of **1a** (1 mmol) with 2.2 mmol of  $I_2$  and 2 mmol of NaCl was conducted in DMSO at r.t. for 4 h and we successfully isolated **5a** in 78% yield (entry 12). Next, three different test reactions of **1a** (1 mmol) with  $I_2$  in DMSO were monitored in the presence of AcOH/TFA (1.0 mmol, entries 13–15). We succeeded in the isolation of *S*-methyl 2-oxo-2-phenylethanethioate **6a** in 69% yield when stirred with TFA (1.0 mmol) at 100 °C (entry 14).

Following these optimized procedures for the selective synthesis of each product, different sets of reactions were carried out to examine the substrate scope. In one set of experiments, different reactions were conducted between phenylacetylenes **1** with iodine in DMSO at 80 °C (Scheme 2, entries **2a**–**2k**). It was observed that both electron-rich and electron-deficient phenylacetylenes could be smoothly transformed into the desired products **2**. However, reactions with phenylacetylenes bearing electron-withdrawing groups, *i.e.*,  $-F$  (**2h**),  $-Cl$  (**2j**),  $-Br$  (**2i**) and  $-CF_3$  (**2k**), produced slightly lower yields than those of unsubstituted **2a** and those containing a donating group, **2b**–**2g**. Another set of experiments was performed at room temperature with different acetylenes (**3a**–**3k**) as per the optimized procedure for the preparation of different tri-iodinated products **3** (Scheme 2, **3a**–**3k**). As observed, the electronic environment of the phenyl ring in **1** affected the product yields to some

Table 1 Optimization of the reaction<sup>a</sup>

Entry	$I_2$ (mmol)	Reagent (mmol)	Temp. (°C)	Time (h)	Yield <sup>a</sup> (%)					
					<b>2a</b>	<b>3a</b>	<b>4a</b>	<b>5a</b>	<b>6a</b>	<b>7a</b>
1	1.2	HCl-NH <sub>2</sub> CH <sub>2</sub> COOCH <sub>3</sub>	80	2	12	19	23	1	7	22
2	1.2	—	80	2	67	16	—	—	—	11
3	1.5	—	80	2	71	11	—	—	—	12
4	2.0	—	80	2	78	8	—	—	—	Trace
5 <sup>a</sup>	2.2	—	80	2	79	7	—	—	—	Traces
6	2.2	—	60	2	56	19	—	—	—	Traces
7	2.2	—	40	2	27	59	—	—	—	Traces
8 <sup>b</sup>	2.2	—	r.t.	4	9	81	—	—	—	Trace
9 <sup>c</sup>	2.2	2 N HCl (0.5 mL)	r.t.	16	—	—	72	11	—	Trace
10	2.5	2 N HCl (0.5 mL)	r.t.	16	—	—	73	19	—	Trace
11	2.2	NaCl (1)	r.t.	2	—	—	11	37	—	34
12 <sup>d</sup>	2.2	NaCl (2)	r.t.	4	—	—	9	78	—	Trace
13	2.2	AcOH (1.0)	100	2	14	19	—	—	27	37
14 <sup>e</sup>	2.2	TFA (1.0)	100	4	Traces	—	—	—	69	11
15	1.0	TFA (1.0)	100	4	—	—	—	—	19	27

Reaction condition: <sup>a</sup> Phenylacetylene **1a** (1.0 mmol) and  $I_2$  (2.2 mmol) in 3 mL of DMSO at 80 °C for 2 h. <sup>b</sup> Phenylacetylene **1a** (1.0 mmol) and  $I_2$  (2.2 mmol) in 3 mL of DMSO at r.t. for 4 h. <sup>c</sup> Phenylacetylene **1a** (1.0 mmol),  $I_2$  (2.2 mmol), and 2 N HCl (0.5 mL) in 3 mL of DMSO at r.t. for 16 h. <sup>d</sup> Phenylacetylene **1a** (1.0 mmol),  $I_2$  (2.2 mmol), and NaCl (2.0 mmol) in 3 mL of DMSO at r.t. for 4 h. <sup>e</sup> Phenylacetylene **1a** (1.0 mmol),  $I_2$  (2.2 mmol), and TFA (1.0 mmol) in 3 mL of DMSO at 100 °C for 4 h.



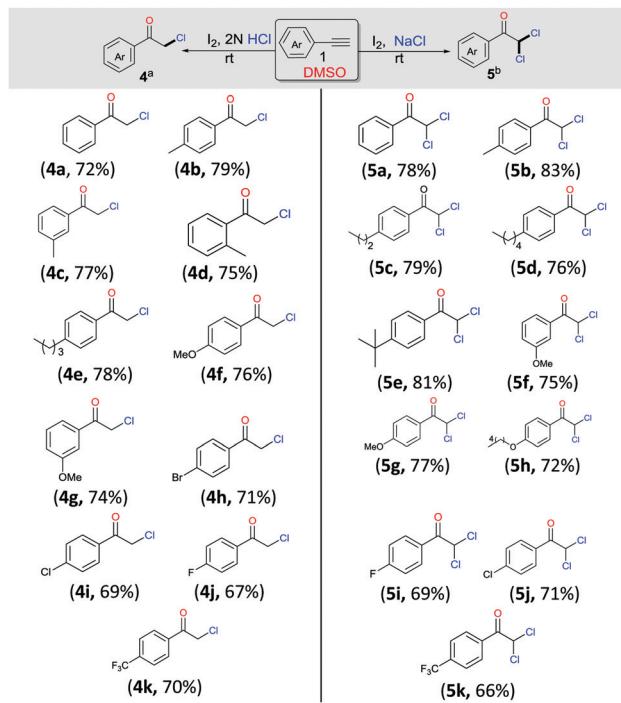
**Scheme 2** Scope of the reaction. Reaction conditions: <sup>a</sup>arylacetylene 1 (1.0 mmol) and I<sub>2</sub> (2.2 mmol) in 3 mL of DMSO at 80 °C for 2 h.  
<sup>b</sup>Arylacetylene 1 (1.0 mmol) and I<sub>2</sub> (2.2 mmol) in 3 mL of DMSO at r.t. for 4 h.

extent. It was observed that the phenylacetylenes bearing electron-withdrawing groups, for example,  $-F$  (3h),  $-Cl$  (3j) and  $-CF_3$  (4m–4o), afforded slightly lower yields in comparison to unsubstituted acetylenes 3a and those containing electron-donating groups (3b–3g).

Having observed that the reaction of phenylacetylene 1a (1 mmol) with 2 N HCl and NaCl (2 mmol), respectively, as per the optimized procedure (Table 1, entries 9 and 12) promoted the selective synthesis of mono- and di-chlorinated acetophenone, we then decided to examine the substrate scope of each process (Scheme 3, 4a–4k and 5a–5k). As compiled, a variety of arylacetylenes 1 with diverse steric and electronic properties were tested and we were gratified to find that in all reactions tested the desired products 4 and 5 were produced predominantly in good yields (66–83%). In general, we observed that both electron-rich and electron-deficient acetylenes could be smoothly transformed into the desired product. However, in these cases the yields were also slightly better for unsubstituted and electron-donating acetylenes.

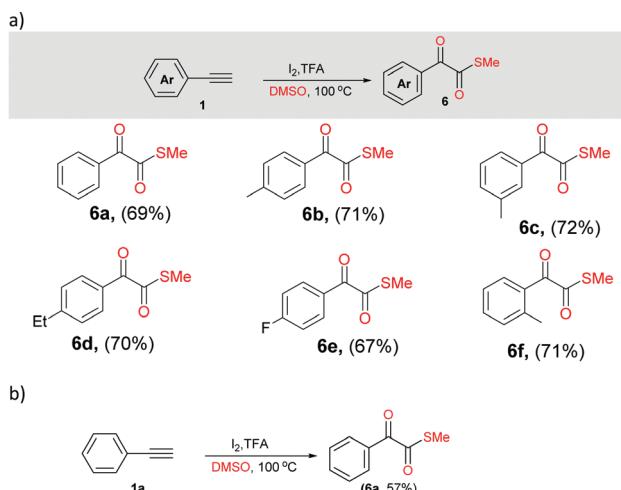
Next, we performed different sets of experiments for the synthesis of  $\alpha$ -ketomethylthioesters as per the optimized conditions. In all the reactions, we isolated the corresponding products 6 in good yields (64–72%) (Scheme 4a, 6a–6f). In addition, gram scale reaction with phenylacetylene was also performed that resulted in the isolation of 6a in 57% yield (Scheme 4b).

In order to probe the mechanism of these reactions, we performed a few controlled experiments using (iodoethynyl)benzene A as the starting material (Scheme 5a). In experiment 1, the reaction of A with I<sub>2</sub> as per the optimization in entry 5, Table 1 at 80 °C generated 2a in 83% yield. Similarly, the reaction of 1a at r.t. as per entry 8, Table 1 selectively generated 3a in 86% yield. On the basis of

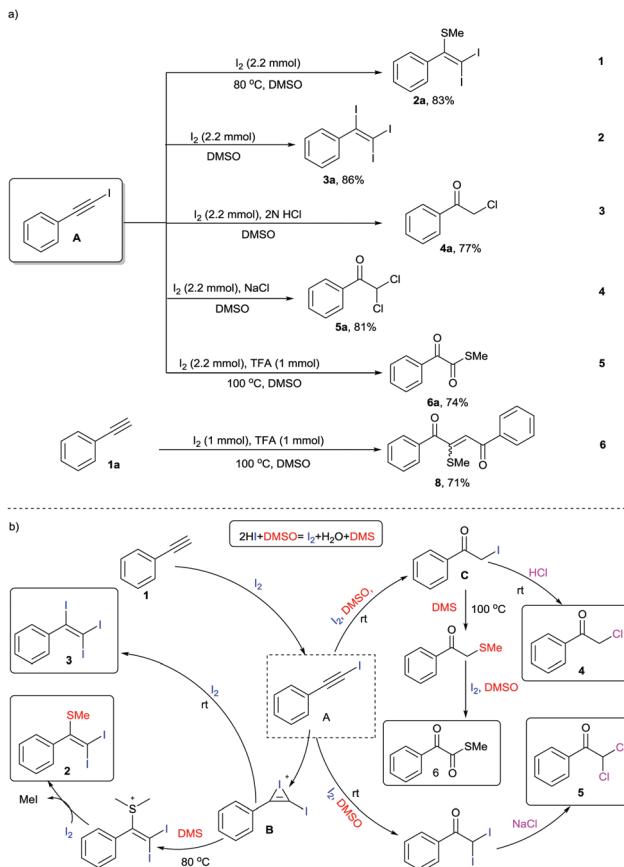


**Scheme 3** Scope of mono- and di-oxychlorination. Reaction conditions: <sup>a</sup>arylacetylene 1 (1.0 mmol), I<sub>2</sub> (2.2 mmol), and 2 N HCl (0.5 mL) in 3 mL of DMSO at r.t. for 16 h. <sup>b</sup>Arylacetylene 1 (1.0 mmol), I<sub>2</sub> (2.2 mmol), and NaCl (2.0 mmol) in 3 mL of DMSO at r.t. for 4 h.

these observations, we speculated that all the reactions are feasible through a common intermediate A. In addition, experiments 3, 4, and 5 also justified that these syntheses primarily involve iodination to A. Further, in experiment 6 reaction of phenylacetylene 1a with 1 mmol of iodine and 1 mmol of TFA at 100 °C as per Shah's procedure generated predominantly product 8.<sup>7a</sup> However, in our reactions, we used 2.2 mmol of iodine, which clearly indicates the



**Scheme 4** Studies related to 2-oxomethylthioesters. (a) Substrate scope. Reaction condition: arylacetylene 1 (1.0 mmol), I<sub>2</sub> (2.2 mmol), TFA (1.0 mmol) in 3 mL of DMSO at 100 °C for 4 h. (b) Gram scale synthesis of S-methyl-2-oxo-2-phenylethanethioate. Reaction condition: arylacetylene 1 (9.8 mmol), I<sub>2</sub> (21.6 mmol), TFA (9.8 mmol) in 30 mL of DMSO at 100 °C for 8 h.



role of excess iodine in the generation of DMS in higher concentration, which stops the phenylglyoxal pathway for generation of **8**.

Based on the preceding literature reports and the above-mentioned studies, we propose the mechanism of these reactions as depicted in Scheme 5b. The initial step for the synthesis of each product **2**, **3**, **4**, **5**, and **6** primarily involves the reaction of acetylene **1** and iodine to give intermediate **A**. This intermediate behaves differently under different conditions. In the additive-free pathway for the synthesis of alkenes **2** and **3**, intermediate **A** undergoes iodination to common iodonium intermediate **B**, which either undergoes conversion to **2** at 80 °C or adds one more mole of iodine to **3** at r.t. However, in the presence of acid/NaCl, intermediate **A** reacts to form mono-**C** and di-iodinated acetophenone **D**, which ultimately led to the synthesis of **4** and **5**, respectively. On the other hand, in the presence of TFA, intermediate **A** through **C** can undergo *S*-methylation followed by I<sub>2</sub>-DMSO-mediated oxidation to compound **6**.

In conclusion, we have revealed a set of different, efficient, atom-economic, economical, mild and novel synthetic methods based around arylacetylenes for the generation of different isolable selective products *via* unconventional I<sub>2</sub>-DMSO-promoted reaction in different environments. Despite the variation in the nature of acetylenes, the reactions presented a broad substrate scope. Further study to expand the scope in one pot for generation of different coupled products is currently underway in our lab.

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## Conflicts of interest

There are no conflicts to declare.

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