

Efficient C–C Double-Bond Formation Reaction via a New Synthetic Strategy: A Self-Sorting Tandem Reaction

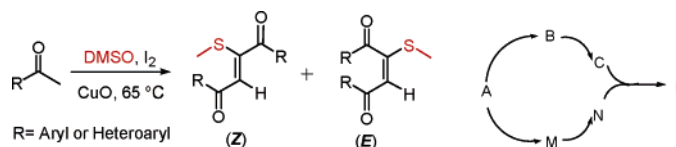
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ABSTRACT

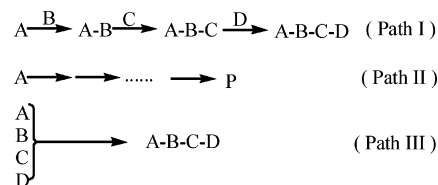


A novel and efficient carbon–carbon double-bond formation reaction via coupling of aryl or heteroaryl methyl ketones has been developed. A dimethyl sulfoxide–iodine–CuO system was proven to be efficient for this reaction and afforded the expected products in good yields. A new synthetic strategy, a self-sorting tandem reaction, was involved in this type of reaction and was presented for the first time.

Tandem reactions and multicomponent reactions (MCRs), in which multiple reactions are combined into one synthetic operation, have been used extensively to form carbon–carbon bonds in organic synthetic chemistry.^{1,2} Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedural step, thus omitting the need for several workup and purification operations and allowing savings of both solvents and reagents. Additionally, they frequently occur with enhanced regio-, diastereo-, and even enantioselectivity for the overall

transformation. All reactions proceed cooperatively or step by step in these strategies (Scheme 1, paths I, II, and III).

Scheme 1. General Tandem Reactions and Multicomponent Reaction Strategy



It has been known that self-sorting is a fundamental property of natural and biological systems. Most notably, self-sorting in synthetic supramolecular systems and polymers has developed rapidly over recent years,^{3,4} which encouraged us to utilize molecular self-sorting behavior in a covalent synthesis employing multiple independent reactions in one pot. In this paper, we present a new synthetic

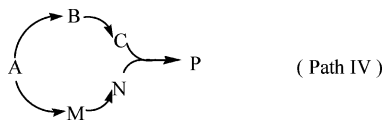
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(1) For recent reviews of tandem reactions, see: (a) Taylor, R. J. K.; Reid, M.; Foot, J.; Raw, S. A. *Acc. Chem. Res.* **2005**, *38*, 851. (b) de Meijere, A.; von Zezschwitz, P.; Bräse, S. *Acc. Chem. Res.* **2005**, *38*, 413. (c) Wasilke, J. C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (d) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551. (e) Ikeda, S. I. *Acc. Chem. Res.* **2000**, *33*, 511. (f) Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959. (g) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167. (h) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137. (i) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103. (j) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed.* **1993**, *32*, 131. (k) Tse-Lok, Ho. *Tandem Organic Reactions*; Wiley-VCH: Weinheim, 1993.

strategy, which is different from classical tandem reactions. As shown in Scheme 2, two parallel tandem reactions

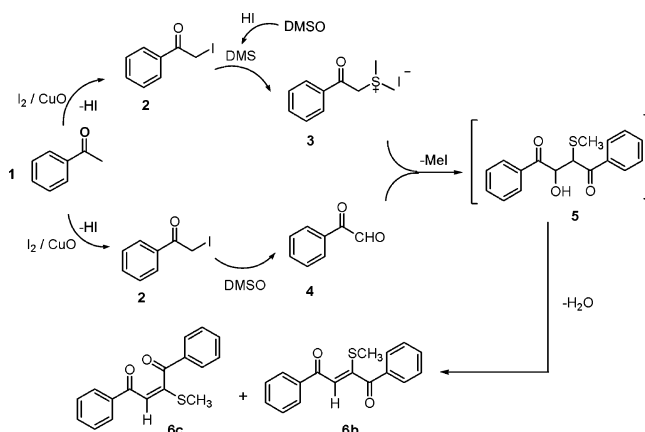
Scheme 2. Self-Sorting Tandem Reaction Strategy



proceed independently, starting from the same reactant **A** and yielding the corresponding intermediates **C** and **N**; then, **C** and **N** combine effectively together to provide the target molecule **P**. We refer to this type of reaction as a self-sorting tandem reaction.

Herein, we report a novel and efficient carbon–carbon double-bond-forming reaction starting from aryl or heteroaryl methyl ketones via the self-sorting tandem reaction strategy (Scheme 3). These olefinic products containing 1,4-dicar-

Scheme 3. Synthesis of Compounds **6b,c** via the Self-Sorting Tandem Reaction



bonyl groups are important precursors for the synthesis of some new pyrroles and furan derivatives by the Paal–Knorr reaction.⁵

According to the previous literature, the following reactions have been reported. First, phenacyl iodide **2**, obtained

by iodination of acetophenone **1** under acid conditions, can be sequentially oxidized by dimethyl sulfoxide to phenylglyoxal **4**.^{6,7} Second, **2** is reacted with dimethyl sulfide (DMS), which is readily reduced from dimethyl sulfoxide in high yield in the presence of HI formed in the first step⁸ to give dimethyl (phenacyl)-sulfonium iodide **3**.⁹ Furthermore, **3** could condense with **4** in an aldol-type reaction to produce intermediate 2-hydroxy-3-(methylthio)-1,4-diphenyl butane-1,4-dione **5** after loss of MeI, which is then dehydrated to yield **6b** and **6c**.¹⁰

On the basis of these analyses, we believe that it is possible to obtain isomers **6b,c** from **1** in a one-pot reaction. Surprisingly, as early as the 1970s, Furukawa reported that the unexpected olefinic products **6b,c** were obtained in poor yield when the dimethyl sulfoxide–iodine–sulfuric acid system was employed to oxidize **1**.¹⁰ Additionally, under acid conditions, the yield for direct oxidation of **1** to **4** by dimethyl sulfoxide was reported to be only 10%,¹¹ which could explain the poor yield of the above-mentioned reaction. Therefore, to obtain isomers **6b,c** from **1** in one pot, the generation of intermediate **2** is a key step. Moreover, iodine and dimethyl sulfoxide are indispensable. On the basis of our research results, we found that a CuO–iodine system could iodinate **1** to **2** in excellent yield¹² after screening various metal catalysts, such as Ag₂O, CuCl, CuCl₂, and CuBr. As a result, the experiments indicated that the dimethyl sulfoxide–CuO–iodine system (the optimal molar ratio of $n(\text{substrate})/n(\text{CuO})/n(\text{iodine})$ equals 1:3:2) was more efficient for this desired reaction.

Next, we also successfully obtained the target products **6b,c** using phenacyl iodide **2** as the reactant, which was powerful evidence in support of the above hypothesis (Scheme 3). In addition, to ensure the self-sorting tandem reaction could be carried out efficiently, the same or approximate reactive rates between the oxidation step from

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(12) When heating the mixture of acetophenone **1** (1 equiv), CuO (1 equiv), and iodine (1 equiv) in methanol at 65 °C for 1 h, compound **2** was obtained in 96% yield.

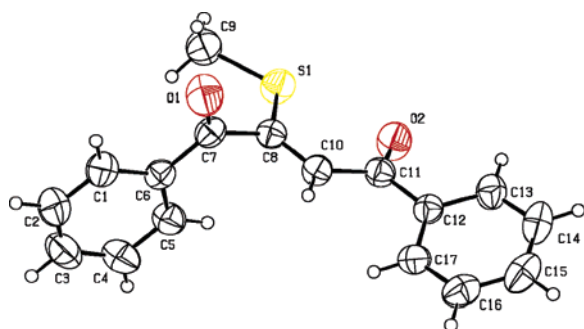


Figure 1. X-ray structure of compound **6b**.

2 to **4** and the formation of sulfonium salt **3** from **2** should be required. Further experimental results showed that these two steps might have approximate reactive rates when the reaction temperature was in the range of 60–65 °C, especially in the presence of CuO. However, if the temperature was elevated to 90 °C, the oxidation step from **2** to **4** might be the main fast reaction in the whole system, and the corresponding aromatic acid was the major product (see Supporting Information for details).

Following the above optimized conditions, a general experimental procedure is as follows: a mixture of acetophenone **1** (1 equiv), CuO (3 equiv), and iodine (2 equiv) in freshly distilled dimethyl sulfoxide was stirred at 65 °C for 18 h. The corresponding products **6b,c** were obtained in overall yields of 86% (*Z/E* = 6:1, Table 1, entry 1), which were determined by X-ray single diffraction analysis (Figures 1 and 2). A series of other aryl methyl ketones (entries 2–11)

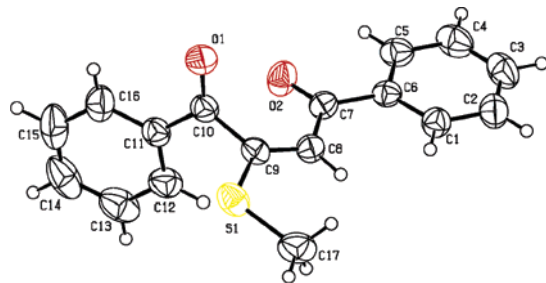
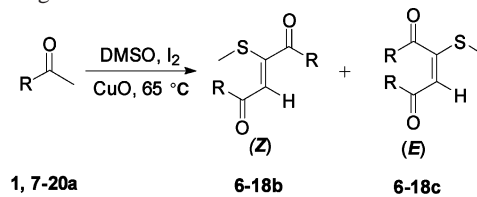


Figure 2. X-ray structure of compound **6c**.

were further investigated. Gratifyingly, all the reactions proceeded smoothly and afforded the expected products in good yields. *Z*-Isomers were the major products in all cases. In particular, when *p*-ethoxyacetophenone (**13a**) was used as a substrate (entry 8), the *Z*-isomer was the exclusive isolated product and only a trace amount of the *E*-isomer was detected by ¹H NMR analysis of the crude reaction mixture.¹³

Encouraged by the results obtained with aryl methyl ketones, we turned our attention to the heteroaryl methyl

Table 1. Formation of Carbon–Carbon Double Bonds via the Self-Sorting Tandem Reaction



entry	substrates	overall yield ^a	<i>Z/E</i> ^b
1	1a	86	6b/6c (6:1)
2	7a	85	7b/7c (7:3)
3	8a	92	8b/8c (5: 2)
4	9a	71	9b/9c (4:3)
5	10a	80	10b/10c (7:3)
6	11a	94	11b/11c (9:2)
7	12a	81	12b/12c (6:1)
8	13a	86	13b ^c
9	14a	89	14b/14c (3:2)
10	15a	88	15b/15c (5:3)
11	16a	89	16b/16c (5:3)
12	17a	81	17b ^c
13	18a	79	18b ^c
14	19a	— ^d	
15	20a	— ^d	

^a Isolated yields of pure products. ^b The ratios of *Z/E*-isomers were estimated from ¹H NMR analysis of crude product mixtures. ^c Trace amounts of the *E*-isomers were not isolated. ^d No olefinic products were observed (see Supporting Information for detailed explanations).

ketones and aryl dimethyl ketones. As shown in Table 1, 2-acetylfuran (**17a**) and 2-acetylthiophene (**18a**) also gave satisfying results (entries 12 and 13). However, no expected products were observed when the substrate was 4-acetylpyridine (**19a**). It was supposed that the HI formed in the first step combined with the nitrogen of 4-acetylpyridine to form

(13) The *Z*-stereoconfiguration of the product was assigned by comparing the chemical shifts of SCH₃ in ¹H NMR with other *Z/E*-isomers reported in this paper. There was an obvious difference in chemical shifts of SCH₃ between *Z*- and *E*-isomers (see Supporting Information).

an ammonium salt which prevented further reaction. As for the dicarbonyl substrate, 1,4-diacetylbenzene (**20a**) gave an unexpected mixture (see Supporting Information for a detailed explanation).

In conclusion, a new synthetic strategy, a self-sorting tandem reaction, for efficient formation of carbon–carbon double bonds from aryl or heteroaryl methyl ketones has been developed. Owing to the readily available starting materials, mild reaction conditions, and good yields, this method should expand the scope of the formation of carbon–carbon double bonds. To the best of our knowledge, this is the first example to utilize molecular self-sorting behavior in covalent synthesis. More significantly, this synthetic strategy will offer another possibility for the efficient construction of complex molecules from simple molecules in a single procedural step.

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Supporting Information Available: Detailed experimental procedures, characterization data for compounds **6–18**, and X-ray crystallography data for compounds **6b,c** and **7c**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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