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Formation of Unsymmetrical 1,4-Enediones via A Focusing Domino Strategy: Cross-Coupling of 1,3-Dicarbonyl Compounds and Methyl Ketones or Terminal Aryl Alkenes

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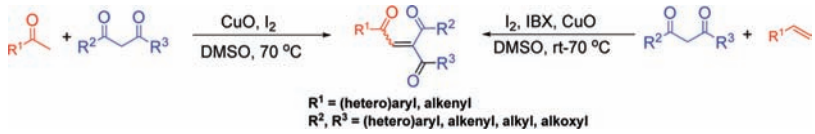
ABSTRACT



A highly efficient synthesis of unsymmetrical 1,4-enediones from 1,3-dicarbonyl compounds and methyl ketones or terminal aryl alkenes has been developed via a focusing domino strategy. Simple and readily available starting materials, mild reaction conditions, and a very simple operation are advantages of the reaction, which allow straightforward synthesis of a variety of unsymmetrical 1,4-enediones.

Domino reactions that perform multiple reactions simultaneously in a single reaction vessel offer possibilities for the efficient construction of complex molecules from readily available starting materials.[1]

Although several domino strategies have been developed (Scheme 1, paths I−IV),[2] the prevalence of diverse domino approaches in nature continues to stimulate organic chemists to develop novel domino strategies in synthetic chemistry. For example, nature utilizes a focusing domino approach that consists of two or more distinct pathways focusing on one final common pathway to afford the same product (Scheme 1, path V).[3] This should be the most efficient design during evolution, as the desired products could be obtained from diverse substrates via a common pathway.[3b] Inspired by the striking efficiency of this graceful strategy, we would like to develop a focusing domino reaction in synthetic chemistry, which would allow changes in substrates and help chemists for their flexibility in synthetic plans.

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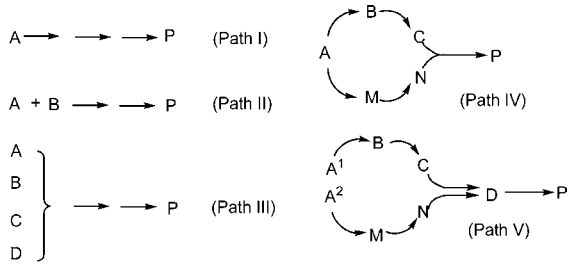
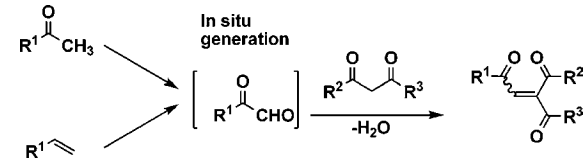
Scheme 1. Strategies of Domino Reaction[a]



[a] Intramolecular domino reaction (Path I); Intermolecular domino reaction (Path II); multicomponent domino reaction (Path III); self-sorting domino reaction (Path IV); focusing domino reaction (Path V).

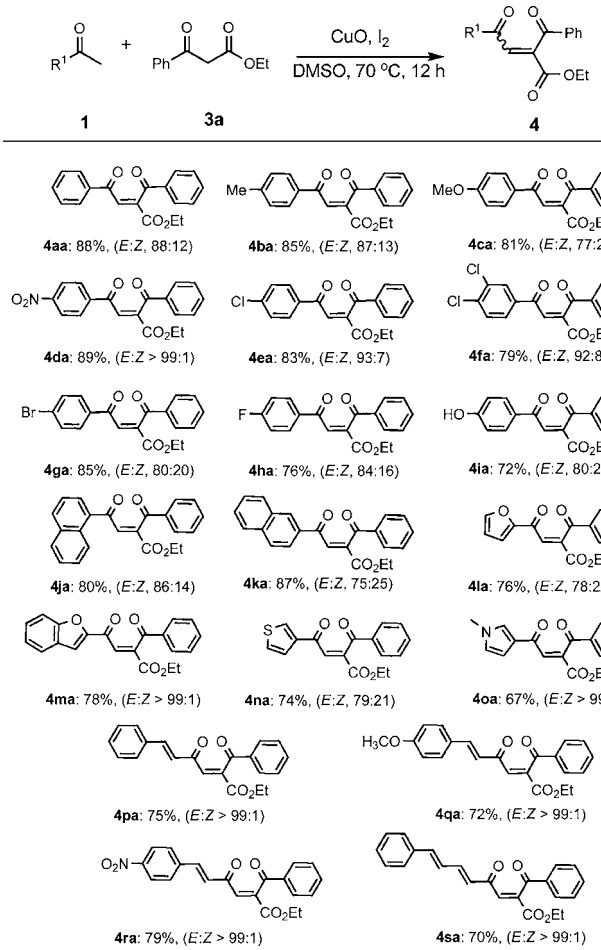
The 1,4-enedione framework is frequently found in bioactive natural products and medicinal compounds.[4] In addition, by virtue of their multifunctional composition, 1,4-enediones could serve as versatile precursors for heterocycle synthesis,[5] Diels−Alder cycloaddition,[6] Michael addition,[7] as well as many other useful transformations.[8] Although a variety of approaches have been developed for the synthesis of this skeleton,[9] a general and practical methodology is still needed for chemists to construct 1,4-enediones from simple and readily available starting materials. In our recent reports, we proposed a novel self-sorting domino strategy for the efficient construction of α-methylthio-substituted 1,4-enediones from readily available methyl ketones, wherein α-ketoaldehydes were generated in situ.[2g−i] However, the direct synthesis of unsymmetrical 1,4-enediones from two different methyl ketones has been proved extremely difficult.[2h] We wondered whether it would be possible for simple methyl ketones or terminal aryl alkenes to focus on the same α-ketoaldehyde intermediates, which further reacted with 1,3-dicarbonyl compounds to afford unsymmetrical 1,4-enediones via a common pathway (Scheme 2).

Scheme 2. Proposal: Preparation of Unsymmetrical 1,4-Enediones via the Focusing Domino Strategy



On the basis of our previous studies,[2g−i] we initially examined the feasibility of the strategy by reaction of acetophenone **1a** with ethyl benzoylacetate **3a**. When **1a** and **3a** were in the presence of copper(II) oxide and iodine in DMSO at 70 °C for 12 h, the desired 1,4-enedione **4aa** was obtained in 88% yield (Scheme 3). The efficient formation

Scheme 3. Scope of Methyl Ketones[a]



[a] The reaction was carried out with 1.0 equiv of **1**, 1.0 equiv of **3a**, 1.1 equiv of CuO and 1.1 equiv of I_2 in DMSO at 70 °C. Isolated yield. *E*:*Z* ratio determined by ^{1}H NMR.

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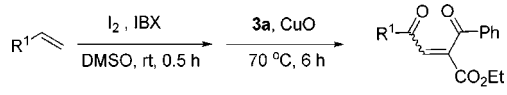
of cross-coupling product prompted us to study the reaction scope further. Pleasingly, all methyl ketones, regardless of their electronic or steric properties, proceed cleanly in good yields to afford the expected 1,4-enediones (67−89%; **4aa**−**4sa**). The conditions were mild enough to be compatible with haologenated and hydroxylated substrates (72−85%; **4ea**−**4ia**). Moreover, the desired 1,4-enediones could also be obtained in good yields from α,β-unsaturated methyl ketones (70−79%; **4pa**−**4sa**).[2i] In most cases, the reaction delivers a mixture of *E*/*Z* isomers, and the thermodynamically stable *E*-isomers were the major products. Although the two isomers could not be separated by column chromatography, pure (*E*)-**4** isomers were obtained by recrystallization from ethanol/petroleum ether. Furthermore, the configuration of (*E*)-**4na** was unambiguously determined by X-ray crystallographic analysis,[10] and other 1,4-enedione products were assigned by analogy on the basis of their similar ^{1}H NMR spectra.

Next, the substrates were extended to terminal aryl alkenes. On the basis of previous reports,[11] we found that a wide range of terminal aryl alkenes in the presence of I_2/IBX in DMSO could be easily transformed to α-iodoketones, which further reacted with ethyl benzoylacetate **3a** to afford the corresponding 1,4-enediones in one-pot. The steric and electronic nature of the alkenes had little influence on the reaction, and generally high yields were obtained (74−86%; Table 1).

Table 1. Scope of Terminal Aryl Alkenes[a,b]



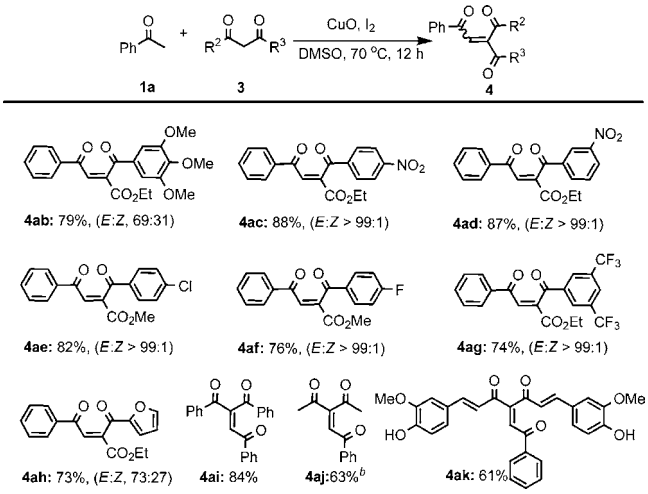
2 **4**

entry	**2** (R^1)	**4**	yield (%)[c]	*E*:*Z*[d]
1	**2a** (C_6H_5)	**4aa**	84	86:14
2	**2b** (4-MeC_6H_4)	**4ba**	83	88:12
3	**2c** (4-MeOC_6H_4)	**4ca**	80	75:25
4	**2d** (4-ClC_6H_4)	**4ea**	78	82:18
5	**2e** (4-BrC_6H_4)	**4ga**	79	87:13
6	**2f** (4-FC_6H_4)	**4ha**	74	80:20
7	**2g** (β-naphthyl)	**4ka**	86	77:23

[a] Reaction was carried out with 1.0 equiv of **2**, 1.1 equiv of I_2, 1.2 equiv of IBX, 1.0 equiv of **3a**, and 1.1 equiv of CuO. [b] IBX = 2-iodoxybenzoic acid. [c] Isolated yield. [d] *E*:*Z* ratio determined by ^{1}H NMR.

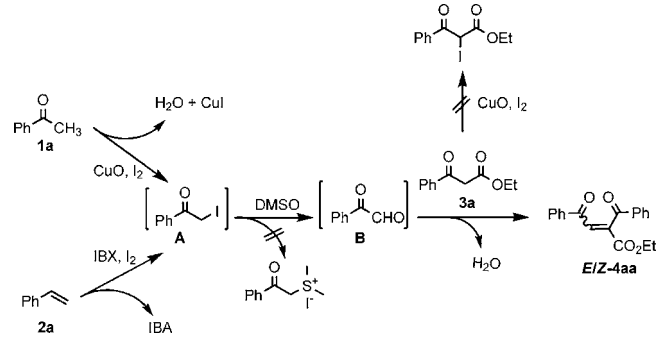
Using acetophenone, structural variations in the 1,3-dicarbonyl compounds were then examined (Scheme 4). The electronic nature of the phenyl ring of the 1,3-dicarbonyl compounds has little effect on the reaction efficiency (79−88%; **4ab**−**4ad**). Significantly, halo, heterocycle containing and sterically encumbered 1,3-diketones are readily tolerated in this transformation (73−84%; **4ae**−**4ai**). To our delight, aliphatic acetylacetone and multifunctionalized curcumin could also give their corresponding products in moderate yields (61−63%; **4aj**−**4ak**).

Scheme 4. Socpe of 1,3-Dicarbonyl Compounds[a]



[a] The reaction was carried out with 1.0 equiv of **1a**, 1.0 equiv of **3**, 1.1 equiv of CuO and 1.1 equiv of I_2 in DMSO at 70 °C. Isolated yield. *E*:*Z* ratio determined by ^{1}H NMR. [b]Reaction time of 3 h.

Scheme 5. Proposed Mechanism[a]



[a] IBA = iodosobenzoic acid.

As shown in Scheme 5, a possible reaction mechanism for this domino reaction is as follows using acetophenone **1a**, styrene **2a** and ethyl benzoylacetate **3a** as an example: Because **1a** was more reactive than **3a** toward iodination under this condition,[10] the phenacyl iodine **A** was preferentially generated either by iodination of **1a** or by consecutive iodination and oxidation of **2a**. Then it was oxidized to give phenylglyoxal **B** via Kornblum oxidation,[12] which further reacted with **3a** by Knoevenagel condensation to afford the desired product **4aa** after loss of water. We speculated that 1,3-dicarbonyl compounds would trap out small equilibrium quantities of α-ketoaldehydes generated in situ from α-io-

(10) See the Supporting Information.

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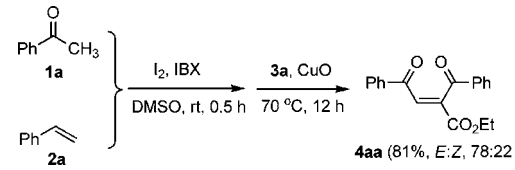
doketones, thus accelerating equilibrium toward the desired products and preventing the pathway toward dimethyl (acyl)-sulfonium iodide.[2g−i] To prove the intermediacy of phenacyl iodine **A** and phenylglyoxal **B** in the proposed mechanism, we used phenacyl iodine and phenylglyoxal hydrate as substrates to react with **3a** and the desired product **4aa** was obtained.[10]

With the success in obtaining 1,4-enediones from individual substrate, we considered the possibility of using diverse substrates in one-pot to focus on the same product. If successful, this would be an excellent example of the focusing domino reaction based on retrosynthetic design from the same intermediates, which further verified the proposed mechanism. Fortunately, these substrates were compatible under this condition and smoothly converted to the desired products. For example, a mixture of acetophenone **1a** and styrene **2a** were successfully converted to the same product **4aa** in 81% yield (Scheme 6). Meanwhile, substrates with different substituents were also successfully converted to their corresponding products.[10] These facts imply the focusing process of two parallel reactions in one-pot via self-sorting behavior.

In conclusion, we have developed a novel focusing domino reaction to prepare unsymmetrical 1,4-enediones from 1,3-dicarbonyl compounds and methyl ketones or terminal aryl alkenes. Owing to the simple and readily available starting materials, mild reaction conditions, and a very simple operation, this reaction should be of great utility in organic chemistry. Particularly noteworthy is the high efficiency of this focusing domino reaction, as diverse substrates could be used to prepare their corresponding products via a common pathway. Further studies on the applications of this strategy will be reported in due course.

Scheme 6. Focusing Domino Reaction of Methyl Ketone **1a** and Terminal Aryl Alkene **2a** in One-Pot[a]



[a] The reaction was carried out with 1.0 equiv of **1a**, 1.0 equiv of **2a,** 2.2 equiv of I_2, 1.2 equiv of IBX, 2.0 equiv of **3a**, 2.2 equiv of CuO. Isolated yield based on **3a**. *E*:*Z* ratio determined by ^{1}H NMR.

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Supporting Information Available: Experimental procedures and compound characterization data including X-ray crystal data for (*E*)-**4na**. This material is available free of charge via the Internet at http://pubs.acs.org.

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