



A concise and efficient way to synthesize polyenic diones directly from α,β -unsaturated methyl ketones

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ABSTRACT

A concise and efficient approach to polyenic compounds containing important diketone structural fragments is developed from readily available α,β -unsaturated methyl ketones in the presence of copper(II) oxide, iodine, and dimethyl sulfoxide. This is a new carbon–carbon double bond-forming reaction from two methyl sp^3 C–H bonds and an attractive route to introduce the SMe group into the molecule from inexpensive dimethyl sulfoxide. The hypothetical self-sorting tandem reaction mechanism is also proposed in this paper.

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1. Introduction

Polyenic compounds containing diketone structural fragments are important intermediates in the preparation of polyenes,¹ natural products,² (e.g., compounds **1** and **2**, Fig. 1), and interesting heterocyclic compounds.³ Although polyenic diones are useful intermediates to afford various products, an advance of its synthetic method has not been performed to date. In particular, previous methods can synthesize only a few derivatives. For instance, they are usually prepared by copper-promoted dimerization of ketone enolates⁴ or furan–diazoketone reaction.¹ Problems in these reactions are the use of expensive reagents under harsh conditions

and cumbersome workup procedures. Therefore, there is a strong driving force to design new and efficient strategies for synthesis of these compounds.

In our recent reports,⁵ we proposed a novel self-sorting tandem reaction pattern and established a simple, efficient method for the preparation of α -methylthio-substituted α,β -unsaturated 1,4-dicarbonyl compounds from readily available (hetero)aryl methyl ketones as substrates. These products are facile substrates for the synthesis of saturated 1,4-dicarbonyl compounds,⁶ substituted furans, pyrroles, and thiophenes.^{5b} Compared with the previously reported methods for synthesis of 1,4-enediones,⁷ this is a new carbon–carbon double bond-forming reaction between the sp^3 C–H bonds of two methyl groups and an attractive way to introduce the methylthio group into these molecules from inexpensive dimethyl sulfoxide.⁸ The self-sorting tandem reaction mechanism shows that the key step is the generation of α -iodinated ketone intermediate **3** from enol form **2**. Probably copper(II) oxide could promote the formation of highly reactive enol form from methyl ketone **1**,⁹ which is stabilized by the aromatic ring through conjugation effect (Scheme 1, $n=0$). According to the proposed mechanism,⁵ we envision that if there exists one or more carbon–carbon double bonds between the aromatic ring and the carbonyl group, due to the possible conjugation effect of the introduced carbon–carbon double bonds and the enol form of ketones, the reaction could give the polyenic diones via methyl-iodinated α,β -unsaturated ketone intermediate^{9c} (Scheme 1, $n=1, 2$). Herein, the detailed research results were discussed.

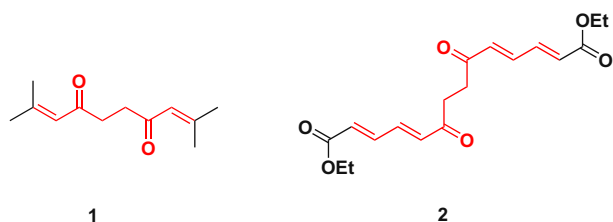
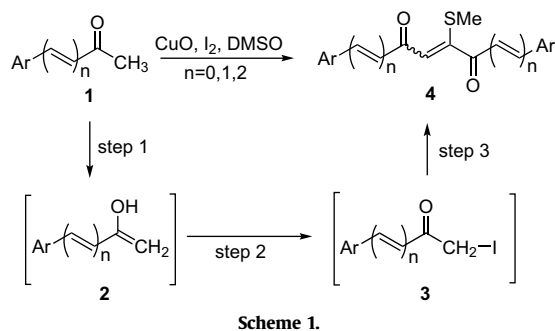


Figure 1.

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2. Results and discussion

To begin our study, benzalacetone (**1a**) was synthesized in 89% yield via the aldol condensation of benzaldehyde with acetone catalyzed by sodium hydroxide according to a modified procedure.¹⁰ Based on our previous studies,⁵ herein we only investigated the effect of reaction temperature and molar ratio of $n(\mathbf{1a})/n(I_2)/n(\text{CuO})$ on the yield of the coupling product **4a** in freshly distilled dimethyl sulfoxide for 20 h using benzalacetone as a model substrate. The experimental results were summarized in Table 1.

Table 1
Effect of reaction temperature and molar ratio of $n(\mathbf{1a})/n(\text{CuO})/n(I_2)$ on the yield of **4a**

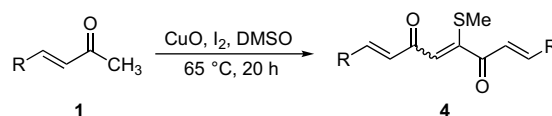


| Entry | $n(\mathbf{1a})/n(\text{CuO})/n(I_2)$ | Temp (°C) | Isolated yield |
|-------|---------------------------------------|-----------|----------------|
| 1 | 1:3:2 | 20 | 0 |
| 2 | 1:3:2 | 45 | 29 |
| 3 | 1:3:2 | 65 | 52 |
| 4 | 1:3:2 | 90 | 10 |
| 5 | 1:1:1 | 65 | 24 |
| 6 | 1:1:2 | 65 | 30 |
| 7 | 1:2:1 | 65 | 37 |
| 8 | 1:2:2 | 65 | 45 |

When the molar ratio of $n(\mathbf{1a})/n(\text{CuO})/n(I_2)$ was fixed at 1:3:2, the expected product **4a** was obtained in 52% yield (*Z/E* isomers) at 65 °C (entry 3). At the room temperature, no reaction was observed (entry 1). When the temperature was 45 °C or 90 °C, **4a** was obtained in 29% and 10% yields, respectively (entries 2 and 4).¹¹ Next we varied the molar ratio of $n(\mathbf{1a})/n(\text{CuO})/n(I_2)$ from 1:1:1 to 1:2:2, the reaction afforded **4a** in 24–45% yield (entries 5–8).

With the successful synthesis of polyenic diketone **4a**, a series of other α,β -unsaturated methyl ketones were prepared (see Supplementary data for details) to investigate the generality of this reaction under the above optimized conditions (Table 2). The substrates bearing electron-donating groups (e.g., -Me, -OMe, -OEt) on the phenyl rings afforded the products **4b–d** in 62–80% yields (entries 2–4). When the substrates bearing electron-withdrawing groups (e.g., -Cl, -Br, -NO₂), the corresponding products **4e–h** were obtained with a slightly lower yields in 49–68% (entries 5–8). In all cases, the products were a mixture of *Z/E* isomers, and the thermodynamically stable *Z*-isomers were the major products. All these target molecules were characterized by ¹H NMR, ¹³C NMR, HRMS, and IR spectra. The structure of compound (*E*)-**4e** was further determined by X-ray single diffraction analysis.¹² The bond distance of C10–C11 and the torsion angle of C(9)–C(10)–C(11)–C(12) are 1.33 Å and 2.2°, respectively, which supports the *E*-configuration of the olefin **4e** (Fig. 2).

Table 2
Formation of carbon–carbon double bonds via the coupling reaction of α,β -unsaturated methyl ketones^a



| Entry | Substrates (R=) | Products | Isolated yield (<i>Z/E</i>) |
|-------|----------------------------------------------------|----------|-------------------------------|
| 1 | C ₆ H ₅ | 4a | 52 (55:45) |
| 2 | 4-MeC ₆ H ₄ | 4b | 62 (55:45) |
| 3 | 4-MeOC ₆ H ₄ | 4c | 78 (62:38) |
| 4 | 4-EtOC ₆ H ₄ | 4d | 80 (62:38) |
| 5 | 4-ClC ₆ H ₄ | 4e | 68 (62:38) |
| 6 | 2,4-Cl ₂ C ₆ H ₃ | 4f | 58 (52:48) |
| 7 | 4-BrC ₆ H ₄ | 4g | 49 (57:43) |
| 8 | 3-NO ₂ C ₆ H ₄ | 4h | 52 (65:35) |
| 9 | 3-MeO-4-HOC ₆ H ₃ | 4i | — ^b |
| 10 | 3-MeO-4-AcOC ₆ H ₃ | 4j | 62 (88:12) |
| 11 | 2-Furyl | 4k | 57 (52:48) |
| 12 | (<i>E</i>)-C ₆ H ₅ -CH=CH- | 4l | 50 (60:40) ^c |

^a Standard conditions: $n(\text{substrate})/n(I_2)/n(\text{CuO})=1:2:3$, $T=65$ °C, 20 h.

^b Complicated mixture.

^c Pure *Z*-isomer was not obtained, the ratio of *Z/E* isomers was estimated from ¹H NMR analysis of the crude reaction mixture.

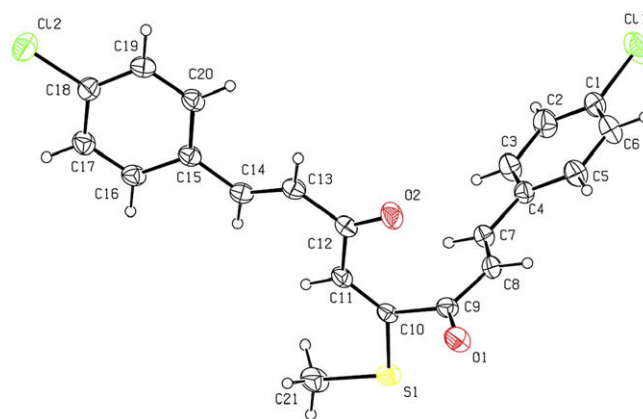
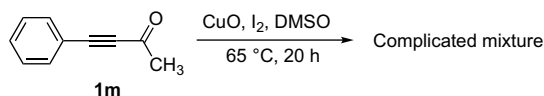


Figure 2. X-ray structures of compound (*E*)-**4e**.

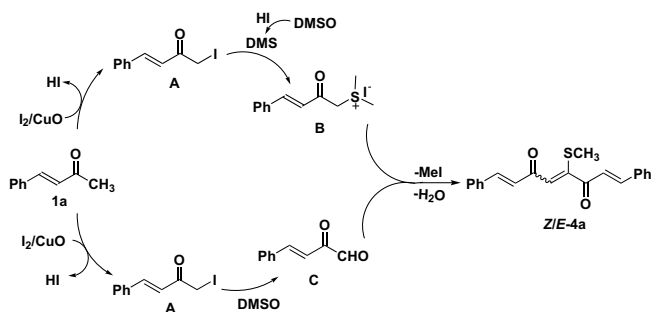
However, it was a pity that this reaction was not suitable for the substrate (**1i**) containing a sensitive hydroxyl group (-OH) probably due to the use of iodine and dimethyl sulfoxide as oxidants (entry 9). Much to our satisfaction, when the hydroxyl group was protected by acetyl group, substrate **1j** gave the product **4j** in 62% yield (entry 10). It should be noted that the coupling reaction did not occur between the methyl carbons of acetoxy owing to the difficulty in the formation of enol form (see Scheme 3 for the reaction mechanism). In addition, (*E*)-4-(furan-2-yl)but-3-en-2-one delivered the corresponding product **4k** in 57% yield. When using (3*E*,5*E*)-6-phenylhexa-3,5-dien-2-one as a substrate, we only separated the pure (*E*)-**4l** from the *Z/E* mixture.

In order to further expand the substrate scope, 4-phenylbut-3-en-2-one (**1m**)¹³ was employed for this reaction, which gave a complicated mixture, possibly because it was difficult for the enolization of this substrate under these conditions (Scheme 2).

As shown in Scheme 3, a possible reaction mechanism is as follows using benzalacetone (**1a**) as an example: First, (*E*)-1-iodo-4-phenylbut-3-en-2-one (**A**) obtained by the selective iodination of **1a** in the presence of copper(II) oxide is sequentially oxidized by dimethyl sulfoxide to give intermediate (*E*)-2-oxo-4-phenylbut-3-enal (**C**).⁵ While **A** is reacted with dimethyl sulfide (DMS), which is



Scheme 2.



Scheme 3. The proposed self-sorting tandem reaction mechanism.

readily produced from reduction of dimethyl sulfoxide by HI formed in the iodination step, to give (*E*)-dimethyl-(2-oxo-4-phenylbut-3-enyl)sulfonium iodide (**B**). Furthermore, **B** condenses with **C** in an aldol-type reaction to give target product *Z/E*-**4a** isomers after loss of MeI and water. It can be seen from Scheme 3 that the starting material benzalacetone displays a self-sorting property during the reaction process.

3. Conclusion

A concise and efficient approach to polyenic compounds containing important diketone structural fragments from α,β -unsaturated methyl ketones in the presence of copper(II) oxide, iodine, and DMSO has been developed. This is an efficient carbon-carbon double bond-forming reaction from two methyl sp^3 C-H bonds and an attractive route to introduce the methylthio group into these molecules from inexpensive dimethyl sulfoxide. The hypothetical reaction mechanism shows the starting material benzalacetone displays a self-sorting property during the reaction process. Further application of this methodology for the synthesis of various substituted heterocyclic compounds and polyenes is under way in our laboratory.

4. Experimental

4.1. General procedure for preparation of **4** (**4a** as an example)

A mixture of benzalacetone (0.73 g, 5 mmol), iodine (2.54 g, 10 mmol), and CuO (1.20 g, 15 mmol) in anhyd DMSO (30 mL) was heated at 65 °C for 20 h. The reaction mixture was poured into brine (150 mL) after filtration and the aqueous layer was extracted with CH_2Cl_2 (4 × 50 mL). The extract was washed with 10% $\text{Na}_2\text{S}_2\text{O}_3$ then a small amount 5% NaOH solution, dried over anhyd Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel using petroleum ether/EtOAc (*v/v*=8:1) as the eluent to give the expected products (*Z*)-**4a** and (*E*)-**4a** as yellow solids in 52% overall yield. Compound (*Z*)-**4a**: 0.24 g, yield 29%; ^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 7.68 (d, $J=16.0$ Hz, 1H), 7.65 (d, $J=16.0$ Hz, 1H), 7.61–7.38 (m, 10H), 6.88 (d, $J=16.0$ Hz, 1H), 6.86 (d, $J=16.0$ Hz, 1H), 6.65 (s, 1H), 2.28 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 191.6, 187.2, 159.2, 149.1, 142.8, 134.5, 133.6, 131.6, 130.3, 129.0, 128.8, 128.7, 128.2, 126.5, 125.1, 119.3, 15.5; IR (KBr, cm^{-1}): 1652, 1603, 1531, 1510, 1245, 1116, 975; MS (EI, 70 eV) m/z (%): 334 (60), 203 (46), 131 (100), 103 (81); HRMS (ESI):

m/z [$\text{M}+\text{Na}$] $^+$ calcd for $\text{C}_{21}\text{H}_{18}\text{NaO}_2\text{S}$: 357.0920; found: 357.0904. Compound (*E*)-**4a**: 0.20 g, yield 23%; ^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 7.62 (d, $J=16.0$ Hz, 1H), 7.56–7.36 (m, 11H), 6.89 (d, $J=16.0$ Hz, 1H), 6.83 (d, $J=16.0$ Hz, 1H), 6.42 (s, 1H), 2.46 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 193.6, 183.8, 160.0, 144.5, 143.7, 134.3, 134.0, 130.5, 130.4, 128.7, 128.6, 128.3, 128.2, 125.6, 125.1, 118.2, 14.8; IR (KBr, cm^{-1}): 1659, 1601, 1534, 1116; MS (EI, 70 eV) m/z (%): 334 (53), 257 (12), 203 (41), 131 (100), 103 (99), 91 (8), 77 (55); HRMS (ESI): m/z [$\text{M}+\text{Na}$] $^+$ calcd for $\text{C}_{21}\text{H}_{18}\text{NaO}_2\text{S}$: 357.0920; found: 357.0913.

Acknowledgements

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Supplementary data

The general experimental methods and the characterizing data for α,β -unsaturated methyl ketones, ^1H NMR, ^{13}C NMR, MS, and HRMS data for compound **4** and X-ray crystallography data for (*E*)-**4e** are available. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.05.050.

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- To ensure that the coupling reaction is carried out efficiently between intermediates **B** and **C**, the reaction rate from **A** to **C** should be close to that from **A** to **B**. However, if the temperature was elevated to 90 °C, the reaction rate for the oxidation step from **A** to **C** might be much faster than that from **A** to **B** in the whole system, and the corresponding aromatic acid would be the major product (see Scheme 3 and Supplementary data for *Org. Lett.* **2006**, *8*, 2245–2248).
- Crystal data for compound (*E*)-**4e**: $\text{C}_{21}\text{H}_{16}\text{Cl}_2\text{O}_2\text{S}$, $MW=425.01$, monoclinic, $a=14.9253(10)$, $b=13.5170(10)$, $c=9.9867(7)$ Å, $\alpha=90.00^\circ$, $\beta=104.2030(10)^\circ$, $\gamma=90.00^\circ$, $V=1953.2(2)$ Å 3 , $T=295(2)$ K, space group $Z=4$, $\mu(\text{Mo K}\alpha)=0.094$ mm $^{-1}$, 21,634 reflections measured, 4260 unique ($R_{\text{int}}=0.0908$), which were used in all calculations. The final wR_2 (F_2) was 0.1378. CCDC 725679 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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