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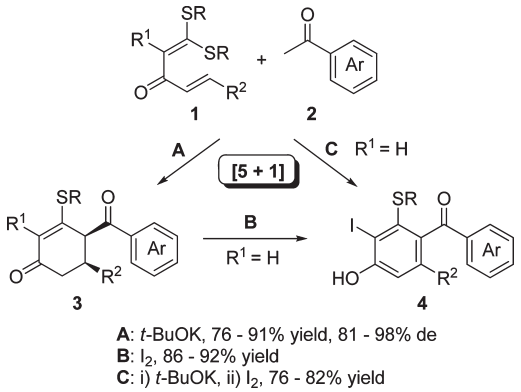
Direct Synthesis of Highly Substituted 2-Cyclohexenones and Sterically Hindered Benzophenones Based on a [5C + 1C] Annulation

Zhenqian Fu,[†] Mang Wang,*[,†,‡] Ying Dong,[†] Jun Liu,[†] and Qun Liu*[,†]

[†]*Department of Chemistry, Northeast Normal University, Changchun 130024, China, and* [‡]*State Key Laboratory of Fine Chemicals, Dalian University of Technology, Dalian 116012, China*

wangm452@nenu.edu.cn

Received June 23, 2009



The regiospecific [5C + 1C] annulation of readily available α-alkenoyl ketene (*S*,*S*)-acetals **1** with aryl methyl ketones **2**, the less active methylene compounds, has been developed. Upon treatment of **1** with **2** in the presence of *t*-BuOK in DMF at room temperature, highly substituted 2-cyclohexenones **3** were synthesized in high to excellent diastereoselectivities with high yields. On the basis of this strategy, sterically hindered benzophenones **4** were conveniently prepared via the iodonation−aromatization of 2-cyclohexenones **3** with I_2 in MeONa/MeOH basic medium. Furthermore, benzophenones **4** were also obtained directly from **1** and **2** following a sequential [5 + 1] annulation−iodonation−aromatization procedure in a one-pot operation.

Introduction

Over the past decades, the utility of α-functionalized ketene (*S*,*S*)-acetals as versatile intermediates in organic synthesis has been well-recognized.[1] During the course of our studies,[2−4] we found that α-alkenoyl ketene (*S*,*S*)-acetals **1** (Scheme 1), the cross-conjugated dienones with *gem*-dialkylthio substituents on the terminal carbon of a C=C double bond, showed promising structural features as novel synthetic intermediates because of their (i) five-carbon 1,5-bielectrophilic nature, (ii) dense substitution patterns, and (iii) flexible alkylthio functionality able to play multiple roles.[3,4] Thus, on the basis of the regiospecific [5C + 1C] annulation reactions (a sequence of inter- and intramolecular Michael additions) of α-alkenoyl ketene (*S*,*S*)-acetals and their equivalents with nitroalkanes,[5] substituted phenols

(1) For reviews on α-oxo ketene (*S*,*S*)-acetals, see: (a) Dieter, R. K. *Tetrahedron* **1986**, *42*, 3029. (b) Junjappa, H.; Ila, H.; Asokan, C. V. *Tetrahedron* **1990**, *46*, 5423. (c) Elgemeie, G. H.; Sayed, S. H. *Synthesis* **2001**, 1747.

(2) Selected examples for C−C bond-forming reactions at the α-position of functionalized ketene (*S*,*S*)-acetals: (a) Yuan, H.-J.; Wang, M.; Liu, Y.-J.; Liu, Q. *Adv. Synth. Catal.* **2009**, *351*, 112. (b) Ma, Y.; Wang, M.; Li, D.; Bekturhun, B.; Liu, J.; Liu, Q. *J. Org. Chem.* **2009**, *74*, 3116. (c) Fu, Z.; Wang, M.; Ma, Y.; Liu, Q.; Liu, J. *J. Org. Chem.* **2008**, *73*, 7625.

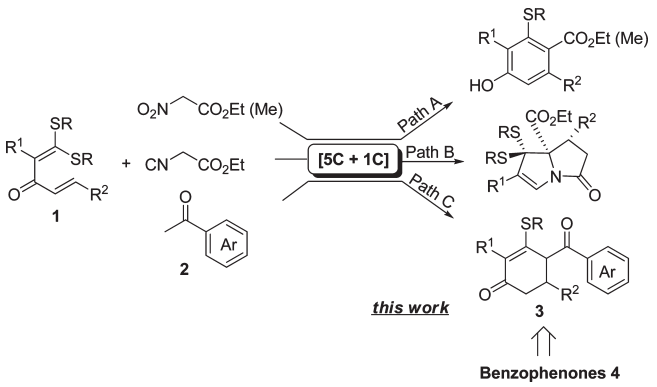
(3) Selected examples of intramolecular anti-Michael addition: (a) Bi, X.; Zhang, J.; Liu, Q.; Tan, J.; Li, B. *Adv. Synth. Catal.* **2007**, *349*, 2301. Domino reaction: (b) Liang, F.; Zhang, J.; Tan, J.; Liu, Q. *Adv. Synth. Catal.* **2006**, *348*, 1986. [5C + 1N] annulations: (c) Dong, D.; Bi, X.; Liu, Q.; Cong, F. *Chem. Commun.* **2005**, 3580. (d) Hu, J.; Zhang, Q.; Yuan, H.; Liu, Q. *J. Org. Chem.* **2008**, *73*, 2442. [5C + 1S] and [5C + 1Se] annulations: (e) Bi, X.; Dong, D.; Li, Y.; Liu, Q. *J. Org. Chem.* **2005**, *70*, 10886. (f) Li, D.; Xu, X.; Liu, Q.; Dong, S. *Synthesis* **2008**, 1895.

(4) Selected examples for [5C + 1C] annulations: (a) Bi, X.; Dong, D.; Liu, Q.; Pan, W.; Zhao, L.; Li, B. *J. Am. Chem. Soc.* **2005**, *127*, 4578. (b) Zhang, L.; Liang, F.; Cheng, X.; Liu, Q. *J. Org. Chem.* **2009**, *74*, 899. (c) Zhang, Q.; Sun, S.; Hu, J.; Liu, Q.; Tan, J. *J. Org. Chem.* **2007**, *72*, 139.

(5) For a review of applications of nitroalkanes in the synthesis of benzene derivatives, see: Ballini, R.; Palmieri, A.; Barboni, L. *Chem. Commun.* **2008**, 2975.

DOI: 10.1021/jo9013386 Published on Web 07/27/2009

SCHEME 1. [5C + 1C] Annulation Strategies Based on α-Alkenoyl Ketene (*S*,*S*)-Acetals 1

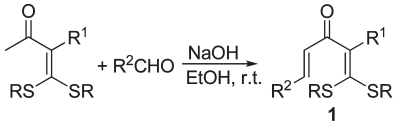


(Scheme 1, Path A),[4a] *p*-terphenyls,[4b] and biaryls[4b] were constructed in a single step. Very recently, we also described the synthesis of pyrrolizidine derivatives through the [5C + 1C] annulation of α-alkenoyl ketene (*S*,*S*)-acetals with ethyl isocyanoacetate (Scheme 1, Path B).[6] As part of a continuing study of the [5 + 1] annulation strategy with the aim to exploit suitable carbon nucleophiles,[4–6] the reactions of easily available α-alkenoyl ketene (*S*,*S*)-acetals **1** with aryl methyl ketones **2**,[7] the less active methylene compounds, as one-carbon component were examined. As a result, highly substituted 2-cyclohexenones **3** were synthesized via the [5C + 1C] annulation reactions of **1** with **2** (Scheme 1, Path C). To our knowledge, this represents the first example of the use of a methyl ketone as one-carbon nucleophile in the sequential inter- and intramolecular Michael additions[4,6–9] and provides a facile and direct method for the synthesis of sterically hindered benzophenones **4**. In this paper, we are pleased to report these experimental results.

Results and Discussion

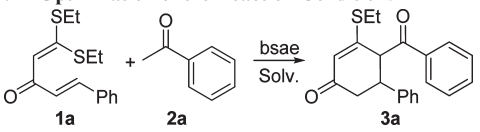
Preparation of α-Alkenoyl Ketene (*S*,*S*)-Acetals 1. According to the procedures described in our previous reports, the selected substrates, α-alkenoyl ketene (*S*,*S*)-acetals **1a**–**j**, were prepared in high to excellent yields by the condensation reaction of the corresponding α-acetyl ketene (*S*,*S*)-acetals with various aldehydes, including aromatic and aliphatic aldehydes, under basic conditions (Scheme 2).[2b,3,4a,6]

SCHEME 2. Preparation of α-Alkenoyl Ketene (*S*,*S*)-Acetals 1



1a: R^1 = H, R^2 = C_6H_5, R,R = Et, 95%
1b: R^1 = H, R^2 = 4-ClC_6H_4, R,R = Et, 93%
1c: R^1 = H, R^2 = 4-MeC_6H_4, R,R = Et, 88%
1d: R^1 = H, R^2 =3, 4-$CH_2O_2C_6H_3$, R,R = Et, 90%
1e: R^1 = H, R^2 = 4-MeOC_6H_4, R,R = Et, 87%
1f: R^1 = H, R^2 = 2-furyl, R,R = Et, 94%
1g: R^1 = H, R^2 = 2-thienyl, R,R = Et, 95%
1h: R^1 = H, R^2 = Cy, R,R = Et, 69%
1i: R^1 = C_6H_5CO, R^2 = C_6H_5, R,R = Et, 90%
1j: R^1 = H, R^2 = C_6H_5, R,R = Me, 95%

TABLE 1. Optimization of the Reaction Conditions[a]



entry	base (equiv)	solvent	time (h)	yield (%)[b]
1	*t*-BuOK (1.0)	DMF	2.0	44[c]
2	*t*-BuOK (2.0)	DMF	1.0	90
3	*t*-BuOK (3.0)	DMF	1.0	87
4	*t*-BuOK (2.0)	THF	1.0	86
5	*t*-BuOK (2.0)	MeCN	1.0	85
6	*t*-BuOK (2.0)	*t*-BuOH	1.0	67
7	NaOH (2.0)	DMF	1.0	49
8	NaH (2.0)	DMF	1.0	82
9	DBU (2.0)	DMF	10	nr[d]

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.1 mmol), solvent (10 mL), rt. [b]Isolated yield. [c]43% of **1a** was recovered. [d]No reaction.

Synthesis of 2-Cyclohexenones 3 Based on [5 + 1] Annulations of α-Alkenoyl Ketene (*S*,*S*)-Acetals 1 with Methyl Ketones 2. 2-Cyclohexenones are useful building blocks in organic synthesis,[10] and the procedures for their synthesis from simple acyclic precursors in a single operation have attracted increasing attention in recent years.[11–14] In this

(6) Tan, J.; Xu, X.; Zhang, L.; Li, Y.; Liu, Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 2868.

(7) For selective reports on the Michael reactions of α-oxo ketene (*S*,*S*)-acetals with acetophenones, see: (a) Potts, K. T.; Cipullo, M. J.; Ralli, P.; Theodoridis, G. *J. Am. Chem. Soc.* **1981**, *103*, 3584. (b) Potts, K. T.; Cipullo, M. J.; Ralli, P.; Theodoridis, G. *J. Am. Chem. Soc.* **1981**, *103*, 3585. (c) Tinggaard, M.; Hansen, P.; Mogensen, P. K.; Simonsen, O.; Becher, J. *J. Heterocycl. Chem.* **1989**, *26*, 439. (d) Kumar, S.; Ila, H.; Junjappa, H. *Tetrahedron* **2007**, *63*, 10067.

(8) For reports on inter- and intramolecular Michael addition of an 1,5-electrophilic double Michael acceptor and certain nucleophilic addend, see: (a) Bergmann, E. D.; Ginsburg, D.; Pappo, R. *Org. React.* **1959**, *10*, 179. (b) Britten-Kelly, M.; Willis, B. J. *Synthesis* **1980**, 27. (c) Gómez-Bengoa, E.; Cuerva, J. M.; Mateo, C.; Echavarren, A. M. *J. Am. Chem. Soc.* **1996**, *118*, 8553. (d) Rule, N. G.; Detty, M. R.; Kaeding, J. E.; Sinicropi, J. A. *J. Org. Chem.* **1995**, *60*, 1665. (e) Chande, M. S.; Khanwelkar, R. R. *Tetrahedron Lett.* **2005**, *46*, 7787. (f) Rosiak, A.; Frey, W.; Christoffers, J. *Eur. J. Org. Chem.* **2006**, 4044. (g) Krishna, P. R.; Sreeshailam, A. *Tetrahedron Lett.* **2007**, *48*, 6924. (h) Rosiak, A.; Hoenke, C.; Christoffers, J. *Eur. J. Org. Chem.* **2007**, 4376.

(9) For reports on intermolecular double Michael additions of methyl ketones to electron-deficient alkenes, see: (a) Basu, B.; Das, P.; Hossain, I. *Synlett* **2004**, 2224. (b) DeGraffenreid, M. R.; Bennett, S.; Caille, S.; Turiso, F. G.-L.; Hungate, R. W.; Julian, L. D.; Kaizeman, J. A.; McMinn, D. L.; Rew, Y.; Sun, D.; Yan, X.; Powers, J. P. *J. Org. Chem.* **2007**, *72*, 7455. (c) Ishikawa, T.; Kudo, K.; Kuroyabu, K.; Uchida, S.; Kudoh, T.; Saito, S. *J. Org. Chem.* **2008**, *73*, 7498.

(10) For selected recent reports of the synthetic applications of substituted 2-cyclohexenones, see: (a) Herzon, S. B.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 5342. (b) Yang, J.; Dewal, M. B.; Shimizu, L. S. *J. Am. Chem. Soc.* **2006**, *128*, 8122. (c) Paczkowski, R.; Maichle-Mo1ssmer, C.; Maier, M. E. *Org. Lett.* **2006**, *8*, 151. (d) Linghu, X.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 7671.

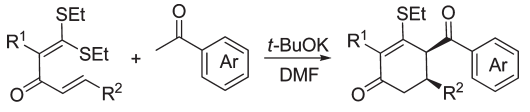
(11) For recent examples of the synthesis of substituted 2-cyclohexenones from acyclic precursors, see: (a) Pei, T.; Wang, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 648. (b) Lee, S. I.; Park, J. H.; Chung, Y. K.; Lee, S. *J. Am. Chem. Soc.* **2004**, *126*, 2714. (c) Seiser, T.; Cramer, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 9294. (d) Zhang, C.; Cui, D.; Yao, L.; Wang, B.; Hu, Y.; Hayashi, T. *J. Org. Chem.* **2008**, *73*, 7811. (e) Sudo, Y.; Shirasaki, D.; Harada, S.; Nishida, A. *J. Am. Chem. Soc.* **2008**, *130*, 12588. (f) Murakami, M.; Ashida, S.; Matsuda, T. *J. Am. Chem. Soc.* **2005**, *127*, 6932.

(12) (a) Magomedov, N. A.; Ruggiero, P. L.; Tang, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1624. (b) Lu, Z.; Chai, G.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 6045. (c) Carlone, A.; Marigo, M.; North, C.; Landa, A.; Jorgensen, K. A. *Chem. Commun.* **2006**, 4928.

(13) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 10204.

(14) (a) Hayashi, Y.; Toyoshima, M.; Gotoh, H.; Ishikawa, H. *Org. Lett.* **2009**, *11*, 45. (b) Inokuchi, T.; Okano, M.; Miyamoto, T.; Madon, H. B.; Takagi, M. *Synlett* **2000**, 1549.

TABLE 2. Synthesis of Highly Substituted 2-Cyclohexenones 3[a]

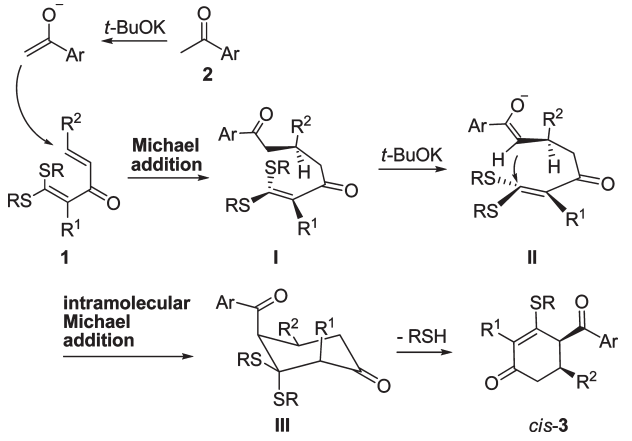


1 2 3

entry	1	R^1	R^2	2	Ar	time (h)	3	yield of 3 (%)[b]	de of 3 (%)[c]
1	**1a**	H	Ph	**2a**	Ph	1.0	**3a**	90	>98
2	**1b**	H	4-ClC_6H_4	**2a**	Ph	1.0	**3b**	90	>98
3	**1c**	H	4-MeC_6H_4	**2a**	Ph	1.0	**3c**	88	>98
4	**1d**	H	3,4-$CH_2O_2C_6H_3$	**2a**	Ph	1.0	**3d**	87	>98
5	**1e**	H	4-$MeOC_6H_4$	**2a**	Ph	1.0	**3e**	89	>98
6	**1f**	H	2-furyl	**2a**	Ph	1.0	**3f**	85	84
7	**1g**	H	2-thienyl	**2a**	Ph	1.0	**3g**	87	82
8	**1h**	H	Cy	**2a**	Ph	1.0	**3h**	84	>98
9	**1i**	PhCO	Ph	**2a**	Ph	20	**3i**	76	>98
10	**1a**	H	Ph	**2b**	4-ClC_6H_4	1.0	**3j**	89	>98
11	**1a**	H	Ph	**2c**	4-MeC_6H_4	1.0	**3k**	88	>98
12	**1a**	H	Ph	**2d**	2-$MeCONHC_6H_4$	1.0	***3l***	84	81
13	**1a**	H	Ph	**2e**	2-furyl	1.0	**3m**	89	>98
14[d]	**1j**	H	Ph	**2a**	Ph	1.0	**3n**	91	>98

[a]Reaction conditions: **1** (1.0 mmol), **2** (1.1 mmol), *t*-BuOK (2.0 mmoL), DMF (10 mL), rt. [b]Isolated yield. [c]Diastereomeric excesses determined by ^1H NMR. [d]The substrate with SMe.

SCHEME 3. Possible Mechanism for the [5 + 1] Annulations of 1 with 2



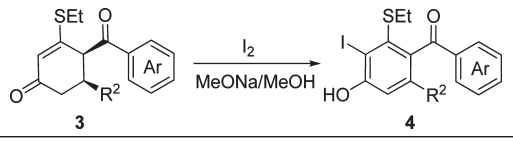
context, cycloaddition reactions, including [3 + 2 + 1],[11b] [3 + 3],[12c,14a] and [4 + 2],[14b] provide direct routes toward 2-cyclohexenones. In the present study, the [5 + 1] cycloaddition of (*E*)-1,1-bis(ethylthio)-5-phenylpenta-1,4-dien-3-one **1a** with acetophenone **2a** was initially selected as a model reaction for the preparation of 2-cyclohexenones. Fortunately, as shown in Table 1, entry 1, 4-benzoyl-3-(ethylthio)-5-phenylcyclohex-2-enone **3a** could be obtained in 44% yield upon treatment of **1a** (1.0 mmol) with **2a** (1.1 mmol) in DMF (10 mL) in the presence of *t*-BuOK (1.0 equiv) under ambient conditions for 2.0 h. It was found that the yield of **3a** was significantly improved to 90% when 2.0 equiv of *t*-BuOK was used (Table 1, entry 2).[15] The reaction media and the base were then examined. Clearly, all of the reactions could proceed to afford **3a** in the tested basic systems, such as *t*-BuOK/THF, *t*-BuOK/MeCN, *t*-BuOK/*t*-BuOH, NaOH/DMF, and NaH/DMF, except that no reaction was detected in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DMF (Table 1, entry 9). By comparison, *t*-BuOK/DMF was a more efficient basic media and was selected for the following investigations.

Encouraged by the above results, the scope and limitations of the reactions between α-alkenoyl ketene (*S*,*S*)-acetals **1** and acetophenones **2** were investigated, and the results are described in Table 2. It is evident that **1** bearing either an aromatic substituent (electro-neutral, electron-rich, or electron-deficient, Table 2, entries 1−7) or an aliphatic substituent (Table 2, entry 8) at the *β*-position of the α-alkenoyl moiety of **1** can efficiently react with acetophenone **2a** to give the desired 2-cyclohexenones **3a**−**h** in high yields with high stereoselectivities in short reaction time. In the case of **1i** (having an α-PhCO group) as substrate, the reaction afforded cyclohexenone **3i** in 76% yield with longer reaction time (Table 2, entry 9). The tolerance of methyl ketones **2** was then examined. It was proved that all the selected aryl methyl ketones **2b**−**e** were efficient nucleophiles and led to the desired 2-cyclohexenones **3j**−**m** in 84−89% yields, respectively (Table 2, entries 10−13). In addition, **1j** (with SMe group) also allowed the formation of **3n** in 91% isolated yield (Table 2, entry 14).

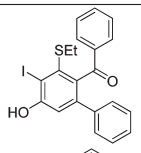
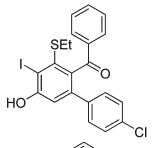
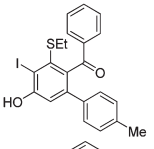
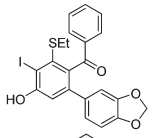
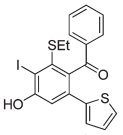
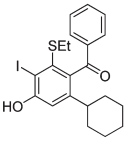
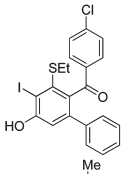
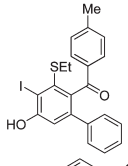
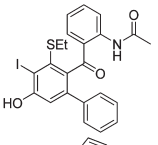
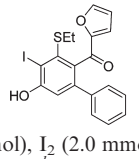
As we know, [5 + 1] annulation reaction of an 1,5-electrophilic double Michael acceptor and certain nucleophilic addend via a sequential inter- and intramolecular Michael addition provides a useful method for the construction of six-membered ring compounds.[8] In this context, as one-carbon components, activated methylene compounds, such as ethyl 2-cyanoacetate, 2-tosylacetonitrile, *β*-ketoesters, dialkyl malonate, Meldrum's acid, or nitroalkanes, are well used for efficiency of the annulation. While Basu et al. reported in 2004 the first example of the intermolecular double Michael additions of aryl methyl ketones, the less active methylene compounds, to electron-deficient alkenes mediated by KF−alumina,[9a] the study on efficient formation of the [5 + 1] cycloadducts by the inter- and intramolecular Michael addition of methyl ketones as one-carbon

(15) For experimental details, see Supporting Information.

TABLE 3. Synthesis of Benzophenones 4 from Cyclohexenones 3[a]



3 4

entry	substrates 3	benzophenones 4	yield (%)[b]
1	**3a**	**4a** 	91
2	**3b**	**4b** 	89
3	**3c**	**4c** 	88
4	**3d**	**4d** 	90
5	**3g**	**4e** 	87
6	**3h**	**4f** 	92
7	**3j**	**4g** 	89
8	**3k**	**4h** 	91
9	**3*l***	**4i** 	86
10	**3m**	**4j** 	88

[a]Reaction conditions: **3** (1.0 mmol), I_2 (2.0 mmol), MeONa/MeOH (10 mL, M = 0.6 mol/L), −78 °C to rt. [b]Isolated yield.

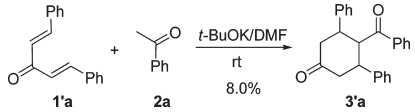
nucleophile with a double Michael acceptor is rare. Obviously, the above [5 + 1] annulations of α-alkenoyl ketene (*S*,*S*)-acetals **1** and acetophenones **2** proceeded smoothly with a broad range of substituents for both components and thus allow for the efficient and divergent synthesis of substituted 2-cyclohexenones in a regiospecific manner under mild reaction conditions.[16] Notably, the reaction proceeded with high to excellent diastereoselectivity based on the ^{1}H NMR spectral analysis of cyclohexenones **3** (de, 81−98%, Table 2). All products **3** were well-characterized by their spectra and analytical data, and the configuration of products **3** was further confirmed as *cis*-isomers by the X-ray diffraction studies of **3i**.[17]

Proposed Mechanism for the [5 + 1] Annulation of 1 with 2. On the basis of all of the obtained results along with our previous work,[3c−f,4,6] a plausible mechanism for the annulation of **1** with **2** is presented in Scheme 3. The reaction begins with the Michael addition of the enol anion of aryl methyl ketone **2**, formed in the presence of *t*-BuOK, to the α-alkenoyl moiety of **1** leading to intermediate **I**.[4a] Then the intramolecular Michael addition of the enol anion **II** to the dithiolacetal moiety in the manner with R^2 away from the SR group to avoid the steric hindrance and subsequent elimination of a thiol leads to the formation of cyclohexenones **3** with *cis* configuration.

Synthesis of Benzophenones 4. Polysubstituted benzophenones are encountered in numerous natural products as well as in organic materials.[18] Therefore, the facile synthesis of sterically hindered benzophenones is highly desired. In the present work, the convenient preparation of 3,5-disubstituted 4-aroyl 2-cyclohexenones **3** may serve as an easy pathway to sterically hindered benzophenones. With the aim to explore the synthetic potential of **3** to benzophenone frameworks, the selected cyclohexenones **3** were thus treated with iodine/sodium methoxide in methanol following the procedures described by Hegde et al.[19] Table 3 summarizes the transformation of 2-cyclohexenones **3** into benzophenones **4**. As shown in Table 3, all substrates **3** were suitable precursors for this tandem double iodination−dehydroiodination−isomerization process[15] and led to benzophenones **4a**−**j** in high yields. Interestingly, benzophenone **4i** with three ortho-substituents was also constructed in 86% yield (Table 3, entry 9).

Furthermore, a one-pot procedure for the direct synthesis of benzophenones **4** starting from **1** and **2** was developed as well. For example, the selected benzophenones **4a**−**d** and **4j** could be obtained in 76−82% isolated yields, respectively, by treatment of an acetonitrile solution of the corresponding **1**

(16) As a comparison, divinyl ketone **1′a** without dithioacetal functionality was prepared toward the [5 + 1] annulation conditions (Table 1, entry 2). It was found that the reaction usually resulted in an unidentified complex mixture. One of the isomers of **3′a** was obtained only in 8.0% isolated yield by careful flash silica gel chromatography and further recrystallization from a mixture of petroleum ether and ethyl ether (3/1, v/v).



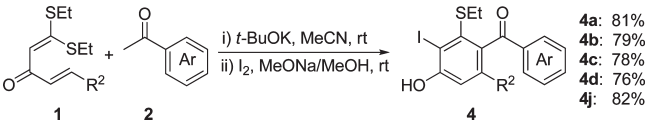
1′a 2a 3′a

(17) Crystal data for **3i**: $C_{28}H_{24}O_3S$, M = 440.53, monoclinic, $P21/n$, a = 13.159(2), b = 14.135(2), c = 13.883(3) Å, V = 2306.3(7) Å^3, α = 90.00, β = 116.723(3), γ = 90.00, Z = 4, T = 293(2) K, $F000$ = 928, R_1 = 0.0618, wR_2 = 0.1112.

(18) For recent examples on the synthesis of benzophenones, see: (a) Srivastava, A. K.; Panda, G. *Chem.—Eur. J.* **2008**, *14*, 4675. (b) Terzidis, M. A.; Tsoleridis, C. A.; Stephanidou-Stephanatou, J.; Terzis, A.; Raptopoulou, C. P.; Psycharis, V. *Tetrahedron* **2008**, *64*, 11611. (c) Chuzel, O.; Roesch, A.; Genet, J.-P.; Darses, S. *J. Org. Chem.* **2008**, *73*, 7800 and references therein. .

(19) Hegde, S. G.; Kassim, A. M.; Ingrum, A. I. *Tetrahedron Lett.* **1995**, *36*, 8395.

SCHEME 4. One-Pot Synthesis of Benzophenones 4 Starting from 1 and 2



and **2** with *t*-BuOK at room temperature for 1.0 h at first and then with iodine and MeONa/MeOH for an additional 10 h (Scheme 4).[15] Some notable features of benzophenones **4** obtained above include the following: (i) the multiple substituents and functional groups incorporated on the benzophenone framework (hydroxy, iodo, ethylthio, aryl, alkyl, etc.) provide the structural diversity and potential for further modification;[20] (ii) the sterically congested structure (at least di-ortho-substituted) is required in the majority of biologically active benzophenones.[18c]

Conclusion

In summary, an efficient and regiospecific [5C + 1C] annulation reaction of α-alkenoyl ketene (*S*,*S*)-acetals with aryl methyl ketones, the less active methylene compounds, was disclosed, and thus highly substituted 2-cyclohexanones were synthesized in high yields with high stereoselectivities. On the basis of this synthetic strategy, a facile route to sterically hindered benzophenones was developed via the iodonation−aromatization of 2-cyclohexenones obtained above with I_2 in MeONa/MeOH basic medium. Furthermore, the direct preparation of benzophenones from α-alkenoyl ketene (*S*,*S*)-acetals and aryl methyl ketones following a sequential [5 + 1] annulation−iodonation−aromatization procedure in a one-pot operation was achieved as well. The synthetic strategy is associated with readily available starting materials, mild conditions, high yields, and wide range of synthetic potential of the products. Further investigations are in progress.

Experimental Section

Representative Procedure for the Preparation of α-Alkenoyl Ketene (*S*,*S*)-Acetals 1 (1e as an Example)[2b,3,4a,6]. To a solution of 4,4-bis(ethylthio)but-3-en-2-one (1.9 g, 10 mmol) and 4-methoxybenzaldehyde (1.33 mL, 11 mmol) in EtOH (10 mL) was added NaOH (200 mg, 5.0 mmol) in one portion at room temperature. The reaction mixture was stirred overnight. After the starting material was consumed as indicated by TLC, the resulting mixture was quenched by ice−water (20 mL) under stirring and neutralized with dilute hydrochloric acid. The precipitate was collected by filtration, washed with water (100 mL), and dried under vacuum to afford the product **1e** (2.68 g, 87%) as a yellow solid.

(*E*)-1,1-Bis(ethylthio)-5-(4-methoxyphenyl)penta-1,4-dien-3-one (1e): Mp 86−88 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 1.36 (t, J = 7.5 Hz, 3H, $SCH_2C\mathbf{H_3}$), 1.41 (t, J = 7.5 Hz, 3H, $SCH_2C\mathbf{H_3}$), 3.01 (q, J = 7.5 Hz, 2H, $SC\mathbf{H_2}CH_3$), 3.06 (q, J = 7.5 Hz, 2H, $SC\mathbf{H_2}CH_3$), 3.83 (s, 3H, $OC\mathbf{H_3}$), 6.28 (s, 1H, COC**H**=C), 6.69 (d, J = 15.5 Hz, 1H, COCH=C**H**), 6.89 (d, J = 9.0 Hz, 2H, 2 × ArH), 7.51 (d, J = 9.0 Hz, 2H, 2 × ArH), 7.57 (d, J = 15.5 Hz, 1H, COC**H**=CH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 184.0, 162.4, 160.9, 140.8, 129.5 (2C), 127.8, 125.1, 114.4 (2C), 114.1, 55.2, 28.1, 25.6, 13.7, 12.4; IR (KBr) ν = 3060, 2967, 2923, 1643, 1584,1478, 1253, 1124, 831; ES−MS calcd m/z 308.1, found 309.0 $[(M + 1)]^+$. Anal. Calcd for $C_{16}H_{20}O_2S_2$: C, 62.30; H, 6.54. Found: C, 62.35; H, 6.52.

Typical Procedure for Preparation of 2-Cyclohexanones 3 (3a as an Example). To a well-stirred solution of acetophenone **2a** (0.13 mL, 1.1 mmol) in DMF (10 mL) was added *t*-BuOK (224 mg, 2.0 mmol) at room temperature. After the reaction mixture was stirred for 10 min, (*E*)-1,1-bis(ethylthio)-5-phenylpenta-1,4-dien-3-one **1a** (278 mg, 1.0 mmol) was added and stirred for an additional 1.0 h at room temperature. After completion of the reaction as indicated by TLC (diethyl ether/petrolum ether, 1/1), the reaction mixture was quenched by saturated aqueous NaCl (100 mL), neutralized with dilute hydrochloric acid, and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phase was washed with water, dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The crude product was purified by flash silica gel chromatography (petroleum ether/ethyl ether = 3/1, v/v) to give **3a** as a white solid (90% yield).

4-Benzoyl-3-(ethylthio)-5-phenylcyclohex-2-enone (3a): Mp 94−96 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 1.30 (t, J = 7.5 Hz, 3H, $SCH_2C\mathbf{H_3}$), 2.56 (dd, J = 4.5, 16.5 Hz, 1H, COC**H**HCH), 2.83−2.88 (m, 2H, $SC\mathbf{H_2}CH_3$), 3.46 (dd, J = 14.5, 16.5 Hz, 1H, COCH**H**CH), 3.82−3.86 (m, 1H, $COCH_2C\mathbf{H}$), 4.69 (d, J = 5.0 Hz, 1H, COC**H**C), 6.13 (s, 1H, COC**H**=C), 7.03−7.06 (m, 1H, ArH), 7.09−7.12 (m, 4H, 4 × ArH), 7.20−7.23 (m, 2H, 2 × ArH), 7.37−7.40 (m, 1H, ArH), 7.48−7.50 (m, 2H, 2 × ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 197.1, 195.7, 161.0, 138.9, 137.4, 133.0, 128.6 (2C), 128.3 (2C), 128.2 (2C), 127.5 (3C), 121.3, 52.4, 44.2, 37.4, 25.7, 12.6; IR (KBr) ν = 3049, 2967, 2923, 1647, 1578, 1248, 1213, 992, 760, 678; ES−MS calcd m/z 336.1, found 337.1 $[(M + 1)]^+$. Anal. Calcd for $C_{21}H_{20}O_2S$: C, 74.97; H, 5.99. Found: C, 74.99; H, 5.95.

General Procedure for Preparation of Benzophenones 4 (4a as an Example). To a well-sirred solution of cyclohexenone **3a** (336 mg, 1.0 mmol) in MeONa/MeOH (10 mL, M = 0.6 mol/L) was added iodine (508 mg, 2.0 mol) in small portions at −78 °C. The reaction was allowed to run at −78 °C for 3.0 h and then at room temperature overnight. The reaction mixture was quenched by dilute HCl to pH 7 and was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phase was washed with saturated aqueous $Na_2S_2O_3$ (2 × 15 mL) and water (1 × 20 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The crude product was purified by flash silica gel chromatography (petroleum ether/ethyl ether = 3/1, v/v) to give **4a** as a colorless oil (419 mg, 91% yield).

(3-(Ethylthio)-5-hydroxy-4-iodobiphenyl-2-yl)(phenyl)methanone (4a): ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 1.12 (t, J = 7.5 Hz, 3H, $SCH_2C\mathbf{H_3}$), 2.70−2.72 (m, 1H, $SC\mathbf{H}HCH_3$), 2.84−2.87 (m, 1H, $SCH\mathbf{H}CH_3$), 5.86 (s, 1H, O**H**), 7.05 (s, 1H, ArH), 7.17−7.22 (m, 5H, 5 × ArH), 7.30 (t, J = 7.5 Hz, 2H, 2 × ArH), 7.43 (t, J = 7.5 Hz, 1H, ArH), 7.60 (d, J = 7.5 Hz, 2H, 2 × ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 195.6, 156.1, 142.3, 138.3, 138.1, 137.7, 136.8, 133.0, 129.4 (2C), 128.9 (2C), 128.3 (2C), 128.1 (2C), 127.7, 116.6, 102.2, 32.3, 13.9; IR (KBr) ν = 3246, 3057, 2924, 2854, 1649, 1565, 1381, 1233, 1073, 957, 698; ES−MS calcd m/z 460.0, found 461.0 $[(M + 1)]^+$. Anal. Calcd for $C_{21}H_{17}IO_2S$: C, 54.79; H, 3.72. Found: C, 54.71; H, 3.66.

Typical Procedure for One-Pot Synthesis of Benzophenones 4 (4a as an Example). To a well-stirred solution of acetophenone **2a** (0.13 mL, 1.1 mmol) and *t*-BuOK (224 mg, 2.0 mmol) in MeCN (10 mL) was added (*E*)-1,1-bis(ethylthio)-5-phenylpenta-1,4-dien-3-one **1a** (278 mg, 1.0 mmol) at room temperature.

(20) For recent examples of the synthetic applications of *o*-iodophenol derivatives, see: (a) Kadnikov, D. V.; Larock, R. C. *Org. Lett.* **2000**, *2*, 3643. (b) Miao, H.; Yang, Z. *Org. Lett.* **2000**, *2*, 1765. (c) Bates, C. G.; Saejueng, P.; Murphy, J. M.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 4727. (d) Kadnikov, D. V.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 9423. (e) Liu, Z.; Larock, R. C. *Org. Lett.* **2004**, *6*, 3739. (f) Bi, H.; Liu, X.; Gou, F.; Guo, L.; Duan, X.; Shu, X.; Liang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 7068.

The reaction was allowed to run at room temperature for 1.0 h. Then, MeONa/MeOH (10 mL, $M = 0.6$ mol/L) and iodine (2.0 mmol) were added. After reacting for an additional 10 h, the resulting mixture was quenched by dilute HCl to pH 7 and was extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were washed with saturated aqueous $Na_2S_2O_3$ (2×15 mL) and water (1×20 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The crude product was purified by flash silica gel chromatography (petroleum ether/ethyl ether = 3/1, v/v) to give **4a** as a colorless oil (81% yield).

Acknowledgment. Financial support of this research by NNSFC-20872015, NENU-STC08007/07007, and the State Key Laboratory of fine chemicals is greatly appreciated.

Supporting Information Available: Experimental details, spectral and analytical data for compounds **1**, **3**, and **4**, copies of ^{1}H NMR and ^{13}C NMR spectra of all new compounds (PDF), and crystallographic data for **3i** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.