ORGANIC LETTERS

2010
Vol. 12, No. 22
5120−5123

Thermally Induced Electrocyclic Reaction of Methylenecyclopropane Methylene Diketone Derivatives: A Facile Method for the Synthesis of Spiro[2.5]octa-3,5-dienes

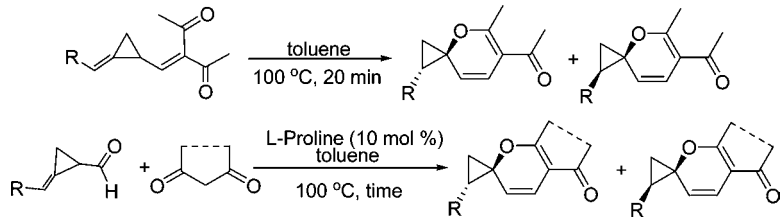
Xiang-Ying Tang, Yin Wei,* and Min Shi*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

weiyin@mail.sioc.ac.cn; mshi@mail.sioc.ac.cn

Received August 24, 2010

ABSTRACT



Thermally induced electrocyclic reactions of methylenecyclopropane (MCP) methylene diketone derivatives afford a novel method for the synthesis of spiro[2.5]octa-3,5-dienes in moderate to good yields. Applying this methodology in a one-pot manner for the reactions of MCP aldehydes with 1,3-diketones, catalyzed by L-proline, also afforded the corresponding spiro derivatives.

Methylenecyclopropanes (MCPs) are generally used as building blocks in organic synthesis for their ready accessibility as well as diverse reactivity driven by the relief of ring strain.[1] The ring-opening reactions of MCPs are synthetically useful protocols in the construction of complex product structures that have been studied extensively thus far. Over the past decades, Lewis acid- and transition metal-catalyzed reactions involving ring-opening of MCPs to form a variety of different carbocycles and heterocycles have been extensively investigated in our group and others.[2−4] To the best of our knowledge, the ring-opening reactions of MCPs

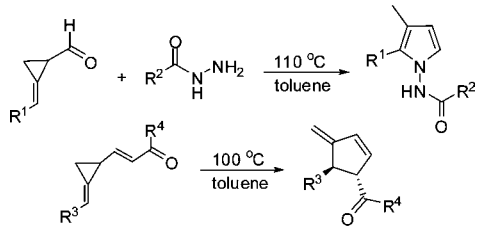
(1) For selected reviews on MCPs, see: (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49–92. (b) de Meijere, A.; Kozhushkov, S. I.; Khlebnikov, A. F. *Top. Curr. Chem.* **2000**, *207*, 89–147. (c) Binger, P.; Wedemann, P.; Kozhushkov, S. I.; de Meijere, A. *Eur. J. Org. Chem.* **1998**, 113–119. (d) de Meijere, A.; Kozhushkov, S. I. A. *Eur. J. Org. Chem.* **2000**, 3809–3822. (e) Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal.* **2002**, *344*, 111–129. (f) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213–1270. (g) Nakamura, E.; Yamago, S. *Acc. Chem. Res.* **2002**, *35*, 867–877. (h) Shao, L.-X.; Shi, M. *Curr. Org. Chem.* **2007**, *11*, 1135–1137. (i) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117–3179. (j) Yamago, S.; Nakamura, E. *Org. React.* **2002**, *61*, 1–217. (k) de Meijere, A.; Kozhushkov, S. I.; Spath, T.; von Seebach, M.; Lohr, S.; Nuske, H.; Pohomann, T.; Es-Sayed, M.; Brase, S. *Pure. Appl. Chem.* **2000**, *72*, 1745–1756.

(2) For Lewis acid-catalyzed ring opening reactions of MCPs, see: (a) Hu, B.; Xing, S. Y.; Wang, Z. W. *Org. Lett.* **2008**, *10*, 5481–5484. (b) Huang, X.; Yang, Y. *Org. Lett.* **2007**, *9*, 1667–1670. (c) Lautens, M.; Han, W. *J. Am. Chem. Soc.* **2002**, *124*, 6312–6316. (d) Lautens, M.; Han, W.; Liu, J. H. *J. Am. Chem. Soc.* **2003**, *125*, 4028–4029. (e) Scott, M. E.; Bethuel, Y.; Lautens, M. *J. Am. Chem. Soc.* **2007**, *129*, 1482–1483. (f) Scott, M. E.; Schwarz, C. A.; Lautens, M. *Org. Lett.* **2006**, *8*, 5521–5524. (g) Scott, M. E.; Han, W.; Lautens, M. *Org. Lett.* **2004**, *6*, 3309–3312. (h) Scott, M. E.; Lautens, M. *Org. Lett.* **2005**, *7*, 3045–3047. (i) Yu, L.; Meng, J. D.; Xia, L.; Guo, R. *J. Org. Chem.* **2009**, *74*, 5087–5089. (j) Lu, L.; Chen, G.; Ma, S. *Org. Lett.* **2006**, *8*, 835–838. (k) Scott, M. E.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 8154–8162. (l) Taillier, C.; Lautens, M. *Org. Lett.* **2007**, *9*, 591–593. (m) Diev, V. V.; Tung, T. Q.; Molchanov, A. P. *Eur. J. Org. Chem.* **2009**, 525–530. (n) Hu, B.; Zhu, J. L.; Xing, S. Y.; Fang, J.; Du, D.; Wang, Z. W. *Chem.—Eur. J.* **2009**, *15*, 324–327. (o) Bagutski, V.; de Meijere, A. *Adv. Synth. Catal.* **2007**, *349*, 1247–1255. (p) Hang, X.-C.; Chen, Q.-Y.; Xiao, J.-C. *Eur. J. Org. Chem.* **2008**, 1101–1106. (q) Huang, X.; Miao, M.-Z. *J. Org. Chem.* **2008**, *73*, 6884–6887.

10.1021/ol102002f
Published on Web 10/29/2010

by thermally induced rearrangements seldom have been reported. Since high temperature is usually required for the thermally induced rearrangements of the analogues of MCPs, such as cyclopropenes and vinylcyclopropanes due to certain activation energy required,[5] this may account for the ring-opening reactions of MCPs by thermally induced rearrangements normally being difficult to occur. Previously, we reported a synthetic route to 2,3-disubstituted pyrrolamides by ring-opening recyclization of benzylidene and alkylidenecyclopropylcarbaldehydes with hydrazides upon heating in toluene in moderate to good yields (Scheme 1).[6]

Scheme 1. Previous Studies on the Ring-Opening Reactions of MCP Derivatives upon Heating

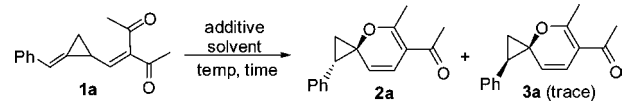


Later, we also reported an efficient method to stereospecifically synthesize trans-substituted cyclopentene derivatives via the thermally induced Cope rearrangement of readily available MCP alkenyl ketone derivatives in moderate to good yields (Scheme 1).[7] Furthermore, Renaud and coworkers reported the addition of enolizable 1,3-diketone to α,β-unsaturated aldehydes leading to substituted 2*H*-pyrans via a formal [3 + 3] cycloaddition.[8] On the basis of these previous works, we hypothesized that MCP methylene diketone might also undergo a rearrangement reaction upon heating, but with a different outcome due to the unique properties of diketones. Herein, we wish to report a novel thermally induced electrocyclic reaction of MCP methylene diketone derivatives to synthesize spiro[2.5]octa-3,5-dienes upon heating.

We initially utilized (*E*)-3-((2-benzylidenecyclopropyl)-methylene)pentane-2,4-dione **1a** as the substrate to investigate its behavior upon heating in toluene at 100 °C. To our surprise, a new cyclopropane-containing product **2a**, which was later confirmed as *trans*-spiro[2.5]octa-3,5-diene, was obtained in 56% yield instead of the cyclopentene product derived from a Cope rearrangement (Table 1, entry 1). When several acids such as Ph_2PO_2H, $FeCl_3$, CF_3CO_2H, and tartaric acid were present in the reaction system, the yields of product **2a** were lower than 56%, indicating that this reaction was not tolerant to acidic conditions (Table 1, entries 2−5). The UV photolytic reaction of **1a** in DCM at room temperature required a reaction time of 1 day, and the yield of **2a** was only 19% (Table 1, entry 6). When this reaction was kept in the dark or heated by microwave at 100 °C, the yields of **2a** dropped to 46% and 42%, respectively (Table 1, entries 7 and 8). Furthermore, phase transfer catalyst $^tBu_4NOAc$ did not work well either in this reaction (Table 1, entry 9). Finally, it was found that free radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) did not inhibit this reaction, rendering unlikely the involvement of a simple radical pathway (Table 1, entry 10).

Repeated attempts to increase the yield of **2a** were unsuccessful. In fact, as shown by TLC, there was a product in addition to **2a**, which was easily decomposed during

Table 1. Optimization of the Reaction Conditions



entry	additive	solvent	temp (°C)	time (min)	yield of **2a** (%)[a]
1		toluene	100	20	56
2	Ph_2PO_2H (10 mol %)	DCE	50	9 h	22
3	$FeCl_3$ (1 0 mol %)	toluene	60	30	complex
4	CF_3CO_2H (5 mol %)	DCM	rt	20	complex
5	tartaric acid (20 mol %)	toluene	100	15	48
6		DCM	rt	1 day	19[b]
7		toluene	100	30	46[c]
8		toluene	100	10	42[d]
9	$^tBu_4NOAc$ (1 equiv)	toluene	100	20	54
10	TEMPO (1 equiv)	xylene	120	10	56

[a] Isolated yields. [b] The reaction mixture was irradiated by ultraviolet light. [c] The reaction was kept in the dark. [d] The reaction was conducted under microwave.

(3) For transition metal-catalyzed ring reactions of MCPs, see: (a) Lautens, M.; Ren, Y. *J. Am. Chem. Soc.* **1996**, *118*, 10668–10669. (b) Ma, S.; Zhang, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 183–187. (c) Ma, S.; Lu, L.; Zhang, J. *J. Am. Chem. Soc.* **2004**, *126*, 9645–9660. (d) Smolensky, E.; Kapon, M.; Eisen, M. S. *Organometallics* **2007**, *26*, 4510–4527. (e) Nakamura, I.; Oh, B. H.; Saito, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1298–1300. (f) Kurahashi, T.; de Meijere, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7881–7884. (g) Huang, X.; Zhou, H. *Org. Lett.* **2002**, *4*, 4419–4422.

(4) For work from our group, see: (a) Shi, M.; Xu, B.; Huang, J.-W. *Org. Lett.* **2004**, *6*, 1175–1178. (b) Jiang, M.; Shi, M. *Tetrahedron* **2009**, *65*, 5222–5227. (c) Shi, M.; Liu, L.-P.; Tang, J. *Org. Lett.* **2006**, *8*, 4043–4046. (d) Yao, L.-F.; Shi, M. *Eur. J. Org. Chem.* **2009**, 4971–4983. (e) Jiang, M.; Liu, L.-P.; Shi, M.; Li, Y.-X. *Org. Lett.* **2010**, *12*, 116–119. (f) Shao, L.-X.; Shi, M. *Tetrahedron* **2010**, *66*, 4551–4554. (g) Jiang, M.; Shi, M. *Org. Lett.* **2010**, *12*, 2606–2609. (h) Huang, X.; Miao, M.-Z. *J. Org. Chem.* **2008**, *73*, 6884–6887.

(5) The thermally induced rearrangements for the analogues of MCPs, such as cyclopropenes and vinylcyclopropanes, have been investigated; please see: (a) Houk, K. N.; Nendel, M.; Wiest, O.; Storer, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 10545–10546. (b) Baldwin, J. E.; Bonacorsi, S., Jr. *J. Am. Chem. Soc.* **1996**, *118*, 8258–8265. (c) Gajewski, J. J. *Hydrocarbons Thermal Isomerizations*; Academic: New York, 1980; pp 81−87. (d) Baird, M. S. *Chem. Rev.* **2003**, *103*, 1271–1294. (e) Baldwin, J. E. *Chem. Rev.* **2003**, *103*, 1197–1212.

(6) Tang, X.-Y.; Shi, M. *J. Org. Chem.* **2009**, *74*, 5983–5986.

(7) Tang, X.-Y.; Shi, M. *J. Org. Chem.* **2010**, *75*, 902–905.

(8) (a) Hubert, C.; Moreau, J.; Batany, J.; Duboc, A.; Hurvois, J.-P.; Renaud, J. L. *Adv. Synth. Catal.* **2008**, *350*, 40–42. (b) Moreau, J.; Hubert, C.; Batany, J.; Toupet, L.; Roisnel, T.; Hurvois, J.-P.; Renaud, J.-L. *J. Org. Chem.* **2009**, *74*, 8963–8973.

purification. Fortunately, the structure of **2a** was finally confirmed as *trans*-spiro[2.5]octa-3,5-diene by its analogue **2j**, whose structure was unambiguously determined by X-ray diffraction (Figure 1).[9] In addition, **3j**, the configurational

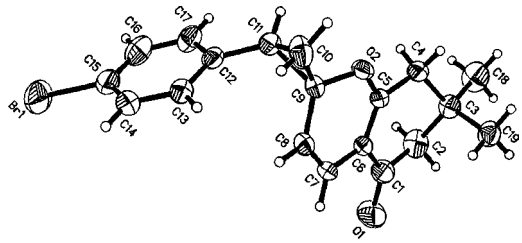


Figure 1. X-ray crystal structure of **2j**.

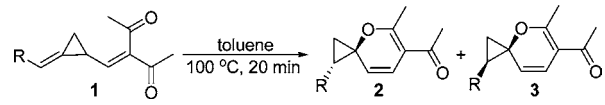
isomer of **2j**, was also obtained and characterized as *cis*-spiro[2.5]octa-3,5-diene on the basis of its spectral and analytical data. According to this result, it was unlikely to increase the yield of **2a** due to the formation of its unstable isomer.

We next turned our attention to the generality of this reaction in toluene. A variety of MCP methylene diketones having either electron-donating or electron-withdrawing groups on the benzene ring as substituents, **1**, were examined under these optimal conditions. When the electron-withdrawing groups Br or Cl were present on the benzene ring (**1b** and **1c**), the corresponding *trans*-spiro[2.5]octa-3,5-diene derivatives **2b** and **2c** were obtained in 62% and 58% yields. The cis-isomers were also isolated but were complex mixtures as shown by ^{1}H NMR spectra (Table 2, entries 1 and 2). Using (*Z*)-3-((2-benzylidenecyclopropyl)methylene)pentane-2,4-dione (Z-**1a**) or **1h** bearing three strongly electron-donating MeO groups on the benzene ring as the substrates, the trans-isomers were afforded in 42% and 55% yields, respectively; but the pure cis-isomers **3a** and **3h** could not be isolated due to their instability (Table 2, entries 5 and 8). As was the case for **1d**, **1f**, and **1g** having electron-donating groups on the benzene ring as well as **1e** bearing a *p*-phenyl group, both the trans- and cis-isomers could be isolated and the total yields were 64−86% (Table 2, entries 3−4 and 6−7). Unfortunately, **1** with aliphatic substituents did not give good results, affording complex mixtures of unidentified products.

Considering that it might be feasible to synthesize the spiro product from more common starting materials, therefore, the reaction was carried out using a one-pot manner by heating MCP aldehyde and 1,3-diketones in toluene catalyzed by 10

(9) The crystal data of **2j** have been deposited with the Cambridge Crystallographic Data Centre; deposition no. 757321. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, UK or via www.ccdc.cam.ac.uk/conts/retrieving.html. Empirical formula: $C_{19}H_{19}BrO_2$; formula weight: 359.25; crystal size: 0.396 × 0.267 × 0.175; crystal color, habit: colorless, prismatic; crystal system: orthorhombic; lattice type: primitive; lattice parameters: a = 25.683(3) Å, b = 12.1372(13) Å, c = 11.0178(12) Å, α = 90°, β = 90°, γ = 90°, V = 3434.5(6) Å^3; space group: *Pbcn*; Z = 8; D_{calc} = 1.390 g/cm^3; F_{000} = 1472; R1 = 0.0488, *w*R2 = 0.1294. Diffractometer: Rigaku AFC7R.

Table 2. Reaction Scope of This Rearrangement

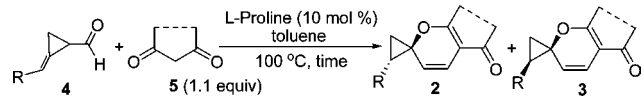


entry	R	2:3	yield of **2** + **3** (%)[a]
1	**1b**, *p*-BrC_6H_4	–[b]	**2b**, 62
2	**1c**, *p*-ClC_6H_4	–[b]	**2c**, 58
3	**1d**, *p*-MeC_6H_4	2.3:1	**2d/3d**, 86
4	**1e**, *p*-PhC_6H_4	2.4:1	**2e/3e**, 64
5	*Z*-**1a**, C_6H_5	–[b]	**2a**, 42
6	**1f**, *p*-MeOC_6H_4	2.7:1	**2f/3f**, 74
7	**1g**, *m*-MeC_6H_4	2:1	**2g/3g**, 76
8	**1h**, 3,4,5-$(MeO)_3C_6H_2$	–[b]	**2h**, 55

[a] Isolated yields. [b] As detected by ^{1}H NMR, product **3** was isolated as complex mixtures due to its instability.

mol % of L-proline at 100 °C. Instead of L-proline, another less expensive base, such as piperidine, has also been tried as a catalyst in this reaction. However, some Michael addition byproduct were generated, leading to low yields of the desired products. With MCP aldehyde **4b** and 1,3-diketone pentane **5b** as the substrates, the reaction became more sluggish, giving the corresponding product **2b** in very low yield (27%) (Table 3, entry 6). It was found that 1,3-

Table 3. Tandem Knoevenagel Condensation−Cope Rearrangement of MCP Aldehydes with 1,3-Diketones in One-Pot



entry	R	5	time (min)	2:3	yield (%)[a] 2+3
1	**4a**, C_6H_5	**5a**	20	6.3:3.7	**2i/3i**, 81
2	**4b**, *p*-BrC_6H_4	**5a**	20	5.7:4.3	**2j/3j**, 58
3	*Z*-**4a**, C_6H_5	**5a**	20	6:4	**2i/3i**, 80
4	**4c**, *p*-MeC_6H_5	**5a**	20	5.5:4.5	**2k/3k**, 67
5	**4d**, 3,4,5-*(*MeO)$_3C_6H_2$	**5a**	20	5.5:4.5	**2l/3l**, 62
6	**4b**, *p*-BrC_6H_4	**5b**	90	–[b]	**2b**, 27
7	**4a**, C_6H_5	**5c**	30	6:4	**2m/3m**, 73[c]
8	**4e**, *p*-ClC_6H_4	**5c**	30	6:4	**2n/3n**, 55[c]
9	**4f**, *p*-PhC_6H_4	**5c**	30	6:4	**2o/3o**, 28[c]
10	**4a**, C_6H_5	**5d**	120	6:4	**2p/3p**, 69
11	**4b**, *p*-BrC_6H_4	**5d**	120	5.5:4.5	**2q/3q**, 61
12	**4c**, *p*-MeC_6H_4	**5d**	90	6:4	**2r/3r**, 61

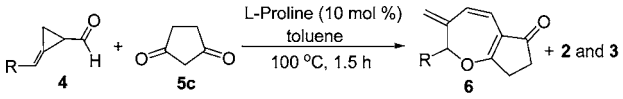
[a] Isolated yields. [b] None of the product **3** was obtained. [c] A new product was formed.

cyclohexanedione **5a** possessed higher activity than **5b** and such reactions were completed within 20 min, giving the configurational isomers (**2i**/**3i**, **2j**/**3j**, **2k**/**3k**, **2l**/**3l**) in 58−81% yields, respectively (Table 3, entries 1, 2, 4, and 5). Probably the pK_a values of cyclic diketones are lower than those

of the corresponding acyclic diketones, then the synthesis of the Knoevenagel adducts is faster, leading to the whole reaction rate being faster. With 1,3-cyclohexanedione **5d** instead of **5a**, as for substrates **4a**, as well as **4b** and **4c** having a para-substituent on the benzene ring, the reaction time was lengthened to 90−120 min and the total yields of the *cis*- and *trans*-spiro[2.5]octa-3,5-diene derivatives were 61−69%, respectively (Table 3, entries 10−12). In addition, 1,3-cyclopentanedione **5c** exhibited unique properties as the reaction of **5c** with **4a**, **4e** (*p*-Cl substituted), and **4f** (*p*-phenyl substituted) gave the corresponding isomers in 28−73% yields along with a set of new products **6** which are discussed later (Table 3, entries 7−9). When *Z*-**4a** was used as the substrate, the reaction went through smoothly to deliver the same isomers **2i**/**3i** in 80% yield (Table 3, entry 3). Unfortunately, **4** with aliphatic substituents did not give good results either, affording complex mixtures of unidentified products.

Interestingly, a new product **6a** was obtained in the reaction of MCP aldehyde **4a** with **5c** though the yield of **6a** was low. On the basis of Renaud's finding and its spectral and analytical data,[8] **6a** was identified as 3-methylene-2-phenyl-7,8-dihydro-2*H*-cyclopenta[*b*]oxepin-6(3*H*)-one. Further investigation revealed that if the reaction mixture was heated for 1.5 h, **6a** was obtained in higher yield (25%). Simultaneously, the corresponding spiro[2.5]octa-3,5-diene isomers **2m** and **3m** were formed in 62% yield (Scheme 2,

Scheme 2. The Reaction of MCP Aldehydes **4** with 1,3-Diketone **5**



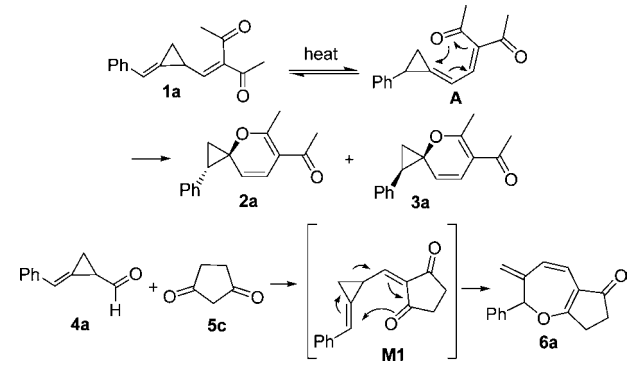
R = C_6H_5, **6a**: 25% **2m/3m**, 62% (1)
R = *p*-ClC_6H_4, **6b**: 19% **2n/3n**, 55% (2)
R = *p*-$C_6H_5C_6H_4$, **6c**: 6% **2o/3o**, 15% (3)

eq 1), slightly lower than 73% (Table 3, entry 7). With **4e** and **4f** as the substrates, the same results were observed as the two isomers were obtained in 19% and 6% yields, respectively (Scheme 2, eqs 2 and 3), suggesting that **6** was a thermally stable product because longer reaction time favors its formation.

A plausible reaction mechanism is outlined in Scheme 3. Initially, **1a** was converted to intermediate **A** upon heating at 100 °C,[10] presumably via a simple sigmatropic rearrangement. After formation of the intermediate **A**, an electrocyclic reaction took place to furnish the corresponding *trans*- and

(10) (a) Skancke, A.; Schaad, L. J.; Hess, B. A., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 5315–5318. (b) Patrick, T. B.; Haynie, E. C.; Probst, W. J. *Tetrahedron Lett.* **1971**, *12*, 423. (c) Patrick, T. B.; Haynie, E. C.; Probst, W. J. *J. Org. Chem.* **1972**, *37*, 1553.

Scheme 3. A Plausible Reaction Mechanism



cis-spiro[2.5]octa-3,5-diene derivatives **2** and **3** (Scheme 3). In addition, **2** is the major product due to its small steric hindrance and stability. It should also be noted that the reaction of **4** with 1,3-cyclopentanedione **5c** may generate intermediate **M1**, which undergoes electrocyclic reaction to give product **6a** (Scheme 3). In principle, we should obtain the six-membered analogue of product **6a** in a low yield in the reaction of **4** with **5d**. However, under our standard reaction conditions, we observed that the reactions of **4** with **5d** afforded several products mixed with small amounts of decomposed compounds from starting materials, which made it very difficult to identify the six-membered analogue of product **6a**. The theoretical investigations are in progress to elucidate further mechanistic details of these reactions.

In conclusion, we have found a thermally induced reaction of MCP methylene diketone derivatives, affording a novel synthetic protocol for the preparation of spiro[2.5]octa-3,5-dienes as well as 3-methylene-2-aryl-7,8-dihydro-2*H*-cyclopenta[*b*]oxepin-6(3*H*)-ones in some cases. A plausible mechanism was proposed. The potential utilization and extension of the scope of the methodology are currently under investigation. Detailed mechanistic investigations are also under way.

Acknowledgment. We thank the Shanghai Municipal Committee of Science and Technology (08dj1400100-2), National Basic Research Program of China (973)-2009CB825300, and the National Natural Science Foundation of China for financial support (20472096, 20872162, 20672127, 20821002, and 20732008) and Dr. Donald D. Bretches for revising our English.

Supporting Information Available: The spectroscopic data (^1H, ^{13}C spectroscopic data), HRMS of the compounds shown in Tables 1−3 and Scheme 2, the X-ray crystal structures of compound **2j**, and a detailed description of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL102002F