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A Synthetic Protocol of Trans-Substituted Cyclopentenes via the Ring-Opening Rearrangement of MCP Alkenyl Derivatives

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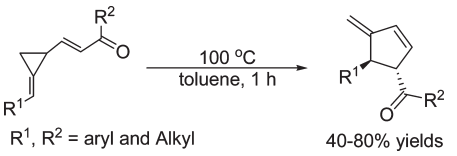

A efficient method to stereospecifically synthesize trans-substituted cyclopentene derivatives via the ring-opening rearrangement of readily available MCP alkenyl derivatives in moderate to good yields has been described. The control experiment based on the deuterium labeling experiment and the addition of TEMPO revealed that this transformation might proceed through a fast concerted pericyclic process rather than a simple radical pathway or an ionic pathway.

Introduction

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.[2] For example, during the last 10 years, Lewis acids and transition metal-catalyzed reactions involving ring-opening of MCPs to form a variety of different carbocycles and heterocycles have been extensively investigated. However, the ring-opening reactions of MCPs by thermally induced rearrangements are relatively limited due to that high temperature is usually required because of the huge activation energy.[3] Previously, we reported an efficient synthetic route to 2,3-disubstituted pyrrolamides by ring-opening cyclization of benzylidene and alkylidenecyclopropylcarbaldehydes with hydrazides upon heating in toluene in moderate to good yields.[4] Such a transformation involves a ring-opening and thermally induced rearrangement of MCPs to produce the five-membered nitrogen atom containing heterocyclic ring. Herein, we wish to report an efficient synthetic method to stereospecifically produce trans-disubstituted cyclopentene derivatives **2**, a class of novel carbocycles, in moderate to good yields (40−80%) by ring-opening rearrangement of MCP alkenyl derivatives **1**.

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(2) For selected examples on the reactions of MCPs, see: (a) Hu, B.; Xing, S. Y.; Wang, Z. W. *Org. Lett.* **2008**, *10*, 5481–5484. (b) Shi, M.; Liu, L.-P.; Tang, J. *Org. Lett.* **2006**, *8*, 4043–4046. (c) Shi, M.; Xu, B.; Huang, J.-W. *Org. Lett.* **2004**, *6*, 1175–1178. (d) Huang, X.; Yang, Y. *Org. Lett.* **2007**, *9*, 1667–1670. (e) Lautens, M.; Han, W.; Liu, J. H. *J. Am. Chem. Soc.* **2003**, *125*, 4028–4029. (f) Lautens, M.; Ren, Y. *J. Am. Chem. Soc.* **1996**, *118*, 10668–10669. (g) Yu, L.; Meng, J. D.; Xia, L.; Guo, R. *J. Org. Chem.* **2009**, *74*, 5087–5089. (h) Ma, S.; Zhang, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 183–187. (i) Ma, S.; Lu, L.; Zhang, J. *J. Am. Chem. Soc.* **2004**, *126*, 9645–9660. (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) Smolensky, E.; Kapon, M.; Eisen, M. S. *Organometallics* **2007**, *26*, 4510–4527. (n) Diev, V. V.; Tung, T. Q.; Molchanov, A. P. *Eur. J. Org. Chem.* **2009**, 525–530. (o) Hu, B.; Zhu, J. L.; Xing, S. Y.; Fang, J.; Du, D.; Wang, Z. W. *Chem.—Eur. J.* **2009**, *15*, 324–327. (p) Bagutski, V.; de Meijere, A. *Adv. Synth. Catal.* **2007**, *349*, 1247–1255. (q) Hang, X.-C.; Chen, Q.-Y.; Xiao, J.-C. *Eur. J. Org. Chem.* **2008**, 1101–1106. (r) Nakamura, I.; Oh, B. H.; Saito, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1298–1300. (s) Kurahashi, T.; de Meijere, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7881–7884. (t) Huang, X.; Zhou, H. *Org. Lett.* **2002**, *4*, 4419–4422.

(3) In fact, the thermally induced rearrangement of MCPs is rare. However, vinylcyclopropane is investigated extensively and there are a few examples; 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.

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

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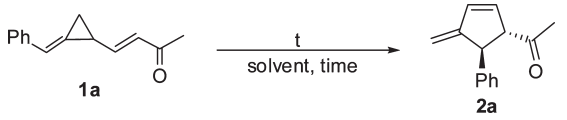
TABLE 1. Rearrangement of MCP Alkenyl Derivative (1a) under Various Reaction Conditions



entry[a]	solvent	t (°C)	time (h)	yield (%)[b] of **2a**
1	toluene	90	12.0	25
2	toluene	90	2.0	48
3	toluene	100	1.5	57
4	toluene	100	1.0	80
5	toluene	100	0.8	69
6	toluene	110	0.7	70
7	xylene	120	0.5	63
8	DCE	100	1.0	60
9	dioxane	100	1.0	55
10	isopropanol	100	1.0	56
11	CH_3NO_2	100	1.0	78
12	DMSO	100	1.0	58

[a]Reaction scale: 0.2 mmol of **1a** in 2.0 mL of toluene. [b]Isolated yields.

Results and Discussion

We initially utilized **1a** as a model to investigate its reaction outcomes upon heating in toluene (Table 1, entries 1−4) (for the synthesis of **1a**, please see the Supporting Information). It was found that treatment of **1a** at 90 °C in toluene for 12 h delivered one major product as a yellow liquid, which was later characterized as 1-(4-methylene-5-phenylcyclopent-2-enyl)ethanone (**2a**), in 25% yield on the basis of its spectral and analytical data after usual workup and purification by column chromatography on silica gel, although the relative configuration of the two substituents on the cyclopentene ring could not be determined on the basis of its ^{1}H NMR spectroscopic data (Table 1, entry 1). Fortunately, its structure was further confirmed by the X-ray single-crystal analysis of its analogue **2p** (Figure 1).[5] Therefore, the configuration of the two substitutes on the cyclopentene ring could be identified as trans.[6] Considering that the reaction time might be the crucial factor in the yield of **2a**, we monitored the reaction proceeding by TLC plates under the same conditions and found that the starting material **1a** was consumed within 2 h, affording **2a** in 48% yield (Table 1, entry 2). Moreover, when raising the reaction temperature to 100 °C and reducing the reaction time to 1.5, 1.0, and 0.8 h, the resulting **2a** was given in 57%, 80%, and 69% yield, respectively (Table 1, entries 3−5). However, if running the reaction at 110 or 120 °C in toluene for 0.7 h or xylene for 0.5 h, **2a** was obtained in 70% and 63% yield, respectively (Table 1, entries 6 and 7). Other solvents such as 1,2-dichloromethane (DCE), dioxane, isopropanol, nitromethane, and dimethyl sulfoxide (DMSO) were also investigated under the standard conditions, leading to formation of **2a** in 55−78% yields, respectively (Table 1, entries 8−12). Therefore, the optimized reaction conditions were determined to carry out the reaction in toluene at 100 °C.

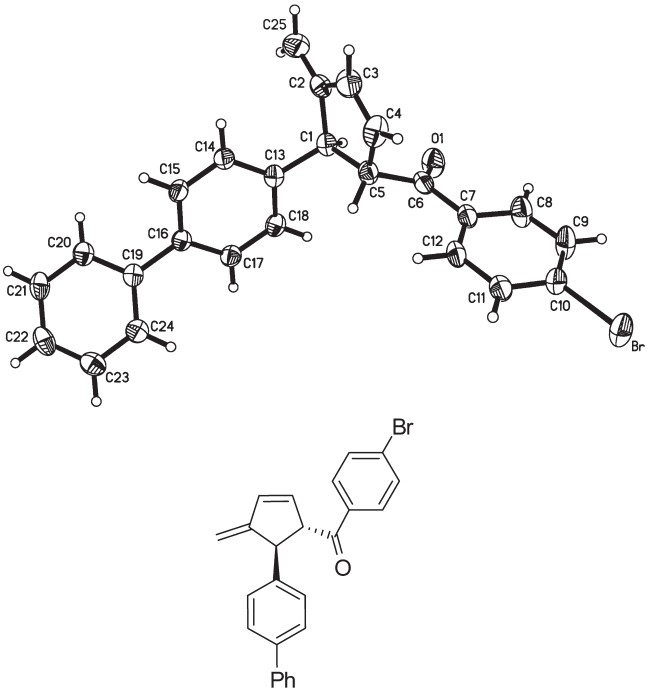
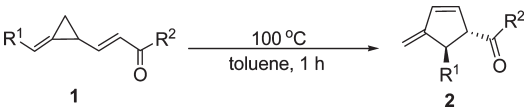


FIGURE 1. X-ray crystal and two-dimensional structure of **2p**.

TABLE 2. Rearrangement of Various MCP Alkenyl Derivatives



entry[a]	R^1	R^2	yield (%)[b] of **2**
1	*p*-BrC_6H_4, **1b**	Me	**2b**, 60
2	*p*-ClC_6H_4, **1c**	Me	**2c**, 63
3	*o*-BrC_6H_4, **1d**	Me	**2d**, 64
4	3,5-$Br_2C_6H_3$, **1e**	Me	**2e**, 51
5	3,4,5-$(MeO)_3C_6H_2$, **1f**	Me	**2f**, 75
6	4-MeC_6H_4, **1g**	Me	**2g**, 76
7	3,4-$Me_2C_6H_4$, **1h**	Me	**2h**, 71
8	*m*-$CH_3C_6H_4$, **1i**	Me	**2i**, 71
9	C_7H_{15}, **1j**	Me	**2j**, 40
10	*Z*-**1a**	Me	**2a**, 70
11	C_6H_5, **1k**	Et	**2k**, 72
12	*p*-BrC_6H_4, **1l**	C_6H_5	**2l**, 66
13	*p*-ClC_6H_4, **1m**	C_6H_5	**2m**, 68
14	*p*-BrC_6H_4, **1n**	*p*-BrC_6H_4	**2n**, 54
15	2-furan, **1o**	Me	**2o**, 76
16	C_6H_5, **1a′**	OEt	no reaction

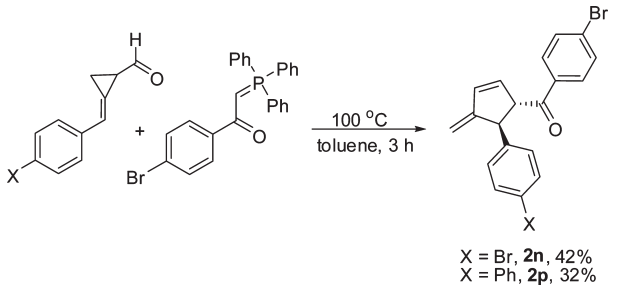
[a]Reaction scale: 0.2 mmol of **1a** in 2.0 mL of toluene. [b]Isolated yields.

With these optimized reaction conditions in hand, we next attempted to study the scope and limitations of this reaction by using a variety of other MCP alkenyl compounds. The results are outlined in Table 2. As for substrates **1b−d** having an electron-withdrawing group substituted aromatic group (R^1), the corresponding cyclopentene derivatives **2b−d** were obtained in 60−64% yields (Table 2, entries 1−3). However, if two electron-withdrawing Br atoms were introduced on the benzene ring of R^1, the yield of **2e** decreased to 51% (Table 1, entry 4). On the other hand, in the cases of substrates **1f−i** in

(5) The crystal data of **2p** have been deposited in CCDC with number 752267. Empirical formula: $C_{25}H_{19}BrO$; formula weight: 415.31; crystal size: 0.397 × 0.269 × 0.172; crystal color, habit: colorless, prismatic; crystal system: monoclinic; lattice type: primitive; lattice parameters: a = 6.3664(10) Å, b = 8.9574(14) Å, c = 34.323(5) Å, α = 90°, β = 94.721(3)°, γ = 90°, V = 1950.7(5) Å^3; space group: $P2(1)/n$; Z = 4; D_{calc} = 1.414 g/cm^3; F_{000} = 848; R1 = 0.0461, wR2 = 0.1036. Diffractometer: Rigaku AFC7R.

(6) No cis isomers were detected in this reaction on the basis of the ^{1}H NMR spectrum of crude **2a**. See the Supporting Information.

SCHEME 1. A One-Pot Manner for the Synthesis of Cyclopentenes

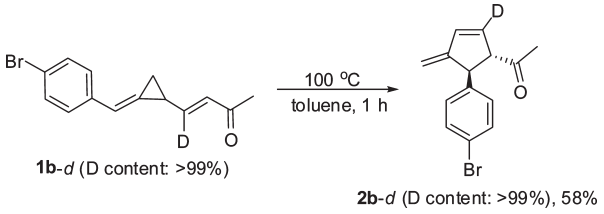


which the aryl groups have electron-donating Me or MeO substitutes, the reaction proceeded more cleanly and smoothly, affording the corresponding products **2f**−**i** in higher yields (71−76%) (Table 2, entries 5−8). We also turned our interest to alkyl group substituted substrate **1i** ($R^1 = C_7H_{15}$). After heating at 100 °C in toluene for 1.0 h, the corresponding cyclopentene product **2i** was given in 40% yield (Table 2, entry 9). It also should be noted that, using (*Z*)-4-[(*E*)-2-benzylidenecyclopropyl]but-3-en-2-one (*Z*-**1a**) as the substrate, the same product **2a** could be formed in 70% yield under identical conditions (Table 2, entry 10). Furthermore, the R^2 group was also not restricted to a methyl group. Changing it into an ethyl and aryl group, to our delight, the corresponding cyclopentene derivatives **2k**−**n** were obtained in 54−72% yields (Table 2, entries 11−14). When a heteroaromatic ring was introduced into the substrate (R^1 = 2-furanyl), the corresponding product **2o** was formed in 76% yield (Table 2, entry 15), suggesting that this synthetic method to cyclopentenes has a broad substrate generality. As for MCP alkenyl derivative **1a**′, no reaction occurred under the standard conditions (Table 2, entry 16).

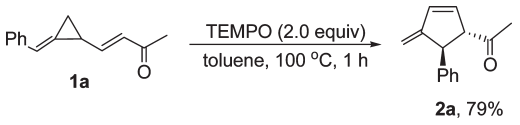
Considering that it might be feasible to synthesize the cyclopentene derivatives from more common starting materials, therefore, two experiments were carried out by using a one-pot manner by heating MCP aldehyde and phosphorane ylide in toluene together. Interestingly, as assumed, the corresponding cyclopentenes **2n** and **2p** were obtained in 42% and 32% yield, respectively, although the reaction time should be prolonged to 3 h because such a Wittig reaction was sluggish under the standard reaction conditions (Scheme 1). The moderate yields of **2n** and **2p** were presumably due to that the prolonged heating time did not favor the formation of cyclopentene derivatives.

To gain more mechanistic insight into the ring-opening/recyclization reaction, two control experiments were conducted under identical reaction conditions. Upon treating **1b**-*d* (D content: >99%) at 100 °C in toluene for 1.0 h, we found that no H-D exchange or migration was observed in product **2b**-*d* (D content: >99%) (Scheme 2, for the details, see the Supporting Information). Another control experiment was carried out by adding 2.0 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as a free radical scavenger into the reaction system to quench the supposed biradical intermediate. However, it was found that the formation of **2a** was unaffected by the addition of the radical inhibitor such as TEMPO since **2a** was formed in 79% yield, rendering unlikely the intervention of a radical pathway (Scheme 3). On the basis of these results, a concerted pericyclic process is a more reasonable mechanism for the formation of **2a**.

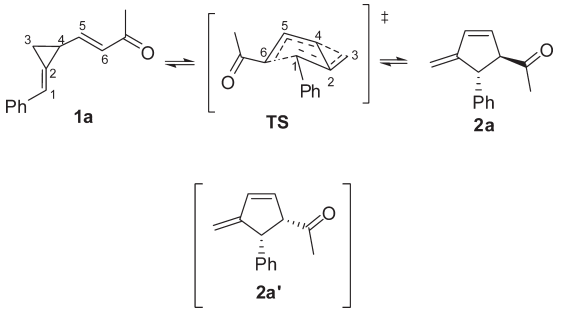
SCHEME 2. Deuterium Labeling Experiment



SCHEME 3. A Control Experiment



SCHEME 4. Plausible Reaction Mechanism



Thereby, we consider that the reaction may proceed through a Cope rearrangement.[7] A plausible mechanism for the formation of **2a** is outlined in Scheme 4, using **1a** as a model. This transformation proceeds via a chairlike transition state (TS) in which the steric interaction between the substituents is minimal. It should also be noted that if using *Z*-**1a** as the substrate, the same product **2a** could be formed in 70% yield under identical conditions (Table 2, entry 10). Moreover, compound **2a**′ was not observed on the basis of NMR spectroscopy, suggesting that **2a**′ is unstable and it might be quickly transformed to **2a** under the standard conditions.[8]

At this stage, we also conducted some simple transformation of **2a** to understand its chemical behavior. Treatment of **2a** with 1.2 equiv of methylmagnesium bromide gave a tertiary alcohol derivative in 88% yield (for the details, see the Supporting Information). On the other hand, after reduction of **2a** with $NaBH_4$ in dichloromethane (DCM), the resulting alcohol was condensed without purification with 3,5-bis(benzyloxy)benzoic acid in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 4-*N*,*N*-dimethylpyridine (DMAP) in DCM, yielding the corresponding ester in 74% yield (for the details, see the Supporting Information).

In summary, a convenient and efficient method for the synthesis of novel cyclopentene derivatives **2** has been

(7) (a) Baird, M. S. *Chem. Rev.* **2003**, *103*, 1271–1294. (b) Cope, A. C.; Hardy, E. M. *J. Am. Chem. Soc.* **1940**, *62*, 441. (c) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765.

(8) It can be seen from the ^1H NMR spectrum of crude **2a** (see the Supporting Information) that none of **2a**′ is contained in the reaction mixture. According to this result, we assume that **2a**′ is unstable and it might be quickly transformed to **2a** under the standard conditions.

developed through the thermally induced ring-opening rearrangement of MCPs **1**. This synthetic protocol is associated with readily available starting materials, a wide rang of substrates, and easy control of the reaction conditions. Furthermore, the plausible reaction mechanism has been discussed on the basis of deuterium labeling and control experiments, rendering that a pericyclic mechanism may be responsible for this thermally induced rearrangement. The potential utilization and extension of the scope of the methodology are currently under investigation.

Experimental Section

General Procedure for the Preparation of 1a. To 5 mL of DCM in a 25 mL round-bottomed flask was added (*E*)-2-benzylidenecyclopropanecarbaldehyde (158.0 mg, 1.0 mmol) and ylide (380.0 mg, 1.2 mmol); the mixture was then stirred at room temperature (rt, 20 °C) until most of the aldehyde was consumed (ca. 24 h). The solvent was removed under reduced pressure and the residue was purified by a flash column chromatography to give **1a** (143.0 mg, 0.72 mmol, 72% yield).

General Procedure for the Thermally Induced Rearrangement of (*E*)-4-((*E*)-2-Benzylidenecyclopropyl)but-3-en-2-one, 1a. A Schlenk tube was charged with (*E*)-4-((*E*)-2-benzylidenecyclopropyl)but-3-en-2-one (**1a**) (39.6 mg, 0.2 mmol) and toluene (2.0 mL), cooled with liquid nitrogen, then vacuumed by pump and subsequently vented with Ar. After being warmed to rt, the reaction was stirred at 100 °C for 1 h. The solvent was removed under reduced pressure and then the residue was purified by flash column chromatography.

Compound 1a: yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 1.63−1.67 (m, 1H), 2.08−2.21 (m, 1H), 2.22 (s, 3H, CH_3), 2.32−2.38 (m, 1H), 6.25 (d, J = 16 Hz, 1H, CH), 6.39 (dd, J = 16, 9.2 Hz, 1H), 7.23−7.28 (m, 1H, Ar), 7.32−7.37 (m, 2H, Ar), 7.50−7.53 (m, 2H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 14.6, 17.0, 26.8, 120.8, 126.0, 126.8, 127.5, 128.5, 129.5, 136.7, 149.7, 197.7; IR (CH_2Cl_2) ν 3060, 3028, 3003, 2922, 1783, 1713, 1626, 1495, 1452, 1360, 1256 cm^{-1}; MS (EI) m/z (%) 198 [M^+] (19.2), 172 (50.7), 157 (29.8), 155 (100.0), 129 (43.9), 128 (36.2), 115 (30.4), 43 (29.2); HRMS (EI) calcd for $C_{14}H_{14}O$ (M^+) requires 198.1045, found 198.1044.

Compound 2a: yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 2.17 (s, 3H, CH_3), 3.78−3.80 (m, 1H, CH), 4.18−4.21 (m, 1H, CH), 4.64 (br s, 1H, CH), 5.07 (d, J = 2.4 Hz, 1H, CH), 6.13−6.16 (m, 1H, CH), 6.39 (dd, J = 5.6, 2.4 Hz, 1H), 7.18−7.25 (m, 3H, Ar), 7.28−7.32 (m, 2H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 28.5, 49.1, 69.1, 107.5, 126.6, 127.8, 128.6, 133.4, 136.0, 144.3, 156.5, 206.5; IR (CH_2Cl_2) ν 3057, 2938, 2838, 1712, 1633, 1588, 1505, 1460, 1423 cm^{-1}; MS (EI) m/z (%) 198 [M^+] (37.8), 156 (29.9), 155 (100.0), 154 (23.6), 153 (33.0), 152 (14.3), 115 (15.3), 43 (15.7); HRMS (EI) calcd for $C_{14}H_{14}O$ (M^+) requires 198.1045, found 198.1044.

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