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Rapid Preparation of Cycloheptane Ring from 1,2-Diketone and Bis(iodozincio)methane via Oxy-Cope Rearrangement Using Microflow System

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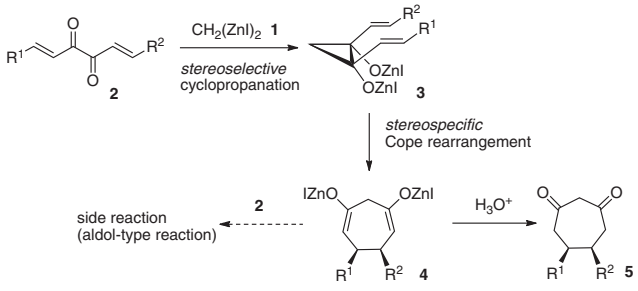
Treatment of 1,6-dialkylhexa-1,5-diene-3,4-diones with bis(iodozincio)methane at −78 °C for several hours gave *cis*-dialkenylcyclopropane-1,2-diols which rearranged into the zinc alkoxides of *cis*-5,6-dialkylcyclohepta-3,7-diene-1,3-diol in good yields at room temperature as a one-pot reaction. The reaction should be performed under the careful temperature control. When the reaction was performed using a microflow system, these two-step reactions were able to be performed in a few seconds at room temperature.

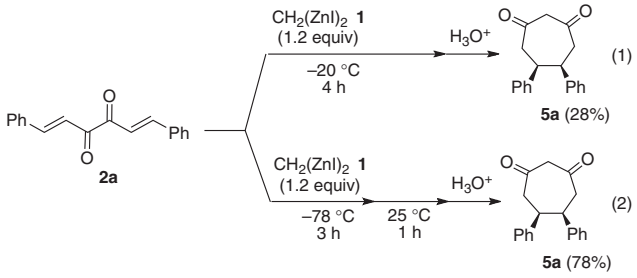
A cycloheptane ring is often observed in natural products, and its preparation has been well studied.[1] To construct it, cycloaddition reactions have been vigorously developed. In the meanwhile, the cyclization strategy to a seven-membered ring has been also examined in spite of unfavorable entropic factors.[2] Among the cyclization method, the Cope rearrangement of *cis*-divinylcyclopropane has been recognized as an efficient route to obtain a cycloheptane skeleton. The disadvantageous entropic factor to form a seven-membered ring is compensated with a favorable configuration of *cis*-divinylcyclopropane. The difficulty of the selective preparation of the *cis*-isomer of the substrate, however, often causes the transformation to be less valuable. Although some practical methods for the preparation of the *cis*-isomer have been shown,[3] most methods yielded the *trans*-isomers that require a temperature of over 100 °C to perform the Cope rearrangement.[3d,4] During the course of our research concerning bis(iodozincio)methane (**1**), we found the nucleophilic cyclopropanation of 1,2-diketone, which gave *cis*-cyclopropane-1,2-diol stereoselectively.[5,6] When 1,6-dialkylhexa-1,5-diene-3,4-diones **2** were treated with **1**, the products would be zinc alkoxides of *cis*-divinylcyclopropane-1,2-diols **3**. The alkoxides of *cis*-divinylcyclopropane derivatives **3** would undergo the Cope rearrangement more rapidly due to acceleration by the alkoxide groups (Scheme 1).[7] These two reactions may be performed sequentially without isolation.



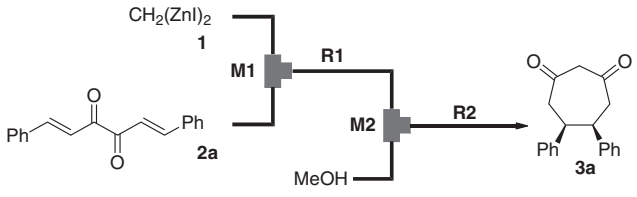
Scheme 1. Syntheses of cycloheptane derivatives.

As an addition of (1*E*,5*E*)-1,6-diphenylhexa-1,5-diene-3,4-dione (**2a**) to bis(iodozincio)methane (**1**) at 0 °C gave a messy mixture, the same procedure was examined at −20 °C. Although the desired seven-membered ring product **5a** was obtained in 28% yield, the aldol adduct of the zinc enolate **4a** to the ketone **2a** was also obtained in 40% yield (Scheme 2(1)). This result implied that the first reaction, that is, the cyclopropanation of **2a** with **1** should complete before the start of Cope rearrangement to prevent the side reactions. For this purpose, we treated the diketone **2** with **1** at the lower temperature, which does not allow the Cope rearrangement, for an appropriate period, until the completion of cyclopropanation, and the resulting mixture was warmed up to promote the rearrangement. Actually, as shown in Scheme 2(2), (1*E*,5*E*)-1,6-diphenylhexa-1,5-diene-3,4-dione (**2a**) was treated with **1** for 3 h at −78 °C, and the resulting mixture was warmed up to 25 °C gradually to give the 7-membered ring **5a** in 78% yield.[8]

The microflow system (space integration)[9] may improve the problem of the one-pot procedure described above, as it can supply the minimum amount of the substrate to be consumed at the micromixer. Thus, as shown in Scheme 3, we constructed a microflow system consisting of two T-shaped SUS micromixers (**M1** and **M2**; $\Phi = 0.5$ mm) and two SUS microtube reactors (**R1** and **R2**; $\Phi = 1.0$ mm). A THF solution of **1** (0.16 M, 3.92 mL min^{-1}) and a THF solution of 1,2-diketone (0.09 M, 3.92 mL min^{-1}) were introduced by a syringe pump, and quenched

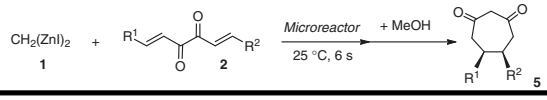


Scheme 2. Preparation of (5*R*,6*S*)-5,6-diphenylcycloheptane-1,3-dione in a batch.



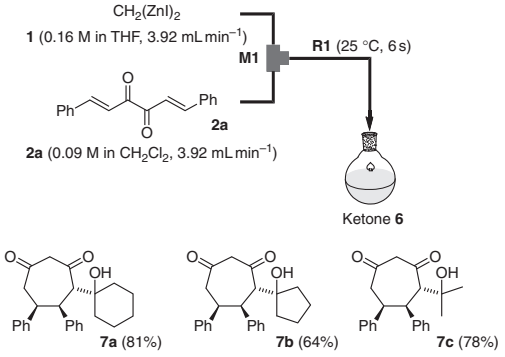
Scheme 3. Microflow system for the preparation of cycloheptane-1,3-dione.

Table 1. Preparation of cycloheptane-1,3-diones using microflow system[a]



Entry	2	R^1	R^2	Solvent	5/%
1	**2a**	Ph	Ph	THF	85
2	**2b**	*p*-Anisyl	*p*-Anisyl	THF	55
3	**2c**	4-F-C_6H_4	4-F-C_6H_4	THF	82
4	**2d**	2-Furyl	2-Furyl	THF	77
5	**2e**	4-*t*-Bu-C_6H_4	4-*t*-Bu-C_6H_4	THF	74
6	**2f**	Me	Me	THF	51
7	**2g**	Ph	Ph	CH_2Cl_2/THF	>99
8	**2h**	*p*-Tol	*p*-Tol	CH_2Cl_2/THF	>99
9	**2i**	*p*-Anisyl	*p*-Anisyl	CH_2Cl_2/THF	92
10	**2j**	4-*t*-Bu-C_6H_4	4-*t*-Bu-C_6H_4	CH_2Cl_2/THF	81
11	**2k**	Me	Me	CH_2Cl_2/THF	70

[a]The reaction was performed with the microflow system in Scheme 3: T-shaped SUS micromixer: **M1** (inner diameter: 0.5 mm) and **M2** (inner diameter: 0.5 mm), SUS microtube reactor: **R1** ($\Phi = 1.0$ mm, length = 1 m), **R2** ($\Phi = 1.0$ mm, length = 1 m), a solution of **1**: 3.92 mL min^{-1}, 0.16 M; a solution of **2**: 3.92 mL min^{-1}, 0.09 M; methanol: 7.85 mL min^{-1}.



Scheme 4. Sequential reaction using microflow system.[11]

the excess amount of **1** with methanol in the **M2**. The residence time was optimized by the length of the microtube reactor. As shown in Table 1 (Entries 1–6), the products were obtained in reasonable yields at 25 °C for 6 s continuously. In addition, the system allowed us to use dichloromethane as a cosolvent. As the structure change of the dizinc **1** in THF based on the Schlenk equilibrium, which is often induced by an addition of any other solvent, spoils the nucleophilicity,[10] dichloromethane is difficult to use as a cosolvent in a one-pot reaction. In the system, a THF solution of **1** (0.16 M, 3.92 mL min^{-1}) and a dichloromethane solution of 1,2-diketone (0.09 M, 3.92 mL min^{-1}) were introduced by a syringe pump, and quenched the excess amount of **1** with methanol at the **M2**. The yields of the products were improved dramatically (Entries 7–11, Table 1).

The further integrated syntheses were demonstrated in Scheme 4. The reaction mixture, which ran out from the microflow system, was treated with excess amount of a ketone. Although the mixture containing a dienolate **4** was treated with an excess amount of the ketone, the mono-aldol product was obtained in a moderate yield.[12–14]

Thus, we can show an efficient use of a microflow system for the transformation of divinyl-1,2-diketones into cycloheptane-1,3-diones. While the classical batch reaction required a careful temperature control to suppress the sidereaction between the product and the starting substrate, the microflow system did exclude the product from the reaction site continuously. The one-pot reaction, which is difficult to control in the conventional vessel, can be carried out efficiently using the space integration concept.

References and Notes

1 C. H. Heathcock, S. L. Graham, M. C. Pirrung, F. Plavac, C. T. White, in *The Total Synthesis of Natural Products*, ed. by J. ApSimon, Wiley, New York, **1983**, pp. 333–384.

2 a) H. M. L. Davies, *Tetrahedron* **1993**, *49*, 5203. b) D. A. Foley, A. R. Maguire, *Tetrahedron* **2010**, *66*, 1131. c) G. A. Molander, *Acc. Chem. Res.* **1998**, *31*, 603. d) Y. Ni, J. Montgomery, *J. Am. Chem. Soc.* **2004**, *126*, 11162.

3 a) H. Lebel, J.-F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977. b) K. Takeda, M. Takeda, A. Nakajima, E. Yoshii, *J. Am. Chem. Soc.* **1995**, *117*, 6400. c) V. Vuligonda, M. E. Garst, R. A. S. Chandraratna, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 589. d) N. J. Wallock, W. A. Donaldson, *Org. Lett.* **2005**, *7*, 2047. e) S. Pantke-Böcker, G. Pohnert, I. Fischer-Lui, W. Boland, *Tetrahedron* **1995**, *51*, 7927. f) J. P. Olson, H. M. L. Davies, *Org. Lett.* **2008**, *10*, 573.

4 a) P. A. Wender, M. P. Filosa, *J. Org. Chem.* **1976**, *41*, 3490. b) E. Thomas, A. N. Kasatkin, R. J. Whitby, *Tetrahedron Lett.* **2006**, *47*, 9181. c) H. M. L. Davies, T. J. Clark, H. D. Smith, *J. Org. Chem.* **1991**, *56*, 3817. d) H. M. L. Davies, B. D. Doan, *J. Org. Chem.* **1999**, *64*, 8501. e) J. E. Baldwin, K. E. Gilbert, *J. Am. Chem. Soc.* **1976**, *98*, 8283.

5 a) K. Ukai, K. Oshima, S. Matsubara, *J. Am. Chem. Soc.* **2000**, *122*, 12047. b) S. Matsubara, K. Ukai, H. Fushimi, Y. Yokota, H. Yoshino, K. Oshima, K. Omoto, A. Ogawa, Y. Hioki, H. Fujimoto, *Tetrahedron* **2002**, *58*, 8255. c) K. Nomura, K. Asano, T. Kurahashi, S. Matsubara, *Heterocycles* **2008**, *76*, 1381.

6 a) M. Sada, S. Komagawa, M. Uchiyama, M. Kobata, T. Mizuno, K. Utimoto, K. Oshima, S. Matsubara, *J. Am. Chem. Soc.* **2010**, *132*, 17452. b) M. Sada, S. Matsubara, *J. Am. Chem. Soc.* **2010**, *132*, 432. c) S. Ueno, M. Sada, S. Matsubara, *Chem. Lett.* **2010**, *39*, 96.

7 D. A. Evans, A. M. Golob, *J. Am. Chem. Soc.* **1975**, *97*, 4765.

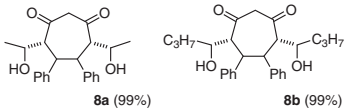
8 Y. Takada, K. Nomura, S. Matsubara, *Org. Lett.* **2010**, *12*, 5204.

9 a) S. Suga, D. Yamada, J.-i. Yoshida, *Chem. Lett.* **2010**, *39*, 404. b) J.-i. Yoshida, K. Saito, T. Nokami, A. Nagaki, *Synlett* **2011**, 1189. c) Y. Takada, S. Matsubara, *Chem. Lett.* **2011**, *40*, 364.

10 M. Sada, S. Matsubara, *Tetrahedron* **2011**, *67*, 2612.

11 Crystallographic data have been deposited with The Cambridge Crystallographic Data Centre: Deposition number CCDC-878671 for compound **7a**. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif (or from The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; e-mail: data_request@ccdc.cam.ac.uk).

12 Instead of ketone, an excess amount of aldehyde and the reaction mixture from the microflow system gave the bis-aldol products **8a** and **8b**. The diastereomeric ratio was quite high, but the relative stereochemistry has not been determined.



13 The low reactivity of the ketones **6** caused an isomerization of the monoenolate, which had been formed by the reaction with an equimolar ketone **6**, into the stable 1,3-diketone enolate. It cannot react with the ketone.

14 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

