One-Pot Coupling of Two Alkynes and One Alkene for Formation of Cyclohexene Derivatives via Zirconacyclopentadienes

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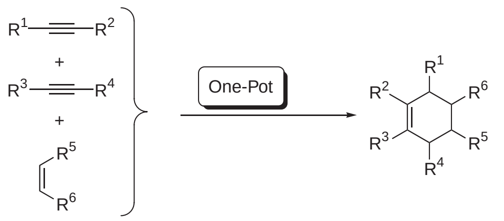
One-pot synthesis of cyclohexene derivatives from two alkynes and one maleic acid derivative could be achieved. Two alkynes were treated with [Cp_2ZrBu_2] to give zirconacyclopentadienes. Addition of 2 equiv of H_2O followed by the reaction with maleic anhydride at 100 °C in toluene for 12 h afforded the cyclohexene derivatives in high yields. The corresponding titanacyclopentadiene did not give the desired product under the same conditions. In the case of Hf, only 8% of the product was obtained. Dienylzirconocene, which could be prepared by the addition of one equiv of EtOH or *t*-BuOH to the zirconacyclopentadiene, also reacted with maleic anhydride to give the cyclohexene derivative in 82 and 62% yield, respectively.

The cyclohexene skeleton is an important structural unit of some natural compounds.[1–6] A number of methods have been developed for constructing cyclohexene derivatives.[7–11] Among them, the most notable reaction is the Diels–Alder reaction using dienes and alkenes.[11] Dienes can be prepared from two alkynes using transition metals.

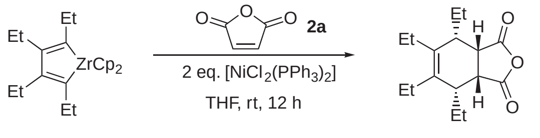


(1)

Therefore, from the point of view of synthetic chemistry, one-pot synthesis of cyclohexene derivatives from two alkynes and one alkene is very attractive. In this paper, we would like to report the one-pot synthesis of cyclohexene derivatives from two alkynes and maleic acid derivatives via zirconacyclopentadienes.

Results and Discussion

We have investigated various reactions of zirconacyclopentadienes,[12] which are conveniently prepared by the reaction of [Cp_2ZrBu_2] or [Cp_2ZrEt_2] with two alkynes or a diyne. During the course of our study on the reaction of the zirconacyclopentadiene **1a** with maleic anhydride in the presence of two equiv of [$NiCl_2(PPh_3)_2$], the cyclohexene derivative **3a** was obtained as shown in Eq. 2.



(2)

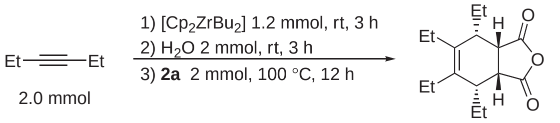
1a

3a
73% isolated yield

In order to find the source of two protons in this reaction, the resulting mixture was quenched with D_2O. However, there is no significant incorporation of deuterium in the product. This reaction was quite mysterious and confusing for us, but it indicated the possibility of the one-pot synthesis of cyclohexene derivatives from two alkynes and one alkene via zirconacyclopentadienes.[12]

It is well known that low-valent early transition-metal compounds react with two alkynes to afford diene derivatives after hydrolysis and the isolated dienes can be used for Diels–Alder reactions.[13] Nugent et al. reported the first example for Diels–Alder reaction using diene derivatives prepared from titanacyclopentadienes.[13a] They isolated the dienes after hydrolysis of titanacyclopentadienes. However, there have been no example for the one-pot formation of such cyclohexene derivatives from two alkynes and one alkene via metallacyclopentadienes.

After various investigations, we found that the addition of 2 mmol of H_2O to the reaction mixture prepared from 1.2 mmol of [Cp_2ZrBu_2] and 2.0 mmol of 3-hexyne is very effective for the one-pot reaction. The desired product **3a** was obtained in 90% GC yield.

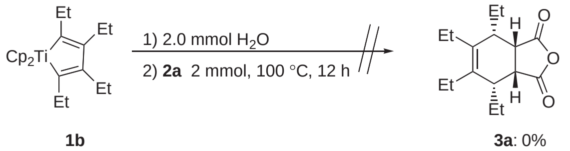


(3)

3a: 90%

Without the addition of water, the desired product **3a** was not obtained. It is clearly understood that the zirconacyclopentadiene **1a** prepared from 3-hexyne and [Cp_2ZrBu_2] was hydrolyzed with water and that thus-formed 4,5-diethyl-3,5-octadiene reacted with maleic anhydride. In fact, 95% of 4,5-diethyl-3,5-octadiene was detected when **1a** was treated with 2.0 mmol of H_2O at 100 °C for 1 h.

It is interesting to note that under the same conditions, when the titanocene compound was used instead of zirconocene, the desired product **3a** was not obtained.



(4)

1b

3a: 0%

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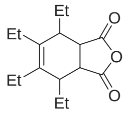
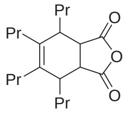
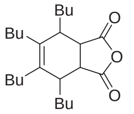
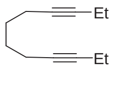
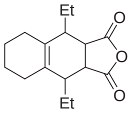
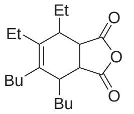
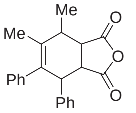
Although the Diels–Alder reaction has been known using the isolated dienes prepared from titanacyclopentadienes after hydrolysis,[13a] a one-pot procedure with ca. 2 equiv of water did not give **3a** at all. In order to understand the origin of the difference between Zr and Ti, reactions of **1a** and **1b** with 2 equiv of D_2O were investigated. When **1a** was treated with D_2O at room temperature for 3 h, 33% of **1a** reacted to open the ring of the zirconacycle. In contrast, in the case of the titanium **1b**, no reaction with D_2O was observed. This indicates that the reactivity of **1a** and **1b** towards water is the origin of the difference observed here.

When the tetraethylhafnacyclopentadiene **1c** was used for the same reaction under identical conditions with maleic anhydride, **3a** was given only in 8% yield. Therefore, the one-pot cyclohexene formation from two alkynes and maleic anhydride using zirconocene under the conditions used here is very unusual but useful.

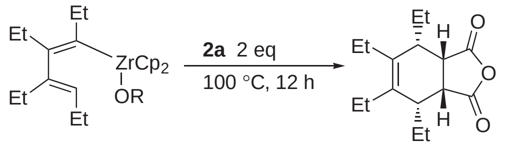
We have reported that when zirconacyclopentadienes were treated with one equiv of an alcohol such as EtOH and *t*-BuOH,[14] one of the two carbon–zirconium bonds of zirconacyclopentadienes was selectively cleaved to afford dienylzirconocene derivatives. It is notable that such dienylzirconocenes **4a** and **4b** reacted with maleic anhydride at 100 °C for 12 h to give **3a** in 82 and 62% yields, respectively, after hydrolysis.

Further study involving the use of diyne or a combination of two different alkynes resulted in the formation of the tetrahydroisobenzofuran-1,3-dione products **3a**–**3f** in high yields. The results are summarized in Table 1.

Table 1. Reaction of Alkynes with Maleic Anhydride **2a**

Entry	Alkyne	Product		Yield/%[a),b)]
1	Et—≡—Et		**3a**	90(71)
2	Pr—≡—Pr		**3b**	88(74)
3	Bu—≡—Bu		**3c**	87(77)
4			**3d**	84(72)
5	Et—≡—Et Bu—≡—Bu		**3e**	75(61)
6	Me—≡—Me Ph—≡—Ph		**3f**	86(75)

a) GC yield. b) Isolated yields are given in parentheses.



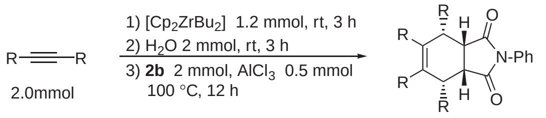
(5)

4a: R=Et
4b: R = t-Bu

3a

82% from **4a**
62% from **4b**

When the *N*-phenylmaleimide (**2b**) was used instead of maleic anhydride, the expected products **5a**–**5c** were obtained as shown in Eq. 6. It is noteworthy that in this reaction with **2b**, 0.5 mmol of anhydrous aluminum chloride was necessary to obtain the desired products.[15,16]



(6)

5a: R = Et 77 (64) %
5b: R = Pr 80 (68) %
5c: R = Bu 76 (65) %

Conclusion

A convenient method for the preparation of cyclohexene derivatives has been developed based on the one-pot coupling of two alkynes and one alkene via zirconacyclopentadienes.

Experimental

General. All reactions involving organometallic compounds were carried out using standard Schlenk techniques under nitrogen. Toluene was distilled from sodium/benzophenone. Zirconocene dichloride was purchased from Aldrich Chemical Co., Ltd. The other starting materials were purchased from commercial sources and used as received. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-ECA 300 MHz spectrometer in $CDCl_3$ solutions. Chemical shifts are reported in ppm with internal reference to TMS. GC analysis was performed with a Shimadzu GC-14B, equipped with a fused-silica capillary column. The appropriate alkanes were used as internal standards.

Formation of Tetrahydroisobenzofuran-1,3-diones from Two Alkynes and Maleic Anhydride. To a solution of $[Cp_2ZrCl_2]$ (0.35 g, 1.2 mmol) in toluene (5 mL) were added *n*-butyllithium (1.6 M in a hexane solution, 1.5 mL, 2.4 mmol) and alkynes (2.0 mmol) at −78 °C. The mixture was stirred at −78 °C for 15 min and then warmed to room temperature for 3 h. Water (2.0 mmol) was added to the above mixture and the mixture was kept at room temperature for 3 h. Then, maleic anhydride (2.0 mmol) was added. The mixture was heated to 100 °C for 12 h. The reaction mixture was quenched with water, extracted with ethyl acetate, and dried over $MgSO_4$. Filtration, evaporation, and separation by column chromatography on silica gel afforded the products.

3a,4,7,7a-Tetrahydro-4,5,6,7-tetraethylisobenzofuran-1,3-dione (3a): Yield 90%. ^1H NMR ($CDCl_3$, Me_4Si) δ 0.90 (t, $J = 7.5$ Hz, 6H), 1.10 (t, $J = 7.5$ Hz, 6H), 1.83–1.95 (m, 2H), 2.04–2.20 (m, 8H), 3.40–3.42 (m, 2H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 12.57, 14.95, 20.07, 20.68, 41.07, 42.71, 138.29, 172.37. HRMS calcd for $C_{16}H_{24}O_3$ 264.1725, found 264.1721.

3a,4,7,7a-Tetrahydro-4,5,6,7-tetrapropylisobenzofuran-1,3-

dione (3b): Yield 88%. ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.92 (t, $J = 7.5$ Hz, 6H), 1.03 (t, $J = 7.5$ Hz, 6H), 1.20–1.38 (m, 6H), 1.63–1.78 (m, 4H), 2.00–2.14 (m, 6H), 2.24–2.32 (m, 2H), 3.34–3.36 (m, 2H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 14.34, 14.65, 21.32, 23.91, 29.51, 30.49, 39.15, 43.40, 137.36, 172.38. HRMS calcd for $C_{20}H_{32}O_3$ 320.2351, found 320.2355.

3a,4,7,7a-Tetrahydro-4,5,6,7-tetrabutylisobenzofuran-1,3-dione (3c): Yield 87%. ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.90 (t, $J = 7.5$ Hz, 6H), 0.96 (t, $J = 7.5$ Hz, 6H), 1.15–1.46 (m, 16H), 1.54–1.67 (m, 2H), 1.73–1.84 (m, 2H), 2.02–2.14 (m, 4H), 2.21–2.29 (m, 2H), 3.33–3.38 (m, 2H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.79, 14.10, 22.89, 23.17, 27.02, 27.86, 30.40, 32.62, 39.35, 43.47, 138.28, 172.38. HRMS calcd for $C_{24}H_{40}O_3$ 376.2977, found 376.2974.

3a,4,5,6,7,8,9,9a-Octahydro-4,9-diethylnaphtho[2,3-*c*]furan-1,3-dione (3d): Yield 84%. ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.08 (t, $J = 7.5$ Hz, 6H), 1.48–1.58 (m, 4H), 1.82–2.08 (m, 8H), 2.16–2.24 (m, 2H), 3.40–3.42 (m, 2H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 12.67, 19.91, 22.62, 25.38, 40.99, 43.37, 134.24, 172.08. HRMS calcd for $C_{16}H_{22}O_3$ 262.1569, found 262.1570.

3a,4,7,7a-Tetrahydro-4,5-dibutyl-6,7-diethylisobenzofuran-1,3-dione (3e): Yield 75%. ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.88–0.98 (m, 9H), 1.10 (t, $J = 7.5$ Hz, 3H), 1.18–1.48 (m, 8H), 1.72–1.94 (m, 2H), 2.02–2.18 (m, 6H), 2.20–2.29 (m, 2H), 3.34–3.43 (m, 2H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 12.59, 13.81, 14.09, 14.95, 20.13, 20.86, 22.85, 23.16, 26.90, 27.69, 30.36, 32.70, 39.31, 41.08, 42.77, 43.37, 137.03, 138.47, 172.37(2C). HRMS calcd for $C_{20}H_{32}O_3$ 320.2351, found 320.2353.

3a,4,7,7a-Tetrahydro-4,5-dimethyl-6,7-diphenylisobenzofuran-1,3-dione (3f): Yield 86%. ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.67 (d, $J = 7.5$ Hz, 3H), 1.73 (s, 3H), 2.88 (m, 1H), 3.46 (dd, $J = 8.4$, 8.7 Hz, 1H), 3.68 (dd, $J = 8.8$, 7.2 Hz, 1H), 4.10 (d, $J = 7.2$ Hz, 1H), 6.84–6.88 (m, 2H), 7.05–7.18 (m, 8H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 15.64, 18.28, 33.59, 44.18, 46.30, 46.78, 126.68, 127.69, 127.94, 128.08, 129.10, 130.19, 134.17, 135.34, 136.12, 140.45, 170.87. Anal. Calcd for $C_{22}H_{20}O_3$: C, 79.50; H, 6.06%. Found: C, 79.62; H, 6.18%.

Formation of 3a,4,7,7a-Tetrahydro-2-phenyl-2*H*-isoindole-1,3-diones 5. A brown homogeneous toluene solution of zirconacyclopentadiene was prepared in situ as described. Water (2.0 mmol) was added to the above mixture at room temperature for 3 h. *N*-Phenylmaleimide (2.0 mmol) and anhydrous aluminum chloride (0.5 mmol) were added to the above reaction mixture and the mixture was heated to 100 °C for 12 h. Then, the reaction mixture was quenched with water, extracted with ethyl acetate, and dried over $MgSO_4$. Filtration, evaporation, and separation by column chromatography on silica gel afforded the compounds.

3a,4,7,7a-Tetrahydro-4,5,6,7-tetraethyl-2-phenyl-2*H*-isoindole-1,3-dione (5a): Yield 77%. ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.94 (t, $J = 7.5$ Hz, 6H), 1.16 (t, $J = 7.5$ Hz, 6H), 1.84–1.96 (m, 2H), 2.08–2.30 (m, 8H), 3.27–3.33 (m, 2H), 7.15–7.46 (m, 5H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 12.91, 15.20, 20.55, 20.83, 41.70, 41.80, 126.34, 128.16, 128.87, 132.01, 137.55, 177.38. HRMS calcd for $C_{22}H_{29}NO_2$ 339.2198, found 339.2195.

3a,4,7,7a-Tetrahydro-2-phenyl-4,5,6,7-tetrapropyl-2*H*-isoindole-1,3-dione (5b): Yield 80%. ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.90 (t, $J = 7.5$ Hz, 6H), 1.01 (t, $J = 7.5$ Hz, 6H), 1.14–1.44 (m, 6H), 1.66–1.80 (m, 4H), 2.00–2.08 (m, 4H), 2.16–2.26 (m, 2H), 2.32–2.38 (m, 2H), 3.20–3.25 (m, 2H), 7.13–7.43 (m, 5H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 14.17, 14.50, 21.31, 23.86, 29.85, 30.53, 39.40, 42.18, 126.10, 128.00, 128.63, 131.87, 136.39, 177.14. HRMS calcd for $C_{26}H_{37}NO_2$ 395.2824, found 395.2827.

3a,4,7,7a-Tetrahydro-4,5,6,7-tetrabutyl-2-phenyl-2*H*-isoindole-1,3-dione (5c): Yield 76%. ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.88 (t, $J = 7.5$ Hz, 6H), 0.95 (t, $J = 7.5$ Hz, 6H), 1.16–1.48 (m, 14H), 1.64–1.81 (m, 4H), 2.05–2.10 (m, 4H), 2.17–2.24 (m, 2H), 2.28–2.37 (m, 2H), 3.20–3.28 (m, 2H), 7.17–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.61, 13.98, 22.82, 23.07, 27.34, 27.86, 30.50, 32.84, 39.70, 42.34, 126.16, 127.96, 128.63, 131.90, 136.39, 177.23. HRMS calcd for $C_{30}H_{45}NO_2$ 451.3450, found 451.3453.

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