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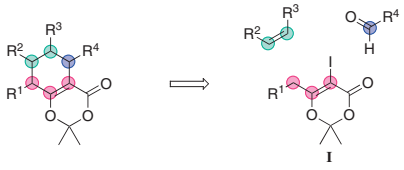
# Expeditious Modular Assembly of Multisubstituted Cyclohexanes via Dioxanone–Dienes

Yoshifumi Aoki, Yuta Mochizuki, Tomohiro Yoshinari, Ken Ohmori, and Keisuke Suzuki*
*Department of Chemistry, Tokyo Institute of Technology, 2-12-1 O-okayama, Meguro-ku, Tokyo 152-8551*

(Received August 4, 2011; CL-110655; E-mail: ksuzuki@chem.titech.ac.jp)

An effective route to multisubstituted cyclohexanes has been developed by exploiting the Diels–Alder reaction of easily available dienes within a dioxanone moiety with electron-deficient dienophiles.

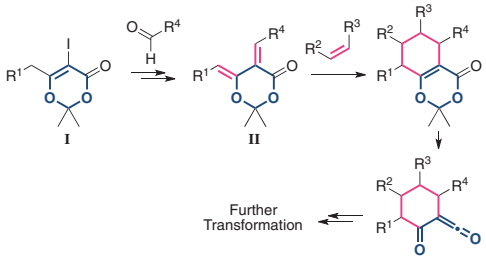
Modular assembly of organic molecules with sizable molecular weight and/or complexity is gaining increasing importance for developing effective routes to architecturally complex, biologically active natural/unnatural products.[1] Associated with the importance of *cyclohexane* motifs with functional and stereochemical complexity,[2] we report herein assembly of a cyclohexane skeleton from three components, that is, an olefin, an aldehyde, and a $\beta$-keto ester equivalent, that is, iododioxinone **I** (Scheme 1).



**Scheme 1.** Cyclohexane modular assembly.

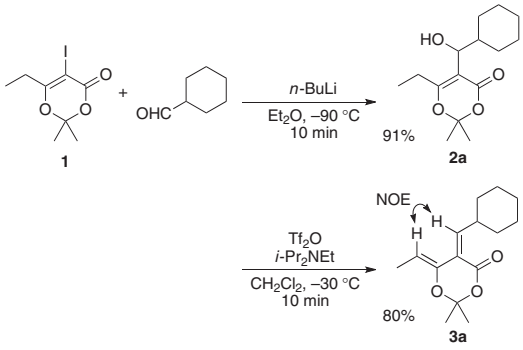
As the key conjunctive agent of our plan for assembling three components, we focused on diene **II** as the synthetic platform, which could be derived from iododioxinone **I** and an aldehyde (Scheme 2). Three promising features in **II** are, (1) high Diels–Alder reactivity expected from two vicinal exocyclic alkenes (*s-cis* diene), (2) characteristic reactivity by donor/acceptor substitution pattern,[3] and (3) capability of generating acyl ketene species from the dioxinone moiety[4] that is regenerated by the Diels–Alder reaction, amenable for various synthetic manipulations. In addition, the dioxanone scaffold may also provide a platform for stereoselective reactions.[5]

We report herein facile synthesis of dienes **II** and their excellent behaviors in the Diels–Alder reactions.




**Scheme 2.** Synthetic plan.

Readily available iododioxinone **1**[6,7] served as a platform to various dienes. The protocol is exemplified by the preparation of diene **3a** (Scheme 3). To a mixture of iodide **1** and cyclohexanecarbaldehyde in $Et_2O$ (−90 °C) was added *n*-BuLi, where a rapid halogen–lithium exchange followed by the carbonyl addition gave alcohol **2a** in 91% yield.[8] Alcohol **2a**, thus obtained, was treated with triflic anhydride in the presence of Hünig's base, giving cleanly diene **3a** as the single product in 80% yield. The (*Z*,*Z*) stereochemistry was proven by NOE study.




**Scheme 3.** Synthesis of diene **3a**.

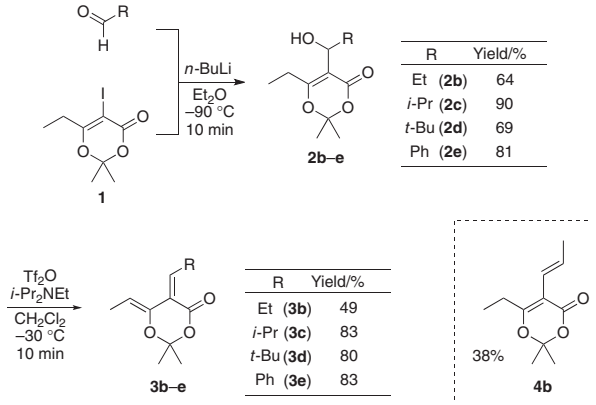
Scheme 4 shows a rationale for the (*Z*,*Z*)-selectivity; Given the 1,4-elimination occurred from the intermediary triflate with the *anti* and/or *syn* relationship of the proton and the triflate,[9] the 1,3-allylic strain[10] suggests that the reaction would occur from conformers **A** and/or **B**, either of which gives the (*Z*,*Z*) isomer.


**Scheme 4.** Possible conformations for 1,4-elimination.

This protocol allowed facile access to several other dienes **3b**–**3e** from the corresponding aldehydes (Scheme 5). Rigorous (*Z*,*Z*)-selectivity applied in all of these cases. A limitation was that the reaction of alcohol **2b**, the propanal adduct, produced also a positional isomer **4b** in 38% yield.

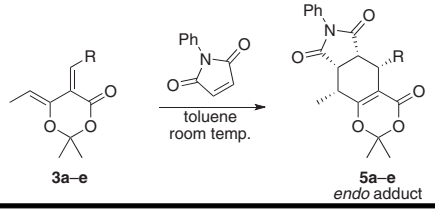
Having these dienes in hand, we examined their reactivity in the Diels–Alder reactions[7] (Table 1). Upon reaction of **3a** with *N*-phenylmaleimide (toluene, room temp., 1 h), the *endo* cycloadduct **5a** was obtained as a single diastereomer in 95% yield (Run 1). The stereochemistry of **5a** was confirmed by X-ray analysis[11] (Figure 1). Other dienes were also subjected to the reaction with *N*-phenylmaleimide, giving good to excellent yield of the respective *endo* cycloadduct as a single isomer. Although the diene **3c** with *sec*-alkyl substituent provided the *endo* cycloadduct **5c** in excellent yield in a short time (Run 3), the yields remained moderate for the reaction of *prim*-alkyl or




**Scheme 5.** Preparation of other dienes.

**Table 1.** Diels–Alder reaction of dienes **3a**–**3e**




| Run | Substrate | R | Time/h | Product | Yield/% |
|---|---|---|---|---|---|
| 1 | **3a** | Cy[a] | 1 | **5a** | 95 |
| 2 | **3b** | Et | 0.5 | **5b** | 46 |
| 3 | **3c** | *i*-Pr | 4 | **5c** | 90 |
| 4 | **3d** | *t*-Bu | 18 | **5d** | 80 |
| 5 | **3e** | Ph | 17 | **5e** | 52 |

[a]Cy: cyclohexyl.

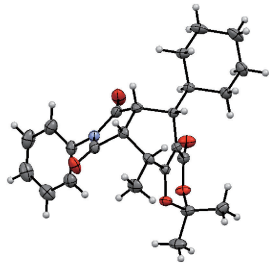
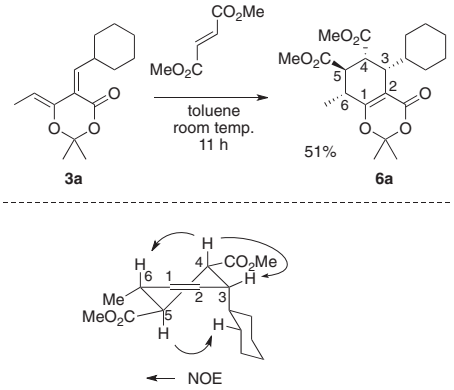


**Figure 1.** X-ray structure of **5a**.

phenyl-substituted ones **3b** and **3e** (Runs 2 and 5). *tert*-Alkyl-substituted diene **3d** gave the *endo* cycloadduct **5d** in high yield, although longer reaction time was required (Run 4).

The reaction of diene **3a** with dimethyl fumarate afforded cycloadduct **6a** in 51% yield as a single isomer among two possible diastereomers (Scheme 6). The stereochemistry of cycloadduct **6a** was determined by NOE study.

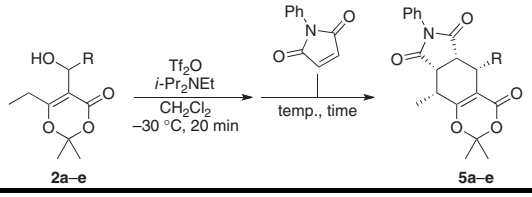
These data convinced us of the successive one-pot reaction of the diene formation and the Diels–Alder reaction, which proved indeed the case[7,12] (Table 2). Starting with the treatment of alcohol **2a** with $Tf_2O$, and after confirming the formation of diene **3a** by TLC analysis, successive addition of *N*-phenylmaleimide cleanly affected the cycloaddition, giving the cycloadduct **5a** in excellent yield (Run 1).




**Scheme 6.** Reaction with dimethyl fumarate.

This one-pot protocol could be applied to the reactions of alcohols **2** with various substituents, although the reaction temperature and time were slightly different (Runs 2–5).

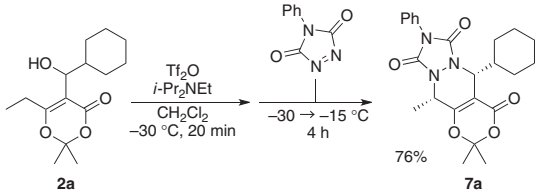
**Table 2.** One-pot reaction




| Run | Substrate | R | Temp. /°C | Time /h | Product | Yield /% |
|---|---|---|---|---|---|---|
| 1 | **2a** | Cy[a] | −30 → −15 | 4 | **5a** | 95 |
| 2 | **2b** | Et | −30 | 0.5 | **5b** | 43 |
| 3 | **2c** | *i*-Pr | −30 | 1 | **5c** | 81 |
| 4 | **2d** | *t*-Bu | −30 → 25 | 8.5 | **5d** | 68 |
| 5 | **2e** | Ph | −30 → 0 | 4 | **5e** | 81 |

[a]Cy: cyclohexyl.

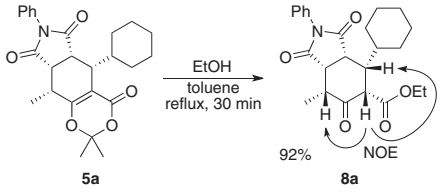
The one-pot protocol was further applicable to a trinitrogen heterocycle (Scheme 7). When 4-phenyl-1,2,4-triazole-3,5-dione was subjected to the one-pot reaction with alcohol **2a**, the cycloadduct **7a** was obtained in 76% yield.




**Scheme 7.** One-pot reaction with another dienophile.

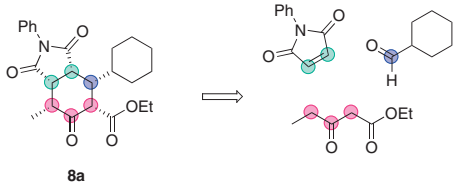
The cycloadduct is amenable to various transformations by exploiting the dioxinone moiety. An example is the following:[7] upon heating of dioxinone **5a** in toluene in the presence of ethanol, $\beta$-keto ester **8a** was obtained in 92% yield as the single diastereomer, which has five contiguous stereogenic centers (Scheme 8). The stereochemistry of **8a** was determined by NOE study. Interestingly, the $\beta$-keto ester **8a** existed completely in the keto form in $CDCl_3$ as well as acetone-$d_6$.




**Scheme 8.** Transformation to $\beta$-keto ester **8a**.

The $\beta$-keto ester **8a** is regarded as an assemblage of three components (Scheme 9), implying promising potential of this approach in the modular synthesis of various natural/unnatural compounds with a cyclohexane structure motif.




**Scheme 9.** Three components assembly.

Further work is in progress on the exploration of the synthetic potential of diene **II**, including its ambiphilic reactivity coming from the substitution pattern with an electron-donating and -withdrawing group.

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10 For a review, see: R. W. Hoffmann, *Chem. Rev.* **1989**, *89*, 1841.

11 Crystallographic data reported in this manuscript have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-838020. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

12 *A typical procedure for the one-pot reaction is described for the reaction of alcohol* ***2a***: To a solution of alcohol **2a** (20.2 mg, 75.3 µmol) in $CH_2Cl_2$ (0.75 mL) was added *i*-$Pr_2NEt$ (52.5 µL, 301 µmol) at −30 °C followed by $Tf_2O$ (19.0 µL, 113 µmol). After stirring for 20 min, *N*-phenylmaleimide (130 mg, 753 µmol) was added, and the stirring was continued for 0.5 h. The resulting solution was allowed to warm slowly to −15 °C. After stirring for 3 h at −15 °C, phosphate buffer (pH 7) was added. Usual extractive workup followed by purification by preparative TLC (hexane/EtOAc = 4/1, three times) gave **5a** (29.9 mg, 95%) as a white powder.


  