

Expeditious Modular Assembly of Multisubstituted Cyclohexanes via Dioxanone–Dienes

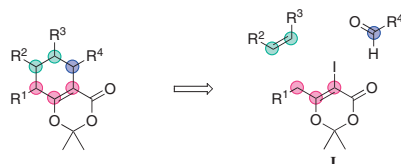
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An effective route to multisubstituted cyclohexanes has been developed by exploiting the Diels–Alder reaction of easily available dienes within a dioxanone moiety with electron-deficient dienophiles.

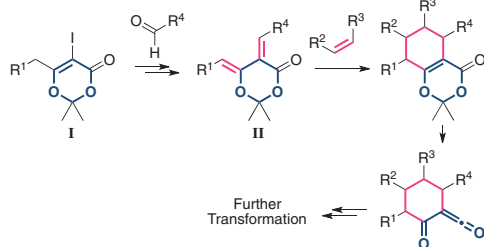
Modular assembly of organic molecules with sizable molecular weight and/or complexity is gaining increasing importance for developing effective routes to architecturally complex, biologically active natural/unnatural products.¹ Associated with the importance of *cyclohexane* motifs with functional and stereochemical complexity,² we report herein assembly of a cyclohexane skeleton from three components, that is, an olefin, an aldehyde, and a β -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 moiety⁴ 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

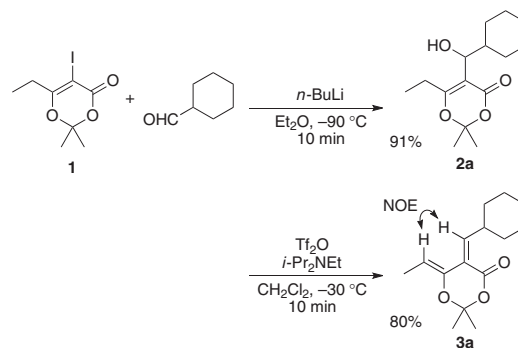
We report herein facile synthesis of dienes **II** and their excellent behaviors in the Diels–Alder reactions.



Scheme 2. Synthetic plan.

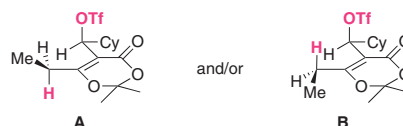
Readily available iododioxinone **1**^{6,7} served as a platform to various dienes. The protocol is exemplified by the preparation of

diene **3a** (Scheme 3). To a mixture of iodide **1** and cyclohexanecarbaldehyde in Et₂O (−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**.

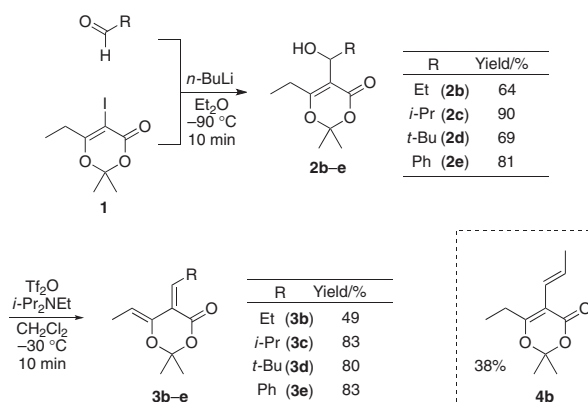
Scheme 4 shows a rationale for the (*Z,Z*)-selectivity; Given the 1,4-elimination occurred from the intermediary triflate with the *anti* and/or *syn* relationship of the proton and the triflate,⁹ the 1,3-allylic strain¹⁰ suggests that the reaction would occur from conformers **A** and/or **B**, either 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.

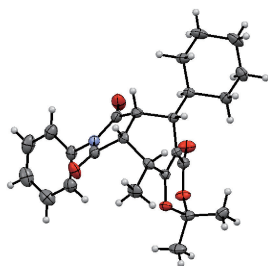
Having these dienes in hand, we examined their reactivity in the Diels–Alder reactions⁷ (Table 1). Upon reaction of **3a** with *N*-phenylmaleimide (toluene, room temp., 1 h), the *endo* cycloadduct **5a** was obtained as a single diastereomer in 95% yield (Run 1). The stereochemistry of **5a** was confirmed by X-ray analysis¹¹ (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**

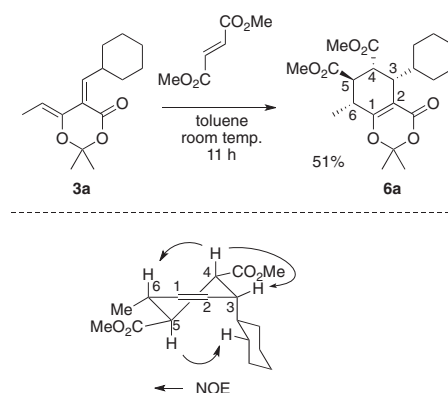
Run	Substrate	R	Time/h	Product	Yield/%
1	3a	Cy ^a	1	5a	95
2	3b	Et	0.5	5b	46
3	3c	<i>i</i> -Pr	4	5c	90
4	3d	<i>t</i> -Bu	18	5d	80
5	3e	Ph	17	5e	52

^aCy: 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 Tf₂O, 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.

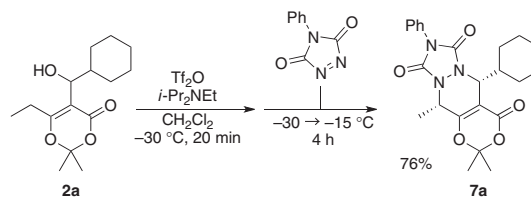
This one-pot protocol could be applied to the reactions of alcohols **2** with various substituents, although the reaction temperature and time were slightly different (Runs 2–5).

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>i</i> -Pr	−30	1	5c	81
4	2d	<i>t</i> -Bu	−30 → 25	8.5	5d	68
5	2e	Ph	−30 → 0	4	5e	81

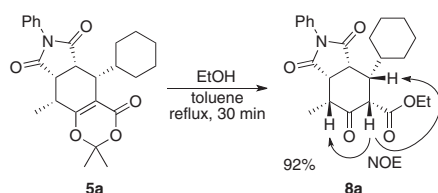
^aCy: cyclohexyl.

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.



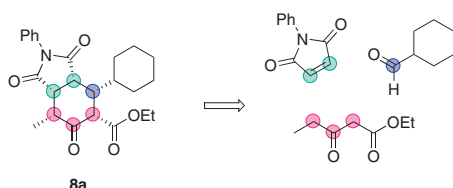
Scheme 7. One-pot reaction with another dienophile.

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, β -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 β -keto ester **8a** existed completely in the keto form in CDCl₃ as well as acetone-*d*₆.



Scheme 8. Transformation to β -keto ester **8a**.

The β -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.

References and Notes

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- For a review, see: R. W. Hoffmann, *Chem. Rev.* **1989**, *89*, 1841.
- 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).
- 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 μ mol) in CH_2Cl_2 (0.75 mL) was added *i*-Pr₂NEt (52.5 μ L, 301 μ mol) at -30°C followed by TiF_2O (19.0 μ L, 113 μ mol). After stirring for 20 min, *N*-phenylmaleimide (130 mg, 753 μ mol) 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.