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Synthesis of Tetrahydroisoindolinones via a Metal-Free Dehydrogenative Diels-Alder Reaction

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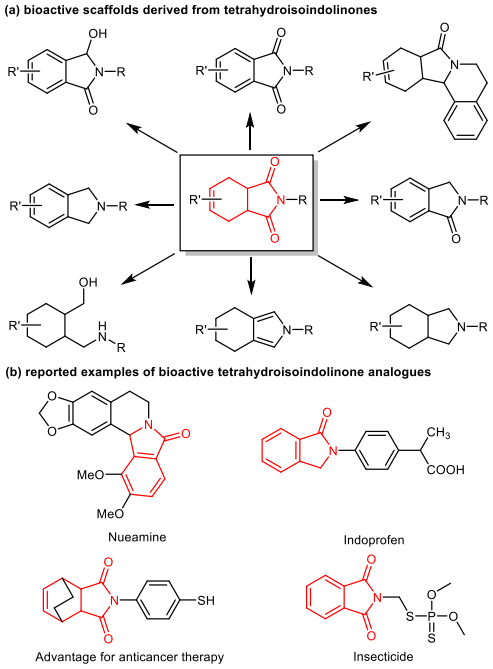
Abstract. A metal-free dehydrogenative Diels-Alder reaction of substituted alkenes for the synthesis of tetrahydroisoindolinones has been exploited for the first time. This new method features functional group tolerance and broad substrate scope, providing an efficient access to biologically active tetrahydroisoindolinone skeletons with *endo* steroselectivity in good to excellent yields.

Keywords: alkenes; cycloaddition; Diels-Alder reaction; dehydrogenation

Synthesis of functional building blocks associated with nature products and biologically relevant molecules have attracted significant attention of organic chemists, because the resulting scaffolds exhibit vital value in functional molecules, organic materials and clinical drugs.[1] The development of synthesis methods and improvement of structural diversity are important factors of organic chemistry research.[2] Diels-Alder (DA) reaction is one of the most efficient and synthetically useful reactions, remaining a powerful tool for synthesis of cyclohexene derivatives.[3] However, one limitation of the reaction is that the diene component is sometimes unavailable and need to be pre-prepared. Therefore, to develop more efficient variation of DA reaction is highly desirable.

Tetrahydroisoindolinone, a privileged structural motif, is widespread in bioactive natural and unnatural products.[4] Many compounds derived from tetrahydroisoindolinone also exhibit considerable biological activities in pharmaceuticals and agrochemicals, such as anti-inflammatory,[5] anticancer,[6] anti-insect.[7] Therefore, great efforts have been made by synthetic and medicinal chemists to construct novel structural motifs of tetrahydroisoindolinone and its derivatives.[8,4c] Among various strategies, DA reaction has been proved as an efficient method for the synthesis of tetrahydroisoindolinones starting from dienes and *N*-substituted maleimides. However, as mentioned above, prefunctionalization to prepare the dienes is always required, which limited the practicability of DA reaction in the synthesis efficiency.



Scheme 1. Bioactive tetrahydroisoindolinone analogues.

Consequently, variation of DA reaction has been emerged for the synthesis of tetrahydroisoindolinones. In 2010, Lee's group reported a Pd-catalyzed tandem DA/cross-coupling reaction of organoindium reagents to form tetrahydroisoindolinones.[8d] Later, Liu's group employed gold-catalyst to isomerize unactivated allenes into 1,3-dienes, and developed an isomerization-DA reaction cascade with *N*-substituted maleimide to give tetrahydroisoindolinones.[8f] Very recently, the direct

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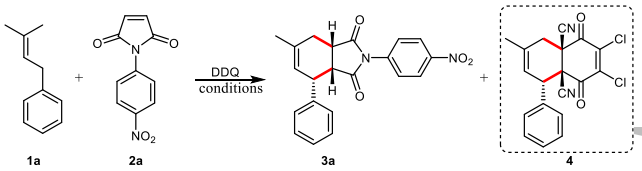
functionalization of C(sp^3)-H bonds, cross-dehydrogenative coupling (CDC) reactions have attracted much attention.[9] As an important member of CDC reactions, dehydrogenative Diels-Alder (DHDA) reaction has irreplaceable advantages in forming cyclohexene derivatives from unprefunctionalized starting materials.[10,2] Owing to the wide application value of tetrahydroisoindolinones, our group has attempted to realize the cross DHDA reaction between prenyl derivatives with *N*-substituted maleimide in the presence of DDQ. Unfortunately, no desired product was observed, only DDQ-adduct was obtained, in which DDQ played a dual role as both oxidant and dienophile.[10c] With our continued effort on DDQ-involved DHDA reaction of prenyl derivatives, we anticipated that the DDQ-adducts could react with *N*-substituted maleimide to give tetrahydroisoindolinones via a thermal Retro-Diels-Alder reaction process.[10h] In which DDQ-adducts would break down into DDQ and dienes, the resulting dienes undergo the DA reaction with *N*-substituted maleimide to form tetrahydroisoindolinones. Retro-Diels-Alder reaction had been studied for almost 90 years,[11] cyclohexene derivatives could release diene and dienophile with an appropriate driving force such as heat, acid or base mediation.[12] To the best of our knowledge, synthesis of functional tetrahydroisoindolinones by using cross DHDA reaction strategy has not been reported. Herein, we report the first efficient DDQ-mediated DHDA reaction via a metal-free thermal reversible process for the synthesis of tetrahydroisoindolinone derivates with high *endo*-selectivity and good to excellent yields in one-pot.

We started to evaluate the cross DHDA reaction of prenyl benzene **1a** with *N*-(4-nitrophenyl)maleimide **2a** for the synthesis of tetrahydroisoindolinone in the presence of DDQ in a ratio of 1:2:1.2 in DCM. To our gratification, the desired product **3a** was obtained when the reaction was conducted under an N_2 atmosphere at room temperature for 72h, even though only a small amount of product **3a** (9%) accompanying with the DDQ-adduct product **4** in 41% yield was detected (Table 1, entry 1). As we mentioned above, temperature is the crucial factor of the retro-DA reaction. Therefore, various temperatures were tested, and the increase of temperature led to higher yield (Table 1, entries 1-4). To our delight, the yield of product was reached 91% and no side-product **4** was observed when the reaction was conducted at 110 °C (Table 1, entry 4). A further increase of temperature did not result to an improved yield (Table 1, entry 5). These results indicated that higher temperature could realize to convert DDQ-adduct **4** into the desired product **3a**, and validated our initial hypothesis. Following this, investigation of solvents (Table 1, entries 4, 6-8), including chlorobenzene, toluene, fluorobenzene, bromobenzene, suggested chlorobenzene to be the best choice (Table 1, entry 4). Screening of different ratio of starting materials (Table 1, entries 4, 9-11), showed that prenyl benzene, *N*-phenylmaleimide and DDQ in a ratio of 2:1:1.5 gave the best result.

Table 1. Optimization of the reaction conditions.[a,b]



Entry	**1a**:**2a**: DDQ	Solvent	T [°C]	T [h]	**3a** Yield [%][b]	**4** Yield [%][b]
1	1:2:1.2	DCM	20	72	9	41
2	2:1:1.5	PhCl	50	72	26	19
3	2:1:1.5	PhCl	80	72	42	11
4	2:1:1.5	PhCl	110	60	91	0
5	2:1:1.5	PhCl	115	72	91	0
6	2:1:1.5	PhF	110	60	71	0
7	2:1:1.5	PhBr	110	60	83	0
8	2:1:1.5	toluene	110	60	78	0
9	1:2:1.2	PhCl	110	60	67	4
10	1.5:1:1.2	PhCl	110	60	84	0
11	2:1:1.2	PhCl	110	60	86	0

[a] Reactions were conducted on a 0.1 mmol scale in solvent under N_2.
[b] Isolated yield.

With the optimized conditions established, we then probed a variety of prenyl derivatives by applying this new method to improve the structural diversity of tetrahydroisoindolinone. The reaction conducted very well with prenyl benzene containing electron-deficient (F, Cl, Br) or electron-rich (Me, OMe, NHAc) substituents at any position of the aryl group, giving the corresponding tetrahydroisoindolinone with high *endo* selectivity and excellent yields (**3a**-**3p**, 87-96%). Moreover, this new reaction worked smoothly even for relatively electron-withdrawing prenyl benzene bearing a CF_3 substituent at the para-position of the phenyl ring and afforded the corresponding tetrahydroisoindolinone with good yield (**3l**, 78%). As shown in table 2, naphthalenyl- and furyl- substituted substrates were well tolerated, furnishing the corresponding product in satisfactory yield (**3q** and **3r**, 95% and 57%). Interestingly. *n*-octyl-substituted Substrate was also amenable to the DHDA reaction, and only single isomer was obtained in 51% yield although there is more than one reaction site of **1s** resulting of diene.

To further extend the scope of this DHDA reaction, more dienophiles were examined under the optimized

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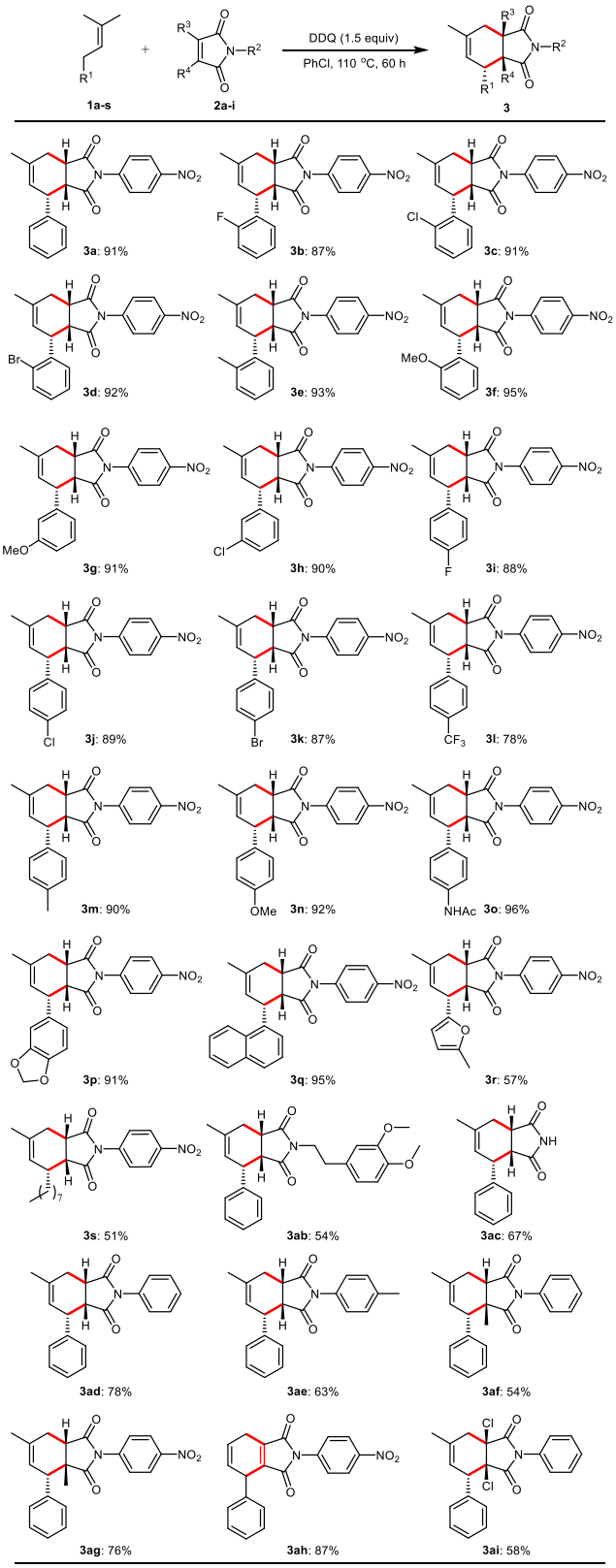
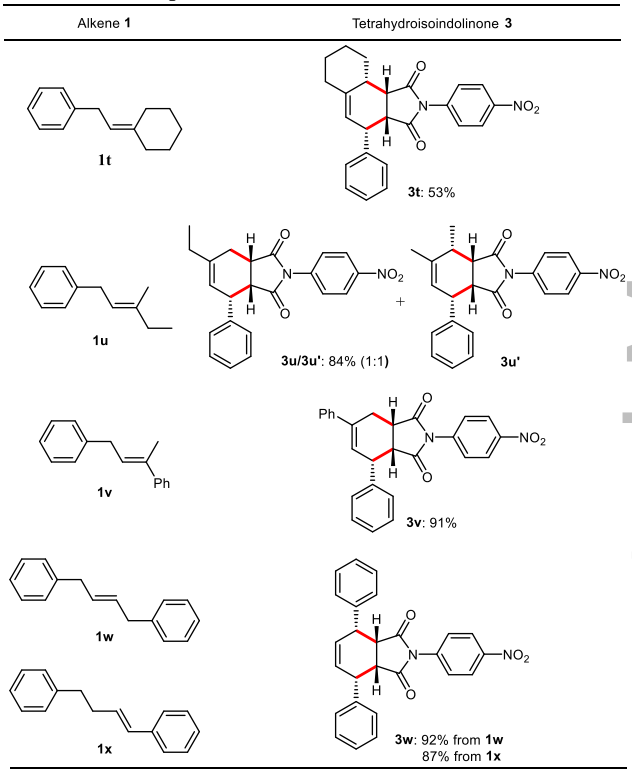
Table 2. Substrate scope of prenyl derivatives and dienophiles.[a,b]



[a] Reactions were conducted with **1a-s** (0.4 mmol), **2a-e** (0.2 mmol), DDQ (0.3 mmol) in PhCl at 110 °C under N_2 for 60 h.
[b] Isolated yields.

conditions. As outlined in Table 2, when prenyl benzene **1a** was treated with maleimide **2c**, tetrahydroisoindolinone **3ac** was obtained in 67% yield. Moreover, maleimides (**2d**, **2e**) with an *N*-aryl group bearing H, CH_3 substituents were also amenable to the DHDA reaction, producing **3ad** and **3ae** in obviously lower yields (78% and 63%), probably owing to the decrease of dienophilicity. Satisfyingly, good result was also obtained for *N*-alkylmaleimide **2b** (54%). Furthermore, maleimides with substituents at the olefinic position were also tolerated. Methyl substituted maleimides (**2f**, **2g**) provided the corresponding tetrahydroisoindolinones (**3af**, **3ag**) in good yields (54% and 76%) with excellent regioselectivities. Bromo-substituted maleimide (**2h**) was also tested, while dihydroisoindolinone (**3ah**) was obtained in excellent yield (87%), a result of eliminating HBr after DHDA reaction. Additionally, dichloro-substituted maleimide was also compatible and afforded the desired product **3ai** in 58% yield.

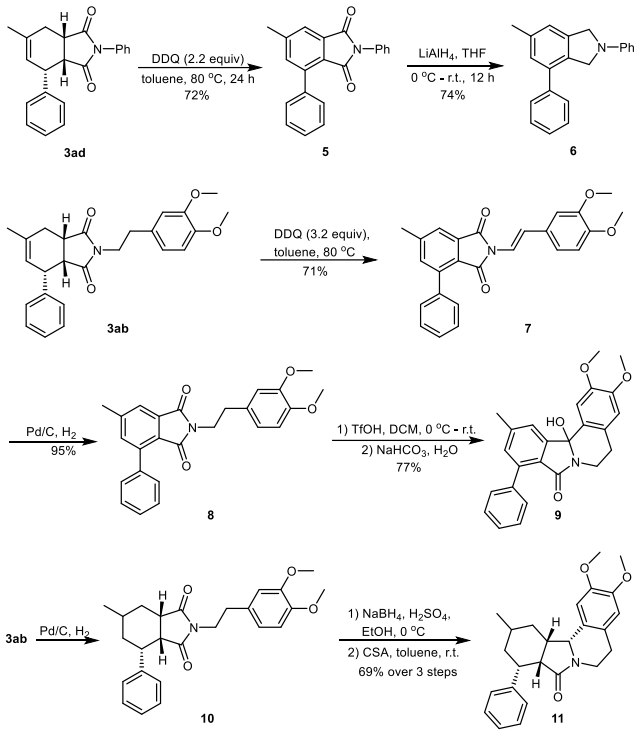
Table 3. Scope of other substituted alkenes.[a,b]



[a] Reactions were conducted with **1t-y** (0.4 mmol), **2a** (0.2 mmol), DDQ (0.3 mmol) in PhCl at 110 °C under N_2 for 60 h.
[b] Isolated yields.

Notably, this synthetic mothed is not limited to prenyl derivatives, trisubstituted and disubstitutedalkenes were also well tolerated (table 3, **1t-x**). Alkene **1t** provides the corresponding tricyclic carbocycle **3t** in moderate yield (53%). Trisubstituted alkene **1u** returned a mixture of **3u**/**3u'** in total 84% yield. Moreover, the synthesis proceeded smoothly for aryl substituted alkene **1v** and afforded the corresponding product **3v** in excellent yield (91%). It

is worth mentioning that disubstituted alkenes **1w**, and **1x** both showed highly reactive efficiency, producing the same product **3w** in excellent yield (92% and 87%).

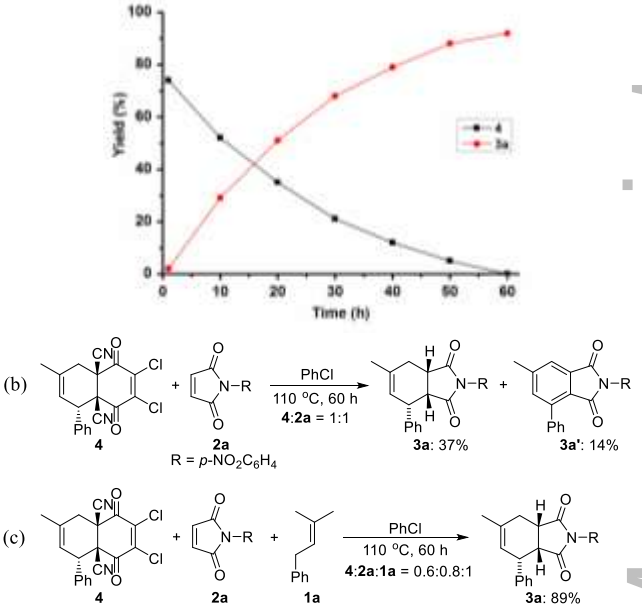


Scheme 2. Demonstration of synthetic utility of products.

The multifunctional characteristics of the products were further instantiated by the synthesis of biologically valuable compounds (scheme 2). For example, **3ad** can be further converted to 6-isoindoline-1,3-dione **5** and isoindoline **6** by aromatization and reduction in good yields (72% and 74%). Which are priviledged structure and widely spread in agrochemicals and natural products.[13] Tetrahydroisoindolinone **3ab** is also an important intermediate of isoindoloquinoline polycycle **9** and **11** (Scheme 2). The isoindoloquinoline framework is often found in alkaloids, such as nuevamine, a potential therapeutic agents for the treatment of inflammatory diseases.[14]

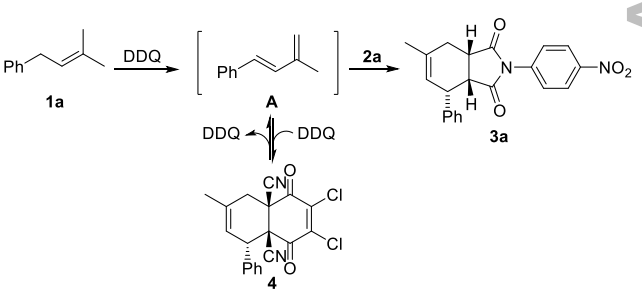
To elucidate the mechanism of this DHDA reaction, a number of control experiments were performed (Scheme 3). Seven parallel model reactions (**1a** and **2a**) under the optimized conditions with various times (1, 10, 20, 30, 40, 50 and 60 h) were conducted (Scheme 3). The yields of **3a** and **4** changed with the reaction time. A decrease of the yield of **4** is accompanied with an increase of the yield of **3a** (Scheme 3, a). The dynamic change of the yields of **3a** and **4** indicates that **4** could be converted into **3a** through a thermal reversible process. To further validate this process, reaction of the DDQ-adduct **4** with **2a** (in 1:1 ratio) under the optimal conditions was conducted (Scheme 3, b), the desired product **3a** and its aromatization product **3a'** was isolated in 37% and 14% yield, respectively. Moreover, in the presence of excess **1a**, the above control experiment returned **3a** in 89% yield without **3a'** (Scheme 3, c). These results suggest that this DHDA reaction involves a thermal reversible process.

(a) The correlation between the yields of **3a**/**4** with the reaction time of the model reaction.



Scheme 3. Control experiments.

A plausible mechanism was described on the basis of the experimental results above (Scheme 4). First, the intermediate diene A is formed from **1a** under the oxidization of DDQ. Next the DA reaction occurs between intermediate A and maleimide **2a** (or DDQ) and provides the desired product **3a** (or by-product **4**). Then the DDQ adduct **4** breaks down into the intermediate diene A and DDQ at high temperature, while compound **3a** is stable at this temperature. Finally, DDQ and the intermediate A will be totally consumed to product **3a** after a long time.



Scheme 4. Plausible reaction mechanism.

In summary, we have developed an efficient synthesis of biologically active products via a metal-free thermal reversible DHDA process. This reaction features broad substrate scope with various substituted alkenes, and excellent endo selectivity and good to excellent yields. In addition, the practical transformations of the tetrahydroisoindolinones reveal the potential utility of the new reaction. Further investigations on the development of new DHDA reactions are underway in our laboratory.

Experimental Section

General procedure for synthesis of tetrahydroisoindolinone derivatives.

In a dry Schlenk tube, a mixture of substituted alkenes **1** (0.4 mmol), maleimides **2** (0.2 mmol) and DDQ (0.3 mmol) in PhCl (2 mL), was stirred at 110 °C until the maleimides **2** was disappeared nearly (monitored by TLC analysis, about 60 h). After removed the solvent under reduced pressure, the residue was purified by column chromatography on silica gel to afford the desired product.

Acknowledgements

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