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Practical access to fluorescent 2,3-naphthalimide derivatives *via* didehydro-Diels–Alder reaction†

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A practical and efficient approach for the synthesis of fluorescent 2,3-naphthalimide derivatives has been developed from readily available starting materials *via* an intramolecular didehydro-Diels–Alder reaction, which proceeded well under room temperature, exhibiting a wide substrate scope and good functional group tolerance. The practicability of this methodology has been verified by one-step synthesis of the environmentally sensitive fluorophore 6-DMN on a gram scale with a shorter time, fewer steps and less waste disposal, and without the utilization of toxic transition metals. The present experimental and computational studies support the crucial role of the propiolimide moiety in the transformation.

Naphthalimides are an important class of heterocyclic compounds that have been studied for their unique properties: their photoinduced-electron-transfer properties have been explored in photophysical studies, and these materials have been used for fluorescent labeling in molecular biology, as optoelectronic materials,[1] typically as environmentally sensitive fluorescent probes,[1b,2] and as potent enzyme inhibitors (Fig. 1).[3,4] Consequently, some developments have taken place for the construction of 2,3-naphthalimides. These advances mainly include Pd-catalyzed carbonylation[5] of aryl C–H bonds in naphthene-2-carboxamide with CO_2, silver-catalyzed C(sp^2)-H/C(sp)-H functionalization of β-ketoesters and alkynes[6] and the development of o-xylylene analogs as reactive dienes to undergo Diels–Alder reactions with a wide range of dienophiles to produce aromatic imides.[2b,3b,7] Despite the individual merits and significance of these synthetic methods, 2,3-naphthalimide's application has severely lagged behind compared to its analogue 1,8-naphthalimide. Thus, a versatile and general route to 2,3-naphthalimide is still highly desirable.

The class of Diels–Alder reaction[8] in which one double bond is replaced by a triple bond is called the didehydro-Diels–Alder reaction (DDDA),[9] that is, a diene and an alkyne react to produce a cyclohexa-1,4-diene. Using a styrene moiety as the diene to react with alkyne dienophiles represents a valuable and atom-economical route for the rapid construction of substituted polyaromatic cycloadducts (Scheme 1).[9a,9b,10] However, in the case of unfavorable dearomatization, this reaction usually requires the use of elevated temperature,[11] Lewis acids, transition-metal catalysts or microwave conditions. For instance (Scheme 1), Chackalamannil developed a thermally-promoted DDDA reaction to form naphthalene and dihydronaphthalene derivatives.[12] Ruijter[13] and Brummond[14] demonstrated microwave assisted intramolecular DDDA reaction of styrene-yne for rapid access to cyclized compounds. In 2015, Bi described a tunable intramolecular annulation for the synthesis of benzo[*f*]-1-indanone with regio- and chemo-selectivity.[15] In 2018, Kang reported a Fe-catalyzed DDDA reaction of stryenyl alkyne substrates to produce polyaromatic compounds, which indicated that Fe catalyst can activate the styrenyl diene.[16] Recent progress mainly concentrated on photo- and electro-initiated DDDA reactions *via* radical-cation intermediates,[17] which mainly focused on electron-rich substrates. DDDA reaction is undoubtedly one of the most ideal ways to facilitate the synthesis of naphthalene or dihydronaphthalene moieties; however, they still suffer from low selectivity, limited substrate scope, longer reaction times and harsh reaction conditions. Herein, we disclosed a novel,

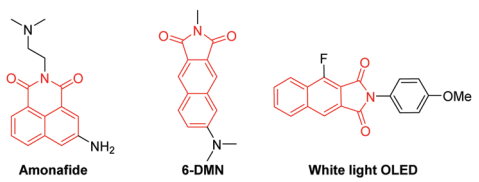

Fig. 1 Examples of naphthalimides.

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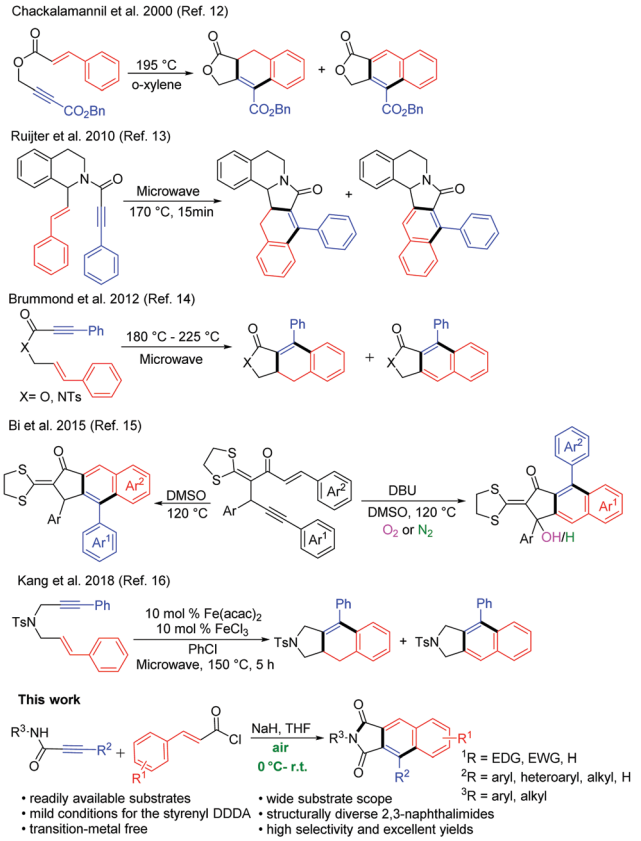
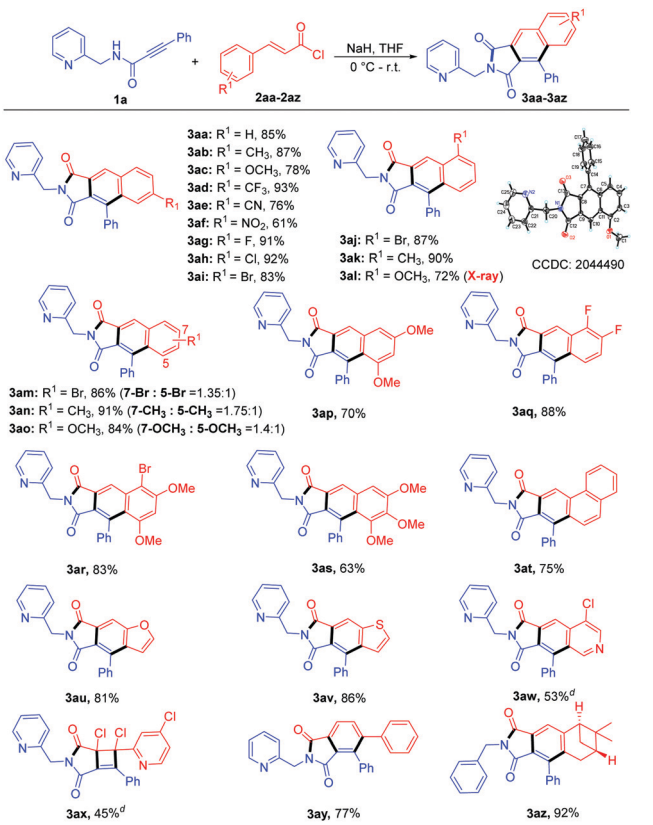


Scheme 1 Didehydro-Diels–Alder reactions of styrene-ynes.

efficient and transition-metal-free DDDA reaction for the preparation of fluorescent 2,3-naphthalimide derivatives from readily available propiolamides and aryl acryoyl chlorides at ambient temperature. This simple approach to obtain 2,3-naphthalimide displays wide substrate scope and can be performed using the one-step synthesis of environment-sensitive fluorescent material **6-DMN** and **6-ClNP** at gram-scale.

Having determined the optimized reaction conditions (Table S1, see ESI† for details), we evaluated the generality of this approach (Tables 1 and 2). Firstly, the substituents on the phenyl ring of cinnamoyl chloride were explored (Table 1). Both electron-donating groups (–Me, –OMe) and electron-withdrawing groups (–CF_3, –CN, and –NO_2) at the *para*-position of the phenyl ring led to the desired products in good to excellent yields (**3ab–3af**). Halo-substituted substrates, such as *p*-F, *p*-Cl, and *p*-Br, can also smoothly produce **3ag–3ai** in excellent yields, providing opportunities for further derivatization. Steric hindrance for substituents on the ortho position has only a slight effect on the reaction (**3aj–3al**), and the structure of **3al** was determined by single-crystal X-ray analysis (CCDC 2044490†). The reaction proceeded smoothly for substitution at the *meta*-position (**3am–3ao**), providing the products with low regioselectivity. Multiple substituted phenyl and 1-Naphthyl substrates exhibited good reactivity (**3ap–3at**). Heteroaromatic substrates containing a thiophene, furan, and pyridine ring reacted efficiently to afford the corresponding annulated products in moderate to good yields (**3au–3aw**). To our delight, open-chain diene

Table 1 Substrate scope of the diene[abc]

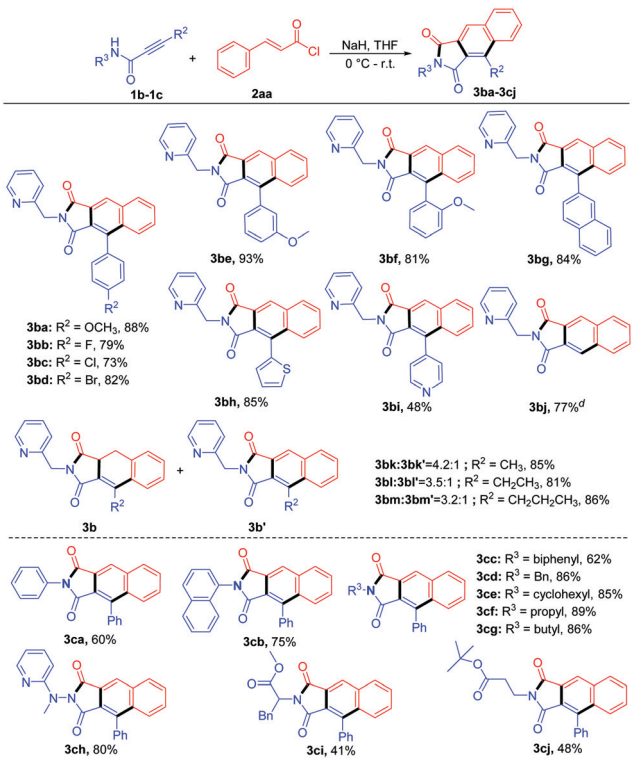


[a] Reaction conditions: **1a** (0.25 mmol), **2aa–2az** (1.3 equiv.), NaH (1.5 equiv.) and THF (2.0 mL) in a reaction bottle under air for 3 h. [b] Isolated yields. [c] T: **2aa–2az** was added at 0 °C, and then the mixture was warmed to room temperature and stirred. [d] n-BuLi was used instead of NaH.

and carbocyclic inner-outer-ring diene also possess high reactivity in the reaction (**3ay** and **3az**). Interestingly, a moderate yield of the cyclobutene product (**3ax**) was obtained from (*E*)-2,3-dichloro-3-(3-chloropyridin-2-yl)acryoyl chloride.

Next, the scope of substituents on the propiolamide and amine were investigated (Table 2). Aromatic propiolamides substituted with CH_3O, F, Cl, and Br, worked well to furnish **3ba–3bf** in good to excellent yields, as well as naphthyl **3bg** and heteroaromatic propiolamaides **3bh–3bi**. Noteworthily, unsubstituted naphthalimide **3bj** was obtained in good yield. Aliphatic propiolamides were accommodated under the optimal conditions. However, methyl, ethyl, or propyl-substituted substrates resulted in mixed products of naphthalene and dihydronaphthalene compounds, **3bk** and **3bk′** (4.2 : 1), **3bl** and **3bl′** (3.5 : 1), and **3bm** and **3bm′** (3.2 : 1) in yields of 85%, 81%, and 86%, respectively. Finally, different kinds of amines were evaluated. Alkyl amines, aryl amines, and amino acid derivatives were all compatible under the reaction conditions, and the corresponding products were obtained in moderate to excellent yields (**3ca–3cj**). All of the above results demonstrated the potential of the approach to prepare substituted 2,3-naphthalimides.

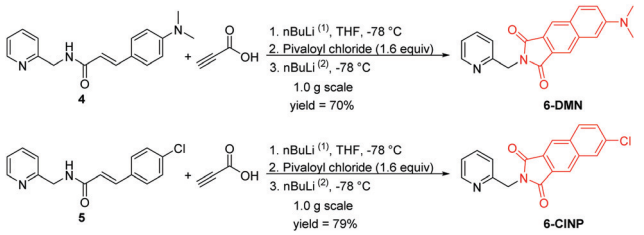
Table 2 Substrate scope of the dienophile and amine[abc]



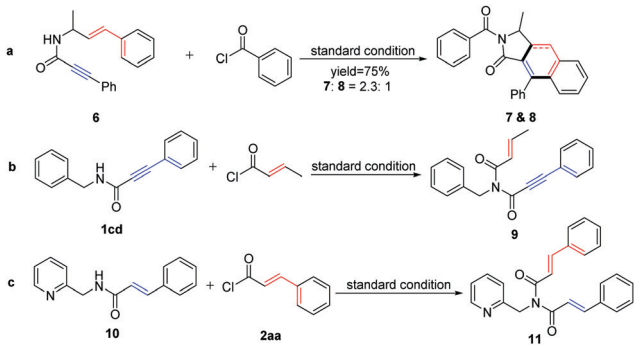
[a] Reaction conditions: **1b–1c** (0.25 mmol), **2aa** (1.3 equiv.), NaH (1.5 equiv.) and THF (2.0 mL) in a reaction bottle under air for 3 h. [b] Isolated yields. [c] T: **2aa** was added at 0 °C, and then the mixture was warmed to room temperature and stirred. [d] Method is presented in the ESI.

To further elucidate the generality and synthetic utility of this methodology, a one-step synthesis of fluorescent materials was presented. 6-Dimethylaminonaphthalimide (**6-DMN**) exhibited excellent fluorescent properties and sensitivity to the local polarity, and has been developed as a probe for the detection of biological interactions and phosphorylation events.[18] Qian[19] presented a scalable three-stage synthesis of an anhydride precursor for the construction of **6-DMN** with an overall yield of about 55%. Herein, we report the one-step synthesis of fluorescent substance **6-DMN** and **6-ClNP** in 70% and 79% yield, respectively, which was completed with a shorter time and less waste disposal, and without the utilization of toxic transition metals. (Scheme 2).

We carried out several control experiments to gain insight into the DDDA reaction. Firstly, to clarify the imide group or the cross-conjugation structure in the imide intermediate, which will facilitate the reaction, reaction **a** (Scheme 3) was carried out. This is because it has been reported that a naphthalene product can be obtained from compound **6** only through a high-temperature intramolecular DDDA reaction. Rreaction **a** proceeded smoothly at ambient temperature, delivering the corresponding cyclized products **7** and **8** in good yields (7 : 8 = 2.3 : 1), which suggested that the imide moiety was of vital significance in the DDDA reaction. Then, two reactions (**b–c**) under standard conditions cannot provide DA products



Scheme 2 Gram-scale synthesis of **6-DMN** and **6-ClNP**.

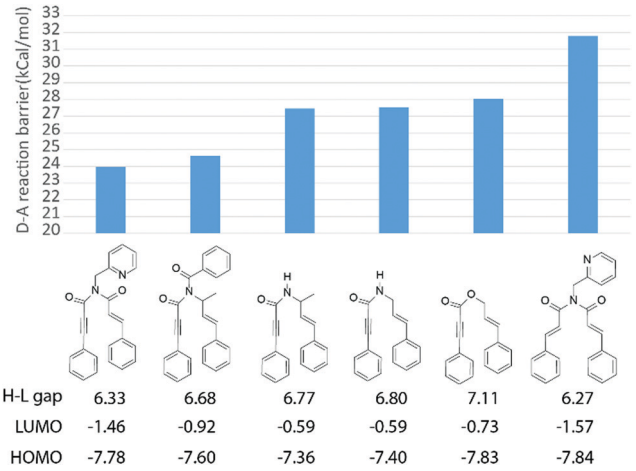


Scheme 3 Control experiments. DFT calculation of the DA reaction barrier and HOMO–LUMO levels (eV) of various structures.

but only stable imide compounds. Combined with the results in the substrate scope, it is inferred that the alkyne part acts as the dienophile and the styrene part acts as the diene in the presented DDA reaction. It could also be speculated from the above experimental results that the propiolimide moiety is of vital importance in the mild and transition-metal-free DDDA reaction.

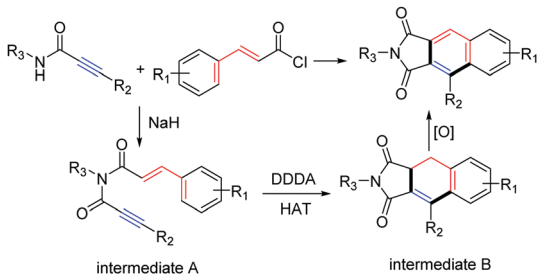
To gain an understanding of some of the critical thermodynamic features associated with the DDDA ring forming step, we turned to computational analysis of the reaction. DFT calculations at the M062X-D3/def2-SVP level[20] were performed to obtain the D–A reaction barrier and HOMO–LUMO gap of the reactant (Scheme 4). The imide structures have a smaller D–A reaction barrier than the others, which is in accordance with the experimental results. The HOMO–LUMO gap of the reactant follows the same trend of reaction barrier, which suggests that the orbital gap may be responsible for the reaction activity as expected. Imide structures have one more acyl group, which leads to the reduction of both the HOMO and LUMO level. Since the LUMO level decreases more than the HOMO level, the gap of the imide structure is smaller.

A plausible mechanism for this cycloaddition reaction is proposed in Scheme 5. The reaction was initiated to generate an intermediate A-imide compound, and then the intermediate A underwent DDDA reaction and hydrogen atom transfer to provide the dihydronaphthalene B, which was subsequently oxidized to deliver the desired naphthalene product. In summary, a protocol to access 2,3-naphthalimides, as well as the one-step synthesis of fluorescent substance **6-DMN** was disclosed *via* an efficient DDDA reaction from easily available



H-L gap	6.33	6.68	6.77	6.80	7.11	6.27
LUMO	-1.46	-0.92	-0.59	-0.59	-0.73	-1.57
HOMO	-7.78	-7.60	-7.36	-7.40	-7.83	-7.84

Scheme 4 DFT calculation.



Scheme 5 Proposed mechanism.

substituted propiolamides and aryl acryoyl chlorides. The main features of this reaction are listed as follows: (1) without the utilization of transition metals or high temperatures; (2) readily available starting materials; (3) operationally simple, insensitive to air and moisture; (4) a wide substrate scope; (5) facile synthesis of the fluorophore **6-DMN** on a gram scale with a shorter time, fewer steps and less waste disposal. The corresponding works are currently being studied in our laboratory and will be presented in future publications.

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Conflicts of interest

There are no conflicts to declare.

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