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The Construction of Polysubstituted Aromatic Core Derivatives *via* a Cycloaddition/Oxidative Aromatization Sequence from Quinone and β-Enamino Esters

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Abstract: An unexpected strategy has been discovered for the construction of polysubstituted aromatic core derivatives from the reaction of quinones or *N*-substituted maleimides with β-enamino esters by a cycloaddition/oxidative aromatization sequence that provides products contrary to those delivered by the Nenitzescu reaction. The current method provides a highly favorable synthetic strategy for the efficient construction of important therapeutic agents containing polysubstituted aromatic core structures.

Keywords: cycloaddition; β-enamino esters; oxidative aromatization; quinone; *N*-substituted maleimides

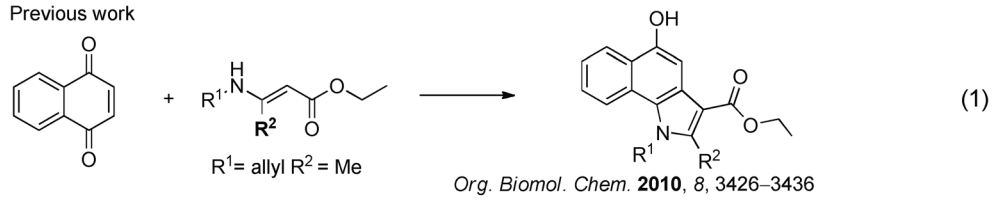
β-Enamino esters are versatile intermediates, which are often used for the synthesis of heterocycles, and compounds of this class are also common pharmacophores in a number of important medicinal agents.[1] Furthermore, β-enamino esters are employed as key starting reagents for the synthesis of substituted pyrazoles,[2] substituted aromatic amines,[3] substituted pyrroles,[4] 1,4-dihydropyridine derivatives,[5] functionalized pyrimidines,[6] benzo[*g*]isoquinolines,[7] 2-azaspiro[4,5]decatrienes,[8] 1,2,3-triazole derivatives,[9] indolequinones,[10] 2-substituted-1,4-quinones,[11] *C*-glycosides,[12] 2-pyrrolidone derivatives,[13] 2-oxo-[1,4]oxazino[3,2-*e*]indoles,[14] 4-thioxopyrimidines,[15] and 5-hydroxyindole derivatives.[16]

Quinones represent one of the most widely distributed structural classes in nature,[17] and compounds belonging to this class can be found in a large number of important pharmacophores[18] associated with anticancer, antibacterial, antimalarial, fungicidal, and antiparasitic agents.[19] Based on the recent resurgence of interest in the functionalization of quinone structures[20] and the application of β-enamino esters in organic synthesis,[21] we became interested in further exploring the reactions of β-enamino esters with quinones.

During the course of our research in this area, an unexpected product, diethyl 9,10-anthraquinone-1,3-dicarboxylate (**3a**), was discovered involving the reaction of 1,4-naphthoquinone (**1a**) with ethyl-3-(methylamino)acrylate (**2a**) [Eq. (2)]. Contrary to similar work reported by Menéndez et al. [Eq. (1)],[22] however, where the Nenitzescu reaction was used to obtain fused indoles, our own work led to the formation of a different product **3a**, with the difference in the products being attributed to the presence of an H atom instead of a methyl group at the R^2 position of the β-enamino esters under the same conditions as reported by Menéndez (Table 1, entry 1).

Furthermore, among various kinds of naturally occurring substances, quinone derivatives are common and very important.[23] For example, rhein,[24] physcion,[23d,25] aloe-emodin;[26] emodin[27] and chrysophanol[28] exhibit antifungal activity.[23d,29] Especially emodin, which is purified from the Chinese medicinal herb rhubarb, has inhibitory activity against ERK phosphorylation in PC3 cells induced by EGF.[30] Moreover, aloe-emodin might represent a conceptually new lead antitumor drug taking into account its unique cytotoxicity profile and mode of action.[26a] Besides, DMAC, aloesaponarin I and aloesaponarin II also show good antibacterial activity (Figure 1).[31]

Based on this initial result and the significance of these unexpected polysubstituted aromatic cores in related drugs, we became interested in developing a greater understanding of this reaction between 1,4-



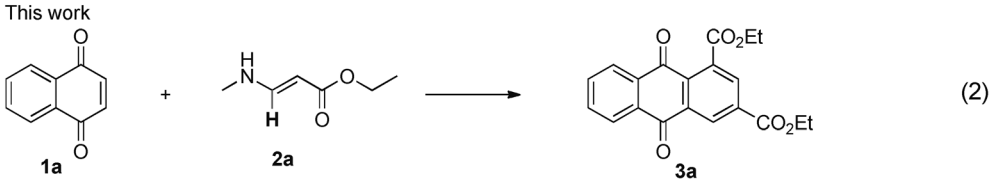
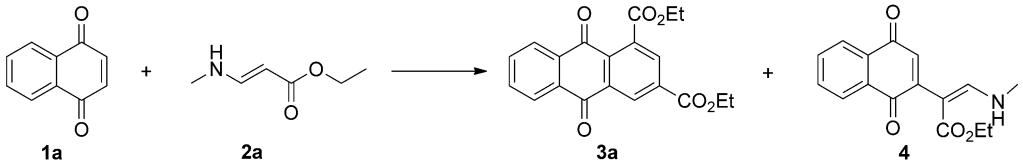


Table 1. Initial evaluation of the reaction conditions.[a]



Entry	Solvent	Temperature	Additive	Yield of **3a** [%][b]	Yield of **4** [%][b]
1	ethanol	reflux	CAN (0.05)	23	60
2	$CHCl_3$	reflux	–	18	58
3	CH_2Cl_2	reflux	–	25	49
4	toluene	reflux	–	10	–
5	CH_3CN	reflux	–	20	54
6	CH_3CN	reflux	$FeCl_3$ (1.0)	30	40
7	CH_3CN	reflux	$FeCl_3$ (0.1)	29	46
8	HOAc	reflux	–	52	–
9	HOAc	80 °C	–	60	–
10	HOAc	70 °C	–	64	–
11	HOAc	60 °C	–	62	–
12	HOAc	r.t.	–	42	–
13	HOAc	70 °C	TBHP (1.0)	75	–
14	HOAc	70 °C	O_2	85	–
15	HOAc	70 °C	N_2	37	–

[a] *Reaction conditions:* the mixture of **1a** (1.0 mmol) and **2a** (3.0 mmol) in solvent (5.0 mL) was stirred for 6 h at the corresponding temperature in an open flask.
[b] Isolated yield.

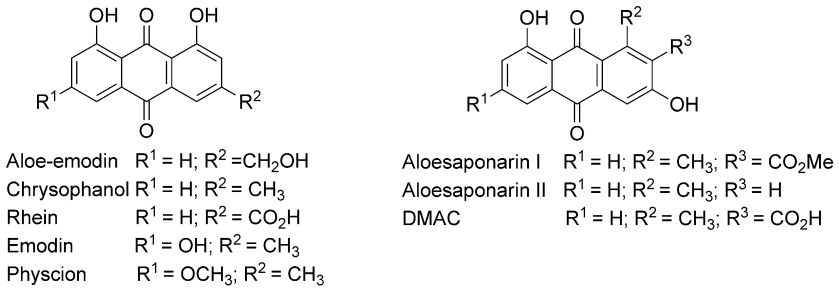


Figure 1. Several important anthraquinone derivatives.

naphthoquinone and ethyl-3-(methylamino)acrylate with a view of determining the structure of any possible polysubstituted aromatic core derivatives products and exploiting their synthetic potential. In the current work, we address these challenges and also optimize the reaction conditions for this transformation with the aim of developing a new aromatization method from the β-enamino ester as the raw substrate that

could potentially provide a rapid access to useful polysubstituted aromatic core derivatives in a simple and efficient manner, in contrast to those produced by the Nenitzescu reaction. Herein, we describe the details of our work in this area.

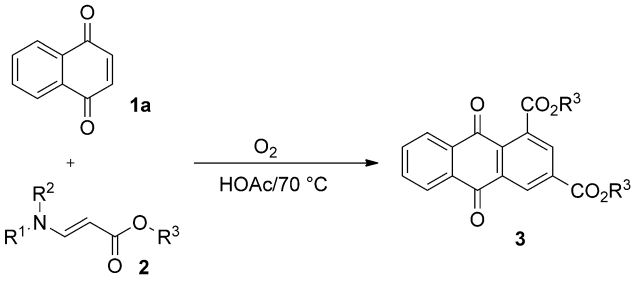
As shown in Table 1, the reaction between 1,4-naphthoquinone **1a** (1.0 mmol) and ethyl β-methylaminoacrylate **2a** (3.0 mmol) gave the unexpected product **3a** in low yields in a range of organic solvents, including ethanol (23%), $CHCl_3$ (18%), CH_2Cl_2 (25%), toluene (10%), and CH_3CN (20%) under reflux conditions for 6 h, with the coupling product **4** being isolated as a major by-product (Table 1, entries 1–5). Pleasingly, the yield of **3a** was slightly increased by the presence of catalytic or stoichiometric amounts of the Lewis acid $FeCl_3$ (Table 1, entries 6 and 7). This result indicated that the acid catalyst was useful for the cyclization process. The yield of **3a** was increased to 52% when HOAc was used as a solvent (Table 1, entry 8), and an investigation of the reaction temperature revealed that the yield could be increased to 64% when the reaction was conducted at 70 °C in HOAc (Table 1, entries 8–12). To further improve the efficiency of the reaction, we investigated the addition of an oxidant to the reaction mixture. Pleasingly, the addition of *tert*-butyl hydroperoxide (1.0 equiv.) to the reaction mixture resulted in a significant increase in the yield of **3a** to 75% (Table 1, entry 13). Interestingly, product **3a** was obtained in 85% yield when **1a** and **2a** were reacted under an oxygen atmosphere (Table 1, entry 14). In contrast, when the reaction was conducted under a nitrogen atmosphere, the yield of product **3a** fell to 34% (Table 1, entry 15).

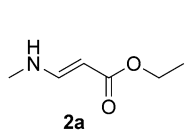
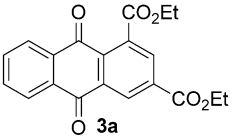
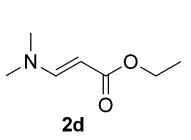
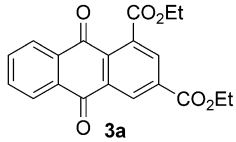
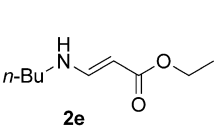
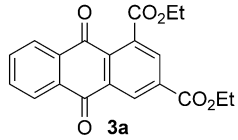
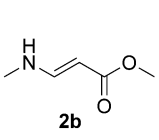
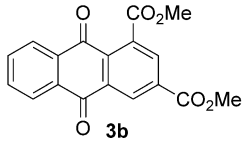
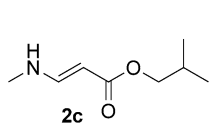
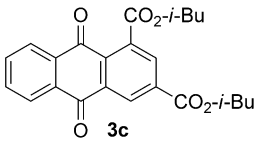
With the optimized conditions in hand, we proceeded to evaluate the substrate scope of this oxidative aromatization using a range of different ethyl amino-substituted acrylates. The same product **3a** was obtained in 62 and 73% yields when ethyl β-dimethylaminoacrylate **2d** and butyl β-methylaminoacrylate **2e** were used instead of **2a**, respectively (Table 2, entries 1–3). A variety of different β-enamino esters bearing structural variation in the ester groups was then reacted with 1,4-naphthoquinone **1a** to give the corresponding products **3a–c** in good to excellent yields (Table 2, entries 1, 4 and 5).

The application of the optimized reaction conditions to 1,4-anthraquinone **1b** proceeded efficiently with the β-enamino esters **2a–c** to give the corresponding products **3d–f** in good to excellent yields (Table 3, entries 1–3). Given the importance of *N*-substituted phthalimide derivatives in pharmacochemistry,[32] a wide range of *N*-substituted maleimides **1c–h** was also investigated under the optimized reaction conditions, and gave the corresponding oxidative aromatization products **3**, albeit in slightly lower yields in the range of 35–71% (Table 3, entries 4–13). Interestingly, when isobutyl methylaminoacrylate was employed as the β-enamino ester, the yield of the product was slightly reduced because of steric effects. Based on these results, we were able to establish that the reaction proceeded smoothly with *N*-aryl-substituted maleimides **1c–f** and that electron-donating substituents on the benzene ring favored the formation of product **3**. In comparison, the use of *N*-alkyl-substituted maleimides resulted in lower yields because the formation of some other by-products that could not be separated and characterized as they were not sufficiently stable under acidic conditions (Table 3, entries 14–19).

On the basis of the results provided above, we have tried the reaction of the isolated coupling product **4** with ethyl β-methylaminoacrylate, but the product **3**

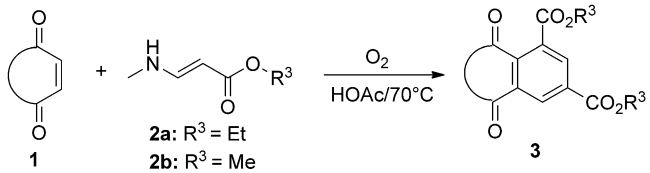
Table 2. Scope of different β-enamino esters.



Entry	2	3	Yield of 3 [%][a]
1			85
2			62
3			73
4			94
5			74

[a] Isolated yields.

Table 3. Scope of the current reaction for the formation of **3**.



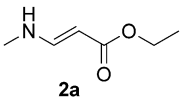
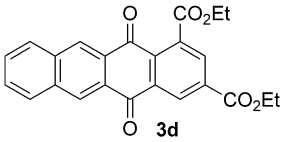
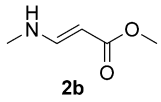
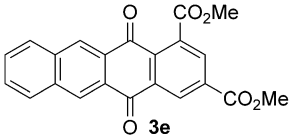
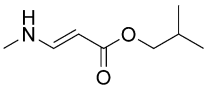
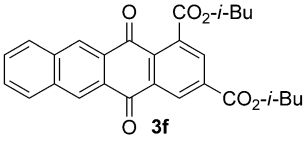
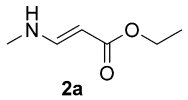
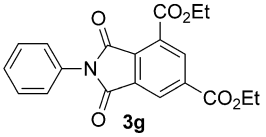
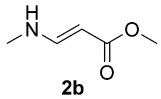
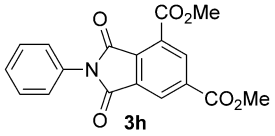
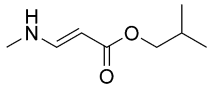
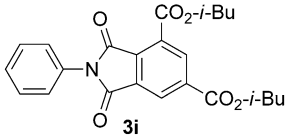
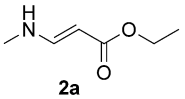
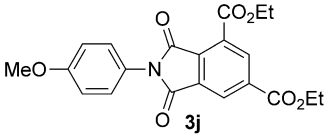
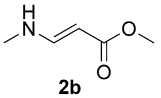
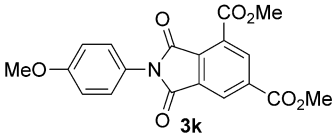
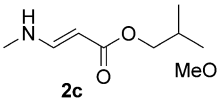
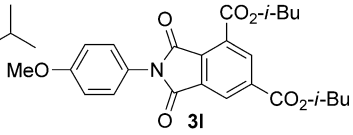
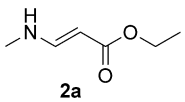
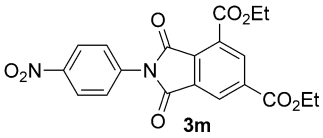
Entry	2	3	Yield of 3 [%][a]
1			92
2			96
3			87
4			68
5			50
6			47
7			71
8			68
9			51
10			52

Table 3. (Continued)

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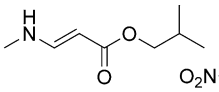
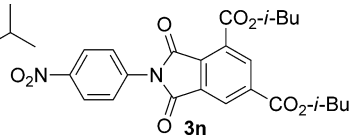
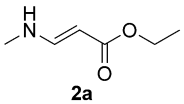
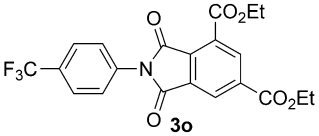
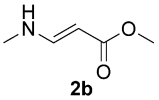
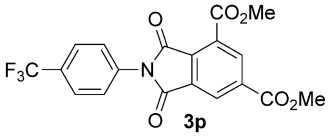
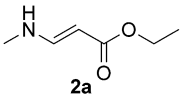
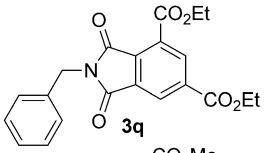
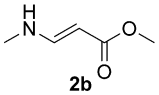
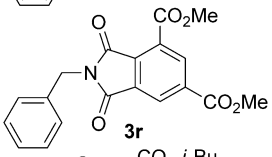
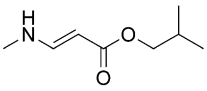
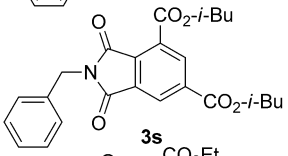
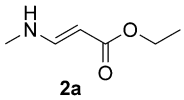
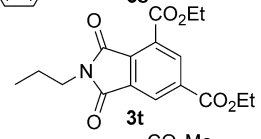
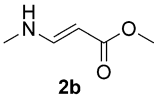
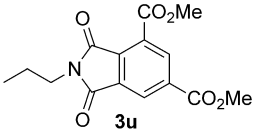
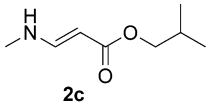
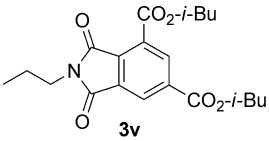
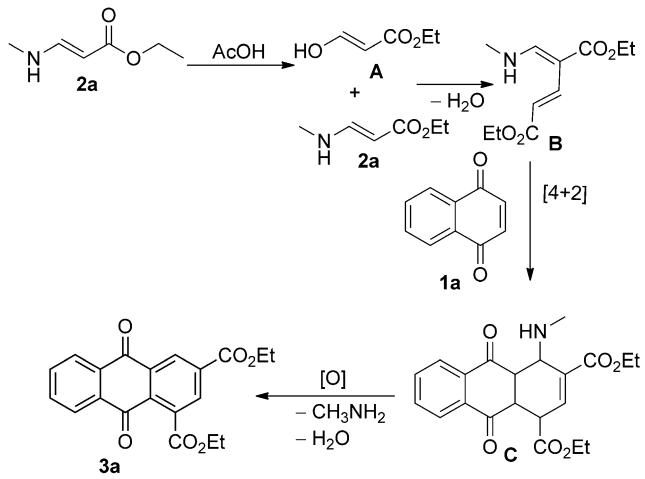
11			43
12			59
13			57
14			42
15			43
16			39
17			32
18			36
19			35

[a] Isolated yields.

was not obtained. To confirm the intermediates of this reaction and elucidate the mechanism for the formation of **3**, the intermediate **B** was isolated and its structure determined by NMR analysis (see the Supporting Information).[33] Then we proposed a tentative mechanism for this oxidative aromatization process (Scheme 1).

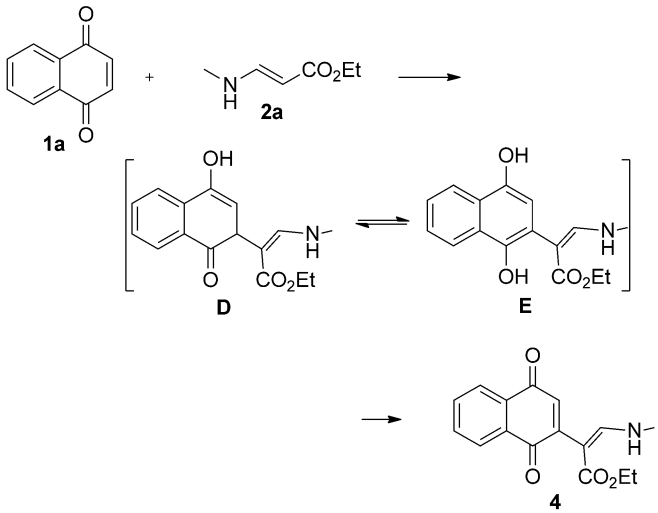
Firstly, ethyl 3-hydroxyacrylate **A** was formed from **2a** under acidic conditions,[34] with a subsequent cou-



Scheme 1. Plausible reaction mechanism.

pling reaction between **A** and **2a** giving rise to intermediate **B**. Intermediate **C** was then formed through a Diels–Alder reaction between **1a** and **B**,[35] with a subsequent oxidative aromatization giving rise to product **3a** under an oxygen atmosphere. Besides, the by-product **4** was formed through an initial Michael addition followed by sequential tautomerization to the corresponding hydroquinone species and oxidation by air (Scheme 2).[22]

In conclusion, we have developed an exciting new strategy for the construction of polysubstituted aromatic core derivatives from the oxidative aromatization reaction of quinones or *N*-substituted maleimides with β-enamino esters under an oxygen atmosphere. This novel protocol provides a rapid and efficient access to biologically important polysubstituted aromatic core derivatives in a highly concise fashion. Although detailed mechanistic descriptions and the development of milder reaction conditions are still desired, we believe that this new protocol will provide a platform for the development of new methods from the β-enamino ester as the raw substrate for the practical construction of polysubstituted aromatic core derivatives.



Scheme 2. Possible route for the formation of by-product **4**.

Experimental Section

Representative Procedure for the Synthesis of 3

A mixture of 1.4-naphthoquinone (**1a**, 1.0 mmol, 0.158 g, 1.0 equiv.), ethyl β-methylaminoacrylate (**2a**, 3.0 mmol, 0.387 g, 3.0 equiv.) and HOAc (5.0 mL) was stirred for 6 h at 70 °C under an atmosphere of oxygen. Upon completion of the reaction, as determined by GC-MS and TLC, the mixture was cooled to ambient temperature and the solvent was removed under vacuum to give the crude product, which was purified by column chromatography on silica gel using CH_2Cl_2 as the eluent to give **3a** as a yellow solid; yield: 0.300 g (84%): mp 156–157 °C.

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