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Generation and Application of *o*-Quinone Methides Bearing Various Substituents on the Benzene Ring

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This paper is dedicated to Professor Dr. Masakatsu Shibasaki, who has made enormous contributions to chemistry, on the occasion of his 60th birthday.

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Abstract: *o*-Quinone methides (*o*-QMs) are highly reactive, short-lived intermediates, which have potential synthetic applicability. However, few studies on the generation of *o*-QMs bearing an electron-withdrawing group have been reported. Herein we present a general method for the generation of *o*-QMs, particularly those substituted with an electrophilic substituent, from new precursors, 4*H*-1,2-benzoxazines **2**. We have also studied systematically the Diels–Alder reactions of *o*-QMs with various dienophiles, such as vinyl ethers, enamines and imines. The reactions provide a versatile route to substituted chromans, phenols and 3,4-dihydro-2*H*-benzo[*e*]-[1,3]oxazines (3,4-dihydro-1,3-benzoxazines). Furthermore, we applied the new method to the derivatization of some natural products.

Keywords: 4*H*-1,2-benzoxazines; chromans; inverse electron demand Diels-Alder reaction; phenols; *o*-quinone methide

Introduction

o-Quinone methides (*o*-QMs) are highly reactive, short-lived intermediates, which have been used in the synthesis of several natural products.[1,2] They undergo 1,4-conjugate addition with nucleophiles, and Diels–Alder cycloadditions with various dienophiles.[3] Many methods to generate *o*-QMs *in situ* from various precursors have been reported (Figure 1). However, they have various disadvantages, including inaccessibility of precursors,[2] undesirably high reaction temperatures,[2,4] long reaction time,[2–5] a need for additional catalysts,[2,6] and acidic[2,6] or basic[2,3m,7] conditions, and in all cases side reactions can occur. In addition, there have been few systematic studies of the generation and applications of *o*-QMs with various substituents, particularly electrophilic substituents, on the benzene ring. While some information is available on the generation of *o*-QMs with electron-donating groups, only a nitro group has been reported as an electron-withdrawing group.[8] *o*-QMs bearing a variety of electron-withdrawing groups have not been investigated. Very recently a reversible generation of some substituted *o*-QMs from the conventional precursors and their reactivities in conjugate addition have been reported.[3p]

Structurally novel chroman derivatives have been isolated from nature,[9] and are of interest because many display interesting biological properties, such as anti-malaria activity,[10] phytotoxicity,[11] and enhancement of erythropoietin gene expression.[12] Furthermore, 3,4-dihydro-1,3-benzoxazines, which are akin to chromans having a carbon atom replaced with nitrogen at the 3 position, show cytotoxic activity *in vitro* against some cancer cell lines.[13] Thus, both chromans and 3,4-dihydro-1,3-benzoxazines are potential synthetic targets in the pursuit of compounds with interesting biological activities.

Unsubstituted 4*H*-1,2-benzoxazines have been reported to afford the prototype *o*-QM by gentle heating, through a retro-Diels–Alder reaction.[14a] This method has an advantage over the conventional methods with respect to the mildness of the reaction conditions. Some derivatives of 4*H*-1,2-benzoxazine were synthesized for the first time by means of a Friedel–Crafts-type reaction of nitroalkenes with benzene in the presence of a strong Brønsted acid, such as trifluoromethanesulfonic acid (TFSA),[14b–d] but this method turned out to have limited applicability for the synthesis of 4*H*-1,2-benzoxazine derivatives bearing substituents on the benzene ring, because biaryl

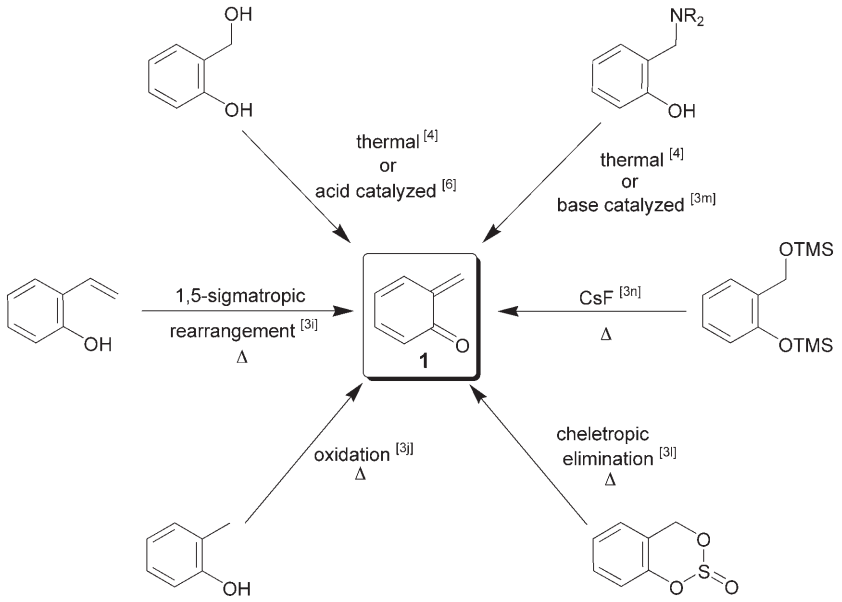
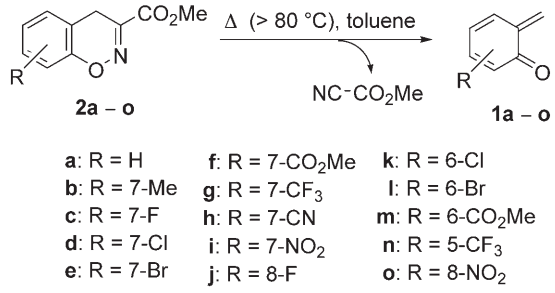


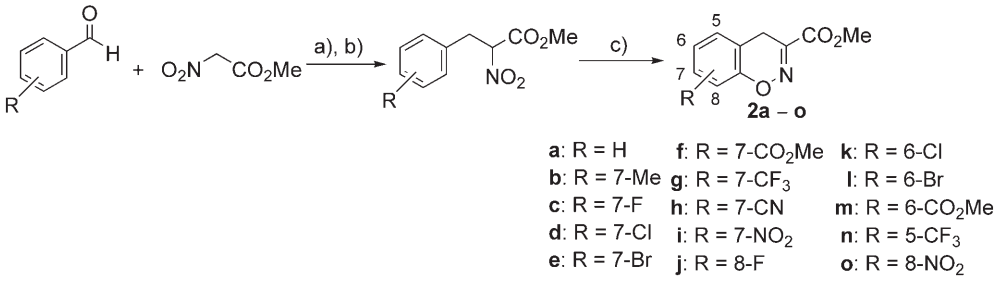
Figure 1. Conventional precursors for the thermal generation of *o*-QMs.

compounds were obtained as major products when substituted benzenes were used. This unexpected result was due to an intermolecular reaction between the substituted benzenes and nitroalkenes.[14d] While subsequent reports also described the synthesis of 4*H*-1,2-benzoxazine derivatives,[14e–k] the yields were low and the methods lacked generality, since only limited starting materials could be employed, and the products were not amenable to further modification. Recently, we have reported the synthesis of 4*H*-1,2-benzoxazines bearing various substituents on the benzene ring, from saturated nitroalkanes and methyl 3-aryl-2-nitropropionates.[15] These starting materials are readily obtained by condensation of substituted benzaldehyde and methyl nitroacetate, followed by sodium borohydride reduction of the olefin to give methyl 3-aryl-2-nitropropionates. Methyl 3-aryl-2-nitropropionates cyclized to give 4*H*-1,2-benzoxazine in the presence of TFSA (Scheme 1).

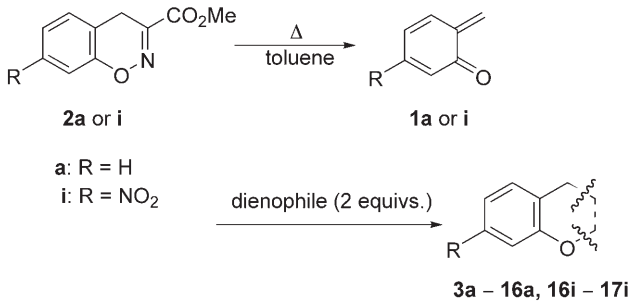
The chemical nature of 4*H*-1,2-benzoxazine derivatives bearing various substituents on the benzene moiety has not been well studied because of the lack of suitable general synthetic methods. 4*H*-1,2-Benzoxazines afford *o*-QMs with various substituents on the benzene ring simply upon heating at low temperature (Scheme 2).



Scheme 2. Generation of *o*-QMs from 4*H*-1,2-benzoxazines.



Scheme 1. *Reagents and conditions*: a) $TiCl_4$ (2 equivs.), *N*-methylmorpholine (4 equivs.), THF, 0 °C to room temperature, 18 h; b) $NaBH_4$ (0.5 equivs.), $CHCl_3$, room temperature, 3 h; c) trifluoromethanesulfonic acid (10 equivs.), $CHCl_3$, 50 °C, 30 min.



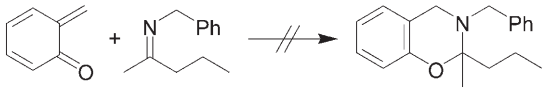
Scheme 3.

The Diels–Alder reactions of *o*-QMs with some dienophiles have been reported previously,[1-3] but the combinatorial reactions of various *o*-QMs with various dienophiles have not been fully reported yet. In addition, the reactivity of substituted *o*-QMs in terms of the Diels–Alder diene has not been investigated. In this paper, we have established a general method for the generation of *o*-QMs from the new precursors, 4*H*-1,2-benzoxazines **2**, and systematically studied the Diels–Alder reactions of *o*-QMs with various dienophiles.[16] Furthermore, we applied this method to derivatize some natural products.

Results and Discussion

Diels–Alder Reactions of *o*-Quinone Methides with Various Dienophiles

In the presence of a dienophile, heating of a solution of unsubstituted **2a** and nitro-substituted 4*H*-1,2-benzoxazine **2i** in toluene afforded chroman derivatives in high yield (Scheme 3 and Table 1). This supports the formation of unsubstituted *o*-QM **1a** and nitro-substituted *o*-QM **1i** upon the elimination of methyl cyanoformate *in situ*. In the presence of nitrile compounds such as acetonitrile and diethylcyanamide, no cyclized product, such as 4*H*-1,2-benzoxazine derivatives, was formed, indicating the generation of *o*-QMs from **2** was irreversible. Since Diels–Alder reactions of *o*-QMs are known to be of reverse electron-demand,[2] electron-rich dienophiles react more efficiently. Indeed, as shown in Table 1, reactions with vinyl ethers **20a–d** and enamines **20j–l** gave products in good yields. Even in the cases of vinyl ethers and enamines bearing a bulky substituent, such as vinyl ethers **20a–c** and enamines **20j–l**, the yields are high, probably because the dienophiles are sufficiently electron-rich to allow the reactions with *o*-QM (Table 1, entries 1–3 and 11–13). In most cases, reactions of vinyl ethers and enamines gave the chroman structure. In the case of vinyl silyl acetal **20c** as a dienophile, however, the cyclized compound could not be isolated, probably because the cyclized intermediate is an unstable orthoester compound.[17] Thus, after desilylation with tetrabutylammonium fluoride (TBAF), the intermediate silyl acetal was converted to the corresponding *o*-substituted phenol in a good yield (Table 1, entry 4). Imines also gave products, but the yields varied from imine to imine. The imines of formaldehyde **20e** and **f**, which have only hydrogen atoms on the carbon atom of the C=N bond, gave 3,4-dihydro-1,3-benzoxazines in moderate yields (Table 1, entries 6 and 7). The imines which bear OEt (**20g**) and Ph (**20h** and **i**) on the carbon atom of the C=N bond gave the unstable orthoester and aminoacetal derivatives, respectively, which were difficult to isolate. Subsequent acid-catalyzed hydrolysis without isolation of the intermediates gave *o*-substituted phenol derivatives (Table 1, entries 8–10). In the case of the imines **20h** and **i** with a phenyl group on the carbon atom of the C=N bond, the existence of the unstable cyclized intermediate aminoacetal was observed by ^{1}H NMR spectroscopy (Table 1, entries 9 and 10). When aliphatic ketimines were used as dienophiles, the expected products were not obtained (Scheme 4),

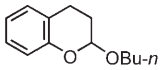
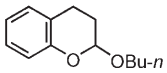
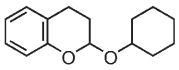
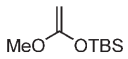
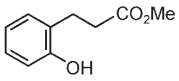
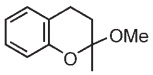
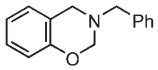
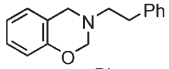
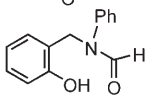
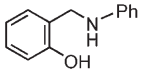
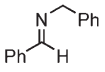
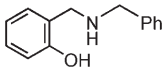
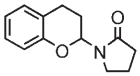
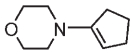
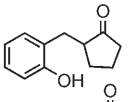
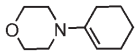
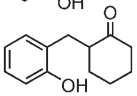
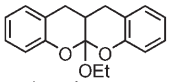
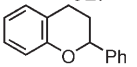
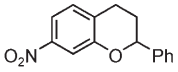
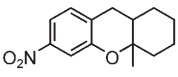
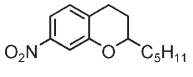


Scheme 4. Diels–Alder reaction of *o*-QM with an aliphatic ketimine.

while the corresponding vinyl ether **20d** gave the cyclized product in moderate yield (Table 1, entry 4). A possible reason for this result is that, when imines are used as dienophiles, this Diels–Alder reaction is influenced by the bulk of the substituents on the carbon atom of C=N bond. The reactivity of the imine is not high enough to allow *o*-QMs to react with bulky imines such as ketimine. Because the length of the C=N bond of imines (1.27 Å) is shorter than that of vinyl ethers (1.34 Å), steric congestion might have more impact on the reactivity of the imine moiety.

The substituent effects on the reactants of the *o*-QMs (**1a** and **i**) become clearer when the reactivities toward relatively electron-poor dienophiles **20n–p** are compared. In the case of styrene **20n** as a dienophile, while unsubstituted *o*-QM **1a** gave the product in 69% yield (Table 1, entry 15), nitro-substituted *o*-QM **1i** gave the product in 80% yield (Table 1, entry 16) under similar reaction conditions. When a trisubstituted or monosubstituted olefin (less electron-rich than styrene) is used as a dienophile, unsubstituted *o*-QM **1a** failed to react (Table 1, entries 17 and 19), but nitro-substituted *o*-QM **1i** gave the products, even though in low yields (Table 1, entries 18 and 20). The nitro group on the benzene ring of the *o*-QM **1i** lowers the $LUMO_{diene}$ energy, so that the $LUMO_{diene}$–$HOMO_{dienophile}$ energy gap becomes smaller and the

Table 1. Diels–Alder reactions of *o*-QMs generated from 4*H*-1,2-benzoxazines with various dienophiles.[a]

Entry		R	Dienophile	Temperature [°C]	Time [h]	Product	Yield [%]
1	**2a**	H	**20a** 	80	8	**3a** 	92
2	**2a**	H	**20a** 	90	3	**3a** 	91
3	**2a**	H	**20b** 	90	3	**4** 	93
4[b]	**2a**	H	**20c** 	100	2	**5** 	85
5	**2a**	H	**20d** 	100	2	**6** 	66
6	**2a**	H	**20e** 	100	6	**7a** 	79
7	**2a**	H	**20f** 	100	6	**8** 	43
8	**2a**	H	**20g** 	100	6	**9** 	48
9[b]	**2a**	H	**20h** 	100	8	**10a** 	92
10[b]	**2a**	H	**20i** 	100	8	**11** 	67
11	**2a**	H	**20j** 	100	6	**12** 	62
12	**2a**	H	**20k** 	100	6	**13** 	100
13	**2a**	H	**20l** 	100	6	**14** 	85
14	**2a**	H	**20m** 	100	12	**15** 	23
15	**2a**	H	**20n** 	120	12	**16a** 	69
16	**2i**	NO_2	**20n** 	120	12	**16i** 	80
17	**2a**	H	**20o** 	120	12	—	0
18	**2i**	NO_2	**20o** 	120	12	**17i** 	44
19	**2a**	H	**20p** 	120	12	—	0
20	**2i**	NO_2	**20p** 	120	12	**18i** 	16

[a] A solution of 3-methoxycarbonyl-4*H*-1,2-benzoxazine (**2a** or **2i**) and 2 equivs. of dienophile in 15 mL of dry toluene was heated at 80–120 °C with stirring for 2–12 h.

[b] The products were obtained after acid-catalyzed hydrolysis or tetrabutylammonium fluoride deprotection of the cyclized products obtained in footnote[a].

orbital interaction between *o*-QM and the dienophile becomes stronger. These results clearly indicate that the nitro group of *o*-QM accelerates the Diels–Alder reaction.

Diels–Alder Reactions of *o*-Quinone Methides with Various Substituents on the Benzene Ring

4*H*-1,2-Benzoxazines with various substitutents on the benzene ring can afford correspondingly substituted *o*-QMs. Formation of the chroman derivatives, the Diels–Alder products with *n*-butoxyethene **20a**, supports the formation of *o*-QMs substituted with various substituents on the aromatic ring (Scheme 5 and Table 2). Although the temperature had to be varied in order to force the reaction to completion, the yields are generally high (Table 2). The reactions of substituted *o*-QMs with the imines, such as *N*-methylidenebenzylamine **20e** and benzylidenephenylamine **20h** (Scheme 6), are shown in Table 3.

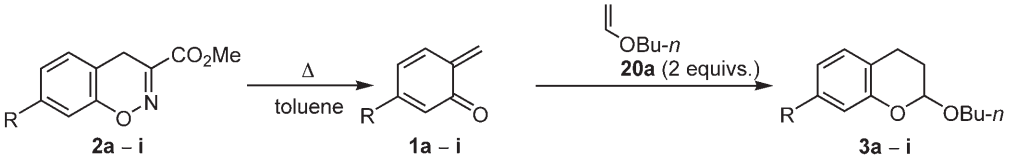
Depending on the substituents of the imines, the 3,4-dihydro-1,3-benzoxazines or open-chain phenol derivatives (after hydrolysis) were obtained in moderate to high yields (Table 3). The electron-withdrawing ability of the substituent on the benzene ring of the 4*H*-1,2-benzoxazines **2** affected the reaction rate. The stronger the electron-withdrawing ability of the substituent, the more slowly the reaction proceeded (Tables 2 and 3). For example, when the nitro-substituted 4*H*-1,2-benzoxazine **2i** was used as a precursor, it slowly reacted with the dienophiles at below 100 °C. 4*H*-1,2-Benzoxazines with a strongly electron-withdrawing substituent, such as CF_3 (**2g**), CN (**2h**), or NO_2 (**2i**), on the benzene ring reacted with the dienophiles at a higher reaction temperature, 120 °C.

These results showed that the generation of *o*-QMs from 4*H*-1,2-benzoxazines bearing various substitutents on the benzene ring is general with the present method, which should be widely applicable in the synthesis of chromans, 3,4-dihydro-1,3-benzoxazines and *o*-substituted phenols having various substituents on the benzene ring.

Application of *o*-Quinone Methides to Synthesis of Euglobal G1 and G2 Analogues

Euglobal G1 and G2, derivatives of phloroglucinol, isolated from *Eucalyptus* spp. have potent inhibitory activity against Epstein-Barr virus activation.[18] These compounds have a chroman structure fused with a unique bicyclic structure (Figure 2). Biogenetically, the euglobals have been proposed to be formed by Diels–Alder type cycloaddition of *o*-QMs derived from oxidation of grandinol with α-pinene **20q**, as depicted in Figure 2.[19] Some euglobal derivatives were synthesized *via* *o*-QMs, and their antivirus activity was examined by Singh et al.[19]

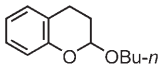
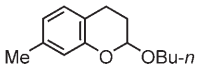
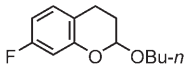
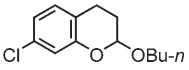
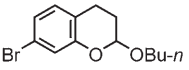
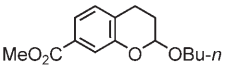
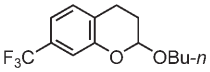
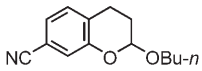
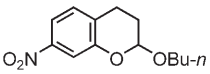
To demonstrate the utility of our method of generation of *o*-QMs, we applied the present procedure to the synthesis of skeletal analogues of euglobals **19a–o** (Scheme 7). Substituted *o*-QMs, derived from various substituted 4*H*-1,2-benzoxazines, were reacted with α-pinene **20q** to give the basic skeleton of euglobals in moderate yield (Table 4, entries 3–16). However, unsubstituted *o*-QM **1a** did not react with α-pinene **20q** (Table 4, entry 1). This is a similar situation to that of **1a**, which did not react with the trisubstituted olefin **20o** at 120 °C (Table 1, entry 17) because of the higher-lying $LUMO_{diene}$ of **1a**. At a higher temperature (150 °C), however, **1a** reacted with α-pinene **20q** to give the product in 28 % yield (Table 4, entry 2). When the *o*-QM **1b**, which has a methyl group on the benzene ring, is used as the diene, it did not give the product even at 150 °C, probably because of its higher-lying $LUMO_{diene}$ (Table 4, entry 3). When *o*-QMs with an electron-withdrawing group on the benzene ring were used, they gave the expected products in moderate yield (Table 4, entries 4–16). These results support the idea that the reactivity of *o*-QM with an electron-withdrawing group on the benzene ring is higher than that of *o*-QM with an electron-donating group. In addition, there is no significant effect of the substituent of *o*-QMs on the regioselectivity (Table 4, entries 3/4, 5/6, 7/8, 9/10, 11/12, and 14/15). The stereochemistry of the products was confirmed by means of NOE experiments in ^{1}H NMR spectros-



a: R = H **f**: R = CO_2Me
b: R = Me **g**: R = CF_3
c: R = F **h**: R = CN
d: R = Cl **i**: R = NO_2
e: R = Br

Scheme 5.

Table 2. Diels–Alder reactions of various substituted *o*-QMs generated from substituted 4*H*-1,2-benzoxaizines with butoxyethene **20a**.[a]

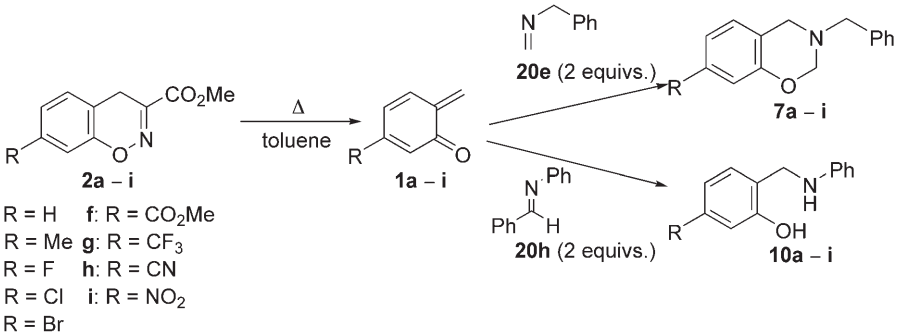
Entry		R	Dienophile	Temperature [°C]	Time [h]		Product	Yield [%]
1	**2a**	H	**20a** 	90	3	**3a**		91
2	**2b**	Me		80	3	**3b**		80
3	**2c**	F		100	3	**3c**		89
4	**2d**	Cl		100	3	**3d**		85
5	**2e**	Br		100	3	**3e**		86
6	**2f**	CO_2Me		110	8	**3f**		86
7	**2g**	CF_3		120	8	**3g**		100
8	**2h**	CN		120	8	**3h**		100
9	**2i**	NO_2		120	8	**3i**		98

[a] A solution of substituted 3-methoxycarbonyl-4*H*-1,2-benzoxazine and 2 equivs. of *n*-butoxyethene **20a** in 15 mL of dry toluene was heated at 80–120 °C with stirring for 3–8 h. The solvent was evaporated under reduced pressure to give the product.

copy. Generally, the stronger the electron-withdrawing ability, the higher is the yield of the cycloaddition.

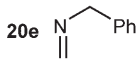
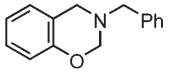
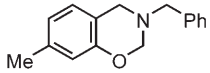
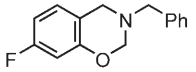
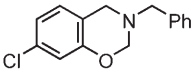
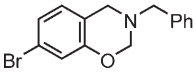
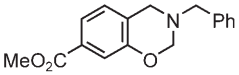
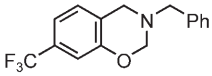
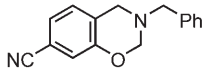
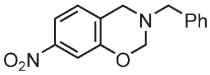
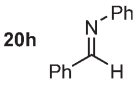
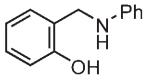
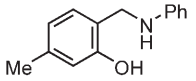
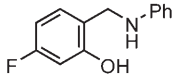
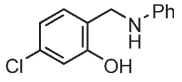
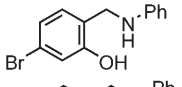
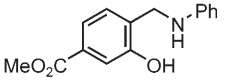
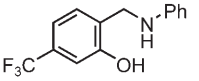
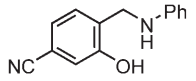
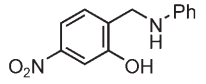
Conclusions

We have developed a new and efficient method for the generation of various substituted *o*-QMs from the versatile precursors 4*H*-1,2-benzoxazines. In this method *o*-QMs substituted with various substituents can be generated and trapped with dienophiles. The method requires heating, but to a much lower temperature than in the cases of the conventional precursors, and no additional acid or base catalysts are required for the formation of the Diels–Alder adducts. This method can allow the generation of various substituted *o*-QMs simply by moderate heating. The Diels–Alder reaction proceeds efficiently with a variety of



Scheme 6.

Table 3. Diels–Alder reactions of various substituted *o*-QMs generated from substituted 4*H*-1,2-benzoxazines with benzylmethyleneamine **20e** and benzylidenephenylamine **20h**.[a,b]

Entry	R	Dienophile	Temperature [°C]	Time [h]	Product	Yield [%]
1	**2a** H	**20e** 	90	6	**7a** 	79
2	**2b** Me		80	6	**7b** 	58
3	**2c** F		100	6	**7c** 	62
4	**2d** Cl		100	6	**7d** 	83
5	**2e** Br		100	6	**7e** 	96
6	**2f** CO_2Me		110	8	**7f** 	100
7	**2g** CF_3		120	8	**7g** 	91
8	**2h** CN		120	8	**7h** 	100
9	**2i** NO_2		120	8	**7i** 	100
10	**2a** H	**20h** 	100	8	**10a** 	92
11	**2b** Me		90	8	**10b** 	75
12	**2c** F		100	8	**10c** 	73
13	**2d** Cl		100	8	**10d** 	81
14	**2e** Br		100	8	**10e** 	72
15	**2f** CO_2Me		110	10	**10f** 	77
16	**2g** CF_3		120	10	**10g** 	89
17	**2h** CN		120	10	**10h** 	81
18	**2i** NO_2		120	10	**10i** 	56

[a] A solution of substituted 3-methoxycarbonyl-4*H*-1,2-benzoxazine and 2 equivs. of *N*-methylidene benzylamine **20e** in 15 mL of dry toluene was heated at 80–120 °C with stirring for 6–8 h. Then the solvent was evaporated under reduced pressure to give the product.

[b] A solution of substituted 3-methoxycarbonyl-4*H*-1,2-benzoxazine and 2 equiv of benzylidene phenylamine **20h** in 15 mL of dry toluene was heated at 90-120 °C with stirring for 8-10 h. After acid-catalyzed hydrolysis of the cyclized intermediate, the solvent was evaporated under reduced pressure to give the product.

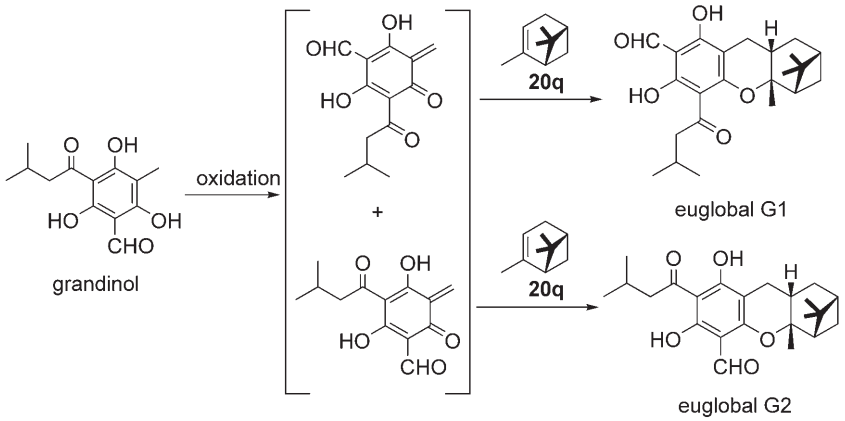
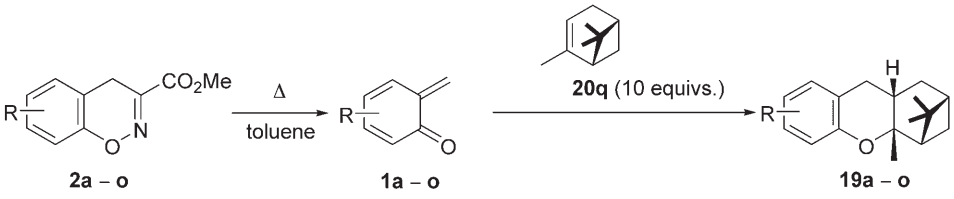


Figure 2. Grandinol and euglobals G1 and G2.



a: R = H **f**: R = 7-CO_2Me **k**: R = 6-Cl
b: R = 7-Me **g**: R = 7-CF_3 **l**: R = 6-Br
c: R = 7-F **h**: R = 7-CN **m**: R = 6-CO_2Me
d: R = 7-Cl **i**: R = 7-NO_2 **n**: R = 5-CF_3
e: R = 7-Br **j**: R = 8-F **o**: R = 8-NO_2

Scheme 7.

electron-rich dienophiles to give chromans, 3,4-dihydro-1,3-benzoxazines and *o*-substituted phenols in good yields with high regio-, chemo- and stereoselectivities. The generation of various substituted *o*-QMs allowed us to investigate the reactivity of these *o*-QMs. This novel method has been applied to the rapid synthesis of complex natural product derivatives. The present findings greatly enhance the applicability of *o*-QMs in synthetic chemistry.

Experimental Section

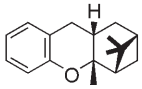
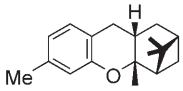
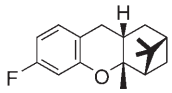
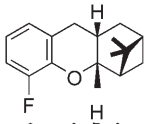
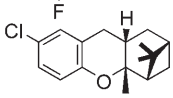
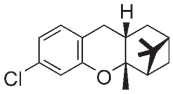
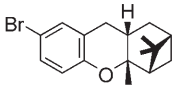
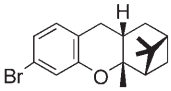
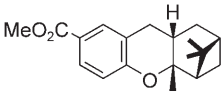
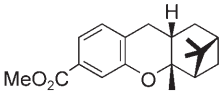
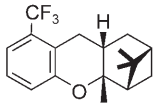
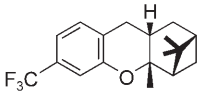
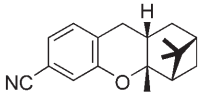
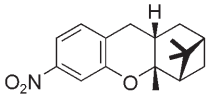
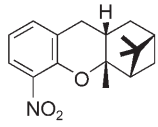
General Methods

All moisture-sensitive reactions were carried out under an argon atmosphere unless otherwise noted. All other reagents were commercially available and used without further purification. Thin-layer chromatography was carried out on precoated glass plates (E. Merck Brinkman, Kieselgel 60 F254, 0.25 mm thickness). Column chromatography was carried out on silica gel [silica gel 60 N (100–210 μm), Merck]. All the melting points were measured with a Yanaco Micro Melting Point Apparatus and are uncorrected. Proton (400 MHz) NMR spectra were measured on a Bruker AV400 NMR spectrometer with TMS as an internal reference in $CDCl_3$ as the solvent, unless otherwise specified. Chemical shifts are shown in ppm. Coupling constants are given in Hertz. Electron spray ionization time-of-flight mass spectra (ESI-MS) and high-resolution ESI mass spectra (HR-MS) were recorded on a Bruker Daltonics (micro-TOF-05). Low-resolution FAB mass spectra (MS, FAB^+) and high-resolution FAB mass spectra (HR-MS, FAB^+) were recorded on JEOL MStaton JMS-700 and JEOL JMS-SX 102A spectrometers. The combustion analyses were carried out in the microanalytical laboratory of this faculty.

Synthesis of 3-Methoxycarbonyl-4*H*-1,2-benzoxazine (2a)

To ice-cooled dry THF (25 mL) a solution of $TiCl_4$ (2.3 mL, 22.6 mmol, 2.4 equivs.) in CCl_4 (10 mL) was added at 0 °C. Then, to this solution a solution of benzaldehyde (1.00 g, 9.44 mmol) and methyl nitroacetate (1.14 g, 9.53 mmol, 1.0 equiv.) in dry THF (10 mL) was added, and the whole was stirred for 2 h at 0 °C. A solution of *N*-methylmorpholine (3.81 g, 37.8 mmol, 4.0 equivs.) in dry THF (20 mL) was slowly added over 2 h, and the whole was stirred vigorously for 20 h at 18 °C. Then, water (100 mL) was added, and the whole was extracted with ether. The organic phase was washed with brine, dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to give a residue (2.24 g), which was column-chromatographed on silica gel

Table 4. Diels–Alder reactions of various substituted *o*-QMs generated from substituted 4*H*-1,2-benzoxazines with α-pinene **20q**.[a]

Entry		R	Dienophile	Temperature [°C]	Time [h]	Product	Yield [%]
1	**2a**	H	**20q** 	120	6	—	0
2	**2a**	H		150	6	**19a** 	28
3	**2b**	7-Me		150	6	**19b** 	trace
4	**2c**	7-F		150	6	**19c** 	32
5	**2j**	8-F		150	6	**19j** 	38
6	**2k**	6-Cl		150	6	**19k** 	43
7	**2d**	7-Cl		150	6	**19d** 	42
8	**2l**	6-Br		150	6	**19l** 	48
9	**2e**	7-Br		150	6	**19e** 	56
10	**2m**	6-CO_2Me		150	6	**19m** 	51
11	**2f**	7-CO_2Me		150	6	**19f** 	48
12	**2n**	5-CF_3		150	6	**19n** 	72
13	**2g**	7-CF_3		150	6	**19g** 	52
14	**2h**	7-CN		150	6	**19h** 	44
15	**2i**	7-NO_2		150	6	**19i** 	78
16	**2o**	8-NO_2		150	6	**19o** 	70

[a] To a solution of 10 equivs. of α-pinene **20q** in toluene, a solution of substituted 3-methoxycarbonyl-4*H*-1,2-benzoxazine in toluene was slowly added at 150 °C. Then the whole was stirred for 6 h at 150 °C, and the solvent was evaporated under reduced pressure to give the product.

(eluent: *n*-hexane-ethyl acetate = 6:1) to afford the *intermediate nitroolefin*; yield: 1.70 g.

This crude intermediate was dissolved in a mixture of $CHCl_3$ (70 mL) and *i*-PrOH (20 mL). To this solution, SiO_2 (6.00 g) and $NaBH_4$ (0.309 g, 4.72 mmol) were added, and the reaction mixture was stirred at room temperature for 4 h. Then, aqueous 12 N HCl (5 mL) was carefully added, and the whole was filtered to remove silica gel. The solution was evaporated under reduced pressure to give a residue, which was column-chromatographed on silica gel (eluent: *n*-hexane-ethyl acetate = 10:1) to afford *methyl 2-nitro-3-phenylpropionate* as a white solid; yield: 0.953 g, 4.56 mmol, overall 48%, based on benzaldehyde).

To a solution of methyl 2-nitro-3-phenylpropionate (204 mg, 0.98 mmol) in ice-cooled dry $CHCl_3$ (20 mL), TFSA (0.90 mL, 10.0 mmol, 10 equivs.) was added slowly. The mixture was stirred at 50 °C for 30 min, then the whole was poured into ice-water (100 mL), and extracted with $CHCl_3$. The organic phase was washed with brine, dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to give a residue (196 mg), which was column-chromatographed on silica-gel (eluent: *n*-hexane-ethyl acetate = 6 :1) to afford *3-methoxycarbonyl-4H-1,2-benzoxazine* **2a** as white powder; yield: 155 mg (0.81 mmol, 83%); mp 64–66 °C (colorless plates, recrystallized from *n*-hexane/$CHCl_3$). ^{1}H NMR ($CDCl_3$/TMS): δ = 7.26–7.23 (m, total 1H), 7.11–7.04 (m, total 3H), 3.94 (s, 3H), 3.66 (s, 2H); ^{13}C NMR ($CDCl_3$): δ = 163.2, 151.4, 149.3, 128.6, 128.1, 125.0, 114.8, 114.3, 53.2, 22.3; anal. calcd. for $C_{10}H_9NO_3$: C 62.82, H 4.74, N 7.33; found: C 62.74, H 4.86, N 7.32.

Preparation of Imines 20e and 20f; Typical Procedure for Benzylmethyleneamine (20e)

To a solution of benzylamine (524 mg, 4.89 mmol) and paraformaldehyde (149 mg, 4.95 mmol) in dry $CHCl_3$, $MgSO_4$ (1.10 g) was added. The solution was stirred at room temperature for 6 h. Then, the whole was filtered to remove $MgSO_4$. The solvent was evaporated under reduced pressure to give a solid, which was recrystallized from *n*-hexane/ether to afford benzylmethyleneamine **20e** as a white powder; yield: 361 mg (3.03 mmol, 62%); mp 46–47 °C (white powder, recrystallized from *n*-hexane/ether). ^{1}H NMR ($CDCl_3$/TMS): δ = 7.35–7.22 (m, total 5H), 3.97 (s, 2H), 3.45 (s, 2H); ^{13}C NMR ($CDCl_3$): δ = 138.4, 128.9, 128.2, 127.0, 73.8, 57.1; anal. calcd. for C_8H_9N: C 80.63, H 7.61, N 11.75; found: C 80.35, H 7.77, N, 11.66.

Cyclization Reaction of *o*-Quinone Methides Generated from 4*H*-1,2-Benzoxazines; Typical Procedure for 2-Butoxychroman (3a)

A solution of **2a** (180 mg, 0.940 mmol) and *n*-butoxyethene (200 mg, 2.00 mmol, 2.1 equivs.) in dry toluene (15 mL) was heated at 90 °C with stirring for 3 h. Then the solvent was evaporated under reduced pressure to give a residue, which was column-chromatographed on silica gel (eluent: *n*-hexane-ethyl acetate = 10:1) to afford 2-butoxychroman **3a** as a colorless oil; yield: 176 mg, 0.860 mmol, 91%). ^{1}H NMR ($CDCl_3$/TMS): δ = 7.05 (dd, J = 7.9, 7.3 Hz, 2H), 6.86–6.79 (m, total 2H), 5.21 (t, J = 2.8 Hz, 1H), 3.83–3.80 (m, total 1H), 3.58–3.54 (m, total 1H), 1.54–1.49 (m, total 2H), 1.31–1.26 (m, total 2H), 0.91–0.83 (m, total 3H); ^{13}C NMR ($CDCl_3$): δ = 152.6, 129.2, 127.2, 122.7, 120.5, 116.9, 97.1, 68.0, 31.7, 26.6, 20.6, 19.3, 13.8; anal. calcd. for $C_{13}H_{18}O_2$: C 75.69, H 8.80, N, 0.00; found: C 75.64, H 8.65, N 0.00.

Methyl 3-(2-Hydroxyphenyl)propionate (5)

A solution of **2a** (180 mg, 0.940 mmol) and *tert*-butyl(1-methoxyvinyloxy)dimethylsilane (377 mg, 2.00 mmol, 2.1 equivs.) in dry toluene (15 mL) was heated at 100 °C with stirring for 2 h. Then the solvent was evaporated under reduced pressure to give an intermediate. 1.0 M TBAF solution in THF (1.0 mL) was added to the intermediate at 0 °C. The solvent was stirred for 5 min. Then the solvent was evaporated under reduced pressure to give a residue, which was column-chromatographed on silica gel (eluent: *n*-hexane-ethyl acetate = 3:1) to afford methyl 3-(2-hydroxyphenyl)propionate **5** as a white solid; yield: 144 mg (0.800 mmol, 85%); mp 40–41 °C (white powder, recrystallized from *n*-hexane/ether). ^{1}H NMR (DMSO-d_6): δ = 9.37 (s, 1H), 7.06–6.99 (m, total, 2H), 6.78 (d, J = 8.0 Hz, 1H), 6.80 (dd, J = 7.4, 7.4 Hz, 1H), 3.58 (s, 3H), 3.34 (s, 2H), 2.77 (t, J = 7.4 Hz, 2H), 2.56 (t, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 176.0, 154.2, 130.5, 128.0, 127.3, 120.9, 117.1, 52.3, 34.9, 24.7; anal. calcd. for $C_{10}H_{12}O_3$: C 66.65, H 6.71, N 0.00; found: C 66.52, H, 6.71, N, 0.00.

2-Phenylaminomethylphenol (10a)

A solution of **2a** (190 mg, 0.990 mmol) and benzylidenephenylamine (363 mg, 2.00 mmol, 2.0 equivs.) in dry toluene (15 mL) was heated at 100 °C with stirring for 8 h. Then the solvent was evaporated under reduced pressure to give an intermediate. Aqueous 2 N HCl (5 mL) and THF (5 mL) were added to the intermediate. The solvent was stirred for 2 h. The whole was extracted with water. The aqueous phase was neutralized by aqueous 2 N NaOH. The whole was extracted with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4. Then the solvent was evaporated under reduced pressure to give a residue, which was column-chromatographed on silica gel (eluent: *n*-hexane-ethyl acetate = 1:1) to afford 2-phenylaminomethylphenol **10a** as a white solid; yield: 182 mg (0.910 mmol, 92%); mp 131–132 °C (white powder, recrystallized from *n*-hexane/ether). ^{1}H NMR ($CDCl_3$/TMS): δ = 8.18 (s, 1H), 7.30–7.18 (m, total 5H), 6.97–6.87 (m, total 4H), 4.45 (s, 2H), 4.00 (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 155.4, 149.3, 129.3, 128.6, 127.9, 126.2, 119.2, 116.0, 115.3, 112.6; anal. calcd. for $C_{13}H_{13}NO$: C 78.36, H 6.58, N 7.03; found: C 78.23, H 6.77, N 7.24.

Supporting Information

Characterization data for all compounds made are given in the electronic Supporting Information.

Acknowledgements

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