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New type of a stable *p*-quinone methide possessing a pendant malonate moiety: synthesis and reactions with C-nucleophiles

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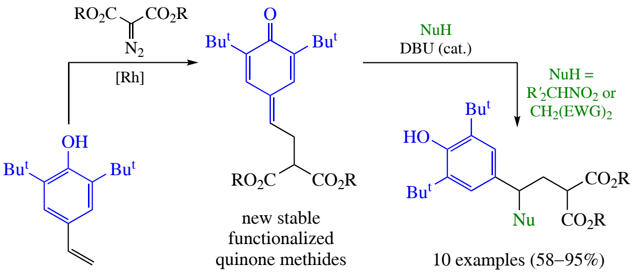
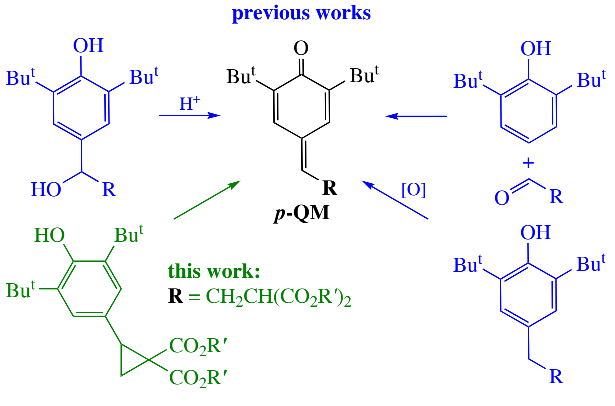
Cyclopropanation of 2,6-di-*tert*-butyl-4-vinylphenol with diazomalonates affords 4-hydroxyaryl-substituted cyclopropane dicarboxylates prone to easy ring opening into *p*-quinone methides tethered to malonate unit. The resulting quinone methides react with various C-nucleophiles to form the corresponding adducts thus serving as synthetic equivalents for donor–acceptor cyclopropanes in the homo-Michael addition. Side processes, namely, isomerization and dimerization of the quinone methides under basic conditions, were found.



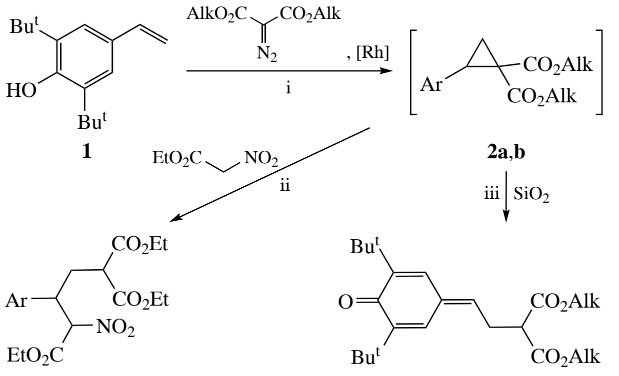
Keywords: quinone methides, donor–acceptor cyclopropanes, cyclopropanation, ring opening, nitro compounds, diazo compounds, malonates.

p-Quinone methides (*p*-QMs) are valuable synthons in organic synthesis and important intermediates in various biological processes. They are strong Michael acceptors that smoothly undergo 1,6-addition reactions accompanied by rearomatization of the *p*-hydroxyphenyl ring.[1–3] This unique reactivity pattern can be used in the preparation of polysubstituted phenols as well as be incorporated in tandem processes leading to complex heterocycles.[4–8] Common approaches[2,9] to stable *p*-QMs involve dehydration of the corresponding *p*-hydroxybenzyl alcohols and their derivatives,[10,11] base-promoted condensation of aromatic aldehydes with phenols[11–13] and oxidation of *p*-alkylphenols[14,15] (Scheme 1). Despite this, the scope of available *p*-QMs appears limited. The most used *p*-QMs possess two main structural features: the presence of two bulky substituents (usually $\mathrm{Bu^t}$-groups)[1,2] shielding carbonyl group and six-membered ring, and the presence of an aryl substituent at exocyclic methylidene site. The conjugation of the latter with π-bonds of *p*-QM moiety increases the stability of *p*-QMs allowing them to be isolated in a pure state. *p*-Quinone methides with an exocyclic alkylidene residue are essentially less explored.[3,15] It can be attributed to their inherent reactivity as well as lability under conditions used for the preparation of aryl-substituted congeners. Recently, two reports[16,17] appeared on the *p*-QMs as proposed intermediates in the nucleophilic ring opening of donor–acceptor cyclopropanes (DACs) with hydroxyaryl substituent.[18–20] We envisioned that appropriate structural modification would improve the stability of the intermediate *p*-QMs and enable their isolation. Not only could it lead to the establishment of a novel type of *p*-QMs, but could also provide an experimental evidence for the intermediacy of *p*-QMs in the ring opening of DACs. Therefore, it would provide a new type of synthetic equivalent of DAC.[18,21–23] Hereby we report the synthesis of stable *p*-quinone methides with a pendant malonate moiety and its reactions with C-nucleophiles.



Scheme 1

We initiated our study with the preparation of the proposed precursor of a stable *p*-QM. Since di-*tert*-butylated *p*-QMs are most frequently employed, we aimed for the corresponding cyclopropane which could be accessed from the parent 2,6-di-*tert*-butyl-4-vinylphenol **1** (Scheme 2). For this purpose, we tried to implement the same reaction sequence that was used in our previous report.[16] Hence, at the first step, 4-vinylphenol **1** was prepared by methylenation of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde in 60% yield according to a modified literature procedure.[24] However, attempts to install a silyl group on the phenolic hydroxy function (TBSCl/ImH or TBSOTf/ImH or TMSOTf/ImH, room temperature, 1–3 days) failed due to the bulkiness of *tert*-butyl and silyl groups. It encouraged us to use unprotected phenol **1** in the reaction with diazomalonate under catalysis by $Rh_2(Oct)_4$. Gratifyingly, it worked pretty well and gave the target cyclopropane **2a** with *ca.* 78% yield. Presumably, hydroxy group in **1** is shielded by *tert*-butyl substituents and cannot participate in side reactions with metal carbenes.[25] Additionally, $\mathrm{Bu^t}$ groups increased the solubility of 4-vinylphenol **1** in CH_2Cl_2 as compared to its unsubstituted analog.



4a (63% from **1**, *dr* = 1.3:1)
Ar = 3,5-Bu^t_2-4-HOC_6H_2

3a Alk = Et (79%)
3b Alk = Me (75%)

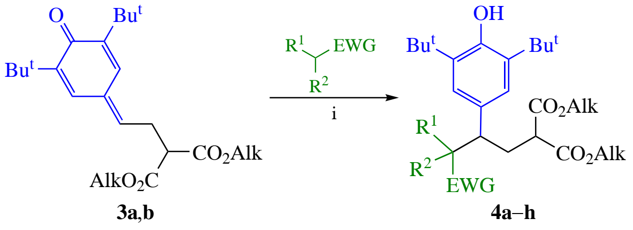
Scheme 2 *Reagents and conditions*: i, Rh_2Oct_4 (0.5 mol%) or $Rh_2(esp)_2$ (0.2 mol%), MS 4Å, CH_2Cl_2, 25 °C, 3 h; ii, $O_2NCH_2CO_2Et$ (1.1 equiv.), DBU (0.1 equiv.), MeCN, 25 °C, 1.5 h; iii, column chromatography.

Overall, it allowed smooth preparation of DAC **2a** (see Scheme 2). Since no noticeable amounts of impurities were observed, crude DAC **2a** was involved in the ring opening reaction with nitroacetate to give malonate **4a** isolated in 63% overall yield. Thus, we confirmed that DAC **2a** behaved in a way similar to that of its analogs possessing no *tert*-butyl groups.[16]

Next we proceeded to the detailed investigations on the synthesis of 4-hydroxyaryl-substituted DACs **2**. Intriguingly, attempted purification of DAC **2a** by column chromatography on silica resulted in a clean conversion into *p*-QM **3a** with 68% total yield. Indeed, related examples of the cleavage of small cycles at silica are known.[26,27] Aiming to increase the yield of the target *p*-QM **3a**, we briefly screened the conditions for the cyclopropanation and tested other common Rh-catalysts. Carboxylates $Rh_2(OAc)_4$ and $Rh_2(CF_3COO)_4$ did not lead to improvement, while $Rh_2(OPiv)_4$ and $Rh_2(esp)_2$ (esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionate)[28] gave better results. Finally, the use of $Rh_2(esp)_2$ allowed us to decrease the amount of catalyst and to increase the yield of **3a** to 79%. Cyclopropanation–ring opening sequence worked well for methyl and ethyl diazomalonates, affording DACs **2a**,**b** and corresponding *p*-QMs **3a** and **3b**. Their structure was confirmed by NMR, HRMS, and UV-vis spectra data.

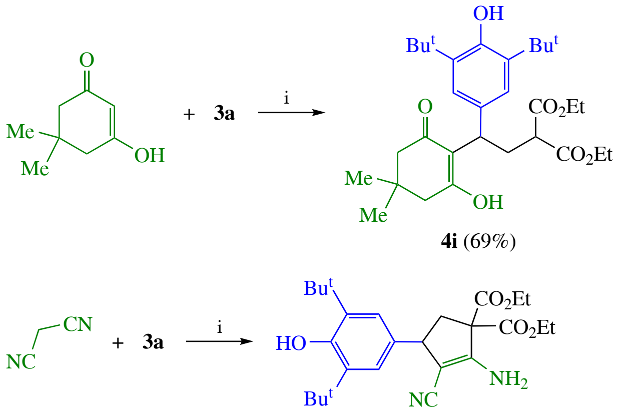
With *p*-QMs **3** in hand, we proceeded to the evaluation of their reactivity toward nucleophiles. Using *p*-QM **3a** and ethyl nitroacetate as model substrates, we performed a variation of reaction conditions. To our delight, a number of bases (DBU, NEt_3, *N*-methylmorpholine, DMAP) in various solvents (MeCN, CH_2Cl_2, PhMe, THF, EtOH) gave adduct **4a** in high yields of 83–94% (see Online Supplementary Materials for details). Therefore, we chose DBU in CH_2Cl_2 to elucidate the reaction scope. Active methylene compounds were used as reaction partners (Scheme 3). High yields were observed for nitroacetates (products **4a–c**), nitroacetophenone (**4d**), and α-nitrotoluene (**4e**). In the case of less acidic nitroethane, an excess of nitrocompound was used that led to product **4f** in 58% yield. Among other common CH-acids, dibenzoylmethane and dimedone gave smoothly products **4g** and **4i**, respectively. While the reaction with diethyl malonate did not provide a satisfactory yield of the corresponding product, use of bis(2,2,2-trichloroethyl) malonate possessing two electron-withdrawing moieties afforded adduct **4h** in 83% yield. Finally, addition of malononitrile was accompanied by a cyclization leading to aminocyclopentene **5**.[16,29]

Considering the presence of two reactive functionalities (*i.e.*, electron-deficient conjugated system and malonate moiety) in compounds **3** we proceeded to the investigation of their behavior under basic conditions. Thus, *p*-QM **3a** was treated with NEt_3 and DBU in the absence of other reactants (Scheme 4). While NEt_3 caused isomerization of *p*-QM **3a** to styrene **6**, a stronger base DBU gave a mixture of linear (**7**) and cyclic (**8**) dimers (paths *a* and *b*, respectively). Their structures were proved by 1D and 2D NMR as well as HRMS data (see Online Supplementary Materials for details). We found out, that these processes took place even in the presence of weak nucleophiles. That is, for less acidic (*e.g.*, nitrocyclopentane) or sterically hindered [*e.g.*, (1-nitroethyl)benzene] substrates attempted reactions with *p*-QM **3a** were sluggish with predominant formation of styrene **6** and dimerization of **3a** to products **7** and **8**. These side processes are also attributed to the low yields of adducts **4** in case of nitroethane and diethyl malonate (see above). The following mechanisms for the observed transformations were proposed. The first thing to note is that there are two acidic centers in *p*-QM **3a**, namely the allylic position (H_A in Scheme 4) and the malonate moiety (H_B). In case of abstraction of H_A, an anion conjugated with a quinone methide is formed. It can easily isomerize with the reconstruction of aromatic system and formation of styrene **6**. Another possible option, *i.e.*, deprotonation of the malonate moiety (abstraction of H_B) in **3a** can be followed by the subsequent addition to another molecule of **3a**. Next, proton transfer leads to linear product **7** (path *a*), while 1,6-addition at the quinone methide moiety provides cyclic



3a Alk = Et
3b Alk = Me

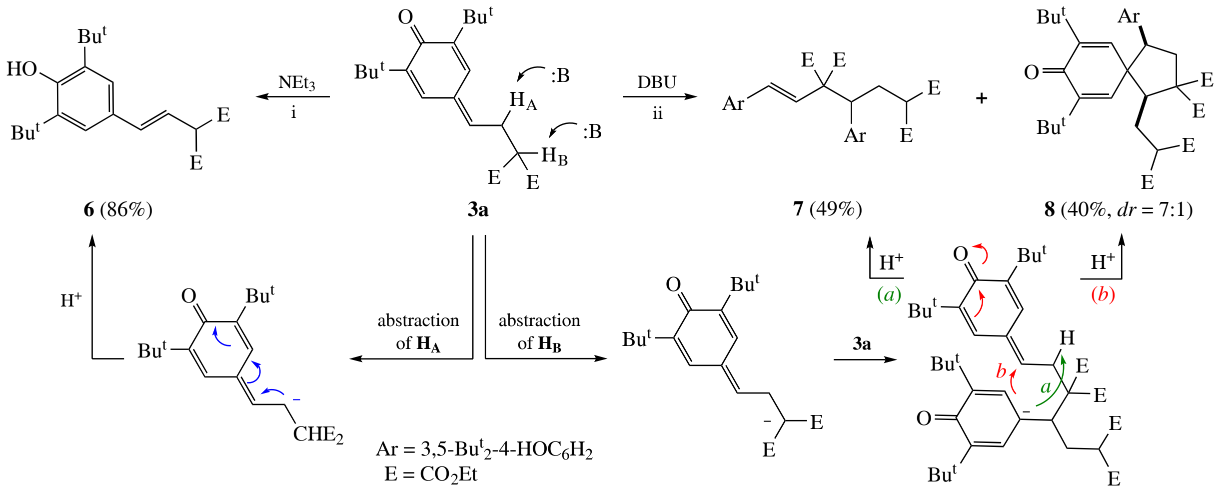
4a Alk = Et, R^1 = H, R^2 = CO_2Et, EWG = NO_2 (93%, *dr* = 1.3:1)
4b Alk = Me, R^1 = H, R^2 = CO_2Me, EWG = NO_2 (87%, *dr* = 1:1)
4c Alk = Et, R^1 = Me, R^2 = CO_2Et, EWG = NO_2 (95%, *dr* = 1:1)
4d Alk = Et, R^1 = H, R^2 = C(O)Ph, EWG = NO_2 (94%, *dr* = 2.7:1)
4e Alk = Et, R^1 = H, R^2 = Ph, EWG = NO_2 (88%, *dr* = 2.3:1)
4f Alk = Et, R^1 = H, R^2 = Me, EWG = NO_2 (58%, *dr* = 1.3:1)
4g Alk = Et, R^1 = H, R^2 = EWG = C(O)Ph (65%)
4h Alk = Et, R^1 = H, R^2 = EWG = $CO_2CH_2CCl_3$ (83%)



4i (69%)

5 (85%)

Scheme 3 *Reagents and conditions*: i, 1.1 equiv. of CH-acid (or 5 equiv. of $EtNO_2$ for **4f**), DBU (0.1–0.5 equiv.), CH_2Cl_2, 25 °C, 1.5–5 h. Relative configuration of stereocenters in **4a**–**d** was not determined, while for **4e**,**f** it could be hypothesized based on the similarities in the NMR spectra (*cf.* ref. 16).



Scheme 4 *Reagents and conditions*: i, NEt_3 (0.1 equiv.), CH_2Cl_2, room temperature, 1 day; ii, DBU (0.1 equiv.), CH_2Cl_2, room temperature, 3 h.

product **8** (path *b*). Formation of linear dimer **7** is also possible *via* the intermediacy of styrene **6**. We can note that such behavior of *p*-QMs **3** resembles those of the corresponding DACs which are known to produce isomers and dimers under Lewis acid catalysis.[18,30–35]

In conclusion, the synthesis and reactivity of stable *p*-quinone methides possessing a malonate moiety were studied. Cyclopropanation of 2,6-di-*tert*-butyl-4-vinylphenol with diazomalonate smoothly proceeded under catalysis with Rh^{II} carboxylates, and formed cyclopropanes underwent ring opening during silica chromatography leading to *p*-QMs. Nucleophilic addition of active methylene compounds to *p*-QMs afforded corresponding products in high yields for substrates with pK_a of ~7–14. For less active nucleophiles, isomerization and dimerization of *p*-QMs became major processes. Further studies on the reactivity of hydroxyaryl-substituted DAC and corresponding *p*-QMs, including its dimerization, are currently underway.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7746.

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