Synlett H. Yu, G. A. Kraus Letter

Base-Promoted Reactions of Hydroxyquinones with Pyrones: A Direct and Sustainable Entry to Anthraquinones and Naphthoquinones

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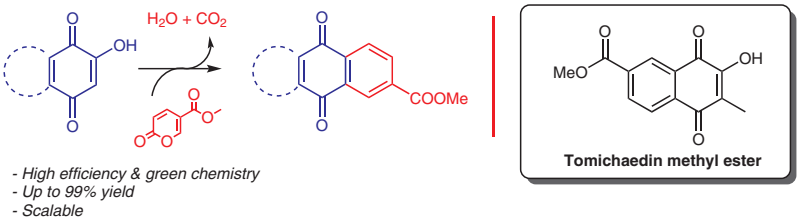


Received: 11.04.2019
Accepted after revision: 07.06.2019
Published online: 08.07.2019
DOI: 10.1055/s-0039-1690106; Art ID: st-2019-v0207-l

Abstract Hydroxybenzoquinones and hydroxynaphthoquinones react with methyl coumalate and 5-cyanopyrone to generate anthraquinones and naphthoquinones in good to excellent yields.

Key words anthraquinone, naphthoquinone, pyrone, base-promoted, synthesis

Direct and sustainable routes to quinones are important to a number of sectors, including the polymer and pharmaceutical sectors. Anthracene diesters have been employed as monomers for poly(ethylene anthracenates) (PEAs). PEAs such as 2,6-PEA (**1**) have barrier properties and UV-blocking ability that are superior to polyethylene terephthalate (PET; **2**) (Figure 1).[1] As a result, the structure-function relationships of PEAs, a necessary foundation for the rational design of commercially viable specialty polymers, is of current interest. In the pharmaceutical sector, natural products such as AM5221 (**3**), and tomichaedin (**4**) are naphthoquinones.[2]

Scheme 1 shows our approach to anthracene **5** from anthraquinone **6** which, in turn, might be derived from methyl coumalate and a benzoquinone (**7**). Although only the dimethoxy version of **5** is shown, this strategy will permit the ready synthesis of tunable monomers with different alkyl groups and thus different properties. Methyl coumalate is available from malic acid in a one-pot process.[3] We evaluated a variety of X groups in benzoquinone **7**, including methoxyl (**7a**), morpholinyl (**7b**), and hydroxyl (**7c**). Only dihydroxybenzoquinone reacted to give **6**. Previous routes to **6** have utilized starting materials derived from petroleum sources and some routes involved multistep pathways.[4] Importantly, the monomers described herein are derived from renewable sources, aligning well with the current sustainable plastics initiatives and the goals of the recent OECD global forum on plastics in a circular economy.[5]

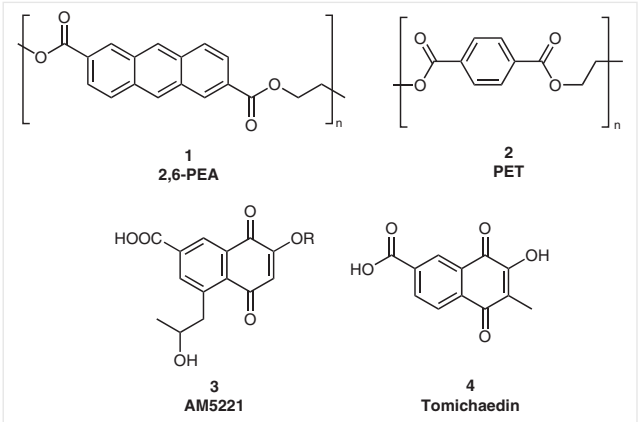
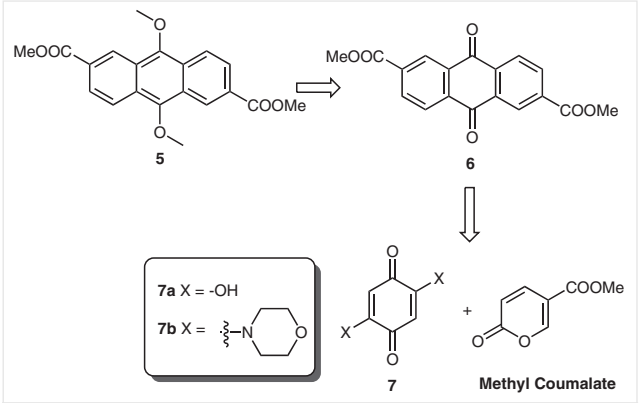


Figure 1 Structures of 2,6-PEA, PET, AM5221 and tomichaedin



Scheme 1 Retrosynthetic analysis of **6**

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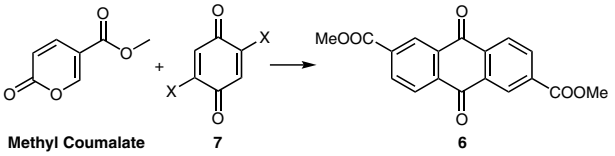
After screening solvents and conditions (Table 1), the addition of base was found to be essential for the conversion of **7** into **6**. The dimethoxyquinone **7a** and dimorpholinylquinone **7b** did not show any Diels–Alder reactivity under thermal conditions. The best result was obtained by reacting methyl coumalate with dihydroxyquinone **7c**, with a catalytic amount of triethylamine in acetonitrile under reflux for one day:

Table 1 Screening for Optimal Conditions



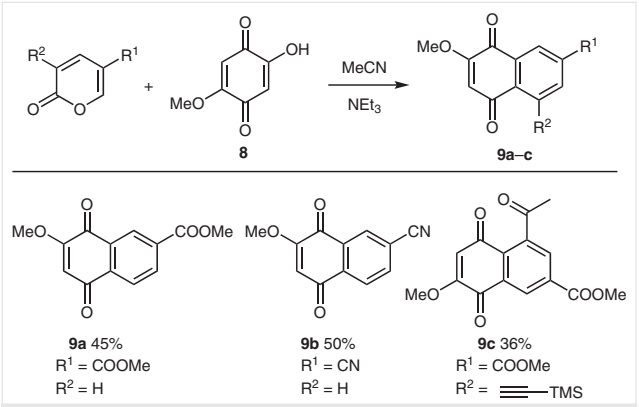
Methyl Coumalate 7 6

Entry	Reactant	Solvent	Temp (°C)	Base	Yield
1	**7a**	MeCN	80	–	no reaction
2	**7a**	toluene	80	–	no reaction
3	**7b**	MeCN	80	–	no reaction
4	**7b**	DMF	80	–	no reaction
5	**7b**	DMSO	150	–	0[a]
6	**7c**	toluene	80	–	no reaction
7	**7c**	CH_2Cl_2	40	–	no reaction
8	**7c**	MeCN	80	–	no reaction
9	**7c**	MeCN	80	NEt_3	67
10	**7c**	MeCN (Ar)	80	NEt_3	98
11	**7c**	DMF	80	NEt_3	<5
12	**7c**	DMSO	80	NEt_3	trace
13	**7c**	water	100	NEt_3	0[a]

[a] Full decomposition of starting materials.

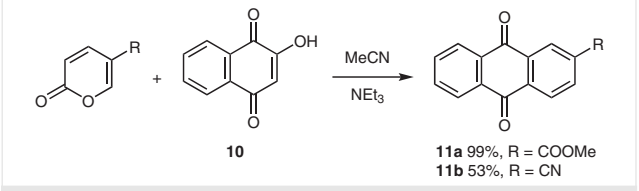
Dimethyl 2,6-anthraquinonedicarboxylate **6** was obtained in 98% yield. Conducting the reaction in the absence of oxygen was critical for excellent yields. Taking advantage of the low solubility of the anthraquinone diester, the crude material was isolated on a 20-gram scale simply by heating to reflux in ethyl acetate followed by filtration. Since base promotion is essential, these reactions are likely not concerted cycloadditions in the Diels–Alder mode and seem to be mechanistically different from the classic quinone cycloaddition chemistry of Jung, Houk and Hendrickson.[6] We believe that the reaction occurs via an intermolecular Michael addition followed by an intramolecular aldol reaction and loss of water and carbon dioxide.

With the optimal conditions in hand, other hydroxyquinones and substituted pyrones were tested as substrates. Some of them showed good reactivities with a moderate yield (Scheme 2). The corresponding products **9a–c** were isolated as a single regioisomer. The reaction of methyl coumalate with 5-methoxy-2-hydroxybenzoquinone **8** required a stoichiometric amount of triethylamine as base at a lower temperature for the best result. It is worth mentioning that the reaction between methyl 3-propynylcoumalate with corresponding quinone afforded the product **9c**, wherein the intermediate alkyne was transformed into a methyl ketone through a hydration process.



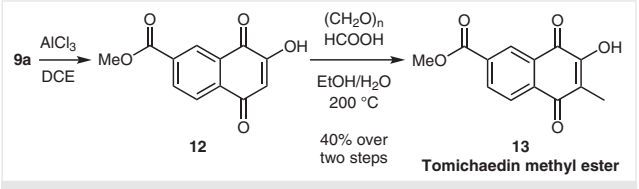
Scheme 2 Scope of the reaction (naphthoquinone)

Base-promoted reactions were carried out under the same conditions using lawsone (**10**) as the substrate. The reaction with methyl coumalate and 5-cyanopyrone afforded anthraquinones **11a** and **11b** in moderate yield (Scheme 3).



Scheme 3 Scope of the reaction (anthraquinone)

Tomichaedin methyl ester, readily derived from chaetomidin, was previously prepared by Thomson in a nine-step route.[7] Our synthesis used naphthoquinone **9a**. Cleavage of the methyl ether with $AlCl_3$ followed by methylation using paraformaldehyde with formic acid afforded tomichaedin methyl ester in two steps from **9a**, as illustrated in Scheme 4.



Scheme 4 Total synthesis of tomichaedin methyl ester

To conclude, methyl coumalate and 5-cyanopyrone react readily with hydroxyquinones under slightly basic conditions.[8] Dimethyl 2,6-anthraquinone dicarboxylate can be

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obtained on a 20-gram scale. Tomichaedin methyl ester was synthesized in three steps from commercially available compounds.

Funding Information

We thank the NSF Engineering Center for Biorenewable Chemicals (CBiRC) which awarded NSF grant EEC-0813570 for support of this research.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690106.

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(8) **Diels–Alder Reaction of Methyl Coumalate with Hydroxyquinone; Typical Procedure for Methyl 6-Methoxy-5,8-dioxo-5,8-dihydronaphthalene-2-carboxylate (9a)**
To a solution of methyl coumalate (555 mg, 3.6 mmol, 0.9 equiv) and hydroxyquinone **8** (552 mg, 4.0 mmol, 1.0 equiv) in acetonitrile (20 mL), triethylamine (405 mg, 4.0 mmol, 1.0 equiv) was added, and the solution turned dark-red immediately. The mixture was stirred under argon at 45 °C for 24 hours (monitored by ^{1}H NMR) then was cooled to ambient temperature. 0.5 M HCl solution was added, and the mixture was extracted with ethyl acetate three times. The organic phase was washed with brine and was dried over Na_2SO_4. Purification by column chromatography gave the product **9a** (45% yield) as a light-brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.75 (d, *J* = 1.6 Hz, 1 H), 8.39 (dd, *J* = 8.0, 1.5 Hz, 1 H), 8.16 (d, *J* = 8.1 Hz, 1 H), 6.23 (s, 1 H), 3.98 (s, 3 H), 3.93 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 184.2, 179.5, 165.6, 160.9, 135.2, 134.9, 134.8, 131.3, 128.2, 126.8, 110.4, 56.8, 53.0. HRMS (ESI-QTOF): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{10}O_5$: 247.0601; found: 247.0600.
Synthesis of Tomichaedin Methyl Ester
Methyl 7-Hydroxy-5,8-dioxo-5,8-dihydronaphthalene-2-carboxylate (12)
Under argon, a suspension of methoxy quinone **9a** (180 mg, 0.73 mmol, 1.0 equiv) and $AlCl_3$ (195 mg, 1.46 mmol, 2.0 equiv) in DCE (5 mL) was stirred under reflux for 1 hour. The reaction mixture was allowed to cool, 0.5 M HCl was added, and the mixture was extracted with ethyl acetate three times, and the organic phase was dried over Na_2SO_4. Filtration through a thin silica pad followed by removal of solvent afforded the product **12** as a solid, which was pure enough to use in the next step. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.75 (d, *J* = 1.7 Hz, 1 H), 8.44 (dd, *J* = 8.0, 1.7 Hz, 1 H), 8.20 (d, *J* = 8.0 Hz, 1 H), 7.39 (s, 1 H), 6.43 (s, 1 H), 4.00 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 184.3, 181.4, 165.4, 156.9, 136.1, 135.7, 134.7, 129.7, 128.0, 127.3, 111.4, 53.1. HRMS (ESI-QTOF): *m*/*z* [M]$^-$ calcd for $C_{12}H_8O_5$: 232.0370; found: 232.0323.
Tomichaedin Methyl Ester (13)
To a stainless-steel reactor, hydroxy quinone **12** (68 mg, 0.3 mmol, 1.0 equiv) was dissolved in a mixture of ethanol/water (1:1 ratio, 2 mL), and paraformaldehyde (40 mg, 1.2 mmol, 4.0 equiv) was added. The reactor was sealed under air, and was heated to 200 °C for 3 hours. After cooling, the mixture was diluted with 0.5 M HCl, and extracted with ethyl acetate. Filtration through a thin silica pad (the compound was found to be unstable on silica) afforded tomichaedin methyl ester **13** (40% over two steps) as a light-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.71 (d, *J* = 1.7 Hz, 1 H), 8.39 (dd, *J* = 8.0, 1.8 Hz, 1 H), 8.20 (d, *J* = 8.0 Hz, 1 H), 3.99 (s, 3 H), 2.13 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 184.5, 180.6, 165.5, 153.7, 135.8, 135.7, 134.5, 129.7, 127.6, 127.3, 121.5, 53.0, 9.0. HRMS (ESI-QTOF): *m*/*z* [M – H]$^-$ calcd for $C_{13}H_9O_5$: 245.0455; found: 245.0456.

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