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PARA-QUINONE METHIDE INITIATED INTRAMOLECULAR ELECTROPHILIC SUBSTITUTION REACTIONS

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ABSTRACT: A study on the reactivity of *para*-quinone methides in intramolecular cyclization reactions is presented. The *para*-quinone methides were isolated and completely characterized prior to cyclization. A furan, a pyrrole and a mono-alkyl substituted benzene were used as cyclization terminators.

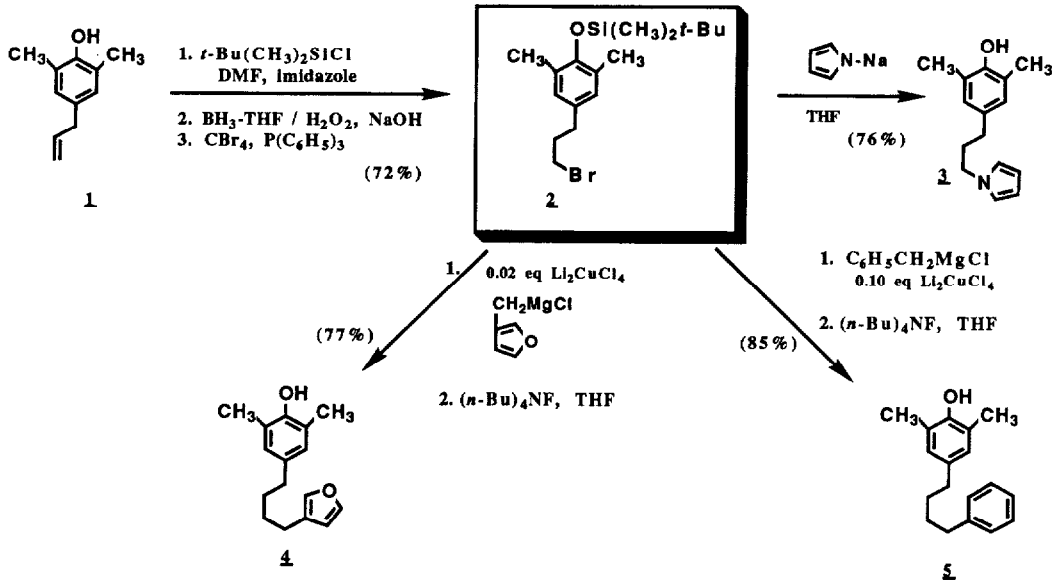
Quinone methides are believed to play an important role in biosynthesis[1] and in the biological activity of many quinonoid antitumor compounds.[2] However, their application as intermediates in synthesis has been quite limited.[3,4] As part of our program to better define the chemistry of quinone methides and utilize them in synthesis, we report herein the use of *para*-quinone methides as electrophiles in intramolecular electrophilic substitution reactions.

Earlier work from our laboratory has shown β-keto esters and allylsilanes to be excellent terminators for quinone methide initiated cyclizations.[5] The goal of the present study is to define the nature of the terminator in these cyclization reactions to help answer the question: How nucleophilic must a terminator be in order to capture a quinone methide before it decomposes? We elected to utilize electrophilic substitution reactions to probe this question. The relative reactivities of the terminators toward electrophiles have already been determined and vary over a wide range (benzene = 1, furan = 10^4, pyrrole = 10^9),[6] thus the results of the study can be used to predict the reactivity of quinone methides with other terminators of intermediate reactivity.

The use of *para*-quinone methides as synthetic intermediates has been limited largely to their use as transient intermediates,[4d,e] and there are only a few examples where a reactive quinone methide has been unambiguously characterized.[7,8a] 2,6-Disubstitution imparts considerable stability to *para*-quinone methides,[3] and the systems studied incorporate this substitution pattern. The quinone methides were fully characterized by normal spectroscopic methods (^{1}H-NMR, ^{13}C-NMR, IR, and MS), thus we can make definitive conclusions about their reactivity and synthesis potential.

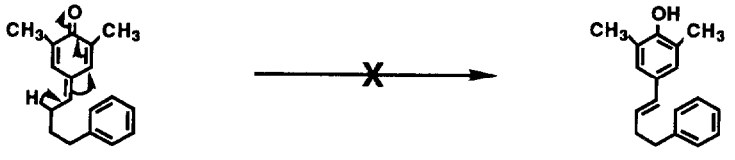
The cyclization substrates were prepared from readily available 2,6-dimethyl-4-(2-propenyl)-phenol[9] **1** (scheme 1). Protection of **1** as the *tert*-butyldimethylsilyl ether followed by hydroboration and oxidation afforded the primary alcohol, which was converted to bromide **2** using the method of Hooz and Gilani.[10] Treatment of **2** with the sodium salt of pyrrole[11] (5 eq, DMF, 0°C, 20min) gave phenol **3** in 76% yield.[12] Coupling of **2** with the Grignard reagent derived from 3-chloromethyl furan[13] was achieved using the Kochi-Tamura catalyst[14] (2 eq RMgCl, 0.02 eq Li_2CuCl_4, THF, 0°, 3h). Cleavage of the *tert*-butyldimethylsilyl ether (1.2 eq $(n\text{-}Bu)_4NF$, THF, 2h) afforded phenol **4** in 77% overall yield. Similarly, coupling of bromide **2** with benzyl-magnesium chloride (5.0 eq; 0.10 eq Li_2CuCl_4, THF, 0°, 3h) and desilylation [2.5 eq $(n\text{-}Bu)_4NF$, THF, 1.5h] afforded phenol **5** in 85% yield.[12]

SCHEME 1



The results of the cyclization studies are summarized in Table 1. The phenols were oxidized to the corresponding quinone methides with Ag_2O (4 to 10 eq) using the method of Dyall and Winstein.[5,8a] Each quinone methide could be easily handled in solution, or neat, and was fully characterized using normal spectroscopic methods.[16-18] Treatment with $ZnCl_2$ (1.0 to 10.0 eq) to increase the electrophilic character of the quinone methide triggered the cyclization reaction. The cyclizations were all complete within 1 minute of $ZnCl_2$ addition. The modest yield of pyrrole **7** (62%) is due to the instability of the compound, which rapidly decomposes upon handling. It is interesting to note the yield of **7** is concentration dependent. At low concentrations (0.001M to 0.005M), the desired product was the only compound observed in the ^{1}H-NMR spectrum of crude **7**; at higher concentrations (0.01M to 0.10M), a significant amount (20 to 80%) of intractable products were produced. We did not detect any concentration effects in the other cyclizations.

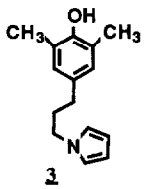
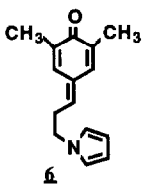
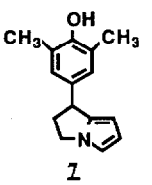
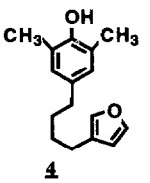
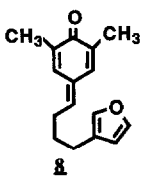
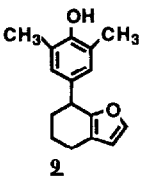
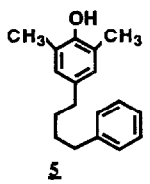
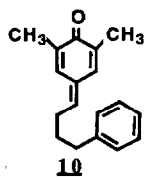
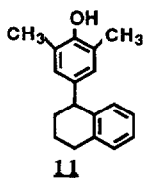
The conversion of **10** to **11** is important; the monosubstituted aromatic ring is reactive enough to capture the quinone methide before it has a chance to undergo formal enolization to styrene **12**. Enolization is a major decomposition pathway for quinone methides,[3] however, we do not detect any styrene **12** in the crude ^{1}H-NMR of cyclization product **11**.



10 **12** NOT OBSERVED

This result bodes favorably for the use of *para*-quinone methides as cyclization initiators with relatively unreactive cyclization terminators. In addition, one would anticipate that any aryl ring substituted with an alkyl group or other electron donating groups would also be a viable terminator for a quinone methide initiated cyclization reaction.

TABLE 1. *PARA*-QUINONE METHIDE INITIATED CYCLIZATION REACTIONS.

ENTRY	PHENOL	QUINONE METHIDE[a]	PRODUCT	YIELD %[b]
1	 **3**	 **6**	 **7**	62
2	 **4**	 **8**	 **9**	83
3	 **5**	 **10**	 **11**	67

[a] Oxidations were run in CH_2Cl_2 or $CDCl_3$ at 25°C using the procedure of Dyall and Winstein (ref 8a). All quinone methides were treated with $ZnCl_2$ (1.0 to 10.0 eq) to induce cyclization. [b] Yields refer to isolated material spectroscopically and chromatographically homogeneous.

In conclusion, we have demonstrated the viability of *para*-quinone methides as cyclization initiators in intramolecular electrophilic substitution reactions using three different terminators of widely varying reactivity (pyrrole, a very reactive nucleophile; furan, a moderately reactive; a monosubstituted benzene, a relatively poor nucleophile). We are currently examining the diastereofacial selectivity of the cyclization, the use of less substituted quinone methides, and the use of even less reactive terminators in the cyclization reaction.

ACKNOWLEDGMENT This work was supported by a grant from the the National Institutes of Health (GM 39354).

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7. This obviously excludes cases where the quinone methide derives stability from extensive substitution on the exocyclic methylene group and *ortho* to the carbonyl. For the direct observation of reactive *para*-quinone methides see: (a) Zanarotti, A. **Tetrahedron Lett.** *1982*, **23**, 3815. (b) Zanarotti, A. **J. Org. Chem.** *1985*, **50**, 941. (c) Ralph, J.; Young, R.A. **J. Wood Chem. and Tech.** *1983*, **3**, 161.
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15. Quinone methide **6**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.11(s, 1H, =CH), 6.85(s, 1H, =CH), 6.65(t, 2H, $NCH{=}C\underline{H}$), 6.15(m, 3H, $NC\underline{H}{=}CH$, $=C\underline{H}CH_2$), 4.07(t, J = 7 Hz, 2H, NCH_2), 2.93(q, J = 7 Hz, 2H, $NCH_2C\underline{H_2}$), 2.01(s, 3H, CH_3), 1.99(s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.4, 141.6, 137.9, 136.7, 134.9, 133.3, 129.2, 120.2, 108.4, 48.3, 31.0, 16.5, 15.8; IR (CH_2Cl_2) cm^{-1} 2928, 1641, 1631, 1621, 1576, 1501, 1483, 1376, 1366, 1336, 1212, 1146, 1088, 906, 613; MS (EI, 20eV) m/z(rel %) 227(M^+, 47%), 212(13), 179(15), 161(30), 81(100); HRMS (EI, 20eV) m/z 227.1308 (227.13101 calculated for $C_{15}H_{17}NO$).
16. Quinone methide **8**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37(s, 1H, $OC\underline{H}{=}CH$), 7.25(s, 1H), 7.22, (s, 1H), 6.89(s, 1H), 6.30(t, J = 6 Hz, 1H, $C{=}C\underline{H}CH_2$), 6.27(s, 1H, =CH), 2.56-2.47(m, 4H, $=CHC\underline{H_2}C\underline{H_2}C\underline{H_2}$), 2.04(s, 3H, CH_3), 2.00(s, 3H, CH_3), 1.80(t, t, J = 7Hz, 7Hz, 2H, $CH_2C\underline{H_2}CH_2$); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 187.7, 147.5, 142.9, 139.0, 138.5, 136.4, 134.7, 132.2, 129.8, 124.0, 110.7, 29.4, 28.3, 24.3, 16.7, 16.0; UV ($CDCl_3$, λmax, nm) 242, 282; IR (CCl_4) cm^{-1} 2978, 2827, 2899, 1646, 1627, 1579, 1505, 1445, 1380, 1150, 1119, 1027, 907, 745; MS (EI, 70eV) m/z 242(M+, 100%), 161(74), 145(22), 108(27), 91(39); HRMS (EI, 70 eV) m/z 242.1316 (242.13068 calculated for $C_{16}H_{18}O_2$).
17. Quinone methide **10**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.33-7.16(m, 6H), 6.88(s, 1H, =CH), 6.30(t, J = 8.0Hz, 1H, $=C\underline{H}CH_2$), 2.69(t, J = 7.5Hz, 2H, CH_2Ph), 2.51(q, J = 7.5Hz, 2H, $=CHC\underline{H_2}CH_2$), 2.03(d, J = 0.9Hz, 3H, CH_3), 2.00(d, J = 0.7Hz, 3H, CH_3), 1.87(p, J = 7Hz, 2H, $CH_2C\underline{H_2}CH_2$); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 187.7, 147.4, 141.3, 138.5, 136.4, 134.7, 132.2, 129.8, 128.4, 126.1, 35.3, 30.8, 28.3, 16.7, 16.0; UV (CH_3CN, λmax, nm) 210, 288, 322; IR (CCl_4)cm^{-1} 2978, 2935, 2928, 2863, 1628, 1579, 1120; MS (EI, 70eV) m/z 252(M+, 19%), 174(9), 161(65), 146(11), 135(15), 117(19), 91(100); HRMS (EI, 70 eV) m/z 252.1508 (252.15141 calculated for $C_{18}H_{20}O$).

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