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The Carroll Rearrangement: A Facile Entry into Substituted Arylacetones and Related Derivatives

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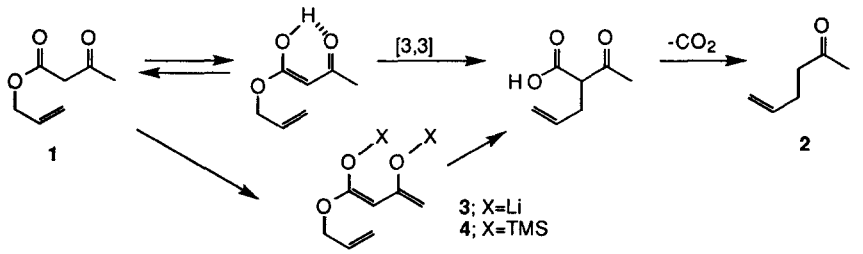
Abstract: Acetoacetates, easily prepared from substituted *p*-quinols, undergo a mild room temperature Carroll rearrangement to afford substituted arylacetones and related derivatives in moderate to good yields.

The Carroll rearrangement,[1] a variant to the ester Claisen rearrangement,[2] is a useful method for preparing γ,δ-unsaturated ketones (**2**) from allylic acetoacetates (Scheme 1). The reaction has found limited use in synthetic organic chemistry,[3] probably because of the harsh thermal conditions (130 - 220°C) needed to induce the [3,3] sigmatropic rearrangement. However, these thermal barriers are lowered through modifications to the starting β-keto-ester (**1**). Wilson and Price[4] and others[5] conducted the rearrangement of keto-ester bis-enolates (i.e. **3**; X = Li) in refluxing THF while Gilbert and Kelly[6] effected a room temperature rearrangement of the silyl ketene acetal analog (i.e. **4**; X = TMS). We now report that allylic acetoacetates prepared from *p*-quinols[7] undergo a surprisingly facile room temperature Carroll rearrangement under neutral conditions to provide substituted arylacetone derivatives in moderate to good yields.[8]

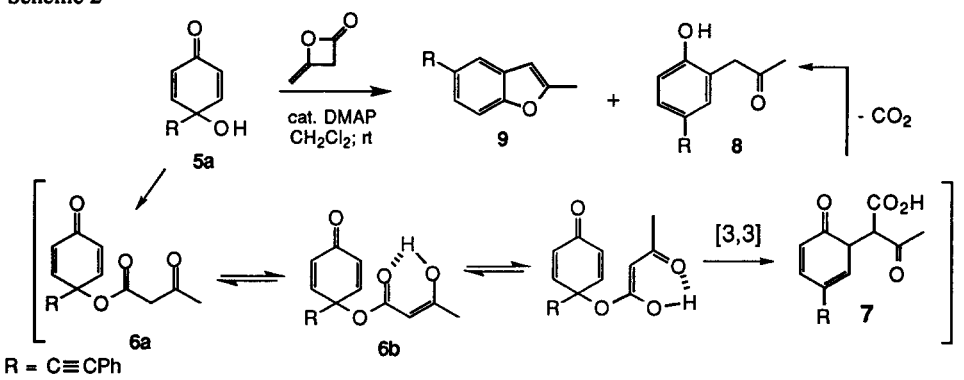
Scheme 1



We found that reaction of *p*-quinol **5a** with diketene and a catalytic amount of 4-dimethylaminopyridine (DMAP) at room temperature[9] produces the trisubstituted arylacetone **8** in a 72% isolated yield along with minor amounts of benzofuran **9**. Monitoring this reaction by ^{1}H NMR (300 MHz, $CDCl_3$), we observed the instantaneous and quantitative formation of acetoacetate **6a** (82%) and its enol tautomer **6b** (18%). Within several hours, the reaction produces arylacetone **8** as the major product (Scheme 2). The presumed keto-acid intermediate **7** was not observed, most likely due to a rapid aromatization/decarboxylation.

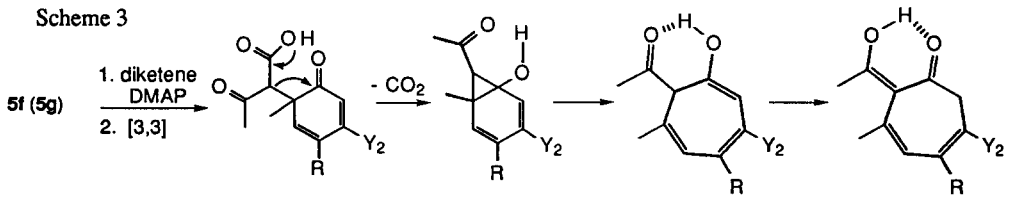
We examined a variety of substituted *p*-quinols. Table 1 summarizes our initial results.[10] A typical procedure involves adding a catalytic amount of DMAP (2 mol %) to a stirring mixture of *p*-quinol and diketene (1.1-1.4 equiv) in CH_2Cl_2 at room temperature. Isolation and purification of the products consists of simply removing the solvent in vacuo followed by recrystallization or chromatography.

Scheme 2



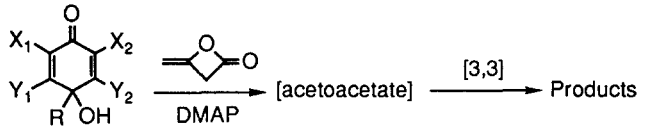
The simple *p*-quinol **5a** and the symmetrical 3,5-dimethyl *p*-quinol **5b** led to good yields of rearrangement products. A good overall yield was also obtained using the 3-methyl substituted *p*-quinol **5c**, though regiochemical competition between the termini resulted in a 1.3:1 ratio of isomeric arylacetones **12** and **13**. To gain further insight into the effect of substitution at the termini on the rearrangement, we treated the 2,6-disubstituted quinols **5d** and **5e** with diketene and a catalytic amount of DMAP and found the rearrangement still took place to generate the 1,4-diketones **14** and **15** in excellent yields, respectively. Thus, in addition to the successful generation of the 1,4-diketone functionality, the rearrangement allows an effective introduction of a quaternary carbon center.[11] Further regiochemical competition was examined with the 2-methyl and 2,5-dimethyl quinols **5f** and **5g**. A 10:1 mixture of arylacetone **16** and the 1,4-diketone **17** was obtained from **5f**, while the disubstituted quinol **5g** led to 5:2:1 mixture of arylacetone **19**, benzofuran **20**, and the 1,4-diketone **21**. The regiochemical competition observed between the termini parallels that found in the Claisen rearrangement.[12, 2c-d] Interestingly, we also isolated the cycloheptadienones **18**[13] and **22** from the reactions involving *p*-quinols **5f** and **5g**. Mechanistically, these products may be viewed as arising from the initial Carroll rearrangement to the substituted terminus followed by ring expansion[14] involving a norcaradiene-like intermediate (Scheme 3).

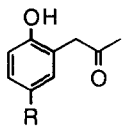
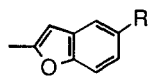
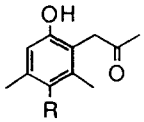
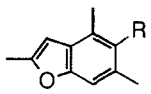
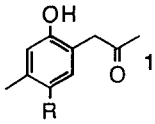
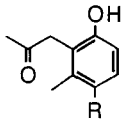
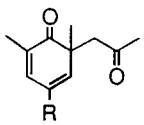
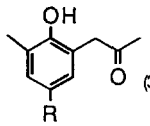
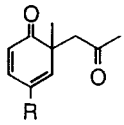
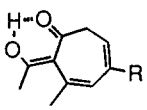
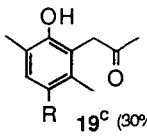
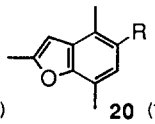
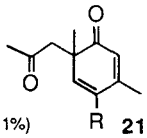
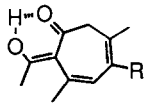
Scheme 3



In general, good overall yields of rearrangement products are realized. However, a steric component to the methodology was encountered with sterically congested *p*-quinols. For example, with *p*-quinol **5h**, in which the acetoacetate moiety is flanked by two methyl substituents, none of the expected rearrangement

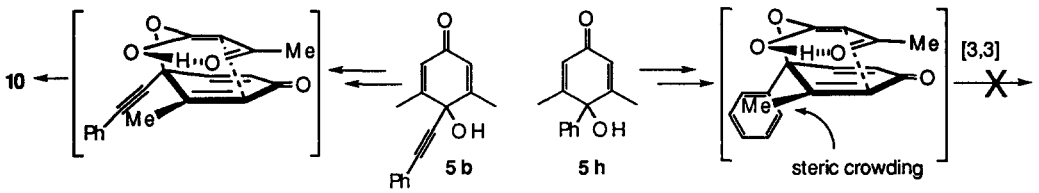
Table 1. Carroll Rearrangement of Substituted *p*-Quinols



p-Quinol	Products (Isolated Yields)
5a; X_1, X_2 = H; Y_1, Y_2 = H; R = C≡C-Ph	 **8** (72%)  **9** (5%)
5b; X_1, X_2 = H; Y_1, Y_2 = Me; R = C≡C-Ph	 **10**[a] (71%)  **11** (16%)
5c; X_1, X_2 = H; Y_1 = Me; Y_2 = H; R = C≡C-Ph	 **12** (41%)  **13**[b] (31%)
X_1, X_2 = Me; Y_1, Y_2 = H; **5d**; R = C≡C-Ph; **5e**; R = Ph	 **14**; R = C≡C-Ph (87%); **15**; R = Ph (83%)
5f; X_1 = Me; X_2 = H; Y_1, Y_2 = H; R = C≡C-Ph	 **16** (30%)  **17** (3%)  **18** (30%)
5g; X_1 = Me; X_2 = H; Y_1 = H; Y_2 = Me; R = C≡C-Ph	 **19**[c] (30%)  **20** (11%)  **21** (6%)  **22** (30%)
5h; X_1, X_2 = H; Y_1, Y_2 = Me; R = Ph	No rearrangement

a) Exists as a 55:45 mixture of ring-chain tautomers in $CDCl_3$.
b) Exists as a 66:33 mixture of ring-chain tautomers in $CDCl_3$.
c) Exists as a 77:23 mixture of ring-chain tautomers in $CDCl_3$.

product was found, even upon heating to 75 °C. The failure of **5h** to rearrange may be explained by severe steric crowding experienced within the developing transition state[15] between the phenyl group and the two adjacent methyl groups. In comparison, this steric interaction apparently is lessened in the transition state for quinol **5b** by having the acetylene group act as a spacer and thus allow the phenyl group to avoid the adjacent methyl groups.



In summary, the reaction of substituted *p*-quinols with diketene and a catalytic amount of DMAP affords acetoacetylated *p*-quinols which undergo facile [3,3] sigmatropic rearrangements at room temperature to generate substituted arylacetones and related derivatives in moderate to good yields.

Acknowledgments. We are very grateful to Dr. Gregory Leo for NMR spectroscopic analysis.

References and Notes

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2 (a) Claisen, L. *Chem. Ber.* **1912**, *45*, 3157. (b) Rhoads, S. J.; Raulins, N. R. *Org. Reactions* **1975**, *22*, 1. (c) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227. (d) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423.
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4. Wilson, S. R.; Price, F. M. *J. Org. Chem.* **1984**, *49*, 722.
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7. Preparation of *p*-quinols from benzoquinones see; (a) Fischer, A.; Henderson, G. N. *Tetrahedron Lett.* **1980**, *21*, 701. (b) Liotta, D.; Saindane, M.; Barnum, C. *J. Org. Chem.* **1981**, *46*, 3369. (c) Cherry, D. A.; Maryanoff, C. A.; Mills, J. E.; Olofson, R. A.; Rodgers, J. D. U.S. Patent 4,798,893, **1985**.
8. A facile room temperature Claisen rearrangement has been observed in similar systems. See; Swenton, J. S.; Bradin, D.; Gates, B. D. *J. Org. Chem.* **1991**, *56*, 6156.
9. Use of dimethylaminopyridine as an acetoacetylation catalyst has been reported. See ref. 3 and Nudelman, A.; Kelner, R.; Broida, N.; Gottlieb, H. E. *Synthesis* **1989**, 387.
10. Satisfactory ^{1}H and ^{13}C NMR, IR, and mass spectroscopic data were obtained for all new compounds.
11. See reference 4 for similar introduction of quaternary carbon centers.
12. (a) Cresson, P.; Lecour, L. *C.R. Seances Acad. Sci., Ser. C*, **1966**, *262*, 1157. (b) Cresson, P.; Bancel, S. *Ibid.* **1968**, *266*, 409. (c) Bancel, S.; Cresson, P. *Ibid.* **1969**, *268*, 1535.
13. Cycloheptadienone **18**; ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.13 (s, 3H), 2.21 (s, 3H), 2.78 (dd, J = 12.1, 5.8 Hz, 1H), 3.09 (dd, *J* = 12.1, 8.0 Hz, 1H), 6.03 (dd, *J* = 8.0, 6.0 Hz, 1H), 6.29 (s, 1H), 7.31-7.35 (m, 2H), 7.41-7.45 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1 (CH_3), 25.4 (CH_3), 39.3 (CH_2), 88.1 (Cq), 89.0 (Cq), 113.4 (Cq), 123.0 (Cq), 123.3 (Cq), 127.3 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 131.5 (CH), 136.2 (Cq), 190.0, 190.5; HRMS (M^+) m/z calcd for $C_{18}H_{16}O_2$ 264.1150, found 264.1135. Further studies concerning the structure analysis of **18** will be reported in detail at a later date.
14. For a similar ring expansion see: Kogler, H.; Fehlhaber, H-W.; Leube, K.; Dürckheimer, W. *Chem Ber.* **1989**, *122*, 2205.
15. Preliminary AM1 calculations show the boat and chair-like transition states involving the acetoacetate intermediate to be of near equal energies.

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