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 γδ-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 Price4 and others5 conducted the rearrangement of keto-ester bis-enolates (i.e. 3; X = Li) in refluxing THF while Gilbert and Kelly6 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-quinols7 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 temperature9 produces the trisubstituted arylacetone 8 in a 72% isolated yield along with minor amounts of benzofuran 9. Monitoring this reaction by 1H NMR (300 MHz, CDCl3), we observed the instantaneous and quantitative formation of acetooacetate 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. 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$_2$Cl$_2$ at room temperature. Isolation and purification of the products consists of simply removing the solvent in vacuo followed by recrystallization or chromatography.

Scheme 2

![Scheme 2](image)

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. 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. Interestingly, we also isolated the cycloheptadienones 18 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 involving a norcaradiene-like intermediate (Scheme 3).

Scheme 3

![Scheme 3](image)

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

\[
\begin{align*}
\text{DMAP} \quad \text{[acetoacetate]} \quad \text{[3,3]} \quad \text{Products}
\end{align*}
\]

<table>
<thead>
<tr>
<th>( p )-Quinol</th>
<th>Products (Isolated Yields)</th>
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<tbody>
<tr>
<td>5a; ( X_1, X_2 = H ) ( Y_1, Y_2 = H ) ( R = C=C-Ph )</td>
<td>( 8 ) (72%) ( 9 ) (5%)</td>
</tr>
<tr>
<td>5b; ( X_1, X_2 = H ) ( Y_1, Y_2 = Me ) ( R = C=C-Ph )</td>
<td>( 10^a ) (71%) ( 11 ) (16%)</td>
</tr>
<tr>
<td>5c; ( X_1, X_2 = H ) ( Y_1 = Me; Y_2 = H ) ( R = C=C-Ph )</td>
<td>( 12 ) (41%) ( 13^b ) (31%)</td>
</tr>
<tr>
<td>( X_1, X_2 = Me ) ( Y_1, Y_2 = H ) 5d; ( R = C=C-Ph ) 5e; ( R = Ph )</td>
<td>( 14; R = C=C-Ph ) (87%) ( 15; R = Ph ) (83%)</td>
</tr>
<tr>
<td>5f; ( X_1 = Me; X_2 = H ) ( Y_1, Y_2 = H ) ( R = C=C-Ph )</td>
<td>( 16 ) (30%) ( 17 ) (3%) ( 18 ) (30%)</td>
</tr>
<tr>
<td>5g; ( X_1 = Me; X_2 = H ) ( Y_1 = H; Y_2 = Me ) ( R = C=C-Ph )</td>
<td>( 19^c ) (30%) ( 20 ) (11%) ( 21 ) (8%) ( 22 ) (30%)</td>
</tr>
<tr>
<td>5h; ( X_1, X_2 = H ) ( Y_1, Y_2 = Me ) ( R = Ph )</td>
<td>No rearrangement</td>
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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 state15 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

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 1H and 13C NMR, IR, and mass spectroscopic data were obtained for all new compounds.
11. See reference 4 for similar introduction of quaternary carbon centers.
13. Cycloheptadienone 18; 1H NMR (360 MHz, CDCl3) 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), 7.31-7.45 (m, 2H); 13C NMR (100 MHz, CDCl3) δ 25.1 (CH3), 25.4 (CH3), 39.3 (CH2), 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 C18H16O2 264.1150, found 264.1135. Further studies concerning the structure analysis of 18 will be reported in detail at a later date.
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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