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An Approach to Benzannelated [5,6]-Spiroketals
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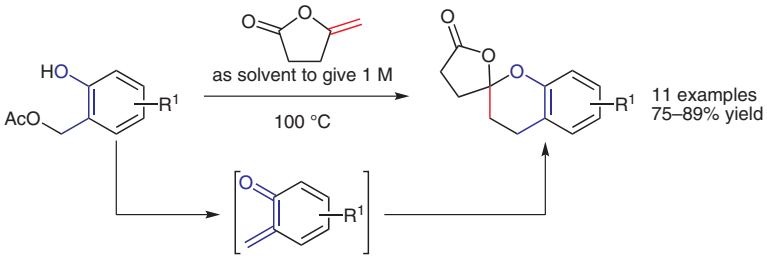
A Diels–Alder Approach to Benzannulated [5,6]-Spiroketals



R^1 = H, 4-Me, 4-OAc, 4-CO_2Me, 4-Cl, 5-Me, 5-CO_2Me, 5-OMe, 5-NO_2, 5-Cl, 5-Br

Significance: Reported is the synthesis of aryl-substituted benzannulated [5,6]-spiroketals from the thermal reaction of 2-hydroxybenzylacetates with γ-methylene-γ-butyrolactone. The reaction proceeds via an *ortho*-quinone methide which then undergoes Diels–Alder cycloaddition to give the spiroketal products. The starting acetates were synthesized in high yield through selective acetylation of the requisite 2-hydroxybenzyl alcohols.

Comment: Due to their range of biological activity, spiroketals have come to be considered privileged pharmacophores. However, methods for their formation are few and usually require a starting material synthesized using a difficult and protracted process, such as a keto-diol (see Book below). In contrast, the current method uses Diels–Alder chemistry to form the spiroketal unit in one step. This should prove extremely useful due to the ease of the reaction, high yields, and the ready availability and relative inexpense of the starting materials. The scope of the reaction was explored based only on 4- and 5-substituted benzylacetates. Nevertheless, these were intelligently chosen examples that demonstrate a tolerance to both electron-withdrawing and -donating groups at the 4- and 5-position of the aromatic ring.

Book: S. V. Ley, L.-G. Milroy, R. M. Myers, In *Science of Synthesis*, Vol. 29; S. Warriner, Ed.; Georg Thieme Verlag: Stuttgart, New York, **2007**, 613-690.

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Synthesis of Heterocycles

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Diels–Alder reaction
hydroxybenzyl-acetates
quinone methide