

## Hetero-Diels–Alder Reactions of Ketones: a High-yielding Synthesis of 2,2-Disubstituted 2,3-Dihydropyran-4-ones

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2,2-Disubstituted 2,3-dihydropyran-4-ones may be prepared in high yields by the Lewis acid-catalysed hetero-Diels–Alder reactions of electron-rich dienes with ketones bearing strongly electron-withdrawing substituents.

As a part of our interest in tetrahydropyrones we required a general high-yielding preparative method for 2,2-disubstituted 2,3-dihydropyran-4-ones (**1**). A number of syntheses of pyran-4-ones appear in the literature,<sup>1</sup> for example the cyclisation of 1,3,5-triketones in various guises, the acid-catalysed condensations of aliphatic carboxylic acids or anhydrides at 200 °C, the acid-catalysed rearrangement of furan derivatives or dihydropyran-3-ones, cycloaddition reactions of ketones, and transformations of 4-hydroxypyran-2-ones. These methods often suffer from lack of generality, variable yields, or severe reaction conditions; further, for our purposes, they still require the regiospecific removal or functionalisation of one double bond.

Substituted 2,3-dihydro-3-hydroxy-6-trifluoromethylpyran-4-ones (**2**) have been prepared by the reaction of ethyl trifluoroacetate with aliphatic or alicyclic acetyl epoxides in the presence of sodium ethoxide,<sup>2</sup> and Kosower and Sorensen have reported the isolation of dihydropyrene (**3**) from the acid-catalysed cyclisation of 5-hydroxy-1-methoxy-5-methylhex-1-en-3-yne;<sup>3</sup> however as a general route this procedure depends for its success upon ready and efficient access to the methoxy-enol starting materials, and in our hands did not prove satisfactory.

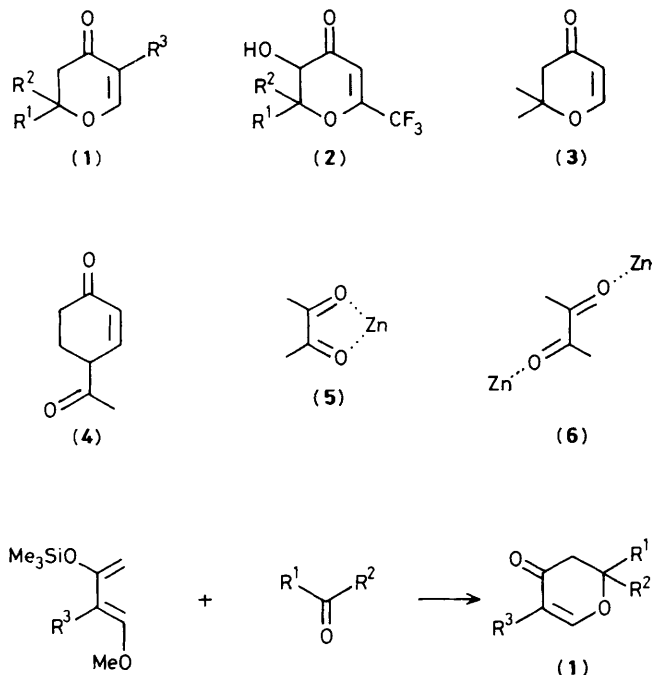
One might expect that 2,2-disubstituted 2,3-dihydropyran-4-ones should be available from the hetero-Diels–Alder

reactions of appropriately substituted butadienes with suitable carbonyl compounds, but whereas Lewis acid-catalysed ‘cycloadditions’ of reactive dienes with aldehydes are now well known,<sup>4</sup> examples of such reactions of any conjugated diene with ketones are very rare in the literature<sup>5</sup> or require high-pressure conditions.<sup>6</sup>

Table 1.

R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	% Yield of ( <b>1</b> )
Me	CO <sub>2</sub> Et	H	72
Me	COMe	H	69
Me	CN	H	78
Me	CO <sub>2</sub> Me	H	75
CH <sub>2</sub> Br	CO <sub>2</sub> Et	H	81
CO <sub>2</sub> Et	CO <sub>2</sub> Et	H	88
Me	CO <sub>2</sub> Me	OAc <sup>a</sup>	74
CO <sub>2</sub> Et	CO <sub>2</sub> Et	OAc <sup>a</sup>	86

<sup>a</sup> 2-Acetoxy-1-methoxy-3-trimethylsilyloxybutadiene was prepared from 1-methoxybut-1-en-3-one by the sequential action of lead tetra-acetate (68%), pyridine (88%), and trimethylsilyl trifluoromethane sulphonate (78%).<sup>7,8</sup>



We are therefore pleased to report that Danishefsky's diene<sup>4</sup> and other electron-rich dienes undergo 'cycloadditions' with ketones bearing strongly electron-withdrawing substituents in the presence of Lewis acids to give the corresponding 2,2-disubstituted 2,3-dihydropyran-4-ones (**1**) in very good yields (Table 1).

In a typical experiment the ketone is shaken with Danishefsky's diene (1 equiv.) and zinc(II) chloride (2.5 equiv.) in degassed, purified benzene solution at ambient temperature for 12 h using glassware washed with base and hexamethyldisilazane. After dilution with ether the mixture is stirred with hydrochloric acid (0.005 M) for 15 min before normal work-up.

Successful substrate types include 1,2-diketones, pyruvates, acyl nitriles, and oxomalonates. Less electron-deficient carbonyl compounds give poor results; for example no reactions were observed with acetone, 2-acetyl-*N*-methylpyrrole, ethyl dehydrolaevulinate, 2-acetylthiophene, pentane-2,4-dione, *p*-nitroacetophenone, phenyl isocyanate, diethyl oxalate, methyl formate, thioacetamide, trifluoroacetone, or 1,1,1-

trifluoropentane-2,4-dione. Reaction with methyl vinyl ketone gave only the 'normal' Diels-Alder reaction product (**4**).

The choice and quantity of Lewis acid used also appears to be of vital importance for efficient reaction. Neither titanium tetrachloride nor tin tetrachloride proved to be a successful mediator; use of less catalyst (1 or 1.25 equiv.) normally gives only low yields of products, perhaps indicating a double template or chelation effect with the two electron-rich centres of each reacting molecule. Interestingly, in the case of butane-2,3-dione no reaction was observed when 2.5 equiv. of catalyst were employed, although use of 1.2 equiv. gave a 69% yield of the desired product. This may suggest that a *cisoid* conformation of the diketone, with both carbonyl oxygen atoms co-ordinated to one zinc atom, as in (**5**), is necessary for reactions to take place rather than a conformation involving two zinc atoms [e.g. (**6**)].

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