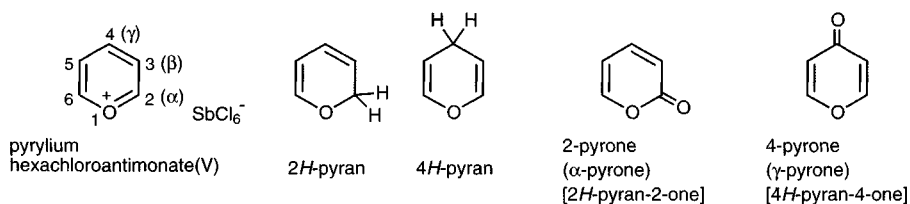


## 8 Piryliums, 2- and 4-pyrones: reactions and synthesis



Pyrylium salts,<sup>1,2</sup> especially perchlorates, tetrafluoroborates, and hexachloroantimonates(V), are stable but reactive compounds. Perchlorates have been used extensively, since pyrylium perchlorates tend to be sparingly soluble, however all perchlorates should be treated with CAUTION: perchlorates, particularly dry perchlorates can decompose explosively. No pyrylium salts have been identified in living organisms, though the benzo[b]pyrylium system plays an important role in the flower pigments (section 9.1.6).

Almost all the known reactions of the pyrylium nucleus involve addition of a nucleophile, usually at an  $\alpha$ -position, occasionally  $\gamma$ , as the first step. A feature of pyrylium chemistry is the ring opening of adducts produced by such additions, followed by cyclisation in a different manner to give a new heterocyclic or homocyclic product (ANRORC processes).

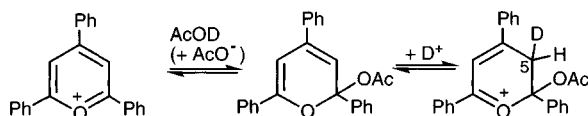
Straightforward electrophilic or radical substitutions at ring positions are unknown. Controlled oxidations, like those of pyridinium salts to 2-pyridones, are likewise not known in pyrylium chemistry.

### 8.1 Reactions of pyrylium cations

#### 8.1.1 Reactions with electrophilic reagents

##### 8.1.1.1 Proton exchange

2,4,6-Triphenylpyrylium undergoes exchange at the 3- and 5-positions in hot deuterioacetic acid, but the process probably involves not protonation of the pyrylium cation, but formation of an equilibrium concentration of an adduct, with acetate added to C-2, allowing enol ether protonation and thus exchange.<sup>3</sup>



##### 8.1.1.2 Nitration

Nitration of 2,4,6-triphenylpyrylium proceeds on the benzene rings;<sup>4</sup> no nitrations of pyrylium rings are known.

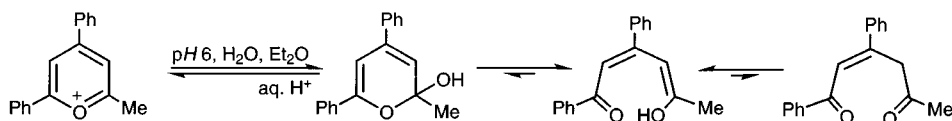
### 8.1.2 Addition reactions with nucleophilic reagents

Pyrylium salts usually add nucleophiles at a carbon adjacent to the oxygen, and in many ways, such reactions are analogous with those of *O*-protonated carbonyl compounds.

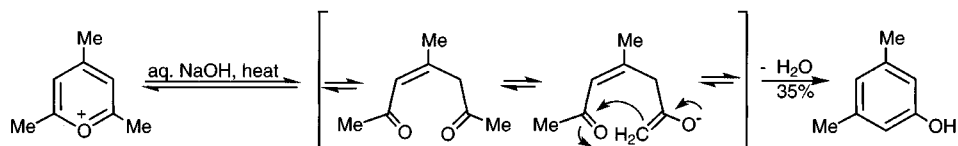
#### 8.1.2.1 Water and hydroxide ion

The degree of susceptibility of pyrylium salts to nucleophilic attack varies widely: pyrylium cation itself is even attacked by water at 0°C, where 2,4,6-trimethylpyrylium is stable in water at 100°C. Hydroxide anion, however, adds very readily to C-2 in all cases.

The reaction of 2-methyl-4,6-diphenylpyrylium is typical:<sup>5</sup> the immediate 2-hydroxy-2-*H*-pyran, which is a cyclic enol hemiacetal, is in equilibrium with a dominant concentration of the acyclic tautomer, reached probably *via* a proton-catalysed process, since methoxide adducts remain cyclic.<sup>6</sup> Treatment of such acyclic unsaturated diketones with acid regenerates the original pyrylium salt (section 8.3.1).

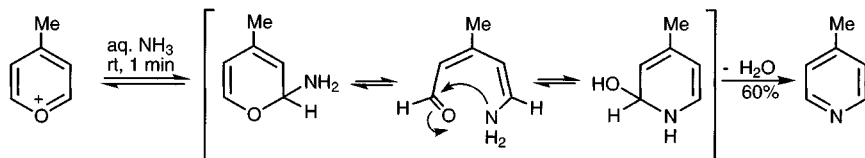


With pyryliums carrying  $\alpha$ -alkyl groups, more vigorous alkaline treatment leads to an alternative closure producing arenes, for example reaction of 2,4,6-trimethylpyrylium with warm alkali causes a subsequent cyclising aldol condensation of the acyclic intermediate to give 3,5-dimethylphenol as shown below.<sup>7</sup>

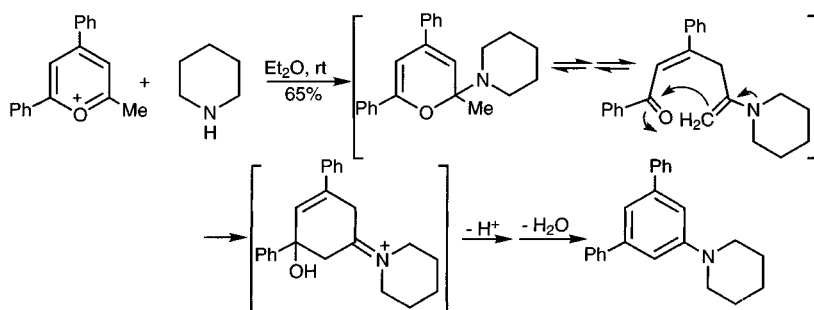


#### 8.1.2.2 Ammonia and primary and secondary amines

Ammonia and primary amines react with pyrylium salts to give pyridines and *N*-alkyl- or *N*-arylpyridinium salts respectively.<sup>7a,8</sup> The transformation represents a good method for preparing the nitrogen heterocycles, providing the pyrylium salt can be accessed in the first place. The initial adduct exists as one of a number of ring-opened tautomeric possibilities,<sup>9</sup> depending upon conditions; it is probably the amino-dienone which recloses to give the nitrogen heterocycle.



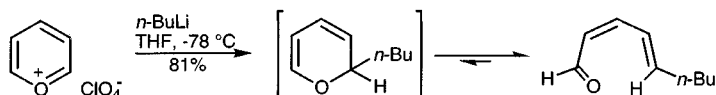
The reaction of a secondary amine cannot, of course, lead to a pyridine, however in pyryliums carrying an  $\alpha$ -methyl, ring closure to an arene can occur, this time *via* an enamine as illustrated.<sup>7a</sup>



Other reactants containing a primary amino group will also convert pyryliums into *N*-substituted nitrogen heterocycles: *N*-aminoheterocycles<sup>10</sup> are amongst several types of hydrazine derivatives to have been utilised: these give 1-(substituted)aminopyridiniums. Reaction of pyryliums with hydroxylamine comparably leads (predominantly) to the formation of pyridine *N*-oxides.<sup>1,11</sup>

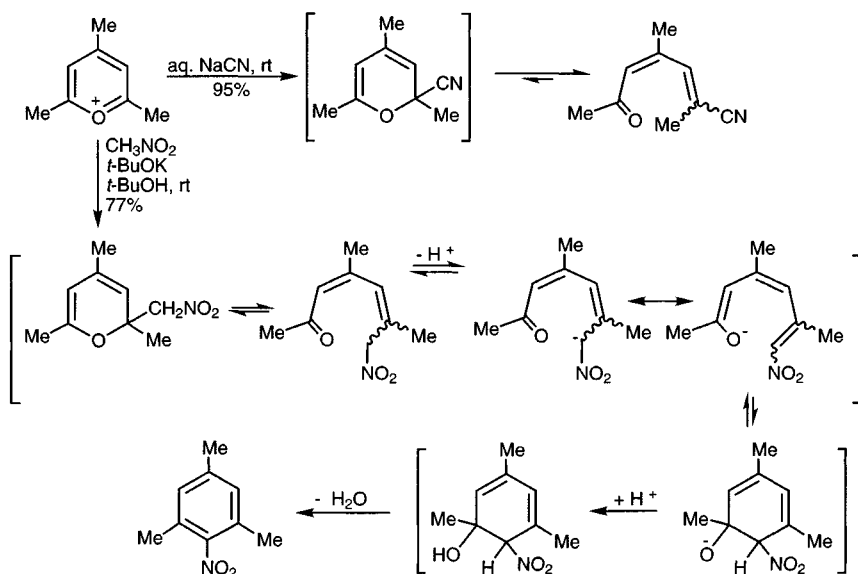
### 8.1.2.3 Organometallic addition

Organometallic addition takes place at an  $\alpha$ -position, or occasionally at C-4 when the  $\alpha$ -positions are substituted and C-4 is unsubstituted,<sup>12</sup> or with organocuprates.<sup>13</sup> The initial 2*H*-pyrans undergo electrocyclic ring opening (and more rapidly than the comparable cyclohexadiene/hexatriene transformation<sup>14</sup>) affording dienones or dienals with retention of geometrical integrity.

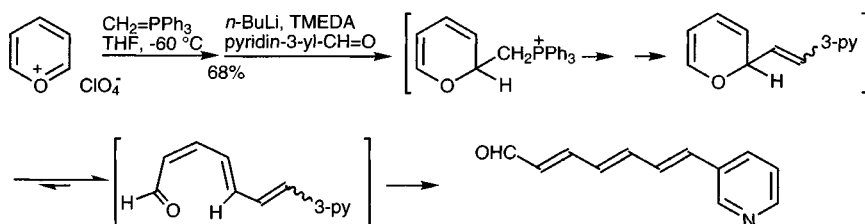


### 8.1.2.4 Other carbanionic additions

By processes comparable to organometallic addition, cyanide addition to 2,4,6-trimethylpyrylium leads to a ring-opened dienone.<sup>15</sup> Reactions with stabilised anions, such as those from nitromethane or 1,3-dicarbonyl compounds, proceed though a series of equilibria to recyclised, aromatic compounds.<sup>7a</sup>

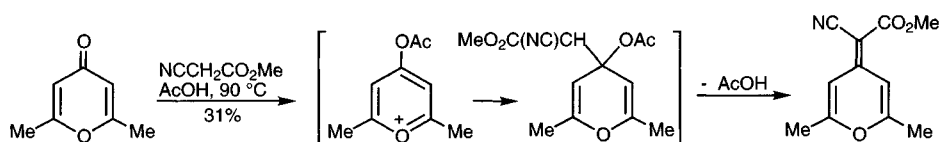


Following addition of triphenylphosphonium methyllide, Wittig condensation, electrocyclic ring opening and double bond equilibration, all *trans* 2,4,6-trienals can be accessed, as illustrated below.<sup>16</sup>



### 8.1.3 Substitution reactions with nucleophilic reagents

There are a small number of pyrylium reactions which fall into the category of nucleophilic substitutions. 4-Pyrones react with acetic anhydride at carbonyl oxygen to produce 4-acetoxypyryliums, *in situ*, allowing nucleophilic substitution at C-4: the reaction of 2,6-dimethylpyrone with methyl cyanoacetate is typical.<sup>17</sup> Phosphoryl chloride likewise converts 4-pyrones into 4-chloropyryliums.<sup>1</sup>

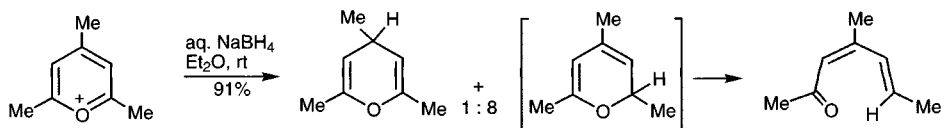


### 8.1.4 Reactions with radical agents

4-Alkylation of 2,6-disubstituted pyryliums has been achieved using tetraalkyltin compounds in the presence of light; the initial adducts are re-oxidised *in situ* to produce 4-substituted pyrylium salts.<sup>18</sup>

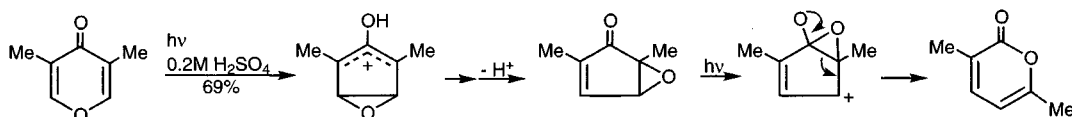
### 8.1.5 Reactions with reducing agents

The addition of hydride to pyryliums takes place mainly at an  $\alpha$ -position, generating 2*H*-pyrans which rapidly open to form the isolated products, dienones best extracted immediately into an organic solvent; the minor products are the isomeric 4*H*-pyrans.<sup>19</sup> One-electron polarographic reduction generates radicals which dimerise (*cf.* 5.6.3).<sup>20</sup>



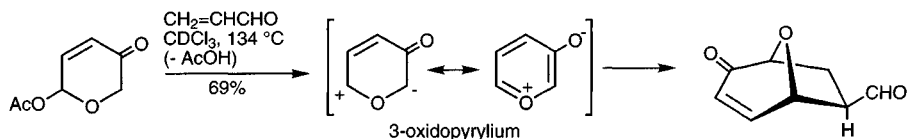
### 8.1.6 Photochemical reactions

At first sight, the photochemistry of 4-hydroxypyryliums, i.e. of 4-pyrones in acid solution, seems extraordinary, in that they are converted into 2-pyrones, however a rationalisation involving first, a bicyclic hydroxyallyl cation, secondly a bicyclic epoxycyclopentenone, and then a second photo-excitation, makes the transformation clear, the sequence is shown below.<sup>21</sup> Irradiation at higher pH leads to a trapping of first-formed photo-intermediate by solvent and thus the isolation of dihydroxycyclopentenones.<sup>22</sup>

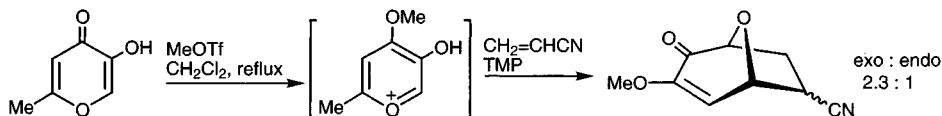


### 8.1.7 Reactions with dienophiles; cycloadditions

There has been strong interest in dipolar cycloaddition reactions of 3-oxidopyryliums,<sup>23</sup> formally, 3-hydroxypyryliums rendered overall neutral by loss of the phenolic proton, though this is not always the method for their formation. These species undergo cycloadditions across the 2,6-positions and in so doing parallel the reactivity of 3-oxidopyridiniums (section 5.8).

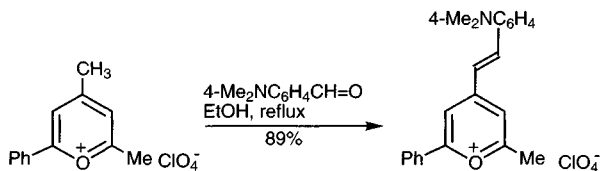


An ingenious route for the generation of the dipolar species involves the carbonyl-*O*-alkylation<sup>24</sup> or *O*-silylation<sup>25</sup> of 3-oxygenated 4-pyrones as shown below for the former case. Even unactivated alkenes will cycloadd when tethered and thus the process is intramolecular.<sup>25</sup> The example below shows *O*-methylation of a kojic acid derivative then deprotonation of the 3-hydroxyl using a hindered base to allow dipolar cycloaddition.



### 8.1.8 Alkylpyryliums<sup>26</sup>

Hydrogens on alkyl groups at the  $\alpha$ - and  $\gamma$ -positions of pyrylium salts are, as might be expected, quite acidic: reaction at a  $\gamma$ -methyl is somewhat faster than at an  $\alpha$ -methyl.<sup>27</sup> Condensations with aromatic aldehydes (illustrated below),<sup>28</sup> triethyl orthoformate,<sup>29</sup> and dimethylformamide<sup>30</sup> have been described.



## 8.2 2-Pyrones and 4-pyrones (2H-pyran-2-ones and 4H-pyran-4-ones; $\alpha$ -pyrones and $\gamma$ -pyrones)

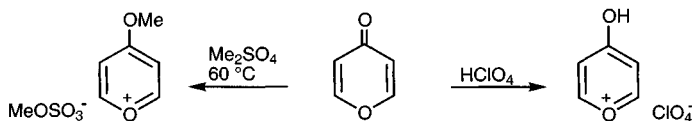
### 8.2.1 Structure of pyrones

2- and 4-Hydroxypyrylium salts are quite strongly acidic and are therefore much better known as their conjugate bases, the 2- and 4- ( $\alpha$ - and  $\gamma$ -) -pyrones. The simple 4-pyrones are quite stable crystalline substances, whereas the 2-pyrones are much less stable, 2-pyrone itself, which has the smell of fresh-mown hay, polymerising slowly on standing. There are relatively few simple pyrone natural products in great contrast with the widespread occurrence and importance of their benzo-derivatives (section 9.2), the coumarins and chromones, in nature.

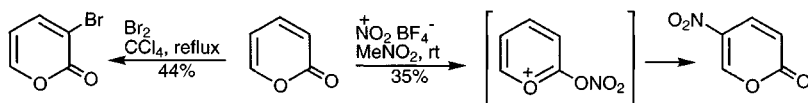
### 8.2.2 Reactions of pyrones

#### 8.2.2.1 Electrophilic addition and substitution

4-Pyrone is a weak base,  $\text{p}K_{\text{a}} -0.3$  which is protonated on the carbonyl oxygen to afford often crystalline 4-hydroxypyrylium salts. The reaction of 2,6-dimethyl-4-pyrone with *t*-butylbromide in hot chloroform provides a neat way to form the corresponding 4-hydroxy-2,6-dimethylpyrylium bromide.<sup>31</sup> 2-Pyrones are much weaker bases and though they are likewise protonated on carbonyl oxygen in solution in strong acids, salts cannot be isolated. This difference is mirrored in reactions with alkylating agents: the former give 4-methoxypyrylium salts with dimethyl sulfate,<sup>32</sup> whereas 2-pyrones require Meerwein salts,  $\text{MeO}^+ \text{BF}_4^-$ , for carbonyl-*O*-methylation. Acid-catalysed exchange in 4-pyrone, presumably *via* C-protonation of a concentration of neutral molecule, takes place at the 3/5-positions.<sup>33</sup>

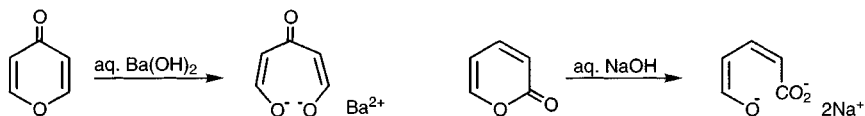


With bromine, 2-pyrone forms an unstable adduct, which gives the substitution product 3-bromo-2-pyrone on warming.<sup>34</sup> With nitronium tetrafluoroborate, the electrophile is assumed to attack first at carbonyl oxygen leading subsequently to 5-nitro-2-pyrone.<sup>35</sup> Simple examples of electrophilic substitution of 4-pyrones are remarkably rare, however bis-dimethylaminomethylation of the parent heterocycle takes place under quite mild conditions.<sup>36</sup>

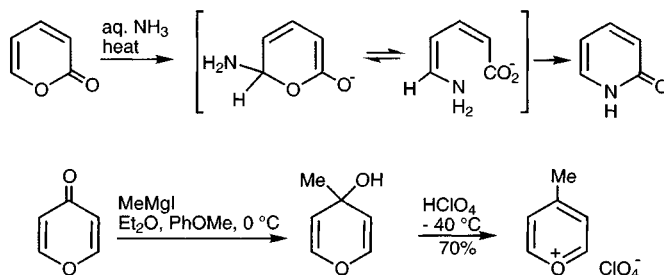


### 8.2.2.2 Attack by nucleophilic reagents

2-Pyrones are in many ways best viewed as unsaturated lactones, and as such they are easily hydrolysed by aqueous alkali; 4-pyrones, too, easily undergo ring-opening with base, though for these vinylogous lactones, initial attack is at C-2, in a Michael fashion.<sup>37</sup>

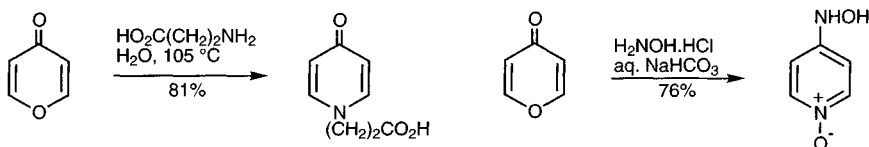


2-Pyrones can in principle add nucleophilic reactants at either C-2 (carbonyl carbon), C-4, or C-6: their reactions with cyanide anion,<sup>38</sup> and ammonia/amines are examples of the latter, whereas the addition of Grignard nucleophiles occurs at carbonyl carbon.



4-Pyrones also add Grignard nucleophiles at the carbonyl carbon, C-4; dehydration of the immediate tertiary alcohol product with mineral acid provides an important access to 4-mono-substituted pyrylium salts.<sup>39</sup> More vigorous conditions lead to the reaction of both 2- and 4-pyrones with two mol equivalents of organometallic reagent and the formation of 2,2-disubstituted-2H- and 4,4-disubstituted-4H-pyrans respectively.<sup>40</sup> Perhaps surprisingly, hydride (lithium aluminium hydride) addition to 4,6-dimethyl-2-pyrone takes place, in contrast, at C-6.<sup>41</sup>

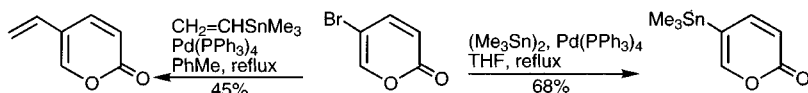
Ammonia and primary aliphatic and aromatic amines convert 4-pyrones into 4-pyridones:<sup>42</sup> this must involve attack at an  $\alpha$ -position, then ring opening and reclosure; in some cases ring opened products of reaction with two mols of the amine have been isolated, though such structures are not necessarily intermediates on the route to pyridones.<sup>43</sup> The transformation can also be achieved by first, hydrolytic ring opening using barium hydroxide (see above), and then reaction of the barium salt with ammonium chloride.<sup>44</sup>



The reactions of 4-pyrones with hydrazines and hydroxylamine, can lead to recyclisations involving the second heteroatom of the attacking nucleophile, producing pyrazoles and isoxazoles respectively, however in the simplest examples 4-pyrones react with hydroxylamine giving either 1-hydroxy-4-pyridones or 4-hydroxyaminopyridine-*N*-oxides;<sup>45</sup> again, prior hydrolytic ring opening using barium hydroxide has been employed.<sup>44</sup>

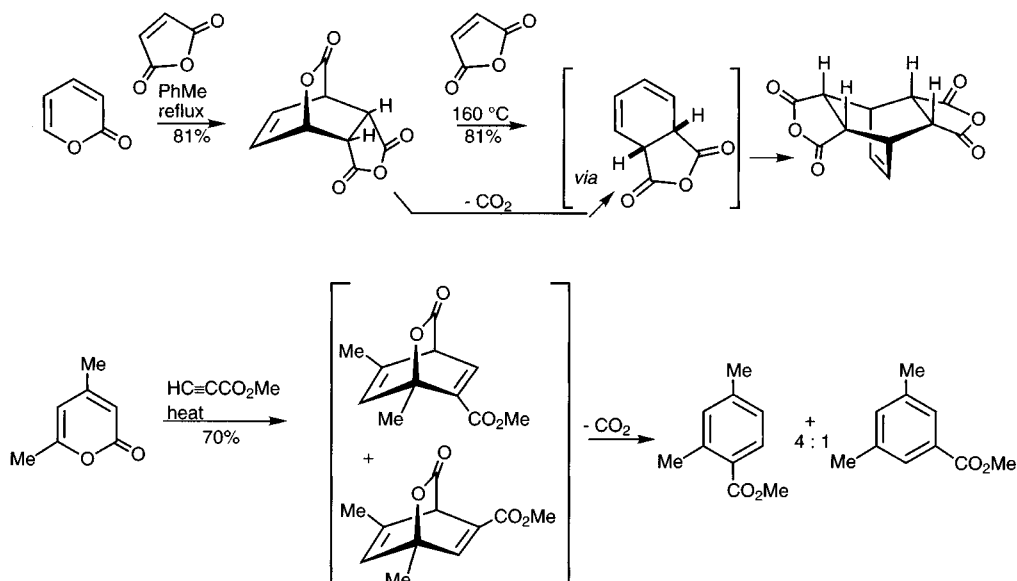
### 8.2.2.3 Organometallic derivatives

3-Bromo-2-pyrone does not undergo exchange (or C-H-deprotonation) with *n*-butyllithium, however it has been transformed into a cuprate, albeit of singularly less nucleophilic character than typical cuprates.<sup>46</sup> Palladium-catalysed coupling with tin compounds or transformation into a tin derivative allows for further elaborations.<sup>47</sup>



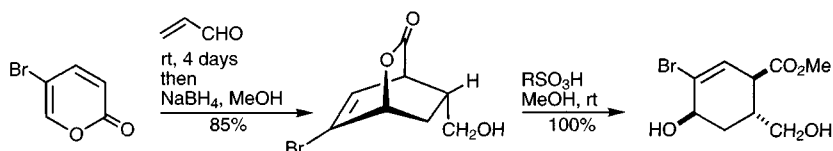
### 8.2.2.4 Cycloaddition reactions<sup>48</sup>

When 2-pyrone acts as a diene in a Diels-Alder addition the initial adduct often loses carbon dioxide, generating a second diene which then adds a second mol of the dienophile; reaction with maleic anhydride, shown below, is typical – a monoadduct can be isolated, which under more vigorous conditions loses carbon dioxide and undergoes a second addition.<sup>49</sup> When the dienophile is an alkyne, methyl propiolate for example, benzenoid products result from the expulsion of carbon dioxide.<sup>50</sup> Primary adducts, which have not lost carbon dioxide, can be obtained from reactions conducted at lower temperatures under very high pressure or in the presence of lanthanide catalysts.<sup>51</sup>

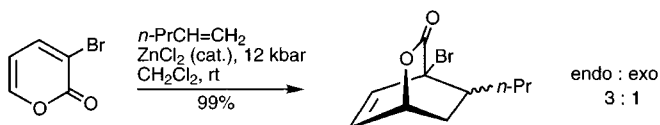


3-<sup>52</sup> and 5-Bromo<sup>53</sup> -2-pyrones present remarkable properties in their abilities to act as efficient dienes towards both electron-rich and electron-poor dienophiles

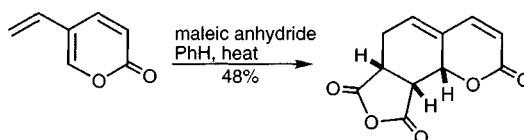
(illustrated below); 3-(*para*-tolylthio)-2-pyrone also undergoes ready cycloadditions with electron-deficient alkenes.<sup>54</sup>



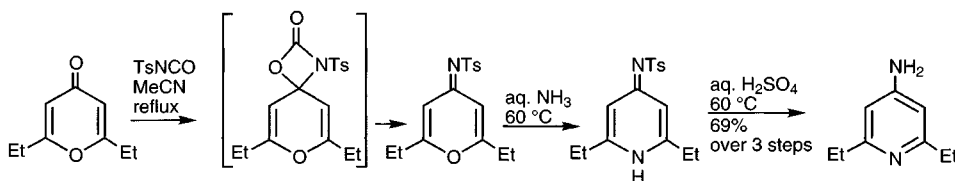
Under appropriate conditions, even unactivated alkenes will take part in intermolecular cycloadditions with 3- and 5-bromo-2-pyrones and with 3-methoxycarbonyl-2-pyrone.<sup>55</sup> Reactions can be conducted at  $100^\circ\text{C}$ , or at room temperature under 10–12 kbar and with zinc chloride catalysis.



2-Pyrone takes part in a  $4\pi + 6\pi$  cycloaddition with a fulvenketene acetal.<sup>56</sup> 5-Alkenyl-2-pyrones, react with dienophiles as dienes, as indicated below.<sup>57</sup>

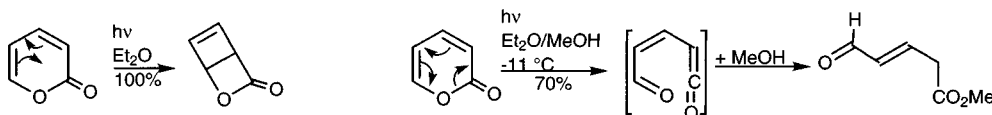


The useful conversion of 4-pyrones into 4-imines on reaction with tosyl isocyanate may involve a  $2 + 2$  cycloadduct, as shown, from which carbon dioxide is then lost.<sup>44,58</sup>



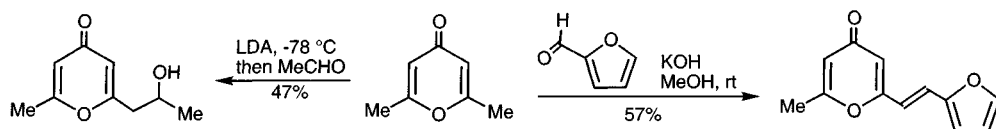
### 8.2.2.5 Photochemical reactions

In addition to the photocatalysed rearrangement of 4-pyrones in acid solution (section 8.1.5) the other clear cut photochemical reactions undergone are the transformation of 2-pyrone into a bicyclic  $\beta$ -lactone on irradiation in a non-hydroxylic solvent and into an acyclic unsaturated ester-aldehyde on irradiation in the presence of methanol.<sup>59</sup>



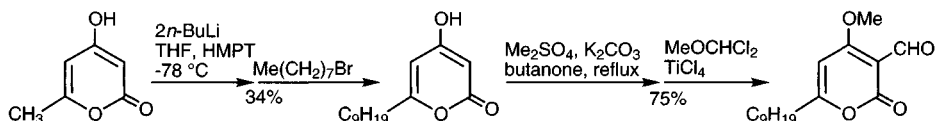
### 8.2.2.6 Side-chain reactions

4-Pyrones<sup>60</sup> and 2-pyrones<sup>61</sup> condense with aromatic aldehydes at 2- and 6-methyl groups respectively and 2,6-dimethyl-4-pyrone has been lithiated at a methyl and thereby substituted as illustrated.<sup>62</sup>



### 8.2.2.7 2,4-Dioxygenated pyrones

2,4-Dioxygenated pyrones exist as the 4-hydroxy tautomers. Such molecules are easily substituted by electrophiles, at the position between the two oxygens (C-3)<sup>63</sup> and can be side-chain deprotonated using two mol equivalents of strong base.<sup>64</sup>

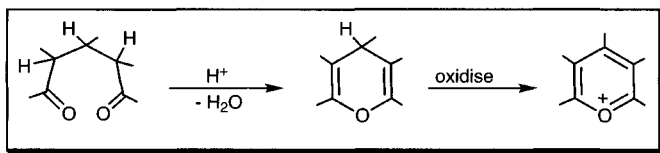


## 8.3 Synthesis of pyryliums<sup>1,8a</sup>

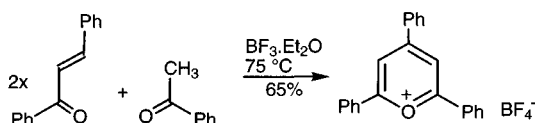
Pyrylium rings are assembled by the cyclisation of a 1,5-dicarbonyl precursor, separately synthesised or generated *in situ*.

### 8.3.1 From 1,5-dicarbonyl compounds

1,5-Dicarbonyl compounds can be cyclised, with dehydration and in the presence of an oxidising agent.

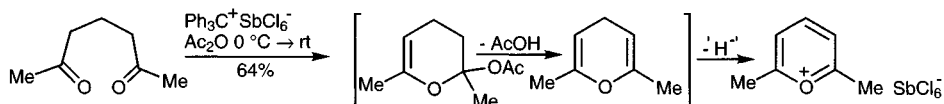


Mono-enolisation of a 1,5-diketone, then the formation of a cyclic hemiacetal, and its dehydration, produces dienol ethers (4*H*-4-pyrans) which require only hydride abstraction to arrive at the pyrylium oxidation level. The diketones are often prepared *in situ* by the reaction of an aldehyde with two mols of a ketone (compare Hantzsch synthesis, section 5.15.1.2) or of a ketone with a previously prepared conjugated ketone – a ‘chalcone’ in the case of aromatic ketones/aldehydes. It is the excess chalcone which serves as the hydride acceptor in this approach.

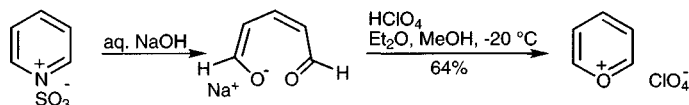


Early work utilised acetic anhydride as solvent with the incorporation of an oxidising agent (hydride acceptor), often iron(III) chloride (though it is believed that it is the acylium cation which is the hydride acceptor); latterly the incorporation of

2,3-dichloro-5,6-dicyano-1,4-benzoquinone,<sup>65</sup> 2,6-dimethylpyrylium or most often, the triphenylmethyl cation<sup>66</sup> have proved efficient. In some cases the 4*H*-pyran is isolated then oxidised in a separate step.<sup>67</sup>

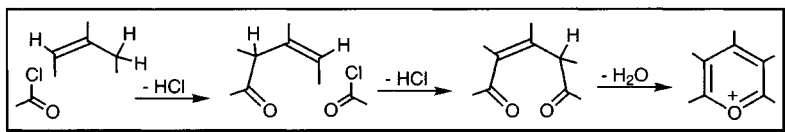


If an unsaturated dicarbonyl precursor is available, no oxidant needs to be added: a synthesis of the perchlorate of pyrylium itself, shown below, falls into this category: careful acid treatment of either glutaconaldehyde, or of its sodium salt, produces the parent salt<sup>13,68</sup> (CAUTION: potentially explosive).

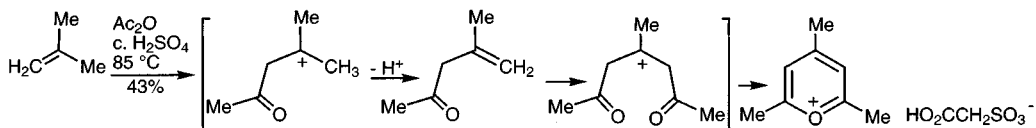


### 8.3.2 Alkene acylation

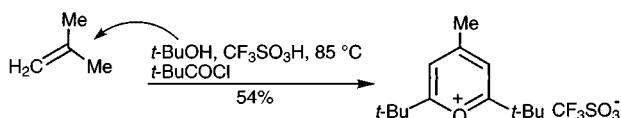
Alkenes can be diacylated with an acid chloride or anhydride generating an unsaturated 1,5-dicarbonyl compound which then cyclises with loss of water.



The aliphatic version of the classical aromatic Friedel-Crafts acylation produces, by loss of proton, a non-conjugated enone which can then undergo a second acylation thus generating an unsaturated 1,5-diketone. Clearly, if the alkene is not symmetrical, two isomeric diketones are formed.<sup>69</sup> Under the conditions of these acylations, the unsaturated diketone cyclises, loses water and forms a pyrylium salt. The formation of 2,4,6-trimethylpyrylium, best as its much more stable and non-hygroscopic carboxymethanesulfonate,<sup>70</sup> illustrates the process.

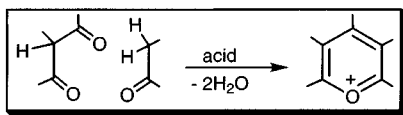


Common variations are the use of an alcohol, which dehydrates *in situ*,<sup>71</sup> or of a halide which dehydrohalogenates<sup>72</sup> to give the alkene.

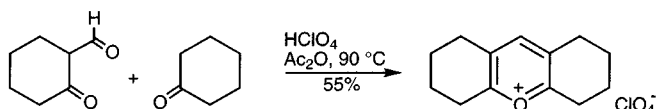


### 8.3.3 From 1,3-dicarbonyl compounds and ketones

The acid-catalysed condensation of a ketone with a 1,3-dicarbonyl compound, with dehydration *in situ* produces pyrylium salts.



Aldol condensation between a 1,3-dicarbonyl component and a ketone carrying an  $\alpha$ -methylene under acidic, dehydrating conditions, produces pyrylium salts.<sup>73</sup> It is likely that the initial condensation is followed by a dehydration before the cyclic hemiacetal formation and loss of a second water molecule. The use of the bis-acetal of malondialdehyde, as synthon for the 1,3-dicarbonyl component is one of the few ways available for preparing  $\alpha$ -unsubstituted pyryliums.<sup>1</sup>

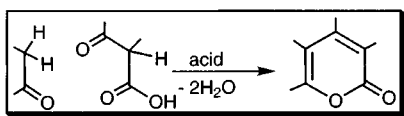


Successful variations on this theme include the use, as synthons for the 1,3-dicarbonyl component, of  $\beta$ -chloro- $\alpha,\beta$ -unsaturated ketones,<sup>74</sup> or of conjugated alkynyl aldehydes.<sup>75</sup>

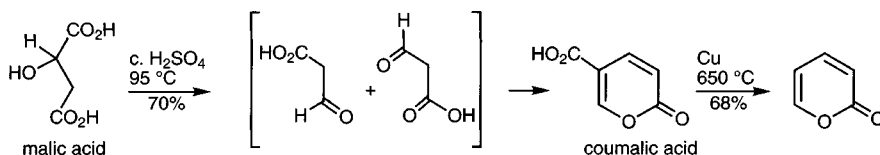
## 8.4 Synthesis of 2-pyrones

### 8.4.1 From 1,3-keto(aldehydo)-acids and carbonyl compounds

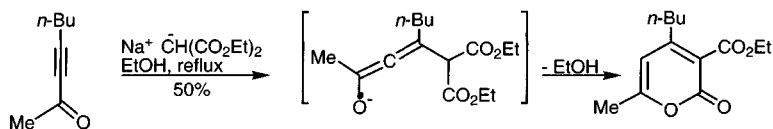
The classical general method for constructing 2-pyrones is that based on the cyclising condensation of a 1,3-keto(aldehydo)-acid with a second component which provides the other two ring carbons.



The long known synthesis of coumalic acid from treatment of malic acid with hot sulfuric acid illustrates this route: decarboxylation produces formylacetic acid, *in situ*, which serves as both 1,3-aldehydo-acid component and the second component.<sup>76</sup> Decarboxylation of coumalic acid is still used to access 2-pyrone itself.<sup>77</sup>

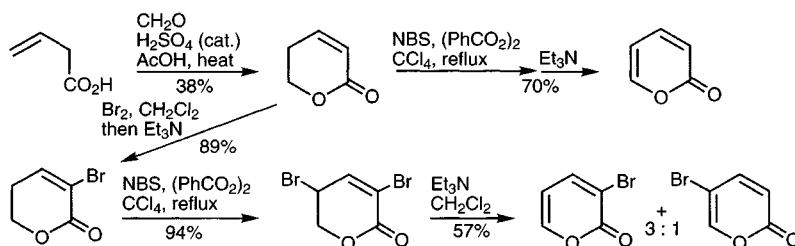


Conjugate addition of enolates to alkynyl-ketones<sup>78</sup> and to alkynyl-esters<sup>79</sup> are further variations on the synthetic theme.

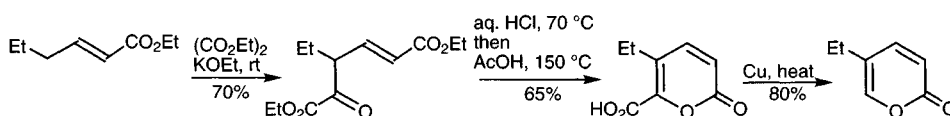


## 8.4.2 Other methods

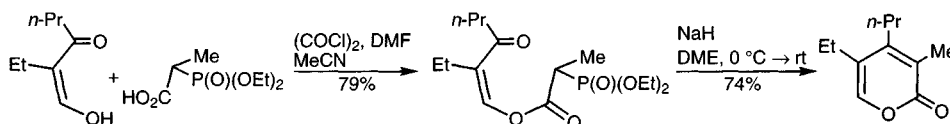
2-Pyrene itself can be prepared via Prins alkylation of but-3-enoic acid with subsequent lactonisation giving 5,6-dihydro-2-pyrene which *via* allylic bromination and then dehydrobromination is converted into 2-pyrene as shown below.<sup>80</sup> Alternative manipulation<sup>81</sup> of the dihydropyrene affords a convenient synthesis of a separable mixture of the important 3- and 5-bromo-2-pyrones (see section 8.2.2.4).



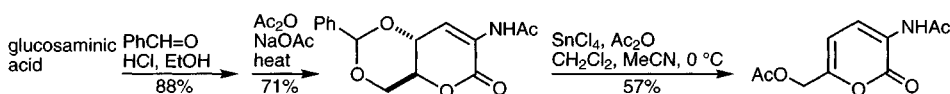
Formation of the 5,6-bond is also involved in the Claisen condensation between diethyl oxalate and an  $\alpha,\beta$ -unsaturated ester at its  $\gamma$  position, to generate an intermediate in which ring closure via the ketone enol produces a 2-pyrene.<sup>82</sup>



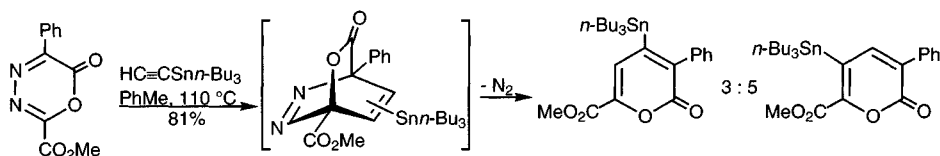
The esterification of a 1,3-ketoaldehyde enol with a diethoxyphosphinylalkanoic acid, forming the ester linkage of the final molecule first, allows ring closure *via* an intramolecular Horner-Emmons reaction.<sup>83</sup>



The conversion of glucosamine into a 3-amino-2-pyrene points up the potential for conversion of sugars into six-membered oxygen heterocycles.<sup>84</sup>



The inverse electron-demand cycloaddition of electron-rich or strained alkynes with 1,3,4-oxadiazin-6-ones leads to 2-pyrones because the adducts lose nitrogen (rather than carbon dioxide).<sup>85</sup> The example below shows the use of ethynyltributyltin giving a mixture of regioisomers; the stannylated pyrones can be utilised in the usual ways, for example for the introduction of halogen.<sup>86</sup>



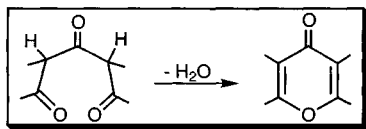
The palladium-catalysed coupling of alkynes with a 3-iodo- $\alpha,\beta$ -unsaturated ester, or with the enol triflate of a  $\beta$ -keto-ester as illustrated below, must surely be one of

the shortest and most direct routes to 2-pyrones.<sup>87</sup> The cycloaddition (non-concerted) of ketenes with silyl enol ethers of  $\alpha,\beta$ -unsaturated esters also provides a simple, direct route to usefully functionalised 2-pyrones.<sup>88</sup>



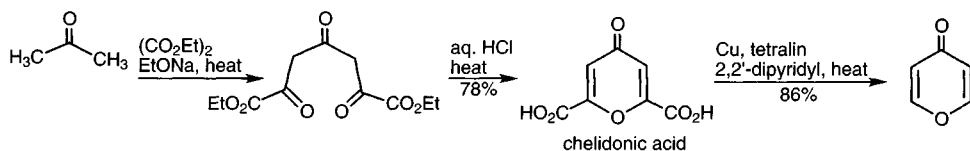
## 8.5 Synthesis of 4-pyrones

4-Pyrones result from the acid-catalysed closure of 1,3,5-tricarbonyl precursors.

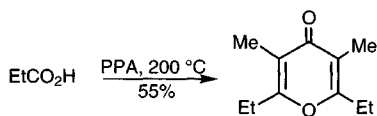


The construction of a 4-pyrone is essentially the construction of a 1,3,5-tricarbonyl compound since such compounds easily form cyclic hemiacetals then requiring only dehydration. Strong acid has usually been used for this purpose, but where stereochemically sensitive centres are close, the reagent from triphenylphosphine and carbon tetrachloride has been employed.<sup>89</sup>

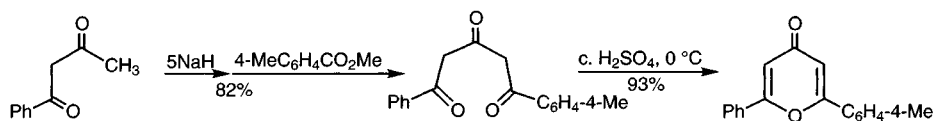
Several methods are available for the assembly of such precursors: the synthesis of chelidonic acid (4-pyrone-2,6-dicarboxylic acid)<sup>90</sup> represents the obvious approach of bringing about two Claisen condensations, one on each side of a ketone carbonyl group. Chelidonic acid can be decarboxylated to produce 4-pyrone itself.<sup>91</sup>



A variety of symmetrically substituted 4-pyrones can be made very simply by heating an alkanedioic acid with polyphosphoric acid;<sup>92</sup> presumably a series of Claisen-type condensations, with a decarboxylation, lead to the assembly of the requisite acyclic, tricarbonyl precursor.

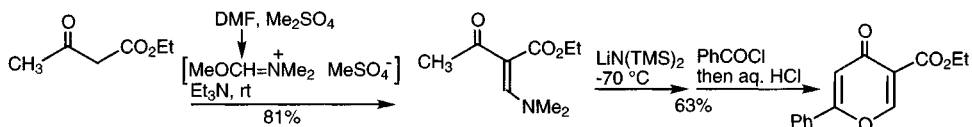


The Claisen condensation of a 1,3-diketone, *via* its dianion, with an ester,<sup>93</sup> or of a ketone enolate with an alkyne ester<sup>94</sup> also give the desired tricarbonyl arrays.

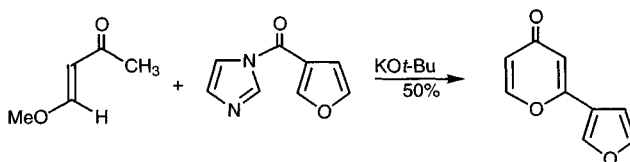


Another strategy to bring about acylation at the less acidic carbon of a  $\beta$ -keto ester, is to condense, firstly at the central methylene, with a formate equivalent; this

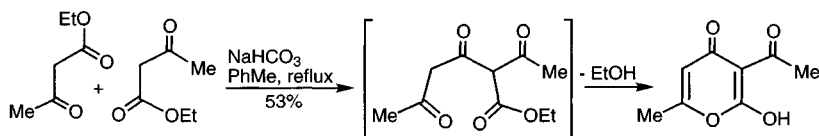
has the added advantage that the added carbon can then provide the fifth carbon of the target heterocycle.<sup>95</sup>



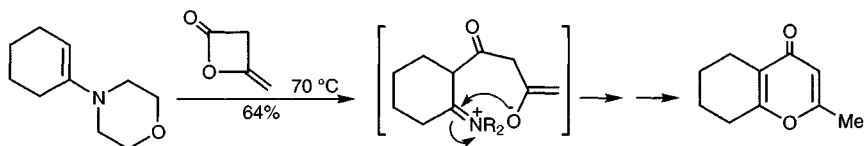
$\alpha$ -Unsubstituted 4-pyrones have similarly been constructed *via* the enolate of methoxymethylene ketones.<sup>96</sup>



Dehydroacetic acid<sup>97</sup> was first synthesised in 1866;<sup>98</sup> it is formed very simply from ethyl acetoacetate by a Claisen condensation between two molecules, followed by the usual cyclisation and finally loss of ethanol. In a modern version,  $\beta$ -keto-acids can be self-condensed using carbonyl diimidazole as the condensing agent.<sup>99</sup>



The acylation of the enamine of a cyclic ketone with diketene leads directly to bicyclic 4-pyrones, as indicated below.<sup>100</sup>



## Exercises for chapter 8

### Straightforward revision exercises (consult chapters 7 and 8)

- Specify three nucleophiles which add easily to pyrylium salts and draw the structures of the products produced thereby.
- Certain derivatives of six-membered oxygen heterocycles undergo 4 + 2 cycloaddition reactions: draw out three examples.
- Draw a mechanism for the transformation of 2-pyrene into 1-methyl-2-pyridone on reaction with methylamine.
- What steps must take place to achieve the conversion of a saturated 1,5-diketone into a pyrylium salt?
- Describe how 5,6-dihydro-2-pyrene can be utilised to prepare either 2-pyrene, or 3- and 5-bromo-2-pyrones.
- 1,3,5-Tricarbonyl compounds are easily converted into 4-pyrones. Describe two ways to produce a 1,3,5-trione or a synthon thereof.

### More advanced exercises

1. Write a sequence for the transformation of 2,4,6-trimethylpyrylium into 1-phenyl-2,4,6-trimethylpyridinium by reaction with aniline.
2. Devise a mechanism to explain the formation of 1,3,5-triphenylbenzene from reaction of 2,4,6-triphenylpyrylium perchlorate on reaction with 2 mol equivalents of  $\text{Ph}_3\text{P}=\text{CH}_2$ .
3. Suggest structures for the compounds in the following sequence: 2-methyl-5-hydroxy-4-pyrone reacted with  $\text{MeOTf} \rightarrow \text{C}_7\text{H}_9\text{O}_3^+ \text{ TfO}^-$  (a salt), then this with 2,2,6,6-tetramethylpiperidine (a hindered base)  $\rightarrow \text{C}_7\text{H}_8\text{O}_3$ , a dipolar substance, and this then with acrylonitrile  $\rightarrow \text{C}_{10}\text{H}_{11}\text{NO}_3$ .
4. Write out a mechanism for the conversion of 4-pyrone into 1-phenyl-4-pyridone by reaction with aniline. Write structures for the products you would expect from reaction of methyl coumalate (5-methoxycarbonyl-2-pyrone) with benzylamine.
5. Deduce structures for the pyrylium salts formed by the following sequences: (i) pinacolone ( $\text{Me}_3\text{CCOMe}$ ) condensed with pivaldehyde ( $\text{Me}_3\text{CCH}=\text{O}$ ) gave  $\text{C}_{11}\text{H}_{20}\text{O}$  which was then reacted with pinacolone in the presence of  $\text{NaNH}_2$ , generating  $\text{C}_{17}\text{H}_{32}\text{O}_2$  and this with  $\text{Ph}_3\text{C}^+ \text{ ClO}_4^-$  in  $\text{AcOH}$  gave a pyrylium salt; (ii) cyclodecene and  $\text{Ac}_2\text{O}/\text{HClO}_4$ ; (iii)  $\text{PhCOMe}$  and  $\text{MeCOCH}_2\text{CHO}$  with  $\text{Ac}_2\text{O}$  and  $\text{HClO}_4$ .
6. When dehydroacetic acid is heated with c.  $\text{HCl}$  2,6-dimethyl-4-pyrone is formed in 97% yield – explain.
7. When ethyl acetoacetate is reacted with  $\text{HCl}$ , isodehydroacetic acid (ethyl 4,6-dimethyl-2-pyrone-5-carboxylate) is formed – explain.
8. Deduce structures for the pyrones formed by the following sequences: (i)  $\text{PhCOCH}_3$  with  $\text{PhC}\equiv\text{CCO}_2\text{Et}$  in the presence of  $\text{NaOEt}$ ; (ii) butanoic acid heated with  $\text{PPA}$  at  $200^\circ\text{C}$ ; (iii)  $n\text{-BuCOCH}_2\text{CO}_2\text{H}$  with carbonyl diimidazole; (iv)  $\text{PhCOCH}_2\text{COCH}_3$  with excess  $\text{NaH}$  then methyl 4-chlorobenzoate; (v)  $\text{CH}_3\text{COCH}=\text{CHOMe}$  with  $\text{KO}t\text{-Bu}$  and  $\text{PhCOCl}$ .

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