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Acid-catalysed acylation of carbonyl compounds

S M Luk'yanov, A V Koblik

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Abstract. Data concerning the *O*- and *C*-acylation of carbonyl compounds under acid catalytic conditions are surveyed. The properties of little-studied products of these reactions, i.e., acylals, α-haloalkyl acylates, and enol acylates are described. The acyloxycarbocations formed by the acylation of aldehydes and ketones are characterised. The recently discovered new reactions of carbonyl compounds that lead to various heterocyclic and polyfunctional compounds are discussed. The bibliography includes 275 references.

I. Introduction

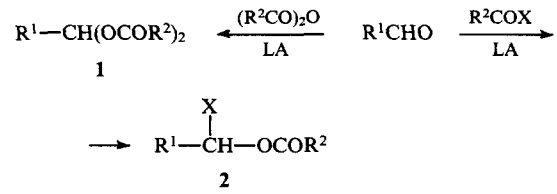
The acylation of carbonyl compounds is traditionally considered as a means of lengthening a carbon chain together with the introduction of the carbonyl function. Such reactions include ester condensation and related reactions (i.e., Claisen, Dieckmann, Darzens reactions, etc.).[1–6] These processes are catalysed by bases, while *O*-acylation which sometimes occurs is usually regarded as an undesirable side reaction. The preparative application of these methods was so successful and fruitful that the analogous acid-catalysed conversions were considered only as theoretically, rather than practically, interesting reactions. Only in some cases, when acid and base catalysis results in different products (e.g., acylation of asymmetric ketones), have syntheses been developed.[1,2] Perhaps only acylation of ketones by anhydrides in the presence of boron trifluoride is an exception.[5,6]

The technique of base-catalysed acylation of carbonyl compounds has been improved and modified (e.g., in Taylor–McKillop and Passerini reactions,[7,8] phase-transfer catalysis,[9] and the application of acyl anions[10]), whereas acid-catalysed reactions have remained much less investigated until now. This is explained by difficulties in the effective stabilisation of cationoid intermediates, as cationoid chemistry has been less well studied than carbanion chemistry.[11]

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Although the importance of the reaction between carbonyl compounds and aprotic acids was noted thirty years ago,[12] few publications concerning this problem are available. On the other hand, two reactions of aldehydes with anhydrides and acid halides in the presence of Lewis acids have been known since the beginning of this century. These reactions lead to the acylals **1** and the α-haloalkyl acylates **2**, respectively.

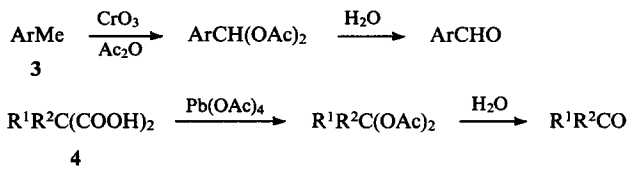


LA — Lewis acid; X = Cl, Br.

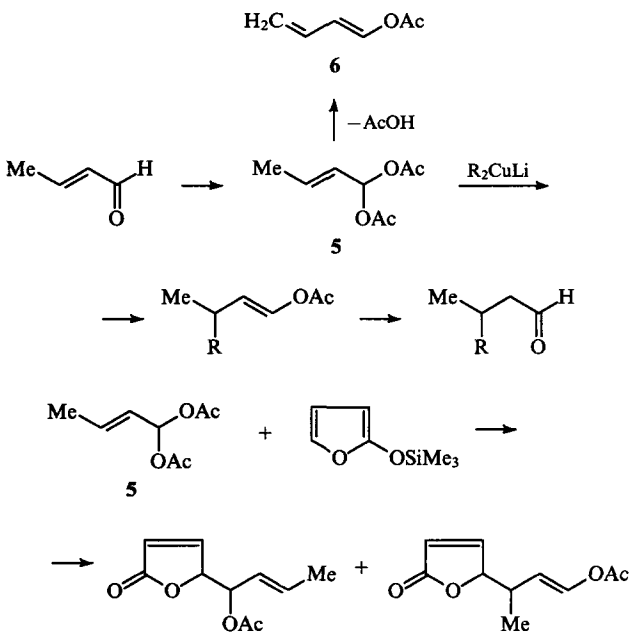
The attitude of synthetic chemists towards acid-catalysed carbonyl reactions can be illustrated by the history of compounds **1** and **2**: the properties of the acylals **1** have been very little investigated until now. The α-haloesters **2** were recalled in the sixties only as subjects of a series of studies under the common title 'A forgotten carbonyl reaction' (see Section IV).

II. Acylals

The esters formed from geminal diols (i.e., acylals, also called aldehyde diacylates) have been known for more than 120 years. Chloral diacetate was described as one of the first acylals.[13] The synthesis based on the acid-catalysed *O*-acylation of aliphatic and aromatic aldehydes by acetic anhydride in the presence of various catalysts was elaborated later.[14,15] Scant information about acylals can be found in some monographs.[5,16–18] For a long time, acylals were regarded only as convenient intermediates for the preparation of aldehydes and ketones from methylarenes **3** by oxidation with a CrO_3–Ac_2O mixture[5,18,19] as well as by oxidative decarboxylation of malonic acid derivatives **4**.[5]

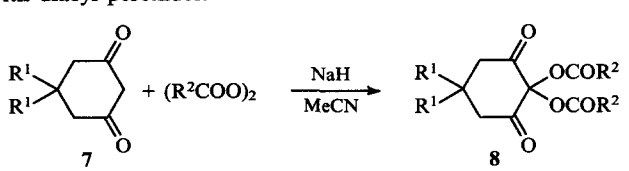


Only recently have acylals attracted special attention as compounds having independent synthetic value. Acylals can serve as convenient precursors of not only aldehydes but also of enol acylates, e.g., in the conversion of crotonaldehyde into 1-acetoxybutadiene **6**[20] and other synthetically difficult compounds.[21,22]



The *gem*-diacetate moiety turned out to be quite stable toward dilute acids, but it is easily removable in weakly alkaline solutions.[21] This group can therefore serve as a suitable complement of the well-known acetal protection for aldehydes.[23] Examples of acylal protection have been mentioned in the literature, but this topic is outside the scope of the present review, which is devoted to the activation rather than the passivation of the carbonyl function.

In the early eighties, several authors reported the preparation of acylals by the acid-catalysed acylation of aldehydes with acetic anhydride. Diacetates of aliphatic and aromatic aldehydes can be obtained in high yields in the presence of PCl_3 (Ref. 24 and the references cited therein). The use of $FeCl_3$ instead of PCl_3 allows one to extend the aldehyde series and to reduce the duration of the acylal synthesis; detailed spectroscopic data (IR, ^1H NMR and ^{13}C NMR) and mass spectra for the acylals were also obtained.[21] The undesirable treatment of reaction mixtures with water can be excluded using the solid superacid 'Nafion-H', which also allows one to simplify the isolation of the acylation products.[25] The preparation of acylals in the presence of protic acids (e.g., sulfuric, perchloric, methanesulfonic acids) was reported in several studies.[26–29] A series of acylals **8** have been obtained by the acyloxylation of cyclohexane-1,3-diones **7** with diacyl peroxides.[30]

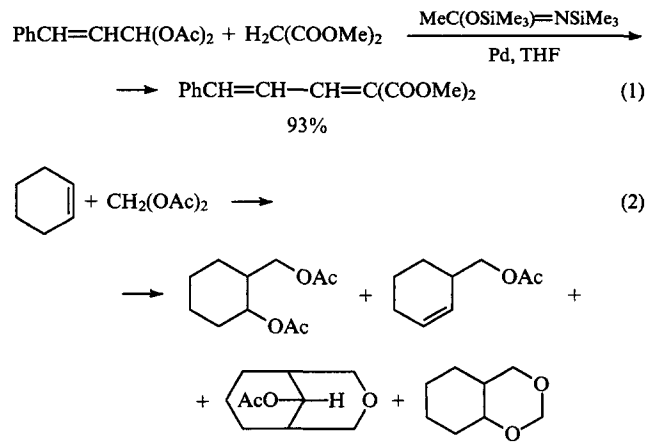


$R^1_2 = Me_2, -(CH_2)_5-$; R^2 = Ar, $PhCH_2O$.

Compounds **8** are ketone acylals. It has been mentioned in earlier publications that ketones do not yield *gem*-diacetates.[14] Subsequently, it was shown that cyclohexanone and its 4-alkyl derivatives react with an $Ac_2O-H_2SO_4$ mixture to form the corresponding enol acetates, but hitherto unknown 1,1-diacetates were also isolated in low yields from these reaction mixtures.[31] However, cyclopentanone affords only an acylal under the same conditions.[32] Mazur and coworkers[33,34] have described the preparation of ketone acylals by the action of trichloroacetic anhydride without a catalyst. However, the reactions of ketones (mainly cyclic ones) with Ac_2O require the presence of an acid.[34] It is remarkable that cyclobutanone reacts with Ac_2O and $HClO_4$ to yield only the 1,1-diacetate.[34] Obviously, the strain in small rings prevents the transformation of acylals into enol acylates.

The mechanism of the formation of acylals derived from both aldehydes and ketones was studied using mixed anhydrides[21] as well as initial ketones labelled with the ^{18}O isotope.[33,34] It has been shown that acylation, which is a reversible reaction, occurs with the participation of two anhydride molecules. Conditions for the conversion of acylals into carbonyl compounds by hydrolysis[35–37] and for the transformation of diacylates into enol acylates were also described.[31,33,38]

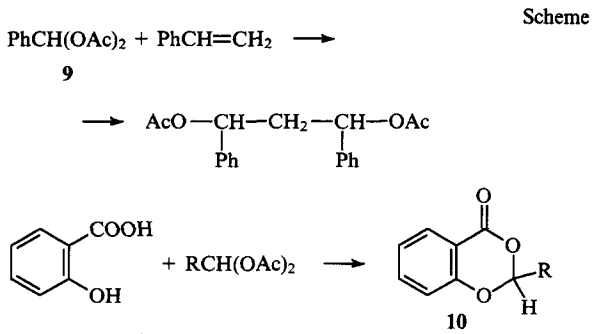
Acylals undergo many reactions typical of aldehydes, such as condensations with CH-acids[39] and with alkenes according to the Prins reaction scheme [Eqns (1) and (2)].[40–42]



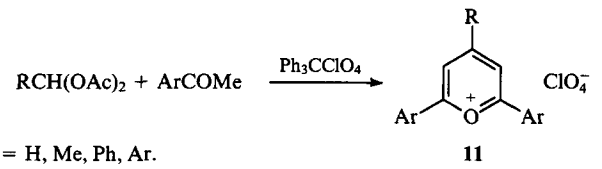
On the other hand, syntheses based on acylals were described in which the aldehydes themselves proved to be ineffective. Thus, in the reaction of benzylidene diacetate **9** with styrene, it is possible to avoid the telomerisation usually occurring in reactions between aldehydes and carboxylic acids (Scheme 1).[43] Acid-catalysed reactions of aldehydes with salicylic acid involve the alkylation of the aromatic ring, whereas the use of acylals yielded a series of 2-substituted 4-oxo-1,3-benzodioxanes **10**.[44] Acylals react with methyl ketones in the presence of triphenylmethyl perchlorate to form the pyrylium salts **11** and the 2-benzopyrylium salts **12**.[29]

Methylene diacetate **13** undergoes self-condensation in the presence of $SnCl_4$ to give the ester and ether derivatives **14**–**16**.[45] It was found recently[46,47] that aliphatic and aromatic aldehyde diacetates **17** react with $CHCl_3$ under phase-transfer catalytic conditions. These reactions proceed with substitution of an acetoxy group by a CCl_3 group with lengthening of the carbon chain by one atom to yield acetates of α-trichloromethyl carbinols **18** (Scheme 2). Apparently, this reaction is general and can also be expanded for other carbanion precursors. For example, analogous conversions were carried out with phenylmethylacetonitrile **19** and phenylacetonitrile **21** (Scheme 2).[48]

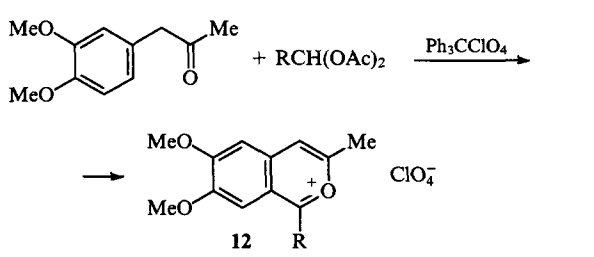
Scheme 1



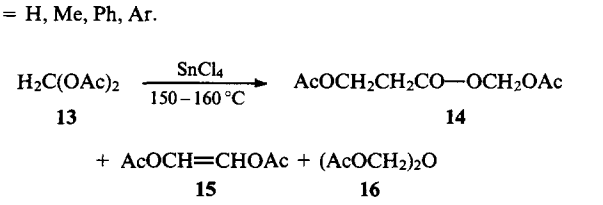
R = Me, Ph, Ar, PhCH=CH.



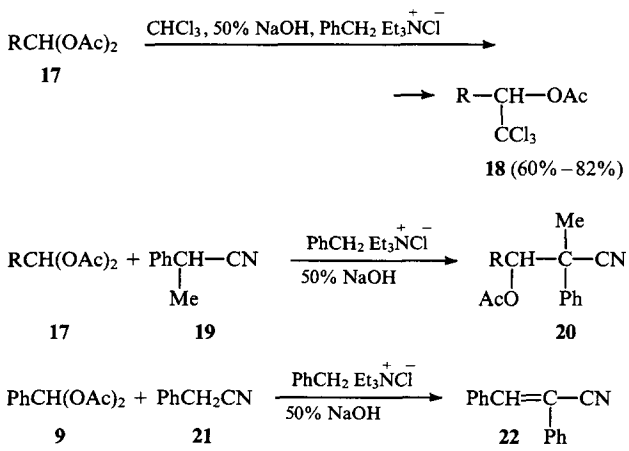
R = H, Me, Ph, Ar.



R = H, Me, Ph, Ar.

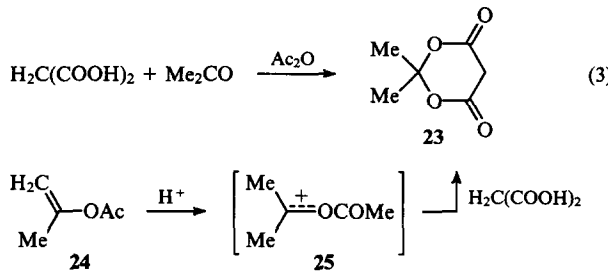


Scheme 2



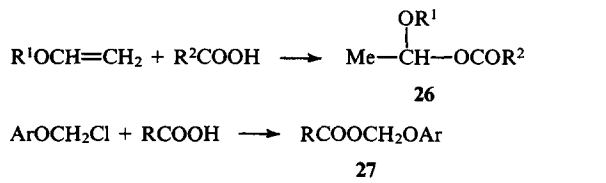
The substitution products obtained (**18**, **20**, and **22**) are valuable intermediates for subsequent transformations.

At present, isopropylidene malonate, Meldrum's acid **23**, is the best known acylal (see the relevant reviews[49–51]). This acid, which is an important precursor of many synthons and carbon suboxide and is a valuable starting material for the preparation of aliphatic-aromatic ketones and synthetically difficult 1,3,5-tricarbonyl compounds,[52,53] has recently attracted keen attention. Meldrum's acid can be prepared by the acid-catalysed acetylation of acetone with acetic anhydride and malonic acid [Eqn (3)][54] as well as by the acidolysis of isopropenyl acetate **24**.[55]



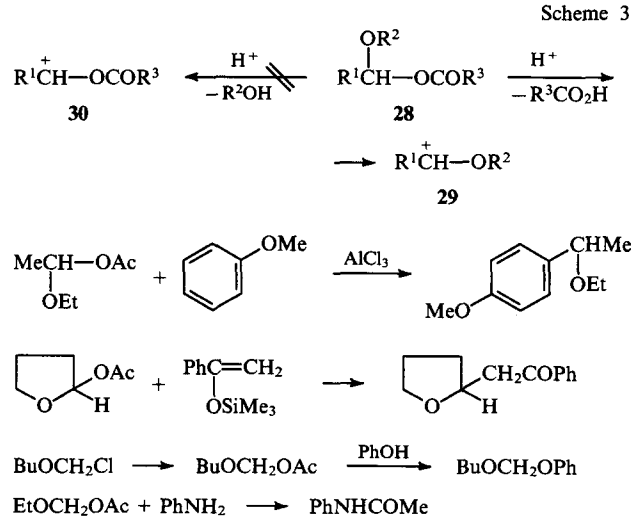
(3)

Mixed geminal α-acyloxyalkyl ethers **26** and **27**, that can be obtained in reactions of carboxylic acids with vinyl ethers[56–59] or aryl chloromethyl ethers,[60] are also called acylals in the chemical literature.

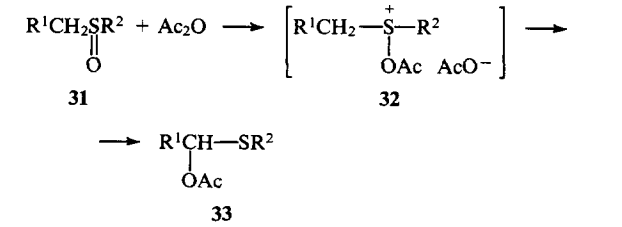


Compounds **26**, **27**, and **28** are noteworthy because their conversions always proceed with substitution of the acyloxy- rather than alkoxy-group, i.e. the more stable alkoxycarbocations **29** arise (see Section V). Kinetic investigations confirmed this observation.[61] Some examples of such reactions are shown in Scheme 3.[62–65]

Scheme 3



It is appropriate to mention in this Section the unusual sulfur-containing hetero-analogues of acylals **33**, which are products of the Pummerer reaction.[7,66] This reaction is, in essence, acylation of the sulfoxides **31**, which are sulfur analogues of ketones.

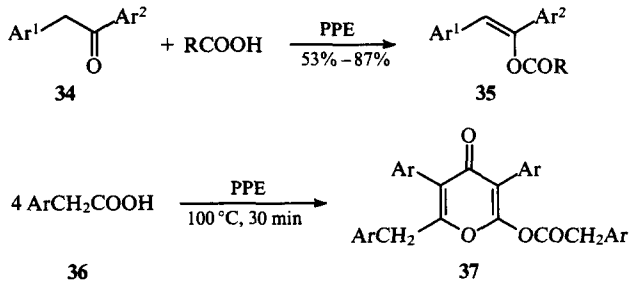


Acylals formed by ketones and an inorganic acid, the geminal diperchlorates $R^1R^2C(OClO_3)_2$, have also been described.[67]

III. Enol acylates

Compared with acylals, vinyl esters, i.e. enol acylates, particularly vinyl acetate, are better known because they are widely used. Syntheses based on enol acylates are of great importance, particularly in steroid chemistry. The extensive literature concerning enol acylates has been surveyed in several reviews.[68-71] A series of papers have been devoted to modifications of well-known preparative methods, for example, the acetoxymercuration of alkynes,[72,73] as well as to the formation of enol acylates under unusual conditions (thermal opening of cyclobutene derivatives,[74] electrochemical acylation of indenones[75]) and the syntheses of unusual enol acylates (benzenesulfonates,[76] triflates[77-79]). The syntheses of enol acylates from α-halogenated aldehydes and ketones by the action of acid halides in the presence of zinc are of interest.[80,81]

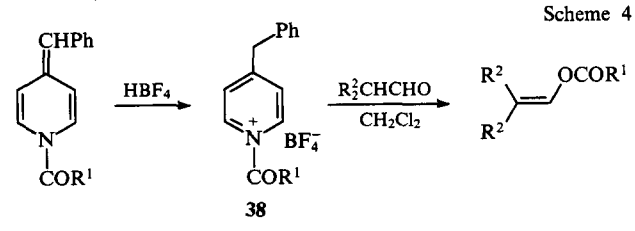
As to syntheses of enol acylates by the acid-catalysed acylation of carbonyl compounds, new variants of this approach were also reported side by side with new examples of traditional procedures (e.g. treatment of ketones with Ac_2O in the presence of perchloric[82] or sulfuric acid[83]). For example, deoxybenzoins **34** react with carboxylic acids or their anhydrides in polyphosphoric ester (PPE) to give the *O*-acylation products **35**.[84] It was found that the arylacetic acids **36** can undergo fourfold self-acylation to form the α-acyloxy-γ-pyrones **37** under these conditions.[85]



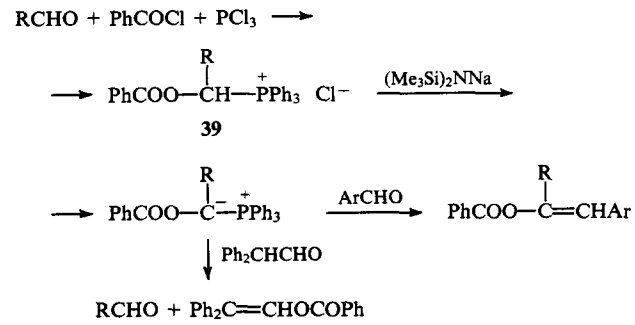
Ar = Ph, 4-$NO_2C_6H_4$.

The use of an Ac_2O + Me_3SiCl mixture represents a new method for the preparation of enol acylates from ketosteroids.[86] This mixture acts as an acylating reagent because trimethylsilyl chloride cleaves Ac_2O to give trimethylsilyl acetate and acetyl chloride.[86] *N*-Acylpyridinium salts **38**[87] and acyloxyacylphosphonium salts **39**[88] have also been used as acylating agents (Scheme 4).

Scheme 4

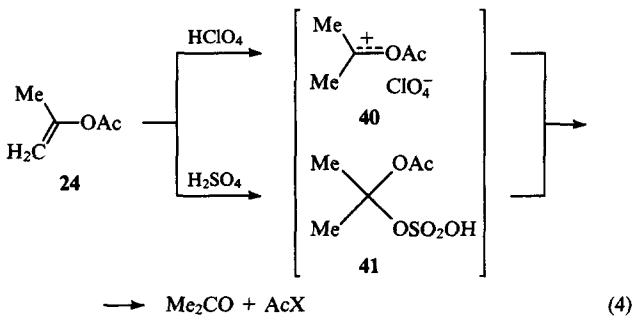


R^1 = Pr^i, Ph, Ar; R^2 = Me, Ph.

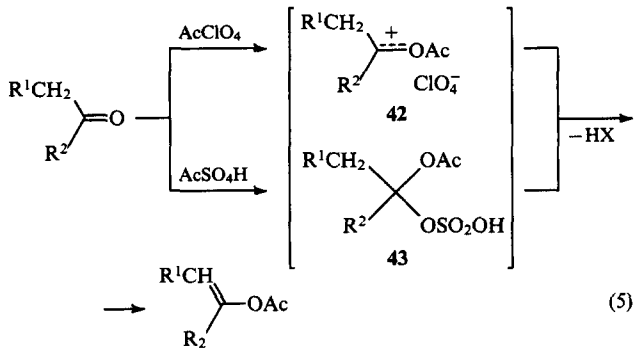


Investigations of the behaviour of labelled (^{18}O) ketones confirmed that acylals are intermediates in the formation of enol acylates by the acid-catalysed acylation of ketones with acetic anhydride.[34] A correlation between the rate of this reaction and the nucleophilicity of the anion of the protic acid was demonstrated. Thus, in the acylation of cyclohexanone by Ac_2O the degree of conversion of the ketone into the corresponding enol acetate reaches 80% after 20 min in the presence of $HClO_4$, in contrast to only 10% after 10 h in the presence of H_2SO_4.[34] The reactions of cyclic ketones with isopropenyl acetate **24** in the presence of both perchloric and sulfuric acids were described in the same paper.[34] According to ^1H NMR data, these reactions occur considerably faster in the presence of $HClO_4$ than with H_2SO_4, because in the former case the intermediates **40** and **42** have a cationoid structure, in contrast to the predominantly covalent nature of the intermediates **41** and **43** in the latter case (Scheme 5).

Scheme 5

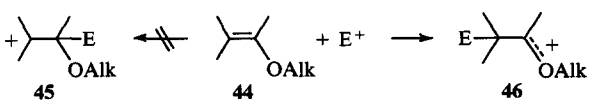


(4)



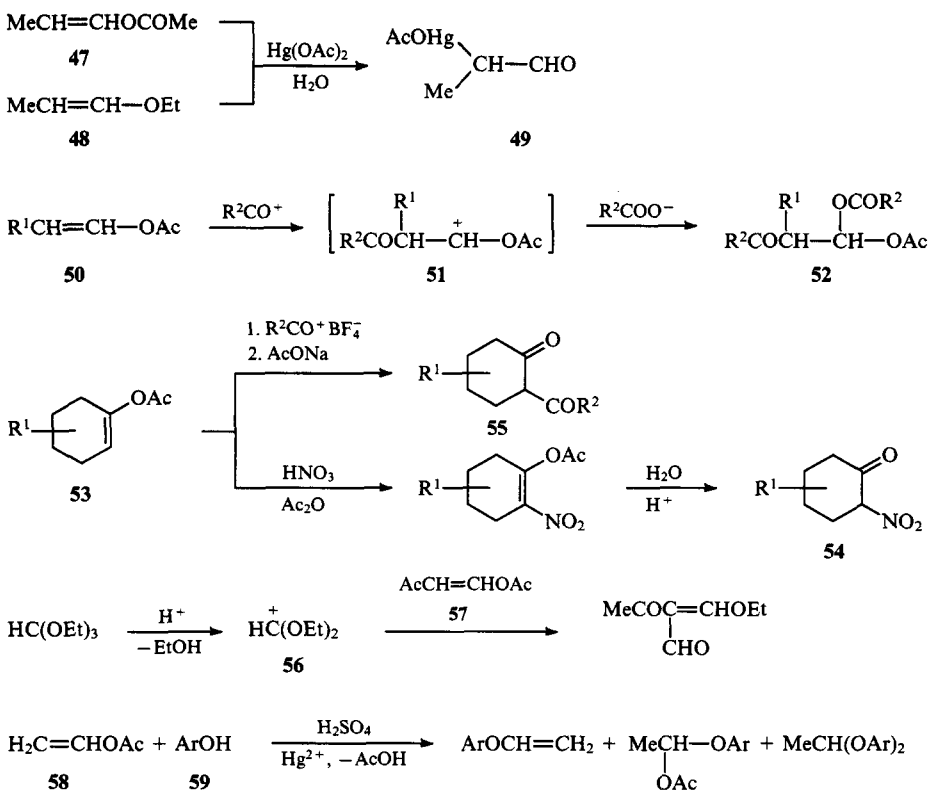
(5)

Among enol acylate reactions, the interaction of the latter with cationoid electrophiles (E) is of particular interest. It is generally known that vinyl ethers **44** always combine with an electrophile at the double bond carbon atom most remote from the oxygen atom and are then converted into carbonyl compounds [see Kulish et al.,[89] Shostakovskii,[90] and also Barton and Ollis[70] (p. 351)]. This is due to the formation of the alkoxycarbenium ions **46**, which are much more stable than the alternative carbocation **45** (even tertiary ones).[91,93]



This difference in the stability of cations **45** and **46** explains the pinacol rearrangement with group migration from the carbon atom linked to the ether oxygen atom[94,95] (see Ref. 1, p. 461). It should be noted that the concept of carbocation resonance stabilisation by heteroatoms at the carbenium centre is so common now that any carboxonium ions are regarded as a priori stable. If this were really so, there would be no need to continue this review.

Scheme 6



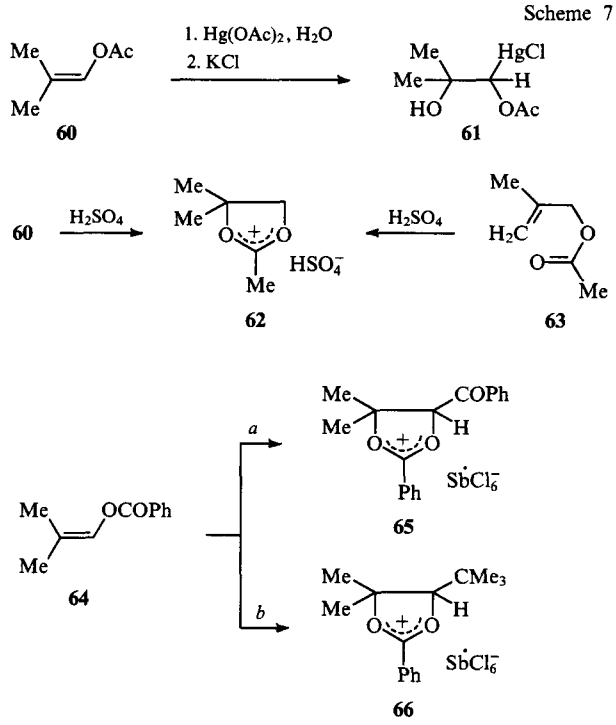
Many of the reactions involving electrophilic addition to vinyl esters reported in the literature are fully consistent with the above ideas. Thus, both the enol acetate of propanal **47** and ethyl propenyl ether **48** react with mercuric acetate to form α-acetoxymercuriopropanal **49** (Scheme 6).[96,97] Acylation of vinyl acetates **50** leads to the β-ketoaldehyde acylals **52** via the acyloxycarbenium ions **51**.[98,99] Nitration of 1-acetoxycyclohexenes **53** gives the nitroketones **54**,[100] while its acylation affords the 1,3-diketones **55**.[101] The diethoxycarbocation **56** formed from ethyl orthoformate also attacks the enol acetate of 3-oxobutanal **57** at the position as the C=C double bond most distant from the ether oxygen atom.[102]

The addition of phenols **59** to the C(α) atom bearing an acetoxy-group in vinyl acetate **58** occurs due to protonation of the latter at the methylene group.[103] All of the enol acylates used in the above reactions contained a primary or secondary carbon atom at the position in the double bond most distant from the oxygen atom (which will be, for convenience, henceforth called the β-carbon atom).

However, it was found recently that enol acylates containing a tertiary β-carbon atom react with electrophiles in a fundamentally different way. Thus, the enol acetate of isobutyraldehyde **60** gives under acyloxymercuration conditions[96] a 1,2-diol derivative **61** rather than an aldehyde.[104] Dissolution of the enol acetate **60** in 98% sulfuric acid yields a 1,3-dioxolanylium salt **62**, the ^{1}H NMR spectrum of which is fully identical to that of the product of protonation of methylallyl acetate **63**.[105] Benzoylation and alkylation of the enol benzoate **64** in weakly nucleophilic media yield 4-benzoyl-**65** and 4-*tert*-butyl-1,3-dioxolanylium salts **66**, respectively.[104] It should be emphasised that the above 1,3-dioxolanylium salts **62**, **65**, and **66** are derivatives of 1,2-glycols, into which they can be readily converted by hydrolysis[106] (Scheme 7).

Thus, if an enol acylate is branched at the position in the C=C double bond most distant from the oxygen atom, the addition of an electrophilic species occurs at the α-carbon atom linked to the oxygen atom. Hence, the energies of the alternative cations, i.e. the acyloxycarbenium cations **67** and the tertiary carbenium cation **68**, are almost the same (see Section VI) (Scheme 8).

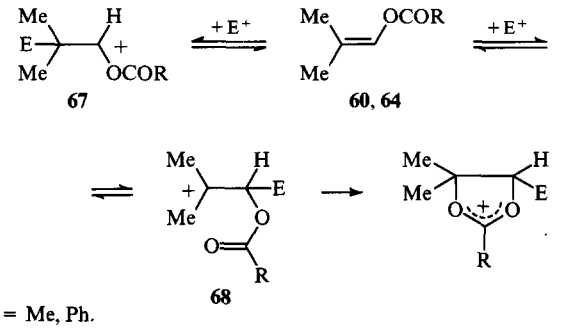
Scheme 7



a: $PhCO^+SbCl_6^-$, −10 °C, CH_3NO_2;

b: $Me_3C^+SbCl_6^-$, −60 °C, CH_2Cl_2.

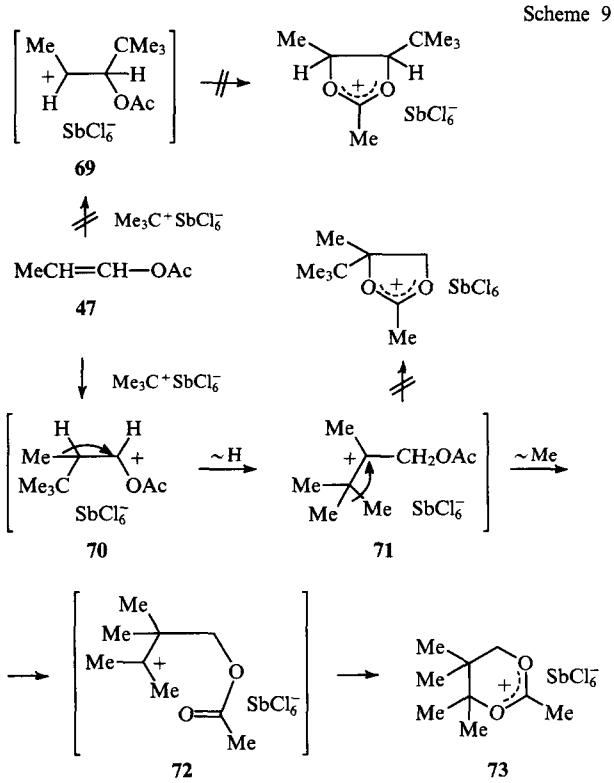
Scheme 8



R = Me, Ph.

This conclusion is in good agreement with the results of the alkylation of the enol acetate **47** under the same conditions leading to 1,3-dioxanylium hexachloroantimonate **73**.[104] The reaction mechanism presupposes the formation of the acyloxycarbenium ion **70**, which is more stable than the secondary carbocation **69**, and two consecutive migrations of a hydrogen atom and the methyl group (Scheme 9).

Scheme 9



It should be noted in conclusion that the acid-catalysed acylation of aldehydes and ketones leads to enol acylates, provided that the reaction mixtures contain bases capable of eliminating a proton from the product of the *O*-acylation of the carbonyl compound. This function can be performed by isopropenyl acetate,[34] pyridine,[87] or the acetate anion at elevated temperatures. In the cold, nucleophilic addition of acylate anions takes place and is accompanied by the formation of acylals. If other acylating reagents are used, such as acyl halides, then the halogen atom should play the role of the nucleophile.

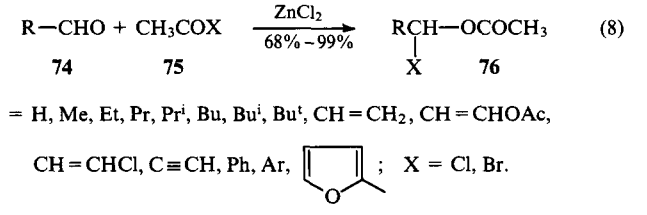
IV. α-Haloalkyl acylates

The acid-catalysed acylation of aldehydes by acid chlorides was discovered in 1901.[107,108] The α-chloroalkyl carboxylates **2** were obtained from formaldehyde and acetaldehyde in the presence of anhydrous zinc chloride. Later several studies were published in which this reaction was extended to higher aldehydes and acrolein.[109–112]

The α-haloalkyl acylates **2** have aroused interest only since the middle of this century. This was connected with the possible use of these compounds for the preparation of vinyl monomers,[113] but primarily for application in studies of the nucleophilic substitution mechanism. In the sixties and seventies, Euranto and coworkers published the results of very detailed investigations of the noncatalytic hydrolysis of various α-haloesters under a wide range of conditions (see the relevant communications[114–120] and the references therein). The methods for the preparation of α-haloalkyl acylates reported up to that time were surveyed in a separate article,[121] in which the merits and drawbacks of ten different approaches were listed. Preference was given to methods involving the chlorination of alkyl carboxylates as well as the halogenation and hydrohalogenation of enol acylates. Five of these procedures, including the acylation of aldehydes, were used for the preparation of samples employed in kinetic investigations.[121] Brief historical surveys concerning the topic discussed were also given in Refs 109 and 113.

However, a preparative application of the reaction of carbonyl compounds with acyl halides was not found until the late sixties, when Neuenschwander and coworkers[122,123] developed a new method to prepare fulvenes. It was found that only α-chloroalkyl acetates are capable of reacting effectively with cyclopentadiene to form differently substituted fulvenes in up to 70% yields.[122–125] Neither their precursors, i.e. carbonyl compounds, nor the related simple α-chloroesters react in this way. A detailed investigation of the mechanism of the formation of the key starting materials, i.e. α-haloalkyl acylates (acyloxychloromethanes), became the subject of a series of papers. Two papers[126,127] reported the applicability of the haloacylation of carbonyl compounds to the synthesis of α-haloalkyl acylates.

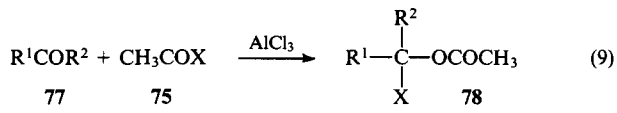
The equilibrium of the reaction between the aliphatic aldehydes **74** and the acetyl halides **75** is so shifted towards the products **76** that the equilibrium constant cannot be determined by ^{1}H NMR spectroscopy. The authors believe that the reaction considered was rarely used for preparative purposes because of the poor yields of the target products **76** resulting from imperfect techniques for the isolation of the latter. This problem can be solved by using low temperatures (from −10 to 0 °C) and by removing the catalyst ($ZnCl_2$) before the fractional distillation of the reaction mixtures.



(8)

The haloacylation of α,β-unsaturated aldehydes occurs readily (68%–94% yields).[127] In contrast to the situation with aliphatic aldehydes, the equilibrium position of the reaction involving aromatic aldehydes is measurable; substituents having +*M* and +*I* effects shift this equilibrium to the left. Therefore, excess acetyl chloride should be used in reactions involving starting aldehydes such as 4-methoxy- and 4-dimethoxy-aminobenzaldehydes. Other aromatic aldehydes afford the products **76** in 96%–99% yields.

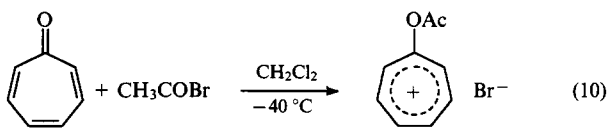
The haloacylation of ketones **77** gives the products **78** in 76%–93% yields, which were observed to depend on the ring size of the alicyclic ketones. In the case of cyclobutanone and cyclohexanone, the equilibrium position is shifted towards the product **78**, whereas for cyclopentanone and cycloheptanone it is nearer to the starting reactants. Aromatic ketones such as acetophenone practically do not form α-haloalkyl esters. Tropone **79**, which gives the acylation product **80** with an ionic structure, occupies a particular position.[127]



(9)

77 75 78

R^1, R^2 = Me, $-(CH_2)_n-$, n = 3, 5; X = Cl, Br



(10)

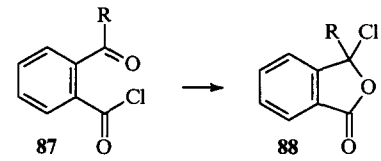
79 80

An analysis of the side products formed by the haloacetylation of aldehydes has been carried out[128] in order to optimise the synthesis conditions. The structure of the aliphatic aldehydes, the reaction time, the concentrations of the catalysts and starting reactants, as well as the polarity of the solvent were varied during this investigation. It was concluded that (*a*) dilute solutions, (*b*) nonpolar solvents, (*c*) higher concentrations of acetyl halides, achieved by the dropwise addition of the aldehyde to the reaction mixture, (*d*) low temperatures, and (*e*) higher concentrations of the catalyst dissolved in the acyl halide should be used for the successful suppression of side reactions mentioned above.

The dependence of the equilibrium position on the reaction conditions in the above processes [Eqns (8) and (9)] was considered in detail in Ref. 129. The equilibrium constants were measured as a function of the structure of the carbonyl component, the composition of the acyl halide, solvent polarity, and temperature. The results of exact measurements[129] fully agree with the practical recommendations specified above.[128]

Finally, the possible mechanisms of the haloacylation of carbonyl compounds, namely, the two 'polar mechanisms' (*a*, *b*), the synchronous mechanism (*c*), and the ketene mechanism (*d*) have been thoroughly discussed[130] (Scheme 10). It was shown by ^{1}H NMR kinetic measurements that aliphatic acyl halides react according to the 'polar mechanism' *b* via the intermediates **84** and **85**, i.e. without ionisation, while aromatic acyl chlorides follow the mechanism *a* with the participation of the acyloxycarbocations **82**.[130] This can be attributed to the lower energy (i.e. higher stability) of the benzoyl cations **81** (R^1 = Ar) in comparison with that of aliphatic acyl cations.

In relation to the facts considered above, we should also mention the long known intramolecular interaction between the functional groups in the chlorides of γ- and δ-keto- and aldehydocarboxylic and *o*-acylbenzoic acids **87**.



87 88

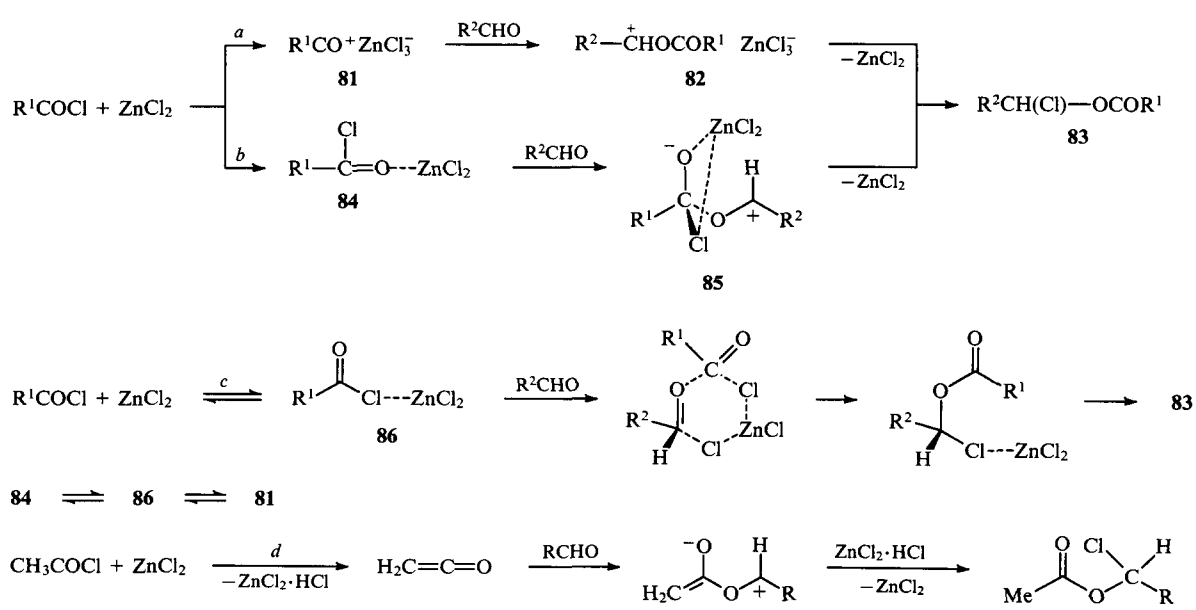
The majority of such compounds are stable only as cyclic α-chloroalkyl acylates **88**, and only a few examples are known where steric hindrance prevents cyclisation.[131–134] More than a hundred of such structures, both aliphatic and aromatic, were considered in a review[135] containing an extensive bibliography. The existence of tautomeric equilibrium between the open form **87** and the cyclic form **88** is completely rejected in Refs 133–135.

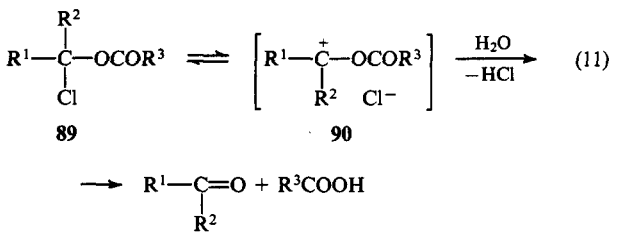
As mentioned above, until now there has been little information about the synthetic application of α-haloalkyl acylates. These compounds can be used as alkylating reagents in reactions with 2-(trimethylsilyloxy)furan,[22] pyridine,[113] secondary amines,[136] silver salts of *N*-nitrosohydroxylamines,[137] and phenols,[138] as well as for forming carbon–manganese bonds.[139] However, the same α-haloesters behave as acylating agents under other conditions.[136,138,140] The chlorine atom in α-chloroalkyl acetates, similarly to that in acylals (see Section II), can be substituted by the trichloromethyl group under phase-transfer catalytic conditions.[141] However, the most interesting properties of α-chloroesters were found when the latter were used for the synthesis of oxygen-containing heterocyclic compounds (see Section V).

V. Acyloxycarbenium ions

It was shown by kinetic studies of the hydrolysis of the α-haloesters **83** and **89** that the majority of the latter react according to a S_N1 mechanism[114–120] via the acyloxycarbenium ions **82** and **90** as intermediates.

Scheme 10

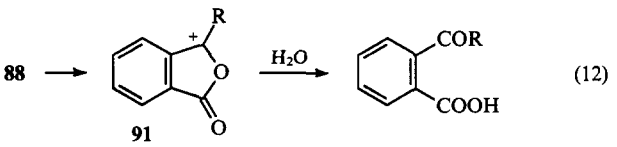




(11)

It was established[115] that α-chloroethyl benzoate **89** (R^1 = Me, R^2 = H, R^3 = Ph) hydrolyses via a unimolecular S_N1 mechanism almost 100 times more quickly than chloromethyl benzoate **89** ($R^1 = R^2$ = H, R^3 = Ph), the solvolysis of which occurs by an S_N2 mechanism. Secondary α-haloalkyl acylates **89** (R^1, R^2 = Alk, R^3 = Me, Et, CCl_3) are hydrolysed a thousand times more quickly than the corresponding primary esters **89** (R^1 = Alk, R^2 = H, R^3 = Ph).[116] α-Chlorobenzyl esters **89** (R^1 = Ar, R^2 = H, R^3 = Ph) also undergo substitution of the chlorine atom by a unimolecular mechanism.[118,119]

The formation of cyclic acyloxycarbocations **91** is suggested by kinetic data for the hydrolysis of the cyclic α-chloroalkyl acylates **88** mentioned above.[133,134,142]



(12)

The hydrolysis of the acylals **1** can also occur by different pathways. Ethylidene diacetate $MeCH(OAc)_2$ reacts by an $A_{AC}2$ mechanism,[36] like *p*-nitrobenzylidene diacetate, $4\text{-}O_2NC_6H_4\text{-}CH(OAc)_2$.[37] However, *p*-methoxybenzylidene diacetate, $4\text{-}MeOC_6H_4CH(OAc)_2$, undergoes unimolecular hydrolysis via acyloxycarbenium ions.[37] It was shown that primary α-chloroalkyl esters react with oxygen- and nitrogen-containing nucleophiles by a bimolecular mechanism,[136,138] whereas the analogous α-chloroalkyl ethers react by an S_N1 mechanism.[94] It is known that vinyl ethers hydrolyse via the same mechanism 10^4 times more quickly than vinyl acetate, which was supposed to form a π-complex with the proton.[89] However, the next homologue, isopropenyl acetate **24**, can be readily transformed into the acyloxycarbocation **40**,[143,144] which was detected by ^1H NMR spectroscopy.[145] It was assumed that both the acetolysis of α-acetoxystyrene, $PhC(OAc)=CH_2$,[146] and the formation of phthalides from *o*-aroylbenzoic acids[147] proceed with formation of acyloxycarbenium ions.

These results allow us to conclude that the generation of the acyloxycarbocations **90** requires a considerably higher energy than the formation of the related alkoxycarbocations **46** and depends very strongly on both the precursor structure (acylal, enol acylate, or α-haloalkyl acylate) and on reaction conditions. The high energy of the acyloxycarbocations follows from the unusual mode of electrophilic addition to β-branched enol acylates (see Section III) and from some indirect evidence, such as the possibility of an equilibrium between the acyloxycarbenium ion **92** (in this case, considerably stabilised) and the acylium ion **93** (Scheme 11).[148]

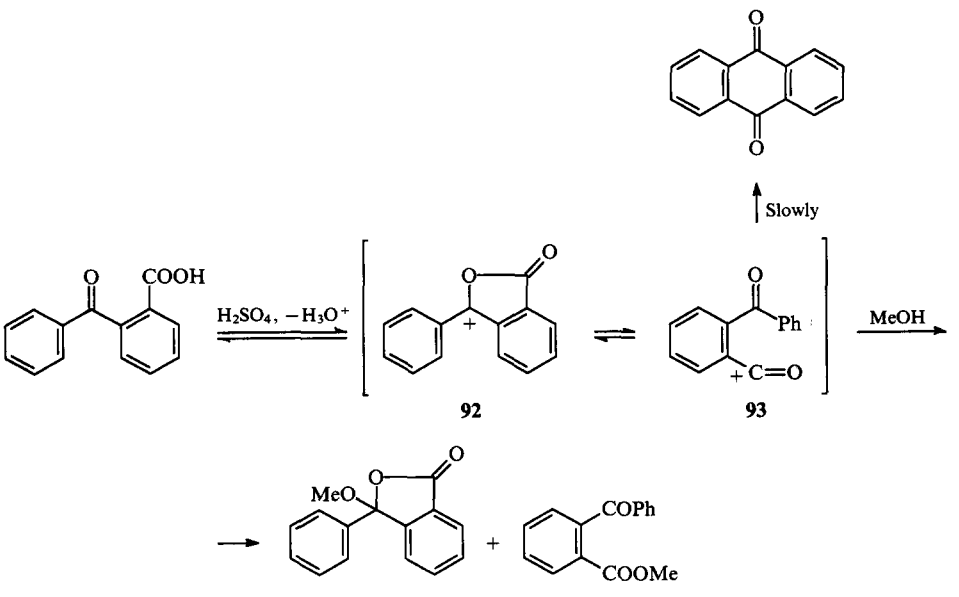
Thus, an acyloxy group linked to a carbenium centre stabilises the latter, but to a much lower extent than a hydroxy- or alkoxy-group. Apparently, the relatively high stability of acylals in weakly acid media[21] (see Section II) can be explained by difficulties in their ionisation (in comparison with acetals).

Perhaps the fact that acyloxycarbenium ions have never been mentioned in any of the reviews dealing with carboxonium ions[91–93] can be explained only by their unpredictable formation conditions and behaviour. At the same time, the information presented above suggests that these species cannot be regarded as just one example of the ion series $R^1R^2C^+-OR^3$. In addition to the high energy of acyloxycarbocations, their tendency to decompose into a carbonyl compound and a quite stable acylium cation should be taken into account as their characteristic feature.[129,149,150] However, since acyloxycarbenium ions are intermediates not only in the acid-catalysed acylation of carbonyl compounds but also in the reactions of its products, it is quite appropriate to make a compilation of the scattered data on these species.

In addition to the instances presented above [reactions (3)–(6), (10)–(13); Schemes 9 and 10], the acyloxycarbocations **95**, **98**, **100**, and **101** were assumed as intermediates in a number of reactions of carbonyl compounds with acylating agents: the reaction of succinic anhydride with 2-acetoxybut-2-ene **94** for the preparation of the key intermediate **96** in steroid syntheses;[151] the conversion of 2,6-diphenyl-4-pyrone **97** into cyanine dyes;[152] the reaction of 3,5-di-*tert*-butyl-1,2-benzoquinone **99** with acetic anhydride (Scheme 12).[153,154]

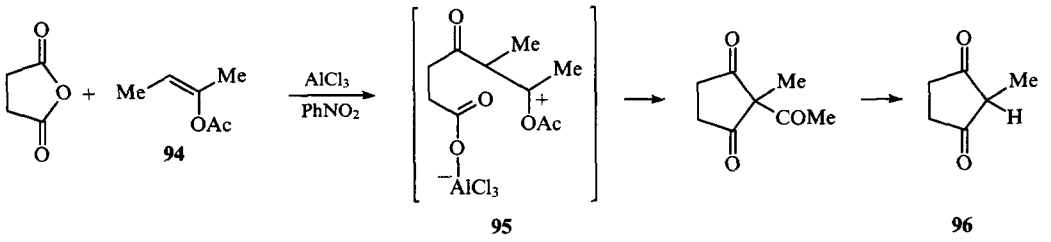
The acyloxycarbenium ions **103**, **104**, and **106** are formed by the acylation of the α,β-unsaturated carbonyl compounds **102** and **105**.[155,156]

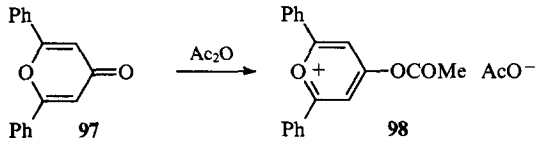
Scheme 11

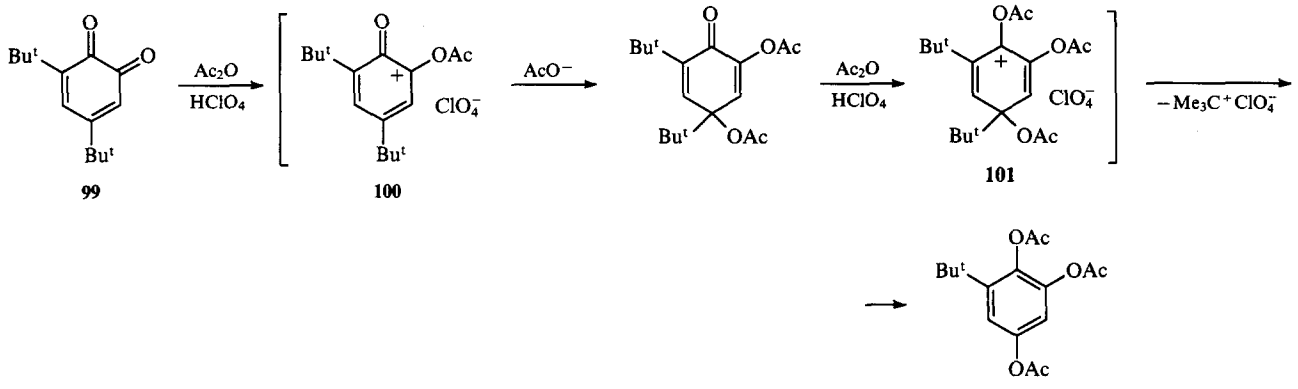


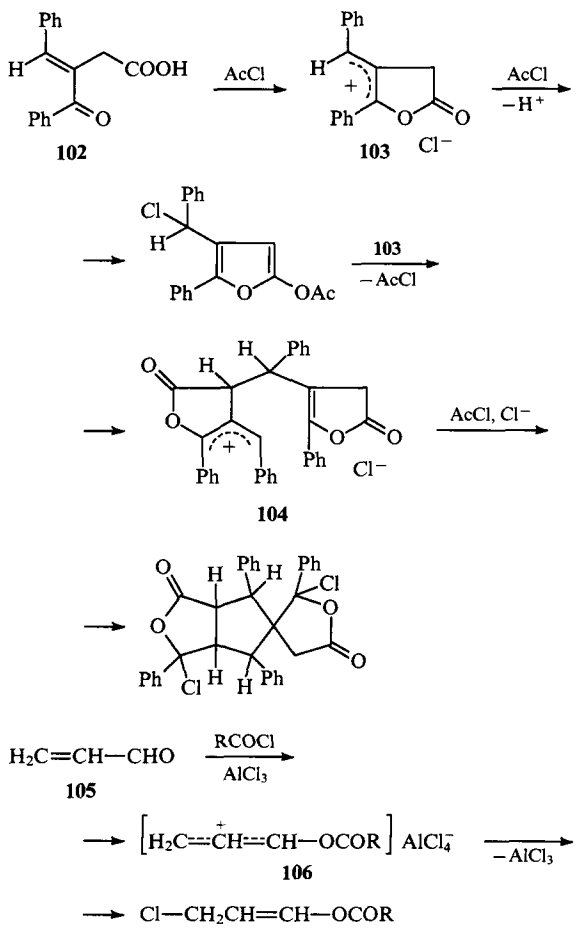
(13)

Scheme 12

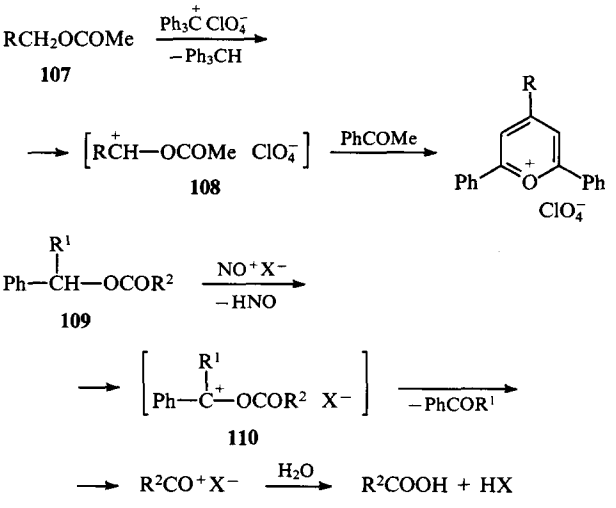








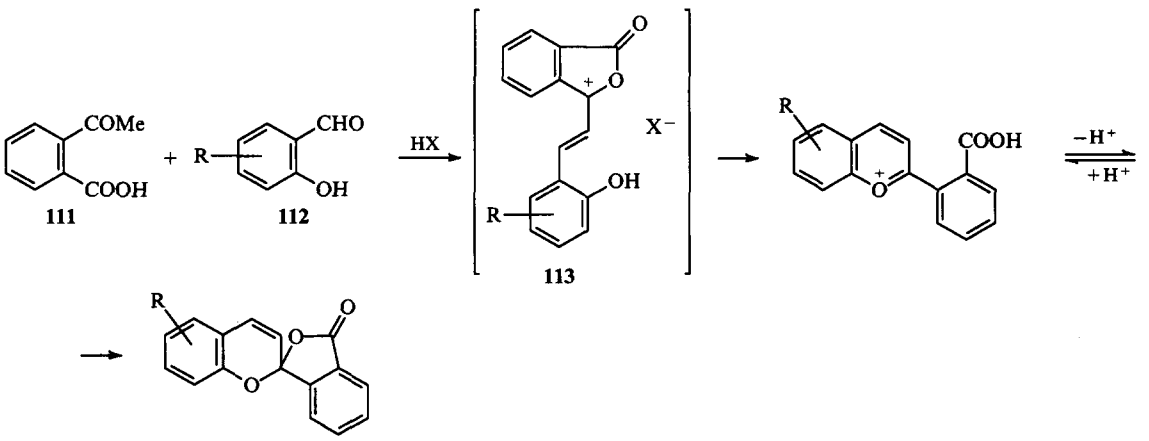
The oxidative dehydrogenation of the esters **107** and **109** occurs with the intermediate formation of the acyloxycarbenium caitons **108** and **110**.[149,157]

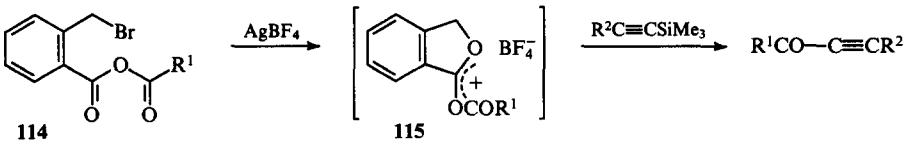


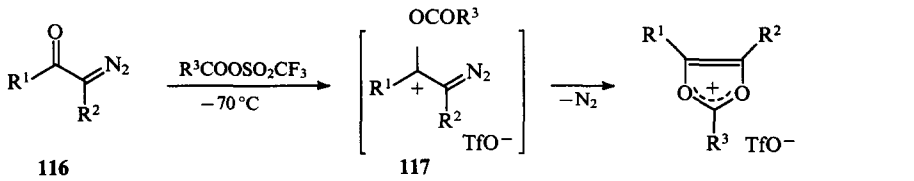
The cyloxycarbenium ions **113**, **115**, **117**, **119**, and **121** are formed in the condensation of *o*-acetylbenzoic acid **111** with the salicyl aldehydes **112**,[158,159] in the ionisation of the mixed anhydrides **114**,[160] in the acylation of the α-diazoketones **116**,[161] in the acid treatment of citral diacetate **118**,[162] and in the liquid-phase oxidation of the ketones **120**[163] (Scheme 13).

Both the nitration of cyclohexanone enol acetates **53**[100] and the formylation of formylacetone monoenol acetate **57**[102] considered above (see Section III) also proceed via acyloxycarbenium ions as intermediates. It was assumed that the latter (compounds **122**–**124**) can serve as intermediates in acid-catalysed transformations of sulfur-containing compounds (Scheme 14).[164–166]

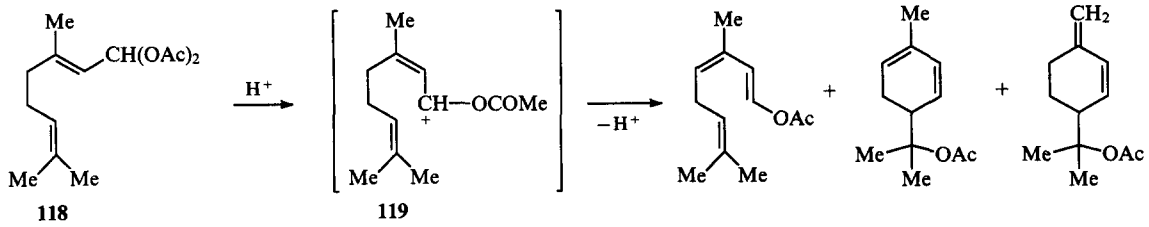
Scheme 13

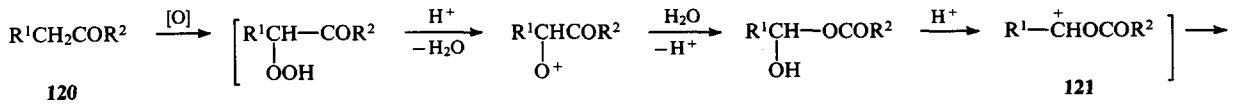




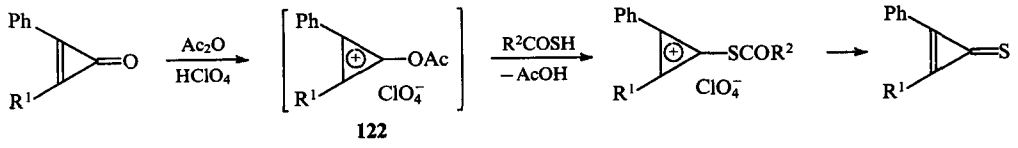


Tf = SO_2CF_3.

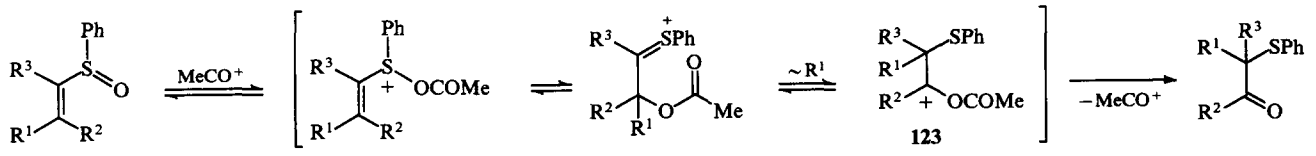




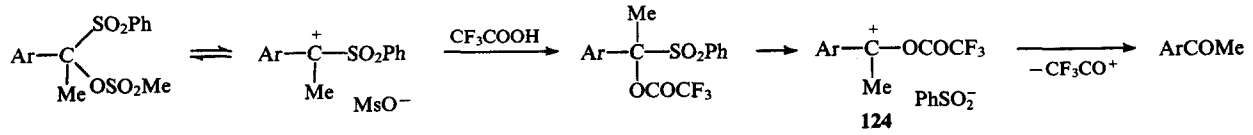
Scheme 14



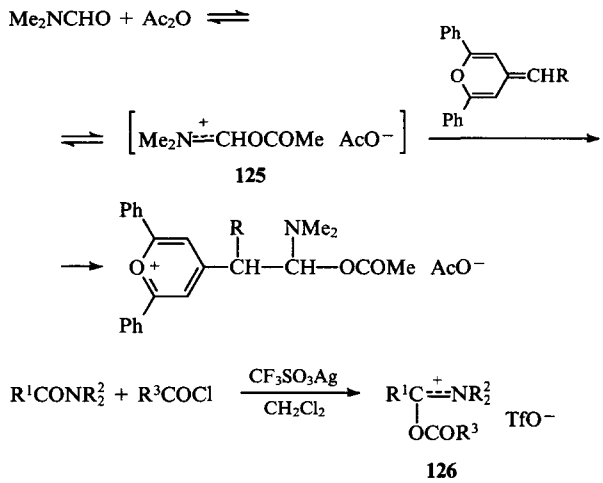
R^1 = Me, Ph; R^2 = Me, Ar.



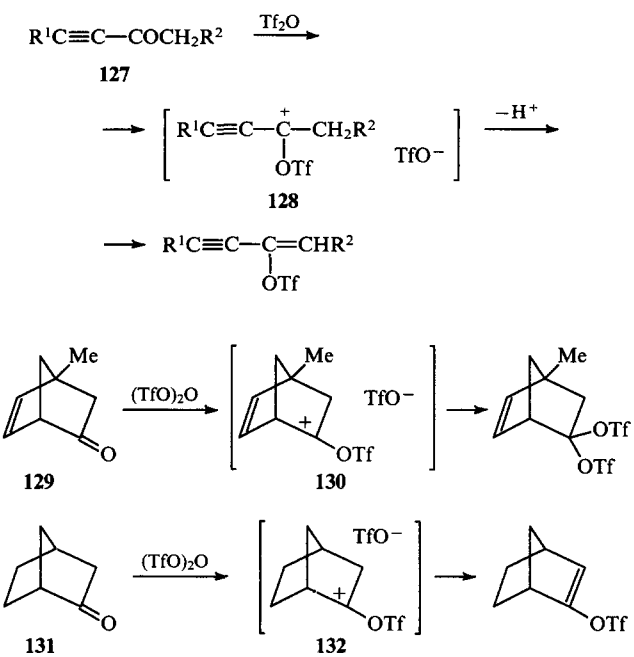
R^1 = H, Me.



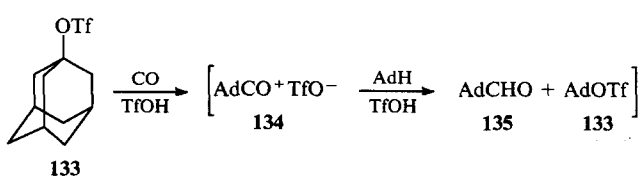
The unusual cationoid species **125** and **126** are formed by the *O*-acylation of amides.[167,168]

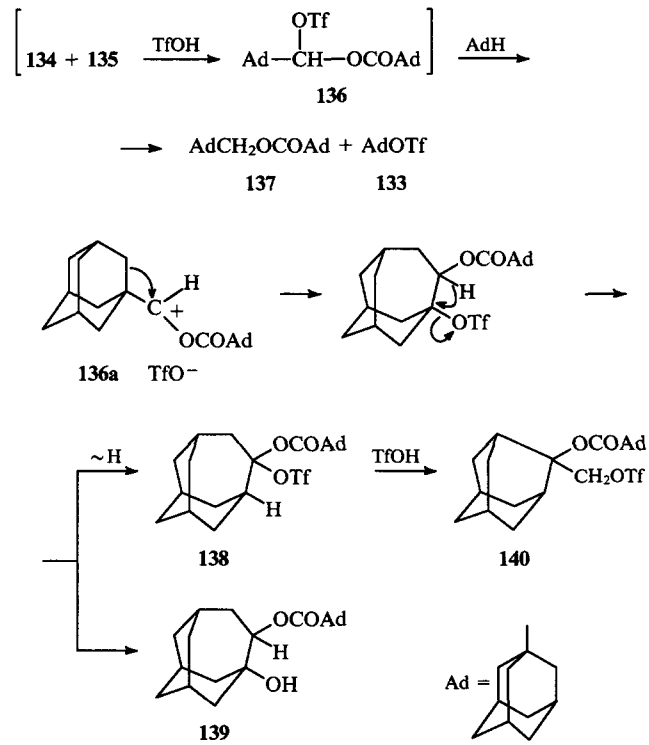


The carbocations **128**, **130**, and **132** are intermediates in reactions of trifluoromethanesulfonic anhydride with the butynones **127**[169] and the terpene ketones **129** and **131**.[170,171]

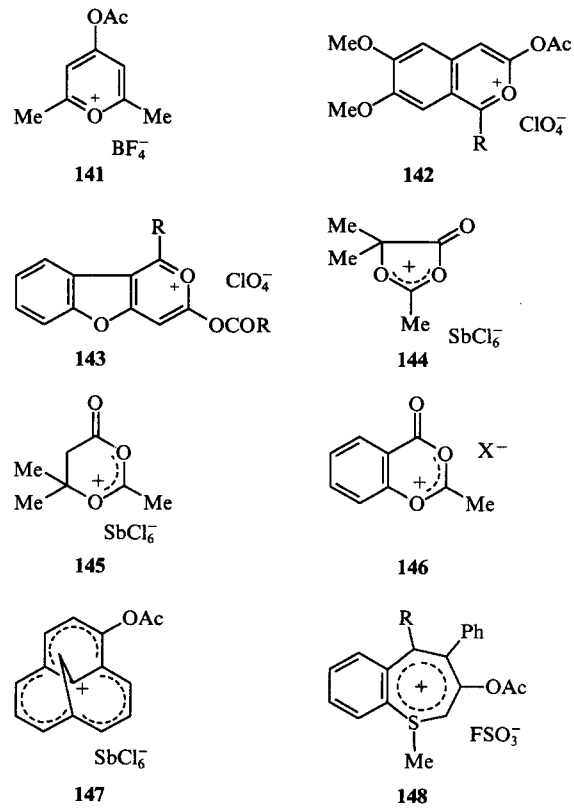


The reaction of 1-adamantyl triflate **133** with carbon monoxide and adamantane (AdH) in the presence of trifluoromethanesulfonic acid (TfOH) gives the products **137**, **139**, and **140**, the formation of which was explained by the participation of acyloxycarbenium intermediates **136**, **136a**, and **138**.[172] Although one of them (**136**) was represented as a covalent structure,[172] its ability to be a hydride acceptor and to undergo a rearrangement suggests that it is readily transformed into the cation **136a** (the low nucleophilicity of the triflate anion is well known[173]).





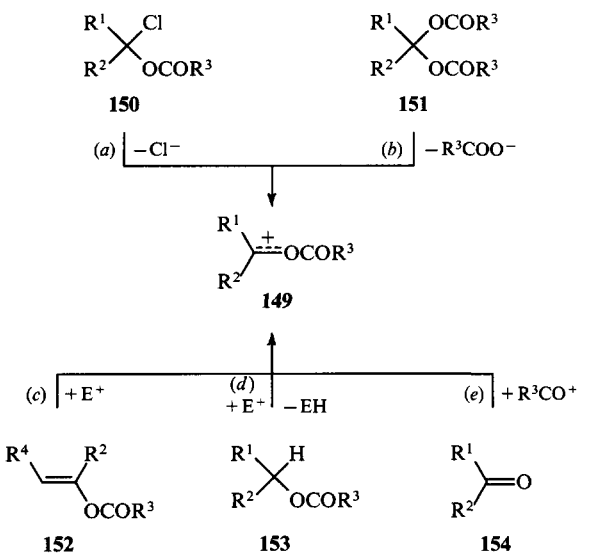
Finally, stable acyloxycarbenium salts have been described: acyloxypyrylium (**141**, **142**, and **143**),[174–176] 4-oxo-1,3-dioxolan-2-ylium (**144**), and 4-oxo-1,3-dioxolan-2-ylium (**145**),[177] as well as 4-oxo-1,3-dioxolan-2-ylium (**146**)[178] salts. Papers dealing with the synthesis of the carbocyclic and heterocyclic systems **147** and **148** containing an acetoxy group as a substituent have been published.[179,180]



To sum up the above information, five general methods for the generation of the acyloxycarbocations **149** can be distinguished: (*a*) ionisation of the α-chloroalkyl acylates **150**;[119]

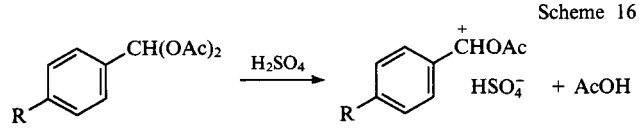
(*b*) ionisation of the acylals **151**;[37] (*c*) addition of cationoid electrophiles to the enol acylates **152**;[145] (*d*) oxidative dehydrogenation of the esters **153**;[149,157] and (*e*) direct *O*-acylation of the carbonyl compounds **154**[156] (Scheme 15).

Scheme 15

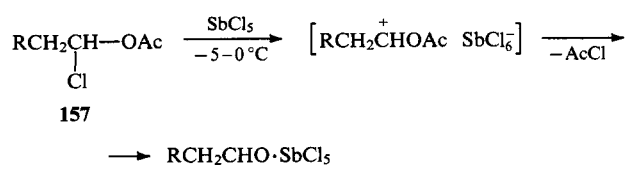


It is known that the stability of highly reactive species such as carbocations can be characterised by the conditions of their existence as salts. Many hydroxy- and alkoxy-carbenium ions are so stable that they can readily be detected in solution by ^{1}H NMR spectroscopy or even isolated as salts with nonnucleophilic anions.[91,92] The conversion of the diacetates of benzaldehyde and its substituted derivatives **155** into arylacyloxycarbenium perchlorates **156**, characterised by ^{1}H NMR spectra of the acylals **155** in solutions in concentrated H_2SO_4, have been reported.[181] The chemical shifts presented[181] agree well with those for methoxycarbenium ions formed from dimethyl acetals of the same aldehydes.[92] However, the author's statement[181] concerning the isolation of solid acyloxycarbenium salts is doubtful. As shown in another study,[182] treatment with $SbCl_5$ of the α-chloroalkyl acetates **157** derived from aliphatic aldehydes leads only to complexes of the latter with $SbCl_5$ (**158**). Mixing the α-chlorobenzyl acylates **159** with $SbCl_5$ at temperatures higher than −60 °C also gives the colourless complexes **161**.[183] Only at −95 °C were bright yellow precipitates of the salts **160** obtained and could be characterised by IR spectra. Heating their suspensions in CH_2Cl_2 to −60 °C results in their decomposition. The product **163** of the reaction between α-chloro-*o*-nitrobenzyl acetate **162** and $SbCl_5$ turned out to be somewhat more stable.[183] Its stability (10 to 15 min at 20 °C) can be explained by the participation of the *ortho*-nitro group in cyclisation[184] (Scheme 16).

Scheme 16

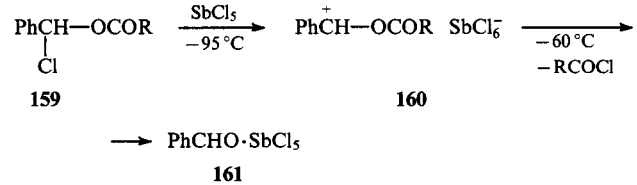


R = H, Me, F, Cl, Br, I.

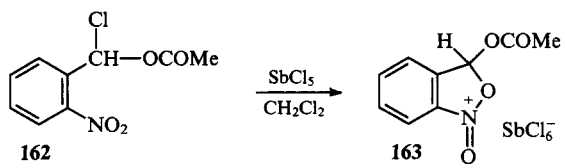


R = Me, Et, Pr^i.

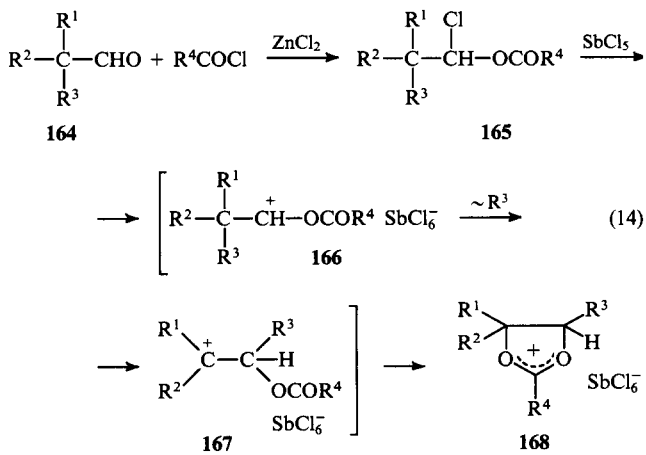
Scheme 16 continued



R = Me, Ph.



As in Ad_E reactions of enol acylates (see Section III), the situation changes sharply when the α-chloroalkyl acylates **165**, obtained from the α-branched aldehydes **164**, are treated with $SbCl_5$. Colourless stable salts were isolated in quantitative yields; according to ^{1}H NMR and IR spectroscopic data, these turned out to be 1,3-dioxolanylium hexachloroantimonates **168**.[182,185,186]

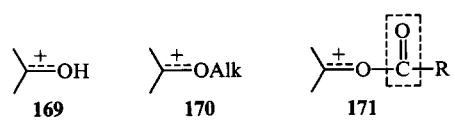


R^1 = Me, Ph;

R^2 = Me, Et, Ph; R^1 + R^2 = −(CH$_2$)$_4$−, −(CH$_2$)$_5$−;

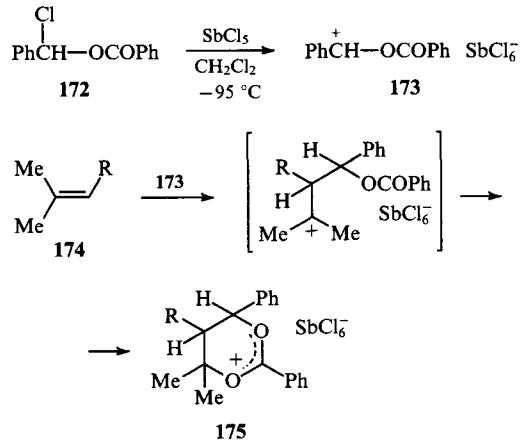
R^3 = H, Ph, PhCH$_2$; R^4 = Me, Et, Ph.

Thus, the same 1,3-dioxolanylium salts as those derived from branched enol acylates **60** and **64** are formed from the α-chloroesters **165**. However, isomerisation of the acyloxycarbenium ions **166** to the tertiary carbenium ions **167**, already shown above (see Scheme 9), occurs in this reaction. It must be emphasised that rearrangements with 1,2-migration to a carbon atom linked to an oxygen atom (see Section VI) are not typical of carboxonium ions and thus differentiate sharply the acyloxycarbenium ions **171** from the well-known hydroxy-(**169**) and alkoxycarbenium (**170**) ions.

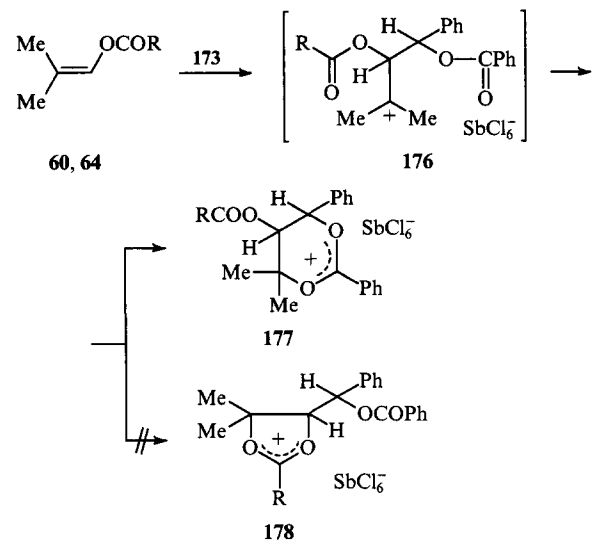


Moreover, an important feature of the cations **171** is the combination of electrophilic (the carbenium atom) and nucleophilic (the carbonyl oxygen atom) centres within the same species. This makes them suitable for interaction with unsaturated compounds in polar 1,4-cycloaddition reactions.[187] Thus, benzoyloxyphenylcarbenium hexachloroantimonate **173**, obtained beforehand from α-chlorobenzyl benzoate **172**, reacts with the

alkanes **174** to give the 1,3-dioxanylium salts **175**.[183] The 5-acyloxy-1,3-dioxanylium salts **177** can be derived from the enol acylates **60** and **64** as unsaturated components.[183]



R = H, Me.



R = Me, Ph.

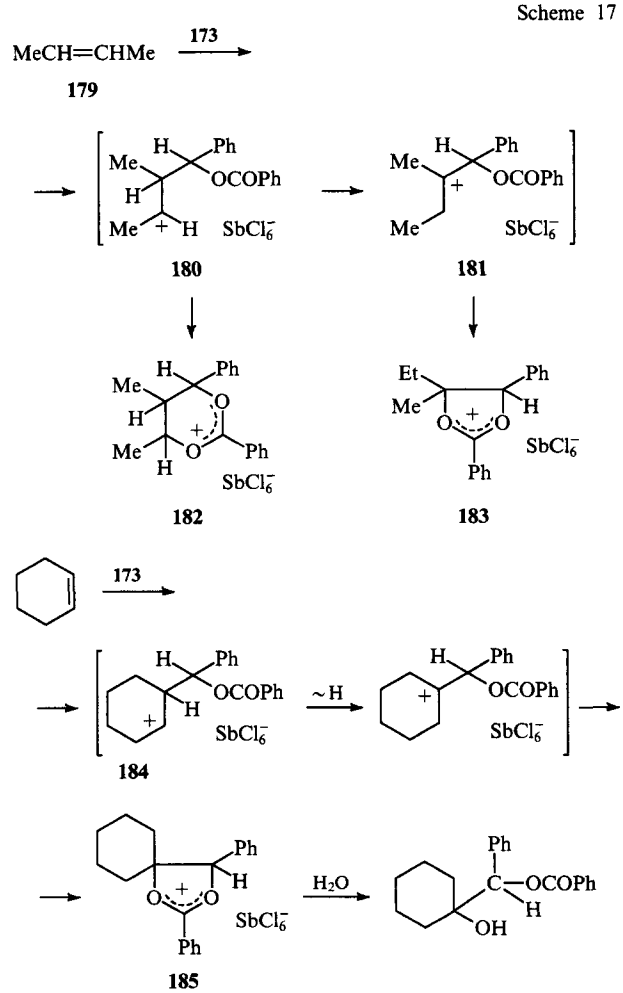
Hydrolysis of 1,3-dioxanylium salts **175** readily yields 1,3-diols with a branched skeleton.[188] Correspondingly, the salts **177** can be precursors of 1,2,3-triol derivatives.

The interaction of the carboxonium salt **173** with 2-butene **179** leads to a separable mixture of the isomers **182** and **183** in a 6:1 molar ratio. It is obvious that cyclisation of the secondary cationoid intermediate **180** is accompanied by partial isomerisation of the latter to the more stable tertiary cation **181**.[183] However, cyclohexene reacts with the salt **173** to give only the 1,3-dioxolanylium derivative **185**. Apparently, immediate cyclisation in the less flexible structure **184** is difficult (Scheme 17).[183]

A contradiction is evident in the above cycloaddition processes. On the one hand, no five-membered heterocycles **178** arise in the reaction of the enol acylates **60** and **64** with the salt **173** by the pathway described in Section III. Cyclisation through one of the two acyloxy groups in the intermediate **176** results only in the 1,3-dioxanylium salts **177**, which supports the concerted 1,4-addition of the cation **173** to the C=C double bond. On the other hand, the addition to cyclohexene has an obviously stepwise mechanism.

As shown by ^{1}H NMR spectroscopy,[188,189] the concerted and stepwise cycloaddition mechanisms can operate simultaneously, and the structure of the end-products is determined by the configuration of at least two transition states arising from the differing chirality of α-chlorobenzyl benzoate **172**.[188]

Scheme 17



VI. Direct *O*-acylation of aldehydes and ketones

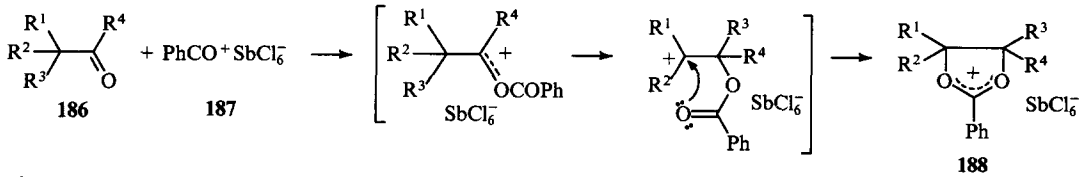
The use of acylals, enol acylates, and α-haloalkyl acylates for preparative syntheses of acyloxycarbocations suffers from several drawbacks. On the one hand, these approaches are in essence 'two steps forward and one step back' because carbonyl compounds acylated under acid catalytic conditions are common starting materials in all these reactions. On the other hand, only aldehydes can be employed successfully, since ketones usually do not form stable acylals and α-haloesters.

Therefore, attempts were made to perform the above syntheses by obtaining the required acyloxycarbocations directly from aldehydes and ketones by path *e* (see Scheme 15). To solve this problem, some requirements had to be fulfilled. First, it was necessary to exclude from the reaction mixtures both any 'external' nucleophiles, such as halide, acylate, and hydroxide anions to avoid the formation of the adducts **1** or **2**, and any bases to prevent the deprotonation of the acyloxycarbocations to give enol acylates or the fragmentation of the former with loss of an acyl cation. Obviously, the presence of protons as competing electrophiles is also undesirable.

All of these requirements can be satisfied by employing cationoid complexes, namely, acylium salts that have recently found extensive use for the controlled and directed functionalisation of unsaturated compounds under Ad_E reaction conditions.[190–192] The benzoyl and *tert*-butyl hexachloroantimonates (see Schemes 7 and 9) can be used as such cationoid complexes.

The interaction of a series of aldehydes and ketones **186** with benzoyl hexachloroantimonate **187** gave the 1,3-dioxolanylium salts **188** in 32%–86% yields.[193–195] It was found that nitromethane is the optimum solvent for these processes as it can

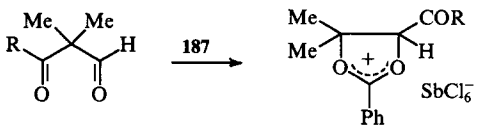
Scheme 18



(15)

186 187 188

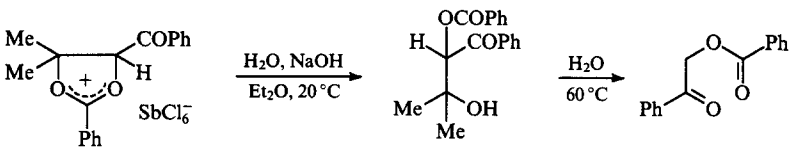
R^1, R^2 = Me, Ph, $PhCH_2$; R^3 = H, Me, Ph, $PhCH_2$; R^4 = H, Me, Et, Pr^i, Ph.



(16)

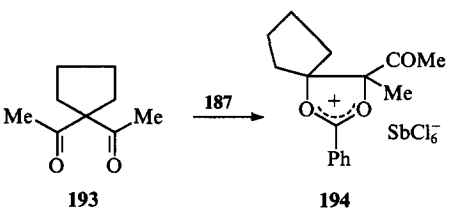
189 190

R = Me, Ph.



(17)

190a 191 192



(18)

193 194

effectively stabilise the cationoid intermediates.[194] The acylation of the ketoaldehydes **189** under the same conditions gave the hitherto unknown 4-acyl-1,3-dioxolanylium salts **190**. Hydrolysis of the salt **190a** yielded the polyfunctional compounds **191** and **192**.[196] 1,3-Diketone **193** behaves similarly (Scheme 18).[196]

Studies of the structures of the products of these reactions, **190** and **194**, and compositions of the reaction mixtures [Eqns (16) and (18)] showed that these processes involve 1,2-acyl migrations.[196] It should be noted that 1,2-shifts of acyl groups between carbon atoms in cations are very rare and have been studied only in the ketoxirane series.[197–200] However, the isomerisation of the acyloxycarbocations already mentioned in Sections V and VI [Eqns (14)–(16) and (18); Scheme 9] is worthy of particular consideration.

Sextet rearrangements so typical of carbenium ions[94,201] are not in any way characteristic of the carboxonium cations **169** and **170**, which arise in acid-catalysed reactions of carbonyl compounds. The Danilov aldehyde–ketone isomerisation,[202] the acyloin rearrangement,[94] as well as the dienone–phenol rearrangement[12] are perhaps the only ones known. Therefore, the isomerisation discovered in reactions involving acyloxycarbocations at once attracted attention. The isomerisation is, in essence, the transformation of carbonyl compounds into 1,2-diols, i.e. is the reverse of the pinacol (diol–ketone) rearrangement; hence it was described as a retropinacol rearrangement. This term is about 90 years old and is most frequently used for the conversion of pinacol into tetramethylethene. However, this conversion is in fact not a retro-reaction relative to the pinacol rearrangement. This fact has been repeatedly noted, and it was even proposed to exclude altogether this inappropriate term.[203]

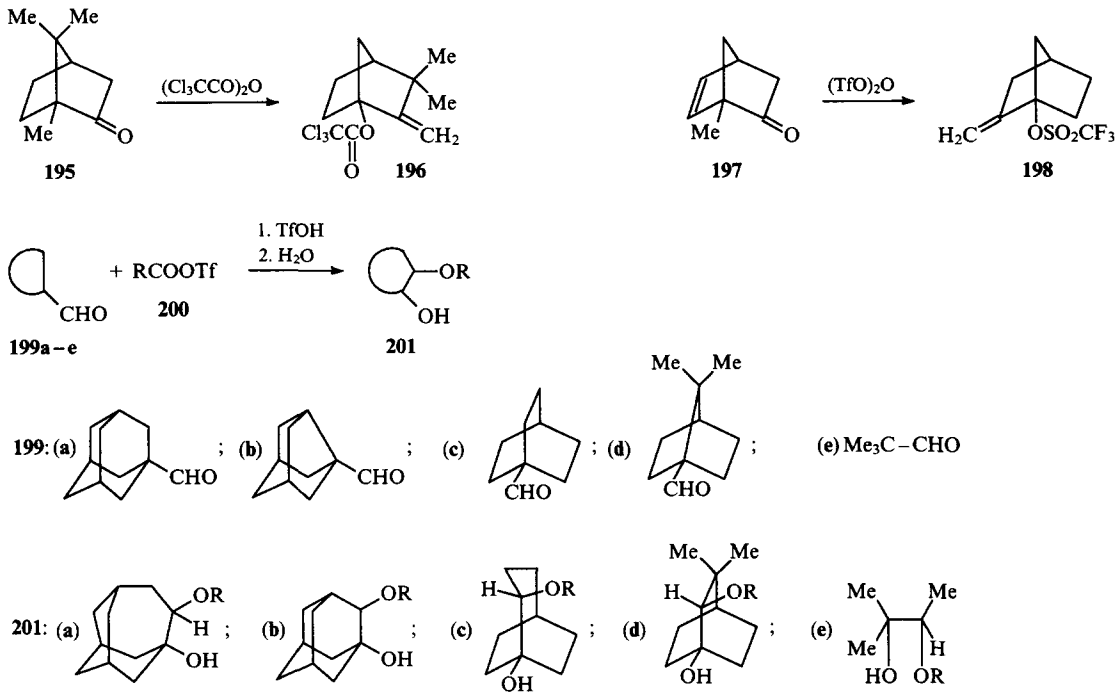
The discovery of a reaction actually corresponding to this concept required reasoned criteria to determine the place of the process among other rearrangements. Structural, functional, and redox features were proposed for this purpose, according to which this conversion of carbonyl compounds is fully the reverse of the pinacol rearrangement.[194,195,204–206]

A few further examples of the retropinacol rearrangement, also proceeding upon acylation of carbonyl compounds, have been described in the literature. The action of trichloroacetic anhydride on camphor **195**[33] and of trifluoromethanesulfonic anhydride on 1-methylnorborn-5-en-2-one **197**[170] leads to the allyl alcohol derivatives **196** and **198**. These reactions are the reverse of the second variant of the pinacol rearrangement, viz. the L'vov–Sheshukov reaction (conversion of allyl alcohols into aldehydes[202]). The acylation of the aldehydes **199** by the acyl triflates **200** also occurs through the retropinacol rearrangement to give the 1,2-diols **201**.[207] An analogous transformation of the aldehyde **199d** by treatment with benzoyl chloride in the presence of $AlCl_3$ was recently described.[208] Pinacolone **202** undergoes a rearrangement on treatment with SO_3 (Scheme 19).[209]

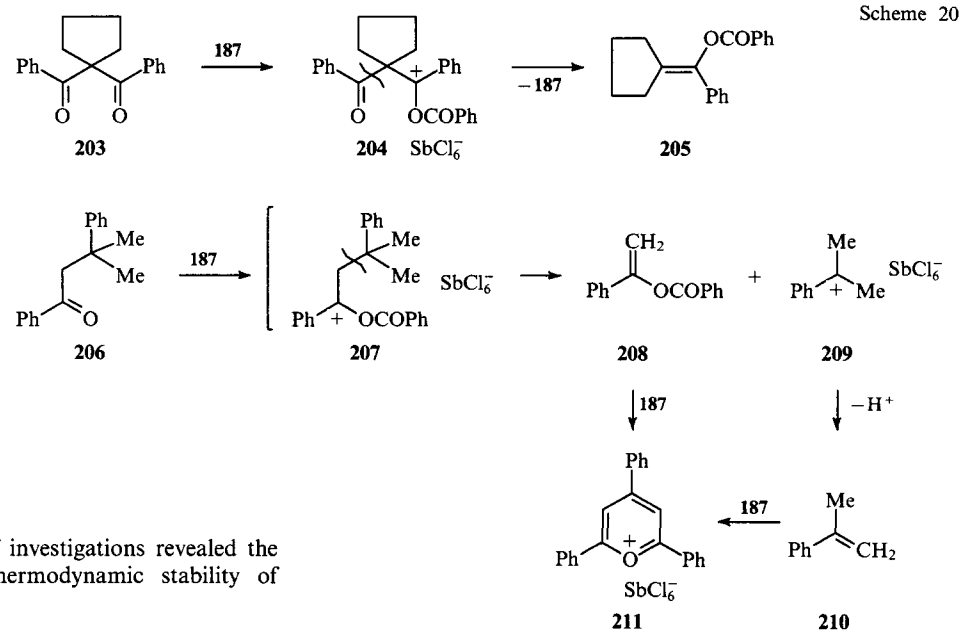
All these reactions are possible owing to the high energy of the acyloxycarbenium intermediates. According to quantum chemical calculations, the energy of the latter is almost equal to that of tertiary carbenium ions [ΔH_f (**166**) = 94.8 kcal mol^{-1}; ΔH_f (**167**) = 97.2 kcal mol^{-1}].[210]

Such a low stability of the acyloxycarbenium ions **171** relative to the carboxonium ions **169** and **170** permits other conversions that are also unusual for carbonyl compounds. Fragmentation of the cationoid intermediate with cleavage of the C–C bond can occur under conditions complicating the rearrangement. Thus, not migration but loss of the benzoyl group in the intermediate **204** takes place upon the benzoylation of 1,1-dibenzoylcyclopentane **203**.[196] Under the same conditions, the β-branched ketone **206** gives the acyloxycarbocation **207**, which is incapable of rearrangement (which would result in a less stable secondary carbocation) and therefore undergoes fragmentation. *C*-Acylation of its products **208–210** gives the pyrylium salt **211**[196] (Scheme 20).

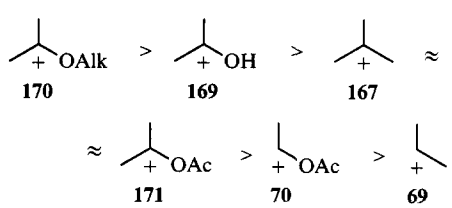
Scheme 19



Scheme 20

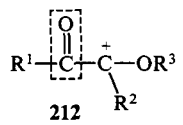


Information from this series of investigations revealed the following series based on the thermodynamic stability of cations.[104]



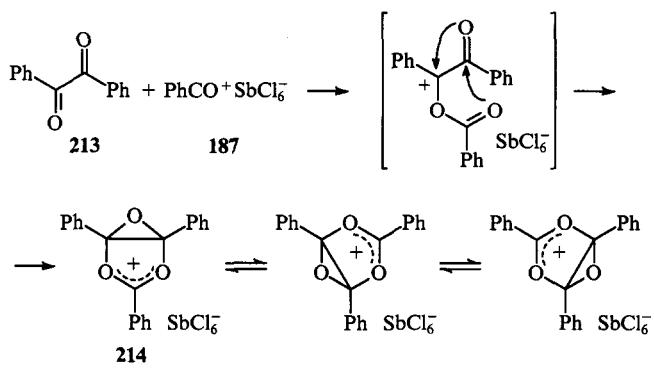
Thus, substitution of a hydroxy- or alkoxy-group at the carbenium centre by an acyloxy group destabilises the carbocation and thereby increases the reaction potentialities of the latter. The term 'destabilised carbocations' that has recently appeared in the chemical literature[166,211] can be quite legitimately applied also to the cations **171**.

Still greater destabilisation of carbocations can be achieved by the 'insertion' of the electron-withdrawing carbonyl group on the other side of the carbenium centre, i.e. into the alkyl fragment of the carboxonium ion. In this way, α-ketocarbenium ions **212** can be obtained.



212

An investigation of these highly reactive species began several years ago.[212–214] Such cations can be generated by the acylation of 1,2-diketones. For example, benzil **213** reacts with benzoyl hexachloroantimonate **187** to form the 4,5-epoxy-1,3-dioxolanylium salt **214**, according to experimental results and quantum-chemical calculations.[215] The possibility of three-fold degenerate intramolecular 1,3-migration of the carbon–carbon bond was assumed.[215]



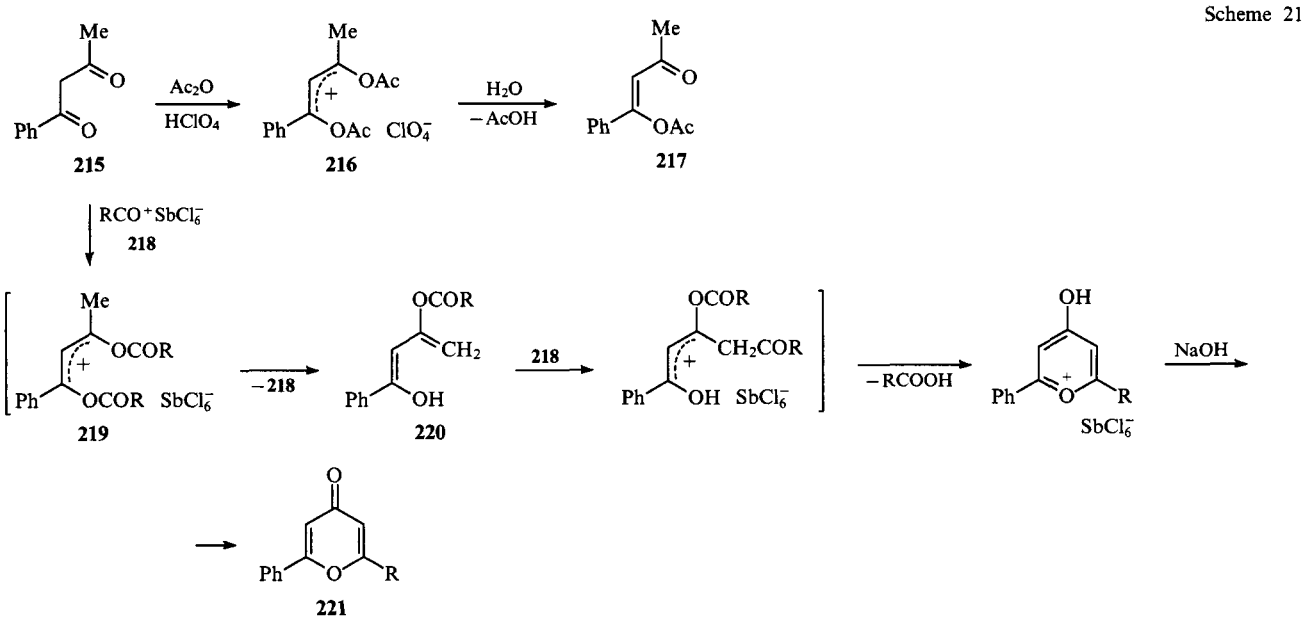
213 **187** **214**

It is known that enolisable 1,3-diketones undergo acylation at the meso-position in the presence of Lewis acids.[216] However, it was recently shown that benzoylacetone **215** reacts with the acylium salts **218** to give the 2,6-diaryl-4-pyrones **221** which are difficult to synthesise.[217] The process mechanism involves the diacyloxyallyl cations **219** which are transformed into the enol acylates **220**; these undergo *C*-acylation at the terminal methylene group. The corresponding allyl cations were isolated as the perchlorate **216**, which was then converted into the enol acetate **217** (Scheme 21).[217]

Apparently, the *C*-acylation of ethylideneacetone **222**, preceded by *O*-acylation and then deprotonation to the key intermediate **224**, should proceed via a similar mechanism.[218]

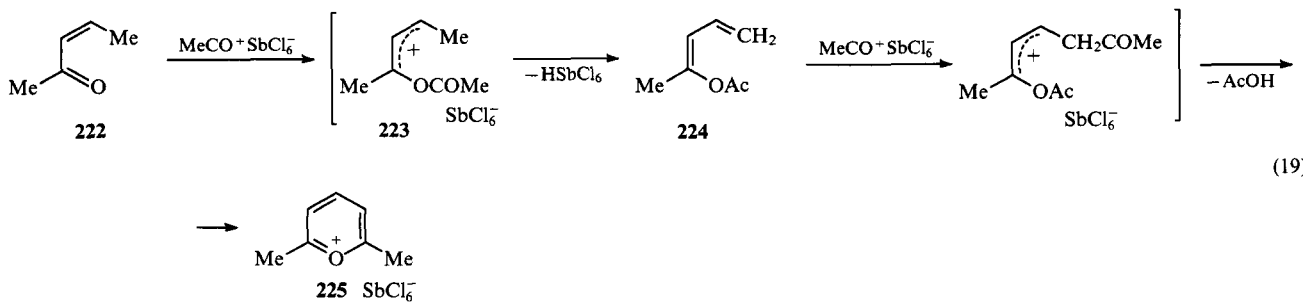
The acid-catalysed *O*-acylation in the last two examples evidently promotes the subsequent lengthening of the carbon chain and final cyclisation.

Scheme 21



215 **216** **217** **218** **219** **220** **221**

R = Ph, 4-MeC$_6$H$_4$.



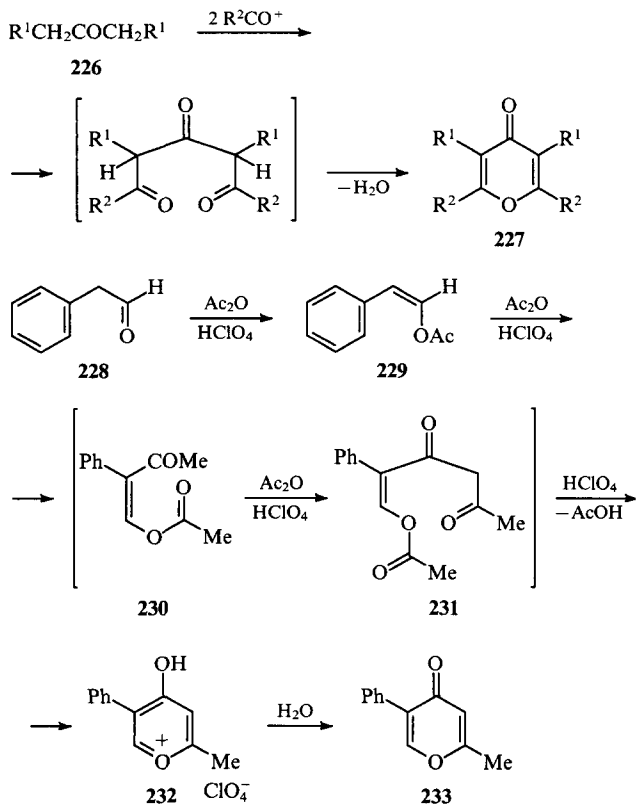
222 **223** **224** **225** $SbCl_6^-$

(19)

VII. Acid-catalysed *C*-acylation of carbonyl compounds

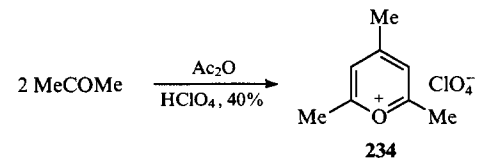
The aforementioned (see Section I) method of synthesis of 1,3-diketones by the acylation of ketones in the presence of boron trifluoride[6] has never been widely used. This was prevented by various side reactions (acylation of diketones, see Section VI) as well as the successful development of alternative approaches using fixed enolic derivatives of ketones, particularly silyl enol ethers (see, for example, Tirpak and Rathke[219] and a review[220]). On the other hand, these side reactions were the basis of many one-pot syntheses of oxygen-containing heterocyclic compounds. These syntheses involve the repeated acylation of the starting carbonyl compounds and intermediates, and are in essence chains of consecutive conversions of cationoid (or similar) structures, terminated by cyclisations to highly stable heterocyclic cations.

Syntheses of the 4-pyrones **227** by the acylation of acetone and its symmetrical homologues **226** have been reported. In these processes, carboxylic acids or their anhydrides in the presence of polyphosphoric acid[221] or acetyl chloride with $AlCl_3$ [222] were used as acylating agents. Repeated acylation of phenylethanol **228** gives the unsymmetrical 4-pyrones **233**.[223] This reaction involves successive lengthening of the carbon chain via the intermediates **230** and **231**, which are represented as uncharged species but can hardly remain uncharged under these reaction conditions.

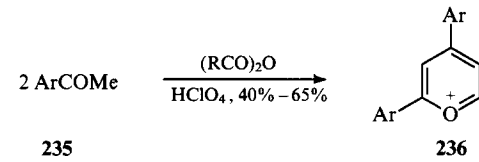


However, pyrylium salts (e.g. **225** and **232**) occupy a dominant position among the heterocyclic compounds discussed. Practically all the information concerning these compounds is concentrated in two comprehensive reviews[224,225] and in several papers.[91,174,226] Therefore, the methods of synthesis of pyrylium salts by the acylation of carbonyl compounds will be outlined only briefly in the present review.

It turned out that the mixture of acetic anhydride with 70% perchloric acid was the most suitable acylating agent for the synthesis of pyrylium salts.[226] This mixture converts acetone into 2,4,6-trimethylpyrylium perchlorate **234**;[227] unsymmetrical 6-alkyl-2,4-diarylpyrylium salts **236** were obtained from the aryl methyl ketones **235** under the same conditions.[174]

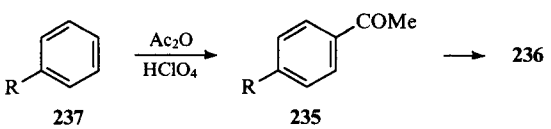


(20)

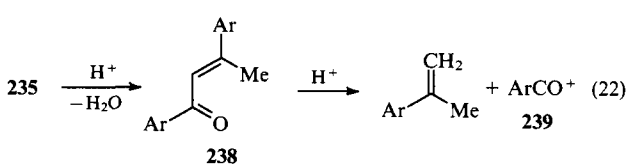


(21)

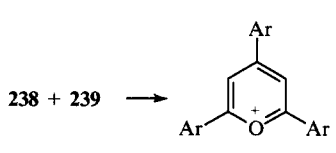
Noteworthy modifications of the latter process are acylation of aromatic compounds **237** having electron-donating substituents and protonation of the aryl methyl ketones **235** with strong inorganic acids.[224] In the former case, the initial Friedel–Crafts ring *C*-acylation to the ketone **235** is followed by its reaction according to Eqn (21). In the latter case, the interaction involves self-condensation of the ketone **235** to the dypnone **238**, which is partially deacylated by the acid [Eqn (22)].[224,228] It should be mentioned that this reaction [Eqn (22)] is of a rather theoretical interest because abundant charring takes place, whereas the yields of the salts **240** do not exceed 12%–15%.



R = Me, OAlk.



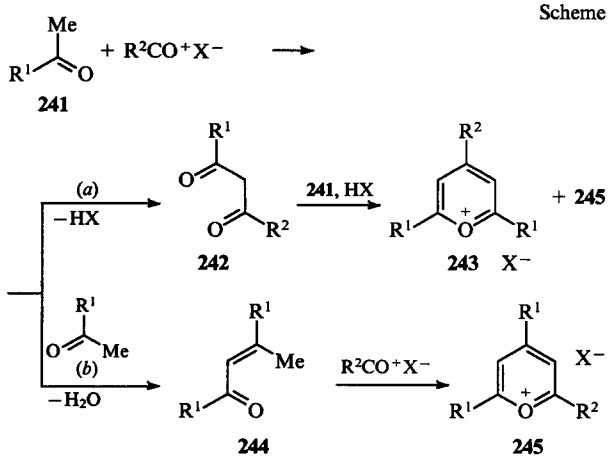
(22)



Ar = Ph, 4-$MeOC_6H_4$, 4-BrC_6H_4.

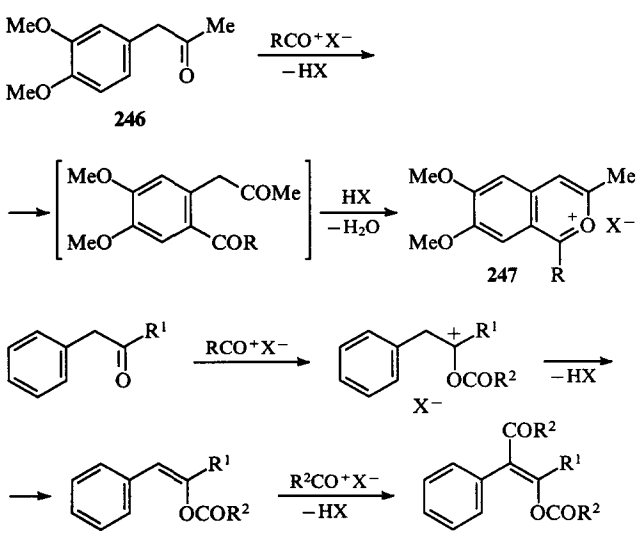
Until recently, there were no commonly accepted opinions concerning the pathway of the methyl ketone acylation [Eqns (20) and (21)]. Arguments have been put forward in the literature both in favour of the initial *C*-acylation of the starting ketones **241** to give the 1,3-diketones **242**, which subsequently react with a second molecule of the ketone **241** (pathway *a*), and in favour of the preliminary crotonic condensation of the ketones **241** to give the α,β-unsaturated ketones **244**, which then undergo *C*-acylation (pathway *b*).[224] Recently, investigations showed that condensations of the unsymmetrical 1,3-diketones **242** ($R^1 \neq R^2$) with methyl ketones **241** always lead to mixtures of isomeric pyrylium salts **243** and **245**, while acylation of the ketones **241** gives only the asymmetric isomers **236** and **245**.[229] Hence, it was concluded that the latter reaction occurs by pathway *b* (Scheme 22).

Scheme 22

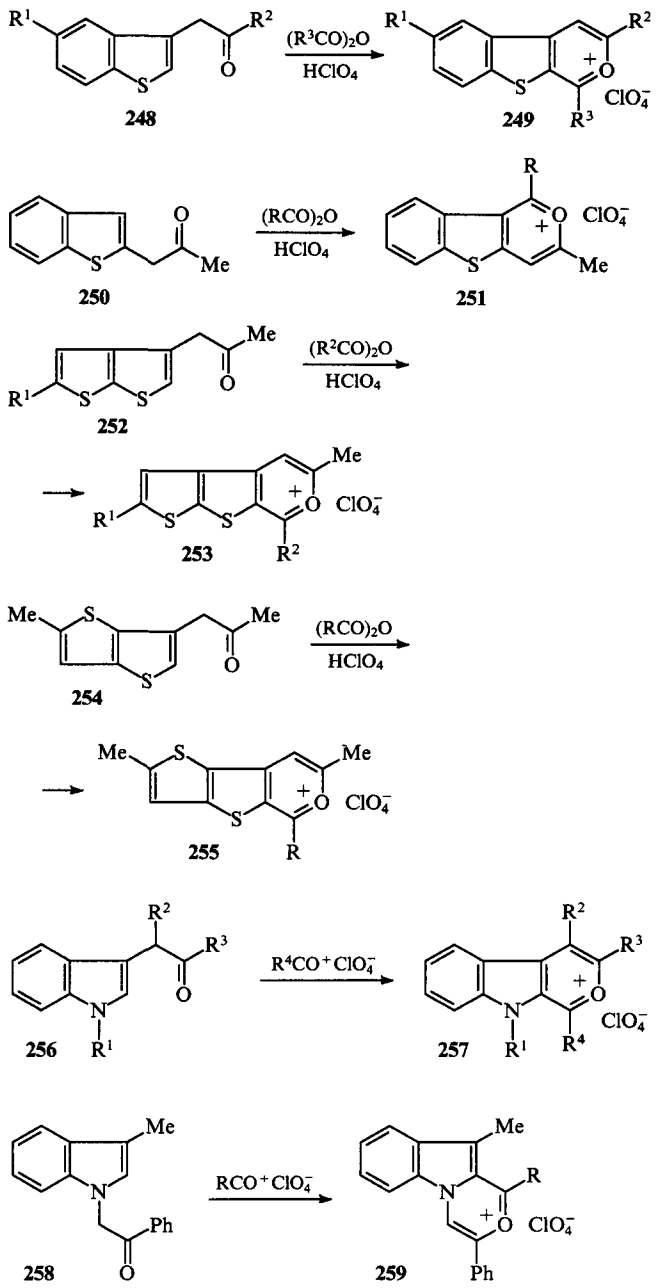


The acylation of the α, β-unsaturated ketones **244** represented by Scheme 22 is one more widely used method for synthesising pyrylium salts,[224] particularly when salts **245** containing definite substituents at positions 2 and 4 are required. The use of dypnone [1,3-diphenyl-2-buten-1-one (Ed.)] and mesityl oxide has been reported most frequently.[224] Evidently, the process occurs by Eqn (19) including isomerisation to a β,γ-unsaturated ketone (or the corresponding enol acylate **224**).[218]

Finally, one more reaction, very important in pyrylium chemistry, cannot be disregarded, namely, the acylation of the benzyl ketones **246** to give the 2-benzopyrylium salts **12** and **247**.[230] These salts can be readily transformed into isoquinolines, including natural alkaloids which are difficult to obtain. The key step of this process is acylation of the aromatic ring which must contain electron-donating substituents (this is possibly the only preparative restriction of this method). In the absence of such substituents, competitive *O*-acylation prevails, which prevents the formation of the target products **247**.



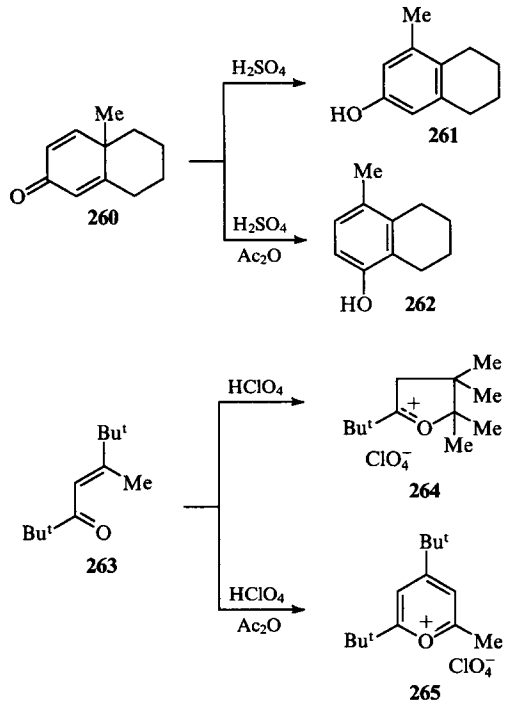
The benzyl ketones **246** can be regarded as fixed β,γ-unsaturated ketones undergoing *C*-acylation at the γ-position.[231,232] The reaction considered was discovered in 1966[233] and was later extended to various heterocyclic ketones (**248**, **250**, **252**, **254**, and **256**). As a result, fused polyheterocyclic derivatives such as the thienopyrylium salts **249**,[234] **251**,[235] **253**, and **255**,[236] as well as the indolopyrylium salts **257**[237] were obtained. These salts can be converted into the corresponding pyridine derivatives, particularly, β-carbolines.[237] The novel indolo-1,4-oxazinium salts **259** were prepared by the acylation of 1-phenacyl-3-methylindole **258**.[238]



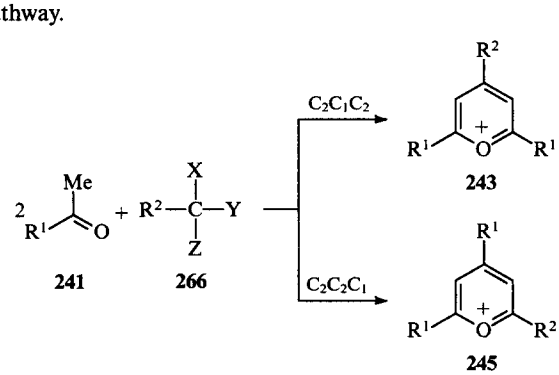
The products **259** are interesting as precursors of indolopyrazines used as phychotropic preparations and antibiotics.[238]

VIII. Electrophilic catalysis by acyl cations

While investigating the acid-catalysed reactions of carbonyl compounds, it was observed long ago that the addition of acetic anhydride to an acidic reaction medium can change the direction of such processes. Thus, isomerisation of dienone **260** occurs by the usual mechanism involving the dienone-phenol rearrangement with migration of the methyl group to form the phenol **261**, but the anomalous product **262** was obtained in the presence of Ac_2O.[239,240] Protonation of the α,β-unsaturated ketone **263** gives the dihydrofurylium salt **264**,[241] while the addition of acetic anhydride leads to the pyrylium salt **265**.[242]

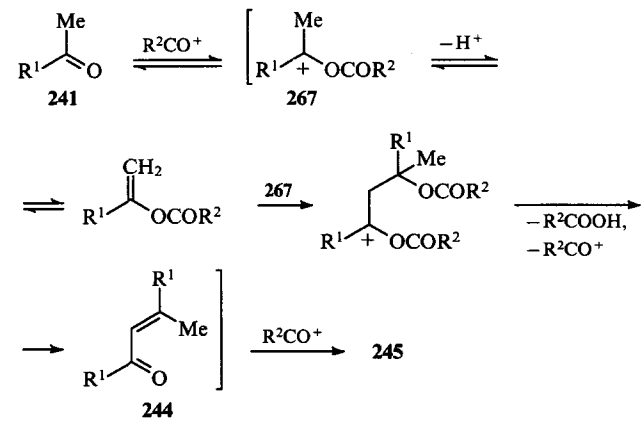


One of the three-component syntheses of pyrylium salts presented above [see Eqns (20) and (21) and Scheme 22, pathway *b*] involves the interaction of the methyl ketone **241** (the C_2-component) with the precursor of the acyl cation (the C_1-component). According to the formation pattern of the five-carbon chain of the ring, this synthetic method can be represented as $C_2C_2C_1$.[224,225] Other precursors of carboxonium ions can be also employed as C_2-components: aromatic aldehydes **266** (X = H, Y + Z = O, hydroxycarbocations), acetals **266** (X = H, Y = Z = OAlk, alkoxycarbocations), orthoesters **266** (X = Y = Z = OAlk, dialkoxycarbocations).[224,225] However, these processes give symmetrical pyrylium salts **243** via the $C_2C_1C_2$ pathway.

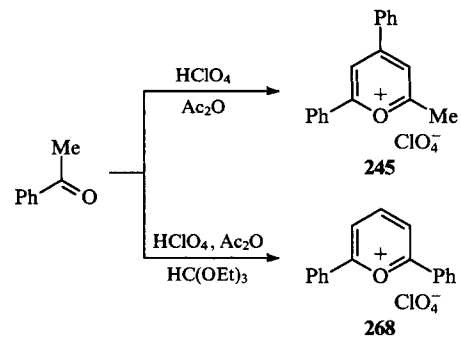


It was found that the reactions of the methyl ketones **241** with analogues of the above C_1-components, e.g. α-chloroalkyl acylates **266** (X = H, Y = Cl, Z = OAc), chloromethyl methyl ether **266** (R^2 = X = H, Y = Cl, Z = OMe), as well as alkyl α,α-dichloromethyl ethers **266** (R^2 = H, X = Y = Cl, Z = OAlk), preferentially follow the $C_2C_2C_1$ path.[224,225,243] This fact evidently implies initial fast self-condensation of the methyl ketone **241** to the α,β-unsaturated ketone **244** (Scheme 22). It should be noted that reactions using these α-chloroethers and α-chloroesters were carried out in AcOH. It was found that the formation of unsymmetrical pyrylium salts **245** predominates when acylium ions are present in the reaction mixture or conditions for the generation of these ions in situ are created.[243]

Hence acyl cations are the factor that promotes the rapid self-condensation of the methyl ketones **241** in accordance with the assumed scheme.[243]

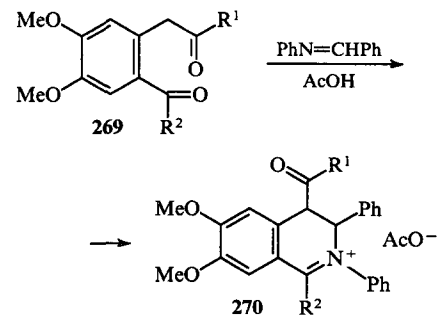


If the *O*-acylation of the keto-component **241** is suppressed, the reaction follows the $C_2C_1C_2$ path. Thus, the addition of ethyl orthoformate (which irreversibly binds the acyl cations to form the corresponding ester and to liberate diethoxycarbenium ions) to the same mixture, 'acetophenone + acetic anhydride + perchloric acid', leads to 2,6-diphenylpyrylium perchlorate (**268**) in high yield.[244]

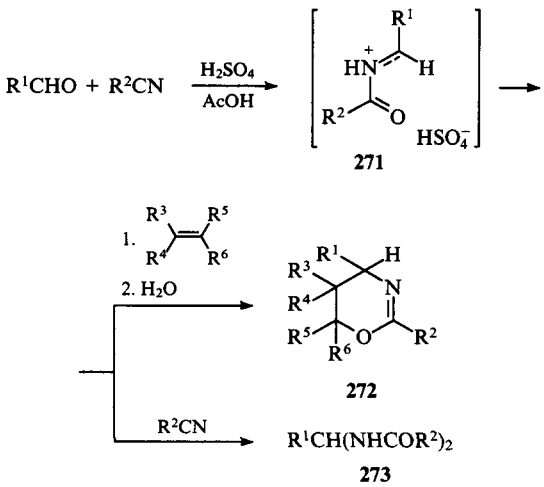


As shown recently, the 1,5-dicarbonyl compounds **269** react with azomethines in AcOH to give the dihydroisoquinolines **270**; this reaction does not occur either in acetonitrile or in *N,N*-dimethylformamide.[245]

Although acyl cations do in fact participate in the conversions of carbonyl compounds considered, they are included among the end-products only provided that the process involves *C*-acylation. In other words, here we deal with electrophilic catalysis by acylium ions in reactions of carbonyl compounds with weak nucleophiles; such catalysis involves the conversion of an aldehyde or ketone into the highly reactive acyloxycarbenium ions **267** (see Section V).

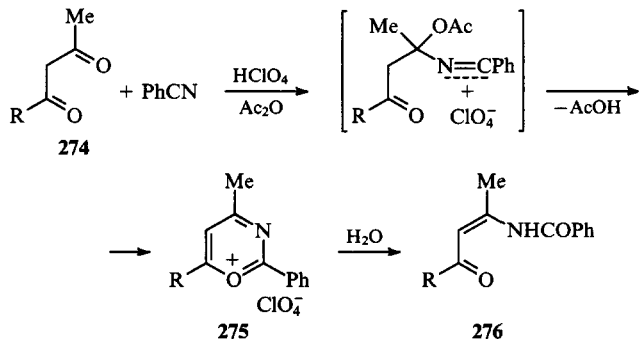


The most typical example of the application of catalysis by acyl cations is the interaction between carbonyl compounds and nitriles. The syntheses of 1,3-oxazine derivatives **272** from aldehydes, nitriles and alkenes are usually carried out with a mixture of sulfuric and acetic acids, although the role of the latter in the reaction has not been clarified.[246–248]



In the absence of an alkane component, the *N*-acyliminium intermediates **271** combine with another nitrile molecule to give the geminal bis-amides **273**.[249]

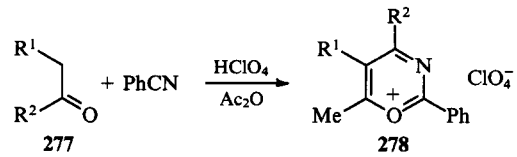
These reactions are well-known in the aldehyde series; however, attempts to extend them to ketones have failed until recently.[249,250] This problem was solved using $HClO_4$ + Ac_2O as the acylating mixture. The 1,3-diketones **274** readily react with benzonitrile in the presence of this mixture to yield the little-known 3-azapyrylium salts **275**, the hydrolysis of which gives the β-acylaminovinyl ketones **276**.[251]



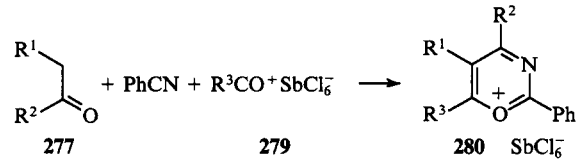
R = Me, Ph.

Under the same conditions, the alkyl aryl ketones **277** give the 3-azapyrylium salts **278**, which are structurally isomeric with compounds **275**.[252] These reactions do not occur in the absence of acetic anhydride (when the nitrile is absent, the reaction follows Schemes 21 and 22).

The large series of 3-azapyrylium salts **280** were obtained by treating mixtures of benzonitrile and the ketones **277** with the acylium salts **279**.[253]



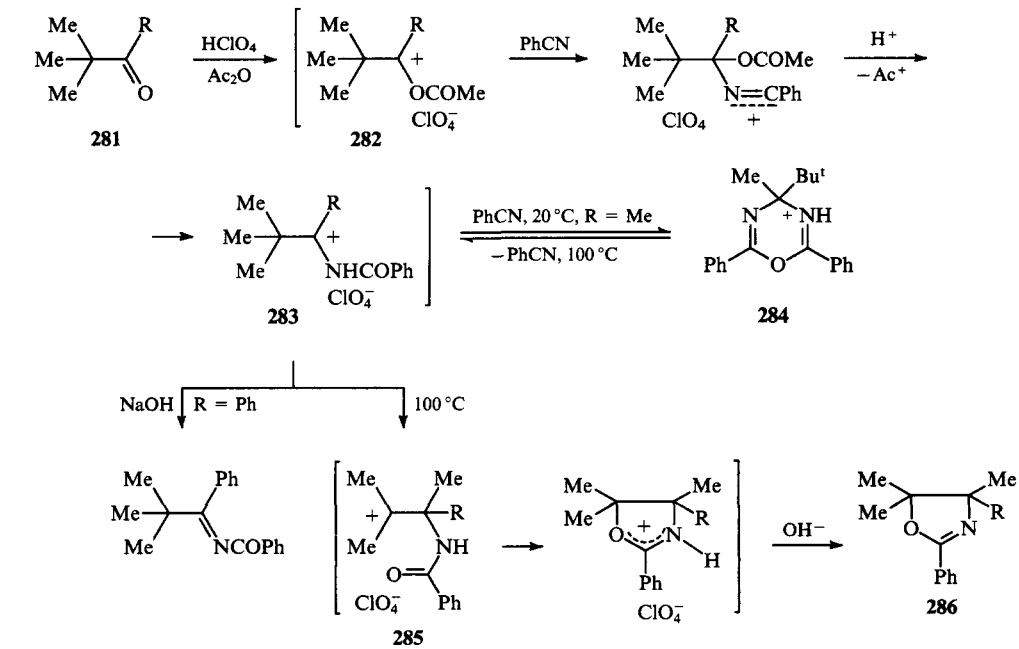
R^1 = H, Me; R^2 = Ph, 4-MeC_6H_4.



R^1 = Me, Et, Bu^t, Ph; R^2 = H, Me; R^1+R^2 = $-(CH_2)_4-$; R^3 = Me, Et.

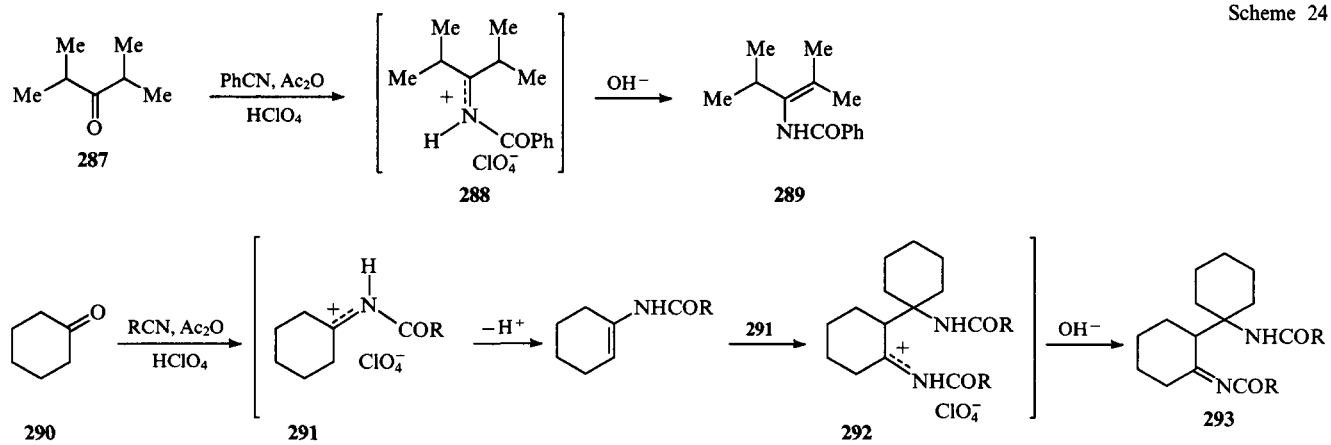
The transformations of a series of aliphatic ketones under the conditions of electrophilic catalysis by acyl cations were described in Ref. 254. Pinacolone **281** (R = Me) combines with benzonitrile in the presence of the $HClO_4$ + Ac_2O mixture to furnish 1,3,5-oxadiazinium perchlorate **284**, which is decomposed on heating to form the *N*-acyliminium intermediate **283**. The latter, which is a heteroanalogue of **282**, can isomerise to the tertiary carbocation **285**. This process is another variant of the retropinacol rearrangement (see Section VI), which is the reverse of the Tiffeneau and MacKenzie reactions[254] (it should be noted that the 2-oxazolines **286** are direct derivatives of 1,2-aminoalcohols). Pivalophenone **281** (R = Ph) behaves similarly. Its transformations also occur in the presence of Ac_2O, but the acyl fragment is not included in the product structure (Scheme 23).

Scheme 23

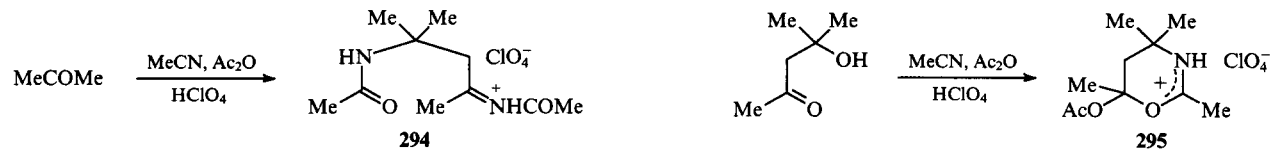


R = Me, Ph.

Scheme 24

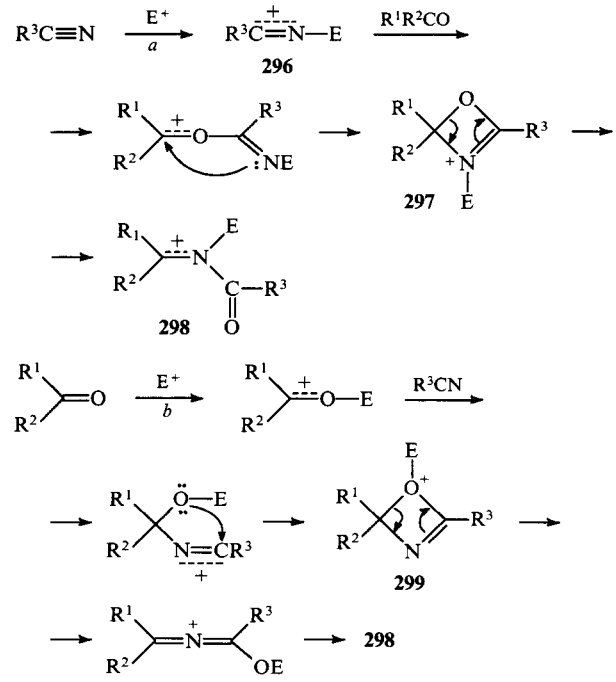


R = Me, Ph.



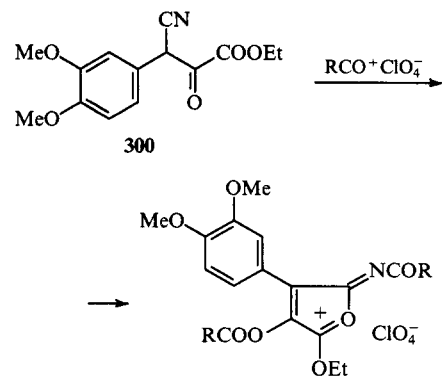
The structure of the products obtained from diisopropyl ketone **287** and cyclohexanone **290** under the same conditions suggest that the *N*-acyliminium ions **288** and **291** are formed as intermediates.[254] The hypothesis that the aldol condensation of the ketone may initially occur has been disproved, for example, by obtaining different products (**294** and **295**) from acetone and diacetone alcohol[254] (Scheme 24).

As shown by experiment and quantum-chemical calculations, the interaction of carbonyl compounds with nitriles occurs by different pathways depending on whether the process is catalysed by protic acids or acylium ions.[255–258] In the former case, the nitrile component undergoes electrophilic activation (protonation, pathway *a*, E = H). The nitrilium cation **296** formed attacks a molecule of the carbonyl compound. On the other hand, in the presence of acylium ions, the carbonyl component undergoes electrophilic activation (pathway *b*, E = Ac). Both pathways lead to the *N*-acyliminium ions **298** via the intermediates **297** and **299**.



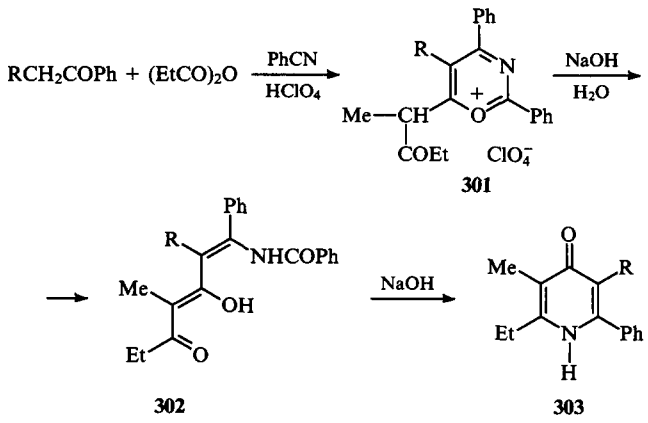
While pathway *b* is analogous to the Ritter reaction (but fundamentally differs from it in a number of features[255,257]), the interaction following pathway *a* was unknown until recently. Only recently has it been found that the nitrilium salts **296** (E = Alk) prepared beforehand (they are, incidentally, heteroanalogues of acylium ions) readily react with carbonyl compounds to give the *N*-acyliminium ions **298** (E = Alk).[259–261] Some aspects of the interaction of aldehydes and ketones with nitriles were thoroughly discussed in a recent review.[262]

Remarkable processes take place in the acylation of compounds containing both a keto-group and a nitrile moiety (e.g. compound **300**).[263–266]

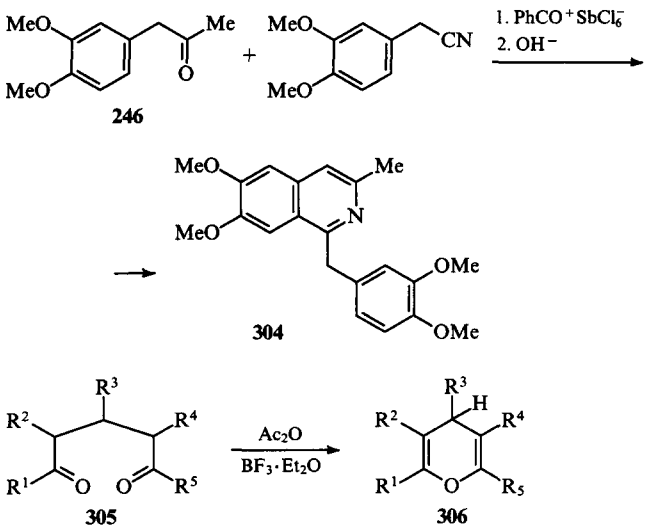


R = Me, Et.

Acylation of propiophenone or butyrophenone with propionic anhydride in benzonitrile leads to the 6-acylmethyl-3-azapyrylium salts **301**, which can be converted into derivatives of the 1,3,5-triketones **302**, which are difficult to synthesise, and into the pyridones **303**.[267]



Electrophilic catalysis by acylium ions was found to be the most effective means for the transformation of the benzyl ketone **246** into a natural alkaloid of the isoquinoline series **304**,[268] as well as for the cyclisation of the polysubstituted 1,5-diketones **305** to the pyrans **306**.[269] These reactions did not occur in the presence of other acid catalysts.



R^1, R^2 = Ar, cyclo-Alk;

R^3 = H, Alk, Ar; R^4 = H, R^5 = Ph.

* * *

The examples presented above illustrate the wide scope of the synthetic application of acyl cations as catalysts in condensations and cylisations of carbonyl substrates. Moreover, going beyond the limits of this review, it should be mentioned that the applicability of the above reactions can be considerably extended using derivatives of carbonyl compounds. Some of them, such as acylals, α-haloalkyl acylates, enol acylates and acetals, have been described in this review. Vinyl halides and ethynes also belong to this series. For example, the reactions of acylium salts with *tert*-butylethyne and the chloroalkenes $R^1-CH=C(Cl)R^2$ present one more example of the retropinacol rearrangement.[270,271] The same rearrangement, i.e. conversion of ketones into vicinal chloroamides, occurs via highly reactive chlorocarbenium ions in the interaction of geminal dichlorohydrocarbons with nitriles.[272] β,γ-Unsaturated chloroketones, allenic 1,5-diketones, and 4-chloropyrylium salts can be obtained by the acylation of vinyl chlorides.[271,273] Vinyl chlorides react with nitriles to give pyrimidines in the presence of trifluoromethanesulfonic acid[274] or 3-azapyrylium hexachloroantimonates in the presence of acylium salts.[253] Finally, pyrimidines and 3-azapyrylium salts can be prepared by the interaction of vinyl chlorides with nitrilium salts.[275]

Thus, the acid-catalysed acylation of carbonyl compounds is not only an alternative to traditional methods using base catalysis but is also a new approach to the activation of aldehydes and ketones in reactions with various carbo- and hetero-nucleophiles. Previously unknown reactions of carbonyl compounds, rearrangements, and fundamentally new methods of synthesis of valuable oxygen- and nitrogen-containing heterocyclic and polyfunctional compounds have already been found in this promising synthetic field.

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