



Reactions of Some Nucleophiles with Pyrylium Salts

FARIBA HEIDARIZADEH* and FATEMEH ABADAST

Department of Chemistry, Faculty of Science, Shahid Chamran University, Ahvaz (Iran).

*Corresponding author: E-mail: heidarizadeh@scu.ac.ir

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ABSTRACT

In this review, we have reported the reaction of substituted pyrylium salts with some of the most important nucleophilic reagents, such as carbon nucleophiles (C-Nucleophiles) and nitrogen nucleophiles (N-Nucleophiles). We also study characteristics and properties of the parent systems.

Key words: Pyrylium salt, Pyridine, Cyanodienone, Nucleophilic Reaction.

INTRODUCTION

Pyrylium salts represent, more than heterocyclic system, a nodal point for many synthetic routes, they can function as intermediates for an extraordinary variety of syntheses¹. They owe their key role both to a high formation tendency²⁻³ and to reactivity toward nucleophiles⁴⁻⁵. These compounds as well as benzo derivatives of these systems appear in many natural products, thus the medicinal and chemical significant of this class of compounds stimulated interest in the synthesis and study of their reactions. Thus, these properties led us to survey some nucleophilic reactions and properties of the parent systems. This review is limited to reactions of pyrylium salts with some C and N-Nucleophiles.

The replacement of CH in benzene by O⁺ modifies the electron distribution much more than any other common heteroatom such as CR, N, NR⁺ or than any substituent R in CR or NR⁺. Thus,

pyrylium salts give no electrophilic substitution, but only addition of nucleophiles. Since the resonance energy in pyrylium is smaller than in benzene or pyridine, unlike these ring systems, the pyrylium ring is as easily opened as it is formed.

The high electronegativity of the oxygen heteroatom leads to charge localization and to lower resonance energy than in benzene or pyridine, the conjugation energy of pyrylium is, however, high enough to make pyrylium salts stable in acid or neutral aqueous solutions (unlike simple oxonium salts), but low enough to enable pyrylium cations to react with many nucleophiles under ring opening.

Reaction of pyrylium salts with nucleophiles, as indicated in Fig. 1 by limiting structures a-d, may occur in positions 2, 4, or 6, where the positive charge appears. Most reactions occur through a primary nucleophilic attack in positions 2 or 6 (α -positions) which have the highest electron deficit (evident from ¹H- and ¹³C-NMR spectrum and from

theoretical calculations), the reaction then usually proceeds through a thermally allowed electrocyclic ring opening of the resulting α -pyran, which valence isomerizes to a 2, 4-pentadien-1-one derivative. In the case of pyrylium salts without γ -substituent or of very strong nucleophiles like Grignard reagents,

nucleophilic attack at position γ competes with attack at α - positions leading to a γ -pyran. As a bisenol ether, this 4*H*-pyran can also undergo ring opening under solvolytic conditions to stable 1, 5-pentanedione derivatives.

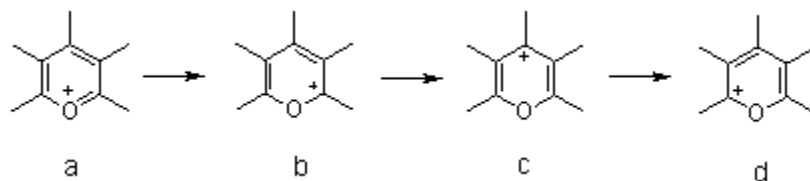
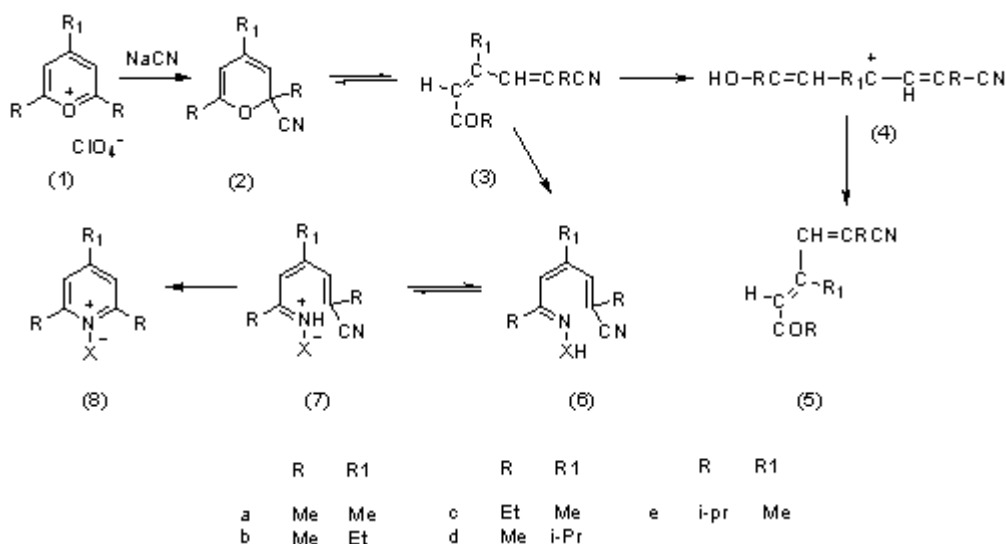


Fig. 1: Different situations to pyrylium salts attack

Reaction with C-Nucleophiles

For the first time, in 1961, A. T. Balaban and C. D. Nenitzescu,⁶ reported reaction of trialkyl pyrylium salts with cyanide ion. As shown in scheme 1, trimethylpyrylium perchlorate (1a) reacts smoothly with cold aqueous sodium cyanide, yielding $C_9H_{11}NO$, which gradually evolves hydrogen cyanide but can be distilled at reduced pressure. It readily yields carbonyl derivatives and is oxidised by

hypobromite to a crystalline acid $C_8H_9NO_2$. Whereas the ketone is resinified by hot alkali, the acid undergoes alkaline hydrolysis to a dibasic acid $C_8H_{10}O_4$. The infrared absorption spectrum of the ketone shows a carbonyl-stretching band at 1616 and a sharp nitrile band at 2216 cm^{-1} and is therefore assigned formula (3a). This accords with the usual addition of nucleophilic agents to the α -position of the pyrylium cation (Scheme 1).



Scheme 1: The preparation of pyridinium compound from the reaction of pyrylium salt with sodium cyanide

The process is depicted as involving a cyclic intermediate (2), though no experimental support has been found in the present case for tautomerism (2) \rightleftharpoons (3).

They believed ketone (3a) shows a surprisingly high basicity, it dissolves at once in concentrated acids, the solution gradually becoming pink. If the solution in concentrated hydrochloric acid is immediately diluted with water, a stable solid isomeric form of the ketone is obtained. The carbonyl derivatives of this and the acid obtained from it by hypobromite melt higher than the corresponding derivatives of the ketone (3a). They postulate a cation, for example (4a), in concentrated acids, that assumes the most stable configuration and on dilution affords the new form (5a), obtained. They postulate a *cis* \rightarrow *trans*-isomerisation on the following grounds: If the double bond next to the cyano-group were also involved, four stereoisomers should be obtained, whereas they obtained only two. The other double bond certainly has a *cis*-configuration in the original product (3).

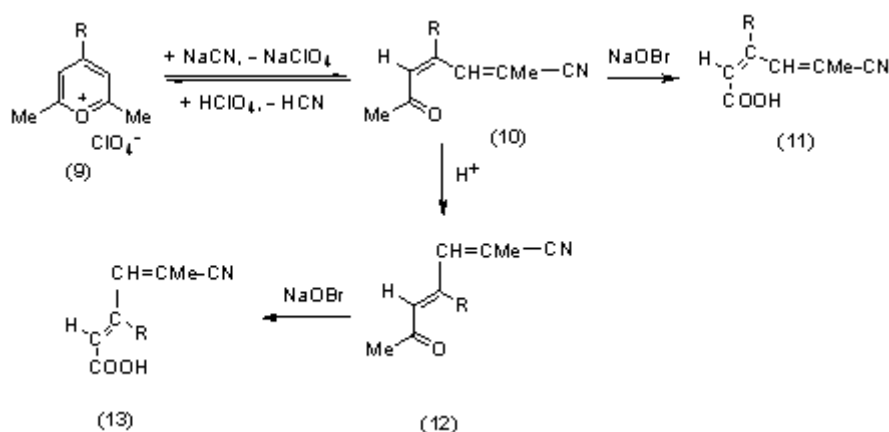
With increasing bulk of the alkyl groups, the *cis* \rightarrow *trans*-isomerisation became more difficult and it did not occur with ketone (3e). All 2,4-dinitrophenylhydrazones of the *cis*-ketones (3a-e) eliminated hydrogen cyanide with formation of higher-melting pyridinium betaines, and no such reaction was observed with any of the derivatives

of the *trans*-ketones (5).

The reaction thus involves the formation of a pyridinium compound (8) pictured as a 1,6-elimination (78).

Balaban and coworkers,⁷ in 1965, also performed reaction of substituted pyrylium salts (9) with aqueous alkali cyanides. This reaction affords 5-cyanopentadienones (2) which are oxidized by hypobromite to 5-cyano-sorbic acids (3). Configurations about the C-2, C-3 double bond are most likely to be those indicated in formulas (2) and (3) (*cis* position of the carbonyl and the CH=CMeCN groups) if ring cleavage of the cyclic starting compound takes place without isomerization.

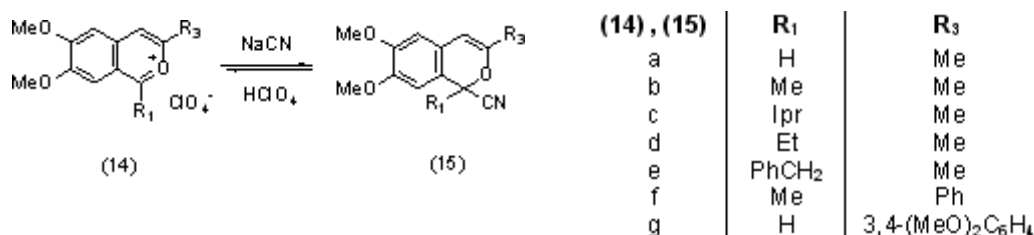
On treatment with concentrated mineral acids the 2-*cis*-5-cyanopentadienones (10) undergo two reactions. They eliminate hydrogen cyanide to re-form the initial pyrylium salt (9) and they isomerize into 2-*trans*-5-cyanopentadienones (12). These latter isomers, and their arylhydrazones, have higher melting points than the 2-*cis* isomers and, unlike them, can no longer be cyclized to pyrylium and pyridinium salts. Hypobromite oxidation of the 2-*trans*-5-cyanopentadienones (12) leads to 2-*trans*-5-cyanosorbic acids (13). No direct conversion of 2-*cis*- into 2-*trans*-5-cyanosorbic acids could be produced under mild conditions. As shown in the following discussion, hot aqueous alkali causes more profound structural changes (Scheme 2).



Scheme 2: Determination of *cis* and *trans* in the products of nucleophilic reaction of cyanide anion with pyrylium salt

In 1987, Balaban and coworkers⁸ carried out the reaction between 2-benzopyrylium salts and sodium cyanide. This reaction was stopped at the stage of the cyanide addition to the heterocycle and

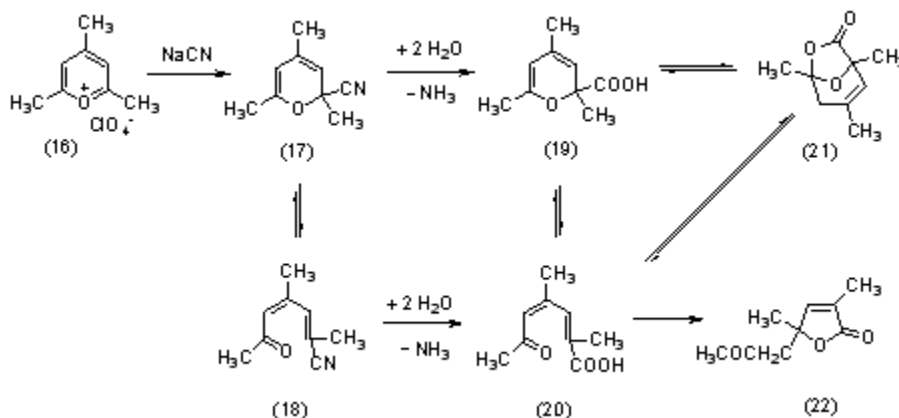
was not accompanied by ring opening. The stability of the addition products supports the nucleophilic attack to α -position with cyanoisochromenes (15a-g) as the result (Scheme 3).



Scheme 3: The reaction of 2-benzopyrylium salts with sodium cyanide

In 2003, Balaban and coworkers,⁹ obtained more details about these reactions. They perform reaction of 2,4,6-trimethylpyrylium cation (16) with sodium cyanide in water at 100°C. In a short reaction time (5 min), the bicyclic lactone (21) (1,3,5-trimethyl-6,8-dioxabicyclo[3.2.1]oct-2-en-7-one) were synthesized along with the two

stereoisomeric 4-Z-2,4-dimethyl-6-oxo-2,4-heptadienonitriles (18). On performing the same reaction at room temperature or at 0°C, no trace of compound (21) was observed by ¹H NMR: the crude reaction product contained only 4-Z-2,4-dimethyl-6-oxo-2,4-heptadienonitriles (Scheme 4).



Scheme 4: The reaction of pyrylium salts in the high temperature

They also performed hydrolysis studies of cyanodienones (18). With aqueous sodium hydroxide (molar ratio (18)/NaOH=2:1) for short reaction times (5 min) in boiling water, compound (21) was obtained along with a substantial amount of 3,5-dimethylphenol (23). On performing the same

reaction with an aqueous solution of sodium acetate at reflux for 3 h, the reaction products were the 3,5-dimethylphenol (23) and another lactonic product, 3,5-dimethyl-5-(2-oxopropyl)-5H-furan-2-one, (24) (Fig. 2).

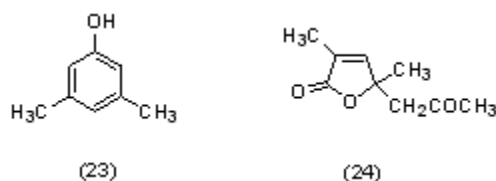


Fig. 2: Other products in high temperature from the reaction of pyrylium salt with sodium cyanide

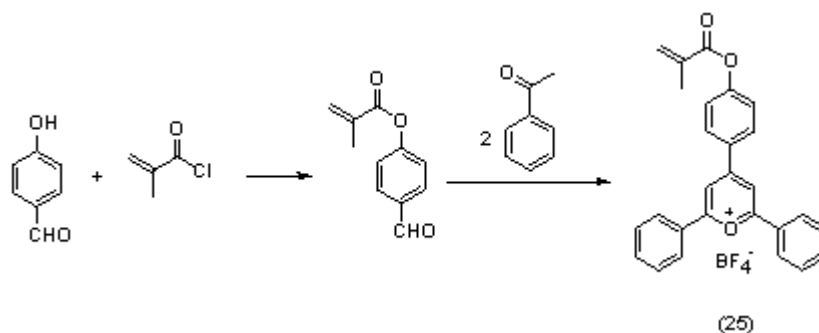
The fact that only at short reaction times needs for isolating of compound (21), suggests two facts: (i) in the reaction of pyrylium salt (16) with sodium cyanide, the elusive pyranic form (17) is the kinetically controlled product, while the isolated cyanodienone is the thermodynamically stable product, (ii) in the hydrolysis, the isomerizations (17) – (18) or (19) – (20) – (21) occurred, the compound (21) being the kinetically controlled product, while the compound (22) is the thermodynamically stable product. The reversibility of the reactions in Scheme 5 was proved by heating the bicyclic compound (21) with an aqueous solution of sodium acetate when the sole product was the lactone (22).

And finally in 2005, Garcia and coworkers,¹⁰ applied this reaction for synthesis of sensory materials for the colorimetric sensing of cyanide in water.

Cyanide is a highly toxic anion that inhibits

mitochondrial cytochrome-oxidase and hence blocks electron transport, resulting in decreasing oxidative metabolism and oxygen utilization and its determination plays an important role in environmental control.

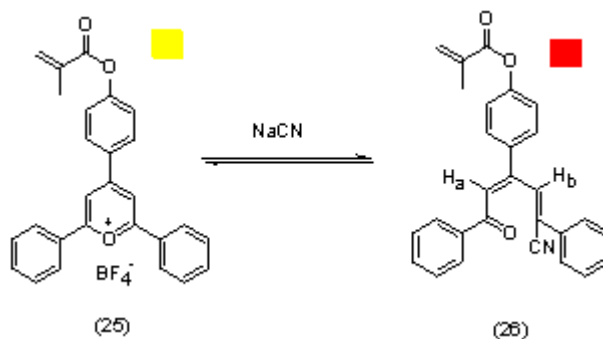
They performed reaction between cyanide and a pyrylium derivative to give the corresponding cyano-enone which could also be used as an output signal in the development of novel sensory materials. In order to incorporate the pyrylium chromophore into a polymeric matrix, the monomer (25) was synthesized by a two step reaction. In the first step, the reaction of methacryloyl chloride with 4-hydroxybenzaldehyde gave 4-formylphenyl methacrylate. The reaction of one equivalent of this compound with two equivalents of acetophenone and two equivalents of boron trifluoride diethyl etherate in 1,2-dichloroethane gave (25) as a yellow powder that was crystallized from acetic acid to yield yellow needles (Scheme 5).



Scheme 5: The synthesis of 2,4,6-triarylpyrylium salt (25)

Preliminary studies revealed that CN⁻ addition to acetonitrile solutions of (25) resulted in a remarkable colour change from yellowish to red due to the formation of the corresponding cyano-

enone derivative (26) via nucleophilic attack of the cyanide anion on the C1 carbon next to the oxygen atom in the pyrylium ring (Scheme 6). This reactivity was confirmed by NMR studies.



Scheme 6: Reactivity of monomer (25) with cyanide

For preparation of sensor films, a series of methacrylic copolymer films containing the pyrylium probe were prepared by radical copolymerization of the monomer (25), 2-ethoxyethyl methacrylate

(27), 2,3-dihydroxypropyl methacrylate¹¹ (28), small quantities of ethylene glycol dimethacrylate as cross-linking agent and 2, 2'- azobis (isobutyronitrile) (AIBN) as radical thermal initiator¹²⁻¹³ (Fig. 3).

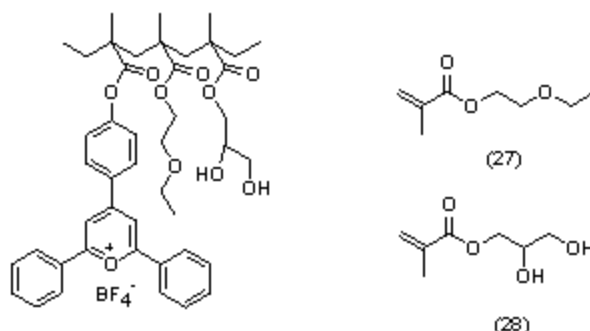


Fig. 3: Structure of the sensing films and monomers (27) and (28)

Various prepared polymers containing the pyrylium derivative are colorless or pale yellow and highly fluorescent. The addition of cyanide into the cell containing the pyrylium-doped films resulted in a change in the absorption spectra with a gradual enhancement of the 537 nm band with the cyanide concentration. In contrast, in the presence of the Cl^- , Br^- , I^- , NO_3^- , H_2PO_4^- , SO_4^{2-} and SCN^- anions, the films remained silent.¹⁴

Reaction with N-Nucleophiles:

Balaban in 1968,¹⁵ has reported the reaction of triphenylpyrylium salts with N-nucleophiles including hydroxylamine, phenylhydrazine and hydrazine.

Reaction of 2,4,6-triphenylpyrylium with hydroxylamine

He surveyed treatment of a suspension of 2,4,6-triphenylpyrylium perchlorate (29) in aqueous ethanol with hydroxylamine (30, $\text{Y} = \text{O}$). This reaction afforded a colorless compound (32), which was very easily convertible into an isomeric compound (35). On treatment with 70% perchloric acid, compound (32) or (35) give a red solution. If this solution is heated at 100-150°C an exothermal reaction takes place. These compound are split into acetophenone (36) (identified as its 2,4-dinitrophenylhydrazone) and 3,5-diphenylisoxazole (38, $\text{Y} = \text{O}$). An intramolecular addition of the nucleophilic YH group to the activated carbon-carbon double bond in (32A) converts (32B) into the isoxazoline derivative (35B)

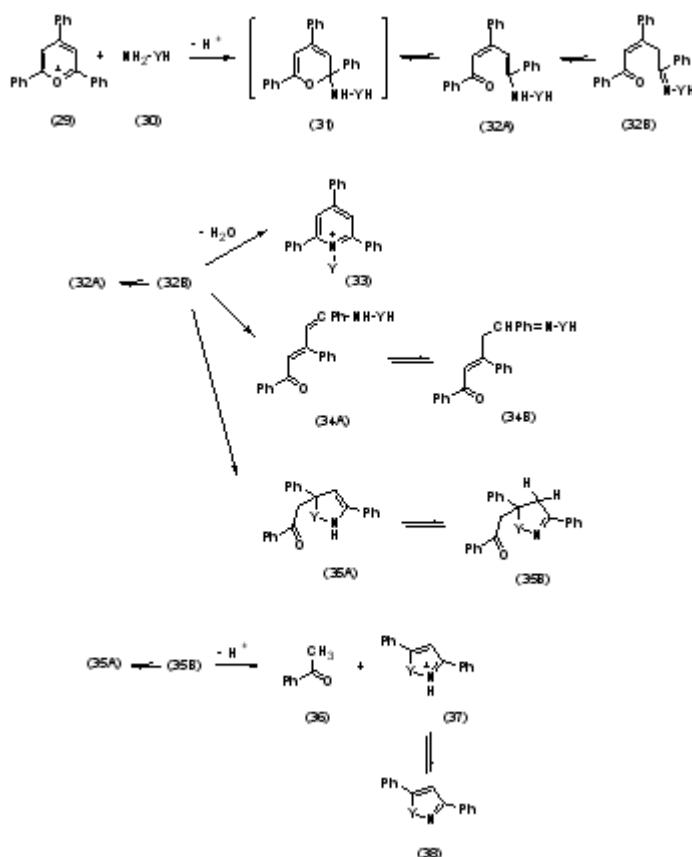
(Y = O) (Scheme 7). Similar ring closures leading to pyrazolines. This intramolecular addition takes precedence in this case over the dehydration which prevails in the alkyl-substituted derivatives leading to pyridine -N-oxides (I, Y = O). An alternative seven-membered dehydration product (39) would be expected to be less stable because 8 δ -electrons cannot be aromatic (Scheme 8).

Reaction of 2,4,6-triphenylpyrylium with phenylhydrazine

The reaction of 2,4,6-triphenylpyrylium perchlorate (29) with phenylhydrazine (30, Y = NPh) was first described by Schneider.¹⁶ The primary crystalline product (α -pyranolhydrazone) underwent an isomerization into a β -pyranolhydrazone on reflux in ethanol. On the basis of UV and IR spectral evidence it was argued that a cis-trans isomerism was probably involved, i.e. that the primary α -pyranolhydrazone had the cis structure

(32B, Y = NPh), whereas the isomerization product (β -pyranolhydrazone) was probably the trans-isomer (34B, Y = NPh). In fact, only the former isomer was able to undergo dehydration in hot acetic acid yielding the pyridinium derivative (33, Y = NPh).

On treatment with 70% perchloric acid, the α -pyranolhydrazone afforded a red solution which darkened on heating. On dilution with water, a tar containing the perchlorate of 1,3,5-triphenylpyrazole (37, Y = NPh) separated in moderate yield. The second reaction product was acetophenone (36). The same two products were obtained in high yield from the β -pyranolhydrazone and perchloric acid: no color developed on mixing these reagents, short heating at 100-120 °C gave acetophenone and the same perchlorate with no side-products. Alkalinization of the perchlorate afforded 1,3,5-triphenylpyrazole (38, Y = NPh) (Scheme 7).

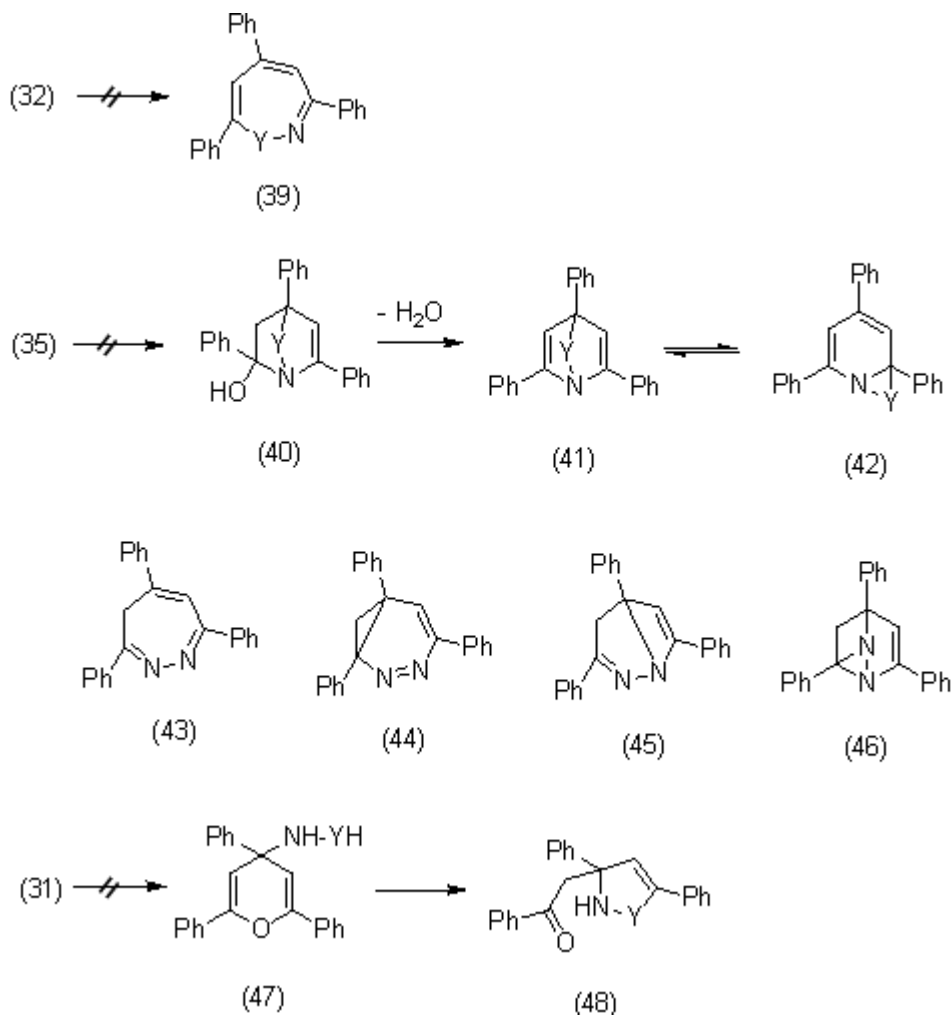


Scheme 7: Reaction of 2,4,6-triarylpyrylium (29) with the nucleophile (30)

Reaction of 2,4,6-triphenylpyrylium with hydrazine

Balaban also studied the reaction between 2,4,6-triphenylpyrylium (29) and hydrazine hydrate (30, Y = NH). NMR data agree with structure (43)

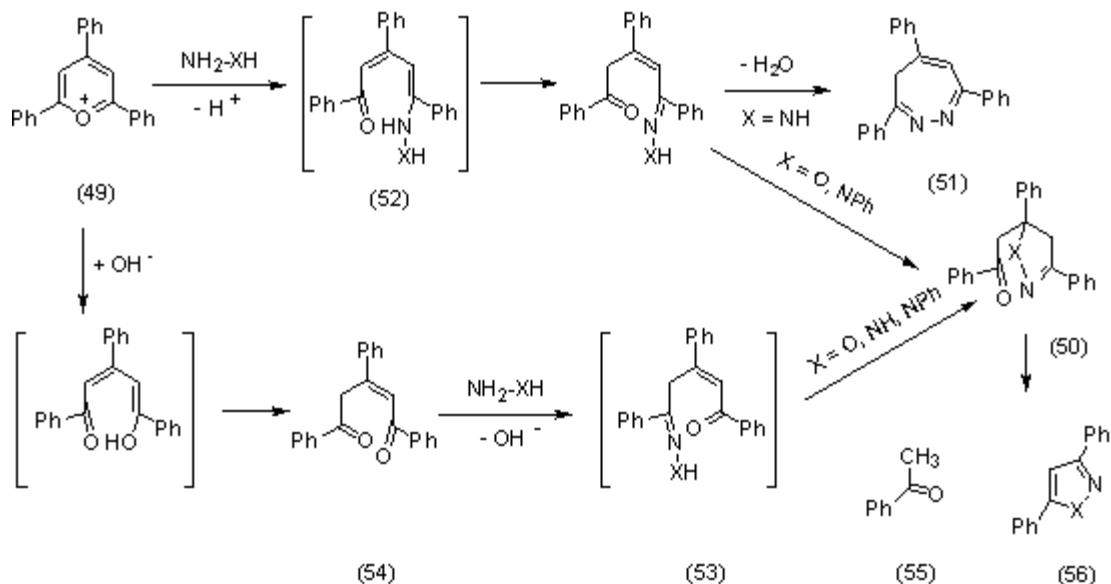
(and also with the less probable structures 44 and 45) better than with other possibilities (39 or 46). This compound does not afford acetophenone and 3,5-diphenylpyrazole on treatment with acids (Scheme 8).



Scheme 8: Uncertain or disproved structures in the reaction of 2,4,6-triarylpyrylium with the nucleophile (30)

In 1970, Balaban¹⁷ also performed the reaction of 2,4,6-triarylpyrylium salts with dilute aqueous hydrazine and ether which a colorless crystalline compound m.p. 108-110°C is obtained. Though, it is stable in the solid state, in solution it dehydrates (half-life ca. 1 h at 40° in CDCl₃) affording 3,5,7-triphenyl-4H-1,2-diazepine (51) and the

solution becomes red-brown (as do the crystals of (52) with traces of solvents). Accordingly, this compound is the monohydrazone of the pseudobase (54) and could have either formula (52, X = NH) or (53, X = NH), i.e. the double bond can be conjugated either with the hydrazo or with the CO group (Scheme 9).



Scheme 9: Reaction of triarylpseudobase with aqueous hydrazine

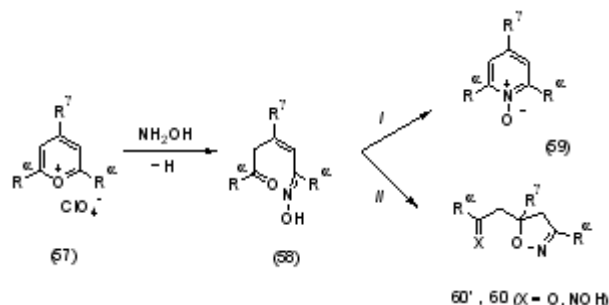
1,3,5-triphenyl-2-penten-1-one (54, pseudobase of 49) reacts in a different fashion with hydrazine in ethanol: with a transient red-brown coloration, a crystalline colorless compound m.p. 133°C is formed (50, X = NH). Similarly to other compounds with formula (50), (but unlike other 2-pyrazolines which afford nitrogen and cyclopropane), this compound (50, X = NH) cleaves on treatment with acids, on recrystallization from acetic acid, or on heating above the m.p. affording acetophenone (55) and an aromatic azole (56).

The pseudobase (54) reacts with hydrazine like other α,β -unsaturated ketones affording a 2-pyrazoline derivative (50, X = NH). Though, no intermediate in this reaction could be detected, the above data make it clear that (52) is not an intermediate in the conversion of (54) into (50, X = NH).

Therefore, the initial attack of nucleophiles like N_2O_4 on the unsaturated 1,5-diketone (54) can either involve a condensation of the more reactive non-conjugated CO group leading to (53, X = NH) which cannot be isolated because it cyclizes, or the addition of N_2H_4 to the activated C=C double bond

followed by intramolecular condensation affording (50, X = NH). Treatment of the pseudobase (54) with hydroxylamine or phenylhydrazine affords 3,5-phenacyl-2-isoxazoline (50, X = O) or 1,3,5-triphenyl-5-phenacyl-2-pyrazoline (50, X = NPh), respectively, identical with the products obtained from triphenylpyrylium (49) and the same reagents by cyclization of the intermediately formed (52, X = O or NPh). Only with hydrazine as the nucleophile is there a difference in these reactions of 2,4,6-triphenylpyrylium (49) and its pseudobase (54) because in this case the intermediate (52, X = NH) reacts more rapidly by intramolecular condensation of CO and NH_2 group to the activated C=C group (a pathway leading to 50).

On the other hand, Uncuta and coworkers in 1998,¹⁸ believed that after the initial α -attack of the nucleophile and the ring-opening to the keto-ketoxime (58), two competing intramolecular cyclizations can occur. The formation of an N-oxide (59) (path *i*) is acid-catalyzed, whereas the intramolecular Michael addition (path *ii*) yielding a 2-isoxazoline derivative 60' (or 60 with another molecule of hydroxylamine) is favoured by the presence of bases (Scheme 10).



Scheme 10: Competing between intramolecular cyclization *i*, *ii*

The stereoelectronic properties of substituent R^{α} also play a significant role in the recyclization step, influencing the relative rate of the paths (*i*) and (*ii*). Indeed, the rate of path (*i*) is much higher than the rate of path (*ii*) for small R^{α} group, namely methyl, either (59a) or (59b) being the sole product under acidic conditions as well as under basic conditions. No influence of the nature of R^{γ} substituent (Me or Ph) on the (59) vs. (60) ratio was observed, as seen by comparing the cases a, b and g, i, in following table. Conversely, the product (60') of path (*ii*) prevails even under acidic conditions for bulky R^{α} such as *t*-Bu, Ph or *o*-MeC₆H₄. The decrease in the rate of path (*i*) may be explained by a high-energy transition state involving three bulky groups in adjacent positions, favouring thereby path (*ii*) leading to 60', in which no such overcrowding exists. The rates of path (*i*) and (*ii*) become comparable for medium-sized groups such as *i*-Pr.

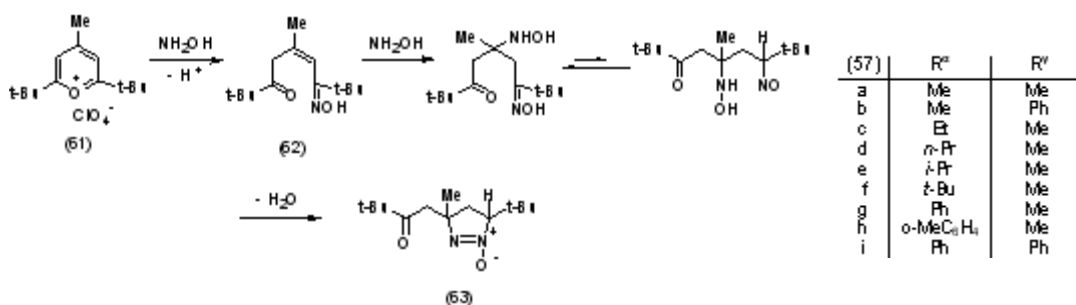
The initial nucleophilic attack at 2,4,6-trisubstituted pyrylium cations having an α -methyl and a different α -substituent R occurring preferentially at the carbon atom adjacent to the α -

methyl group may also be explained by kinetic preference for the smaller group.

A final comment on the results presented in following Table regards the unprecedented formation of 1-pyrazoline-1-oxide (63). A plausible pathway for the formation of (63) involves a Michael addition of hydroxylamine to the keto-ketoxime (62) initially formed from the pyrylium salt, hydrogen shift and dehydration then completes the process.

The explanation of this unprecedented reaction path may reside in the fact that the bulky substituents lower the rate of intramolecular cyclization of the keto-ketoxime (62) to (59) and (60'), allowing thereby the competing intermolecular Michael addition of a second hydroxylamine molecule (Scheme 11).

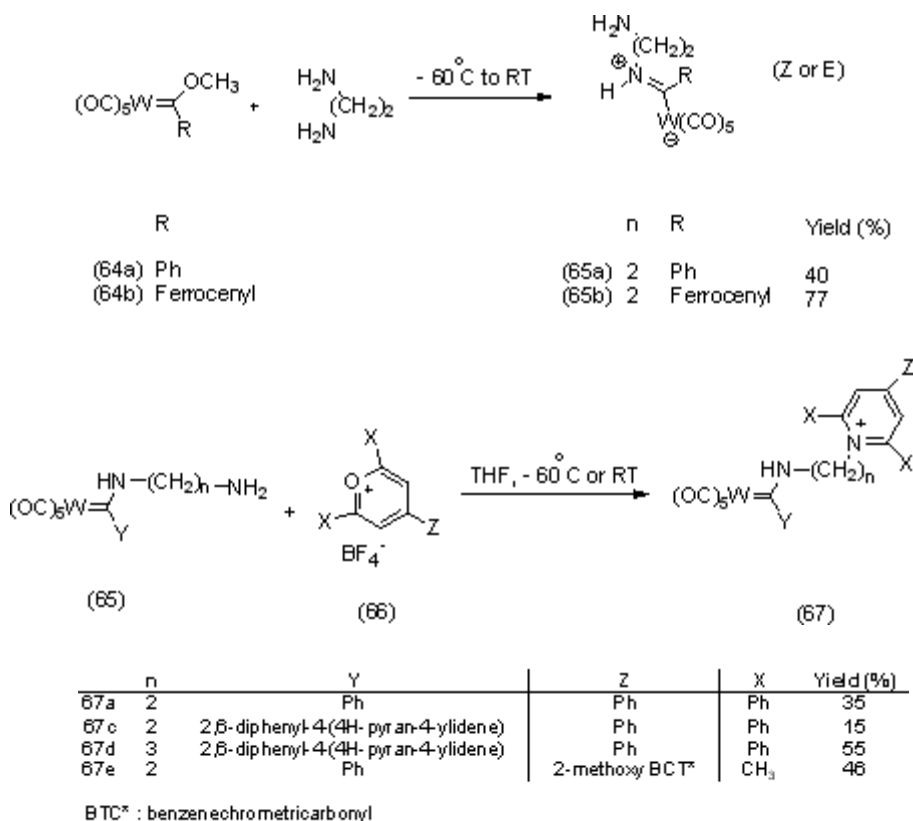
As amines can be used to graft biomolecules, Poul and coworkers in 2007,¹⁹ tested the reactivity of the free nitrogen atom of these organometallic carbenes. Two heterocyclic target molecules, known for a long time for their high affinity with primary amines, were chosen: pyrylium salts²⁰ and 2,4,6-trichloro-1,3,5-triazine.²¹



Scheme 11: Formation of 1-pyrazoline-1-oxide from the reaction of pyrylium salt with NH₂OH

The reaction of pyrylium salts, including organometallic ones, with the NH_2 group of the carbene complex could allow the formation of new complexes containing pyridinium ring. With trichlorotriazine, the successive substitutions by

aminocarbene groups could be expected.²² As the aminocarbene organometallic fragment may be comparable to an amide function, they had in mind that the obtained complexes could play the role of new receptors for anions.²³



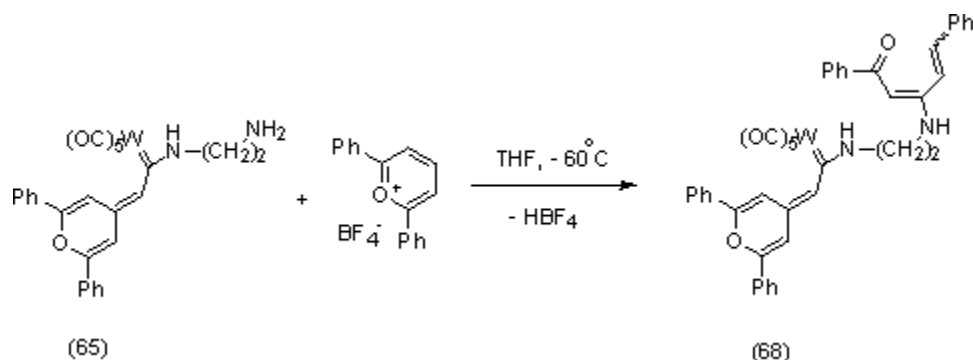
Scheme 12: Reaction of diaminocarbene complexes with 2,4,6-trisubstituted pyrylium salts

The treatment of a solution of carbene (65a) with 2,4,6-triarylpyrylium salt (66a) or (66e) led to the new organometallic carbene pyridinium salt (67a) or to the heterodinuclear pyridinium salt (67e), respectively (Scheme 12).

The same procedure allowed the formation of the organometallic pyridinium salts (67c) and (67d), from reaction between 2,4,6-triphenylpyrylium tetrafluoroborate and the pyran aminocarbenes (65c) and (65d), respectively. It can be noted that the organometallic pyridinium salt (67b) was isolated in lower yield (15%). In that case, unreacted pyrylium salt was recovered from the reaction mixture.

The reactivity of the aminocarbene (65c) with 2,6-diphenylpyrylium salt is interest. As it is repeatedly pointed out, 2,4,6-trisubstituted pyrylium salts usually favor a attack by nucleophiles, whereas 2,6-disubstituted pyrylium cations frequently undergo α attack.¹ The formed 4H-pyrans undergo facile ring opening under acidic influence in order to give unsaturated 1,5- diketone.²⁴ However, the addition of primary amines to the 4-free position of 2,6-disubstituted pyrylium salts is rarely observed and pyridinium salt formation occurs.

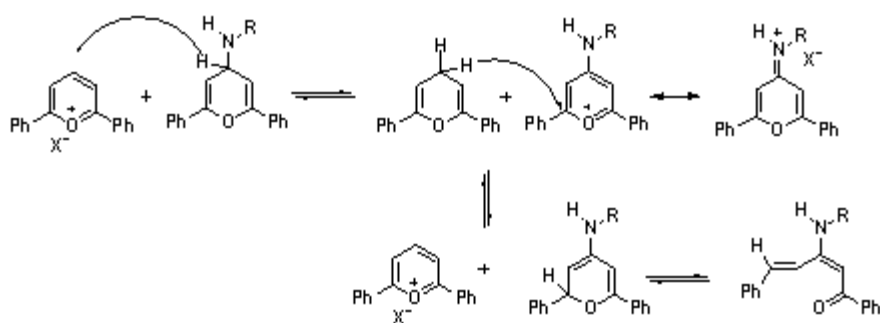
Mixing the aminocarbene (65c) and the 2,6-diphenylpyrylium Salt gave the new unsaturated diaminocarbene (68) (Scheme 13).



Scheme 13: Reaction of diaminocarbene complex (65) with 2,4-disubstituted pyrylium salt

The formation of (68), under these experimental conditions (-60°C), is unprecedented in pyrylium and pyran chemistry. This complex likely results from an initial attack of the amino group in

(65c) onto the C γ of the pyrylium salt. Such an attack leads to a 4*H*-pyran. A 1,3-hydride shift leads to a 2*H*-pyran and subsequent ring opening step gives the final carbene (68) (Scheme 14).



Scheme 14: Suggested intermolecular mechanism for the formation of (68)

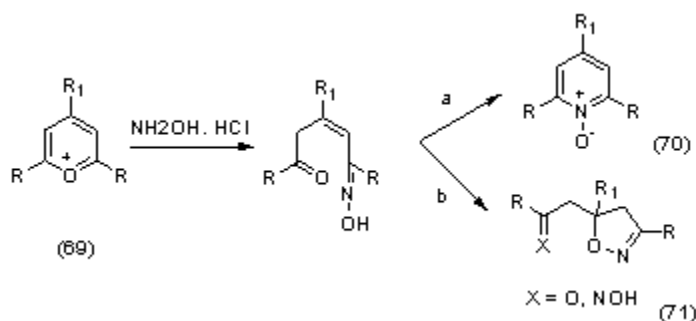
It can be noted that the first step of this process could be kinetically favored by an orbital interaction between the lone pair of the nitrogen atom and the δ^* Molecular Orbital of the C–H bond.

In 2009, Mouradzadegun and coworker,²⁵ effort to improve the conversion of triarylpyryliums to corresponding 2-isoxazolines, these transformations were studied on solid materials such as silica gel, basic alumina and nontraditional solid support material, such as K_2CO_3 , which couple poorly with microwaves. Experiments clearly showed that the traditional solid supports with soft acidic surface is less selective and effective, whereas solid supports with soft basic surface and nontraditional

ones are moderately effective and perform the high selectivity toward desired product.

2-isoxazolines (71), were synthesized from corresponding triarylpyrylium salts with hydroxylamine hydrochloride (Scheme 15).

They believe present solvent-free procedure under microwave irradiation, provide efficient, selective and environmentally friendly methodology for conversion of triarylpyrylium perchlorates in which desired products can be obtained by simple filtration and washing without the need for a chromatographic workup.

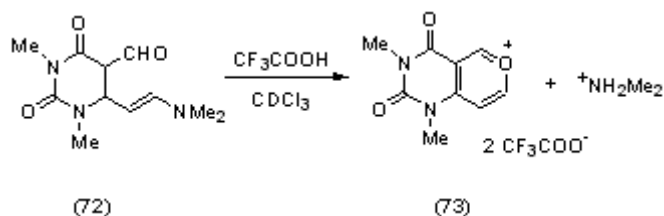


Scheme 15: Synthesis of 2-isoxazolines (71) from corresponding triarylpyrylium salts with hydroxylamine hydrochloride

Tsupak and coworkers,²⁶ in the same year, reported on the generation of 1,3 dimethyl-2,4-dioxo-1*H*,2*H*,3*H*,4*H* pyrano[4,3-*d*]pyrimidinium cation containing no substituents in the pyrylium

ring and its behaviour under the action of N-nucleophiles.

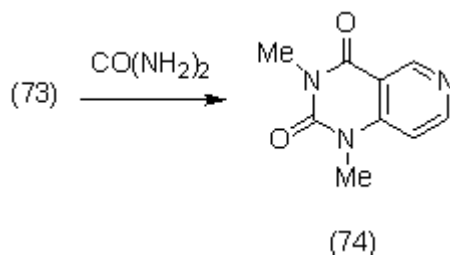
Enamine (72) was used as a starting material for the synthesis of target cation (73) (Scheme 16).



Scheme 16: Synthesis of pyrylium salt (73) from enamine (72)

And they found that cation (73) did not react with ammonium acetate and aliphatic amines. However, using urea as a nucleophile, they isolated

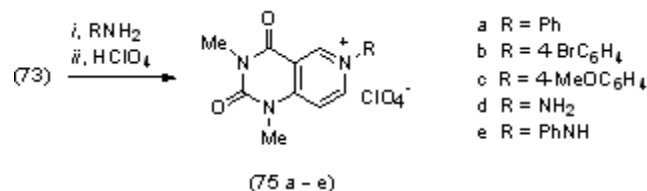
pyrido[4,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (74) described previously²⁷ (Scheme 17) (*cf.* similar interaction of monocyclic pyrylium salts with urea).²⁸



Scheme 17: Reaction of pyrylium salt (73) with urea

It was also shown that cation (73) reacts with aromatic amines, hydrazine and phenylhydrazine under similar conditions,

transforming into corresponding 6-*R*-pyrido[4,3-*d*]pyrimidinium salts (75 a-e) (Scheme 18).

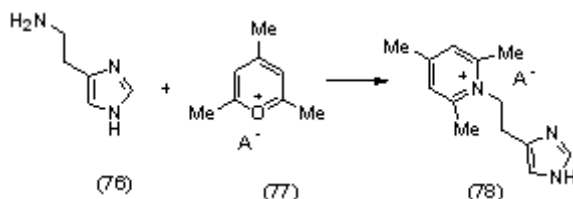


Scheme 18: Synthesis of pyridinium salts from pyrylium salt (73)

Thus, the possibility of nucleophilic substitution is determined by the nature of nucleophile. Ammonium acetate and aliphatic amines are more basic ($pK_b \leq 4.73$) than urea, aromatic amines, and phenylhydrazine ($pK_b \geq 8.71$). Evidently, in the test solution ammonium acetate and aliphatic amines exist completely in protonated forms and do not react with cation 78. The basicity of hydrazine is comparable with ammonium acetate and aliphatic amines ($pK_{b1} = 5.89$). However, it easily enters into the interaction due to the presence of the second nucleophilic centre, which is not protonated under experimental conditions ($pK_{b2} = 14.88$).

And finally, Khyati Dave and coworkers²⁹ in 2011, reported the preparation of the 2,4,6-trimethylpyridinium derivative of histamine (76), its activating properties against several physiologically relevant CA isoforms, and the X-ray crystal structure of this compound in complex with the dominant isoform hCA (78) (h = human enzyme).

Reaction of histamine (76) with 2,4,6-trimethyl pyrylium hexafluorophosphate (77) afforded the pyridinium salt (78) by the Bayer-Piccard synthesis (Scheme 19).³⁰⁻³³



Scheme 19: Reaction of histamine (76) with 2,4,6-trimethylpyrylium salt (77)

Compound (78) has been extensively characterized by physico-chemical procedures,³⁴ and has been investigated as activator of several relevant isoforms, such as hCA I, II and VII (cytosolic) as well as hCA IX, XII and XIV (transmembrane enzymes, with an extracellular active site).³⁵

CONCLUSION

In this review we have studied two of the most important and most commonly used reactions of pyrylium salts with nucleophiles such as C and N-Nucleophiles. The usual products for the reaction of pyrylium salts with C- Nucleophiles such as cyanide anion are cyanodienones. These products

are utilized as a key intermediate to construct complex molecules such as butenolides which are potent antibiotics and also appear as a substructure in peptide analogues and HIV-1 protease inhibitors.

The reaction of pyrylium salts with N-Nucleophiles affords various compounds such as pyridines. These products are used as a precursor to agrochemicals and pharmaceuticals and exhibit several other medicinal applications.

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- The films were prepared by radical polymerization of a mixture of I, III and IV using 1,2 ethanedioldimethacrylate and AIBN (2.0 wt%) as initiator. The nominal cross-linking ratio, i.e., the ratio of the number of moles of monomers to the cross-linking agent, was 100:1, and the film thickness was 110 μ m. The addition of a cross-linking agent is necessary in order to obtain membranes with adequate mechanical properties. The reaction was carried out in a silanized glass mold of 100 μ m thickness in an oxygen-free atmosphere at 65 $^{\circ}$ C for 5 h.
- Layers stored in buffer sodium hydroxide (1023 mol dm⁻³) for 24 hours showed a similar response upon cyanide addition to those only soaked for 30 minutes.
- Under the experimental conditions employed in the cyanide detection, sulfide anion also gives a response, most likely due to a nucleophilic attack on the pyrylium ring. See: Jimenez, D., Martýnez-Mañez, R., Sancenón, F., Ros-Lis, J. V., Benito, A., Soto, J. *J. Am. Chem. Soc.*, **125**: 9000 (2003).
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