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Reactions of pyrylium salts with nucleophiles. Part 26.[1] The reaction with the cyanide anion revisited

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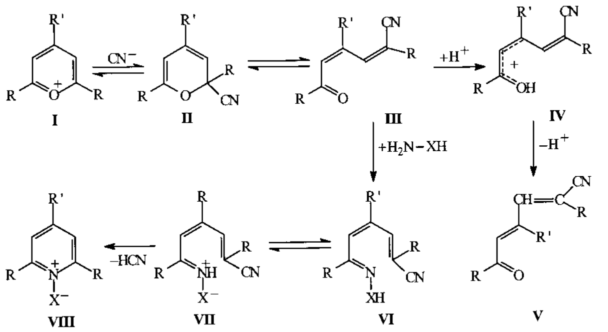
Reaction mechanisms are provided for the formation of diastereomeric 2,4-dialkyl-6-oxo-2,4-heptadienonitriles (including minor diastereoisomers observed for the first time) from 2,4,6-trialkylpyrylium salts and aqueous sodium cyanide.

Keywords: pyrylium salts, nucleophiles, cyanide atom

Almost 40 years ago, the reaction of 2,4,6-trimethylpyrylium salts (I) with sodium cyanide was reported[2] to afford a conjugated acyclic 5-cyano-2,4-dienone (III) by α-addition of the cyanide anion to the pyrylium cation followed by an electrocyclic ring-opening of the 2*H*-pyran (II). The *cis*-configuration of the 2,3-double bond was proved by hypobromite oxidation yielding a 5-cyanosorbic acid that was investigated later by ^{1}H-NMR.[3]

Dienone III is liquid at room temperature, and is soluble in concentrated hydrochloric acid, affording on dilution with water a crystalline *trans*-isomer (V, whose structure was determined by ^{1}H-NMR from that of the corresponding oxidation product with hypochlorite, *i.e.* the 5-cyanosorbic acid[3]). Functional derivatives (VI) of dienone III (oxime, 2,4-dinitro, 2,6-dinitro- and 2,4,6-trinitrophenylhydrazone) evolved hydrogen cyanide on heating, and cyclised affording N-substituted pyridinium salts (VIII);[2,4,5] such salts could not be obtained from the corresponding functional derivatives of the *trans*-isomer (V). Scheme 1 presents structures I–VIII. The reaction of 2,4,6-triphenylpyrylium salts with sodium cyanide led to the formation of a crystalline 5-cyanodienone, which could not be converted into its *trans*-isomer.[4,5]



Scheme 1

On reinvestigating the reaction of 2,4,6-trimethylpyrylium perchlorate (**1**) or fluoroborate with sodium cyanide at room temperature in a stirred mixture of water and ethyl ether and separating the products by chromatography on silica gel, the main product (95%) was **2** (2-*Z*,4-*Z*, 2,4-dimethyl-6-oxo-2,4-heptadienonitrile); a minor product (5%) was its stereoisomer **4** (2-*E*,4-*Z*, 2,4-dimethyl-6-oxo-2,4-heptadienonitrile). Whereas treatment with concentrated hydrochloric acid converted **2** into **3** (2-*Z*, 4-*E*, 2,4-dimethyl-6-oxo-2,4-heptadienonitrile), compound **4** formed **5** (2-*E*,4-*E*, 2,4-dimethyl-6-oxo-2,4-heptadienonitrile) under the same conditions (Fig. 1). Structures were determined by means of IR, ^{1}H-NMR and ^{13}C-NMR spectra, DEPT and HETCOR pulse sequences. A supplementary confirmation of the structural assignment was obtained by the ^{1}H-NMR spectra of **2**, **3**, and **4** in the presence of europium shift reagents.

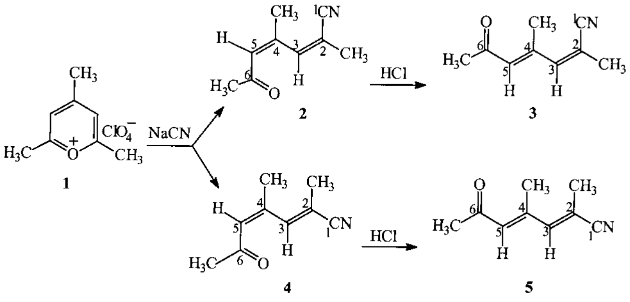
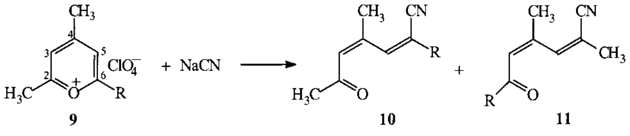


Fig. 1 The formation of stereoisomers **2**, **3**, **4** and **5**

On examining the reaction of sodium cyanide with a pyrylium salt having identical bulkier substituents in the 2 and 6 positions, namely 2,6-di-isopropyl-4-methylpyrylium perchlorate, only one product was obtained with a configuration corresponding to that of compound **2**. It was converted partly by concentrated hydrochloric acid into its diastereoisomer with a configuration corresponding to that of **3**.

Pyrylium salts **9** with different substituents in positions 2 (methyl) and 6 (an R group which is alkyl or phenyl) react regioselectively with sodium cyanide in aqueous solution. With R = alkyl, addition in both α-positions was observed leading to two compounds, **10** and **11** (with a stereochemistry analogous to the major product **2** obtained with R = Me, Scheme 3). The major attack occurred at the α-position adjacent to the larger alkyl group R, affording mainly **10**. This regioselectivity is opposite to that observed in the attack of primary amines[8] or hydroxylamine[1] on pyrylium salts with two different α-substituents. When R = Ph, only one substance was obtained.



9	R	Molar fractions 10	Molar fractions 11
a	Et	0.55	0.45
b	*i*Pr	0.63	0.37
c	Ph	-	1

Scheme 3

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* To receive any correspondence.

It was assigned configuration **11** on the basis of a NOE experiment, indicating that the attack occurred regiospecifically at the α-position adjacent to the methyl group, in agreement with earlier observations on the regiospecificity of the nucleophilic attack by hydroxyl anions on **9**.

The attack of the cyanide anion ought to be equally probable on both faces of the pyrylium cation, leading to a racemic α-pyran **12**. Its electrocyclic, thermally allowed, disrotatory ring opening affords the cyanodienone. There are two possibilities for this ring-opening: "in" and "out", presented in Figure 3, yielding the two diastereoisomers **2** and **4**, respectively. Experiments have shown that the "in" pathway yields the major product. Two alternative explanations come to mind: (i) a higher thermodynamic stability for **2** than for **4**, if one has a thermodynamically-controlled reaction, or (ii) the existence of distinct, non-planar, α-pyranic diastereoisomeric intermediates or transition states $\mathbf{T_1}$ and $\mathbf{T_2}$; it is likely that the former one has a lower energy because of the anomeric effect which favours the axial conformation of the electronegative cyano group. One can also imagine each effect to have some contribution. Molecular mechanics (MM2) calculations were performed for the α-pyranic diastereoisomeric intermediates or transition states $\mathbf{T_1}$ and $\mathbf{T_2}$. Total energies are practically equal, but $\mathbf{T_1}$ is less puckered than $\mathbf{T_2}$, suggesting that it may be preferred.

Similar MM2 calculations indicated for the four cyanodienone stereoisomers that total energies yield the following order: **3** < **5** < **2** < **4**. For the equilibrium mixture, the experimentally determined ratio was about 2:2:3:3 for the four compounds **4**:**2**:**5**:**3**, in rough agreement with the above stability order.

References: 6

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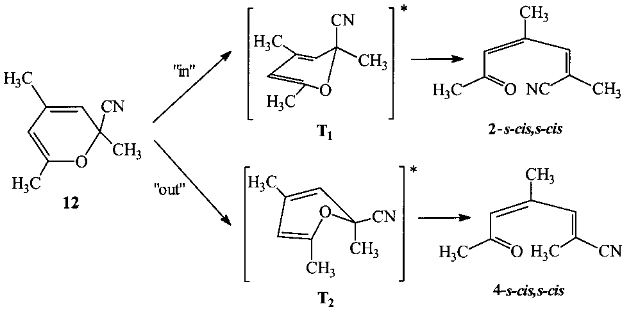

Fig. 3 The two possibilities for the ring-opening of 2-cyano-2,4,6-trimethyl-pyran

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