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Synthesis of 2,4-dimethyl-6-oxo-2,4-heptadienoic acid derivatives from 2,4,6-trimethylpyrylium salts

Alexandru T. Balaban,[a,*] Adriana Tudose[b] and Miron T. Caproiu[b]

[a]*Texas A&M University at Galveston, 5007 Avenue U, Galveston, TX 77553, USA*
[b]*Center of Organic Chemistry, 'C.D. Nenitzescu' of the Romanian Academy, Spl. Independentei 202B, 71141 Bucharest, Romania*

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Abstract—Reaction 2,4,6-trimethylpyrylium salts with sodium cyanide in boiling water yielded the bicyclic lactone 1,3,5-trimethyl-6,8-dioxabicyclo[3.2.1]oct-2-en-7-one (**6**) along with a series of stereoisomers of 2,4-dimethyl-6-oxo-2,4-heptadienonitrile (**5**), which were the sole products when the reaction was carried out at room temperature. Compound **6**, along with 3,5-dimethylphenol (**7**), was also obtained by refluxing **5** briefly in aqueous sodium hydroxide. However, when **5** was refluxed for a prolonged period in aqueous sodium acetate, 3,5-dimethyl-5-(2-oxopropyl)-furan-2-one (**8**), along with some **7**, was generated instead. Compound **8** could also be produced from **6** on prolonged refluxing with aqueous sodium acetate, indicating that **6** was the kinetically-controlled and **8** the thermodynamically-controlled product.

1. Introduction

Since pyrylium salts are readily obtained from simple starting materials, the study of their reactions is of continuous interest. In the present paper we report two interesting isomers of the reaction product of 2,4,6-trimethylpyrylium cation with sodium cyanide followed by hydrolysis of the nitrile group.

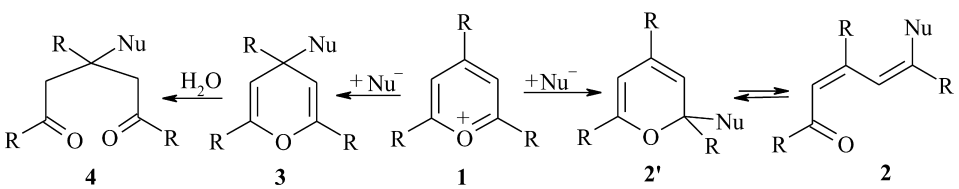
The tautomerism and valence isomerism of heterocyclic compounds is well documented.[1] In all formulas, primed or double-primed numbers will denote valence isomeric intermediates that were not detected experimentally.

In the reaction of pyrylium salts (**1**) with anionic nucleophiles (Nu^-), the first reaction step is the nucleophilic addition of the reactant to the substrate leading either to a 2H-pyran (**2′**) or, less often, to a 4H-pyran structure, **3**.[2,3] (Scheme 1).

The 2H-pyranic form (**2′**) undergoes a thermally-allowed ring opening leading to the acyclic valence tautomer **2**, which may undergo further intramolecular cyclization involving the carbonyl group and either the nucleophile or a methyl(ene) side chain of the initial pyrylium salt. The literature is rich in papers describing the isolated 2H- or 4H-pyranic forms obtained in reaction of pyrylium salts with the methoxy anion,[4–13] secondary amines,[14,15] hydride anion,[16,17] organometallic reagents,[18,19] or 1,3-diketones.[20–21] In several cases the final reaction products are open-chain compounds, e.g. in the reaction of some pyrylium salts with primary amines[22,23] or the hydroxyl anion (yielding products depending on the substitution pattern of the cation, e.g. stable pseudobases from 2,4,6-triarylpyrylium salts),[24–26] or with sodium cyanide.[27–28]

2. Results

Recently, we reinvestigated the reaction of pyrylium salts with the cyanide anion.[27,29] As shown in Scheme 2, we obtained in the reaction of 2,4,6-trimethylpyrylium cation **1**



Scheme 1.

Keywords: stereoisomers; 2,4,6-trimethylpyrylium salts; aqueous sodium acetate; lactones.
* Corresponding author. Tel.: +1-409-740-4706; fax: +1-409-740-4787; e-mail: balabana@tamug.tamu.edu

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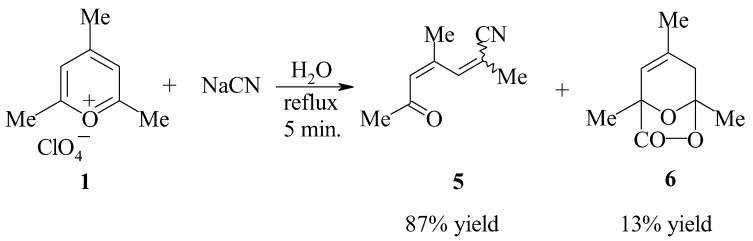


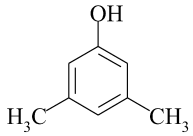
Scheme 2.

(R=Me) with sodium cyanide in water at 100°C for a short reaction time (5 min), the bicyclic lactone **6** (1,3,5-trimethyl-6,8-dioxa-bicyclo[3.2.1]oct-2-en-7-one) along with the two stereoisomeric 4-*Z*-2,4-dimethyl-6-oxo-2,4-heptadienonitriles (**5**), reported earlier[29] with both *E*/*Z* geometries at the double bond (C2–C3). On performing the same reaction at room temperature or at 0°C, no trace of compound **6** was observed by ^{1}H NMR: the crude reaction product contained only 4-*Z*-2,4-dimethyl-6-oxo-2,4-heptadienonitriles.

The initial compounds **5** can be isomerized into two other stereoisomers involving the other double bond between C4 and C5 by concentrated hydrochloric acid.[27,29] The structures of the products obtained in reactions performed at room temperature were described earlier,[27] and the stereochemistry of all possible stereoisomers was unambiguously established by ^{1}H NMR techniques.[29] The structure of compound **6** was determined on the basis of ^{1}H and ^{13}C NMR spectra (COSY and HETCOR), mass spectrometry, and elemental analysis.

It is easily observed that the structure of compound **6** originates in the hydrolyzed product of the cyano group. In the literature no case of isolation of pyranic products in the reaction of 2,4,6-trisubstituted[27] or 2,6-disubstituted[28] pyrylium cations with sodium cyanide was described. In the reaction with sodium borohydride in acetic acid, 2,6-diphenyl-4-methylpyrylium perchlorate give as major product the corresponding 4H-pyranic compound,[17] but in the reaction with cyanide anion 2,6-di-*tert*-butylpyrylium perchlorate led only to the corresponding cyanodienone product.[28] On the other hand, 2-benzopyrylium salts react with sodium cyanide leading only to 2H-pyranic products, in this case the ring opening being disfavored.[30,31]

We performed hydrolysis studies of cyanodienones **5**. With aqueous sodium hydroxide (molar ratio **5**/NaOH=2:1) for short reaction times (5 min) in boiling water, compound **6** was obtained along with a substantial amount of 3,5-dimethylphenol **7**. 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 (**7**) and another lactonic product, 3,5-dimethyl-5-(2-oxopropyl)-5*H*-furan-2-one, **8**. The structure of this latter compound was unambiguously established by ^{1}H and ^{13}C NMR spectral data and elemental analysis.



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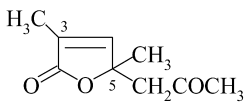

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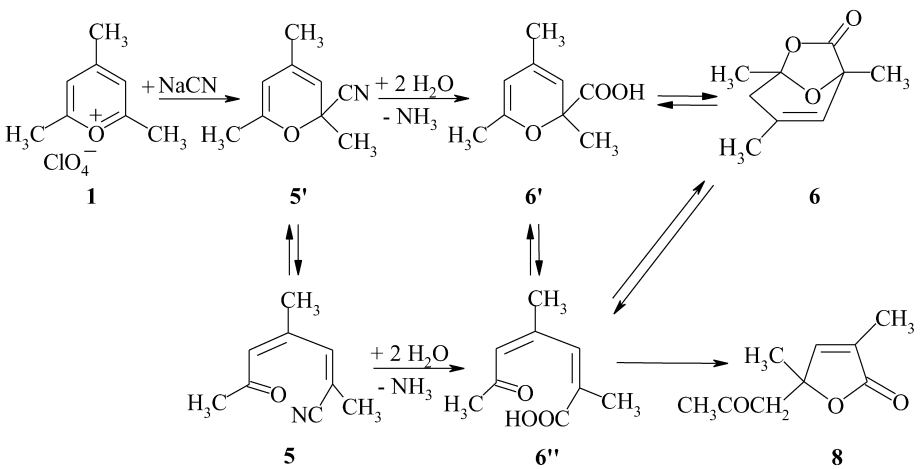
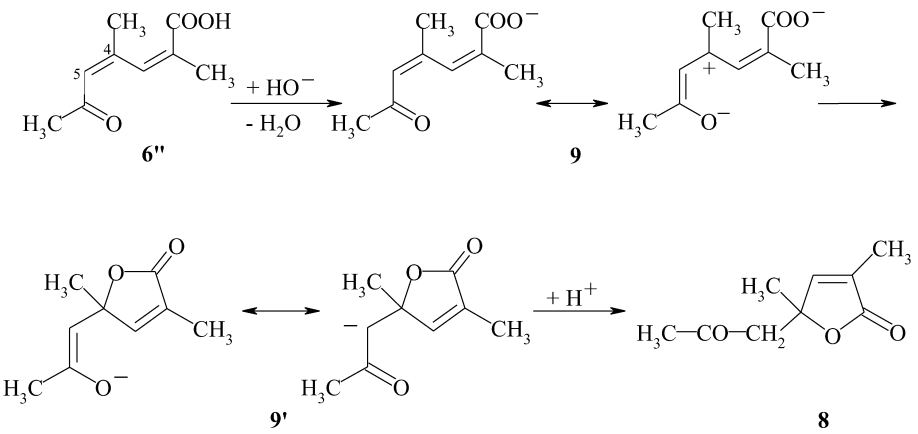
3. Discussion of the results

We explain the formation of both compounds **6** and **8** by reactions outlined in Scheme 3.

The first reaction step affords the α-cyanopyran **5′**. At room temperature or at 0°C the second reaction step is the ring-opening to the valence tautomeric cyanodienone **5**. At 100°C the hydrolysis of the nitrile group competes with the



Scheme 3.



Scheme 4.

ring opening. The fact that only at short reaction times could the compound **6** be isolated suggests two facts: (i) in the reaction of pyrylium salt **1** with sodium cyanide, the elusive pyranic form **5′** is the kinetically controlled product, while the isolated cyanodienone is the thermodynamically stable product; (ii) in the hydrolysis, the isomerizations **5**–**5′** or **6′**–**6″**–**6** occurred, the compound **6** being the kinetically controlled product, while the compound **8** is the thermodynamically stable product. The reversibility of the reactions in Scheme 3 was proved by heating the bicyclic compound **6** with an aqueous solution of sodium acetate when the sole product was the lactone **8** (see Section 5). This explains the absence of compound **6** in the reaction of **5** with sodium acetate. We presume that the reaction pathway is **6**–**6′**–**6″**–**8**, but no detectable amounts of intermediates **6′** or **6″** could be identified by ^{1}H NMR in the crude reaction product. The formation of **6** from the acid **6′**–**6″** or its anion **9** may proceed either from **6′** with a preformed pyranic ring, or from the ring-opened form **6″** simultaneously with the electrocyclic ring closure.

The cyclization to the lactone **8** occurs by an intramolecular 1,4-addition of the carboxylate anion (**9**) of **6″**, to the C4–C5 activated double bond (Scheme 4). On work-up, protonation occurs forming the lactone **8**.

The difference between the two lactones **6** and **8** is not only in the mono/bicyclic structure, but also in the fact that **8** is the intramolecular lactonization product of the carboxylic acid **6″** involving the C4–C5 double bond, whereas **6** is formally derived from the 1,4-addition product of water to the butadienic system of **6″**, placing a hydroxyl group at C2; this hypothetical alcohol intermediate becomes then dehydrated intramolecularly forming the acetal-lactone **6**. The potential lactone ring-opening hydrolysis products of **6** and **8** are isomeric allylic alcohols, namely with the hydroxyl either at C2 (from **6**), or at C4 (from **8**).

The 3,5-dimethylphenol (**7**) may be formed either by decarboxylation of **6″** or by elimination of hydrogen cyanide from **5′** followed by the formation of 4-methyl-2,5-heptenedione (pseudobase of the pyrylium salt **1**) which recyclizes to 3,5-dimethylphenol, **7**. This compound **7** is the usual reaction product when 2,4,6-trimethylpyrylium salts (**1**) are boiled with aqueous sodium hydroxide, and its formation involves an intramolecular condensation of the pseudobase.[2]

4. Conclusions

Brief refluxing of 2,4,6-trimethylpyrylium salts (perchlorate or the less dangerous tetrafluoroborate) with aqueous sodium cyanide affords (along with the two previously reported diastereomeric 4-*Z*-4-methyl-6-oxo-2,4-heptadienonitriles) the bicyclic acetal-lactone **6** (1,3,5-trimethyl-6,8-dioxa-bicyclo[3.2.1]oct-2-en-7-one) isomeric with the carboxylic acids formed by hydrolysis of the above nitriles. Longer refluxing with aqueous sodium acetate converts compound **6** into another lactone under thermodynamic control, namely 3,5-dimethyl-5-(2-oxopropyl)-furan-2(5*H*)-one, **8**. To the best of our knowledge, this is the first example for the formation of lactone products starting from pyrylium salts.

5. Experimental

5.1. Instrumentation

Melting points were determined in a capillary tube with a hot stage and are uncorrected. The NMR spectra were recorded at 300 MHz for ^{1}H, and at 75 MHz for ^{13}C. The δ values are given in ppm from internal TMS, and the coupling constants J in Hz. The ^{1}H and ^{13}C NMR chemical shifts were determined from 1D (^{1}H, ^{13}C) and 2D (HETCOR, COLOC) experiments, as well as from COSY data.

5.2. Reagents, solvents

For preparative column chromatography, silica gel 60 was used. The elution solvents were petroleum ether (bp 35–45°C) and diethyl ether freshly distilled on lithium aluminum hydride. The 2,4,6-trimethylpyrylium perchlorate **1**[32] or the fluoroborate[33] were prepared as described previously.

The cyanodienones **5** undergo isomerization and decomposition on standing for a few days at room temperature, but

keeping the compounds in the refrigerator substantially reduces the rate of this process.

5.3. Reaction of 2,4,6-trimethylpyrylium salts (perchlorate or fluoroborate) with sodium cyanide at 100°C

Sodium cyanide (0.11 g, 2.25 mmol) and 2,4,6-trimethylpyrylium perchlorate **1** (0.5 g, 2.25 mmol) were added into 7 mL of boiling water. The mixture was maintained at reflux with magnetic stirring for 5 min. The cooled reaction mixture was extracted with diethyl ether, then hydrochloric acid was added in the aqueous layer to pH about 2 and the liquid was extracted with chloroform. The ethereal layer was washed with brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure (282 mg of residue, 87% yield of cyanodienones **5**). From the chloroform layer, the bicyclic compound **6** was isolated after evaporation of the solvent (51.3 mg, 13% yield in the crude product). An analytically pure sample of **6** was obtained by column chromatography on silica gel with elution using diethyl ether/petroleum ether 1/20 (v/v).

5.3.1. 1,3,5-Trimethyl-6,8-dioxabicyclo[3.2.1]oct-2-en-7-one (6). Colorless crystals, mp 45–6°C. IR (CCl_4): 1790 cm^{-1} (sharp). EI-MS: 168 [M^+]; 123 [M^+-CO_2-H]; 109 [$M^+-CO_2-CH_3$]. Anal. calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found C, 64.08; H, 7.19%. ^{1}H NMR in $CDCl_3$: 5.61 (2-C*H*, q, *J*=1.6 Hz), 2.43 (CH_AH_B, dq, *J*=18, 0.8 Hz), 2.21 (CH_AH_B, dq, *J*=18, 0.8 Hz), 1.73 (3-CH_3, m, *J*=1.6, 0.8 Hz), 1.66 (5-CH_3, s), 1.54 (1-CH_3, s). ^{13}C NMR in $CDCl_3$: 174.0 (*C*O), 137.3 (3-*C*), 107.3 (5-*C*), 76.2 (1-*C*), 122.6 (2-*C*H), 38.7 (4-CH_AH_B), 23.8 (5-CH_3), 21.8 (3-CH_3), 18.0 (1-CH_3).

5.4. Reaction of 5 with sodium hydroxide

Cyanodienone **5** (150 mg) was heated in 20 mL water under magnetic stirring. When the temperature reached 100°C, 20 mg of sodium hydroxide was added. After 5 min the heating and the magnetic stirring were stopped. The solution was acidified with aqueous hydrochloric acid and the organic products were extracted with chloroform. The crude reaction mixture (136 mg), consisting of 3,5-dimethylphenol, **7** (128 mg) and 8 mg of the lactone **6**, was identified by ^{1}H NMR. *3,5-Dimethylphenol* (**7**) mp 64°C (lit. mp=65–66°C).[34,35]

5.5. Reaction of 5 with an aqueous solution of sodium acetate

The cyanodienone **5** (330 mg, 2.21 mmol) and 300 mg sodium acetate trihydrate (2.21 mmol) were refluxed in 15 mL water for 3 h. The crude reaction mixture was isolated by repeated extractions with chloroform, obtaining 270 mg of lactone **8** and 93 mg of 3,5-dimethylphenol (**7**). The composition of the mixture was established by ^{1}H NMR.

Alternatively, the bicyclic lactone **6** (24 mg, 0.143 mmol) was refluxed under magnetic stirring for 2 h with 2% aqueous solution of sodium acetate. The reaction product was isolated by extraction with chloroform (21.8 mg, 91% yield, lactone **8**).

5.5.1. 3,5-Dimethyl-5-(2-oxopropyl)-5*H*-furan-2-one (8). Oil, purified by column chromatography on silica gel. Anal. calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found C, 64.45; H, 7.02%. IR (CCl_4): 1712, 1750 cm^{-1} for the ketonic and lactonic groups, respectively. ^{1}H NMR: 7.31 (C*H*, q, *J*=1.7 Hz), 3.07 (CH_AH_B, d, *J*=16.6 Hz), 2.72 (CH_AH_B, d, *J*=16.6 Hz), 1.89 (COCH_3, s), 1.50 (3-CH_3, d, *J*=1.7 Hz), 2.19 (5-CH_3, s). ^{13}C NMR: 204.8 (CO), 173.0 (2-*C*O), 152.5 (*C*H), 128.6 (3-*C*), 83.8 (5-*C*), 51.9 (CH_AH_B), 31.1 (CH_3-CO), 23.8 (5-CH_3), 10.4 (3-CH_3).

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