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SYNTHESIS OF NOVEL TRICYCLIC 2H,7H-FURO[3',4':6,7]CYCLOHEPTA-[1,2-*b*]PYRAN SYSTEM

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The reaction of 8-hydroxy-1,3-dimethyl-4H-cyclohepta[c]furan-4-one with the ethoxymethylene derivatives of malononitrile or ethyl cyanoacetate in the presence of KOH gave noncyclic cyanovinyl derivatives as their potassium salts rather than the expected α-pyrone derivatives. They are smoothly cyclized to the target α-pyrones by refluxing with acid. The corresponding 3-benzamido-2H-pyran-2-ones can be obtained in a single vessel from the 2-aryl-4-ethoxymethylene-4H-1,3-oxazol-5-ones using the same scheme.

Keywords: hydroxytropone, enol, 2H-pyran-2-one, α-pyrone, tropolone, tropone, ethoxymethylene-malononitrile, 4-ethoxymethylene-4H-1,3-oxazol-5-one, Michael addition.

Hydroxytropones are an important and interesting class of nonbenzenoid aromatic compounds which are active nucleophiles with many properties resembling phenols [1].

We have studied the recently available 8-hydroxy-1,3-dimethyl-4H-cyclohepta[*c*]furan-4-one (**1**) which can be regarded as a condensed analog of 4-hydroxytropone (γ-tropolone). For us the greatest interest is its reactions with C-electrophiles and principally where this is accompanied by the annelation of a heterocycle to an existing cyclohepta[*c*]furan system. Similar reactions have not been studied either for 4-hydroxytropone and 9-hydroxybenzocyclohepten-5-one closely related to **1** and are virtually unknown for the most investigated hydroxytropone, i.e. tropolone.

In previous work we have found that the hydroxytropone **1** shows typical enol properties in reactions with ylidenemalononitriles to give the novel condensed 4H,7H-furo[3',4':6,7]cyclohepta[1,2-*b*]pyran systems [2].

The aim of this work was to study the reactions of the hydroxytropone **1** with some electrophilic alkenes containing a good leaving group in the β-position of the double bond, e.g. with ethoxymethylene-malononitrile or its analogs. Similar reactions of other enols generally give 2H-pyran-2-one derivatives (α-pyrones) [3-5]. In this case the formation of condensed α-pyrones – novel 2H,7H-furo[3',4':6,7]cyclohepta-[1,2-*b*]pyran system derivatives was expected. These products may possess useful physiological activity (antibacterial, antitumor, etc.). Such activity is seen both in various natural and synthetic condensed α-pyrones [6-9] and in many natural and synthetic heteroannelated tropones [10].

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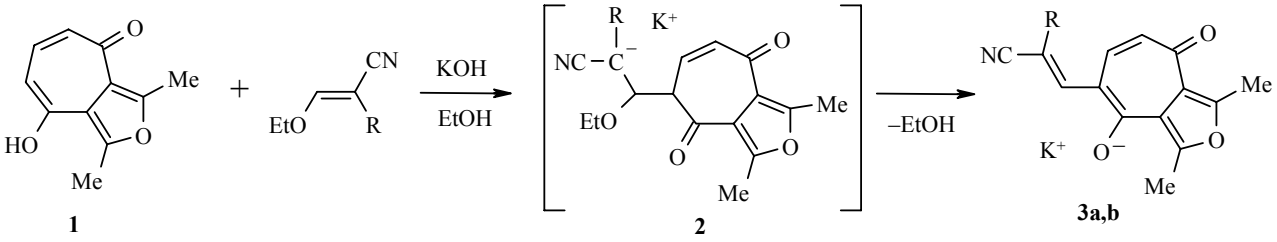
In fact, it was found that the hydroxytropone **1** reacts readily with ethoxymethylenemalononitrile or ethoxymethylenecyanoacetate but to give not the expected 2H-pyran-2-ones but the noncyclic vinyl derivatives **3a,b** as their potassium salts. The reaction occurs by short refluxing of the starting materials with an equimolar amount of potassium hydroxide in ethanol in 45-60% yield. Evidently the electrophilic alkene attacks position 7 in the starting hydroxytropone to form the Michael type adduct **2** with subsequent loss of ethanol to give the conjugated product as its salt.



1 **2** **3a,b**

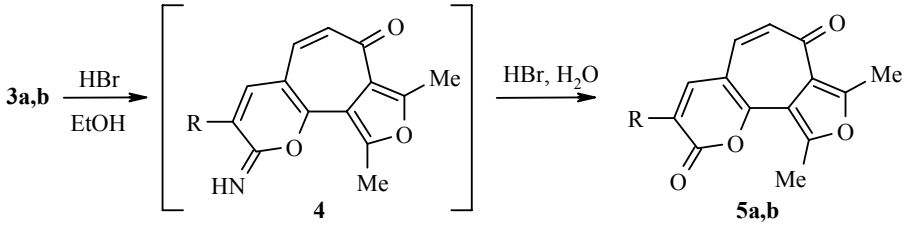
3 a R = CN, **b** R = CO_2Et

Even when heated in DMSO at 190ºC compounds **3a,b** do not undergo cyclization to the expected pyrone or its imine. The high stability of compounds **3a,b** is evidently due to the high degree of delocalization of the negative charge and lowering of the electrophilicity of the nitrile groups of the cyanovinyl substituent.

Compounds **3a,b** are brown, crystalline materials insoluble in chloroform, readily soluble in DMF and DMSO, and soluble in water.

The ^1H NMR spectra of compounds **3a,b** show signals for the furan ring methyl groups as two three – proton singlets at 2.60 ppm, two one-proton methine doublet signals in the seven-membered ring at 5.50-5.60 and 7.60-7.90 ppm, and a singlet signal for the vinyl substituent at 7.90 (**3a**) and 8.60 ppm (**3b**). The IR spectrum of compound **3a** showed sharp, partially overlapping bands for the stretching vibrations of the nitrile groups at 2200 and 2186 cm^{-1}. The broad, strong multiplet band at 1600-1526 cm^{-1} evidently corresponds to C=O and C=C stretching vibrations of the ionized oxodienol fragment in the seven-membered ring. The lowering of the carbonyl stretching frequency is due to the high degree of conjugation and delocalization of the negative charge in this fragment [11].

However, cyclization of compounds **3a,b** can be achieved under acid catalyzed conditions by refluxing with excess 46% HBr in alcohol to give the pyrones **5a,b**. The nitrile group takes part in the cyclization and the intermediate pyroneimine **4** undergoes hydrolysis to pyrone **5**. In the case of compound **3a** the reaction is accompanied by hydrolysis of the second CN group to an amide. A similar acid catalyzed reaction has been reported before [12].



4 **5a,b**

5 a R = $CONH_2$, **b** R = CO_2Et

The synthesis of pyrones **5a,b** can be carried out in one vessel from the hydroxytropone **1** without separation of the compounds **3a,b**.

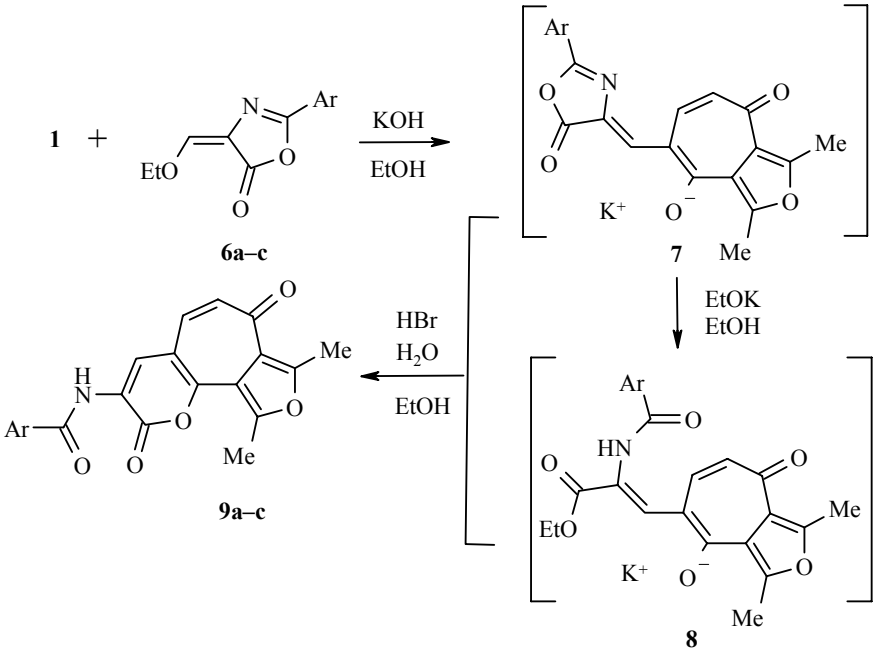
Compounds **5a,b** are yellow, crystalline materials; compound **5a** is soluble in DMF and **5b** readily soluble in chloroform.

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
3a	$C_{15}H_9KN_2O_3$	59.07 / 59.20	3.07 / 2.98	8.97 / 9.20	>300 (dec.)	60
3b	$C_{17}H_{14}KNO_5$	57.95 / 58.11	4.27 / 4.02	3.70 / 3.99	>300 (dec.)	45
5a	$C_{15}H_{11}NO_5$	63.23 / 63.16	3.77 / 3.89	4.71 / 4.91	>300 (dec.)	64
5b	$C_{17}H_{14}O_6$	65.01 / 64.97	4.27 / 4.49	—	190-200	85
9a	$C_{21}H_{15}NO_5$	69.77 / 69.80	4.33 / 4.18	3.52 / 3.88	229-230	55
9b	$C_{21}H_{14}ClNO_5$	63.82 / 63.73	3.61 / 3.57	3.21 / 3.54	220-221	51
9c	$C_{21}H_{14}FNO_5$	66.57 / 66.49	3.91 / 3.72	3.31 / 3.69	231-232	45

The ^{1}H NMR spectra of compounds **5a,b** show singlet signals for the furan ring methyl groups at 2.70-2.90, seven-membered ring methine proton doublets at 6.30-7.30, and a pyran proton singlet at 8.20-8.50 ppm. The spectrum of **5a** also shows the presence of a broad two- proton singlet for the amide group at 7.85 ppm and the spectrum of **5b** a triplet (1.40 ppm) and quartet (4.40 ppm) for the ethyl group protons.

The IR spectrum of pyrone **5b** has bands for the lactone carbonyl of the pyrone ring (1766 cm^{-1}) [13], an ester carbonyl (1700 cm^{-1}), conjugated seven-membered ring carbonyl (1633 cm^{-1}), and a system of conjugated C=C bonds at 1586 cm^{-1}.



6-9 a Ar = Ph, **b** Ar = 2-ClC$_6$H4, **c** Ar = 4-FC$_6$H$_4$

In order to synthesize 3-benzamido-2H-pyran-2-ones the hydroxytropone **1** was treated with the 2-aryl-4-ethoxymethylene-4H-1,3-oxazol-5-ones **6a-c**. The reactions were performed in the presence of KOH in alcohol as before. The potassium salt of the vinyl derivative **7** or **8** formed underwent cyclization without separation using 46% HBr in alcohol. Hence a one vessel synthesis gave the target 3-benzamido-2H-pyran-2-ones **9a-c**.

TABLE 2. Spectroscopic Characteristics of the Compounds Synthesized

Compound	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ , ppm (*J*, Hz)*
3a	2200, 2186, 1600, 1573, 1526	2.56 (3H, s); 2.62 (3H, s); 5.56 (1H, d, *J* = 13); 7.64 (1H, d, *J* = 13); 7.87 (1H, s)
3b	2180, 1666, 1600, 1580, 1526, 1206	1.20 (3H, t, *J* = 8); 2.57 (3H, s); 2.60 (3H, s); 4.14 (2H, q, *J* = 8); 4.20 (1H, s); 5.49 (1H, d, *J* = 13); 7.88 (1H, d, *J* = 13); 8.62 (1H, s)
5a	3446, 3326, 1733, 1680, 1633, 1613, 1586, 1540, 1213	2.64 (3H, s); 2.78 (3H, s); 6.17 (1H, d, *J* = 13); 7.22 (1H, d, *J* = 13); 7.86 (2H, br. s); 8.54 (1H, s)
5b	1766, 1700, 1633, 1613, 1586, 1540, 1226	1.37 (3H, t, *J* = 8); 2.71 (3H, s); 2.88 (3H, s); 4.37 (2H, q, *J* = 8); 6.29 (1H, d, *J* = 13); 6.77 (1H, d, *J* = 13); 8.22 (1H, s)
9a	3446, 1713, 1666, 1633, 1606, 1206	2.75 (3H, s); 2.85 (3H, s); 6.38 (1H, d, *J* = 13); 6.84 (1H, d, *J* = 13); 7.50-7.65 (3H, m); 7.91 (2H, d, *J* = 8); 8.62 (2H, br. s)
9b	3345, 1726, 1673, 1640, 1626, 1540, 1226	2.76 (3H, s); 2.84 (3H, s); 6.39 (1H, d, *J* = 13); 6.85 (1H, d, *J* = 13); 7.36-7.54 (3H, m); 7.80 (1H, d, *J* = 8); 8.62 (1H, s); 8.78 (1H, br. s)
9c	3393, 1713, 1666, 1640, 1620, 1540, 1233	2.77 (3H, s); 2.86 (3H, s); 6.39 (1H, d, *J* = 13); 6.82 (1H, d, *J* = 13); 7.22 (2H, dd, *J* = 9); 7.92 (2H, dd, *J* = 9, *J* = 4)

* The ^1H NMR spectra of compounds **3a,b, 5a** were recorded in DMSO-d_6 and compounds **5b, 9a-c** in $CDCl_3$.

Compounds **9a-c** are yellow-greenish, crystalline materials soluble in DMF, chloroform, and acetonitrile.

The ^1H NMR spectra of pyranones **9a-c** show furan ring three-proton methyl group singlets at 2.86 and 2.83 ppm, seven-membered ring one methine protons doublets at 6.40-6.82, aryl group protons signals at 7.20-7.90, a pyran ring proton singlet at 8.60, and a broad N–H proton singlet at 8.55-8.77 ppm.

The IR spectrum of compound **9a** shows absorption bands for the N–H stretching vibrations at 3446 cm^{-1}, a pyrone ring lactone carbonyl (1713), amide carbonyl (1666), seven-membered ring carbonyl (1633), C=C bond system (1606), and C–O fragment (1240 cm^{-1}).

Hence 8-hydroxy-1,3-dimethyl-4H-cyclohepta[*c*]furan-4-one in the presence of KOH shows a high nucleophilic reactivity when treated with the electrophilic alkenes ethoxymethylene malononitrile, ethylcyanoacetate, and 2-aryloxazol-5-ones. For the first two reagents pure cyanovinyl derivatives can be isolated as their potassium salts. The later readily cyclize to the novel target condensed 2H,7H-furo-[3',4':6,7]cyclohepta[1,2-*b*]pyran system under acid catalyzed conditions. A one vessel reaction of hydroxytropone **1** with the 2-aryl-4-ethoxymethylene-4H-1,3-oxazol-5-ones occurs in two stages, initially base catalyzed and then using acid to give the corresponding 3-benzamido-2H-pyran-2-ones.

EXPERIMENTAL

The IR spectra of the samples prepared were recorded on a Specord IR-71 instrument using vaseline oil. ^1H NMR spectra were taken on Bruker DPX-250 (250 MHz) and Varian VXR-300 (300 MHz) spectrometers using $CDCl_3$ as deuterated solvent. ^{13}C NMR spectra were taken on a Varian VXR-300 (75 MHz) Unity spectrometer using $CDCl_3$. Internal TMS was used as a standard for both.

8-Hydroxy-1,3-dimethyl-4H-cyclohepta[*c*]furan-4-one was prepared by a method developed before [14]. Ethoxymethylenemalononitrile, ethoxymethylenecyanoacetate, and ethoxymethyleneoxazones were prepared by the reaction of the corresponding active methylene compound with triethylorthoformate and acetic anhydride by a known method.

Potassium Salt of [(8-Hydroxy-1,3-dimethyl-4-oxo-4H-cyclohepta[*c*]furan-7-yl)methylene]malononitrile (3a). A solution of KOH (0.14 g) in ethanol (5 ml) was added to a suspension of the 8-hydroxytropone **1** (0.48 g, 2.5 mmol) and ethoxymethylenemalononitrile (0.31 g, 2.5 mmol) in ethanol (5 ml) and refluxed with stirring for 5 min. Precipitation of the product began after 1-2 min. The reaction mixture was left overnight at room temperature. The product was filtered off and washed with ethanol to give pure material. The purity of the product fell with attempts to recrystallized it.

Potassium Salt of Ethyl 2-Cyano-3-(8-hydroxy-1,3-dimethyl-4-oxo-4H-cyclohepta[*c*]furan-7-yl)-acrylate (3b). Obtained similarly to compound **3a** from the 8-hydroxytropone **1** (0.48 g, 2.5 mmol) and ethoxymethylenecyanoacetate (0.42 g, 2.5 mmol). The product was also pure without recrystallization.

8,10-Dimethyl-2,7-dioxo-2H,7H-furo[3',4':6,7]cyclohepta[1,2-*b*]pyran-3-carboxamide (5a). HBr (46%, 1 ml) was added to a suspension of compound **3a** (0.76 g, 2.5 mmol) in ethanol (10 ml). The solution was refluxed for 5 min and water (50 ml) was added portionwise. The reaction mixture was left overnight at room temperature. The product was filtered off, washed with water, dried, and purified by crystallization from $MeNO_2$ to give greenish crystals.

Ethyl 8,10-Dimethyl-2,7-dioxo-2H,7H-furo[3',4':6,7]cyclohepta[1,2-*b*]pyran-3-carboxylate (5b) was prepared similarly to compound **5a** from compound **3b** (0.88 g, 2.5 mmol) and 46% HBr (1 ml) in ethanol 10 ml). Yellow-greenish crystals (MeCN). ^{13}C NMR spectrum, δ, ppm: 14.1, 14.6, 16.6, 61.8, 110.5, 112.1, 112.9, 119.0, 130.3, 134.2, 153.7, 154.8, 157.5, 159.1, 161.9, 162.6, 183.7.

8,10-Dimethyl-2,7-dioxo-2H,7H-furo[3',4':6,7]cyclohepta[1,2-*b*]pyran-3-carboxamide (5a) (one vessel reaction). KOH (0.14 g) in ethanol (5 ml) was added to a suspension of 8-hydroxytropone **1** (0.48 g, 2.5 mmol) and ethoxymethylenemalononitrile (0.31 g, 2.5 mmol) in ethanol (5 ml) and refluxed for 5 min with stirring. 46% HBr (1 ml) was then added. The solution was refluxed for 5 min and water (50 ml) was added portionwise. The reaction mixture was left overnight at room temperature. The product was filtered off, washed with water, dried, and purified by recrystallization from $MeNO_2$. One vessel product yield 41%.

Ethyl 8,10-Dimethyl-2,7-dioxo-2H,7H-furo[3',4':6,7]cyclohepta[1,2-*b*]pyran-3-carboxylate (5b) was prepared in a single vessel similarly to compound **5a**. The precipitate was recrystallized from MeCN. Final product yield 60%.

N-(8,10-Dimethyl-2,7-dioxo-2H,7H-furo[3',4':6,7]cyclohepta[1,2-*b*]pyran-3-yl)benzamide (9a) was prepared in one vessel similarly to compound **5a** from the 8-hydroxytropone **1** (0.48 g, 2.5 mmol) and 4-ethoxymethylene-2-phenyl-4H-1,3-oxazol-5-one (**6a**) (0.54 g, 2.5 mmol). Yellow-greenish crystals (MeCN). ^{13}C NMR spectrum, δ, ppm: 15.1, 16.6, 112.1, 112.5, 119.6, 122.9, 127.5 (2C), 128.9, 129.4 (2C), 131.5, 133.0, 133.7, 135.7, 151.9, 153.6, 157.6, 158.9, 166.4, 184.5.

3-(2-Chlorophenylcarboxamido)-8,10-dimethyl-2,7-dioxo--2H,7H-furo[3',4':6,7]cyclohepta[*b*]pyran (9b) was prepared similarly to compound **9a** from compound **1** (0.48 g, 2.5 mmol) and 2-(2-chlorophenyl)-4-ethoxymethylene-4H-1,3-oxazol-5-one (**6b**) (0.99 g , 2.5 mmol). Yellow-green crystals (MeCN).

8,10-Dimethyl-2,7-dioxo-3-(4-fluorophenylcarboxamido)-2H,7H-furo[3',4':6,7]cyclohepta[b]pyran (9c) was prepared similarly to compound **9a** from tropone **1** (0.48 g, 2.5 mmol) and 4-ethoxy-methylene-2-(4-fluorophenyl)-4H-1,3-oxazol-5-one (**6c**) (0.95 g, 2.5 mmol). Yellow-green crystals ($MeCN–H_2O$, 2:1).

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