Convenient Preparative Methods for *N*-Aryl-γ-pyridones from γ-Pyrones

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2-Hydroxymethyl-5-methoxy-4-*H*-pyran-4-one (**1**) reacts with aniline and six aniline derivatives in very dilute aqueous hydrochloric acid at reflux temperature to give the *N*-aryl-γ-pyridone. A second procedure utilizes the aromatic amine hydrochloride by reacting it with **1** in aqueous medium at reflux temperature. *p*-Nitroaniline hydrochloride and **1** give the *N*-aryl-γ-pyridone in 65% yield, as opposed to 12% from the dilute acid procedure.

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The chemistry of monocyclic γ-pyrones previously has been investigated in this laboratory, including a study of the synthesis and attempted cyclization of β-(4*H*-pyran-4-on-3-yloxy)propionic acid [1], ^{13}C nmr spectra of kojic acid and other 4-pyrone derivatives [2], and formation of novel pyridone derivatives from a bromination product of maltol [3]. In the latter, it was reported that reaction with concentrated aqueous ammonia at room temperature gave the pyridone from bromomaltol methyl ether. In the present paper, we describe two procedures for converting γ-pyrones to *N*-aryl-γ-pyridones.

Studies of pyridone synthesis in other laboratories are extensive [4]. Of considerable interest is synthesis of several *N*-arylpyridones from maltol in which a sealed tube procedure utilizing reaction temperatures of 150° was employed [5]. Use of sealed tubes is a deterrent to large-scale synthesis, although the procedure is quite reliable and has been applied in this laboratory to small-scale synthesis of the pyridone from kojic acid monomethyl ether and ammonium hydroxide.

In an attempt to circumvent sealed tube reactions, **1** was reacted with aniline-water at reflux. In one instance, a very low yield of the pyridone was obtained. Reaction of **1** with aniline and aqueous base at reflux gave no product.

Reaction of **1** with aniline in very dilute hydrochloric acid then was attempted. A reaction period of twenty-four hours at reflux resulted in *N*-phenyl-2-hydroxymethyl-5-methoxy-γ-pyridone (**2**) in 68% yield. The reaction of **1** in very dilute hydrochloric acid then was extended to *p*- and *m*-toluidine, *p*-fluoroaniline, *p*-anisidine, *m*-(trifluoromethyl)aniline, and *m*-chloroaniline to give the *N*-aryl-γ-pyridones **3**, **6**, **4**, **5**, **7**, and **8** respectively. Physical constants for *N*-arylpyridones **2**, **3**, **4**, and **5**, which were isolated and characterized, are reported in Table I. *N*-Arylpyridones **2**, **3**, **5**, **6**, **7**, and **8**, were converted to the hydrochlorides, data for which are listed in Table II. Hydrochlorides of *N*-aryl-γ-pyridones have been reported previously [4c,4e]. Pyridone **4** was converted to the hydrochloride, which was characterized by nmr and ir spectra (Experimental). The hydrochloride then was converted by means of aqueous base to the free *N*-arylpyridone **4** (Table I), which crystallized readily from methanol. The dilute acid-catalyzed procedure with aniline has been extended to 2,6-dimethyl-γ-pyrone and to kojic acid to give the pyridone in 48 and 60% yields respectively. Bromomaltol gave tarry products.

The procedure described herein is similar to that reported for preparing pyridones from meconic acid [4d].

Table I

Physical Constants of *N*-Aryl-γ-pyridones

Pyridone	Mp, °C	Yield, %	Formula	Analysis % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
2	227-228 [b]	68	$C_{13}H_{13}NO_3$	67.52	5.66	6.05	67.40	5.67	5.92
3	191-194 [c]	69	$C_{14}H_{15}NO_3$	[a]	[a]	[a]	[a]	[a]	[a]
4	274-276 [d]	60	$C_{13}H_{12}FNO_3$	62.65	4.85	5.62	62.60	4.86	5.59
5	216-218 [d]	74	$C_{14}H_{15}NO_4$	64.36	5.79	5.36	64.22	5.69	5.29

[a] Characterized as hydrochloride. [b] Crystallized from EtOAc-EtOH (1:2). [c] Crystallized from EtOAc-MeOH (3:1). [d] Crystallized from MeOH.

The reaction of γ-pyrone itself with aniline and other aromatic amines in approximately 6*N* hydrochloric acid gives *N*-aryl-γ-pyridones in excellent yields, as reported several years ago [4e].

Extension of the dilute acid method to *p*-nitroaniline and **1** gives a 12% yield of the pyridone, and a tar. However, a second procedure using the solid amine hydrochloride in aqueous solution with **1** gives N-*p*-nitrophenyl-2-hydroxymethyl-5-methoxy-γ-pyridone in 65% yield. The second procedure also is useful in preparing an ^{15}N-labelled pyridone [6].

The following equilibria may occur under the reaction conditions employed in the pyridone syntheses described:

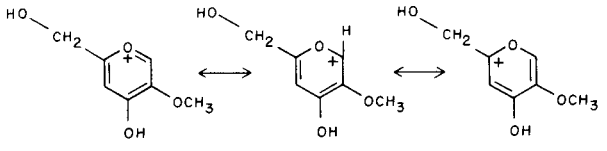
(1) Amine + HCl ⇌ Amine hydrochloride

(2) Pyrone + HCl ⇌ Pyroxonium salt or

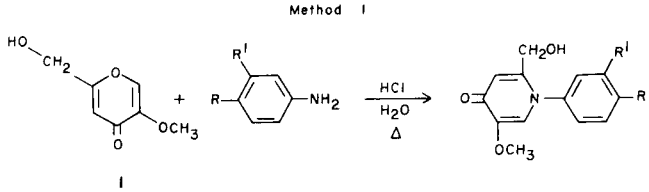
Pyrone + amine hydrochloride ⇌ Pyroxonium salt + amine

(3) Pyroxonium salt + amine → → → Pyridone + H_2O

Presumably, resonance of the following type in the pyroxonium salt is important:



The nitrogen atom of the weakly basic aromatic amine would be sufficiently nucleophilic to explain attack at $C_{(2)}$ [or $C_{(6)}$] of the pyroxonium salt. Attack at similar positions of the free pyrone is not precluded, however. The exact nature of subsequent intermediates leading to the pyridone is not known. Nucleophilic attack at $C_{(2)}$ of structurally related pyrylium salts is well-documented [7].



1

2, R = R^1 = H

3, R = CH_3, R^1 = H

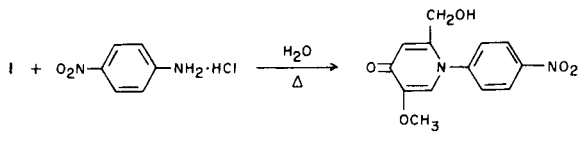
4, R = F, R^1 = H

5, R = OCH_3, R^1 = H

6, R = H, R^1 = CH_3

7, R = H, R^1 = CF_3

8, R = H, R^1 = Cl



EXPERIMENTAL

Melting points were taken in capillary tubes on a Mel-Temp apparatus, and are uncorrected. ^1H nmr spectra were determined with a Varian A-60D spectrometer, with chemical shifts (δ) reported in ppm downfield from internal tetramethylsilane. Infrared spectra were measured on a Beckman Acculab Infrared Spectrometer. Elemental analyses were performed by MicroTech Laboratory, Skokie, Illinois.

2-Hydroxymethyl-5-methoxy-4*H*-pyran-4-one (**1**).

Kojic acid was mono-O-methylated by the literature procedure [8], to give **1**.

N-Phenyl-2-hydroxymethyl-5-methoxy-γ-pyridone Hydrochloride. Method 1.

To 5.00 g of 2-hydroxymethyl-5-methoxy-4*H*-pyran-4-one (**1**), suspended in 100 ml of dilute hydrochloric acid (2 ml concentrated hydrochloric acid diluted to 100 ml), was added 4.0 g aniline. The resulting mixture was heated under reflux for 24 hours. The aqueous solution was extracted with two 25-ml portions of ethyl acetate, which were discarded. The aqueous phase was treated with solid sodium carbonate until basic. Evaporation of the basic solution to *ca.* 50 ml caused precipitation of a tan crystalline product, which was collected by filtration and air-dried. Recrystallization of the tan solid from ethyl acetate-ethanol (1:2) gave *N*-phenyl-2-hydroxymethyl-5-methoxy-γ-pyridone (**2**) in 5.0 g yield (67%). The mp and spectral data were determined from **2** prepared by Method 2.

To 450 mg of the pyridone **2** was added *ca.* 10 ml of concentrated hydrochloric acid, which was heated until solution was complete. Evaporation of the acidic solution to dryness gave a residue, which was dissolved in a small quantity of methanol; addition of methylene chloride to turbidity followed by strong cooling overnight gave the pyridone hydrochloride, which was collected by filtration and air-dried; yield 420 mg, mp 213-215°; nmr (DMSO-d_6): δ 4.00 (s, 3H, OCH_3), 4.30 (s, 2H, $-CH_2O-$), 7.72 (s, 5H, aromatic), 7.81 (s, 1H, pyridone H_3), 8.39 (s, 1H, pyridone H_6); ir (potassium bromide): 3260, 3230, 3060, 3020, 2990-2780 (nine bands), 2680, 2645, 2610, 2560-2410 (six bands), 1640, 1620, 1595, 1580, 1550, 1515, 1495, 1470, 1455, 1430, 1390, 1360, 1355, 1295, 1265, 1240, 1225, 1210, 1190, 1150, 1100, 1080, 1040, 1020, 1000, 985, 885, 855, 785, 760, 710, 675, 645, cm^{-1}. For analytical data, see Table II.

N-Phenyl-2-hydroxymethyl-5-methoxy-γ-pyridone (**2**). Method 2.

To a solution of 1.00 g of aniline hydrochloride in 25 ml of water was added 1.2 g of 2-hydroxymethyl-5-methoxy-4*H*-pyran-4-one (**1**). The resulting mixture was heated under reflux for 24 hours. The reaction mixture was neutralized with solid sodium carbonate and evaporated to dryness. The off-white residual solid was treated with 20 ml methanol, heated gently, and inorganic salts filtered off. The methanolic filtrate was evaporated to dryness, and the residual solid crystallized from ethyl acetate-methanol (5:1) with cooling in a refrigerator overnight; yield of **2**, 500 mg. Mother liquor work-up gave an additional 90 mg of **2**, total yield 590 mg (33%), mp 227-228°; nmr (DMSO-d_6): δ 3.65 (s, 3H, OCH_3), 4.00 (d, 2H, $-CH_2O$), 5.49 (t, 1H, O*H*), 6.37 (s, 1H, pyridone H_3), 7.29 (s, 1H, pyridone H_6), 7.50 (s, 5H, aromatic); ir (potassium bromide): 3220, 3070, 3020, 2970, 2950, 1635, 1570, 1535, 1490, 1460, 1445, 1395, 1365, 1300, 1285, 1240, 1225, 1160, 1100, 1080, 1060, 1035, 1010, 1000, 970, 885, 855, 770, 750, 730, 700, 670, 630 cm^{-1}. For analytical data, see Table I.

N-*p*-Fluorophenyl-2-hydroxymethyl-5-methoxy-γ-pyridone (**4**).

2-Hydroxymethyl-5-methoxy-4*H*-pyran-4-one (1.55 g) was suspended in 50 ml of dilute hydrochloric acid (1 ml of concentrated hydrochloric acid diluted to 50 ml). *p*-Fluoroaniline (2 g) was added, and the resulting mixture heated under reflux for 24 hours. Tan colored crystals precipitated upon cooling to room temperature; yield 2.66 g (2 crops). The product was dissolved in 20 ml concentrated hydrochloric acid by gentle heating. Upon cooling to room temperature, the pyridone hydrochloride (1.5 g, mp 163-166°) precipitated; nmr (DMSO-d_6): δ 3.92 (s, 3H, OCH_3), 4.24 (s,

Table II

Hydrochlorides of *N*-Aryl-γ-pyridones

HCl Salt of	Mp, °C	Molecular Formula	Analysis					
			Calcd.			Found		
			C	H	N	C	H	N
2	213-215 [a]	$C_{13}H_{14}ClNO_3$	58.32	5.27	5.23	58.05	5.01	5.13
3	197-199 [b]	$C_{14}H_{16}ClNO_3$	59.69	5.72	4.97	58.99	5.54	4.82
5	210-211 [c]	$C_{14}H_{16}ClNO_4$	56.48	5.42	4.70	56.72	5.37	4.64
6	202-204 [d]	$C_{14}H_{16}ClNO_3$	59.69	5.72	4.97	59.30	5.63	4.83
7	174-176 [a]	$C_{14}H_{13}ClF_3NO_3$	50.09	3.90	4.17	50.10	3.95	4.17
8	209-211 [b]	$C_{13}H_{13}Cl_2NO_3$	51.67	4.34	4.63	51.59	4.31	4.54

[a] Recrystd. from CH_3OH-CH_2Cl_2. [b] Recrystd. from MeOH-EtOAc. [c] Recrystd. from conc. HCl. [d] Recrystd. from Me_2CO-MeOH (8:1).

2H, CH_2O), 7.23-7.85 (m, 5H, aromatic and pyridone H_3), 8.32 (s, 1H, pyridone H_6); ir (potassium bromide): 3540, 3220, 3080-2890 (seven bands), 2840, 2640, 2500, 1710, 1625, 1575, 1550, 1510, 1470, 1460, 1445, 1425, 1390, 1360, 1330, 1295, 1265, 1235, 1220, 1200, 1165, 1150, 1105, 1095, 1085, 1030, 1020, 1005, 995, 890, 870, 840, 830, 810, 765, 745, 725, 655, 630 cm^{-1}.

N-*p*-Fluorophenyl-2-hydroxymethyl-5-methoxy-γ-pyridone hydrochloride (1.00 g) was suspended in 50 ml of 5% sodium carbonate and the mixture stirred for 10 minutes. The resulting solid was collected by filtration, air-dried, and recrystallized from a small quantity of methanol to give the free pyridone in 708 mg yield, mp 274-276°; nmr (DMSO-d_6): δ 3.65 (s, 3H, OCH_3), 4.02 (d, 2H, CH_2O), 5.45 (t, 1H, O*H*), 6.36 (s, 1H, pyridone H_3), 7.30 (s, 1H, pyridone H_6), 7.18-7.70 (m, 4H, aromatic); ir (potassium bromide): 3220, 3080, 3050, 3000, 2970, 2940, 2900, 2840, 1635, 1575, 1470, 1450, 1425, 1400, 1310, 1270, 1225, 1165, 1155, 1095, 1065, 1025, 1015, 990, 980, 885, 865, 855, 840, 810, 780, 720, 635 cm^{-1}. For analytical data see Table I.

N-*p*-Nitrophenyl-2-hydroxymethyl-5-methoxy-γ-pyridone Hydrochloride. Method 1.

To 3.65 g of 2-hydroxymethyl-5-methoxy-4*H*-pyran-4-one (**1**) suspended in 100 ml of dilute hydrochloric acid (2 ml of concentrated hydrochloric acid diluted to 100 ml) was added 2.65 g of *p*-nitroaniline. The resulting mixture was heated under reflux for 24 hours, filtered to remove tar and excess amine, and the filtrate extracted with 2 x 50 ml of methylene chloride (discarded). The aqueous phase was neutralized with solid sodium carbonate and permitted to evaporate slowly to dryness over 3 days. The solid residue was dissolved as much as possible in 150 ml of boiling water, filtered, and the hot filtrate treated with decolorizing charcoal. After filtration, the aqueous filtrate was cooled in a refrigerator overnight to give the pyridone as a yellow solid, yield 855 mg (12%). The pyridone was dissolved in 10 ml of concentrated hydrochloric acid by heating; evaporation of the acid solution to dryness, followed by recrystallization of the residue from methanol gave 650 mg of the hydrochloride; mp 202-205°, with softening at 194°.

Method 2.

A 0.8 g quantity of **1** was suspended in 30 ml of water, and 1.34 g of *p*-nitroaniline hydrochloride added. The mixture was heated under reflux for 24 hours, a small quantity of tar removed by filtration, and the filtrate neutralized with solid sodium carbonate. The resulting precipitate was collected by filtration. The filtrate was permitted to evaporate to dryness, and the crystalline solid combined with the first precipitate. The combined solids were chromatographed in acetic acid solution on Woelm polyamide (slurry-packed in glacial acetic acid, column diameter 1 inch). Elution with 250 ml of glacial acetic acid gave the pyridone (920 mg, 65%).

The hydrochloride was prepared as described in Method 1, yield 880 mg, mp 202-205°; nmr (DMSO-d_6): δ 3.99 (s, 3H, OCH_3), 5.57 (s, 2H, CH_2O), 7.20-8.33 (m, 6H, aromatic and pyridone protons); ir (potassium bromide): 3460, 3260, 3070, 2850, 2730, 2680, 2540, 1655, 1620, 1590, 1510, 1490, 1460, 1450, 1400, 1345, 1285, 1255, 1215, 1210, 1180, 1175, 1165, 1110, 1000, 995, 895, 885, 870, 850, 805, 750, 665, 630 cm^{-1}.

Anal. Calcd. for $C_{13}H_{13}ClN_2O_5$: N, 8.95. Found: N, 8.61.

N-Phenyl-2-hydroxymethyl-5-hydroxy-γ-pyridone.

To a suspension of 5.5 g kojic acid in 100 ml of dilute hydrochloric acid (2 ml of concentrated hydrochloric acid diluted to 100 ml) was added 5.5 g aniline. The resulting mixture then was heated under reflux for 20 hours. The mixture, while warm, was extracted with 2 x 50 ml of chloroform, which was discarded. The aqueous phase became heterogeneous rapidly, and was neutralized with solid sodium carbonate. The aqueous mixture stood in a hood overnight; filtration followed by further evaporation, gave two crops of the title pyridone. The product was recrystallized from methanol, yield 4.6 g (60%), mp 237-240°, with softening at 233° (lit [9] mp 238°); nmr (DMSO-d_6): δ 4.20 (s, 2H, CH_2O), 6.48 (s, 1H, pyridone H_3), 7.32 (s, 1H, pyridone H_6), 7.50 (s, 5H, aromatic); ir (potassium bromide): 3230, 3050, 1645, 1580, 1520, 1490, 1460, 1390, 1370, 1330, 1315, 1260, 1235, 1155, 1085, 1035, 1000, 980, 855, 840, 795, 785, 775, 705, 645 cm^{-1}.

Anal. Calcd. for $C_{12}H_{11}NO_3$: N, 6.45. Found: N, 6.19.

Dedication

This paper is dedicated to Professor Dr. Karl Kratzl, Organic Chemical Institute of the University of Vienna, Vienna, Austria on the occasion of his seventieth birthday.

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