An Approach to Substituted 4-Hydroxypyran-2-ones

Mai-ly Ramirez,† Donna Garey,† and Michael R. Peña*

Department of Chemistry and Biochemistry, Arizona State University
Box 871604, Tempe, AZ 85287-1604

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We examined a method for the preparation of 4-hydroxypyran-2-ones in two steps from aryl ketones and ethyl malonyl chloride (or ethyl 2-methylmalonyl chloride). These 4-hydroxypyran-2-ones are useful precursors as they may be transformed in two steps to the 2-methoxypyran-4-ones, which is found in phenoxan — a naturally occurring compound discovered to have anti-HIV activity.

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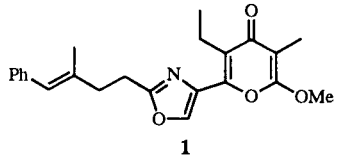
Phenoxan **1** is a recently isolated natural product which was discovered to have anti-HIV activity [1]. The mechanism of action was unknown until recent work by Parke-Davis researchers showed that substituted pyran-2-ones, such as **2**, are effective inhibitors of HIV-protease *in vitro* [2]. During the course of a total synthesis of phenoxan, we needed a method for preparing substituted pyran-2-ones **4** from a ketone (Scheme 1) *via* **3**. The need was dictated by the oxazole portion due to the availability of methyl 3-oxazolecarboxylate or 3-oxazolecarboxaldehyde. We examined



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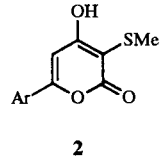

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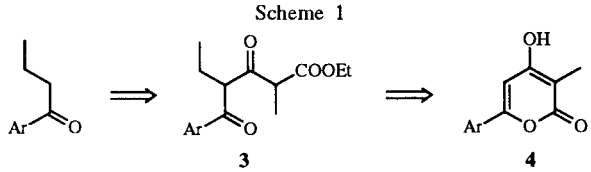
several methods for preparing pyran-2-ones and quickly discovered their limitations. We eventually settled on a two step process for preparing 4-hydroxypyran-2-ones based on the carbon acylation of an enolate with substituted ethyl malonyl chloride followed by an acid-catalyzed cyclization. These 4-hydroxypyran-2-ones are useful precursors as they may be transformed to the desired 2-methoxypyran-4-ones according to a literature procedure [3] which would prove useful in an eventual total synthesis of phenoxan.

Scheme 1

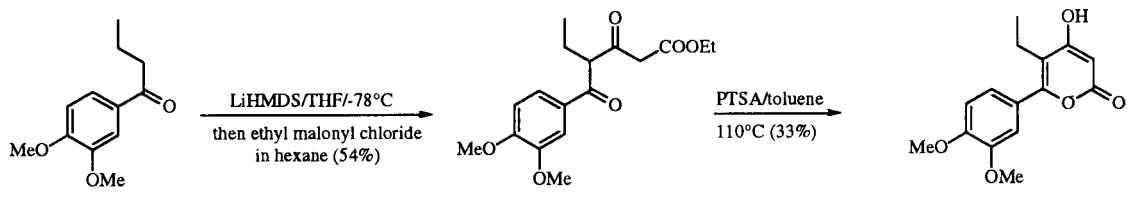


3 **4**

Results and Discussion.

There are a number of methods for preparing substituted 4-hydroxypyran-2-ones [4] and these include addition of a dimethoxyketene acetal enolate to acid chlorides followed by acid catalyzed cyclization [5], carboxylation of dicarbanions followed by cyclization [6], and Friedel-Crafts acylation of glutaconic anhydride followed by cyclization to the pyrone [7]. Some of these methods in our hands were useless for constructing the required pyranone as intermediates were highly unstable or exceedingly difficult to purify [8]. One method that did attract our attention was the carbonyl diimidazole promoted cyclization of diketoacids [6] which, in turn, were prepared by treatment of a diketone dianion with carbon dioxide. This method inspired us to examine diketoesters for preparing pyran-2-ones. The diketoesters were prepared from the appropriate ketone, **5**, **8a**, or **8b**, by treatment with lithium hexamethyldisilylamide [9] and ethyl malonyl chloride (Scheme 2) or ethyl 2-methylmalonyl chloride (Scheme 3). Diluting the reaction mixture with hexane increased the carbon-to-oxygen acylation ratio and gave acceptable yields (46-54% yield) of the desired products after purification by flash column chromatography. Ketones, **5** and **8a-b**, were easily obtained by addition of propylmagnesium bromide to the appropriate aldehyde followed by oxidation using pyridinium chlorochromate [10]. The ^{1}H and ^{13}C-nmr spectra of the diketoesters indicated mostly the keto-form with a trace (~8%) of the enol form. The diketoesters were employed in a variety of reaction conditions to examine cyclization to the pyran-2-one. We discovered that catalytic *p*-toluenesulfonic acid in hot toluene effected an acid-catalyzed ring closure for certain substrates, for

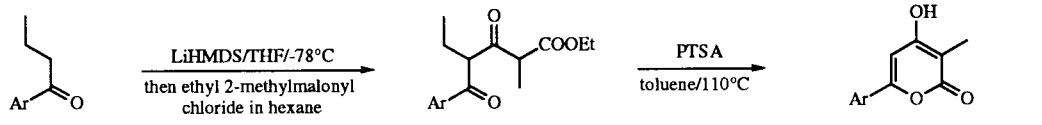
Scheme 2



5 **6** **7**

examples, **6** to **7**, **9a** to **10a**, and **9b** to **10b**. The low yields of the cyclization may be attributed to decomposition of the diketoesters. The pyran-2-ones were found to be in excellent agreement with ^1H, ^{13}C, ms, and elemental analysis. The pyran-2-ones can be converted to the desired 2-methoxypyran-4-ones as found in phenoxan, according to a literature procedure [3]. This was exemplified by conversion of **10a** to **11** (Scheme 4). Spectral data of **11** (^1H and ^{13}C) closely matched the corresponding pyran-4-one portion of phenoxan. Future work will examine optimizing the acylation-cyclization reaction for preparing other pyran-2-ones and adaptation of this methodology to an eventual total synthesis of phenoxan.

Scheme 3

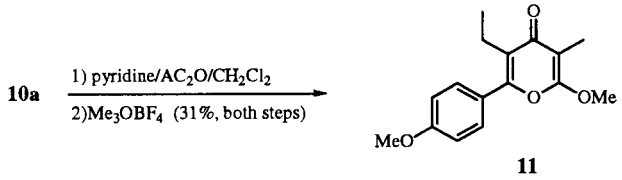


8a Ar = 4-methoxyphenyl
b Ar = 2,4-dichlorophenyl

9a Ar = 4-methoxyphenyl (46%)
b Ar = 2,4-dichlorophenyl (50%)

10a Ar = 4-methoxyphenyl (31%)
b Ar = 2,4-dichlorophenyl (21%)

Scheme 4



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EXPERIMENTAL

General Methods.

All solvents were distilled from calcium hydride prior to use except for tetrahydrofuran which was distilled from molten potassium and ethyl ether which was distilled from sodium-benzophenone. Anhydrous methanol (Mallinckrodt) was distilled from magnesium. All reagents were used as obtained from commercial suppliers unless otherwise noted. Thin layer chromatography was performed with Machery-Nagel glass-backed precoated plates (Si-254F). Column chromatography utilized either EM Science or Baxter Scientific Products silica gel 230-400 mesh, 60Å. The proton and carbon nmr spectra were recorded on a Varian Gemni 300 MHz spectrometer (300 MHz ^1H, 75 MHz ^{13}C). The following deuterated solvents and their following internal reference points were used: deuteriochloroform with tetramethylsilane referenced to tetramethylsilane (0.000 ppm ^1H) or chloroform (77.00 ppm ^{13}C); methanol-d_4 referenced to methanol (3.48 ppm ^1H and 39.00 ppm ^{13}C); and dimethyl sulfoxide-d_6 referenced to dimethyl sulfoxide (2.50 ppm ^1H and 39.5 ppm ^{13}C). Mass spectra were obtained on a Finnigan-MAT Model 312 spectrometer. Melting points were obtained on a Mel-Temp apparatus and are uncorrected. Elemental analysis were performed by Atlantic Microlab, Inc.

1-(3,4-Dimethoxyphenyl)-1-butanone (**5**).

The ketone, prepared in two steps from 3,4-dimethoxybenzaldehyde with propylmagnesium bromide followed by pyridinium chlorochromate oxidation, was obtained as a white crystalline solid [11]; R_f = 0.44 (12% ethyl acetate/hexane), mp 61-62°; ^1H (deuteriochloroform): δ 0.96 (t, 3H, J = 7.35 Hz), 1.74 (m, 2H), 2.8 (t, 2H, J = 7.35 Hz), 3.9, 3.91 (2s, 6H), 6.85 (d, 1H, J = 8.3 Hz), 7.50 (d, 1H, J = 2 Hz), 7.51-7.57 (dd, 1H, J = 2.1, 8.3 Hz); ^{13}C (deuteriochloroform): δ 199.8, 153.6, 149.6, 130.9, 123.1, 110.6, 110.3, 56.2, 56.1, 40.2, 18.2, 14.0; ms: m/z 208 (M^+), 165 (M^+ - C_3H_7), 137 (M^+- C_3H_7O).

1-(4-Methoxyphenyl)-1-butanone (**8a**).

The ketone, prepared in two steps by the reaction of *p*-anisaldehyde with propylmagnesium bromide followed by pyridinium chlorochromate oxidation, was obtained as a viscous oil [12]; R_f = 0.29 (12% ethyl acetate/hexane); ^1H (deuteriochloroform): δ 0.93 (t, 3H, J = 7.3 Hz), 1.65-1.72 (m, 2H), 2.8 (t, 2H, J = 7.2 Hz), 3.76 (s, 3H), 6.84 (d, 2H, J = 8.7 Hz), 7.8 (d, 2H, J = 8.7 Hz); ^{13}C (deuteriochloroform): δ 198.7, 171.0, 163.1, 130.0, 113.4, 55.1, 39.8, 17.7, 13.6; ms: m/z 178 (M^+), 135 (M^+- C_3H_7), 107 (M^+- C_4H_7O).

1-(2,4-Dichlorophenyl)-1-butanone (**8b**).

The ketone, prepared in two steps by the reaction of 2,4-dichlorobenzaldehyde with propylmagnesium bromide followed by pyridinium chlorochromate oxidation, was obtained as a viscous oil [13]; R_f = 0.51 (12% ethyl acetate/hexane); ^1H (deuteriochloroform): δ 0.82 (t, 3H, J = 7.5 Hz), 1.53-1.60 (m, 2H), 2.7 (t, 2H, J = 7.2 Hz), 7.13 (br s, 1H), 7.13-7.16 (dd, 1H, J = 1.8, 8.4 Hz), 7.27 (m, 2H); ^{13}C (deuteriochloroform): δ 202.1, 137.8, 137.0, 131.9, 130.3, 129.9, 127.2, 44.7, 17.6, 13.6; ms: m/z 216 (M^+), 173 (M^+- C_3H_7), 145 (M^+- C_4H_7O).

Ethyl 5-(3,4-Dimethoxyphenyl)-4-ethyl-3,5-dioxopentanoate (**6**).

General Procedure.

Into a 250 ml round bottomed flask, chilled to -78°, was placed 40 ml of tetrahydrofuran, 2.43 ml (11.5 mmoles) of hexamethyldisilazane, 40 ml of tetrahydrofuran, and 6.6 ml (10.56 mmoles) of n-butyllithium. The solution was stirred for 15 minutes before a solution of 2.0 g of ketone **5** (in 5 ml tetrahydrofuran) was added *via* cannula. The enolate was stirred at -78° for 15 minutes before 40 ml of hexane was added. The enolate was slowly treated (over 5 minutes) to 0.73 ml (5.76 mmoles) of ethyl malonyl chloride, dissolved in 30 ml of hexane, *via* cannula. The reaction mixture was stirred at -78° for 30 minutes and then allowed to warm to room temperature for 30 minutes. The reaction mixture was poured into

a separatory funnel containing water and ether. The organic layer was washed several times with water, brine, and dried over magnesium sulfate. Filtration and evaporation of solvent *in vacuo* left an oil which was further purified by column chromatography (25% ethyl acetate/hexane) to give 1.1 g (54% yield) of **6** as a pale yellow viscous oil which slowly crystallized upon standing; R_f = 0.19 (25% ethyl acetate/hexane); ^1H (deuteriochloroform): δ 0.94 (t, 3H, J = 7.4 Hz), 1.05-1.25 (m, 3H), 1.82-1.87 (m, 2H), 3.33 (s, 2H), 3.75, 3.77 (2s, 6H), 4.0-4.1 (q, 2H), 4.51 (t, 1H), 6.8 (d, 1H, J = 8.46 Hz), 7.51 (d, 1H, J = 1.98 Hz), 7.6-7.65 (dd, 1H, J = 2.0, 8.4 Hz); ^{13}C (deuteriochloroform): δ 199.0 194.8, 166.9, 154.0, 149.2, 129.4, 123.5, 110.3, 110.0, 90.1, 62.5, 55.7, 55.5, 46.7, 22.0, 13.4, 11.4; ms: m/z 322 (M^+).

6-(3,4-Dimethoxyphenyl)-5-ethyl-4-hydroxypyran-2-one (**7**).

General Procedure.

Into a 25 ml round bottomed flask was placed 460 mg (1.42 mmoles) of **6**, 5 mg of *p*-toluenesulfonic acid, and 75 ml of toluene. The reaction mixture was heated to reflux under nitrogen until tlc analysis showed complete consumption of starting material (about 2 days). The reaction was chilled in an ice bath for 1 hour and filtered to yield 130 mg (33% yield) of **7**, essentially pure, as judged by ^1H and ^{13}C-nmr, mass spectroscopy, and hplc analysis, R_f = 0.10 (75% ethyl acetate/hexane), mp 189° dec; ^1H (dimethyl sulfoxide-d_6): δ 1.09 (t, 3H, J = 7.29 Hz), 2.34 (q, 2H, J = 7.34 Hz), 3.78, 3.80 (2s, 6H), 5.43 (s, 1H), 7.04-7.1 (m, 3H), 11.92 (s, 1H); ^{13}C (dimethyl sulfoxide-d_6): δ 171.1, 163.5, 158.7, 150.6, 149.0, 125.4, 121.7, 113.5, 112.1, 111.8, 90.0, 55.8, 18.5, 14.3; ms: m/z 276 (M^+).

Anal. Calcd. for $C_{15}H_{16}O_5$: C, 65.20; H, 5.83. Found: C, 64.91; H, 5.77.

Ethyl 5-(4-Methoxyphenyl)-4-ethyl-2-methyl-3,5-dioxopentanoate (**9a**).

This compound was prepared according to the general procedure from **8a** and ethyl 2-methylmalonyl chloride [14]; R_f = 0.37 (25% ethyl acetate/hexane); ^1H (deuteriochloroform): δ 0.83-0.90 (m, 3H), 1.01 (t, 3H), 1.06-1.15 (m, 2H), 1.23 (d, 2H), 1.8-2.0 (m, 2H), 3.8 (s, 3H), 6.8-6.9 (m, 2H), 7.8-7.9 (m, 2H); ^{13}C (deuteriochloroform): δ 201.3, 195.3, 170.2, 164.1, 131.1, 129.4, 114.1, 62.3, 61.4, 55.6, 51.2, 22.6, 13.8, 12.3; ms: m/z 306 (M^+), 178 (M^+- $C_6H_8O_3$).

6-(4-Methoxyphenyl)-5-ethyl-4-hydroxy-3-methylpyran-2-one (**10a**).

This compound was prepared according to the general procedure from **9a** and catalytic *p*-toluenesulfonic acid in toluene, R_f = 0.18 (50% ethyl acetate/hexane), mp 160-161°; ^1H (methanol-d_4): δ 1.17 (t, 3H, J = 7.2 Hz), 1.97 (s, 3H), 2.47 (q, 2H, J = 7.4 Hz), 3.84 (s, 3H), 7.0-7.03 (d, 2H, J = 8.9 Hz), 7.45-7.48 (d, 2H, J = 8.8 Hz); ^{13}C (methanol-d_4): δ 169.2, 169.0, 163.4, 158.2, 132.2, 127.4, 116.9, 116.0, 101.1, 57.0, 21.1, 15.8, 10.1; ms: m/z 260.0 (M^+), 135 (M^+- $C_7H_9O_2$).

Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.21; H, 6.19. Found: C, 68.99; H, 6.21.

Ethyl 5-(2,4-Dichlorophenyl)-4-ethyl-2-methyl-3,5-dioxopentanoate (**9b**).

This compound was prepared according to the general procedure from **8b** and ethyl 2-methylmalonyl chloride, R_f = 0.32 (12% ethyl acetate/hexane); ^1H (deuteriochloroform): δ 1.01 (t, 3H, J = 7.4 Hz), 1.15-1.2 (m, 3H), 1.37 (d, 3H), 2.11 (m, 2H), 3.47 (q, 1H), 4.09-4.13 (q, 2H), 5.46 (t, 1H, J = 7.3 Hz), 7.11-7.30 (m, 3H); ^{13}C (deuteriochloroform): δ 169.3, 167.6, 142.4, 134.6, 133.2, 133.1, 131.7, 129.6, 126.8, 125.8, 61.5, 45.9, 19.2, 13.9, 13.4, 13.2; ms: m/z 344 (M^+), 216 (M^+ - $C_6H_9O_3$), 173 (M^+ - $C_9H_{15}O_3$).

6-(2,4-Dichlorophenyl)-5-ethyl-4-hydroxy-3-methylpyran-2-one (**10b**).

This compound was prepared according to the general procedure from **9b** and catalytic *p*-toluenesulfonic acid in toluene; R_f = 0.43 (75% ethyl acetate/hexane); mp 205-206°; ^1H (methanol-d_4): δ 0.98-1.03 (t, 3H, J = 7.4 Hz), 1.98 (s, 3H), 2.21-2.24 (br q, 2H), 7.42-7.48 (m, 2H), 7.63 (br s, 1H); ms: m/z 298 (M^+), 283 (M^+- CH_3), 263 (M^+ - Cl), 173 (M^+- $C_7H_9O_2$).
Anal. Calcd. for $C_{14}H_{12}Cl_2O_3$: C, 56.21; H, 4.04. Found: C, 56.27; H, 4.05.

6-(4-Methoxyphenyl)-5-ethyl-2-methoxy-3-methylpyran-4-one (**11**).

Into a 50 ml round bottomed flask was placed 100 mg (0.65 mmole) of **10a**, 10 ml of dichloromethane, 0.04 ml (0.460 mmole) of pyridine, and 0.039 ml (0.040 mmole) of acetic anhydride. The reaction mixture was stirred overnight at room temperature. The reaction was worked up by pouring into a separatory funnel containing aqueous sodium bicarbonate and ethyl acetate. The organic layer was washed several times with water, brine, and dried over sodium sulfate. Filtration and evaporation of solvent *in vacuo* left a yellow oil which was quickly carried to the next step. The crude acetate was treated with 65 mg (1.30 mmoles) of trimethyloxonium tetrafluoroborate overnight at 70°. The reaction mixture was worked up by quenching with dilute aqueous sodium bicarbonate and extracting with ethyl acetate. The organic layer was washed with water, brine, and dried over sodium sulfate. Filtration and evaporation of solvent *in vacuo* left a red oil which was further purified by column chromatography (50% ethyl acetate/hexane) to give 33.1 mg (31% yield) of **11** as a tan solid, along with 18.7 mg of **10a**. The product was recrystallized from 12% ethyl acetate/hexane, R_f = 0.34 (50% ethyl acetate/hexane); mp 115-116°;^1H (deuteriochloroform): δ 1.08 (t, 3H, J = 7.4 Hz), 1.84 (s, 3H), 2.39-2.46 (q, 2H, J = 7.4 Hz), 3.80 (s, 3H), 3.90 (s, 3H), 6.91 (d, 2H, J = 8.79 Hz), 7.39 (d, 2H, J = 8.79 Hz); ^{13}C (deuteriochloroform): δ 180.8, 162.3, 160.7, 155.4, 129.7, 124.9, 124.3, 114.0, 99.9, 55.4, 55.4, 19.1, 13.7, 6.9; ms: m/z 274 (M^+), 273 (M^+- 1).
Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 70.11; H, 6.59.

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† Undergraduate research participants.

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