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An Improved Aldol Protocol for the Preparation of 6-Styrenylpyrones

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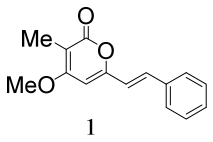
ABSTRACT

An improved aldol protocol for the synthesis of 6-styrenylpyrones is reported. The first synthesis of PTP1B inhibitor **1** and **4** has been described.

Styrenyl pyrones are an emerging class on natural products. Representative examples include penstyrylpyrone (**1**),[1] 5,6-dehydrokawain (**2**),[2] 11-methoxy yangonin (**3**)[3] and pyrone **4**[4]. They exhibit anti-obesity effects,[5] collagenase inhibition,[6] anti-influenza activity,[7] PTP1B inhibitory activity,[1] and HIV neuraminidase inhibition[8].



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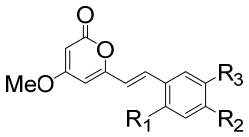

2: $R_1 = R_2 = R_3 = H$
3: $R_1 = H$, $R_2 = R_3 = OMe$
4: $R_1 = OMe$, $R_2, R_3 = OCH_2O$

Figure 1. Representative Styrylpyrones

These compounds have been synthesized from pyrones by Wittig reactions,[9] Heck reactions,[10] Suziki-Miyaura reactions,[11] and aldol reactions[12]. The aldol reaction is the most commonly used strategy for preparing styrenyl pyrones. Typical conditions for the aldol reaction of **5** with aromatic aldehydes involve the reaction of **5** and the aromatic aldehyde with excess magnesium methoxide in boiling methanol. Yields typically range from 20-40%.

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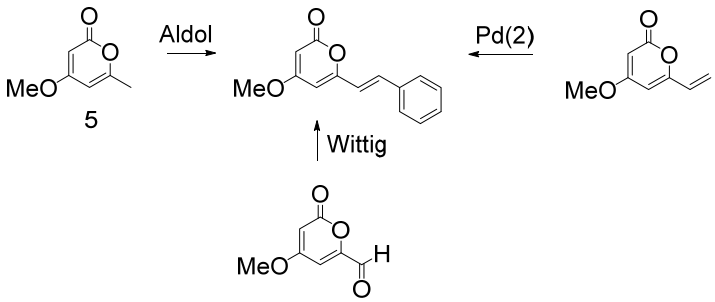
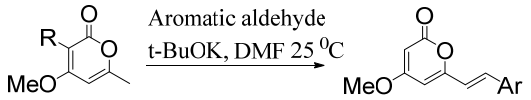


Scheme 1. Synthesis of 6-styrenylpyrones.

We prepared pyrone **2** from **5**[12] using this method and obtained a yield of only 29%. Evaluation of the co-products showed that a Meerwein-Pondorf-Verley reduction of benzaldehyde to benzyl alcohol was a significant side reaction. However, even with three equivalents of benzaldehyde, the yield of **2** was not significantly improved. Deprotonation of **5** with stronger bases has been reported and the results vary with the substitution pattern on the pyrone. Lyga had reported that the reaction of pyrone **5** with lithium diisopropylamide (LDA) furnished the aldol adduct at C-3 of the pyrone.[13] Interestingly, 4-methoxypyrones substituted with alkyl groups at both C-5 and C-6 afforded the deprotonation product at the methyl group at C-6.[14] Additionally, reaction of **5** at -78 °C with n-butyl lithium also produced the C-3 lithiated pyrone.[15]

Because we needed multigram quantities of styrenylpyrones, we sought alternate conditions. Pyrones **5** and **6** (prepared from commercially available 4-hydroxy-3,6-dimethylpyrone by O-methylation) were used. Commercially available bases that might reversibly deprotonate the methyl group at C-6 along with a range of dipolar aprotic solvents were evaluated. The reaction of **5** and benzaldehyde with anhydrous potassium carbonate in DMF at 25 °C or P_4-tBu in DMF gave complicated product mixtures. The reaction with potassium tert-butoxide at 25 °C afforded adduct **2** in 53% yield. Lowering the reaction temperature to 0 °C resulted in the yield of 31%. The reaction of **5** with potassium tert-butoxide in dry DMSO afforded the styrenyl pyrone in low yield. Optimal reaction conditions

involved adding solid potassium tert-butoxide in portions to a solution of the aromatic aldehyde and **5** in DMF at ambient temperature.[16] The use of a commercial solution of 1M potassium tert-butoxide in THF afforded a yield of 30%.



5: R = H
6: R = Me

Scheme 2. Improved aldol conditions.

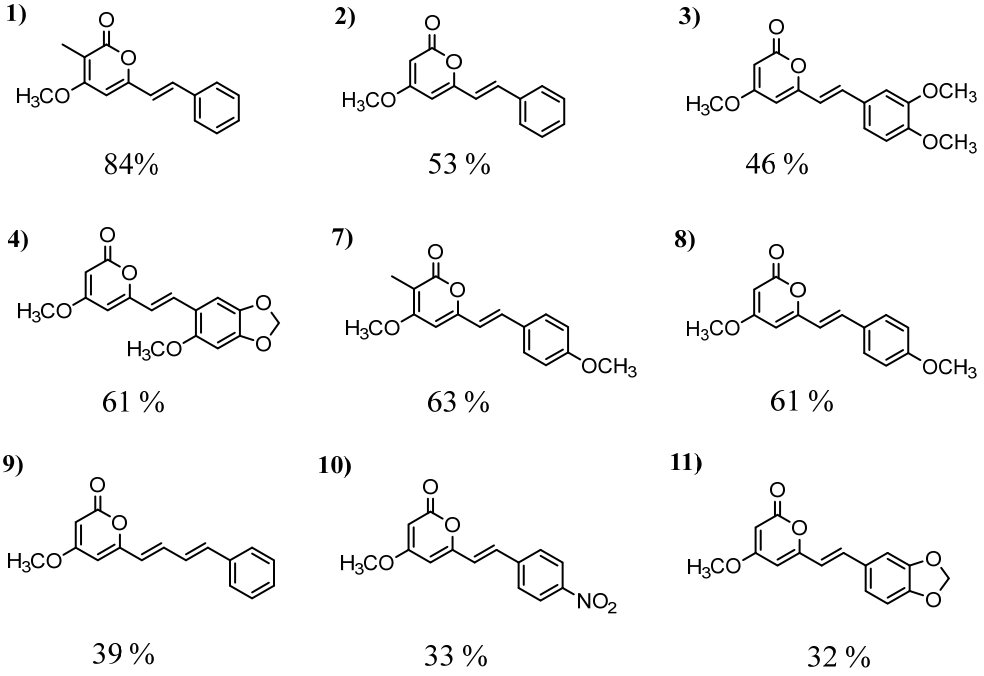


Figure 2. Aldol products.

In summary, an improved preparation of 6-styrenylpyrones has been developed. The reaction proceeds in good yields, is operationally convenient, and is compatible with a variety of functional groups. This reaction has been conducted on a gram scale.

The results from a series of aldol reactions are shown below in Figure 2. Functional groups such as ethers, alkenes, and acetals are compatible with our reaction conditions. Nitro substituted aldehydes afforded adducts in poor yields. Adducts derived from pyrone **6** afforded slightly better yields, presumably due to the absence of the acidic hydrogen atom at C-3.

Acknowledgments

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18. Representative procedure: To a stirred solution of 4-methoxy-6-methyl-2-pyrone (0.067g, 0.47mmol) in DMF (1 mL) at room temperature was added benzaldehyde (0.1 mL, 0.95 mmol). Potassium tert-butoxide solid (0.1g, 0.95mmol) was then added portion wise to it and stirred for 2 days at room temperature. Solution became dark red in color. This was extracted with diethyl ether (3 x 10 mL). For the compounds **3, 4, 8, 9, 10** methylene chloride was used for the extraction. The organic layer was washed with brine (3 x 20 mL), water (5 x 20 mL), dried over MgSO4, and concentrated in vacuo. The crude product was purified by preparative thin layer chromatography (EtOAc/hexanes) to afford the product.

(*E*)-4-methoxy-3-methyl-6-styryl-2H-pyran-2-one (Penstyrylpyrone) (1) (84%) Bright yellow solid: mp 197-199 ^{0}C; ^{1}H NMR (300 MHz, CDCl3) δ 7.53 (d, 2H), 7.49 (d, J = 16 Hz, 1H), 7.40 (d, 2H), 7.35(t, 1H), 6.65 (d, J = 16Hz, 1H), 6.17 (s, 1H), 3.91 (s, 3H), 1.97 (s, 3H) ppm. HRMS (ESI-QTOF) calcd for $C_{15}H_{15}O_3$ $[M+H]^+$ 243.0943, found 243.1016. . ^{13}C NMR data agreed with the literature.[1]

(*E*)-4-methoxy-6-styryl-2H-pyran-2-one (5, 6-dehydrokawain) (2) (53%) Yellow solid: mp 131-133 ^{0}C (Lit[16] 134 – 136 ^{0}C); ^{1}H NMR (300 MHz, CDCl3) δ 7.52 (d, 2H), 7.48(d, J = 16Hz, 1H), 7.37 (d, 2H), 7.35 (t, 1H), 6.60 (d, J = 16Hz, 1H), 5.94 (d, 1H), 5.50 (d, 1H) 3.82 (s, 3H) ppm. HRMS (ESI-QTOF) calcd for $C_{14}H_{13}O_3$ $[M+H]^+$ 229.0859, found 229.0861. . ^{13}C NMR data agreed with the literature.[16]

(*E*)-4-methoxy-6-(2-(6-methoxybenzo[1,3]dioxol-5-yl)vinyl)-2H-pyran-2-one (4) (61%) brown solid: mp 187-189 ^{0}C (Lit[4] 189 – 191 ^{0}C); ^{1}H NMR (300 MHz, CDCl3) δ 7.74 (d, J = 16Hz, 1H), 6.96(s, 1H), 6.52 (s, 1H), 6.47(d, J = 16Hz, 1H), 5.94 (s, 2H), 5.91 (d, 1H), 5.45 (d, 1H) 3.84 (s, 3H), 3.82 (s, 3H) ppm. HRMS (ESI-QTOF) calcd for $C_{16}H_{15}O_6$ $[M+H]^+$ 303.0863, found 303.0867. ^{13}C NMR data agreed with the literature.[4]

(*E*)-4-methoxy-6-(4-methoxystyryl)-2H-pyran-2-one (Yangonin) (8) (61%) yellow solid: mp 146-148 ^{0}C (Lit[16] 148 – 150 ^{0}C); ^{1}H NMR (300 MHz, CDCl3) δ 7.47 (d, 2H), 7.46(d, J = 16Hz, 1H), 6.91 (d, 2H), 6.46 (d, J = 16 Hz, 1H), 5.88 (d, 1H), 5.46 (d, 1H) 3.89 (s, 3H) ppm. HRMS (ESI-QTOF) calcd for $C_{15}H_{15}O_4$ $[M+H]^+$ 259.0892, found 259.0965. ^{13}C NMR data agreed with the literature.[16]

(*E*)-4-methoxy-6-(4-nitrostyryl)-2H-pyran-2-one (10) (33%) yellow solid: mp 209-211 ^{0}C (Lit[17] 211.5 – 214 ^{0}C); ^{1}H NMR (300 MHz, CDCl3) δ 8.25 (d, 2H), 7.62 (d, 2H), 7.57 (d, J = 16Hz, 1H), 6.73 (d, J = 16 Hz, 1H), 6.04 (d, 1H), 5.54 (d, 1H), 3.85 (s, 3H) ppm. HRMS (ESI-QTOF) calcd for $C_{14}H_{12}NO_5$ $[M+H]^+$ 274.0637, found 274.0714. . ^{13}C NMR data agreed with the literature.[12]