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An unexpected ring-opening of a 2-pyrone ring at low temperatures. A mild and expeditious synthesis of novel coumarins

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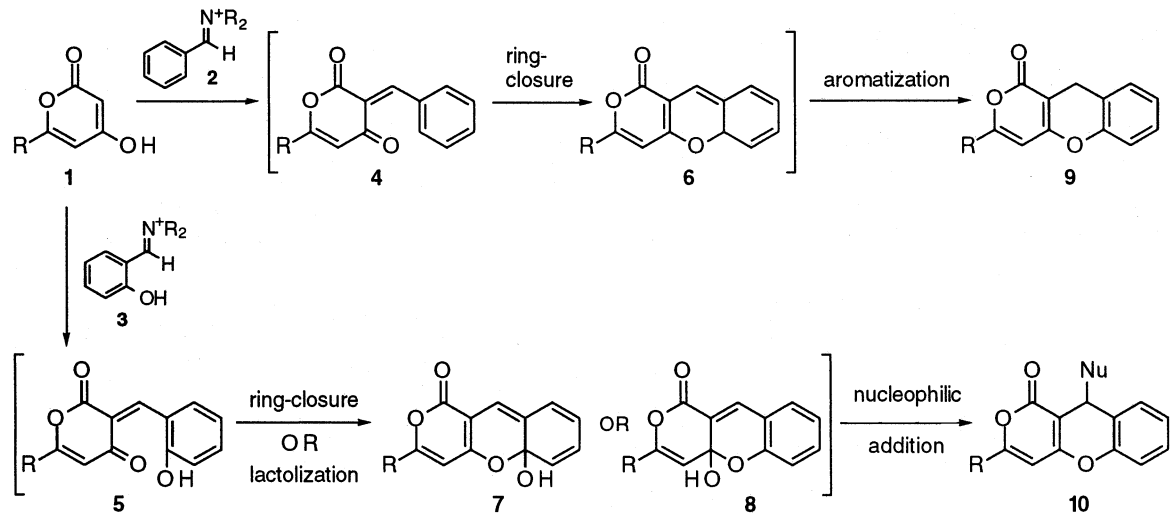
Abstract—When the iminium salts of *ortho*-hydroxy arylaldehydes were condensed with a 4-hydroxy-2-pyrone at room temperature or well below, a series of unique coumarins were isolated via a translactonization at the expense of an unexpected ring-opening of the 2-pyrone nucleus.

Coumarin is an important structural motif present in a variety of natural and unnatural products that possess significant biological activities.[1–3] Given its immense medicinal value, new protocols for the preparation of coumarins have been continuously sought after, ranging from transition metal-catalyzed processes[4] to classical lactonizations.[5] We have been studying reactions of α,β-unsaturated iminium salts with various 1,3-diketo equivalents.[6–9] These reactions proceed in a tandem process consisting of a Knoevenagel condensation,[10,11] followed by a 6π-electron electrocyclic ring-closure,[12] leading to unique approaches for constructing complex heterocycles. These studies led us to also examine the use of iminium salts generated from aromatic aldehydes.[13]

As shown in Scheme 1, we envisioned that reactions of 4-hydroxy-2-pyrones, such as **1**, with the iminium salt **2** or **3** could lead to Knoevenagel condensation products **4** or **5**, and subsequent ring-closure and/or lactol formation could lead to intermediates such as **6**, **7**, or **8**. Aromatization and/or nucleophilic additions could lead



Scheme 1.

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to useful heterocycles such as **9** and **10**.[14] However, instead we isolated a product that was neither **9** nor **10** but a coumarin as a result of translactonization due to an unexpected ring-opening of the 2-pyrone ring under neutral conditions and at temperatures even well below room temperature. We report here our findings and its application as a mild and expeditious synthesis of various novel coumarins.

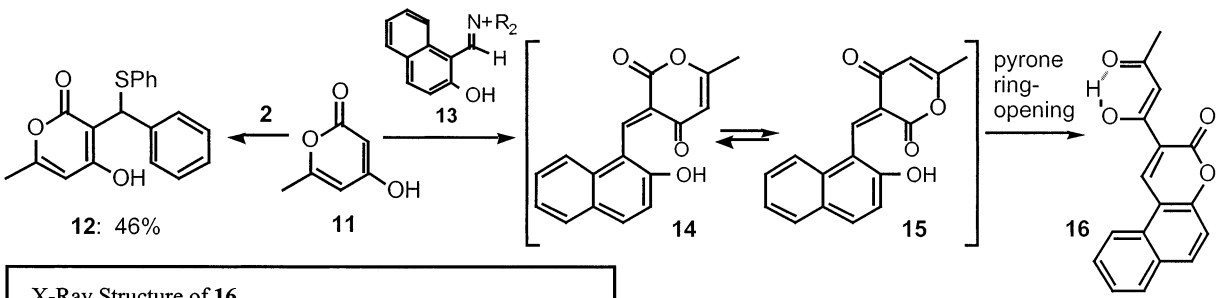
When 6-methyl-4-hydroxy-2-pyrone **11** was heated at 78°C with 1.0 equiv. of the iminium salt **2**, generated in situ by using 0.24 equiv. of piperidinium acetate,[15] and 3.0 equiv. of PhSH in EtOH, the only identifiable product was the pyrone **12** in 46% yield (Scheme 2).[13a] On the other hand, under the identical conditions, the iminium salt **13** provided the coumarin **16**[15] in 75% yield, but the product structure was not assigned until it was revealed by X-ray crystal structure analysis. The same product was also observed in 60% yield in the absence of PhSH.

Given the structural assignment of **16**, it can be suggested that a translactonization had occurred via the intermediate **15** after the initial Knoevenagel condensation, thereby resulting in a rather unexpected ring-opening of the pyrone nucleus in **15**. More significantly, although such a process had been noted by Moreno-Mañas in his studies as a caution at much higher temperatures,[13b–d] we found that it occurs rapidly even at temperatures well below room temperature, and that the nature of the solvents made no apparent differences (Scheme 2).

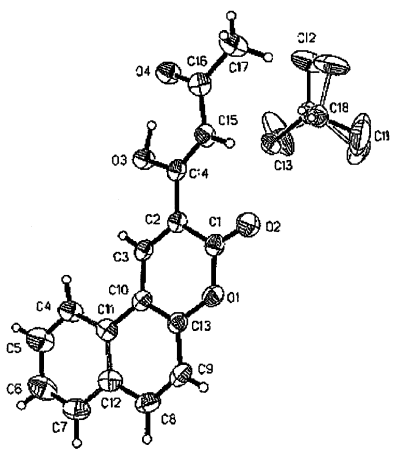
Knoevenagel condensation–lactonization using acyclic β-ketoesters is known to be very useful for the synthesis of coumarins.[5] However, a similar sequence that would involve ring-opening of a 2-pyrone ring is unusual at temperatures well below room temperature and, in this case, many elegant tandem processes involving the Knoevenagel condensation and 4-hydroxy-2-pyrones (and its equivalents) would not have become synthetically attractive.[10,11] While the mechanism leading to the coumarin **16** is quite straightforward after its structural elucidation, it is still noteworthy that none of the other commonly expected products[13] were seen under these conditions.

These results led us to explore the generality of this reaction for the preparation of useful coumarins. As shown in Scheme 3, coumarins such as **17**–**19** may be prepared readily in high yields at room temperature by using the appropriate *ortho*-hydroxy arylaldehydes treated with 0.24 equiv. of piperidinium acetate. Compound **19** closely represents the AB ring of recently isolated sesquiterpene coumarins, pallidones A and B,[3c] and, thus, the methodology described here can be a useful approach to these new natural products.

We have described here an efficient synthesis of coumarins via an unexpected ring-opening of a 2-pyrone nucleus at low temperatures. Given the availability of both starting materials, the *ortho*-hydroxy arylaldehydes and 4-hydroxy-2-pyrones, and given the importance of coumarins, this mild preparation should be synthetically useful leading to coumarin derivatives of high value in medicinal chemistry.



X-Ray Structure of **16**

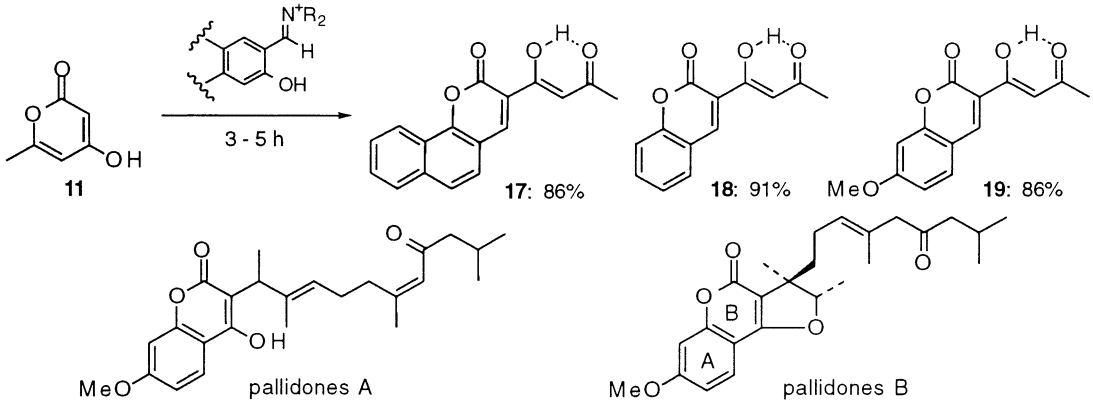


additive	temp [time]	solvent	yield
3.0 eq PhSH	78 °C [18 h]	EtOH	75%
None	78 °C [5 h]	EtOH	60%
None	25 °C [5 h]	EtOH	58%
None	-10 °C [8 h]	EtOH	58%
None	- 50 °C [12 h]	EtOH	58%
None	25 °C [3 h]	EtOAc/ 5% MeOH	86%
None	25 °C [10 h]	CH_3CN	63%

The iminium salt **13** was generated *in situ* from 2-hydroxy-1-naphthaldehyde using 0.24 eq piperidinium acetate salt.

All yields are isolated yields.

Scheme 2.



Scheme 3.

Acknowledgements

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15. **General procedure**. To a stirring solution of 1.00 mmol of an *ortho*-hydroxy arylaldehyde and 0.24 mmol of piperidinium acetate salt in 20 ml of an appropriate solvent was added 1.00 mmol of the 4-hydroxy-2-pyrone **11**. After stirring at 25 or −10°C for 3–10 h, the reaction mixture was concentrated, and the yellow crude solid was either recrystallized from MeOH or chromatographed using silica gel column to provide the desired coumarin product.

Selected characterization. Compound **16**: mp 218–220°C; $R_f=0.84$ (5% v/v MeOH and 45% EtOAc in Et_2O); ^1H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H), 7.08 (s, 1H), 7.42 (d, $J=9.0$ Hz, 1H), 7.59 (ddd, $J=1.5$, 7.8, 7.8 Hz, 1H), 7.73 (ddd, $J=1.8$, 7.8, 7.8 Hz, 1H), 7.89 (d, $J=8.7$ Hz, 1H), 8.05 (d, $J=9.0$ Hz, 1H), 8.32 (d, $J=8.4$ Hz, 1H), 9.33 (s, 1H); ^{13}C NMR (75 Hz, $CDCl_3$): δ 28.9, 101.6, 113.0, 116.4, 118.8, 121.6, 126.6, 129.1, 129.2, 129.4, 130.2, 135.8, 140.8, 154.8, 158.1, 172.5, 199.4; IR (thin film): 3059m, 3004m, 2967m, 2924m, 1715s, 1558m cm^{-1}; MS (EI): *m/e* (% relative intensity) 280 (26) $(M-1)^+$, 237 (12), 223 (100). Anal. calcd for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32. Found: C, 72.68; H, 4.45. Compound **17**: mp 214–216°C; $R_f=0.82$ (5% v/v MeOH and 45% EtOAc in Et_2O); ^1H NMR (300 MHz, $CDCl_3$): δ 2.29 (s, 3H), 7.07 (s, 1H), 7.55 (d, $J=9.0$ Hz, 1H), 7.68 (m, 3H), 7.88 (dd, $J=3.0$, 7.5 Hz, 1H), 8.56 (dd, $J=2.0$, 7.0 Hz, 1H), 8.76 (s, 1H); ^{13}C NMR (75 Hz, $CDCl_3$): δ 27.5, 101.4, 114.0, 115.8, 118.4, 122.9, 124.3, 125.0, 127.1, 128.0, 129.8, 136.0, 146.1, 158.4, 172.0, 198.4 (missing one peak due to overlapping); IR (thin film): 3054m, 2986m, 2305m, 1736s cm^{-1}; MS (EI): *m/e* (% relative intensity) 280 (30) $(M-1)^+$, 237 (16), 223 (100). Anal. calcd for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32. Found: C, 72.66; H, 4.42. Compound **18**: mp 210–212°C; $R_f=0.71$ (50% v/v EtOAc in hexane); ^1H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H), 7.03, (s, 1H), 7.34 (ddd, $J=1.0$ Hz, 6.6 Hz, 9.0 Hz, 2H), 7.63 (ddd, $J=1.0$, 6.6, 9.0 Hz, 2H), 8.66 (s, 1H); ^{13}C NMR (75 Hz, $CDCl_3$): δ 27.7, 101.7, 116.7, 118.4, 120.8, 125.0, 129.6, 134.0, 145.5, 154.2, 158.2, 171.8, 199.9; IR (thin film): 3054s, 2987m, 1735s cm^{-1}; MS (EI): *m/e* (% relative intensity) 230 (10) $(M-1)^+$, 215 (6), 187 (8), 173 (100). Anal. calcd for $C_{13}H_{10}O_4$: C, 66.65; H, 4.66. Found: C, 67.00; H, 4.44. Compound **19**: mp 174–176°C; $R_f=0.64$ (50% v/v EtOAc in hexane); ^1H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H), 4.00 (s, 3H), 7.05 (s, 1H), 7.19 (ddd, $J=1.5$, 7.5, 7.8 Hz, 1H), 7.26 (m, 2H), 8.63 (s, 1H); ^{13}C NMR (75 Hz, $CDCl_3$): δ 27.7, 56.3, 101.7, 105.1, 115.4, 119.1, 120.8, 124.8, 144.2, 145.7, 157.6, 171.8, 200.0 (missing one peak due to overlapping); IR (thin film): 3054s, 2987m, 2305m, 1735s cm^{-1}; MS (EI): *m/e* (% relative intensity) 260 (20) $(M-1)^+$, 245 (6), 217 (10), 203 (100). Anal. calcd for $C_{14}H_{12}O_5$: C, 64.61; H, 4.87. Found: C, 64.68; H, 4.91.