3-(2-BENZOYLALLYL)-4-HYDROXY-6-METHYLPYRAN-2-ONES: SYNTHESIS AND INTRA- AND INTERMOLECULAR NUCLEOPHILIC ADDITIONS

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Abstract - The reaction of 4-hydroxy-6-methylpyran-2-one (6) with 1-aryl-2-(dimethylaminomethyl)prop-2-en-1-ones (2) is investigated systematically in order to assess its suitability in carbon-carbon bond forming reactions as well as to provide the conditions for subsequent ring closure. Using a base-free medium the reaction affords the title 3-(2-benzoylallyl)-4-hydroxy-6-methylpyran-2-ones (7), whereas in the presence of triethylamine the pyrano[4,3-b]pyranes (8) are formed directly. This result is not necessarily contradictory to the Baldwin rules for ring closure. The structures and the mechanism defined is supported by IR and NMR spectroscopy. The intermolecular addition of further nucleophiles to the enone double bond of 7 yields miscellaneous 3-substituted 2-pyrones (14).

Introduction
Enone Mannich bases or rather their hydrochlorides (2)¹ are hitherto overlooked as substrates for ring closure reactions using ambifunctional nucleophiles. Due to the polyfunctional character of both educts, the result of the reaction cannot be predicted. In fact, the first nucleophilic attack at the enone β-position is very likely, but subsequent elimination of the amino group (under formation of a new electrophilic center) as well as direct attack at the carbonyl carbon atom seems to be possible. Our studies revealed that the nucleophilic attack always occurred at the vinyl group.²⁻⁴ We reported recently on the condensation of enone Mannich bases (2) with 2-aminopyridines and amidines as representative N,N-nucleophiles demonstrating that despite the polyfunctional character of both reactants a unique mode of reaction had taken place (see Scheme 1).²⁻³
In order to study the reactivity of other than \(N\)-nucleophiles, we first selected 4-hydroxycoumarines as representative \(O,C\)-nucleophiles and isolated 3-benzoyl-3,4-dihydro-2\(H\),5\(H\)-1-benzopyrano[4,3-\(b\)]pyran-5-

\[
\begin{align*}
\text{Method A or B} & \quad \text{DMF, 125 °C, 1.5 h} \\
\end{align*}
\]

Method A: \((\text{CH}_2\text{O})_n\) (3 equiv), Me\(_2\text{NH}_2\text{Cl}\) (2 equiv); Method B: CH\(_2\text{NMe}_2\text{Cl}\)

\[
\begin{align*}
\text{Method A: } & \quad (\text{CH}_2\text{O})_n \quad (3 \text{ equiv}) , \text{Me}_2\text{NH}_2\text{Cl} \quad (2 \text{ equiv}) ; \\
\text{Method B: } & \quad \text{CH}_2\text{NMe}_2\text{Cl} \\
\end{align*}
\]

\[
\begin{align*}
\text{R}^1 = \text{H}, 4\text{-Br}, 4\text{-Me}, 4\text{-OMe}, 3,4\text{-}(\text{OMe})_2, 3,4\text{-Cl}_2 \\
\text{R}^2 = \text{H}, 6\text{-Me}, 9\text{-Me} \\
\text{R}^3 = \text{H}, \text{t-Bu}, \text{Ph} \\
\text{R}^4 = \text{H}, \text{Me}, \text{Ph} \\
\text{R}^5 = \text{H}, \text{Br}, \text{Cl}, \text{Me} \\
\end{align*}
\]

**Scheme 1**: Synthesis of enone Mannich bases (2) and subsequent ring closures to 3, 4, and 5

ones (5) formed through an addition-elimination mechanism followed by ring closure. Here, we report on the reaction of 4-hydroxy-6-methylpyran-2-one (6) with the hydrochlorides (2) of enone Mannich bases resulting in another type of products when using the reaction conditions applied for 4-hydroxycoumarin (see Scheme 2). The spectroscopic data of the products isolated establish the structure of the 3-(2-benzoarylallyl)-4-hydroxy-6-methylpyran-2-ones (7) which should be capable to cyclize by intramolecular addition yielding pyrano[4,3-\(b\)]pyranes (8) as well as to react by intermolecular addition. According to a literature search the synthesis of such heterocycles has not yet been described. Pyrano[4,3-\(b\)]pyranones (8) bearing a different substitution pattern are well known in the literature. 3,4-Dihydro-2\(H\)-pyrano[4,3-
3,4-ethoxy-2H-pyrano[4,3-b]pyran-5-one was formed by treatment of 3-thiophenoxymethyl-4-hydroxypyran-2-one with piperidine and ethyl vinyl ether, presumably through a Diels-Alder reaction of an intermediate quinonemethide generated in situ.\textsuperscript{12} Treatment of 6-alkyl-4-hydroxypyran-2-ones with α,β-unsaturated acid chlorides led to 3,4-dihydro-2H-pyrano[4,3-b]pyran-2,5-diones or the isomeric pyran 4,5-diones depending on the reaction conditions.\textsuperscript{13-15} Another synthetic approach to 3,4-dihydro-2H-pyrano[4,3-b]pyran-4,5-diones is based upon the base-catalyzed aldol condensation of dehydroacetic acid
with aliphatic aldehydes and subsequent intermolecular Michael-type reaction.\textsuperscript{16,17} A few 3,4-dihydro-2\(H\)-pyrano[4,3-\(b\)]pyran-5-ones have been isolated from natural sources, e.g. radicinin and related molecules.\textsuperscript{13,18} In contrast, much more efforts have been directed to the preparation of 2\(H\)-pyrano[4,3-\(b\)]pyran-2,5-diones or isomeric pyran-4,5-diones. In most cases, 4-hydroxypyran-2-ones were reacted with \(\beta\)-ketoesters,\textsuperscript{19} malic acid\textsuperscript{20} as a synthetic equivalent of formylacetic acid and acetylenes.\textsuperscript{21} Other approaches require starting materials bearing already carbon atoms linked to C-3 of 4-hydroxypyran-2-ones\textsuperscript{22-24} or are produced in the course of the reaction, e.g. three component condensations with triethyl orthoformic acid and methylene active compounds.\textsuperscript{25-27}

The intermediate 3-alk-2´-enyl-4-hydroxypyran-2-ones (7) bearing a different substitution pattern in the side-chain are known in the literature. They were formed by ring closure reaction of ethyl 1-alk-2´-enylpentane-2,4-dione carboxylate\textsuperscript{28,29} or alkylation of 4-hydroxypyran-2-ones by special methods.\textsuperscript{30-33}

**Results and Discussion**

As mentioned above, we found a procedure for preparing the 3-(2-benzoylallyl)-4-hydroxy-6-methylpyran-2-ones (7) in up to 65 % yield by heating the 4-hydroxy-6-methylpyran-2-one (6) with two equivalents of the hydrochlorides (2) in dimethylformamide as the solvent to 120 - 130 °C for 1 hour. The spectroscopic characterization of the isolated products revealed that an addition-elimination mechanism had taken place (Scheme 3). In the first step, the carbon atom 3 adds to the double bond affording the saturated intermediate (9).\textsuperscript{34} Next, the third electrophilic center is generated by elimination of Me\textsubscript{2}NH\textsubscript{2}Cl to form the enone (7). Contrary to the corresponding reaction of 4-hydroxy coumarin the second addition to form the ring closed heterocycle (8) does not take place. But another approach proved successful in the exclusive formation of 8 in yields of 50 to 70 %, when reacting a solution of the educts in \(i\)-propanol in the presence of triethylamine. This cyclization follows the Baldwin rules for ring closure by "stereoelectronic control" and corresponds with 6-endo-trig-reactions. They are not necessarily disfavored for six- and seven-membered rings whereas exo-trig-reactions are favoured in formation of rings five-membered and smaller.\textsuperscript{35,36} The addition of the hydroxy group is without problems since the carbon-carbon double bond can be turned into a position which allows a transition-state-like trajectory of the hydroxy group and the correct distance for bond formation. However, ketalization is unlikely because the approach of the oxygen atom to the carbonyl double bond does not occur at an angle of about 109° as can be shown by molecule models. Obviously, attack at the keto carbonyl group of the enone Mannich base (2) by the 2-pyrone (6) with formation of the corresponding pyrano[4,3-\(b\)]pyran-2-one (10) does not occur.

The possible existence of tautomeric pyran-4-ones and their determination is important to this work, since the structurally different isomers (11) and (13) from 12 are possible ring closure reactions. In fact, NMR
spectroscopy can unambiguously distinguish between the dimethylamino compounds (10) and (11) on the one hand and the pyranocoumarins (8) and (13) on the other hand. This is not easily achieved for the 2-pyranone or 4-pyranone structures of 8 and 13, respectively. Of the methods which have been used for studying the corresponding 4-hydroxycoumarin/2-hydroxychromone tautomerism, only IR spectroscopy

![Chemical structures](attachment:image.png)

**Scheme 3:** Possible reaction mechanism for the formation of 7 and 8

has the capability to distinguish tautomeric substances both in solution and in the crystalline state.\(^{37}\) The IR spectra of the isolated products are not consistent with the conceivable follow-up products (11) and (13) giving evidence that ring closure at C-2 of the pyrane ring does not occur.
The unexpected formation of the ring opened 2-pyranone (7) prompted us to investigate some nucleophilic addition reactions to their enone structure.\textsuperscript{38,39} In first attempts we added amino compounds as examples for N-nucleophiles and obtained the β-amino ketones (14a-e), the β-ethoxy ketone (14f) using sodium ethoxide as O-nucleophile, and the β-benzylmercapto ketone (14g) from benzylthio alcohol as S-nucleophile. It is noteworthy to mention that the nucleophilic addition has to be performed at ambient temperature. Otherwise, follow-up reactions take place, mainly elimination of the nucleophile and ring closure to form 8.

![Scheme 4](image)

**Scheme 4**: Addition of various nucleophiles NuH to 7

**Building Blocks for Combinatorial Chemistry**

The general reaction pathways in nucleophilic additions described above prompted us to investigate the suitability of the enones (7) in the synthesis of small libraries in solution. Thus, the three benzyolallyl derivatives (7a-c) were brought to reaction with a mixture of five amines, namely diethylamine (D), morpholine (M), i-propylamine (I), n-butylamine (Bu), and benzylamine (Bn) (Table 1).

The reaction should afford, in principal, a mixture of 15 racemates, as one stereogenic center is generated. This mixture was analysed using liquid chromatography-MS coupling. Due to the instability of the adducts
(14) with poor abundance of the molecular ion observed in electron-impact ionization the thermospray technique was employed for ionization. The compounds (14) are eluted with an ammonium acetate-methanol gradient. Figure 1 shows the total ion chromatogram and the assignment of the various adducts. Details of the synthesis, chromatographic separation and the recording of the MS are given in the EXPERIMENTAL. The expected adducts (14) are all detectable in similar amounts despite the different reactivities of the enones. Furthermore, small amounts of the starting enones (7) and the cyclization products (8) were found. The order of elution is the same for the different amines. The adducts (14) (which are indicated in Figure 1 by the starting enone (7) and the amine D, M, I, Bu, and Bn) show a typical fragmentation pattern, i.e. the ions with 271, 301, and 339 Dalton yield the information of the starting enones (7). The ion chromatograms for these fragments are given in Figure 2. This library in solution is stable for a couple of weeks when stored at room temperature.

**Table 1: Products Obtained upon Reaction of the Enone Mannich Base (2) with 4-Hydroxy-6-methylpyran-2-one (6) and upon Nucleophilic Addition**

<table>
<thead>
<tr>
<th>Comp.</th>
<th>R</th>
<th>Nu</th>
<th>Yield (%)</th>
<th>Mp (°C)</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>H</td>
<td></td>
<td>65</td>
<td>113</td>
<td>i-propanol</td>
</tr>
<tr>
<td>7b</td>
<td>4´-OMe</td>
<td></td>
<td>50</td>
<td>125</td>
<td>i-propanol</td>
</tr>
<tr>
<td>7c</td>
<td>3´,4´-Cl$_2$</td>
<td></td>
<td>53</td>
<td>178</td>
<td>ethanol</td>
</tr>
<tr>
<td>8a</td>
<td>H</td>
<td></td>
<td>66</td>
<td>158</td>
<td>ether</td>
</tr>
<tr>
<td>8b</td>
<td>4´-OMe</td>
<td></td>
<td>48</td>
<td>171</td>
<td>a)</td>
</tr>
<tr>
<td>8c</td>
<td>3´,4´-Cl$_2$</td>
<td></td>
<td>46</td>
<td>164</td>
<td>a)</td>
</tr>
<tr>
<td>14a</td>
<td>H</td>
<td>NHBn</td>
<td>72</td>
<td>105</td>
<td>a)</td>
</tr>
<tr>
<td>14b</td>
<td>H</td>
<td>NH(CH$_2$)$_3$Me</td>
<td>94</td>
<td>135</td>
<td>ether</td>
</tr>
<tr>
<td>14c</td>
<td>H</td>
<td>NMe$_2$</td>
<td>92</td>
<td>114</td>
<td>ethanol</td>
</tr>
<tr>
<td>14d</td>
<td>H</td>
<td>NHCH$_2$CH$_2$OH</td>
<td>81</td>
<td>171</td>
<td>ethanol</td>
</tr>
<tr>
<td>14e</td>
<td>H</td>
<td>NH-2-Pyrindyl</td>
<td>45</td>
<td>175</td>
<td>a)</td>
</tr>
<tr>
<td>14f</td>
<td>H</td>
<td>OEt</td>
<td>43</td>
<td>94</td>
<td>a)</td>
</tr>
<tr>
<td>14g</td>
<td>H</td>
<td>SBN</td>
<td>70</td>
<td>84-86</td>
<td>a)</td>
</tr>
</tbody>
</table>

* a) purification by column chromatography (see EXPERIMENTAL)
However, upon prolonged standing the formation of bisadducts is observed, i.e. the adducts (14) arising from the reaction of the primary amines butylamine and benzylamine react with another equivalent of enone with formation of bisadducts, the structures of which are tentatively assigned in Figure 1 as \((7b\times7)Bu\) for example.

In summary, treatment of 4-hydroxy-6-methylpyran-2-one (6) with enone Mannich bases (2) offers a very promising, synthetically simple to perform and straightforward route to 3-(2-benzoylallyl)-4-hydroxy-6-methylpyran-2-ones (7) and the ring closed pyrano[4,3-b]pyranes (8) and can be extended to include other enolic heterocycles. The anellated heterocycles are not only interesting targets themselves but are also valuable educts for reduction or condensation processes giving potential drug molecules. Moreover, the lactones (7) are valuable intermediates for the combinatorial chemistry as is illustrated by a few examples presented in this work.
EXPERIMENTAL

General: All reactions were performed using starting materials and solvents as obtained without further purification. EI- and CI-(methane) MS were obtained on a HP5989A mass spectrometer; m/z values are reported followed by the relative intensity in parantheses. 1H and 13C NMR spectra were recorded on a Bruker instrument ARX 300 at 300 K. Chemical shifts are reported in parts per million (δ) downfield from an internal TMS reference. For all new compounds additionally 13C NMR spectra were recorded with the

![Figure 2: Ion chromatograms of characteristic fragments of the addition products (14) in the library](image)

DEPT 135 pulse sequence. IR spectra were recorded as KBr pellets on a Perkin Elmer PC1600 FT IR instrument. Elemental analyses were performed with a Heraeus CHN-analyzer at the Institute of Inorganic Chemistry at the University of Kiel. For chromatographic separation silica gel for chromatography 60 (0.063 - 0.200 mm, Merck) was employed.

3-(2-Benzoylallyl)-4-hydroxy-6-methylpyran-2-one (7a). 250 mg (2.00 mmol) of 4-hydroxy-6-methylpyran-2-one (6) and 900 mg (4.00 mmol) of 2-dimethylaminomethyl-1-phenylprop-2-en-1-one hydrochloride (2a) were suspended in 5 mL of DMF with stirring and the mixture was heated to 120 - 130 °C for 1 h. Then the reaction mixture was allowed to cool to rt, 20 mL of ice water were added and the mixture was stirred for 15 min. The solid was filtered off, washed with two portions of ice water and dried in vacuo. Recrystallization from 2-propanol afforded 352 mg (65 %) of a white solid, mp 158 °C. 1H NMR (300 MHz, CDCl3): δ 2.19 (s, 3 H, CH3), 3.50 (s, 2 H, CH2), 5.88/5.96 (2 × s, 2 × 1 H, =CH2), 6.66 (s, 1 H, =CH), 7.47 (t, J = 7.4 Hz, Phenyl-H), 7.60 (t, J = 7.1 Hz, Phenyl-H), 7.74 (d, J = 7.6 Hz, 2
H, Phenyl-H), 10.39 (br s, 1 H, OH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 19.7, 25.6, 101.1, 101.4, 128.4, 130.0, 133.2, 134.4, 136.3, 144.9, 160.6, 166.1 (2 signals), 202.1. MS (70 eV, EI): $m/z$ 270(M$^+$, 14), 166(10), 165(100), 137(7), 105(52), 85(9), 77(45), 69(9), 51(17), 43(39). IR: $\nu$ 3100 (br), 1650, 1636.

Anal. Calcd for C$_{16}$H$_{14}$O$_4$: C, 71.10; H, 5.22. Found: C, 70.92; H, 5.39.

3-[2-(4-Methoxybenzoyl)allyl]-4-hydroxy-6-methylpyran-2-one (7b). The reaction was performed in the same way and on the same scale as described above using 960 mg (4.00 mmol) of 2b to afford 290 mg (48 %) of a white solid, mp 171 °C. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.19 (s, 3 H, CH$_3$), 3.38 (s, 2 H, CH$_2$), 3.51 (s, 3 H, OCH$_3$), 5.80/5.86 (2 × s, 2 × 1 H, =CH$_2$), 6.56 (s, 1 H, =CH), 6.95 (d, $J$ = 8.9 Hz, 2 H, Phenyl-H), 7.81 (d, $J$ = 8.9 Hz, 2 H, Phenyl-H), 10.74 (s, 1 H, OH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 19.7, 25.8, 55.6, 101.5, 113.8, 128.5, 132.5, 132.8, 145.3, 160.5, 164.2, 166.3 (2 signals), 202.2. MS (70 eV, EI): $m/z$ 300(M$^+$, 11), 165(87), 135(82), 107(19), 92(25), 85(18), 77(49), 69(19), 64(19), 53(19), 43(100). IR: $\nu$ 3098 (br), 1650, 1638. Anal. Calcd for C$_{17}$H$_{16}$O$_5$: C, 67.99; H, 5.37. Found: C, 67.51; H, 5.60.

3-[2-(3,4-Dichlorobenzoyl)allyl]-4-hydroxy-6-methylpyran-2-one (7c). The reaction was performed in the same way and on the same scale as described above, the maximum reaction temperature was but 100 °C, and recrystallization was performed by shortly heating in ethanol. Using 1080 mg of 2c 270 mg (40 %) of 7c, a white solid, mp 164 °C, were obtained. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.34 (s, 3 H, CH$_3$), 3.19 (s, 2 H, CH$_2$), 5.74/5.81 (2 × s, 2 × 1 H, =CH$_2$), 6.60 (s, 1 H, =CH), 7.49 (m, 2 H, Phenyl-H), 7.73 (s, 1 H, Phenyl-H), 9.92 (br s, 1 H, OH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 19.7, 25.6, 100.6, 101.3, 129.0, 130.5, 131.7, 134.2, 134.6, 135.9, 137.8, 144.4, 160.8, 166.0 (2 signals), 199.4. MS (70 eV, EI): $m/z$ 338(M$^+$, 1), 165(87), 135(82), 107(19), 92(25), 85(18), 77(49), 69(19), 64(19), 53(19), 43(100). IR: $\nu$ 3098 (br), 1650, 1638. Anal. Calcd for C$_{16}$H$_{14}$O$_4$: C, 67.99; H, 5.37. Found: C, 67.51; H, 5.60.

3-Benzoyl-7-methyl-3,4-dihydro-2$^H$-pyrano[4,3-b]pyran-5-one (8a). A suspension of 250 mg (2.00 mmol) of 4-hydroxy-6-methylpyran-2-one (6), 900 mg (4.00 mmol) of 2-dimethylaminomethyl-1-phenylprop-2-en-1-one hydrochloride (2a), and 200 µL (140 mg, 1.5 mmol) of triethylamine in 10 mL of i-propanol was heated to reflux for 1 h. The solvent was evaporated in vacuo, the remainder was purified by column chromatography on silica gel with cyclohexane/ethyl acetate (1/1, v/v) to afford after recrystallization from ether, 350 mg (65 %) of 8a, mp 113 °C. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.21 (s, 3 H, CH$_3$), 2.58 (dd, $J$ = 16.9, 10.4 Hz, 1 H, CCH$_2$), 2.88 (ddd, $J$ = 16.9, 5.5, 2.2 Hz, 1 H, CCH$_2$), 3.83 (m, 1 H, CH), 4.21 (dd, $J$ = 11.3, 9.7 Hz, 1 H, OCH$_2$), 4.52 (dd, $J$ = 11.3, 3.5, 2.2 Hz, OCH$_2$), 5.81 (s, 1 H, CH), 7.97 (d, $J$ = 8.9 Hz, 2 H, Phenyl-H), 10.72 (s, 1 H, OH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 19.7, 25.6, 100.6, 101.3, 129.0, 130.5, 131.7, 134.2, 134.6, 135.9, 137.8, 144.4, 160.8, 166.0 (2 signals), 199.4. MS (70 eV, EI): $m/z$ 338(M$^+$, 1), 165(87), 135(82), 107(19), 92(25), 85(18), 77(49), 69(19), 64(19), 53(19), 43(100). IR: $\nu$ 3098 (br), 1650, 1638. Anal. Calcd for C$_{16}$H$_{14}$O$_4$: C, 67.99; H, 5.37. Found: C, 67.51; H, 5.60.
=CH), 7.50 (t, J = 7.6 Hz, 2 H, Phenyl-H), 7.62 (t, J = 7.6 Hz, 1 H, Phenyl-H), 7.94 (d, J = 7.4 Hz, 2 H, Phenyl-H). 13C NMR (75 MHz, CDCl3): δ 19.7, 23.1, 39.0, 67.6, 97.5, 99.8, 128.4, 128.9, 133.8, 135.3, 160.2, 164.36, 164.42, 199.0. MS (70 eV, EI): m/z 270(M+, 6), 166(10), 165(100), 137(8), 105(82), 77(82), 69(10), 53(12), 51(34), 50(9), 43(65). IR: ν 1704, 1678, 1582. Anal. Calcd for C16H14O4: C, 71.10; H, 5.22. Found: C, 71.37; H, 5.40.

3-(4-Methoxybenzoyl)-7-methyl-3,4-dihydro-2H-pyrano[4,3-b]pyran-5-one (8b). The reaction was performed on the same scale as described above starting with 960 mg (4 mmol) of 1-(4-methoxyphenyl)-2-aminomethyl-2-propen-1-one hydrochloride (2b) to afford 300 mg (50 %) of 8b, mp 125 °C. 1H NMR (300 MHz, CDCl3): δ 2.21 (s, 3 H, CH3), 2.57 (dd, J = 16.8, 10.6 Hz, 1 H, CCH2), 2.85 (br dd, J = 16.8, 3.8 Hz, 1 H, CCH2), 3.75 (m, 1 H, CH), 3.89 (s, 3 H, OCH3), 4.20 (dd, J = 11.1, 10.6 Hz, 1 H, OCH2), 4.49 (ddd, J = 11.2, 3.0, 2.3 Hz, OCH2), 5.80 (s, 1 H, =CH), 6.98 (d, J = 8.8 Hz, 2 H, Phenyl-H), 7.96 (d, J = 8.8 Hz, 1 H, Phenyl-H). 13C NMR (75 MHz, CDCl3): δ 19.7, 23.4, 38.6, 55.5, 67.9, 97.6, 99.8, 114.1, 128.3, 130.7, 160.2, 164.34, 164.45, 197.5. MS (70 eV, EI): m/z 300(M+, 8), 166(10), 165(100), 135(74), 107(13), 92(18), 77(33), 64(12), 53(10), 43(40). IR: ν 1700, 1666, 1590. Anal. Calcd for C17H16O5: C, 67.99; H, 5.37. Found: C, 67.50; H, 5.53.

3-(3,4-Dichlorobenzoyl)-7-methyl-3,4-dihydro-2H-pyrano[4,3-b]pyran-5-one (8c). The reaction was performed on the same scale as described above starting with 1080 mg (4 mmol) of 2-aminomethyl-1-(3,4-dichlorophenyl)-2-propen-1-one hydrochloride (2c) to afford 360 mg (53 %) of 8c, mp 178 °C. 1H NMR (300 MHz, CDCl3): δ 2.22 (s, 3 H, CH3), 2.57 (dd, J = 16.8, 10.2 Hz, 1 H, CCH2), 2.85 (br dd, J = 16.8, 5.4, 2.0 Hz, 1 H, CCH2), 3.75 (m, 1 H, CH), 4.21 (dd, J = 11.3, 9.5 Hz, 1 H, OCH2), 4.49 (ddd, J = 11.3, 3.5, 2.0 Hz, OCH2), 5.81 (s, 1 H, =CH), 7.59 (d, J = 8.4 Hz, 1 H, Phenyl-H), 7.78 (dd, J = 8.4, 2.1 Hz, 1 H, Phenyl-H), 8.03 (d, J = 2.1 Hz, 1 H, Phenyl-H). 13C NMR (75 MHz, CDCl3): δ 19.7, 23.0, 39.1, 67.3, 97.2, 99.8, 114.1, 127.3, 130.3, 131.1, 133.8, 134.8, 138.6, 160.5, 164.27, 164.31, 196.9. MS (70 eV, EI): m/z 338(M+ 35Cl2, 2), 175(13), 173(20), 166(10), 165(100), 147(10), 145(14), 69(13), 55(12), 53(12), 43(74). IR: ν 1698, 1690, 1582. Anal. Calcd for C16H12O4Cl2: C, 56.66; H, 3.57. Found: C, 56.62; H, 3.76.

3-(2-Benzoyl-3-benzylaminopropyl)-4-hydroxy-6-methylpyran-2-one (14a). 200 mg (0.74 mmol) of 3-(2-benzoylallyl)-4-hydroxy-6-methylpyran-2-one (7a) and 100 µL (98 mg, 0.92 mmol) of benzylamine were stirred in 10 mL of i-propanol for 3 h at rt. The solvent was evaporated in vacuo and the remainder was stirred with 5 mL of ether while cooling with an ice-bath. The solid crystallized and was filtered off.
and dried in vacuo, to afford 200 mg (72 %) of 14a, mp 105 °C. Attempts to recrystallize 14a led to formation of 8a and was not possible. \textbf{1H NMR} (300 MHz, CDCl3): $\delta$ 2.19 (s, 3 H, CH$_3$), 2.59 (dd, $J = 13.5$, 12.5 Hz, 1 H, CCH$_2$), 2.73 (dd, $J = 12.0$, 4.5 Hz, 1 H, CCH$_2$), 3.04 (d, $J = 11.4$ Hz, 1 H, CCH$_2$), 3.13 (dd, $J = 13.7$, 4.1 Hz, 1 H, CCH$_2$), 3.79/4.02 (2 ×d, $J = 12.0$, 9.0 Hz, 2 × 1 H, NCH$_2$), 3.95 (m, 1 H, CH), 5.30 (very br s, 2 H, NH, OH), 5.83 (s, 1 H, =CH), 7.35-7.65 (m, 8 H, Phenyl-H), 8.20 (d, $J = 7.6$ Hz, 2 H, Phenyl-H). \textbf{13C NMR} (75 MHz, CDCl3): \(\delta\) 19.8, 25.3, 42.6, 47.0, 52.9 96.5, 104.1, 128.7, 128.9, 129.09, 129.10, 129.14, 134.2 134.5, 134.6, 160.0, 166.8, 173.6, 204.9. \textbf{MS} (70 eV, EI): \(m/z\) 377(M+, 2), 272(15), 165(32), 106(66), 91(100), 77(68), 65(20), 55(19), 51(33), 43(86). \textbf{IR}: \(\nu\) 3404 (br), 1664. Anal. Calcd for C$_{23}$H$_{23}$NO$_4$ ⋅ H$_2$O: C, 69.80; H, 6.37; N, 3.54. Found: C, 69.86; H, 6.52; N, 3.58.

3-(2-Benzoyl-3-butylaminopropyl)-4-hydroxy-6-methylpyran-2-one (14b). 200 mg (0.74 mmol) of 3-(2-benzoylallyl)-4-hydroxy-6-methylpyran-2-one (7a) and 70 µL (52 mg, 0.71 mmol) of butylamine were stirred in 10 mL of \(i\)-propanol for 3 h at rt. The solvent was evaporated in vacuo and the remainder was dissolved in 10 mL of refluxing ether, the mixture was then cooled with an ice-bath. The solid which crystallized was filtered off and dried in vacuo, to afford 240 mg (94 %) of 14b, mp 135 °C. \textbf{1H NMR} (300 MHz, CDCl3): $\delta$ 0.99 (t, $J = 7.2$ Hz, 3 H, CH$_3$ of Bu), 1.47 (tq, $J = 7.2$, 7.0 Hz, CH$_2$ of Bu), 1.76 (m, 2 H, CH$_2$ of Bu), 2.14 (s, 3 H, CH$_3$), 2.57 (m, 1 H, NCH$_2$), 2.82 (m, 3 H, CH$_2$ of Bu and CCH$_2$), 3.04 (d, $J = 11.8$ Hz, 1 H, CCH$_2$), 3.18 (dd, $J = 13.8$, 3.2 Hz, 1 H, NCH$_2$), 4.01 (m, 1 H, CH), 5.74 (s, 1 H, =CH), 7.60 (m, 3 H, Phenyl-H), 8.23 (d, $J = 7.4$ Hz, 2 H, Phenyl-H). \textbf{13C NMR} (75 MHz, CDCl3): \(\delta\) 13.5, 19.7, 19.9, 25.5, 29.1, 42.3, 47.4, 48.3, 94.9, 105.4, 129.1 (2 signals), 134.3 (2 signals), 167.2, 176.4, 202.5. \textbf{MS} (70 eV, EI): \(m/z\) 343(M$^+$, 2), 165(70), 105(71), 77(88), 69(18), 55(24), 51(39), 44(21), 43(100), 42(25), 41(32). \textbf{IR}: \(\nu\) 3404 (br), 2400 (br), 1674, 1608. Anal. Calcd for C$_{23}$H$_{23}$NO$_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 70.33; H, 7.72; N, 4.20.

3-(2-Benzoyl-3-dimethylaminopropyl)-4-hydroxy-6-methylpyran-2-one (14c). 200 mg (0.74 mmol) of 3-(2-benzyolallyl)-4-hydroxy-6-methylpyran-2-one (7a) and 200 µL of a solution of dimethylamine in ethanol were stirred in 10 mL of ethanol for 1 h at rt. The solvent was evaporated in vacuo and the remainder was suspended in 10 mL of ether, the mixture was then cooled with an ice-bath. The solid which crystallized was filtered off and dried in vacuo, to afford 240 mg (94 %) of 14c, mp 114 °C. \textbf{1H NMR} (300 MHz, CDCl3): $\delta$ 2.14 (s, 3 H, CH$_3$), 2.54 (s, 6 H, N(CH$_3$)$_2$), 2.61 (dd, $J = 13.0$, 5.4 Hz, 1 H, NCH$_2$), 2.79 (dd, $J = 14.6$, 6.9 Hz, 1 H, CCH$_2$), 2.97 (dd, $J = 14.6$, 3.8 Hz, 1 H, CCH$_2$), 3.18 (dd, $J = 13.0$, 8.5 Hz, 1 H, NCH$_2$), 3.89 (m, 1 H, CH), 5.74 (s, 1 H, =CH), 7.49 (t,
$J = 7.3 \text{ Hz}, 2 \text{ H, Phenyl-H}$, 7.57 (t, $J = 7.2 \text{ Hz}, 1 \text{ H, Phenyl-H}$), 8.11 (d, $J = 7.3 \text{ Hz}, 2 \text{ H, Phenyl-H}$). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 19.6, 24.8, 43.7, 44.3, 56.7, 96.3, 103.5, 128.6, 128.8, 133.2, 135.9, 160.0, 166.6, 172.8, 202.0. MS (70 eV, El): m/z 315(M$^+$, 1), 270(15), 165(97), 105(57), 85(19), 77(57), 58(100), 45(71), 44(71), 43(86), 42(14). MS (CH$_4$, Cl): m/z 356(M+C$_3$H$_5^+$, 3), 344(M+C$_2$H$_5^+$, 6), 317(18), 316(M+H$^+$, 92), 272(18), 271(100). IR: ν 3424 (br), 2200 (br), 1670. Anal. Calcd for C$_{18}$H$_{21}$NO$_4$$\cdot$H$_2$O: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.94; H, 6.97; N, 4.26.

3-[2-Benzoyl-3-(2-hydroxyethylamino)propyl]-4-hydroxy-6-methylpyran-2-one (14d). 270 mg (1.00 mmol) of 3-(2-benzoylallyl)-4-hydroxy-6-methylpyran-2-one (7a) and 125 mg (2.00 mmol) of ethanol-amine were stirred in 10 mL of ethanol for 2 h at rt. The solvent was evaporated in vacuo and the remainder was suspended in 10 mL of ether. The solid was filtered off, dried in vacuo, and recrystallized from ethanol to afford 270 mg (81 %) of 14d, mp 171 °C. $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 2.00 (s, 3 H, CH$_3$), 2.6-3.1 (several m, 4 H, CCH$_2$ and NCH$_2$), 2.95 (t, $J = 5.0 \text{ Hz}, 2 \text{ H, NCH}_2$CH$_2$), 3.69 (t, $J = 5.0 \text{ Hz}, 2 \text{ H, NCH}_2$CH$_2$), 4.06 (m, 1 H, CH), 5.30 (very br s, 1 H, NH), 5.67 (s, 1 H, =CH), 7.50 (br m, 3 H, Phenyl-H), 8.10 (d, $J = 7.4 \text{ Hz}, 2 \text{ H, Phenyl-H}$), 9.70 (br s, 1 H, OH). $^{13}$C NMR (75 MHz, DMSO-d$_6$): $\delta$ 19.2, 24.2, 42.9, 49.4, 56.8, 92.3, 106.2, 128.5, 128.7, 133.3, 135.3, 157.8, 165.8, 177.2, 201.5. MS (70 eV, El): m/z 331(M$^+$, 2), 165(62), 105(52), 85(17), 77(60), 69(14), 60(20), 51(23), 45(38), 43(100), 42(22). IR: ν 3150 (br), 2300, 1660, 1612. Anal. Calcd for C$_{18}$H$_{21}$NO$_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 64.75; H, 6.47; N, 4.27.

3-[2-Benzoyl-3-(2-pyridylamino)propyl]-4-hydroxy-6-methylpyran-2-one (14e). 270 mg (1.00 mmol) of 3-(2-benzoylallyl)-4-hydroxy-6-methylpyran-2-one (7a) and 190 mg (2.00 mmol) of 2-aminopyridine were stirred in 10 mL of THF at rt until a clear solution was formed. The mixture was stored overnight in the refrigerator, the solvent was evaporated in vacuo and the remainder was subjected to column chromatography with dichloromethane/methanol (1/1, v/v) to afford 164 mg (45 %) of 14e, mp 175 °C. $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 1.99 (s, 3 H, CH$_3$), 2.60 (m, 2 H, CCH$_2$), 3.30-3.60 (br m, 2 H, NCH$_2$), 4.16 (m, 1 H, CH), 5.93 (s, 1 H, =CH), 7.10-7.80 (several m, 9 H, Phenyl-H). $^{13}$C NMR (75 MHz, DMSO-d$_6$): $\delta$ 19.2, 24.6, 42.0, 44.1, 99.7, 108.2, 128.0, 128.4, 132.9 136.4, 137.0, 147.2, 158.5, 160.2, 164.8, 166.1, 202.2. MS (70 eV, El): m/z 364(M$^+$, 1), 165(12), 105(18), 94(17), 77(21), 67(16), 60(29), 45(65), 43(100), 42(16), 41(13). IR: ν 3318 (br), 2500, 1678, 1614. Anal. Calcd for C$_{21}$H$_{20}$N$_2$O$_4$: C, 69.22; H, 5.53; N, 7.69. Found: C, 67.92; H, 5.59; N, 8.26.
3-(2-Benzoyl-3-ethoxypropyl)-4-hydroxy-6-methylpyran-2-one (14f). 200 mg (0.74 mmol) of 3-(2-benzoylallyl)-4-hydroxy-6-methylpyran-2-one (7a) was added to a solution of sodium ethoxide (prepared by adding 100 mg of sodium to 10 mL of ethanol) and stirred for 1 h at rt. The solvent was evaporated in vacuo and 10 mL of water were added and the mixture extracted with 3 portions of dichloromethane. After evaporation the remainder was subjected to column chromatography using ethylacetate/cyclohexane (3/1, v/v). The oil was crystallized with a petroleum ether/ether mixture to afford 100 mg (43 %) of 14f, mp 94 °C. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.13 (t, $J$ = 7.0 Hz, 3 H, OCH$_2$CH$_3$), 2.18 (s, 3 H, CH$_3$), 2.75 (dd, $J$ = 14.5, 5.4 Hz, 1 H, CCH$_2$), 3.02 (dd, $J$ = 14.5, 8.1 Hz, 1 H, CCH$_2$), 3.64 (m, 2 H, OCH$_2$), 3.73 (m, 2 H, OCH$_2$CH$_3$), 3.94 (m, 1 H, CH), 5.83 (s, 1 H, =CH), 7.45 (t, $J$ = 7.3 Hz, 2 H, Phenyl-H), 7.59 (t, $J$ = 7.3 Hz, 2 H, Phenyl-H), 8.00 (d, $J$ = 7.4 Hz, 2 H, Phenyl-H), 9.37 (br s, 1 H, OH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 14.6, 19.7, 22.5, 46.2, 67.0, 70.8, 100.0, 101.1, 128.7, 128.8, 133.6, 135.8, 160.3, 166.0, 166.5, 203.8. MS (70 eV, EI): m/z 316(M$^+$, 1), 270(20), 165(100), 105(79), 85(19), 77(55), 69(10), 51(19), 45(17), 43(86). MS (CH$_4$, Cl): m/z 357(M+C$_3$H$_7$+, 4), 345(M+C$_2$H$_5$+, 7), 317(M+H$^+$, 97), 299(15), 271(100). IR: v 3600-2600 (br), 1682, 1580. Anal. calc. for C$_{18}$H$_{20}$NO$_5$: C, 68.34; H, 6.37. Found: C, 67.95; H, 6.47.

3-(2-Benzoyl-3-benzylmercaptpropyl)-4-hydroxy-6-methylpyran-2-one (14g). 270 mg (1.00 mmol) of 3-(2-benzoylallyl)-4-hydroxy-6-methylpyran-2-one (7a) and 290 mg (2.00 mmol) of benzyl mercaptane were stirred in 10 mL of ethanol for one week at rt. The solvent was evaporated in vacuo and the remainder was subjected to column chromatography with ethyl acetate/cyclohexane (1/1, v/v). The tarry oil was crystallized by stirring with petroleum ether/ether for 30 min at 4 °C to afford 275 mg (70 %) of 14g, mp 84-86 °C, as a white solid. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.15 (s, 3 H, CH$_3$), 2.5 (dd, $J$ = 13.3, 7.9 Hz, 1 H, CCH$_2$), 2.89 (m, 3 H, CCH$_2$, SCH$_2$), 3.79 (d, $J$ = 14.0 Hz, 1 H, SCH$_2$Ph), 4.00 (m, 2 H, SCH$_2$Ph, CH), 5.82 (s, 1 H, =CH), 7.2-7.8 (m, 8 H, Phenyl-H), 7.73 (d, $J$ = 7.5 Hz, 2 H, Phenyl-H), 9.12 (br s, 1 H, OH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 19.7, 23.8, 34.0, 35.8, 44.8, 100.5, 101.1, 127.1, 128.6, 128.8, 128.9, 129.0, 134.1, 135.1, 137.4, 160.7, 166.0, 166.1, 205.4. MS (70 eV, EI): m/z 394(M$^+$, not found), 303(M$^+$-C$_7$H$_7$, 1), 165(9), 124(25), 91(77), 77(10), 65(14), 60(69), 45(98), 44(13), 43(100), 42(15). MS (Thermospray, NH$_4$OAc/MeOH): m/z 395(M+H$^+$, 8), 330(1), 303(1), 272(17), 271(100). IR: v 3600 (br), 1674, 1636. Anal. Calcd for C$_{23}$H$_{22}$O$_4$: C, 70.03; H, 5.62. Found: C, 68.97; H, 5.71.

Synthesis and Analysis of the Library. A solution consisting of 0.3 µmol each of the amines diethylamine, benzylamine, morpholine, 2-propylamine, and butylamine were stirred together with 0.5 µmol each
of 7a, 7b, and 7c in 5 mL of ethanol for one day at rt. This mixture was analyzed repeatedly by liquid chromatography using a HP1090 II LC with additional UV detection at 240 nm (HP1050 VWD) and showed only minor changes in composition over 2 weeks, when stored at rt. Chromatography was performed with a Merck RP Select B column (5 µm, 125 × 4 mm) and a guard column (4 × 4 mm) using gradient elution: solvent A: 0.1 M ammonium acetate, solvent B: methanol, and a flow rate of 0.4 mL/min. The gradient was kept for 5 min. at 70 % A and 30 % B and was linearly changed to 20 % A and 80 % B at 120 min. MS spectra were recorded on a HP 5989 A MS Engine equipped with a thermospray interface (stem temperature throughout at 90°C, discharge electrode mode) scanning from 250 to 550 Dalton.

REFERENCES AND NOTES