# A SIMPLE PREPARATION OF SOME 4-METHYL-2*H*-PYRAN-2-ONES

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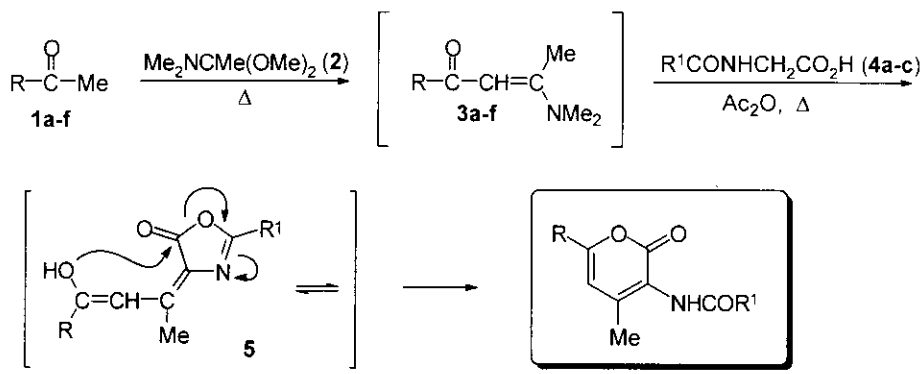
**Abstract** - A method for the preparation of substituted 4-methyl-2*H*-pyran-2-ones (**6-19**) starting from methyl ketones (**1**), *N*,*N*-dimethylacetamide dimethyl acetal (**2**) and *N*-acylglycines (**4**) in acetic anhydride is described.

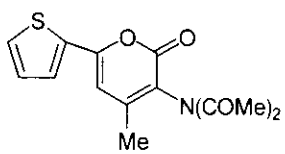
The synthesis of 2*H*-pyran-2-ones and their fused derivatives has been subject of several reviews, which show high importance of this class of compounds.[1] They are useful synthons in organic synthesis and have also found an application as pharmaceuticals, agrochemicals, veterinary products, dyes or pigments, etc.[2] A wide spectrum of their substitution patterns is a reason for the diversity of synthetic approaches to 2*H*-pyran-2-ones. All of the synthetic methods exhibit also some limitations in terms of the number of steps involved, functional groups compatibility, yields, etc. Highly substituted 2*H*-pyran-2-ones containing various substitution patterns are of special interest in the synthesis, because they can be converted into many heterocyclic systems.[1,2a,3,4] Recently, the use of 4-hydroxy-2*H*-pyran-2-ones for the synthesis of some bicyclic derivatives was described.[4] Since the hydroxy group exhibits nucleophilic character, the introduction of other related groups in the position 4 might be of interest for further design of the pyran-2-one derivatives. For this purpose, we wanted to introduce methyl group into position 4 of the pyranone ring, since it would be a part of the conjugate system and for this reason appropriate for the transformation into the carboanionic form and further in various directions by the participation of a neighboring group.

This perception has inspired us to find an efficient way for the preparation of 4-methyl-2*H*-pyran-2-ones containing a substituted amino group in the position 3 and an alkyl or aryl group in the position 6. We hoped that such compounds could be prepared by the one-pot methodology, which had been shown to be very useful for the preparation of 4-unsubstituted 3-acylamino derivatives of 2*H*-pyran-2-ones and fused pyran-2-ones,[5] if the one-carbon synthon would be replaced by its methyl substituted analog. For this purpose, we performed a set of reactions, related to our one-pot methodology, but by using *N*,*N*-

dimethylacetamide dimethyl acetal (**2**) as a synthon of a substituted carbon unit. As given in the Scheme, we prepared a set of 6-substituted 3-acylamino-4-methyl-2*H*-pyran-2-ones (**6-19**) from various methyl ketones (**1**), *N*,*N*-dimethylacetamide dimethyl acetal (**2**) and *N*-acylglycines (**4**). We have used the following ketones: acetone (**1a**), *tert*-butyl methyl ketone (**1b**), acetophenone (**1c**), 2-furyl methyl ketone (**1d**), methyl 2-thienyl ketone (**1e**) and methyl 2-pyridyl ketone (**1f**). As *N*-acylglycines we used hippuric acid (**4a**) in reactions with all ketones, and aceturic acid (**4b**) and *N*-pyrazinylcarbonylglycine (**4c**)[6] were employed only optionally. In the first step a ketone (**1**) was usually refluxed with a two-fold molar excess of acetal (**2**), the volatile components were evaporated under reduced pressure and the resulting crude 3-dimethylamino-2-buten-1-ones (**3**) were used without further purification.

**Scheme**




**19**

| R | R¹ | |
|---|---|---|
| Me | Ph | **6** |
| | Py | **7** |
| *tert*-Bu | Ph | **8** |
| | Me | **9** |
| Ph | Ph | **10** |
| | Py | **11** |

| R | R¹ | |
|---|---|---|
|  | Ph | **12** |
| | Me | **13** |
| | Py | **14** |
|  | Ph | **15** |
| | Me | **16** |
| | Py | **17** |
|  | Ph | **18** |

Py : 2-pyrazinyl

To prepare the compound (**3a**), acetal (**2**) was refluxed with a four-fold molar excess of acetone (**1a**), then the volatile components were removed under reduced pressure and the crude compound (**3a**) was used for further transformation. This modification is required due to high volatility of acetone, which therefore must be present in the reaction mixture in a large excess. Compounds (**3a-f**) are known from the literature and have been prepared by a variety of methods.[7]

In the second step, the equimolar amount of *N*-acylglycine (**4**) and a large excess of acetic anhydride were added to an intermediate (**3**) and the reaction mixture was heated at 90 °C for four hours. Acetic anhydride was removed under reduced pressure and ethanol was added. The products (**6-19**) were isolated either by the column chromatography or by filtering off the precipitated solid. The highest yields were obtained when hippuric acid was used. The reaction conditions and yields are given in the Table.
Under the applied conditions further acylation by acetic anhydride can take place, as shown in the case of diacetamide (**19**), which was isolated by column chromatography in addition to the product (**16**).

**Table.** Synthesis of the compounds (**6-19**):

| ketone (**1**) | compound (**3**) | amount of **3** (mmol) | *N*-acyl-glycine | isolation | yield (%) | product |
|---|---|---|---|---|---|---|
| acetone | **3a** | 2 | **4a** | B | 50 | **6** |
| " | **3a** | 8 | **4c** | B | 11 | **7** |
| *tert*-butyl methyl ketone | **3b** | 4 | **4a** | B | 26 | **8** |
| " | **3b** | 4 | **4b** | B | 14 | **9** |
| acetophenone | **3c** | 2 | **4a** | A | 46 | **10** |
| " | **3c** | 2 | **4c** | A | 14 | **11** |
| 2-furyl methyl ketone | **3d** | 2 | **4a** | A | 69 | **12** |
| " | **3d** | 3 | **4b** | B | 16 | **13** |
| " | **3d** | 2 | **4c** | B | 27 | **14** |
| methyl 2-thienyl ketone | **3e** | 2 | **4a** | A | 72 | **15** |
| " | **3e** | 3 | **4b** | B | 24 | **16** |
| | | | | | 14 | **19** |
| " | **3e** | 5 | **4c** | B | 19 | **17** |
| methyl 2-pyridyl ketone | **3f** | 2 | **4a** | A | 40 | **18** |

In accordance with our previous investigation,[5c] in the present transformation several by-products might be formed, thus reducing the yield of the desired compounds (**6-19**). Considering *N*-acylglycines, as already shown[5b,e,f] the highest yields were obtained when hippuric acid was used, and lower with others.
There is little known about the 3-acylamino-4-methyl-2*H*-pyran-2-ones in the literature.[1-3] The only described direct way for the preparation of this type of compounds is the reaction of a 1,3-dicarbonyl derivative with 4-(1-methoxyethylene)-2-phenyl-5(4*H*)-oxazolone under basic conditions.[8] Namely,

starting from ethyl acetoacetate and methoxyethylene-5(4*H*)-oxazolone derivative in a mixture of pyridine and triethylamine the corresponding *N*-(4,6-dimethyl-5-ethoxycarbonyl-2-oxo-2*H*-pyran-3-yl)benzamide was obtained in 31% yield. In our case, yields with hippuric acid as *N*-acylglycine were generally higher and there was no need for the preparation of the oxazolone intermediate.

In conclusion, the described approach is a useful and simple one-pot method for the preparation of a set of 3-acylamino-4-methyl-2*H*-pyran-2-ones, which might be valuable intermediates in heterocyclic synthesis.

## EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage and are uncorrected. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker Avance DPX 300 spectrometer in $CDCl_3$ (DMSO-$d_6$ in the case of compound (**14**)) using TMS as internal standard. $^1$H NMR spectra were recorded at 300.1 MHz and $^{13}$C NMR spectra at 75.4 MHz. MS spectra were obtained with a VG-Analytical AutospecQ spectrometer. Elemental analyses (C, H, N) were performed on a Perkin-Elmer 2400 CHN Analyzer. TLC was carried out on Fluka silica gel TLC cards. Column chromatography was carried out on Fluka silica gel 60 (220-440 mesh). Compound (**4c**)[6] was prepared as described in the literature. All other compounds were used as received from commercial sources.

### General procedure for the preparation of 4-methyl-2*H*-pyran-2-ones (6-19).

**Synthesis of compounds (3):** A mixture of a ketone (**1b-f**) and a 2-molar excess of *N*,*N*-dimethyl-acetamide dimethyl acetal (**2**) was refluxed for 35 h (in the case of the intermediate (**3b**)) or for 3 h (intermediates (**3c-f**)). The volatile components were evaporated and the residue was used in the next step without any further purification. The intermediate (**3a**) was prepared, due to high volatility of acetone (**1a**), by refluxing the acetal (**2**) with a 4-fold excess of acetone for 18 h. The volatile components were evaporated and the residue was used without further purification.

**2*H*-Pyran-2-ones (6-19):** A mixture of equimolar amounts (2-8 mmol) of a compound (**3**) and *N*-acyl-glycine (**4**) was heated at 90 °C in a large excess of acetic anhydride (1.25 mL per mmol) for 4 h. The acetic anhydride was evaporated, absolute ethanol (0.5 mL per mmol) was added and the mixture was cooled. The separated solid was filtered off and washed with a small amount of ethanol (Isolation A). If no solid precipitated, ethanol was evaporated and the product was isolated by column chromatography on silica gel using a mixture of petroleum benzine and ethyl acetate (1:1) as eluent (Isolation B). Reaction conditions and yields are given in the Table.

**Analytical and spectroscopic data of the compounds (6-19):**

***N*-(4,6-Dimethyl-2-oxo-2*H*-pyran-3-yl)benzamide (6):** mp 165-167 °C (from MeOH); $^1$H NMR δ 2.14 (s, 3H, 4'-Me or 6'-Me), 2.24 (s, 3H, 4'-Me or 6'-Me), 5.98 (s, 1H, 5'-H), 7.40-7.55 (m, 3H, Ph), 7.84-7.87 (m, 2H, Ph), 8.03 (br s, 1H, NH); $^{13}$C NMR δ 19.3, 19.5, 107.93, 118.6, 127.5, 128.6, 132.0, 133.4, 148.5, 157.5, 162.0, 165.8; MS (m/z, %) 243 ($M^+$, 30). Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.98; H, 5.31; N, 5.77.

***N*-(4,6-Dimethyl-2-oxo-2*H*-pyran-3-yl)pyrazinecarboxamide (7):** mp 190-193 °C (MeOH); $^1$H NMR δ 2.18 (s, 3H, 4'-Me or 6'-Me), 2.27 (s, 3H, 4'-Me or 6'-Me), 5.99 (s, 1H, 5'-H), 8.62 (dd, $J$ = 2.2 Hz, $J$ = 1.6 Hz, 1H, 6-H), 8.81 (d, $J$ = 2.4 Hz, 1H, 5-H), 9.35 (br s, 1H, NH), 9.43 (d, $J$ = 1.3 Hz, 1H, 3-H); MS (m/z, %) 245 ($M^+$, 70). Anal. Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.48; H, 4.39; N, 17.17.

***N*-(6-*tert*-Butyl-4-methyl-2-oxo-2*H*-pyran-3-yl)benzamide (8):** mp 163-163.5 °C (MeOH/$CHCl_3$); $^1$H NMR δ 1.29 (s, 9H, *t*-Bu), 2.17 (s, 3H, 4'-Me), 6.02 (s, 1H, 5'-H), 7.42-7.54 (m, 3H, Ph), 7.85-7.88 (m, 2H, Ph), 8.02 (br s, 1H, NH); $^{13}$C NMR δ 20.0, 28.0, 35.7, 104.0, 118.5, 127.6, 128.7, 132.2, 133.6, 147.2, 161.7, 165.9, 167.6; MS (m/z, %) 285 ($M^+$, 22). Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.36; H, 6.88; N, 4.99.

***N*-(6-*tert*-Butyl-4-methyl-2-oxo-2*H*-pyran-3-yl)acetamide (9):** mp 132-136 °C (AcOEt); $^1$H NMR δ 1.26 (s, 9H, *t*-Bu), 2.10 (s, 3H, 4'-Me or Ac), 2.18 (s, 3H, 4'-Me or Ac), 5.95 (s, 1H, 5'-H), 7.18 (br s, 1H, NH); MS (m/z, %) 223 ($M^+$, 30). Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.26; H, 7.84; N, 6.38.

***N*-(4-Methyl-2-oxo-6-phenyl-2*H*-pyran-3-yl)benzamide (10):** mp 220-222 °C ($CHCl_3$/MeOH); $^1$H NMR δ 2.27 (s, 3H, 4'-Me), 6.65 (s, 1H, 5'-H), 7.42-7.58 (m, 6H, two Ph), 7.78-7.82 (m, 2H, Ph), 7.89-7.92 (m, 2H, Ph), 8.07 (br s, 1H, NH); $^{13}$C NMR δ 20.2, 105.8, 119.8, 125.5, 127.6, 128.8, 129.0, 130.6, 131.0, 132.3, 133.6, 146.9, 155.7, 161.1, 165.8; MS (m/z, %) 305 ($M^+$, 64). Anal. Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.70; H, 4.64; N, 4.67.

***N*-(4-Methyl-2-oxo-6-phenyl-2*H*-pyran-3-yl)pyrazinecarboxamide (11):** mp 221-221.5 °C (EtOH/-$CHCl_3$); $^1$H NMR δ 2.31 (s, 3H, 4'-Me), 6.66 (s, 1H, 5'-H), 7.44-7.84 (m, 3H, Ph), 7.80-7.84 (m, 2H, Ph), 8.64 (dd, $J$ = 2.3 Hz, $J$ = 1.5 Hz, 1H, 6-H), 8.82 (d, $J$ = 2.5 Hz, 1H, 5-H), 9.45 (d, $J$ = 1.4 Hz, 1H, 3-H), 9.48 (br s, 1H, NH); MS (m/z, %) 307 ($M^+$, 58). Anal. Calcd for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.26; N, 13.67. Found: C, 66.43; H, 4.19; N, 13.57.

***N*-[6-(2-Furyl)-4-methyl-2-oxo-2*H*-pyran-3-yl]benzamide (12):** mp 163-164 °C (DMF); $^1$H NMR δ 2.23 (s, 3H, 4'-Me), 6.52 (dd, $J$ = 1.8 Hz, $J$ = 3.5 Hz, 1H, 4"-H), 6.57 (s, 1H, 5'-H), 6.93 (d, $J$ = 3.4 Hz, 1H, 3"-H), 7.41-7.55 (m, 4H, 3H of Ph and 5"-H), 7.86-7.88 (m, 2H, Ph), 8.19 (br s, 1H, NH); $^{13}$C NMR δ

20.0, 104.0, 111.3, 112.4, 119.3, 127.6, 128.7, 132.2, 133.4, 144.7, 146.1, 147.8, 147.8, 160.4, 165.8; MS (m/z, %) 295 ($M^+$, 54). Anal. Calcd for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.44; N, 4.74. Found: C, 68.89; H, 4.38; N, 4.76.

***N*-[6-(2-Furyl)-4-methyl-2-oxo-2*H*-pyran-3-yl]acetamide (13):** mp 193-194 °C (MeOH/$CHCl_3$); $^1$H NMR δ 2.17 (s, 3H, 4'-Me or Ac), 2.20 (s, 3H, 4'-Me or Ac), 6.52-6.53 (m, 2H, 5'-H and 4"-H), 6.93 (d, 1H, $J$ = 3.4 Hz, 3"-H), 7.36 (br s, 1H, NH), 7.50 (d, 1H, $J$ = 1.2 Hz, 5"-H); MS (m/z, %) 233 ($M^+$, 41). Anal. Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.79; H, 4.64; N, 6.00.

***N*-[6-(2-Furyl)-4-methyl-2-oxo-2*H*-pyran-3-yl]pyrazinecarboxamide (14):** mp 264-265 °C (decomp, $CHCl_3$ /MeOH); $^1$H NMR (DMSO-$d_6$) δ 2.16 (s, 3H, 4'-Me), 6.74 (dd, $J$ = 1.8 Hz, $J$ = 3.5 Hz, 1H, 4"-H), 6.81 (s, 1H, 5'-H), 7.12 (d, $J$ = 3.5 Hz, 1H, 3"-H), 7.95 (d, $J$ = 1.3 Hz, 1H, 5"-H), 8.82 (dd, $J$ = 2.4 Hz, $J$ = 1.5 Hz, 1H, 6-H), 8.95 (d, $J$ = 2.5 Hz, 1H, 5-H), 9.25 (d, $J$ = 1.4 Hz, 1H, 3-H), 10.16 (br s, 1H, NH); MS (m/z, %) 297 ($M^+$, 11). Anal. Calcd for $C_{15}H_{11}N_3O_4$: C, 60.61; H, 3.73; N, 14.14. Found: C, 60.54; H, 3.64; N, 14.22.

***N*-[4-Methyl-2-oxo-6-(2-thienyl)-2*H*-pyran-3-yl]benzamide (15):** mp 193-195 °C (EtOH/DMF); $^1$H NMR δ 2.23 (s, 3H, 4'-Me), 6.48 (s, 1H, 5'-H), 7.10 (dd, $J$ = 3.9 Hz, $J$ = 4.9 Hz, 1H, 4"-H), 7.42-7.56 (m, 5H, 3H of Ph and 3"-H and 5"-H), 7.87-7.89 (m, 2H, Ph), 8.13 (br s, 1H, NH); $^{13}$C NMR δ 20.0, 104.8, 119.2, 127.0, 127.6, 128.4, 128.6, 128.7, 132.3, 133.5, 134.6, 147.5, 151.6, 160.5, 165.8; MS (m/z, %) 311 ($M^+$, 45). Anal. Calcd for $C_{17}H_{13}NO_3S$: C, 65.58; H, 4.21; N, 4.50. Found: C, 65.39; H, 4.01; N, 4.59.

***N*-[4-Methyl-2-oxo-6-(2-thienyl)-2*H*-pyran-3-yl]acetamide (16):** mp 171-173 °C (MeOH/$CHCl_3$); $^1$H NMR δ 2.17 (s, 3H, Ac or 4'-Me), 2.20 (s, 3H, Ac or 4'-Me), 6.43 (s, 1H, 5'-H), 7.09 (dd, $J$ = 3.8 Hz, $J$ = 4.9 Hz, 1H, 4"-H), 7.42 (dd, $J$ = 0.8 Hz, $J$ = 5.0 Hz, 1H, 5"-H), 7.48 (br s, 1H, NH), 7.53 (dd, $J$ = 0.7 Hz, $J$ = 3.7 Hz, 1H, 3"-H); MS (m/z, %) 249 ($M^+$, 39). Anal. Calcd for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45; N, 5.62. Found: C, 57.64; H, 4.30; N, 5.61.

***N*-[4-Methyl-2-oxo-6-(2-thienyl)-2*H*-pyran-3-yl]pyrazinecarboxamide (17):** mp 259-262 °C (decomp, MeOH/$CHCl_3$); $^1$H NMR δ 2.27 (s, 3H, 4'-Me), 6.49 (s, 1H, 5'-H), 7.12 (dd, $J$ = 3.8 Hz, $J$ = 5.0 Hz, 1H, 4"-H), 7.45 (dd, $J$ = 1.0 Hz, $J$ = 5.1 Hz, 1H, 5"-H), 7.59 (dd, $J$ = 1.0 Hz, $J$ = 3.7 Hz, 1H, 3"-H), 8.63 (dd, $J$ = 1.6 Hz, $J$ = 2.2 Hz, 1H, 6-H), 8.82 (d, $J$ = 2.4 Hz, 1H, 5-H), 9.41-9.47 (m, 2H, 3-H and NH); MS (m/z, %) 313 ($M^+$, 61). Anal. Calcd for $C_{15}H_{11}N_3O_3S$: C, 57.50; H, 3.54; N, 13.41. Found: C, 57.22; H, 3.39; N, 13.29.

***N*-[4-Methyl-2-oxo-6-(2-pyridyl)-2*H*-pyran-3-yl]benzamide (18):** mp 211-214 °C (DMF); $^1$H NMR δ 2.30 (s, 1H, 4'-Me), 7.33 (ddd, $J$ = 1.1 Hz, $J$ = 4.8 Hz, $J$ = 7.5 Hz, 1H, 5"-H), 7.37 (s, 1H, 5'-H), 7.45-7.59 (m, 3H, Ph), 7.80 (dt, $J$ = 1.7 Hz, $J$ = 7.8 Hz, 1H, 4"-H), 7.90-7.97 (m, 3H, 2H of Ph and 3"-H), 8.07 (br s, 1H, NH), 8.65 (ddd, $J$ = 0.9 Hz, $J$ = 1.6 Hz, $J$ = 4.7 Hz, 1H, 6"-H); $^{13}$C NMR δ 20.2, 107.7, 120.2, 121.3,

124.6, 127.7, 128.8, 132.4, 133.6, 137.2, 146.7, 148.7, 149.9, 153.7, 160.7, 165.7; MS (m/z, %) 306 ($M^+$, 55). Anal. Calcd for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15. Found: C, 70.24; H, 4.42; N, 8.97.

***N*-[4-Methyl-2-oxo-6-(2-thienyl)-2*H*-pyran-3-yl]diacetamide (19):** mp 161-163 °C (MeOH/$CHCl_3$); $^1$H NMR δ 2.10 (s, 3H, 4'-Me), 2.38 (s, 6H, two Ac), 6.47 (s, 1H, 5'-H), 7.13 (dd, $J$ = 3.8 Hz, $J$ = 5.0 Hz, 1H, 4"-H), 7.50 (dd, $J$ = 1.0 Hz, $J$ = 5.0 Hz, 1H, 5"-H), 7.64 (dd, $J$ = 1.0 Hz, $J$ = 3.8 Hz, 1H, 3"-H); MS (m/z, %) 291 ($M^+$, 24). Anal. Calcd for $C_{14}H_{13}NO_4S$: C, 57.72; H, 4.50; N, 4.81. Found: C, 57.34; H, 4.36; N, 4.82.

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