One-Pot Synthesis of some 2*H*-Pyran-2-one Derivatives

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A one-pot synthesis of various 2*H*-pyran-2-one derivatives **5-19** starting from methyl ketones **1**, *N,N*-dimethylformamide dimethyl acetal and *N*-acylglycines **3** in acetic anhydride is described.

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Recent development in the field of 2*H*-pyran-2-one derivatives [1] has shown a high importance of this class of compounds in the field of medicinal chemistry [2]. In particular, derivatives of this system represent a new class of HIV protease inhibitors. The use of molecular modeling and the information derived from the X-ray crystal structures of HIV protease complexed with 2*H*-pyran-2-ones enabled a systematic design of novel inhibitors [2]. These results stimulated us to study further applications of the one-pot synthesis [3-7] in order to synthesize 3,6-disubstituted representatives of 2*H*-pyran-2-one system. This method was widely applied for the preparation of several acylamino derivatives of 2*H*-pyran-2-ones and fused pyran-2-ones starting from 1,3-dicarbonyl compounds, one-carbon synthons, *N*-acylglycines and a large excess of acetic anhydride.

For this purpose we have applied our one-pot method to some monoactivated methyl ketones, such as 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**). In all cases the reactions were carried out using *N,N*-dimethylformamide dimethyl acetal as a one-carbon synthon. Hippuric acid (**3a**) was used in reactions with all carbonyls, *N*-acetylglycine (**3b**) and *N*-pyrazinylcarbonylglycine (**3c**) [8] optionally. A previously reported reaction procedure [4] was modified and used in these transformations. In the first step the carbonyls (with the exception of acetone) were heated with two-fold molar excess of *N,N*-dimethylformamide dimethyl acetal and transformed to the corresponding intermediate **2**. The volatile components were evaporated and the remaining intermediate **2** was used without further purification. In the case of acetone, *N,N*-dimethylformamide dimethyl acetal was heated with four-fold molar excess of acetone, then the volatile components were evaporated and the remaining residue was used without further purification in the second step. All compounds of the type **2** are known and have been prepared by various methods [9]. In the second step *N*-acylglycine and acetic anhydride were added to the intermediate **2** and the resulting mixture was heated for four hours at 90°. Derivatives **5-19** have been synthesized in various yields (Scheme, Table). Under the applied conditions, further acetylation by acetic anhydride can take place, as shown in two examples. Thus, diacetamides **18** and **19** were isolated along with the initially formed acetamides **12** and **15**. Both pairs of products were separated by column chro-

Table

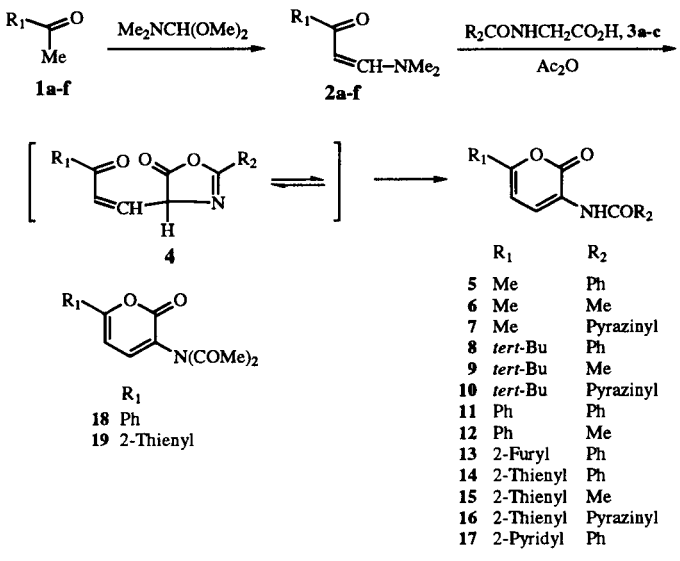
Synthesis of Compounds **5-19** [a]

ketone **1**	intermediate **2**	amount of **2** (mmoles)	*N*-acyl glycine	product	yield (%)	isolation
acetone	**2a**	10	**3a**	**5**	27	A
"	"	10	**3b**	**6**	11	B
"	"	10	**3c**	**7**	11	B
tert-butyl methyl ketone	**2b**	4	**3a**	**8**	69	A
"	"	4	**3b**	**9**	29	B
"	"	4	**3c**	**10**	25	A
acetophenone	**2c**	2	**3a**	**11**	82	A
"	"	5	**3b**	**12**	14	B
				18	10	
2-furyl methyl ketone	**2d**	2	**3a**	**13**	38	A
methyl 2-thienyl ketone	**2e**	2	**3a**	**14**	61	A
"	"	3	**3b**	**15**	10	B
				19	15	
"		5	**3c**	**16**	14	B
methyl 2-pyridyl ketone	**2f**	2	**3a**	**17**	37	B

[a] In all cases yields of crystallized products are given (with the exception of compounds **8**, **11**, and **14**, which were obtained in tlc-pure form as crude products).

matography. Some other by-products might also be formed, in accordance with the previous observation [5]. Compound **6** was earlier detected by gas chromatography-mass spectrometry analysis of pyrolysis of *N*-acetylglucosamine and its structure was tentatively assigned on the basis of the mass spectrum [10]; products **11** and **12** are also known and were satisfactorily characterized [11,12].

Scheme



In conclusion, the described method seems to be very useful for the synthesis of a set of 6-substituted 3-acylamino-2*H*-pyran-2-ones, which might be of interest for further design towards potentially biologically active compounds [2]. The fact that the highest yields were obtained with hippuric acid is in accordance with earlier results [4,7].

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage and are uncorrected. The nmr spectra were recorded on a Bruker Avance DPX 300 spectrometer in deuteriochloroform (if not stated differently), using TMS as an internal standard. Mass spectra were obtained with a VG-Analytical AutospecQ instrument. Elemental analyses (C, H, N) were performed with a Perkin-Elmer 2400 CHN Analyzer. Analysis (tlc) was carried out on Fluka silica gel plates. Fluka silica gel 60 was used for column chromatography. Compound **3c** [8] was prepared as described in the literature. All other compounds were used as received from commercial sources.

Synthesis of 2*H*-Pyran-2-ones **5-19**. General Procedure.

Step 1. Synthesis of Intermediates **2**.

A mixture of a ketone **1** and a 2-fold molar excess of *N,N*-dimethylformamide dimethyl acetal was refluxed for 4 hours (ketones **1c-f**) or 35 hours (ketone **1b**). The volatile components were evaporated and the residue was used without further purification in the second step. Purity of all compounds **2** was determined by nmr spectroscopy and was in all cases at least 95%. The yields were: **2b** 10%, **2c** 78%, **2d** 95%, **2e** 91% and **2f** 90%. Exception to this procedure is the preparation of the compound **2a** [9a]. The mixture of 11.6 ml (80 mmoles) *N,N*-dimethylformamide dimethyl acetal and 23.6 ml (320 mmoles) of acetone was refluxed for 35 hours, then the volatile components were evaporated and the remaining oil (3.43 g, 38%) was used without further purification.

Step 2. Synthesis of Compounds **5-19**.

A mixture of equimolar amounts (2-10 mmoles) of a compound **2** and *N*-acylglycine **3** was heated at 90° in a large excess of acetic anhydride (1.25 ml per mmole) for 4 hours. Acetic anhydride was evaporated, absolute ethanol (0.5 ml per mmole) was added and the mixture was cooled. The products were isolated either by filtration of the solid part, followed by washing with a small amount of ethanol (isolation A), or by column chromatography on silica gel (if no solid separated) with the mixture of petroleum benzine and ethyl acetate (1:1) as the eluent (isolation B). Reaction conditions and yields are given in the table.

N-(6-Methyl-2-oxo-2*H*-pyran-3-yl)benzamide (**5**).

This compound was obtained as light brown crystals, mp 145-148° (from methanol and methylene chloride); ^{1}H nmr: δ 2.27 (s, 3H, Me), 6.09 (d, J = 7.35 Hz, 1H, 5-H), 7.53 (m, 3H, Ph), 7.88 (m, 2H, Ph), 8.35 (d, J = 7.35 Hz, 1H, 4-H), 8.62 (br s, 1H, NH); ^{13}C nmr: δ 19.4, 104.0, 123.2, 124.5, 127.1, 128.9, 132.4, 133.8, 155.1, 160.5, 166.1; ms: m/z 229 (54, M$^+$).

Anal. Calcd. for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 67.82; H, 4.71; N, 6.07.

N-(6-Methyl-2-oxo-2*H*-pyran-3-yl)acetamide (**6**) [10].

This compound was obtained as a yellowish solid, mp 169-172° (methanol/chloroform); ^{1}H nmr: δ 2.19 (s, 3H, Me), 2.25 (s, 3H, Me), 6.02 (d, J = 7.3 Hz, 1H, 5-H), 7.89 (br s, 1H, NH), 8.17 (d, J = 7.3 Hz, 1H, 4-H); ms: m/z 167 (40, M$^+$); tlc: R_f = 0.26 (petroleum benzine and ethyl acetate 1:1).

Anal. Calcd. for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.43; H, 5.41; N, 8.10.

N-(6-Methyl-2-oxo-2*H*-pyran-3-yl)pyrazinecarboxamide (**7**).

This compound was obtained as a yellowish solid, mp 211-214° (methanol/chloroform); ^{1}H nmr: δ 2.29 (s, 3H, Me), 6.11 (d, J = 7.3 Hz, 1H, 5'-H), 8.39 (d, J = 7.3 Hz, 1H, 4'-H), 8.63 (dd, J = 2.4 and 1.5 Hz, 1H, 6-H), 8.81 (d, J = 2.4 Hz, 1H, 5-H), 9.43 (d, J = 1.5 Hz, 1H, 3-H), 10.23 (br s, 1H, NH); ms: m/z 231 (59, M$^+$); hrms: Calcd. mass 231.0644, exact mass 231.0652; tlc: R_f = 0.27 (petroleum benzine and ethyl acetate 1:1).

Anal. Calcd. for $C_{11}H_9N_3O_3 \cdot 0.1H_2O$: C, 56.70; H, 3.98; N, 18.03. Found: C, 56.65; H, 3.74; N, 17.76.

N-(6-*tert*-Butyl-2-oxo-2*H*-pyran-3-yl)benzamide (**8**).

This compound was obtained as white crystals, mp 127-128.5° (ethanol); ^{1}H nmr: δ 1.30 (s, 9H, *tert*-Bu), 6.14 (d, J = 7.5 Hz, 1H, 5-H), 7.53 (m, 3H, Ph), 7.89 (m, 2H, Ph), 8.37 (d, J = 7.5 Hz, 1H, 4-H), 8.63 (br s, 1H, NH); ^{13}C nmr: δ 28.0, 35.8, 100.0, 123.1, 124.4, 127.1, 128.9, 132.3, 133.8, 160.4, 165.8, 166.0; ms: m/z 271 (39, M$^+$).

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.86; H, 6.42; N, 5.17.

N-(6-*tert*-Butyl-2-oxo-2*H*-pyran-3-yl)acetamide (**9**).

This compound was obtained as a white solid, mp 109- 112° (ethyl acetate); ^{1}H nmr: δ 1.27 (s, 9H, *tert*-Bu), 2.19 (s, 3H, Ac), 6.07 (d, J = 7.5 Hz, 1H, 5-H), 7.89 (br s, 1H, NH), 8.18 (d, J = 7.5 Hz, 1H, 4-H); ms: m/z 209 (37, M$^+$); hrms: Calcd. mass 209.1052, exact mass 209.1060; tlc: R_f = 0.43 (petroleum benzine and ethyl acetate 1:1).

Anal. Calcd. for $C_{11}H_{15}NO_3 \cdot 0.2H_2O$: C, 62.07; H, 7.29; N, 6.58. Found: C, 62.22; H, 7.32; N, 6.56.

N-(6-*tert*-Butyl-2-oxo-2*H*-pyran-3-yl)pyrazinecarboxamide (**10**).

This compound was obtained as a white solid, mp 229-230° (methanol/chloroform); ^{1}H nmr: δ 1.31 (s, 9H, *tert*-Bu), 6.15 (d, J = 7.5 Hz, 1H, 5'-H), 8.41 (d, J = 7.5 Hz, 1H, 4'-H), 8.65 (dd, J = 2.3 and 1.5 Hz, 1H, 6-H), 8.82 (d, J = 2.3 Hz, 1H, 5-H), 9.44 (d, J = 1.5 Hz, 1H, 3-H), 10.23 (br s, 1H, NH); ms: m/z 273 (77, M$^+$).

Anal. Calcd. for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.38; H, 5.51; N, 15.40.

N-(2-Oxo-6-phenyl-2*H*-pyran-3-yl)benzamide (**11**) [11].

This compound was obtained as a yellow solid, mp 203-206° (ethanol/*N,N*-dimethylformamide) (lit [11] gives mp 200-201°).

N-(2-Oxo-6-phenyl-2*H*-pyran-3-yl)acetamide (**12**) [12].

This compound was obtained as a yellowish solid, mp 231-232° (chloroform) (lit [12] gives mp 228-229°).

N-[6-(2-Furyl)-2-oxo-2*H*-pyran-3-yl]benzamide (**13**).

This compound was obtained as brownish crystals, mp 212-213.5° (ethanol/*N,N*-dimethylformamide); ^{1}H nmr: δ 6.53 (dd, J = 1.8 and 3.5 Hz, 1H, 4'-H), 6.68 (d, J = 7.7 Hz, 1H, 5-H), 6.90 (d, J = 3.5 Hz, 1H, 3'-H), 7.52 (m, 4H, 3H of Ph, 5'-H), 7.90 (m, 2H, Ph), 8.52 (d, J = 7.7 Hz, 1H, 4-H), 8.69 (br s, 1H, NH); ms: m/z 281 (39, M$^+$).

Anal. Calcd. for $C_{16}H_{11}NO_4$: C, 68.32; H, 3.94; N, 4.98. Found: C, 68.14; H, 3.70; N, 5.10.

N-[2-Oxo-6-(2-thienyl)-2*H*-pyran-3-yl]benzamide (**14**).

This compound was obtained as a yellow solid, mp 208-211° (ethanol/*N,N*-dimethylformamide); ^{1}H nmr: δ 6.60 (d, J = 7.65 Hz, 1H, 5-H), 7.09 (dd, J = 3.77 and 4.95 Hz, 1H, 4'-H), 7.40 (dd, J = 1.10 and 4.95 Hz, 1H, 5'-H), 7.53 (m, 4H, 3H of Ph, 3'-H), 7.90 (m, 2H, Ph), 8.49 (d, J = 7.65 Hz, 1H, 4-H), 8.69 (br s, 1H, NH); ^{13}C nmr: δ 101.4, 123.7, 124.5, 126.2, 127.2, 127.9, 128.3, 128.9, 132.5, 133.7, 134.9, 149.9, 159.1, 166.0; ms: m/z 297 (62, M$^+$).

Anal. Calcd. for $C_{16}H_{11}NO_3S$: C, 64.63; H, 3.73; N, 4.71. Found: C, 64.34; H, 3.50; N, 4.78.

N-[2-Oxo-6-(2-thienyl)-2*H*-pyran-3-yl]acetamide (**15**).

This compound was obtained as a light green solid, mp 220-225° (methanol/methylene chloride); ^{1}H nmr: δ 2.22 (s, 3H, Ac), 6.54 (d, J = 7.65 Hz, 1H, 5-H), 7.09 (dd, J = 3.77 and 5.0 Hz, 1H, 4'-H), 7.39 (dd, J = 1.03 and 5.0 Hz, 1H, 5'-H), 7.49 (dd, J = 1.03 and 3.77 Hz, 1H, 3'-H), 7.96 (br s, 1H, NH), 8.31 (d, J = 7.65 Hz, 1H, 4-H); ms: m/z 235 (52, M$^+$); tlc: R_f = 0.25 (petroleum benzine and ethyl acetate 1:1).

Anal. Calcd. for $C_{11}H_9NO_3S$: C, 56.16; H, 3.86; N, 5.95. Found: C, 56.22; H, 3.96; N, 5.76.

N-[2-Oxo-6-(2-thienyl)-2*H*-pyran-3-yl]pyrazinecarboxamide (**16**).

This compound was obtained as a yellow solid, mp 278-281° (methanol/chloroform); ^{1}H nmr (DMSO-d_6): δ 7.06 (d, J = 7.67 Hz, 1H, 5'-H), 7.22 (dd, J = 3.77 and 4.98 Hz, 1H, 4"-H), 7.70 (dd, J = 1.02 and 3.77 Hz, 1H, 3"-H), 7.78 (dd, J = 1.02 and 4.98 Hz, 1H, 5"-H), 8.39 (d, J = 7.67 Hz, 1H, 4'-H), 8.86 (dd, J = 1.45 and 2.45 Hz, 1H, 6-H), 9.00 (d, J = 2.45 Hz, 1H, 5-H), 9.33 (d, J = 1.45 Hz, 1H, 3-H), 10.17 (br s, 1H, NH); ms: m/z 299 (87, M$^+$); tlc: R_f = 0.30 (petroleum benzine and ethyl acetate 1:1).

Anal. Calcd. for $C_{14}H_9N_3O_3S$: C, 56.18; H, 3.03; N, 14.04. Found: C, 55.89; H, 2.87; N, 13.97.

N-[2-Oxo-6-(2-pyridyl)-2*H*-pyran-3-yl]benzamide (**17**).

This compound was obtained as a white solid, mp 198-200° (ethanol/*N,N*-dimethylformamide); ^{1}H nmr: δ 7.29 (ddd, J = 1.0, 4.85 and 7.6 Hz, 1H, 5'-H), 7.47 (d, J = 7.7 Hz, 1H, 5-H), 7.54 (m, 3H, Ph), 7.79 (ddd, J = 1.7, 7.6 and 7.6 Hz, 1H, 4'-H), 7.92 (m, 3H, 2H of Ph, 3'-H), 8.60 (d, J = 7.7 Hz, 1H, 4-H), 8.64 (deg. ddd, 1H, 6'-H), 8.78 (br s, 1H, NH); ^{13}C nmr: δ 104.4, 119.6, 124.0, 124.2, 125.7, 127.2, 129.0, 132.5, 133.6, 137.1, 148.8, 149.9, 152.3, 159.3, 166.0; ms: m/z 292 (51, M$^+$).

Anal. Calcd. for $C_{17}H_{12}N_2O_3$: C, 69.86; H, 4.14; N, 9.58. Found: C, 69.48; H, 3.87; N, 9.55.

N-(2-Oxo-6-phenyl-2*H*-pyran-3-yl)diacetamide (**18**).

This compound was obtained as a yellowish solid, mp 186-189° (ethyl acetate); ^{1}H nmr: δ 2.41 (s, 6H, two Ac), 6.75 (d, J = 7.3 Hz, 1H, 5-H), 7.38 (d, J = 7.3 Hz, 1H, 4-H), 7.49 (m, 3H, Ph), 7.85 (m, 2H, Ph); ms: m/z 271 (13, M$^+$); tlc: R_f = 0.29 (petroleum benzine and ethyl acetate 1:1).

Anal. Calcd. for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.36; H, 4.69; N, 5.22.

N-(2-Oxo-6-(2-thienyl)-2*H*-pyran-3-yl]diacetamide (**19**).

This compound was obtained as a yellowish solid, mp 163-165° (methanol); ^{1}H nmr: δ 2.40 (s, 6H, two Ac), 6.58 (d, J = 7.3 Hz, 1H, 5-H), 7.15 (dd, J = 3.9 and 5.0 Hz, 1H, 4'-H), 7.32 (d, J = 7.3 Hz, 1H, 4-H), 7.52 (dd, J = 0.95 and 5.0 Hz, 1H, 5'-H), 7.65 (dd, J = 0.95 and 3.9 Hz, 1H, 3'-H); ms: m/z 277 (22, M$^+$); tlc: R_f = 0.32 (petroleum benzine and ethyl acetate 1:1).

Anal. Calcd. for $C_{13}H_{11}NO_4S$: C, 56.31; H, 4.00; N, 5.05. Found: C, 56.06; H, 3.84; N, 5.02.

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