ONE-POT SYNTHESIS OF SOME FUSED PYRAN-2-ONES

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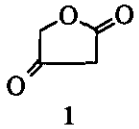
Abstract - A one-pot synthesis of different fused pyran-2-ones starting from some less commonly used activated methylene compounds (cyclic lactones, a thiolactone and a lactam), one-carbon sources and *N*-acylglycines in acetic anhydride is described.

There are numerous synthetic methods for the preparation of 2*H*-pyran-2-ones and fused pyran-2-ones.[1] Some recent papers are dealing with a simple one-pot synthesis of several acylamino derivatives of this type starting from 1,3-dicarbonyl compounds, one-carbon synthons, such as triethyl orthoformate (TOF), diethoxymethyl acetate (DEMA) or *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA), *N*-acylglycines and a large excess of acetic anhydride.[2-6] Since this method seems to be the simplest way for the synthesis of several pyranone ring containing systems, we have tried to find its further applications.

For this reason we have applied our method to less commonly used 1,3-dicarbonyl compounds, such as tetronic acid (**1**), thiotetronic acid (**2**), 4-hydroxy-6-methyl-2*H*-pyran-2-one (**3**), 4-hydroxy-2*H*-1-benzopyran-2-one (**4**) and 4-hydroxyquinolin-2(1*H*)-one (**5**). They all possess an unsymmetrically substituted diactivated methylene group and might exist in two or more tautomeric forms.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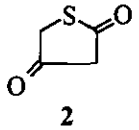
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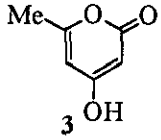
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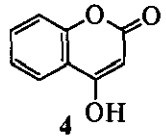
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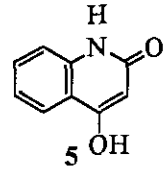
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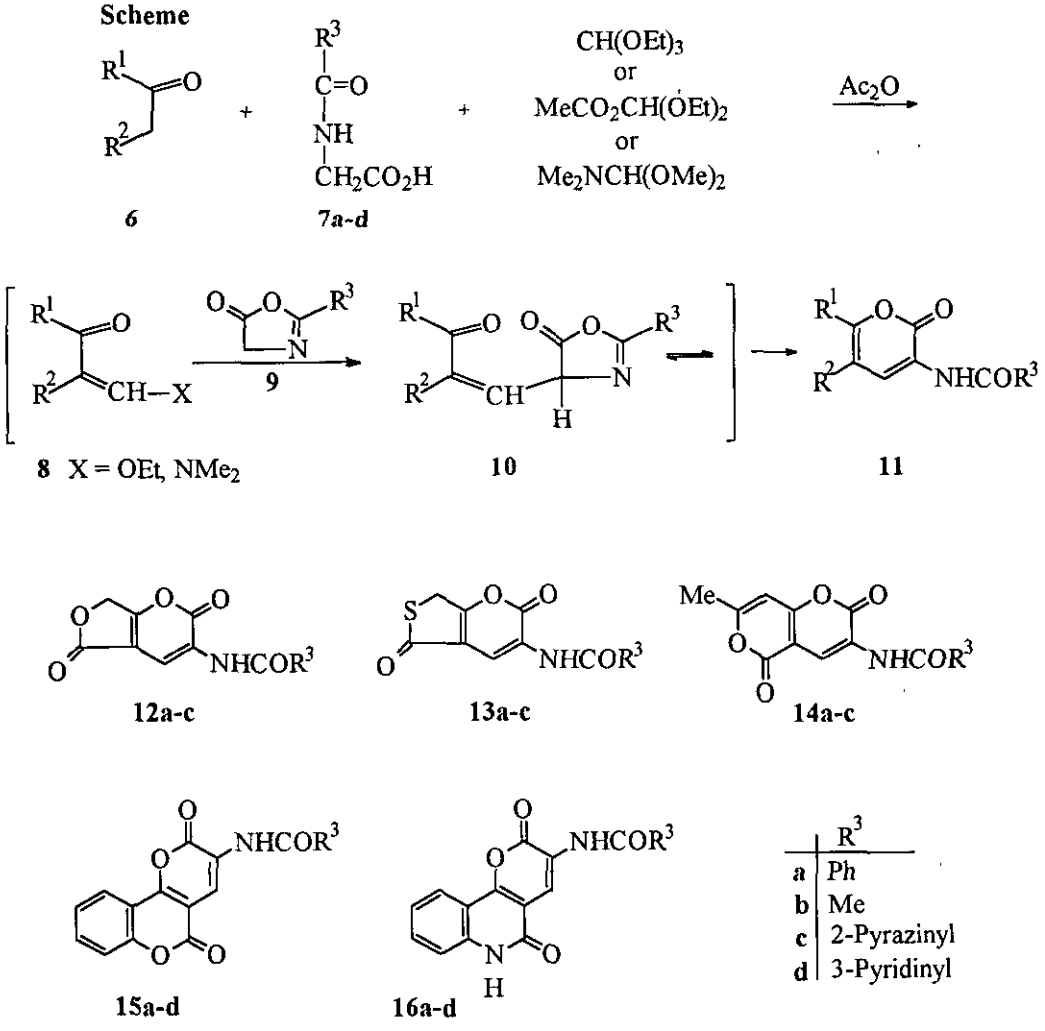
Two previously reported reaction procedures[3] were slightly modified and used in these transformations. In all cases the reactions were carried out using TOF as one of the cheapest one-carbon sources; DEMA and DMFDMA were used optionally. Hippuric acid (**7a**), *N*-acetylglycine (**7b**) and *N*-pyrazinylcarbonylglycine (**7c**)[7]

were used in reactions with all carbonyls and *N*-(3-pyridinylcarbonyl)glycine (**7d**)[8] only in the case of compounds (**4**) and (**5**). Derivatives of 5,7-dihydro-2*H*-furo[3,4-*b*]pyran-2,5-dione (**12a-c**), 5,7-dihydro-2*H*-thieno[3,4-*b*]pyran-2,5-dione (**13a-c**), 2*H*,5*H*-pyrano[4,3-*b*]pyran-2,5-diones (**14a-c**), 2*H*,5*H*-pyrano[3,2-*c*][1]-benzopyran-2,5-dione (**15a-d**), and 2*H*-pyrano[3,2-*c*]quinoline-2,5-dione (**16a-d**) have been synthesized (Scheme). Reaction conditions and yields are given in the Table.

Scheme



In all cases two different products of pyranone type might be formed, since the activated methylene group is unsymmetrically substituted. The formation of the compounds (**14-16**) is in accordance with the previous observations, where some representatives of these systems were formed by different methodologies.[5,9,10] The structure of the compounds (**12**) and (**13**) was determined on the basis of already known transformations of tetronic and thiotetronic acid, in which 4-oxo group has been shown to be more reactive than 2-oxo group.[11-16]

Table: Synthesis of the compounds **(12-16):**

Active methylene compound	*N*-Acylglycine	One-carbon synthon	Procedure	Reaction conditions step 1	step 2	Yield (%)	Product
1	**7a**	TOF	B	10 min;	4 h 90 °C	66[a]	**12a**
1	**7a**	DEMA	B	5 min;	1 h 90 °C	75[a]	**12a**
1	**7b**	TOF	A	4 h 90 °C		26[b]	**12b**
1	**7b**	DEMA	B	10 min;	2 h 90 °C	24	**12b**
1	**7c**	TOF	B	5 min;	4 h 90 °C	24	**12c**
1	**7c**	DEMA	B	10min;	2 h 90 °C	36a	**12c**
2	**7a**	TOF	B	10min;	4 h 90 °C	42	**13a**
2	**7a**	DEMA	A	4 h 90 °C		74	**13a**
2	**7b**	TOF	B	5 min;	4 h 90 °C	17[a,b]	**13b**
2	**7b**	DEMA	B	5 min;	2 h 90 °C	9[a]	**13b**
2	**7c**	TOF	B	5 min;	4 h 90 °C	19[a,b]	**13c**
3	**7a**	TOF	B	10 min;	4 h 90 °C	26	**14a**[10]
3	**7a**	DEMA	B	10 min;	2 h 90 °C	16	**14a**
3	**7a**	DMFDMA	A	2 h 90 °C		22	**14a**
3	**7b**	TOF	A	4 h 90 °C		18	**14b**
3	**7b**	DMFDMA	A	2 h 90 °C		9	**14b**
3	**7c**	TOF	A	4 h 90 °C		10	**14c**
3	**7c**	DMFDMA	A	2 h 90 °C		6	**14c**
4	**7a**	TOF	B	10 min;	4 h 90 °C	57	**15a**
4	**7a**	DEMA	A	4 h 80 °C		70	**15a**[5]
4	**7b**	TOF	A	4 h 80 °C		21	**15b**
4	**7c**	TOF	B	10 min;	4 h 80 °C	17	**15c**
4	**7d**	TOF	A	4 h 80 °C		61	**15d**
5	**7a**	TOF	A	4 h 90 °C		71	**16a**[5]
5	**7b**	TOF	A	4 h 90 °C		46	**16b**
5	**7c**	TOF	A	4 h 90 °C		9	**16c**
5	**7d**	TOF	A	4 h 90 °C		31	**16d**

[a]For the isolation of this product a few drops of DMF were added to the ethanol mixture.

[b]Product was purified by radial chromatography on silica gel plates with a mixture of chloroform and methanol (5:1) as eluent.

On the basis of these data one could predict a similar reactivity in our conversions, too.

In conclusion, the described method seems to be very useful for the synthesis of different fused pyran-2-ones. Considering *N*-acylglycines, the highest yields of pyranones were usually obtained when hippuric acid was used, and lower with others.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage, and are uncorrected. ^{1}H Nmr spectra were recorded with a Varian EM360L spectrometer, 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. Tlc was carried out on Fluka silica gel tlc cards. Compounds (**7c**)[7] and (**7d**)[8] were prepared as described in the literature. All other compounds were used as received from commercial sources.

Procedure A: Equimolar amounts of a 1,3-dicarbonyl compound, a one-carbon synthon and an *N*-acylglycine were heated in acetic anhydride (1.25 ml per mmol) for 2-4 h, the solvent was evaporated *in vacuo* and a small volume of ethanol (0.5 ml per mmol) was added. Upon cooling the crude product was filtered off and washed with a small amount of ethanol.

Procedure B: An equimolar mixture of a methylene compound and a one-carbon synthon was heated in acetic anhydride (1.25 ml per mmol) for a short period of time (step 1), then an equimolar amount of an *N*-acylglycine was added and heating was continued for 1-4 h (step 2). Isolation of the products was the same as described above.

Analytical and spectroscopic data of the compounds 12-16:

***N*-(5,7-Dihydro-2,5-dioxo-2*H*-furo[3,4-*b*]pyran-3-yl)benzamide (12a):** mp 225-228 °C (decomp. from DMF/EtOH); ^{1}H nmr (DMSO-d_6) δ 5.32 (s, 2 H, 7-CH_2), 7.67 (m, 3H, Ph), 8.03 (m, 2H, Ph), 8.28 (s, 1H, 4-H), 9.92 (br s, 1H, NH); ms (m/z, %) 271 (25) [M^+]. Anal. Calcd for $C_{14}H_9NO_5$: C, 62.00; H, 3.34; N, 5.16. Found: C, 62.09; H, 3.35; N 5.40.

***N*-(5,7-Dihydro-2,5-dioxo-2*H*-furo[3,4-*b*]pyran-3-yl)acetamide (12b):** mp 197-200 °C (decomp., MeCN); ^{1}H nmr (DMSO-d_6) δ 2.15 (s, 3H, Ac), 5.22 (s, 2H, 7-CH_2), 8.25 (s, 1H, 4-H), 9.92 (br s, 1H, NH); ms (m/z) 209 (29) [M^+]. Anal. Calcd for $C_9H_7NO_5$: C, 51.68; H, 3.37; N, 6.70. Found: C,51.55; H, 3.29; N, 6.83.

***N*-(5,7-Dihydro-2,5-dioxo-2*H*-furo[3,4-*b*]pyran-3-yl)pyrazine-2-carboxamide (12c):** mp above 270 °C (decomp., MeCN); ^{1}H nmr (DMSO-d_6) δ 5.30 (s, 2H, 7'-CH_2), 8.37 (s, 1H, 4'-H), 8.88 (dd, J = 2.5 and 1.5 Hz, 1H, 6-H), 9.05 (d, J = 2.5 Hz, 1H, 5-H), 9.37 (d, J = 1.5 Hz, 1H, 3-H), 10.25 (br s, 1H, NH); ms (m/z) 273 (75) [M^+]. Anal. Calcd for $C_{12}H_7N_3O_5$: C, 52.76; H, 2.58; N, 15.38. Found: C, 52.92; H, 2.47; N, 15.32.

***N*-(5,7-Dihydro-2,5-dioxo-2*H*-thieno[3,4-*b*]pyran-3-yl)benzamide (13a):** mp 220-220 °C (DMF/EtOH); ^{1}H nmr (DMSO-d_6) δ 4.61 (s, 2H, 7-CH_2), 7.60 (m, 3H, Ph), 7.94 (m, 2H, Ph), 8.20 (s, 1H, 4-H), 9.78 (br s, 1H, NH); ms (m/z) 287 (36) [M^+]. Anal. Calcd for $C_{14}H_9NO_4S$: C, 58.53; H, 3.16; N, 4.88. Found. C, 58.59, H, 3.16; N 4.84.

***N*-(5,7-Dihydro-2,5-dioxo-2*H*-thieno[3,4-*b*]pyran-3-yl)acetamide (13b):** mp 195-197 °C (decomp., DMF/EtOH); ^{1}H nmr (DMSO-d_6) δ 2.15 (s, 3H, Ac), 4.55 (s, 2H, 7-CH_2), 8.23 (s, 1H, 4-H), 9.88 (br s, 1H, NH), ms (m/z) 225 (36) [M^+]. Anal. Calcd for $C_9H_7NO_4S$: C, 48.00; H, 3.13; N, 6.22. Found: C, 48.30; H, 2.82; N, 6.18.

***N*-(5,7-Dihydro-2,5-dioxo-2*H*-thieno[3,4-*b*]pyran-3-yl)pyrazine-2-carboxamide (13c):** mp 232-235 °C (decomp., MeCN); ^{1}H nmr ($CDCl_3$) δ 4.33 (s, 2H, 7'-CH_2), 8.67-8.80 (m, 2H, 4'-H, 6-H), 8.93 (d, J = 3 Hz, 1H, 5-H), 9.53 (d, J = 1.5 Hz, 1H, 3-H), 10.38 (br s, 1H, NH); ms (m/z) 289 (100) [M^+]. Anal. Calcd for $C_{12}H_7N_3O_4S$: C, 49.83; H, 2.44; N, 14.53. Found: C, 50 07; H, 2 20; N, 14.23.

***N*-(2,5-Dioxo-7-methyl-2*H*,5*H*-pyrano[4,3-*b*]pyran-3-yl)benzamide (14a)[10]:** mp 261-263 °C (DMF/EtOH) (lit.,[10] mp 258-260 °C)

***N*-(2,5-Dioxo-7-methyl-2*H*,5*H*-pyrano[4,3-*b*]pyran-3-yl)acetamide (14b):** mp 281-283 °C (MeCN); ^{1}H nmr (DMSO-d_6) δ 2.18 (s, 3H, Ac), 2.37 (s, 3H, Me), 6.83 (s, 1H, 8-H), 8.70 (s, 1H, 4-H), 10.00 (br s, 1H, NH); ms (m/z) 235 (25) [M^+]. Anal. Calcd for $C_{11}H_9NO_5$: C, 56 17, H, 3 86; N, 5.96. Found: C, 56.50; H, 3.66; N, 5 96.

***N*-(2,5-Dioxo-7-methyl-2*H*,5*H*-pyrano[4,3-*b*]pyran-3-yl)pyrazine-2-carboxamide (14c)**: mp 304-306 °C (decomp., DMF); ^{1}H nmr (DMSO-d_6) δ 2.40 (s, 3H, Me), 6.92 (s, 1H, 8'-H), 8.88 (s, 1H, 4'-H), 9.17 (dd, J = 2.5 and 1.5 Hz, 1H, 6-H), 9.33 (d, J = 2.5 Hz, 1H, 5-H), 9.66 (d, J = 1 5 Hz, 1H, 3-H), 10.55 (br s, 1H, NH); ms (m/z) 299 (100) [M^+]. Anal. Calcd for $C_{14}H_9N_3O_5$: C, 56 19; H, 3.03; N, 14.04. Found: C, 56.56; H, 2.97; N, 13.75.

***N*-(2,5-Dioxo-2*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-3-yl)benzamide (15a)[5]:** mp 309-311 °C (DMF) (lit.,[5] mp 309-311 °C).

***N*-(2,5-Dioxo-2*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-3-yl)acetamide (15b):** mp 300-301 °C (EtOH/DMF); ^{1}H

nmr (DMSO-d_6) δ 2.22 (s, 3H, Ac), 7.45-8.22 (m, 4H, 7-H, 8-H, 9-H, 10-H), 8.75 (s, 1 H, 4-H), 10.18 (br s, 1H, NH); ms (m/z) 271 (32) [M^+]. Anal Calcd for $C_{14}H_9NO_5$: C, 62.00; H, 3.34; N, 5.16. Found: C, 62.25; H, 3.31; N, 5.48.

***N*-(2,5-Dioxo-2*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-3-yl)pyrazine-2-carboxamide (15c):** mp above 360 °C (DMF); ^{1}H nmr (CF_3CO_2D) δ 7.00-7.87 (m, 4H, 7'-H, 8'-H, 9'-H, 10'-H), 8.77 (s, 1H, 4'-H), 8.80 (d, J = 1.5 Hz, 1H, 5-H), 9.12 (deg. dd, 1H, 6-H), 9.32 (br s, 1H, 3-H); ms (m/z) 335 (100) [M^+]. Anal. Calcd for $C_{17}H_9N_3O_5$: C, 60.90; H, 2.71; N, 12.53. Found: C, 60.71; H, 2.58; N, 12.43.

***N*-(2,5-Dioxo-2*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-3-yl)pyridine-3-carboxamide (15d):** mp 315-317 °C (DMF); ^{1}H nmr (CF_3CO_2D) δ 7.00-8.07 (m, 5H, 7'-H, 8'-H, 9'-H 10'-H, 5-H), 8.57-8.93 (m, 2H, 4'-H, 4-H, 6-H), 9.13 (m, 1H, 2-H); ms (m/z) 334 (46) [M^+]. Anal. Calcd for $C_{18}H_{10}N_2O_5$: C, 64.67; H, 3.02; N, 8.38. Found: C, 64.91; H, 2.78; N, 8.32.

***N*-(5,6-Dihydro-2,5-dioxo-2*H*-pyrano[3,2-*c*]quinoline-3-yl)benzamide (16a)[5]:** mp above 360 °C (DMF) (lit.,[5] mp above 360 °C).

***N*-(5,6-Dihydro-2,5-dioxo-2*H*-pyrano[3,2-*c*]quinoline-3-yl)acetamide (16b):** mp above 360 °C (DMF); ^{1}H nmr (CF_3CO_2D) δ 2.05 (s, 3H, Ac), 7.07-8.05 (m, 4H, 7-H, 8-H, 9-H, 10-H), 8.83 (s, 1H, 4-H); ms (m/z) 270 (29) [M^+]. Anal. Calcd for $C_{14}H_{10}N_2O_4$: C, 62.22, H, 3.73; N, 10.37. Found: C, 62.43, H, 3.75; N, 10.53.

***N*-(5,6-Dihydro-2,5-dioxo-2*H*-pyrano[3,2-*c*]quinoline-3-yl)pyrazine-2-carboxamide (16c):** mp above 360 °C (DMF); ^{1}H nmr (CF_3CO_2D) δ 7.08-8.08 (m, 4H, 7'-H, 8'-H, 9'-H, 10'-H), 8.88 (d, J = 3.0 Hz, 1H, 5-H), 9.02 (s, 1H, 4'-H), 9.22 (dd, J = 3.0 and 1.5 Hz, 1H, 6-H), 9.43 (d, J = 1.5 Hz, 1H, 3-H); ms (m/z) 334 (100) [M^+]. Anal. Calcd for $C_{17}H_{10}N_4O_4$: C, 61 08; H, 3.02; N, 16.76. Found: C, 61.28; H, 2.96; N, 16.47.

***N*-(5,6-Dihydro-2,5-dioxo-2*H*-pyrano[3,2-*c*]quinoline-3-yl)pyridine-3-carboxamide (16d):** mp above 350 °C (DMF); ^{1}H nmr (CF_3CO_2D) δ 7.10-8.12 (m, 5H, 5-H, 7'-H, 8'-H, 9'-H, 10'-H), 8.67-9.03 (m, 3H, 4-H, 6-H, 4'-H), 9.22 (m, 1H, 2-H), ms (m/z) 333 (51) [M^+]. Anal Calcd for $C_{18}H_{11}N_3O_4$: C, 64.87; H, 3.33; N, 12.61. Found: C, 64.65; H, 3.31; N, 12.54.

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