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A SIMPLE AND GENERAL ONE-POT SYNTHESIS OF SOME 2H-PYRAN-2-ONES AND FUSED PYRAN-2-ONES

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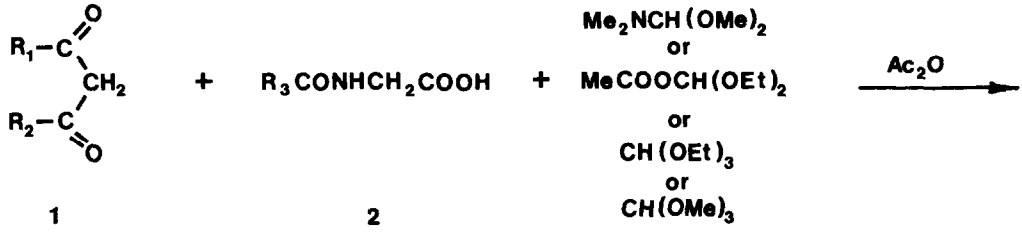
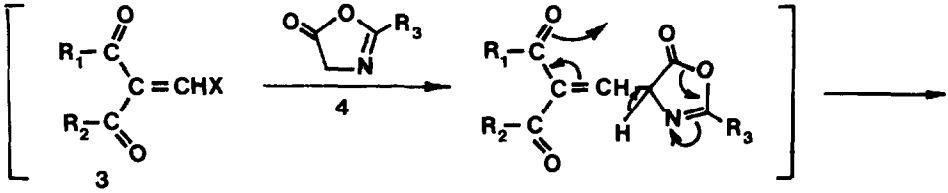
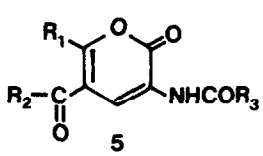
Abstract. A general one-pot synthesis of some 2H-pyran-2-ones and fused pyran-2-ones starting from 1,3-dicarbonyl compounds, N-acylglycines and one-carbon synthons (trialkyl orthoformates, diethoxymethyl acetate or N,N-dimethylformamide dimethyl acetal) in acetic anhydride (or in a mixture of acetic anhydride and acetic acid) is described.

There are several synthetic approaches to 2H-pyran-2-ones and fused pyran-2-ones.[1] For example, the 2-pyrone ring was formed by lactonization of the oxo-carboxylic acids.[2] 4,5-Disubstituted 3-benzoylamino-2H-pyran-2-ones and 3-benzoylamino-5-oxo-5,6,7,8-tetrahydrocoumarin were prepared from 1,3-dicarbonyl compounds and 4-ethoxymethylene-2-phenyl-5(4H)-oxazolone in the presence of triethylamine.[3] 2-(Ureidomethylene)cyclohexane-1,3-diones and activated acetonitriles in the presence of a strong base resulted in 5-oxo-5,6,7,8-tetrahydrocoumarins.[4] 2-Bis(methylthio)methylene-1,3-indandione was transformed in a two-step procedure to 4-(methylthio)indeno[1,2-*b*]pyran-2,5-dione,[5] 2H-pyrano[2,3-*d*]pyrimidine-2,4,7(1H,3H)-triones were prepared from barbituric acid or its derivatives,[6] etc. None of these methods has been declared to be a general procedure for the synthesis of various 2-pyrone ring containing systems.

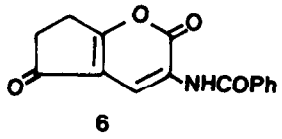
We describe here a convenient and general one-pot synthesis of some 2H-pyran-2-ones and fused pyran-2-ones starting from 1,3-dicarbonyl compounds (an acyclic 1,3-diketone and β-ketoester, cyclic 1,3-diketones and heterocyclic 1,3-dioxo compounds), N-acylglycines [hippuric acid (2, R_3=Ph), N-(pyrazinecarbonyl)glycine (2, R_3=2-pyrazinyl)[7] or aceturic acid (2, R_3=Me)(in one case)] and one-carbon synthons (triethyl orthoformate-TOF, diethoxymethyl acetate-DEMA, N,N-dimethylformamide dimethyl acetal-DMFDMA or trimethyl orthoformate) in acetic anhydride (or a mixture of acetic anhydride and acetic acid). Under the applied reaction conditions, the corresponding 2H-pyran-2-ones **5a-d**, 6,7-dihydrocyclopenta[*b*]pyran-2,5-dione derivative **6**, 5-oxo-5,6,7,8-tetrahydrocoumarins **7a-g**, 2H-pyrano[2,3-*d*]pyrimidine-

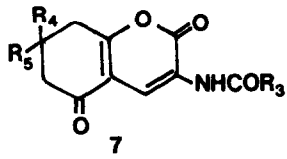




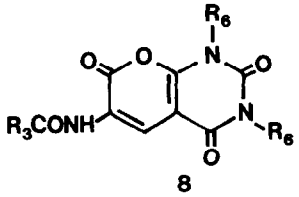


	R_1	R_2	R_3
a	Me	Me	Ph
b	Me	Me	Py
c	Me	OEt	Ph
d	Me	OEt	Py

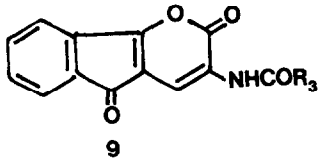




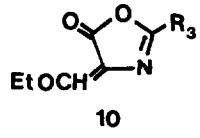
	R_3	R_4	R_5
a	Ph	H	H
b	Py	H	H
c	Ph	H	Me
d	Py	H	Me
e	Ph	Me	Me
f	Py	Me	Me
g	Me	H	Me



	R_3	R_6
a	Ph	H
b	Ph	Me
c	Py	Me



	R_3
a	Ph
b	Py



	R_3
a	Ph

Scheme

Table: Yields of the compounds 5, 6, 7, 8, 9 and 10

1,3-Dicarbonyl compound 1	Glycine derivative 2	C_1 synthon	"Solvent"	Procedure	Product	Yield
	R_3=Ph	TOF	Ac_2O	A	10a[a]	41%
	R_3=Ph	TOF	Ac_2O	B	10a	39%
	R_3=Ph	TOF	Ac_2O	C	5a[a]	16%
$CH_3COCH_2COCH_3$	R_3=Ph	TOF	Ac_2O/AcOH	C	5a	37%
	R_3=Ph	DEMA	Ac_2O	B	5a	17%
	R_3=Ph	DMFDMA	Ac_2O	B	5a	23%
	R_3=Py	DMFDMA	Ac_2O	B	5b	12%
	R_3=Py	DMFDMA	Ac_2O	C	5b	11%[a]
	R_3=Ph	TOF	Ac_2O/AcOH	C	5c[a]	21%
	R_3=Ph	DMFDMA	Ac_2O/AcOH	C	5c	42%
CH_3COCH_2COOEt	R_3=Ph	DMFDMA	Ac_2O	A	5c	9%[a]
	R_3=Py	DMFDMA	Ac_2O	B	5d	12%
	R_3=Py	DMFDMA	Ac_2O	C	5d	20%[a]
	R_3=Py	DMFDMA	Ac_2O/AcOH	C	5d	31%[a]
1,3-Cyclopentanedione	R_3=Ph	TOF	Ac_2O/AcOH	C	6	30%
	R_3=Ph	DEMA	Ac_2O	A	6	32%
	R_3=Ph	DMFDMA	Ac_2O	A	6	15%
	R_3=Ph	$CH(OMe)_3$	Ac_2O	A	7a[a]	25%
1,3-Cyclohexanedione	R_3=Py	TOF	Ac_2O	A	7b	17%[a]
	R_3=Py	DEMA	Ac_2O	A	7b	20%
	R_3=Py	DMFDMA	Ac_2O	A	7b	30%[a]
5-Methyl-1,3-cyclohexanedione[14]	R_3=Ph	$CH(OMe)_3$	Ac_2O	A	7c[a]	33%
	R_3=Py	TOF	Ac_2O	A	7d	17%
	R_3=Py	DEMA	Ac_2O	A	7d	21%
	R_3=Py	DMFDMA	Ac_2O	A	7d	19%
	R_3=Ph	$CH(OMe)_3$	Ac_2O	A	7e[a]	34%
5,5-Dimethyl-1,3-cyclohexanedione	R_3=Py	TOF	Ac_2O	A	7f	25%
	R_3=Py	DEMA	Ac_2O	A	7f	27%
	R_3=Py	DMFDMA	Ac_2O	A	7f	28%
	R_3=Me	TOF	Ac_2O	A	7g	7%[a]
Barbituric acid	R_3=Ph	DMFDMA	Ac_2O	A	8a	20%[a]
	R_3=Ph	TOF	Ac_2O	A	8b	60%
1,3-Dimethylbarbituric acid	R_3=Ph	DEMA	Ac_2O	A	8b	65%
	R_3=Ph	DMFDMA	Ac_2O	A	8b	59%
	R_3=Py	DEMA	Ac_2O	A	8c	39%[a]
	R_3=Py	DMFDMA	Ac_2O	A	8c	18%[a]
	R_3=Ph	TOF	Ac_2O	A	9a	20%[a]
1,3-Indandione	R_3=Ph	DEMA	Ac_2O	A	9a	55%
	R_3=Ph	DMFDMA	Ac_2O	A	9a	55%
	R_3=Py	DMFDMA	Ac_2O	A	9b	68%

Py=2-Pyrazinyl
a) Yield of the crystallized product.

2,4,7(1H,3H)-triones **8a-c**, and indeno[1,2-*b*]pyran-2,5-diones **9a-b** were obtained in various yields (see Table).

The method is based on a procedure used for the synthesis of some 3-benzoylamino-5-oxo-5,6,7,8-tetrahydrocoumarins.[9] This procedure was successfully applied to 1,3-cyclopentanedione, 1,3-cyclohexanediones, barbituric acid, 1,3-dimethylbarbituric acid and 1,3-indandione (Procedure A).

When the described procedure was used in order to prepare the pyrone derivative **5a** from acetylacetone (**1**, R_1=R_2=Me), TOF and hippuric acid (**2**, R_3=Ph) in the presence of a large excess of acetic anhydride, 4-ethoxymethylene-2-phenyl-5(4H)-oxazolone **10a**[9] was isolated instead of the expected derivative **5a**. In a similar experiment, but using DEMA instead of TOF, a mixture of the expected derivative **5a** and the oxazolone derivative **10a** was obtained. Two other procedures were used in order to avoid the formation of the oxazolone derivative **10a**:

1. A one-carbon synthon was first heated with a 1,3-dicarbonyl compound, until the corresponding intermediate **3** is formed. The reaction was continued by the addition of N-acylglycine and acetic anhydride, followed by heating of the reaction mixture (Procedure B). In such an experiment from acetylacetone and hippuric acid, after work-up the pyrone derivative **5a** was separated from the reaction mixture in 17-23% yield, and was not accompanied by the oxazolone derivative **10a** when using DEMA or DMFDMA. With TOF no pyrone derivative **5a** was obtained and the oxazolone derivative **10a** was again isolated.

2. A one-carbon synthon and a 1,3-dicarbonyl compound were first heated in acetic anhydride or a mixture of acetic anhydride and acetic acid (4:1), then N-acylglycine was added and the reaction was continued as in the previous case (Procedure C). Applying this procedure to TOF, acetylacetone and hippuric acid in acetic anhydride and acetic acid, the pyrone derivative **5a** was obtained in 37% yield. When a similar experiment with TOF and acetylacetone was carried out in acetic anhydride, the pyrone derivative **5a** was isolated in only 16% yield.

The method seems to be applicable to practically all the previously mentioned 1,3-dicarbonyl compounds which react with one-carbon synthons to give the corresponding intermediates **3** (X=NMe_2, OEt, OMe),[10] and to the N-acylglycines which can be converted, under the applied reaction conditions, to the intermediate **4**.[11] As expected, side reactions are acetylation of the dicarbonyl compounds, condensation of the dicarbonyl compounds in the presence of one-carbon synthons, or eventually decomposition of the starting dicarbonyl compounds or intermediates **3** in acetic anhydride (or in acetic anhydride and acetic acid). On the other hand, the oxazolone intermediates **4** can be converted with one-carbon synthons into the 4-substituted oxazolones **10**, which cannot be transformed to the corresponding pyrone derivatives.[12] Procedure A is suitable for 1,3-dicarbonyl compounds which are very reactive

towards one-carbon synthons. For less reactive 1,3-dicarbonyl compounds, procedures B or C are recommended, especially for dicarbonyl compounds which do not give condensation products with one-carbon synthons under the applied reaction conditions.[13] The reaction temperature also depends on the N-acylglycine, and must be high enough for the formation of the oxazolone derivative 4. For N-(pyrazinecarbonyl)glycine and aceturic acid higher temperatures (90-110 °C in acetic anhydride) are needed when compared to the reaction with hippuric acid (75-80 °C). In some cases at lower temperatures the starting glycine derivative 2 was recovered. Although it is well known that a basic catalyst can improve the yield or shorten the reaction time in various reactions of oxazolones,[11] the use of sodium acetate as a catalyst in our one-pot synthesis is not recommended, because it favors formation of the oxazolone derivatives 10.[12]

The main advantage of this method when compared to method which starts from 1,3-dicarbonyl compounds and 4-ethoxymethylene-2-phenyl-5(4H)-oxazolone,[3,8] and which may lead to the same products in all cases, is the fact that one can avoid the synthesis of the ethoxymethylene derivatives 10.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage. NMR spectra were recorded on a JEOL JNM FX90Q and Varian EM360L, using TMS as internal standard. Mass spectra were recorded on a CEC-20-110 C instrument. Elemental analyses (C, H, N) were performed on a Perkin-Elmer 240C Analyzer. TLC was carried out on Fluka Silica gel TLC-Cards.

General Procedures:

Procedure A. A mixture of a one-carbon synthon (TOF, DEMA, DMFDMA, trimethyl orthoformate; 4 mmol), a 1,3-dicarbonyl compound 1 (4 mmol), N-acylglycine 2 (4 mmol) and acetic anhydride (5 ml) was heated at 75-80 °C (when hippuric acid was used) or at 90-100 °C (when N-pyrazinecabonylglycine or aceturic acid were used) for 4 h with occasional shaking. The reaction mixture was evaporated in vacuo and the residue was treated with ethanol (2 ml). Upon cooling the solid was filtered and washed with a small amount of ethanol. (The yields of TLC pure products are given in the Table.)

Procedure B. A mixture of a one-carbon synthon (4 mmol) and a 1,3 dicarbonyl compound (4 mmol) was heated for 10-35 min at 75-80 °C, then N-acylglycine 2 (4 mmol) and acetic anhydride (5 ml) were added and the reaction mixture was heated for 4 h at 75-80 °C (with hippuric acid) or 90-100 °C (with N-pyrazinecarbonylglycine). Thereafter the reactions were continued as described in "Procedure A."

Procedure C. A mixture of a one-carbon synthon (4 mmol), a 1,3-dicarbonyl compound (4 mmol) and acetic anhydride (5 ml) (or a mixture of acetic anhydride and acetic acid, 4 ml and 1 ml) was heated at 75-80 °C for 2,5 h (exception: with 1,3-cyclopentanedione 1 h), then N-acylglycine (4 ml) was added and the reaction mixture was heated for 4 h at 75-80 °C (or 100-110 °C with N-pyrazinecarbonylglycine). Thereafter the reactions were continued as described in "Procedure A.

Analytical and spectroscopic data of the compounds:

2H-Pyran-2-ones:

5a: mp 137-138 °C (from EtOH); mp lit[3] 139-140 °C.

5b: mp 215-218 °C, dec (AcOEt); ^{1}H NMR (60 MHz, DMSO-d_6) δ 2.52 (3H, s, Me), 2.57 (3H, s, Me), 8.78 (1H, s, 4-H), 8.92 (1H, dd, J=2.4 and 1.5 Hz, 6′-H), 9.08 (1H, d, J=2.4 Hz, 5′-H), 9.42 (1H, d, J=1.5 Hz, 3′-H), 10.02 (1H, s, NH). Anal. Calcd for $C_{13}H_{11}N_3O_4$ (273.24): C, 57.14; H, 4.06; N, 15.38. Found: C, 57.29; H, 4.22; N, 14.97.

5c: mp 133-136 °C (EtOH); mp lit[3] 135-138 °C.

5d: mp 162-165 °C, dec (EtOH); ^{1}H NMR (60 MHz, DMSO-d_6) δ 1.31 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 2.59 (3H, s, Me), 4.28 (2H, q, J=7 Hz, $O\underline{CH_2}CH_3$), 8.61 (1H, s, 4-H), 8.80 (1H, dd, J=2.5 and 1.6 Hz, 6′-H), 8.97 (1H, d, J=2.5 Hz, 5′-H), 9.28 (1H, d, J=1.6 Hz, 3′-H), 10,0 (1H, s, NH). Anal. Calcd for $C_{14}H_{13}N_3O_5$ (303.27): C, 55.44; H, 4.32; N, 13.86. Found: C, 55.45; H, 4.33; N, 13.80.

3-Benzoylamino-6,7-dihydrocyclopenta[*b*]pyran-2,5-dione (6):

mp 211-214 °C (EtOH); ^{1}H NMR (60 MHz, DMSO-d_6) δ 2.50-3.15 (4H, m, 6-CH_2, 7-CH_2), 7.60 (3H, m, Ph), 7.95 (2H, m, Ph), 8.13 (1H, s, 4-H), 9.70 (1H, s, NH); ms (m/z) 269 (M^+, 15%). Anal. Calcd for $C_{15}H_{11}NO_4$ (269.25): C, 66.91; H, 4.12; N, 5.20. Found: C, 66.74; H, 4.18; N, 5.13.

5-Oxo-5,6,7,8-tetrahydrocoumarins:

7b: mp 230-232 °C, dec (AcOEt); ^{1}H NMR (60 MHz, DMSO-d_6) δ 1.90-3.05 (6H, m, 6-CH_2, 7-CH_2, 8-CH_2), 8.56 (1H, s, 4-H), 8.88 (1H, dd, J=2.4 and 1.5 Hz, 6′-H), 9.04 (1H, d, J=2.4 Hz, 5′-H), 3.95 (1H, d, J=1.5 Hz, 3′-H), 10.15 (1H, s, NH). Anal. Calcd for $C_{14}H_{11}N_3O_4$ (285.25): C, 58.94; H, 3.89; N, 14.73. Found: C, 58.95; H, 3.89; N, 14.52.

7d: mp 231-233 °C (EtOH); ^{1}H NMR (90 MHz, DMSO-d_6, 60 °C) δ 1.10 (3H, d, J=5.6 Hz, Me), 2.20-3.05 (5H, m, 6-CH_2, 7-H, 8-CH_2), 8.52 (1H, s, 4-H), 8.81 (1H, dd, J=2.5 and 1.5 Hz, 6′-H), 8.97 (1H, d, J=2.5 Hz, 5′-H), 9.31 (1H, d, J=1.5 Hz, 3′-H), 10.07 (1H, s, NH). Anal. Calcd for $C_{15}H_{13}N_3O_4$ (299.28): C, 60.19; H, 4.38; N, 14.04. Found: C, 60.04; H, 4.44; N, 13.75.

7f: mp 215-218 °C (MeOH); ^{1}H NMR (90 MHz, DMSO-d_6, 60 °C) δ 1.10 (6H, s, two Me), 2.45 (2H, s, CH_2), 2.82 (2H, s, CH_2), 8.53 (1H, s, 4-H), 8.82 (1H, dd,

J=2.5 and 1.5 Hz, 6'-H), 8.98 (1H, d, J=2.5 Hz, 5'-H), 9.31 (1H, d, J=1.5 Hz, 3'-H), 10.05 (1H, s, NH). Anal. Calcd for $C_{16}H_{12}N_2O_4$ (313.30): C, 61.33; H, 4.83; N, 13.41. Found: C, 61.70; H, 4.87; N, 13.52.

7g: mp 210-212 °C (EtOH); ^{1}H NMR (60 MHz, DMSO-d_6) δ 1.07 (3H, broad, Me), 1.45 (3H, s, COMe), 2.30-2.95 (5H, m, 6-CH_2, 7-H, 8-CH_2), 8.40 (1H, s, 4-H), 9.70 (1H, s, NH); ms (m/z) 235 (M^+, 25%). Anal. Calcd for $C_{12}H_{13}NO_4$ (235.23): C, 61.27; H, 5.57; N, 5.96. Found: C, 61.14; H, 5.60; N, 5.93.

2H-Pyrano[2,3-*d*]pyrimidine-2,4,7(1H,3H)-triones:

8a: mp above 300 °C (DMSO/MeOH); ^{1}H NMR (60 MHz, DMSO-d_6) δ 7.60 (3H, m, Ph), 7.97 (2H, m, Ph), 8.25 (1H, s, 5-H), 9.70 (1H, s, NH); ms (m/z) 299 (M^+, 25%). Anal. Calcd for $C_{14}H_8N_2O_5$ (299.24): C, 56.19; H, 3.03; N, 14.07. Found: C, 55.97; H, 3.07; N, 13.90.

8b: mp 271-274 °C (DMF/MeOH); ^{1}H NMR (60 MHz, DMSO-d_6) δ 3.27 (3H, s, Me), 3.42 (3H, s, Me), 7.57 (3H, m, Ph), 7.95 (2H, m, Ph), 8.30 (1H, s, 5-H), 9.80 (1H, s, NH); ms (m/z) 327 (M^+, 19%). Anal. Calcd for $C_{16}H_{13}N_2O_5$ (327.29): C, 58.71; H, 4.00; N, 12.84. Found: C, 58.82; H, 4.15; N, 13.02.

8c: mp 300-303 °C, dec (DMF/MeOH); ^{1}H NMR (60 MHz, DMSO-d_6) δ 3.30 (3H, s, Me), 3.45 (3H, s, Me), 8.68 (1H, s, 5-H), 8.87 (1H, dd, J=2.4 and 1.5 Hz, 6'-H), 9.03 (1H, d, J=2.4 Hz, 5'-H), 9.35 (1H, d, J=1.5 Hz, 3'-H), 10.07 (1H, s, NH); ms (m/z) 329 (M^+, 56%). Anal. Calcd for $C_{14}H_{11}N_3O_5$ (329.27): C, 51.06; H, 3.37; N, 21.27. Found: C, 50.82; H, 3.49; N, 20.88.

Indeno[1,2-*b*]pyran-2,5-diones:

9a: mp 227-229 °C (DMSO/MeOH); ^{1}H NMR (60 MHz, DMSO-d_6) δ 7.55 ((7H, m, 6-H, 7-H, 8-H, 9-H, and 3H of Ph), 7.94 (2H, m, Ph), 8.23 (1H, s, 4-H), 9.72 (1H, s, NH); ms (m/z) 317 (M^+, 16%). Anal. Calcd for $C_{19}H_{11}NO_4$ (317.29): C, 71.92; H, 3.49; N,4.41. Found: C, 71.86; H, 3.56; N, 4.39.

9b: mp 273-275 °C, dec (DMF/MeOH); ^{1}H NMR (60 MHz, DMSO-d_6, 145 °C) δ 7.50 (4H, m, 6-H, 7-H, 8-H, 9-H), 8.35 (1H, s, 4-H), 8.75 (1H, dd, J=2.2 and 1.5 Hz, 6'-H), 8.88 (1H, d, J=2.2 Hz, 5'-H), 9.27 (1H, d, J=1.5 Hz, 3'-H); ms (m/z) 319 (M^+, 60%). Anal. Calcd for $C_{17}H_9N_3O_4$ (319.27): C, 63.95; H, 2.84; N, 13.16. Found: C, 63.82; H, 3.13; N, 13.27.

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