4-ETHOXYMETHYLENE-2-PHENYL-5(4H)-OXAZOLONE AS A SYNTHON FOR THE SYNTHESIS OF SOME 2H-PYRAN-2-ONES

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Abstract - Treatment of 4-ethoxymethylene-2-phenyl-5(4H)-oxazolone with activated methylene compounds under acidic or basic conditions leads to 2H-pyran-2-ones and fused pyran-2-ones. On the other hand, methyl (3-benzoylamino-5-methoxycarbonyl-2-oxo-2H-pyran-6-yl)-acetate (4) has also been prepared by a one-pot synthesis from dimethyl 1,3-acetonedicarboxylate, diethoxymethyl acetate, hippuric acid and acetic anhydride.

Several substitutions of the ethoxy group in 4-ethoxymethylene-2-phenyl-5(4H)-oxazolone (1) with different nucleophiles have been described.[1,2] Almost all of them were carried out under basic conditions, and only few in acidic medium. Transformations of oxazolone (1) with double-activated methylene compounds into 2H-pyran-2-ones and fused pyran-2-ones under basic conditions have also been described.[3,4]

We describe here transformations of compound (1) with activated methylene compounds (2) into 2H-pyran-2-one derivative (4) and fused pyran-2-ones

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Dedicated to Dr. Masatomo Hamana, Professor Emeritus of Kyushu University, on the occasion of his 75th birthday.

(5-10) under acidic as well as under basic conditions. We also describe the synthesis of compound **(4)** by a one-pot synthesis[4-6] starting from equimolar amounts of activated methylene compound, diethoxymethyl acetate and hippuric acid in the presence of a large excess of acetic anhydride.

The reactions under acidic conditions have been carried out in boiling acetic acid and the reactions under basic conditions either in mixtures of ethanol (in one case methylene chloride) and triethylamine at room temperature or in boiling mixtures of pyridine and triethylamine (Method A). The course of reactions has been followed by tlc. In comparison to the reactions under basic conditions the reactions in acetic acid have required more severe conditions; higher temperature or sometimes longer heating periods (see Table).

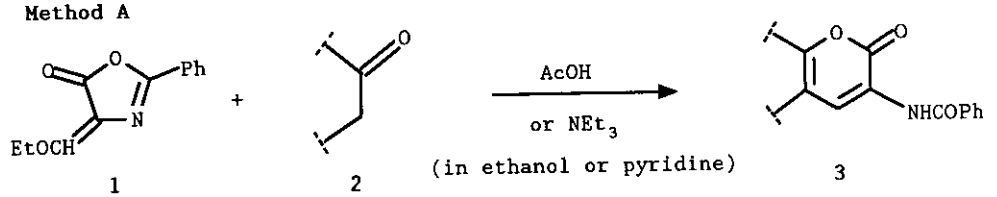
In the one-pot synthesis of compound **(4)** (Method B) diethoxymethyl acetate was first heated with dimethyl 1,3-acetonedicarboxylate until the corresponding intermediate **(12)** was formed. The reaction was continued by the addition of hippuric acid and acetic anhydride, followed by heating of the reaction mixture.

The reactions with 4-hydroxy-2H-1-benzopyran-2-one or 4-hydroxy-2(1H)-quinolinone might give two isomeric types of products **(9)** or **(11)**, respectively. The structures **(9a)** and **(9b)** for these two compounds have been ascribed on the basis of their ir and ^{1}H nmr data. Their formations are also in agreement with the formations of some derivatives of these heterocyclic systems starting from (ethoxymethylene)malononitrile and 4-hydroxy-2H-1-benzopyran-2-one or different 4-hydroxy-2(1H)-quinolinones.[7]

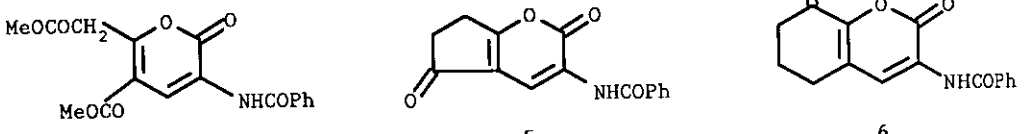
EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage. ^{1}H Nmr spectra were recorded with a JEOL JNM FX90Q and Varian EM360L instruments, using TMS as internal standard. Infrared spectra were obtained with a Perkin

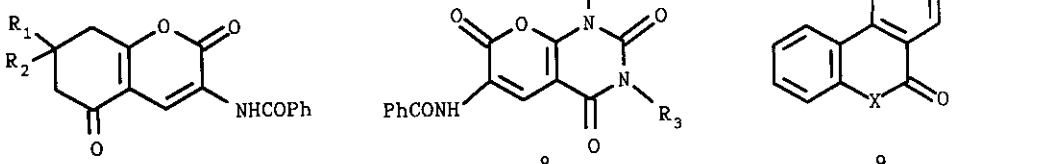
Method A



1 2 3



4 5 6



7 8 9

	R_1	R_2
a	H	H
b	H	Me
c	Me	Me

	R_3
a	H
b	Me

	X
a	O
b	NH

10 11

Method B

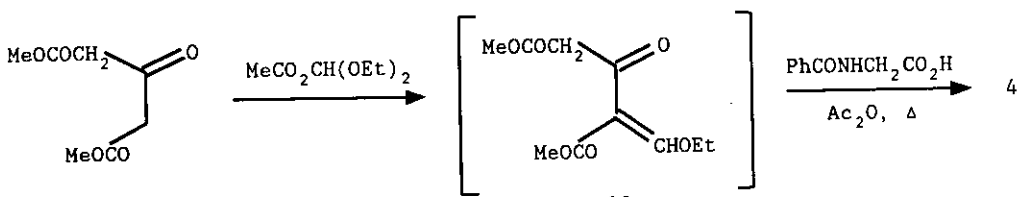


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Table: Yields of the compounds (4-10) by method A:

Active methylene compound	Solvent	Reaction conditions	Product	Yield
Dimethyl 1,3-acetone-dicarboxylate	AcOH	8 h, Δ	4	7%
	CH_2Cl_2/NEt_3	48 h, rt	4	54%
1,3-Cyclopentanedione	AcOH	4 h, Δ	5	23%
	Py/NEt_3	4 h, Δ	5	-
1,2-Cyclohexanedione	AcOH	4 h, Δ	6	-
	Py/NEt_3	4 h, Δ	6	20%
1,3-Cyclohexanedione	AcOH	4 h, Δ	7a[3]	32%
5-Methyl-1,3-cyclo-hexanedione	AcOH	7.5 h, Δ	7b[3]	35%
	AcOH	4 h, Δ	7b	31%
5,5-Dimethyl-1,3-cyclo-hexanedione	AcOH	4 h, Δ	7c[3]	36%
Barbituric acid	AcOH	8 h, Δ	8a[4]	80%
	$EtOH/NEt_3$	72 h, rt	8a	40%[a]
1,3-Dimethylbarbituric acid	AcOH	8 h, Δ	8b[4]	62%
	$EtOH/NEt_3$	72 h, rt	8b	76%
2H-1-Benzopyran-2-one	AcOH	4 h, Δ	9a	24%
	Py/NEt_3	4 h, Δ	9a	77%
4-Hydroxy-2(1H)-quinolinone	AcOH	5 h, Δ	9b	traces
	Py/NEt_3	4 h, Δ	9b	69%
1,3-Indanedione	AcOH	1 h, Δ	10[4]	9%[a]
	$EtOH/NEt_3$	72 h, rt	10	52%

a) Yield of the crystallized product

Py) Pyridine

rt) Room temperature

Δ) Reflux

Elmer 1310 spectrophotometer. Mass spectra were recorded with a CEC-20-110 C 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. Compound **(1)**[8] and 5-methyl-1,3-cyclohexanedione[9] were prepared as described in the literature. All other reagents were used as received from commercial sources.

Method A: A mixture of the corresponding activated methylene compound (2 mmol) and 4-ethoxymethylene-2-phenyl-5(4H)-oxazolone **(1)** (434 mg, 2 mmol), 2 ml of dry ethanol (or methylene chloride) and triethylamine (31-41 mg, 0.3-0.4 mmol) [or 4 ml (50 mmol) of pyridine and 121 mg (1.2 mmol) of triethylamine; or 4 ml of acetic acid] was left at room temperature (or heated). (see Table)

When ethanol (or methylene chloride) was used as a solvent, the reaction mixture was cooled and the solid product was filtered and washed with a small amount of ethanol.

When the reaction was carried out in pyridine or acetic acid, the solvent was first evaporated, then 1-2 ml of ethanol were added to the residue. Upon cooling the solid product was taken by filtration and washed with ethanol. (The yields are given in the Table.)

Method B: Synthesis of compound 4. A mixture of diethoxymethyl acetate (325 mg, 2 mmol) and dimethyl 1,3-acetonedicarboxylate (349 mg, 2 mmol) was heated for 1 h at 80-90 °C, then hippuric acid (359 mg, 2 mmol) and acetic anhydride (2.5 ml) were added and the reaction mixture was heated for 4 h at 80-90 °C. The reaction mixture was evaporated in vacuo and the residue was treated with 1-2 ml of ethanol. Upon cooling the solid was filtered and washed with ethanol. Yield of tlc pure compound 4: 168 mg (24%).

Analytical and spectroscopic data of the compounds:

Methyl (3-Benzoylamino-5-methoxycarbonyl-2-oxo-2H-pyran-6-yl)acetate (4):

mp 155-158 °C (MeOH); ir (KBr) 1735br, 1713, 1664 cm^{-1}; ^1H nmr (90 MHz, DMSO-d_6) δ 3.68 (3H, s, Me), 3.83 (3H, s, Me), 4.13 (2H, s, CH_2), 7.56 (3H, m, Ph), 7.95 (2H, m, Ph), 8.48 (1H, s, 4-H), 9.77 (1H, s, NH). Anal. Calcd for $C_{17}H_{15}NO_7$: C, 59.13; H, 4.38; N, 4.06. Found: C, 59.36; H, 4.63; N, 4.01.

N-(5,6,7,8-Tetrahydro-2,8-dioxo-2H-1-bezopyran-3-yl)benzamide (6):
mp 248-250°C (DMF/MeOH); ir (KBr) 1705, 1680 cm^{-1}; ^1H nmr (60 MHz, DMSO-d_6) δ 2.10 (2H, m, 6-CH_2), 2.50-2.93 (4H, m, 5-CH_2, 7-CH_2), 7.68 (3H, m, Ph), 8.05 (2H, m, Ph), 8.30 (1H, s, 4-H), 9.82 (1H, s, NH); ms (m/z) 283 (M^+, 6%). Anal. Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.62; N, 4.94. Found: C, 67.72; H, 4.56; N, 5.17.

7a: mp 188-189 °C (EtOH); mp lit.,[4] 188-189 °C.

7b: mp 191-192 °C (EtOH); mp lit.,[4] 191-192 °C

7c: mp 179-179.5 °C (EtOH), mp lit.,[4] 179-179.5 °C.

8a: mp above 300 °C (DMSO/MeOH); mp lit.,[5] above 300 °C.

8b: mp 271-274 °C (DMF/MeOH); mp lit.,[5] 271-274 °C.

N-(2,5-Dioxo-2H,5H-pyrano[3,2-c][1]benzopyran-3-yl)benzamide (9a):
mp 309-311 °C (DMF); ir (KBr) 1720br cm^{-1}; ^1H nmr (60 MHz, DMSO-d_6) δ 7.50-8.22 (9H, m, Ph, 7-H, 8-H, 9-H, 10-H), 8.68 (1H, s, 4-H), 9.95 (1H, s, NH); ms (m/z) 333 (M^+, 24%). Anal. Calcd for $C_{19}H_{11}NO_5$: C, 68.47; H, 3.33; N, 4.20. Found: C, 68.69; H, 3.32; N, 4.29.

N-(5,6-Dihydro-2,5-dioxo-2H-pyrano[3,2-c]quinoline-3-yl)benzamide (9b):
mp above 360 °C; ir (KBr) 1718, 1660br cm^{-1}; ^1H nmr (DMSO-d_6, 150 °C) δ 7.23-8.13 (9H, m, Ph, 7-H, 8-H, 9-H, 10-H), 8.75 (1H, s, 4-H), 9.40 (1H, broad s, NH), 11.75 (1H, br s, NH); ms (m/z) 332 (M^+, 31%). Anal. Calcd for $C_{19}H_{12}N_2O_4$: C, 68.67; H, 3.64; N, 8.43. Found: C, 68.91; H, 3.67; N, 8.62.

10: mp 227-229 °C (DMSO/MeOH); mp lit.,[5] 227-229 °C.

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