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Reactions of Cyclic Oxalyl Compounds, Part 29 [1]: A Simple Synthesis of Functionalized 1*H*-Pyrimidines**

Behzat Altural[1], **Yunus Akcamur**[1], **Emin Saripinar**[1], **Ismail Yildirim**[1], and **Gert Kollenz**[2,*]

[1] Fen Edebiyat Faculty, Erciyes University, TR-38039 Kayseri, Turkey
[2] Institute of Organic Chemistry, Isotope Department, University of Graz, A-8010 Graz, Austria

Summary. 4-Benzoyl-5-phenylfuran-2,3-dione (**1**) and the semicarbazones **2**, ureas and thioureas **6**, respectively, combine with loss of water and carbondioxide yielding the 1*H*-pyrimidine derivatives **3** and **7**, respectively, in moderate yields (30–75%). Hydrolysis of **3b** leads to the 1-amino-pyrimidine-2-one **4**.

Keywords. 5-Benzoyl-1-methyleneamino-4-phenyl-1*H*-pyrimidine-2-ones; 1-Alkyl-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-ones; 1,4,5-Substituted pyrimidine-2-thiones; Cyclocondensation reactions.

Reaktionen cyclischer Oxalylverbindungen, 29. Mitt. [1]: **Eine einfache Synthese funktionalisierter 1*H*-Pyrimidine**

Zusammenfassung. 4-Benzoyl-5-phenylfuran-2,3-dion (**1**) cyclisiert mit den Semicarbazonen **2** sowie den Harnstoffen bzw. Thioharnstoffen **6** unter Verlust von H_2O und CO_2 zu einer Reihe von 1,4,5-substituierten 1*H*-Pyrimidinen in Ausbeuten von 30—75%. Die an **3b** exemplarisch durchgeführte Hydrolyse liefert die 1-Amino-Verbindung **4**.

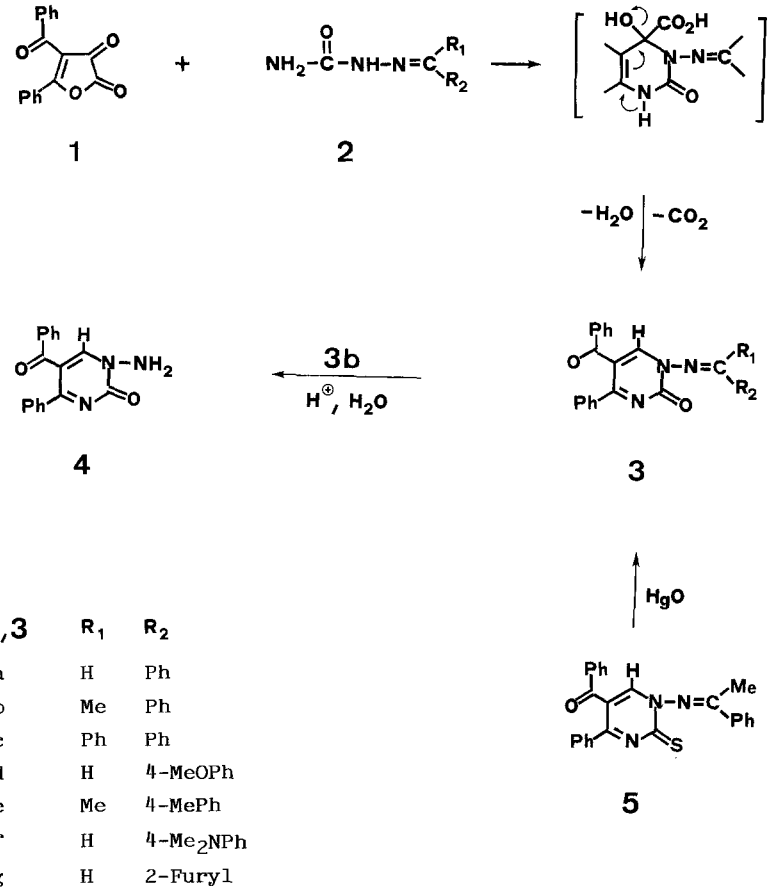
Introduction

Concerning the attempts to gain some insight into the chemical behaviour of five-membered heterocyclic 2,3-diones against NH-nucleophiles [2, 3], a convenient preparation of functionalized 1*H*-pyrimidine-2-thiones from the furan-2,3-dione **1** and several thiosemicarbazones has been reported recently [1]. Since pyrimidines in general have found much interest for biological and medicinal reasons [4], we now have extended our investigations to reactions of **1** with various semicarbazones, thioureas and ureas.

Results and Discussion

A number of 1*H*-pyrimidine-2-ones **3** were obtained in moderate yields (30–75%) from the reaction of the furandione **1** and the corresponding semicarbazones **2**. The formation of **3** obviously is proceeding via a reaction pathway quite similar to that discussed with the thiosemicarbazones [1]. It is outlined briefly in Scheme 1.

** Cordially dedicated to o. Univ.-Prof. Dr. Hans Junek on the occasion of his 60th birthday



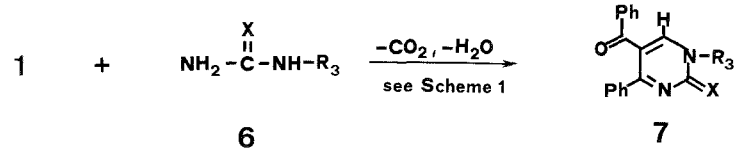
2,3	R_1	R_2
a	H	Ph
b	Me	Ph
c	Ph	Ph
d	H	4-MeOPh
e	Me	4-MePh
f	H	4-Me_2NPh
g	H	2-Furyl

Scheme 1

Structure elucidation of **3** is deduced mainly from elemental analysis, ir and ^{1}H nmr spectroscopic data (see Experimental), based on the X-ray confirmed structure of the corresponding 1*H*-pyrimidine-2-thiones [1]. In addition, the pyrimidine-2-thione **5** exemplary can be converted into the pyrimidine-2-one **3b** by desulfuration reaction with yellow HgO [5]. The structural analogy of all compounds **3** is easily seen from the ir and ^{1}H nmr spectra. Absorption bands at about 1 685 and 1 650 cm^{-1}, and the CH-proton of C-6, which is detected on the lower edge of the aromatic protons region at 8.0–8.5 ppm, respectively, are structural characteristics. H^+-catalysed hydrolysis of **3b**, as an example, leads to cleavage of the C=N-double bond finally yielding the aminopyrimidine **4**. A quite similar behaviour had been found with the corresponding pyrimidine-2-thiones [1].

1,4,5-substituted 1*H*-pyrimidines **7** are obtained also from the cyclisation reaction of **1** and several ureas or thioureas respectively. Ir and ^{1}H nmr spectroscopic data—C=O absorption bands at about 1 650 cm^{-1} (**7a–c**) or 1 680, 1 650 cm^{-1} (**7d–g**) and the proton of C-6 in the region 8.2–8.8 ppm—as well as comparison with the analogues **3** and **5** [1] confirm the structural identification of **7**.

The formation of all compounds **7** should proceed again via an analogous key-intermediate and subsequent elimination of CO_2 and H_2O as described in Scheme 1.



6 7

6,7	X	R_3
a	S	Me
b	S	Et
c	S	Ph
d	O	H
e	O	Me
f	O	n-Bu
g	O	$-CH_2-CH=CH_2$

Scheme 2

Experimental

Melting points are uncorrected. The ir spectra were recorded on a Perkin-Elmer 421 spectrometer using samples in potassium bromide disks. The ^1H nmr spectra were determined on a Varian EM 360 L spectrometer using *TMS* as an internal standard.

Synthesis of the 1H-Pyrimidine-2-ones **3**. *General Procedures*

Method A. An equimolar mixture of **1** and the corresponding semicarbazone **2** is heated to 110–120°C for 10–20 min without any solvent. After cooling to room temperature the residue is treated with dry ether and the so formed crude product crystallized from a suitable solvent (ethanol, *n*-butanol).

Method B. The equimolar mixture of the reactants (**1** + **2**) is refluxed in boiling toluene/or benzene for 1–6 h. After evaporation the oily residue is worked up as described in Method A.

5-Benzoyl-4-phenyl-1-(phenyl-methyleneamino)-1H-pyrimidine-2-one (**3a**)
3a was prepared following Method A: 0.28 g (1 mmol) **1** and 0.165 g (1 mmol) **2a** were heated to 115°C for 10 min yielding 0.11 g (30%) **3a**, m.p. 182°C (*n*-butanol). Ir: 1685 s, 1650 s (CO), 1600 m, 1480 m cm^{-1}. Anal. calc. for $C_{24}H_{17}N_3O_2$: C 75.97, H 4.52, N 11.08; found: C 76.07, H 4.53, N 11.01.

5-Benzoyl-1-(methylphenylmethyleneamino)-4-phenyl-1H-pyrimidine-2-one (**3b**)

0.28 g **1** and 0.18 g **2b** (molar ratio 1 : 1) were refluxed in boiling toluene for 45 min (Method B) finally yielding 0.14 g (38%) **3b**, m.p. 195°C. Ir: 1695 s, 1650 s (CO), 1610 s, 1480 m cm^{-1}. ^1H nmr (*DMSO*): $\delta = 2.3$ (s, 3 H), 7.2–8.1 (m, 15 H), 8.5 (s, 1 H at C-6). Anal. calc. for $C_{25}H_{19}N_3O_2$: C 76.31, H 4.87, N 10.68; found: C 76.25, H 4.81, N 10.62.

5-Benzoyl-1-(diphenylmethyleneamino)-4-phenyl-1H-pyrimidine-2-one (**3c**)

0.2 g (44%) **3c**, m.p. 125°C (ethanol), were obtained from reaction of 1 mmol **1** and **2c** respectively, in boiling benzene for 2 h (Method B). Ir: 1680 s, 1650 s (CO), 1600 s, 1480 m cm^{-1}. ^1H nmr ($CDCl_3$): $\delta = 7.1$–7.9 (m, 20 H), 8.0 (s, 1 H at C-6). Anal. calc. for $C_{30}H_{21}N_3O_2$: C 79.10, H 4.65, N 9.22; found: C 78.72, H 4.83, N 9.18.

5-Benzoyl-1-(4-methoxyphenylmethyleneamino)-4-phenyl-1H-pyrimidine-2-one (**3d**)

1 g **1** and 0.7 g **2d** (molar ratio 1 : 1) were heated to 115°C for 25 min (Method A); yield 0.9 g (62%), m.p. 195°C (ethanol). Ir: 1680 s, 1650 s (CO), 1600 s, 1510 m, 1480 m cm^{-1}. ^1H nmr ($CDCl_3$): $\delta = 3.9$ (s, 3H), 6.9–7.9 (m, 14H), 8.4 (s, 1H at C-6), 9.5 (s, 1H). Anal. calc. for $C_{25}H_{19}N_3O_3$: C 73.34, H 4.67, N 10.26; found: C 73.24, H 4.72, N 10.53.

5-Benzoyl-1-(4-methylphenyl-methylmethyleneamino)-4-phenyl-1H-pyrimidine-2-one (**3e**)

A mixture of 1.12 g **1** and 0.8 g **2e** (molar ratio 1 : 1) was kept at 115°C for 15 min (Method A) yielding 0.8 g (50%) **3e**, m.p. 228°C (*n*-butanol). Ir: 1685 s, 1640 s (CO), 1600 s, 1470 m cm^{-1}. ^1H nmr ($CDCl_3$): $\delta = 2.35$ (s, 3H), 2.45 (s, 3H), 7.1–8.0 (m, 14H), 8.1 (s, 1H at C-6). Anal. calc. for $C_{22}H_{15}N_3O_3$: C 71.54, H 4.09, N 11.38; found: C 71.65, H 4.06, N 11.17.

5-Benzoyl-1-(4-dimethylaminophenyl-methyleneamino)-4-phenyl-1H-pyrimidine-2-one (**3f**)

Under identical reaction conditions as described for **3e** (Method A) 1.68 g **1** and 1.25 g **2f** (molar ratio 1 : 1) yield 1.4 g (55%) **3f**, m.p. 204°C (*n*-butanol). Ir: 1680 s, 1660 s (CO), 1610 s, 1590 s, 1540 m, 1470 m cm^{-1}. ^1H nmr ($CDCl_3$): $\delta = 3.1$ (s, 6H), 6.7–7.8 (m, 12H), 8.4 (s, 1H at C-6), 9.3 (s, 1H). Anal. calc. for $C_{26}H_{22}N_4O_2$: C 73.92, H 5.24, N 13.26; found: C 73.87, H 5.02, N 13.04.

5-Benzoyl-1-(2-furylmethyleneamino)-4-phenyl-1H-pyrimidine-2-one (**3g**)

Heating of 1 g **1** and 0.56 g **2g** (molar ratio 1 : 1) in boiling benzene for 6 h (Method B) leads to isolation of 1 g (76%) of **3g**, m.p. 192°C (*n*-butanol). Ir: 1680 s, 1660 s (CO), 1620 m, 1470 s cm^{-1}. ^1H nmr ($CDCl_3$): $\delta = 6.6$ (m, 1H), 7.0–7.8 (m, 12H), 8.4 (s, 1H at C-6), 9.7 (s, 1H). Anal. calc. for $C_{22}H_{15}N_3O_3$: C 71.54, H 4.09, N 11.38; found: C 71.65, H 4.06, N 11.17.

1-Amino-5-benzoyl-4-phenyl-1H-pyrimidine-2-one (**4**)

15 ml of water were added to a solution of 1 g **3b** in 5 ml of acetic acid and the mixture was then heated under reflux for 15 min. With cooling 0.37 g (50%) of **4** precipitated; m.p. 204°C (*n*-butanol). Ir: 3300, 3190 (NH_2), 1680 s, 1650 s (CO), 1600 m, 1480 s cm^{-1}. ^1H nmr (*DMSO*): 6.5 (s, 2H, exchangeable with D_2O), 7.2–8.08 (m, 10H), 8.5 (s, 1H at C-6). Anal. calc. for $C_{17}H_{13}N_3O_2$: C 70.09, H 4.50, N 14.42; found: C 70.05, H 4.54, N 14.36.

Desulfuration of the 1H-Pyrimidine-2-thione **5**

A suspension of 0.5 g yellow HgO in 10 ml dry dioxane, containing 100 mg **5** [1], was shaken at room temperature for one week. After filtration from the precipitate (HgS/HgO), treating the clear solution with charcoal and evaporation, the oily residue was dissolved in hot ethanol, with cooling finally yielding a small amount of **3b** (10 mg, 10%), identified by comparison with an authentic sample.

Synthesis of 1H-Pyrimidines **7**. *General Procedure*

The furandione **1** and the corresponding urea or thiourea, respectively, (molar ratio 1 : 1) are refluxed in boiling benzene for 3–5 h. After evaporation the residue is crystallized from a suitable solvent (acetic acid or alcohols), in some cases previously treated with dry ether.

5-Benzoyl-1-methyl-4-phenyl-1H-pyrimidine-2-thione (**7a**)

From 0.28 g **1** and 0.1 g **6a** 0.185 g (60%) **7a** were obtained after 4 h reaction time; m.p. 223°C (acetic acid). Ir: 1655 s (CO), 1605 s, 1500 s, 1230 s cm^{-1}. ^1H nmr (*DMSO*): $\delta = 3.8$ (s, 3H), 7.2–8.0 (m, 10H), 8.8 (s, 1H at C-6). Anal. calc. for $C_{18}H_{14}N_2OS$: C 70.58, H 4.57, N 9.15; found: C 70.36, H 4.70, N 9.11.

5-Benzoyl-1-ethyl-4-phenyl-1H-pyrimidine-2-thione (**7b**)

0.23 g (72%) **7b** were isolated from reaction of 0.28 g **1** and 0.105 g **6b** and treating the oily residue with dry ether; m.p. 214°C (acetic acid). Ir: 1650 s (CO), 1610 s, 1480 s, 1440 m cm^{-1}. ^1H nmr (*DMSO*): $\delta = 1.3$ (t, 3H), 4.4 (q, 2H), 7.2–7.9 (m, 10H), 8.7 (s, 1H at C-6). Anal. calc. for $C_{19}H_{16}N_2OS$: C 71.20, H 5.03, N 8.74; found: C 71.30, H 5.20, N 8.76.

5-Benzoyl-1,4-diphenyl-1H-pyrimidine-2-thione (**7c**)

An equimolar mixture of **1** and **6c** (1 mmol) was refluxed in boiling benzene for 3.5 h. After cooling the crude product precipitated and was crystallized from acetic acid yielding 0.13 g (35%) pure **7c**; m.p. 224°C. Ir: 1660 s (CO), 1605, 1480 cm^{-1}. ^1H nmr (*DMSO*): $\delta = 8.2$ (s, 1H at C-6), 7.2–7.8 (m, 15H). Anal. calc. for $C_{23}H_{16}N_2OS$: C 75.00, H 4.35, N 7.60, S 8.69; found: C 74.78, H 4.59, N 7.85, S 8.72.

5-Benzoyl-4-phenyl-1H-pyrimidine-2-one (**7d**)

An identical procedure as described with **7c** leads to the isolation of 0.1 g (36%) **7d**, m.p. 228°C (isopropanol) from the reaction of 0.28 g **1** and 0.05 g urea. Ir: 3100 b (NH), 1660 s (CO), 1615 s, 1420 s cm^{-1}. ^1H nmr (*DMSO*): 7.2–7.8 (m, 10H), 8.3 (s, 1H at C-6), 12.5 (b, 1H).

5-Benzoyl-1-methyl-4-phenyl-1H-pyrimidine-2-one (**7e**)

After heating an equimolar (1 mmol) mixture of **1** and **6e** in boiling benzene for 5.5 h and evaporation, the oily residue was treated with dry ether and the crude product crystallized from *n*-butanol yielding 0.22 g (75%) **7e**, m.p. 196°C. Ir: 1675, 1650 s (CO), 1620 m, 1490 s cm^{-1}. ^1H nmr (*DMSO*): $\delta = 3.6$ (s, 3H), 7.1–7.8 (m, 10H), 8.2 (s, 1H at C-6).

5-Benzoyl-1-n-butyl-4-phenyl-1H-pyrimidine-2-one (**7f**)

Using a procedure identical with that leading to **7e**, 0.25 g (76%) **7f** were obtained from the reaction of equimolar amounts (1 mmol) **1** and **6f**; m.p. 193°C (*n*-butanol). Ir: 1670 s, broad (CO), 1500 s, 1460 m cm^{-1}. ^1H nmr ($CDCl_3$): $\delta = 1.0$ (t, 3H), 1.1–2.1 (m, 4H), 4.0 (t, 2H), 7.1–7.8 (m, 10H), 8.2 (s, 1H at C-6). Anal. calc. for $C_{21}H_{20}N_2O_2$: C 75.88, H 6.06, N 8.43; found: C 76.06, H 5.90, N 8.30.

1-Allyl-5-benzoyl-4-phenyl-1H-pyrimidine-2-one (**7g**)

An equimolar mixture of **1** and **6g** was heated in boiling benzene for 3.5 h. After evaporation the crude product was purified from ethanol yielding 0.24 g (74%) **7g** (the compound crystallized with 0.5 mole of water); m.p. 157°C (ethanol). Ir: 3550 (H_2O), 1670 s, 1640 s (CO), 1490 m, 1420 m cm^{-1}. ^1H nmr ($CDCl_3$): $\delta = 2.2$ (s, H_2O), 4.6 (m, 2H), 5.4 (m, 2H), 6.0 (m, 1H), 7.1–7.8 (m, 10H), 8.2 (s, 1H at C-6). Anal. calc. for $C_{20}H_{16}N_2O_2 \cdot 0.5\,H_2O$: C 73.84, H 5.23, N 8.62; found: C 73.92, H 5.34, N 8.48.

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