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Reactions of Cyclic Oxalyl Compounds, Part 30 [1]: Some Reactions with N-Amino-pyrimidine Derivatives**

Behzat Altural[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. 1-Amino-5-benzoyl-4-phenyl-1*H*-pyrimidine derivatives **1** add arylisocyanates **2** to give the N,N′-disubsituted ureas **3** which can be cyclized by use of oxalyl dichloride to the imidazolyl-pyrimidinones(thiones) **4**. In addition, **1** is transferred into the desaminated pyrimidines **6** either by diazotation reaction or by thermolysis of the parental functionalized pyrimidine derivatives **7**.

Keywords. 1-Pyrimidinyl-3-aryl-ureas; 2,4,5-Trioxo-perhydro-imidazolyl-pyrimidine-2(*H*)-ones(thiones); 4,5-Substituted pyrimidine-2-one(thione); Addition- and Cyclocondensation reactions.

Reaktionen cyclischer Oxalylverbindungen, 30. Mitt. [1]: Einige Reaktionen mit N-Aminopyrimidinen

Zusammenfassung. 1-Amino-5-benzoyl-4-phenyl-1*H*-pyrimidin-2-one(thione) **1** addieren Arylisocyanate **2** in guten Ausbeuten (60–95%) zu den Pyrimidinylharnstoff-Derivaten **3**, die ihrerseits mit Oxalylchlorid zu den Imidazolyl-pyrimidinen **4** cyclisierbar sind. Versuche, die Amino-Verbindungen **1** zu diazotieren, führen unter N_2-Eliminierung zu den desaminierten Pyrimidinen **6**, die andererseits auch durch einfache Thermolyse der Methylenamino-pyrimidine **7** entstehen.

Introduction

A convenient synthesis of 1-methylenamino-pyrimidines of type **7** has been reported recently [1, 2]. Their hydrolysis afforded the 1-amino-pyrimidine derivatives **1** exhibiting a free $N-NH_2-$moiety, which should apply to several subsequent reactions. In particular following the improved method to synthesize substituted ureas by adding amines to isocyanates [3], pyrimidinyl-aryl urea derivatives should be available, which by cyclization reaction with oxalyl dichloride could be transferred into bicyclic systems thus combining pyrimidine and imidazole nuclei within one molecule. Both ring systems in general are well known for their potential biological activities [4, 5].

Results and Discussion

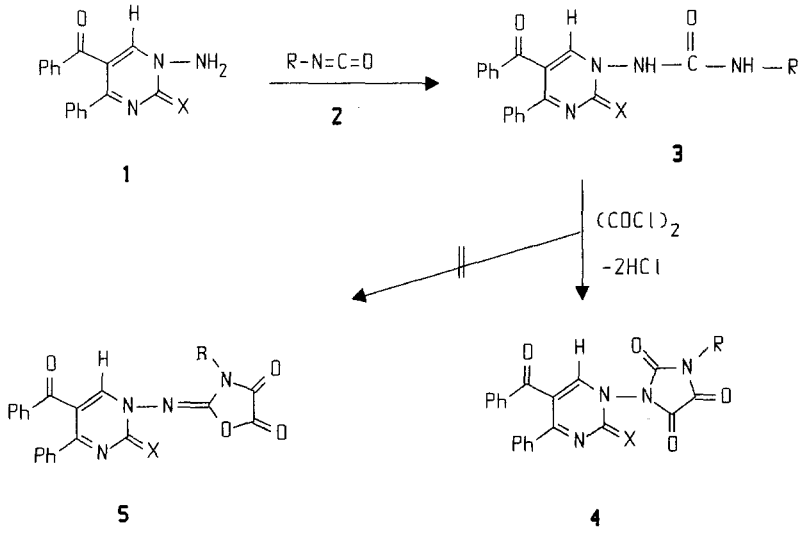
Several N,N′-disubstituted ureas **3** were easily obtained in good yields (60–95%) from nucleophilic addition of **1** to the corresponding arylisocyanates **2** [3]. The

** Dedicated to o. Univ. Prof. Dr. F. Sauter on the occasion of his 60th birthday

reactions were performed either in boiling acetonitrile or heating without solvent up to 80–110°C (see Experimental). Structural confirmation of **3** was based on elemental analysis, ir- and ^{1}H nmr (**3a, b** as examples) spectroscopic data.

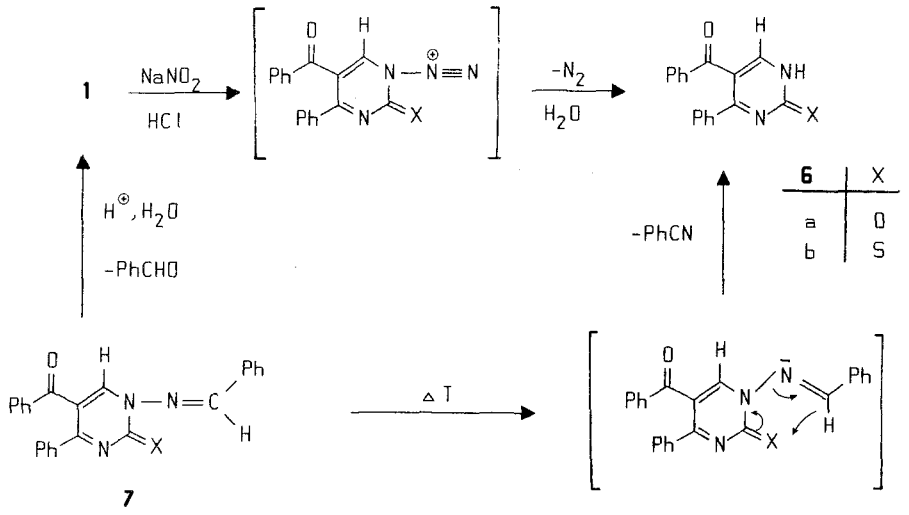
The highest C=O absorption bands are found within the region 1 690–1 720 cm^{-1} which agrees with findings from substituted semicarbazides [6]. In particular the strong absorption at 1 720 cm^{-1} for the pyrimidine-thiones **3a, c, e** – found from KBr-spectra as well as in *DMSO*-solution – indicates a possible contribution of a zwitterionic species (N-1 bearing the positive, S bearing the negative charge $=NH-N^{\oplus}=C-S^{\ominus}$) thus slightly increasing the vibrational frequencies of the side chain carbonyls [7] as well as introducing an additional deshielding effect to the proton at C-6 of the pyrimidine nucleus found from comparison of the ^{1}H nmr spectra of **3a** (C-6 at 8.9 ppm) and **3b** (C-6 at 8.5 ppm), respectively. Some evidence for the possible contribution of that dipolar form to the overall electronic distribution in **3a, c, e** could be deduced from the experimental fact that similar 1-amino-pyrimidine-2-thiones can easily be S-methylated to afford 1-amino-2-methylthiopyrimidinium salts [8]. Strong deshielding of C-6 in general obviously is due to the anisotropic effect of the benzoyl group and was observed with **1** and several similar benzoyl-substituted pyrimidine-2-ones(thiones) [1, 2]. The signals of the two NH-protons are detected as one singlet at 9.8 ppm (**3a**) and as two singlets at 9.5 and 9.6 ppm (**3b**), respectively.

All compounds **3** undergo cyclocondensation reactions using oxalyl dichloride to give the 1-imidazolyl-pyrimidines **4**. The formation of an imidazole-trione ring system instead of the isomeric oxazolidine-dione moiety (**5**) is easily deduced from ir spectroscopic data: All compounds **4** exhibit broad C=O absorption bands at 1 750–1 760 cm^{-1} with nearly identical intensities and line shapes characteristic for



1 - 4	X	R
a	S	Ph
b	O	Ph
c	S	pTol
d	O	pTol
e	S	1-Napht
f	O	1-Napht

Scheme 1



Scheme 2

parabanic acid derivatives [9, 10]. The latter are usually synthesized via similar cyclocondensation reactions from corresponding ureas and oxalyl dichloride [10, 11]. Oxazolidine-diones, made f.e. from amides and oxalyl dichloride, on the other hand show characteristic ir absorptions somewhat above 1 800 cm^{-1} [12], therefore a clear distinction can be made between those heterocyclic systems.

Attempts to get fairly stable diazonium salts by diazotation reaction of **1** failed. The only reaction product obtained was the corresponding pyrimidine derivative **6** irrespective to change of reaction conditions. The formation of **6** obviously is the result of a desamination process proceeding via a primarily formed diazonium salt intermediate and subsequent elimination of nitrogen. This agrees well with earlier results reported on compounds possessing similar $N-NH_2$ moieties [13], but nevertheless it is worthwile to note that concerning the reaction mechanism, a reductive process seems to be essential to explain all the transformations of $N-NH_2$ into NH groups.

A different approach to **6** was made following a procedure to prepare nitriles via thermolysis of heterocyclic aldimines [14a] or to obtain triazino[4,3-a]-quinazolines on the same synthetic pathway, respectively [14b]. This reaction was suggested to be a thermally allowed concerted process similar to the retro-ene reactions [15] and is outlined briefly in Scheme 2. Starting with the 1-methyleneamino-pyrimidines **7**, the parental compounds of **1**, the corresponding target products **6** were obtained in rather poor yields (15–20%) – obviously due to the high temperatures required to initiate this thermolysis reaction. As expected, benzonitrile could be detected chromatographically as by-product.

Experimental Part

Melting points are uncorrected. The ir spectra were recorded on a Perkin-Elmer 421 spectrometer using samples in potassium bromide disks (**3a** in *DMSO*-solution too). The ^1H nmr spectra were determined on a Varian EM 360 L spectrometer using *TMS* as an internal standard.

Synthesis of the Urea Compounds **3.** *General Procedures*

Method A. The mixture of **1** and the corresponding isocyanate **2** (molar ratio 1 : 20, approximately) is heated to 80–110°C for 0.5–3 h without any solvent. As soon as the precipitate is formed it is filtered from the hot solution, extensively washed with anhydrous ether and recrystallized from a suitable solvent (ethanol, *n*-butanol).

Method B. A mixture of the reactants **1** and **2** (molar ratio 1 : 1.2) is refluxed in boiling acetonitrile for 2–6 h and stirred at room temperature for additional 12 h. The precipitate formed is treated further as described in Method A.

1-(5-Benzoyl-2-thioxo-4-phenyl-1,2-dihydro-pyrimidine-1-yl)-3-phenyl-urea (**3a**)

3a was prepared following Method A: 100 mg (0.32 mmol) **1a** and 1 ml (9.2 mmol) **2a** were heated at 110°C for 1 h yielding 125 mg (90%) **3a**, m.p. 186°C (ethanol). Ir: 3280, 3080 (NH), 1720 s, 1640 m (CO), 1600 s cm^{-1}. ^1H nmr (*DMSO*): δ = 7.0–7.9 (m, 15 H), 8.9 (s, 1 H), 9.8 (s, 2 H). Anal. calc. for $C_{24}H_{18}N_4O_2S$: C 67.61, H 4.22, N 13.15, S 7.51; found: C 67.70, H 4.33, N 13.09, S 7.58.

1-(5-Benzoyl-2-oxo-4-phenyl-1,2-dihydro-pyrimidine-1-yl)-3-phenyl-urea (**3b**)

50 mg (0.17 mmol) **1b** and 0.5 ml (4.6 mmol) **2a** were heated at 100°C for 2 h (Method A) yielding 63 mg (90%) **3b**, m.p. 221°C (*n*-butanol). Ir: 3300, 3240 (NH), 1710 w, 1660 s, 1650 s (CO), 1600 cm^{-1}. ^1H nmr (*DMSO*): δ = 7.0–7.9 (m, 15 H), 8.5 (s, 1 H), 9.4 (s, 1 H), 9.5 (s, 1 H). Anal. calc. for $C_{24}H_{18}N_4O_3$: C 70.24, H 4.39, N 13.66; found: C 70.09, H 4.38, N 13.53.

1-(5-Benzoyl-2-thioxo-4-phenyl-1,2-dihydro-pyrimidine-1-yl)-3-p-tolyl-urea (**3c**)

100 mg (0.32 mmol) **1a** and 0.035 ml (0.38 mmol) **2c** were refluxed in 2 ml acetonitrile for 6 h (Method B) yielding 50 mg (65%) **3c**, m.p. 195°C (ethanol). Ir: 3270 (NH), 1725 s, 1640 m (CO), 1600 s cm^{-1}. Anal. calc. for $C_{25}H_{20}N_4O_2S$: C 68.18, H 4.55, N 12.73; found C 68.33, H 4.63, N 12.71.

1-(5-Benzoyl-2-oxo-4-phenyl-1,2-dihydro-pyrimidine-1-yl)-3-p-tolyl-urea (**3d**)

70 mg (95%) **3d**, m.p. 238–240°C (*n*-butanol) were obtained (Method A) from heating 50 mg (0.17 mmol) **1b** in 0.5 ml (4 mmol) **2c** for 0.5 h at 80–85°C. Ir: 3280, 3060 (NH), 1690 s, 1660 m, 1640 m (CO), 1600 cm^{-1}. Anal. calc. for $C_{25}H_{20}N_4O_3$: C 70.75, H 4.72, N 13.21; found: C 70.63, H 4.98, N 12.83.

1-(5-Benzoyl-2-thioxo-4-phenyl-1,2-dihydro-pyrimidine-1-yl)-3-1-naphthyl-urea (**3e**)

500 mg (1.63 mmol) **1a** and 0.28 ml (1.95 mmol) **2e** were refluxed in 10 ml of acetonitrile for 2 h (Method B) yielding 460 mg (60%) **3e**, m.p. 191–192°C (ethanol). Ir: 3260, 3060 (NH), 1715 m, 1660 s (CO), 1600 s cm^{-1}. Anal. calc. for $C_{28}H_{20}N_4O_2S$: C 70.59, H 4.20, N 11.76; found: C 70.23, H 4.22, N 11.70.

1-(5-Benzoyl-2-oxo-4-phenyl-1,2-dihydro-pyrimidine-1-yl)-3-1-naphthyl-urea (**3f**)

3f was synthesized according to Method B: 250 mg (0.86 mmol) **1b** and 0.15 ml (1.05 mmol) **2e** react in boiling acetonitrile (3 ml) for 3 h affording 320 mg (81%) **3f**, m.p. 222°C (ethanol). Ir: 3240, 3060 (NH), 1690 s, 1660 s (CO), 1620 m, 1600 m cm^{-1}. Anal. calc. for $C_{28}H_{20}N_4O_3$: C 73.04, H 4.34, N 12.17; found: C 73.13, H 4.48, N 12.02.

Synthesis of Compounds **4**. *General Procedure*

To the solution or suspension of **3** (0.24 mmol) in 2 ml of benzene at 60–65°C oxalyl dichloride (0.48 mmol) is added drop by drop with stirring. After few minutes a clear solution is obtained and refluxed for 2–4 h. By cooling either a product precipitates or the solution is evaporated to dryness. The crude solids are washed with anhydrous ether and recrystallized from benzene or toluene. The yields range from 53–79%.

5-Benzoyl-4-phenyl-1-(2,4,5-trioxo-3-phenyl-perhydro-imidazol-1-yl)-pyrimidine-2(H)-thione (**4a**)

3a and oxalyl dichloride react for 2 h to give 40 mg (68%) **4a**, m.p. 202°C dec. (benzene). Ir: 1 770 s, 1 670 s (C=O), 1 610 m cm^{-1}. Anal. calc. for $C_{26}H_{16}N_4O_4S$: C 65.00, H 3.33, N 11.67; found: C 64.95, H 33.97, N 11.42.

5-Benzoyl-4-phenyl-1-(2,4,5-trioxo-3-phenyl-perhydro-imidazol-1-yl)-pyrimidine-2(H)-one (**4b**)

After 2 h the reaction mixture of **3b** and oxalylchloride in benzene was evaporated and the residue treated with anhydrous ether finally affording 90 mg (80%) **4b**, m.p. 148–150°C (toluene). Ir: 1 770 s, 1 700 s, 1 660 s (CO), 1 600 m cm^{-1}. Anal. calc. for $C_{26}H_{16}N_4O_5$: C 67.24, H 3.45, N 12.07; found: C 67.21, H 3.69, N 11.85.

5-Benzoyl-4-phenyl-1-(2,4,5-trioxo-3-p-tolyl-perhydro-imidazol-1-yl)-pyrimidine-2(H)-thione (**4c**)

3c and oxalyl dichloride reacted for 3 h to afford 30 mg (53%) **4c**, m.p. 209–210°C (toluene). Ir: 1 760 s, 1 670 s, 1 650 m (CO), 1 600 m cm^{-1}. Anal. calc. for $C_{27}H_{18}N_4O_4S$: C 65.59, H 3.64, N 11.34; found C 65.67, H 3.75, N 11.26.

5-Benzoyl-4-phenyl-(2,4,5-trioxo-3-p-tolyl-perhydro-imidazol-1-yl)-pyrimidine-2(H)-one (**4d**)

90 mg (80%) **4d**, m.p. 150–152°C (toluene) are obtained after 4 h reaction of **3d** and oxalyl dichloride. Ir: 1 760 s, 1 700 s, 1 660 m (CO), 1 600 s cm^{-1}. Anal. calc. for $C_{27}H_{18}N_4O_5$: C 67.78, H 3.76, N 11.71; found: C 67.60, H 3.78, N 11.51.

5-Benzoyl-4-phenyl-(2,4,5-trioxo-3-1-naphthyl-perhydro-imidazol-1-yl)-pyrimidine-2(H)-thione (**4e**)

3e and oxalyl dichloride react for 4 h. Then the precipitate of **4e** is worked up as described in the general procedure. Yield: 40 mg (59%); m.p. 207–209°C (benzene). Ir: 1 760 s, 1 670 s (CO), 1 600 m cm^{-1}. Anal. calcd. for $C_{30}H_{18}N_4O_4S$: C 67.92, H 3.39, N 10.56; found: C 67.91, H 3.82, N 10.21.

5-Benzoyl-4-phenyl-1-(2,4,5-trioxo-3-1-naphthyl-perhydro-imidazol-1-yl)-pyrimidine-2(H)-one (**4f**)

3f and oxalyl dichloride react for 4 h and then the reaction mixture is stirred for additional 14 h at 20°C. The so formed precipitate is worked up according to the general procedure finally yielding 90 mg (73%) **4f**, m.p. 183–185°C (toluene). Ir: 1 760 s, 1 670 s, 1 640 m (CO), 1 600 s cm^{-1}. Anal. calc. for $C_{30}H_{18}N_4O_5$: C 70.04, H 3.50, N 10.89; found: C 69.80, H 3.60, N 10.75.

5-Benzoyl-4-phenyl-1H-pyrimidine-2(H)-one (**6a**) [2]

a) To 100 mg (0.34 mmol) **1a**, 95 mg (1.34 mmol) $NaNO_2$, suspended in 10 ml of ethanol, 5 drops of water and conc. HCl are added and the mixture is stirred at 20°C for 2 h. Addition of 5 ml of water then precipitates a colourless product which, recrystallized from ethanol, gives 40 mg (87%) **6a**. It is by m.p. and Ir spectrum identical with an authentic sample [2].

b) 100 mg dry **7a** were heated up to 300°C in a metal bath for 30 min untill the evolution of benzonitrile has stopped. After cooling the residue is crystallized from ethanol to give 16 mg (22%) **6a**.

5-Benzoyl-4-phenyl-1H-pyrimidine-2(H)-thione (**6b**)

a) As described with the preparation of **6a** from 100 mg (0.32 mmol) **1b** and 60 mg (0.87 mmol) $NaNO_2$ 44 mg (46%) **6b** were obtained, m.p. 162°C (ethanol). Ir: 1660 s (CO), 1600 cm^{-1}. Anal. calc. for $C_{17}H_{12}N_2OS$: C 69.86, H 4.11, N 9.59, S 10.96; found: C 70.11, H 3.83, N 9.62, S 11.15.

b) Heating of 100 mg dry **7b** up to 250°C for 30 min gives 10 mg (15%) **6b**, recrystallized from ethanol.

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