A Convenient Synthesis of Functionalized 1*H*-Pyrimidine-2-thiones [1]

Yunus Akcamur, Behzat Altural and Emin Saripinar

Fen Edebiyat Faculty, Erciyes University,
38039 Kayseri, Turkey

Gert Kollenz* and Oliver Kappe

Institute of Organic Chemistry, Isotope Department, University of Graz,
A-8010 Graz, Austria

Karl Peters, Eva-Maria Peters and Hans-Georg von Schnering

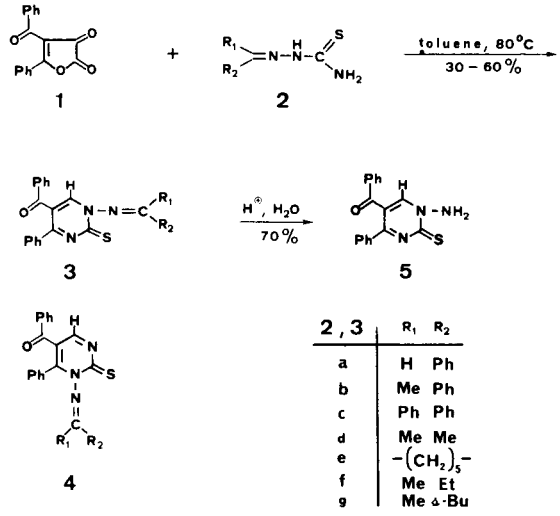
Max-Planck Institut für Festkörperforschung, Heisenbergstrasse 1,
D-7000 Stuttgart 80, West Germany

Received March 11, 1988

The furan-2,3-dione **1** and the thiosemicarbazones **2** combine with loss of carbon dioxide and water yielding the 1-methylenaminopyrimidine-2-thione derivatives **3** in moderate yields (30-60%). Their molecular skeleton is confirmed with aid of an X-ray structure determination of **3c**. Hydrolysis of **3** leads to the 1-aminopyrimidine-2-thione **5**.

J. Heterocyclic Chem., **25**, 1419 (1988).

Pyrimidines in general have found much interest for biological and medicinal reasons, thus their chemistry has been investigated extensively [2]. In particularly various analogues of thiopyrimidines possess effective antibacterial, antifungal, antiviral, insecticidal and miticidal activities [3-5]. From the reaction of the furan-2,3-dione **1**, easily made from dibenzoylmethane and oxalyl dichloride [6], and the thiosemicarbazones **2** a number of 1,4,5-substituted 1*H*-pyrimidine-2-thiones **3** can be obtained in moderate yields (30-60°).



2, 3	R_1	R_2
a	H	Ph
b	Me	Ph
c	Ph	Ph
d	Me	Me
e	-(CH$_2$)$_5$-	
f	Me	Et
g	Me	t-Bu

Formula Scheme 1

The confirmation of the pyrimidine skeleton of **3** is based on a X-ray study of **3c** thus excluding the possible isomer **4**.

The pyrimidine ring is not completely planar, the interplanar angle of the two planes formed by the ring atoms C-4/C-3/N-2 and C-1/N-6/C-5 respectively is 5.3°.

The structural analogy of all compounds **3** is easily

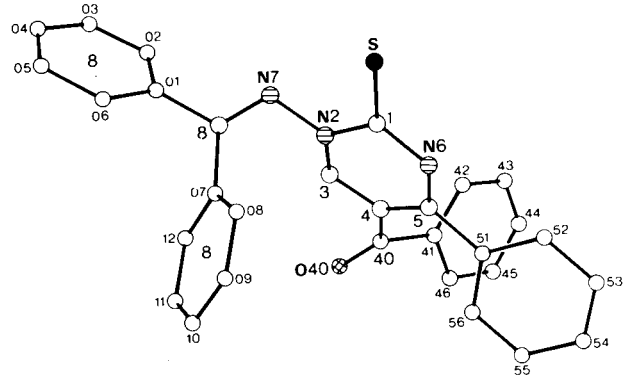
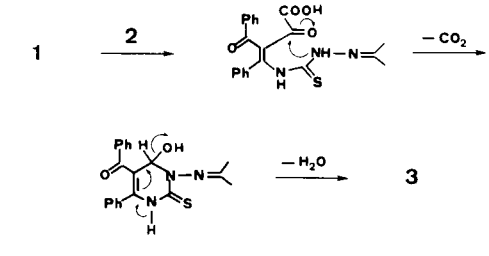


Figure. Stereo View of **3c**

found from the ir and ^{1}H-nmr spectroscopic data. Absorption bands at 1640-1650 cm^{-1} and the CH-proton of C-6, which is detected on the lower edge of the aromatic protons region at 7.9-8.9 ppm respectively, are structural characteristics.

Hydrolysis of **3** in acetic acid or concentrated hydrochloric acid leads to cleavage of the C=N double bond with loss of the corresponding C=O compound finally yielding the aminopyrimidine **5** [ir: 1650 cm^{-1}; ^{1}H-nmr: 6.2 (NH_2), 7.1-7.7 (aromat), 8.5 ppm (CH)].

A reasonable reaction pathway leading to the pyrimidines **3** is outlined briefly in Formula Scheme 2.



Formula Scheme 2

It should start with a nucleophilic attack of the NH_2-group of **2** at the C-5 position of the furandione ring [7] similar to a Michael-type addition. Syntheses of pyrimidines systems *via* Michael-type additions of ureas, thioureas, amidines, and similar compounds of this type onto α,β-unsaturated carbonyls are well established [8]. Ring opening, decarboxylation reaction of an α-oxocarbonic acid intermediate, eventually initiated by the subsequent ring closure *via* addition of the NH to the C=O moiety [9], and finally loss of water *via* a fragmentational process [10] should be the additional steps.

Table 1

Atomic Coordinates (x10⁴) and Isotropic Thermal Parameters (pm^2x10^{-1})

	x	y	z	U
S(1)	−887(1)	1474(1)	−1580(1)	59(1)*
C(1)	−131(1)	1625(2)	−587(2)	44(2)*
N(2)	90(1)	1433(1)	308(1)	42(1)*
C(3)	703(1)	1431(2)	1112(2)	43(2)*
C(4)	1145(1)	1723(2)	1106(2)	43(2)*
C(5)	903(1)	2095(2)	207(2)	43(2)*
N(6)	301(1)	2009(2)	−586(1)	45(1)*
N(7)	−338(1)	1065(2)	370(1)	47(1)*
C(8)	−446(1)	1848(2)	706(2)	43(1)*
C(40)	1816(1)	1570(2)	2021(2)	47(2)*
O(40)	2001(1)	1898(2)	2771(1)	66(1)*
C(41)	2235(1)	943(2)	1990(2)	44(2)*
C(42)	2012(1)	26(2)	1390(2)	56(2)*
C(43)	2418(1)	−603(2)	1419(2)	68(2)*
C(44)	3034(1)	−286(3)	2016(2)	68(2)*
C(45)	3253(1)	634(3)	2595(2)	71(2)*
C(46)	2859(1)	1249(2)	2599(2)	64(2)*
C(51)	1304(1)	2674(2)	118(2)	51(2)*
C(52)	1147(1)	2611(2)	−737(2)	63(2)*
C(53)	1517(2)	3164(3)	−826(2)	81(3)*
C(54)	2019(2)	3785(3)	−90(3)	100(4)*
C(55)	2171(2)	3888(3)	754(3)	99(3)*
C(56)	1813(1)	3334(2)	857(2)	71(3)*
C(801)	−838(1)	1514(2)	886(2)	54(2)*
C(802)	−790(2)	449(3)	1219(2)	80(3)*
C(803)	−1144(2)	177(3)	1416(3)	115(5)*
C(804)	−1542(2)	951(4)	1262(3)	126(5)*
C(805)	−1603(1)	2013(3)	924(2)	101(3)*
C(806)	−1245(1)	2323(3)	733(2)	72(2)*
C(807)	−219(1)	3044(2)	937(2)	43(2)*
C(808)	−470(1)	3835(2)	233(2)	70(2)*
C(809)	−305(2)	4963(3)	460(2)	82(3)*
C(810)	117(1)	5315(2)	1390(2)	72(3)*
C(811)	387(1)	4526(2)	2102(2)	69(2)*
C(812)	211(1)	3398(2)	1875(2)	58(2)*

*Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table 2

Bond Lengths (pm)

S(1)-C(1)	166,3(2)	C(1)-N(2)	139,4(4)
C(1)-N(6)	136,4(5)	N(2)-C(3)	134,0(2)
N(2)-N(7)	143,4(4)	C(3)-C(4)	137,1(5)
C(4)-C(5)	142,8(4)	C(4)-C(40)	149,4(2)
C(5)-N(6)	132,0(2)	C(5)-C(51)	148,9(5)
N(7)-C(8)	129,4(4)	C(8)-C(801)	149,2(5)
C(8)-C(807)	148,3(3)	C(40)-O(40)	121,7(4)
C(40)-C(41)	148,8(5)	C(41)-C(42)	137,3(3)
C(41)-C(46)	138,2(3)	C(42)-C(43)	138,4(5)
C(43)-C(44)	137,0(4)	C(44)-C(45)	135,7(4)
C(45)-C(46)	138,3(6)	C(51)-C(52)	139,0(6)
C(51)-C(56)	138,7(3)	C(52)-C(53)	139,4(7)
C(53)-C(54)	135,4(4)	C(54)-C(55)	138,2(8)
C(55)-C(56)	138,2(7)	C(801)-C(802)	137,0(4)
C(801)-C(806)	139,8(5)	C(802)-C(803)	139,2(10)
C(803)-C(804)	135,1(8)	C(804)-C(805)	136,1(6)
C(805)-C(806)	140,5(7)	C(807)-C(808)	137,1(4)
C(807)-C(812)	137,6(3)	C(808)-C(809)	137,1(4)
C(809)-C(810)	136,7(5)	C(810)-C(811)	137,1(4)
C(811)-C(812)	137,6(4)		

Table 3

Bond Angles (°)

S(1)-C(1)-N(2)	120,9(3)	S(1)-C(1)-N(6)	123,0(2)
N(2)-C(1)-N(6)	116.0(2)	C(1)-N(2)-C(3)	122,3(3)
C(1)-N(2)-N(7)	119,5(2)	C(3)-N(2)-N(7)	117,6(2)
N(2)-C(3)-C(4)	121,2(3)	C(3)-C(4)-C(5)	115,4(2)
C(3)-C(4)-C(40)	116,8(3)	C(5)-C(4)-C(40)	127,7(3)
C(4)-C(5)-N(6)	121,7(3)	C(4)-C(5)-C(51)	122,1(2)
N(6)-C(5)-C(51)	116,1(3)	C(1)-N(6)-C(5)	122,2(3)
N(2)-N(7)-C(8)	112,6(2)	N(7)-C(8)-C(801)	116,7(2)
N(7)-C(8)-C(807)	127,0(3)	C(801)-C(8)-C(807)	116,3(3)
C(4)-C(40)-O(40)	120,3(3)	C(4)-C(40)-C(41)	118,1(3)
O(40)-C(40)-C(41)	121,5(2)	C(40)-C(41)-C(42)	120,3(2)
C(40)-C(41)-C(46)	120,0(2)	C(42)-C(41)-C(46)	119,7(3)
C(41)-C(42)-C(43)	119,7(2)	C(42)-C(43)-C(44)	120,3(3)
C(43)-C(44)-C(45)	120,1(4)	C(44)-C(45)-C(46)	120,4(3)
C(41)-C(46)-C(45)	119,8(3)	C(5)-C(51)-C(52)	119,7(2)
C(5)-C(51)-C(56)	121,0(4)	C(52)-C(51)-C(56)	119,2(4)
C(51)-C(52)-C(53)	119,9(2)	C(52)-C(53)-C(54)	120,0(5)
C(53)-C(54)-C(55)	120,9(5)	C(54)-C(55)-C(56)	119,7(3)
C(51)-C(56)-C(55)	120,2(4)	C(8)-C(801)-C(802)	121,0(3)
C(8)-C(801)-C(806)	118,7(3)	C(802)-C(801)-C(806)	120,3(4)
C(801)-C(802)-C(803)	119,7(4)	C(802)-C(803)-C(804)	120,3(4)

C(803)-C(804)-C(805)	121,3(6)	C(804)-C(805)-C(806)	120,0(4)
C(801)-C(806)-C(805)	118,5(3)	C(8)-C(807)-C(808)	121,4(2)
C(8)-C(807)-C(812)	119,5(2)	C(808)-C(807)-C(812)	118,9(2)
C(807)-C(808)-C(809)	120,4(3)	C(808)-C(809)-C(810)	120,7(3)
C(809)-C(810)-C(811)	119,4(3)	C(810)-C(811)-C(812)	119,9(2)
C(807)-C(812)-C(811)	120,7(3)		

EXPERIMENTAL

Melting points are uncorrected, ir spectra were recorded on a Perkin Elmer 421 spectrometer; ^{1}H nmr spectra were determined on Varian EM 360 L and XL 200 spectrometers.

Synthesis of 5-Benzoyl-1-(methylenamino)-4-phenyl-1*H*-pyrimid-2-thiones **3**. General Procedure.

Compounds **1** and **2** (molar ratio 1:1.1) were heated to 80° in dry toluene for 1-2 hours. After 12 hours at room temperature, the yellow coloured products **3** either have separated and were isolated by suction, **3a** and **3b**, or were obtained after evaporation of the solvent and trituration the residue with dry ether.

5-Benzoyl-1-(phenylmethylenamino)-4-phenyl-1*H*-pyrimidine-2-thione (**3a**).

Compound **1** (0.5 g) and 0.32 g of **2a** in 20 ml of toluene for 1.5 hours gave 0.25 g (35%) of **3a**, mp 185° (from acetic acid); ir (potassium bromide): 1650 (C=O), 1560 cm^{-1}; ^{1}H-nmr (DMSO-d$_6$) δ 7.3-8.0 (m, 15H), 8.9 (s, 1H), 9.0 (s, 1H).

Anal. Calcd. for $C_{24}H_{17}N_3SO$: C, 72.89; H, 4.33; N, 10.63; S, 8.11. Found: C, 72.75; H, 4.36; N, 10.55; S, 7.85.

5-Benzoyl-1-(methylphenylmethylenamino)-4-phenyl-1*H*-pyrimidine-2-thione (**3b**).

Compound **1** (0.5 g) and 0.35 g of **2b** in 20 ml of toluene for 1 hour gave 0.24 g (33%) of **3b**, mp 226-281° (from acetic acid); ir (potassium bromide): 1650 (C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.4 (s, 3H), 7.2-8.0 (m, 15H), 8.1 (s, 1H) ppm.

Anal. Calcd. for $C_{25}H_{19}N_3OS$: C, 72.80; H, 4.58; N, 10.33; S, 8.05. Found: C, 73.04; H, 4.64; N, 10.26; S, 7.82.

5-Benzoyl-1-(diphenylmethylenamino)-4-phenyl-1*H*-pyrimidine-2-thione (**3c**).

Compound **1** (2 g) and 1.85 g of **2c** were heated (100°) without solvent for 20 minutes. After triturating with dry ether 2 g (60%) of **3c** was obtained, mp 195-197° (from 1-butanol); ir (potassium bromide): 1660 (C=O) cm^{-1}.

Anal. Calcd. for $C_{30}H_{21}N_3OS$: C, 76.40; H, 4.89; N, 8.91; S, 6.79. Found: C, 76.25; H, 4.54; N, 8.83; S, 6.72.

5-Benzoyl-1-(dimethylmethylenamino)-4-phenyl-1*H*-pyrimidine-2-thione (**3d**).

Compound **1** (1 g) and 0.5 g of **2d** in 50 ml of toluene for 2 hours gave 0.42 g (34%) of **3d**, mp 148-150° (from absolute ethanol); ir (potassium bromide): 1670 (C=O), 1600 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.2 (s, 6H), 7.0-7.7 (m, 10H), 7.9 (s, 1H) ppm.

Anal. Calcd. for $C_{20}H_{17}N_3OS$: C, 69.14; H, 4.93; N, 12.09. Found: C, 68.90; H, 5.03; N, 12.19.

5-Benzoyl-1-(pentamethylenemethylenamino)-4-phenyl-1*H*-pyrimidine-2-thione (**3e**).

Compound **1** (1 g) and 0.62 g of **2e** in 50 ml of tolulene for 10 hours yielded 0.42 g (30%) of **3e**, mp 167-168° (from 1-butanol); ir (potassium bromide): 1660 (C=O), 1600 cm^{-1}; ^{1}H-nmr (DMSO-d$_6$): δ 1.77-2.7 (m, 10H), 7.2-7.9 (m, 10H), 8.5 (s, 1H) ppm.

Anal. Calcd. for $C_{23}H_{21}N_3OS$: C, 71.29; H, 5.46; N, 10.84; S, 8.27. Found: C, 71.45; H, 5.57; N, 10.62; S, 8.01.

5-Benzoyl-1-(ethylmethylmethylenamino)-4-phenyl-1*H*-pyrimidine-2-thione (**3f**).

Compound **1** (1 g) and 0.52 g of **2f** in 50 ml of toluene for 2 hours yielded 0.62 g (48%) of **3f**, mp 168-169° (from 1-butanol); ir (potassium bromide): 1665 (C=O), 1600 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.3 (t, 3H), 2.0 (s, 3H), 2.6 (q, 2H), 7.0-7.7 (m, 10H), 8.0 (s, 1H) ppm.

Anal. Calcd. for $C_{21}H_{19}N_3OS$: C, 69.78; H, 5.30; N, 11.62. Found: C, 69.91; H, 5.41; N, 11.54.

5-Benzoyl-1-(isobutylmethylmethylenamino)-4-phenyl-1*H*-pyrimidine-2-thione (**3g**).

Compound **1** (1 g) and 0.62 g of **2g** in 50 ml of toluene for 2 hours yielded 0.95 g (68%) of **3g**, mp 144-146° (from 1-butanol); ir (potassium bromide): 1660 (C=O), 1600 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.1 (d, 6H), 2.1 (s, 3H), 2.6 (m, 3H), 7.1-7.8 (m, 10H), 8.0 (s, 1H) ppm.

Anal. Calcd. for $C_{23}H_{23}N_3OS$: C, 70.92; H, 5.95; N, 10.79. Found: C, 70.93; H, 6.03; N, 10.76.

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

General Procedure a.

Fifteen ml of water was added to a solution of 1 g **3** in 5 ml of acetic acid and the mixture was then heated under reflux for 10-15 minutes. With cooling 0.5 g (70%) of **5** precipitated and was recrystallized from acetic acid, mp 195°.

General Procedure b.

Compound **3** (0.5 g) was dissolved in 25 ml of concentrated hydrochloric acid and 200 ml of water was added thus precipitating 0.25 g (70%) of **5**; ir (potassium bromide): 1660 (C=O), 1610 cm^{-1}.

Anal. Calcd. for $C_{17}H_{13}N_3OS$: C, 66.43; H, 4.26; N, 13.67. Found: C, 66.37; H, 4.09; N, 13.59.

Crystal Data of **3c**.

The crystals are monoclinic, space group C2/c, Z = 8; a = 2985.9(19), b = 1172.0(10), c = 1960.9(14) pm, β = 134.44(3)°, V = 4899(4) pm^3.10^{-6}, d_{calc} = 1.279 g cm^{-3}; number of reflexions: 3970. Intensity measurements were made on a Syntex P3 four circle diffractometer using MoKα-radiation in the ω-scan mode. The structure was solved by direct methods by the computer program SHELXTL [11]. Several refinement circles led to an R value of 0.046.

Further details of the crystal structure investigations are available on request from the Fachinformationszentrum Energie, Physik, Mathematik, GmbH, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD 52858, the names of the authors, and the journal citation.

REFERENCES AND NOTES

[1] This is part **28** in a series "Reactions of Oxalyl Compounds", Part **27**, G. Kollenz, R. Theuer, W. Ott, K. Peters, E. M. Peters and H. G. von Schnering, *Heterocycles*, **27**, 479 (1988).

[2] Recent Reviews: D. J. Brown in "The Chemistry of Heterocyclic Compounds", "The Pyrimidines", Suppl II, A. Weissberger and E. C. Taylor eds, Interscience Publishers, John Wiley & Sons, 1985, p 1 ff; D. J. Brown in: "Comprehensive Heterocyclic Chemistry", Vol **3**, Chapter 2.13, A. R. Katritzky and C. W. Rees eds, Pergamon Press, 1984, p 57 ff.

[3] C. C. Cheng, *Prog. Med. Chem.*, 67 (1969).

[4] D. B. McNair-Scott, T. L. V. Ulbricht, M. L. Rogers, E. Chu and C. Rose *Cancer Res.*, **19**, 15 (1959).

[5] Sankyo Co., Ltd., Ube Industries, Ltd., Japanese Patent 5936,667 [8436,667]; *Chem. Abstr.*, **101**, 1109392 (1984).

[6] E. Ziegler, M. Eder, C. Belegratis and E. Prewedourakis, *Monatsh. Chem.*, **98**, 2249 (1967).

[7] Y. Akcamur, G. Penn, E. Ziegler, H. Sterk, G. Kollenz, K. Peters, E. M. Peters and H. G. von Schnering, *Monatsh. Chem.*, **117**, 231 (1986);

Y. Akcamur and G. Kollenz, *Org. Prep. Proced. Int.*, **19**, 52 (1987).
[8] A. L. Weis in "Advances in Heterocyclic Chemistry", Vol **38**, A. R. Katritzky, ed, Academic Press, Inc, 1985, p 45 ff.
[9] O. Bayer in: "Methoden der Organische Chemie", Bd. VII/1, Houben-Weyl-Müller, eds, Georg Thieme Verlag, 1954, p 317 ff.
[10] C. A. Grob, *Angew. Chem., Int. Ed. Engl.*, **8**, 535 (1969).
[11] G. M. Sheldrick, SHELXTL, Universität Göttingen, 1985, unpublished.