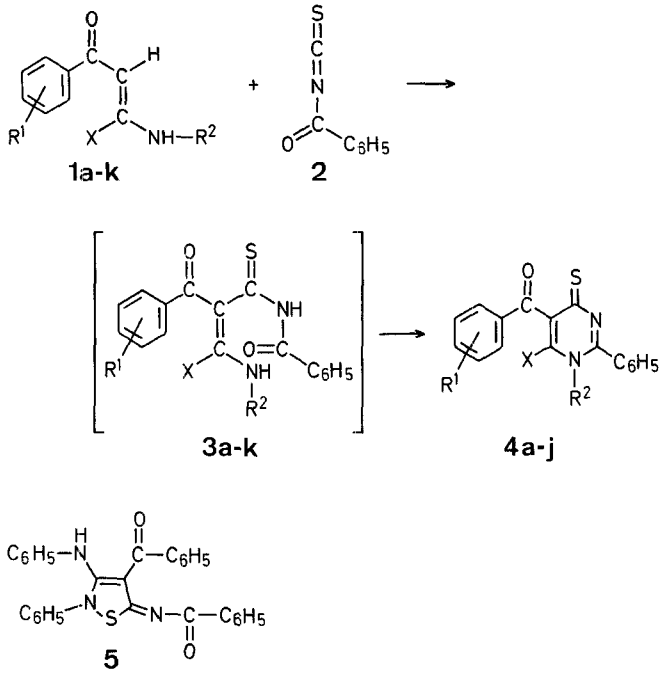
Reactions of Polarized Ketene *S,N*- and *N,N*-Acetals with Benzoyl Isothiocyanate: Synthesis of Novel 1-*N*-Aryl(alkyl)-2-phenyl-5-aroyl-6-methylthio(*N*-alkylamino)-4-thioxopyrimidines[1]

V. AGGARWAL, H. ILA*, H. JUNJAPPA*

Department of Chemistry, North-Eastern Hill University, Shillong 793003, Meghalaya, India

While 2-thioxopyrimidines may be directly prepared by reacting thiourea with three-carbon fragments, the corresponding 4-thioxopyrimidines have mostly been prepared involving several steps using hydroxypyrimidines[2]. Direct thiation of hydroxypyrimidines is reported to give good yields of the corresponding thioxopyrimidines except when nitro and amino groups are present on the pyrimidine ring[2]. Chloropyrimidines or their thiouronium salts, on treatment with sodium hydrogen sulphide followed by hydrolysis, also yield thioxopyrimidines[2]. Apparently, these methods involve multiple steps coupled with the overall poor yields of the desired thioxopyrimidines. The only efficient, direct synthesis of 4-thioxopyrimidines is reported to involve the reaction of enamines with acyl isothiocyanates[3-7]. These 4-thioxopyrimidines carry alkyl substitution at the 6-position, limiting their synthetic elaboration for fused ring construction leading to biologically important purine analogues. Therefore, a method for the synthesis of 4-thioxopyrimidines carrying functional groups in the 5- and 6-positions suitable for the construction of fused ring systems is desirable.

In continuation of our interest in ketene *S,N*- and *N,N*-acetals[1], we report here, the reaction of these acetals **1** with benzoyl isothiocyanate **(2)** which yields 5,6-functionalised 4-thioxopyrimidines **4.**



Thus, when **1a** and **2** were refluxed in either ether or tetrahydrofuran for 18 h, **4a** was obtained in 80% yield. Similarly, **1b** and **1c** reacted with **2** to give the corresponding **4b** and **4c** in 78 and 76% yields, respectively. However, the corresponding *S,N*-diethylacetal **1d** and **2,** in refluxing ether, gave only the open chain adduct **3d** (80% yield) while the desired pyrimidine **4d** was obtained in 68% yield, when **1d** and **2** were reacted in tetrahydrofuran at room temperature. The pyrimidines **4e-g** were similarly prepared from the respective **1e-g** and **2** in 67-70% overall yields (Table 1).

When the *N,N*-acetals **1h-k** reacted with **2,** compound **1h** in refluxing ether gave only an open chain adduct **3h** (75% yield), while the same reaction mixture in refluxing tetrahydrofuran yielded **4h** in 42% yield. Similarly **1i** and **1j** with **2** in refluxing tetrahydrofuran gave the corresponding **4i** and **4j** in 35 and 38% yields, respectively. The *N,N*-diphenylacetal **1k** and **2** reacted readily in refluxing ether to give the open chain adduct **3k** in excellent yield. However, in refluxing tetrahydrofuran, the desired pyrimidine **4k** was not formed and the product isolated (35% yield) was characterised as the isothiazoline **5,** formed by oxidative cyclisation of **3k.** The structure of **5** was further confirmed by subjecting **3k** to bromine oxidation[5] which gave **5** in 48% yield (m.p., m.m.p., superimposable I.R.). Further attempts to cyclise **3k** to **4k** in different solvents (benzene, chloroform, and acetonitrile) and in the presence of a base such as triethylamine were not successful.

When the reaction of **2** was extended to nitroketene *S,N*- and *N,N*-acetals **6a-d, 6a** and **2** remain unchanged in both refluxing tetrahydrofuran and ether, while on refluxing for a longer period in benzene, **8a** was obtained in 39% yield and the corresponding **9a** was not formed at all. Similarly **6b-d** with **2** in boiling tetrahydrofuran yielded directly the corresponding **8b-d** in 46-55% overall yields, while in boiling ether the respective open chain adducts **7b-d** were formed, which were

0039-7881/82/0132-0065 $ 03.00

Table 1. Preparation of Products **4a–j**, **3d**, **3h**, **3k**, and **5**

Product No.	R^1	R^2	X	Reaction conditions time/solvent	Yield [%]	m.p. [°C]	Molecular formula[a]	I.R. (nujol)[b] ν [cm^{-1}]	^{1}H-N.M.R. (CF_3COOH) δ [ppm]	M.S. *m/e* (M^+)
4a	H	C_6H_5	H_3C—S	18 h/ether	80	158–160°	$C_{24}H_{18}N_2OS_2$ (414.5)	1665 (C=O); 1595 (C=N)	1.60 (s, 3H); 7.1–7.5 (m, 13H); 7.86 (dd, 2H)	414
4b	4-Cl	C_6H_5	H_3C—S	24 h/ether	78	185–186°	$C_{24}H_{17}ClN_2OS_2$ (449.0)	1673 (C=O); 1585 (C=N)	1.58 (s, 3H); 6.8–7.1 (m, 12H); 7.54 (dd, 2H)	—
4c	4-H_3CO	C_6H_5	H_3C—S	20 h/ether	76	149–150°	$C_{25}H_{20}N_2O_2S_2$ (444.6)	1660 (C=O); 1600 (C=N)	1.62 (s, 3H); 3.52 (s, 3H); 6.64 (d, 2H); 6.98 (br s, 10H); 7.60 (dd, 2H)	—
4d	H	C_2H_5	H_3C—S	20 h/THF	68	202°	$C_{20}H_{18}N_2OS_2$ (366.5)	1665 (C=O); 1595 (C=N)	1.01 (t, 3H); 2.06 (s, 3H); 4.20 (q, 2H); 7.3–7.6 (m, 8H); 7.66–7.90 (dd, 2H)	366
4e	4-Cl	C_2H_5	H_3C—S	22 h/THF	70	200–201°	$C_{20}H_{17}ClN_2OS_2$ (401.0)	1670 (C=O); 1585 (C=N)	1.01 (t, 3H); 2.10 (s, 3H); 4.13 (q, 2H); 7.10 (d, 2H); 7.35 (br s, 5H); 7.60 (d, 2H)	—
4f	4-H_3CO	C_2H_5	H_3C—S	26 h/THF	68	172–174°	$C_{21}H_{20}N_2O_2S_2$ (396.5)	1660 (C=O); 1595 (C=N)	1.00 (t, 3H); 2.11 (s, 3H); 3.56 (s, 3H); 4.10 (q, 2H); 6.66 (d, 2H); 7.30 (br s, 5H); 7.58 (dd, 2H)	396
4g	4-H_3C	C_2H_5	H_3C—S	20 h/THF	67	193–195°	$C_{21}H_{20}N_2OS_2$ (380.5)	1660 (C=O); 1600 (C=N)	1.00 (t, 3H); 2.05 (br s, 6H); 4.05 (q, 2H); 6.90 (d, 2H); 7.28 (br s, 5H); 7.44 (d, 2H)	—
4h	H	C_2H_5	C_2H_5—NH	24 h/THF	42	179–181°	$C_{21}H_{21}N_3OS$ (363.5)	3230 (br, NH); 1625 (C=O); 1590 (C=N)[c]	0.60 (t, 3H); 0.80 (t, 3H); 3.05 (br q, 4H); 7.0–7.3 (m, 8H); 7.55 (dd, 2H)	363
4i	4-Cl	C_2H_5	C_2H_5—NH	10 h/THF	35	159–161°	$C_{21}H_{20}ClN_3OS$ (397.9)	3220 (br, NH); 1625 (C=O); 1580 (C=N)	0.95–1.60 (2 br t, 6H); 3.10–3.90 (2 br q, 4H); 7.2–8.4 (m, 9H)	—
4j	4-H_3CO	C_2H_5	C_2H_5—NH	32 h/THF	38	151–152°	$C_{22}H_{23}N_3O_2S$ (393.5)	3230 (br, NH); 1625 (C=O); 1605 (C=N)	1.14–1.55 (2 br t, 6H); 3.32–3.78 (2 br q, 4H); 3.96 (s, 3H); 7.0–7.5 (m, 2H); 7.6–7.8 (m, 5H); 8.02 (dd, 2H)	—
3d	H	C_2H_5	H_3C—S	0.5 h/ether	80	125–126°	$C_{20}H_{20}N_2O_2S_2$ (384.5)	3140 (br, NH); 1685 (C=O); 1600 (Ar—C=O)	1.30 (t, 3H); 2.43 (s, 3H); 3.42 (br q, 2H); 5.60 (br, 1H); 7.2–8.1 (m, 10H)[d]	—
3h	H	C_2H_5	C_2H_5—NH	0.5 h/ether	78	129–130°	$C_{21}H_{23}N_3O_2S$ (381.5)	3250, 3150 (NH); 1690 (C=O); 1625 (Ar—C=O)[c]	1.05 (br t, 6H); 3.25 (br q, 4H); 7.3 (m, 8H); 8.0 (m, 2H)	—
3k	H	C_6H_5	C_6H_5—NH	10 h/ether	82	126–127°	$C_{29}H_{23}N_3O_2S$ (477.6)	3350–3200 (br, NH); 1688 (C=O); 1600 (Ar—C=O)	6.2–9.3 (m, 23H)	—
5	—	—	—	45 h/THF	35	196–198°	$C_{29}H_{21}N_3O_2S$ (475.6)	3175 (NH); 1600–1500 (br, C=O, C=N)	6.1–8.1 (m, 21H)	475

[a] Satisfactory microanalyses obtained: C ±0.43, H ±0.30, N ±0.33; exceptions: **4e**, C −0.67.

[b] All open chain adducts (**3d**, **3h**, **3k** and **7b–7d**) showed strong band for carbonyl group between ν = 1685–1695 cm^{-1} (Ref.[3]); all isothiazolines (**5** and **8a–8d**) showed strong bands between ν = 1500–1600 cm^{-1} (Ref.[5]).

[c] KBr disc.

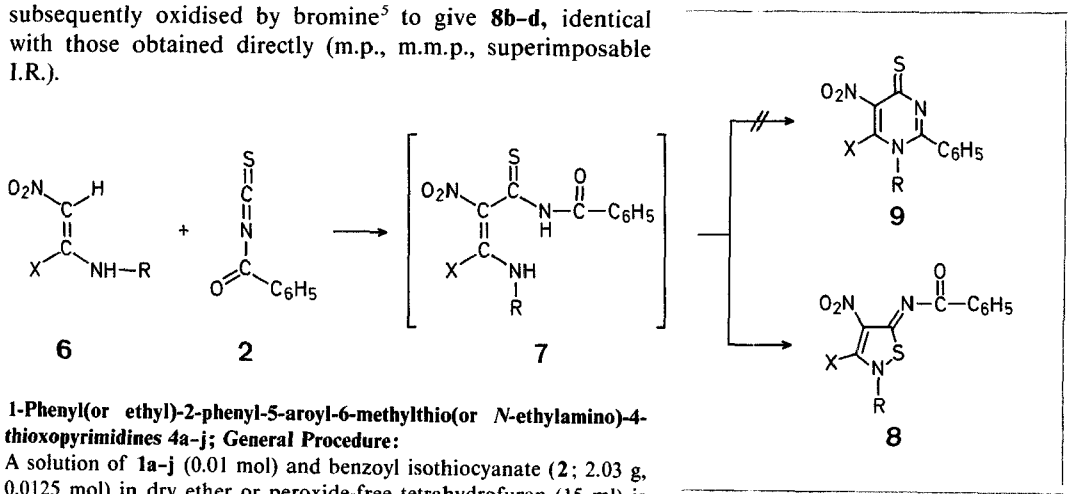
[d] $CDCl_3$ solution.

Table 2. Preparation of Products **8a–d** and **7b–d**

Product No.	R	X	Reaction conditions time/solvent	Yield [%]	m.p. [°C]	Molecular formula[a]	I.R. (nujol) ν [cm^{-1}][b]	^{1}H-N.M.R. (CF_3COOH) δ [ppm]	M.S. *m/e* (M^+)
8a	C_6H_5	H_3C—S	54 h/benzene	39	210–212°	$C_{17}H_{13}N_3O_3S_2$ (371.4)	1590, 1530 (C=O, C=N)[c]	1.76 (s, 3H); 7.2–7.5 (m, 8H); 7.6–8.0 (m, 2H)	371
8b	C_2H_5	H_3C—S	54 h/THF	55	151–153°	$C_{13}H_{13}N_3O_3S_2$ (323.4)	1590, 1535 (C=O, C=N)[c]	1.40 (t, 3H); 2.52 (s, 3H); 4.12 (q, 2H); 7.3–7.6 (m, 3H); 8.3–8.4 (m, 2H)[d]	323
8c	C_2H_5	C_2H_5—NH	45 h/THF	52	173–174°	$C_{14}H_{16}N_4O_3S$ (320.4)	3265 (NH); 1600, 1532 (C=O, C=N)[c]	1.30 (t, 3H); 1.33 (t, 3H); 3.48 (br q, 2H); 3.80 (q, 2H); 7.2–7.6 (m, 3H); 8.2–8.5 (m, 2H); 8.80 (br t, 1H)[d]	320
8d	C_6H_5	C_6H_5—NH	52 h/THF	46	257–258°	$C_{22}H_{16}N_4O_3S$ (416.5)	3200 (br, NH); 1590, 1560 (C=O, C=N)	6.6–10.3 (m, 16H)	416
7b	C_2H_5	H_3C—S	8 h/ether	77	125–127°	$C_{13}H_{15}N_3O_3S_2$ (325.4)	3200 (br, NH); 1693 (C=O)	1.58 (t, 3H); 2.71, 2.80 (2 s, 3H); 3.85, 4.61 (2 q, 2H); 7.5–8.2 (m, 5H)	—
7c	C_2H_5	C_2H_5—NH	2 h/ether	78	130–131°	$C_{14}H_{18}N_4O_3S$ (322.4)	3220, 3210 (br, NH); 1695 (C=O)	1.42 (2 br t, 6H); 3.55 (br q, 4H); 7.5–8.2 (m, 5H)	—
7d	C_6H_5	C_6H_5—NH	15 h/ether	75	148–150°	$C_{22}H_{18}N_4O_3S$ (418.5)	3470, 3400 (br, NH); 1688 (C=O)	7.0–10.3 (m, 18H)	—

[a] Satisfactory microanalyses obtained: C ±0.38, H ±0.28, N ±0.28.
[b] See Table 1, footnote b.
[c] KBr disc.
[d] $CDCl_3$ solution.

subsequently oxidised by bromine[5] to give **8b–d**, identical with those obtained directly (m.p., m.m.p., superimposable I.R.).



6 2 7

1-Phenyl(or ethyl)-2-phenyl-5-aroyl-6-methylthio(or *N*-ethylamino)-4-thioxopyrimidines 4a–j; General Procedure:

A solution of **1a–j** (0.01 mol) and benzoyl isothiocyanate (**2**; 2.03 g, 0.0125 mol) in dry ether or peroxide-free tetrahydrofuran (15 ml) is either stirred at room temperature (**4d–g**) or refluxed (**4a–c** and **4h–j**) for the stated time (Table 1). Bright orange or yellow solids separate out, are filtered, washed with ether (2 × 10 ml), and the crude pyrimidines further purified by crystallisation from either ethyl acetate (**4a–c**) or ether/chloroform (**4d–g**).

In the reaction of **1h–j** with **2**, no solid separates and the residue obtained after evaporation of the solvent is passed through a silica gel column. Elution with ethyl acetate/benzene (1 : 1) yields pure pyrimidines **4h–j**.

***β*-Methylthio(or *N*-ethylamino or anilino)-*β*-*N*-ethylamino(or anilino)-*α*-benzoylthiocarbamoyl-*α*-benzoyl(or nitro)-ethylenes 3d, 3h, 3k and 7b–d; General Procedure:**

All open chain adducts **3d, 3h, 3k** and **7b–7d** are prepared by stirring (**3d, 3h, 3k**) or refluxing (**7b–7d**), a solution of the respective *S,N*- or *N,N*-acetals (**1d, 1h, 1k** and **6b–6d**; 0.01 mol) with benzoyl isothiocyanate (**2**; 2.03 g, 0.0125 mol) in ether (15 ml) for 0.5–10 h (Table 1 and

2). The products are further purified by crystallisation from chloroform.

2-*N*-Ethyl(or *N*-phenyl)-3-methylthio(or *N*-ethyl- or -*N*-phenylamino)-4-benzoyl(or nitro)-5-benzoylimino-Δ^3-isothiazolines (5 and 8a–d); General Procedure:

Method A: The isothiazolines (**5** and **8a–d**) are obtained by refluxing the respective *S,N*- and *N,N*-acetals (**1k** and **6a–d**; 0.01 mol) and benzoyl isothiocyanate (**2**; 2.03 g, 0.0125 mol) in either benzene (15 ml for **6a**) or dry, peroxide free-tetrahydrofuran (20 ml for **1k** and **6b–d**) for 45 to 54 h. The isothiazolines **8a–d** separate as light brown solids which are further purified by crystallisation from methanol/benzene (**8a–c**) and chloroform (**8d**). The isothiazoline **5** is obtained by silica gel column chromatography of the residue obtained by evaporation of the solvent from the reaction mixture. Elution with hexane/benzene (3:1) gives pure **5** as a light brown solid.

Method B[5]: To an ice-cooled solution of the open chain adducts **3k** and **7b–d** (0.001 mol) in dry chloroform (5 ml), bromine (160 mg, 0.001 mol) in dry chloroform (5 ml) is added dropwise during 10–15 min. After stirring at room temperature for 0.5 to 1 h (monitored by T.L.C.), the reaction mixture is neutralised with 2 normal sodium hydroxide solution, diluted with water (20 ml), and extracted with chloroform (2 × 20 ml). The chloroform layer is dried with sodium sulphate and evaporated to a residue from which isothiazolines **5** and **8b–d** crystallise out as light brown crystals.

One of us (V. A.) thanks UGC, New Delhi, for Junior Research Fellowship.

Received: July 27, 1981

[1] Part XVI of the series, Part XV: V. Aggarwal, A. Kumar, H. Ila, H. Junjappa, *Synthesis* **1981**, 157 and references therein.

[2] D. J. Brown in, *The Pyrimidines*, Chapter VIII, p. 272–282; Chapter VII, p. 251; Interscience Publishers, 1962; Supplement I, Chapter VIII, p. 202 and references therein, 1970.

[3] G. deStevens, B. Smolinsky, L. Dorfman, *J. Org. Chem.* **29**, 1115 (1964).

[4] J. Goerdeler, H. W. Pohland, *Chem. Ber.* **96**, 526 (1963).

[5] J. Goerdeler, J. Gnad, *Chem. Ber.* **98**, 1531 (1965) and references therein.

[6] R. W. Lamon, *Tetrahedron Lett.* **1970**, 3957.

[7] R. W. J. Carney, J. Wojtkunski, G. deStevens, *J. Org. Chem.* **29**, 2887 (1964).

0039-7881/82/0132-0068 $ 03.00