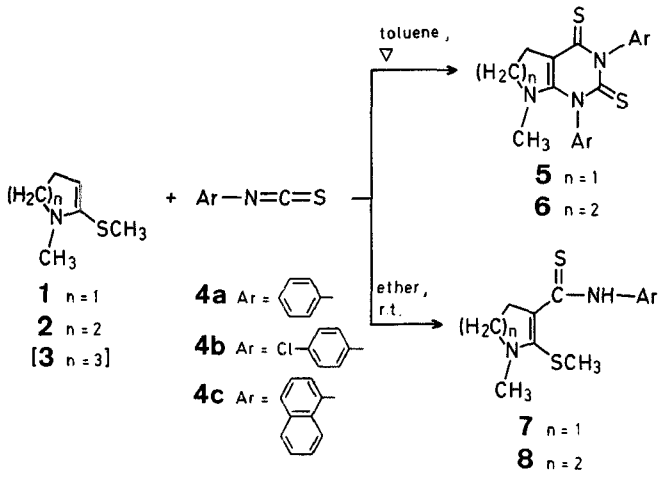
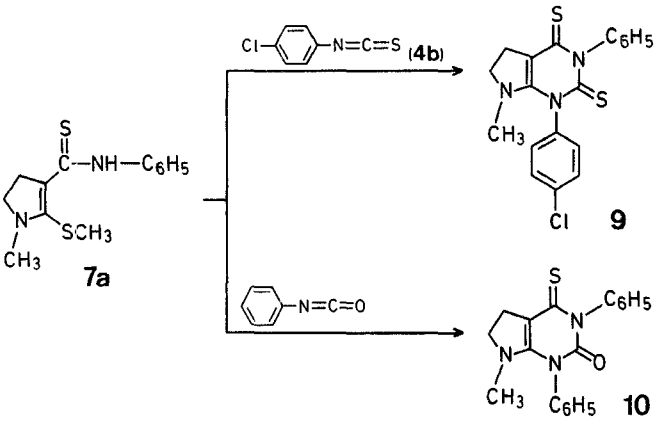


Compound **7a** was converted into the 1,2,3,4,5,6-hexahydro-7*H*-pyrrolo[2,3-*d*]pyrimidine derivatives **9** and **10** by reaction with 4-chlorophenyl isothiocyanate **(4b)** or phenyl isocyanate, respectively.



Activated Lactams: Reaction of Semicyclic Ketene *S,N*-Acetals with Aryl Isothiocyanates

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We have been interested in developing new syntheses of heterocycles using ketene *S,N*-acetals **(1, 2, 3)** as activated lactams[1-4]. In a recent communication, we reported a new synthesis of 1,3-diaryl-2,4-dioxo-*N*-methylazacycloalka[2,3-*d*]pyrimidines by the reaction of **1, 2,** or **3** with aryl isocyanates[2]. The present paper describes new syntheses of 1,3-diaryl-2,4-dithio-*N*-methylazacycloalka[2,3-*d*]pyrimidines with biological interest and semicyclic *β*-aminothiocarbonyl-*α*-methylthioenamines as potential intermediates in the synthesis of fused *N*-heterocyclic systems by reaction of compounds **1** and **2** with aryl isothiocyanates **(4)**.

The reaction of 1-methyl-5-methylthio-2,3-dihydropyrrole **(1)** with 2 equivalents of an aryl isothiocyanate **(4a, b, c)** in boiling toluene affords 1,3-diaryl-7-methyl-2,4-dithioxo-1,2,3,4,5,6-hexahydro-7*H*-pyrrolo[2,3-*d*]pyrimidines **(5a, b, c)**; the analogous reaction of **2** with **4a, b, c** affords 1,3-diaryl-8-methyl-2,4-dithioxo-1,2,3,4,5,6,7,8-octahydropyrido[2,3-*d*]pyrimidines **(6a, b, c)**. When only 1 equivalent of isothiocyanate **4a, b, c** is used and the reactions are carried out in ether at room temperature 1-methyl-2-methylthio-4,5-dihydropyrrole-3-(*N*-arylcarbothioamides) **(7a, b, c)** or 1-methyl-2-methylthio-1,4,5,6-tetrahydropyridine-3-(*N*-arylcarbothioamides) **(8a, b, c)**, respectively, are obtained. Compounds **7** and **8** are attractive intermediates for further heterocyclic syntheses[5].

The tetrahydroazepine derivatives **3** do not react with the aryl isothiocyanates **4a, b, c** (neither in boiling toluene nor in ether) whereas they undergo an analogous cyclocondensation reaction with aryl isocyanates[2,3]. This result may be rationalized by the fact that the reactivity of semicyclic ketene *S,N*-acetals (such as compounds **1, 2,** and **3**) decreases with increasing ring size[4,6] and that the reactivity of aryl isothiocyanates **(4)** is lower than that of aryl isocyanates.

1,3-Diaryl-7-methyl-2,4-dithioxo-1,2,3,4,5,6-hexahydro-7*H*-pyrrolo[2,3-*d*]pyrimidines (5) and 1,3-Diaryl-8-methyl-2,4-dithioxo-1,2,3,4,5,6,7,8-octahydropyrido[2,3-*d*]pyrimidines (6); General Procedure:

To a stirred solution of an aryl isothiocyanate (**4**; 2 mmol) in toluene (10 ml) is added the semicyclic ketene *S,N*-acetal **1** or **2** (1 mmol) and the mixture is refluxed with stirring over the period of time indicated in Table 1. The solvent is evaporated and the residual oil is crystallized from diisopropyl ether to afford a solid. Recrystallization of the solid from dichloromethane/diisopropyl ether gives **5** or **6**, respectively.

1-Methyl-2-methylthio-4,5-dihydropyrrole-3-(*N*-arylcarbothioamides) (7); General Procedure:

To a stirred solution of an aryl isothiocyanate (**4**; 1 mmol) in ether (10 ml) is added the ketene *S,N*-acetal **1** (1 mmol) and stirring is continued for 4 h at room temperature. The precipitate is isolated by suction and recrystallized from diisopropyl ether to afford **7** as pale yellow crystals.

1-Methyl-2-methylthio-1,4,5,6-tetrahydropyridine-3-(*N*-arylcarbothioamides) (8); General Procedure:

To a stirred solution of the aryl isothiocyanate (**4**; 1 mmol) in ether (10 ml) is added compound **2** (1 mmol) and stirring is continued for 20 h at room temperature. The precipitate is isolated by suction and recrystallized from diisopropyl ether to afford **8** as pale yellow crystals.

1-(4-Chlorophenyl)-2,4-dithioxo-7-methyl-3-phenyl-1,2,3,4,5,6-hexahydro-7*H*-pyrrolo[2,3-*d*]pyrimidine (9):

A mixture of compound **7a** (1 mmol) and 4-chlorophenyl isothiocyanate (**4b**; 1 mmol) in toluene (10 ml) is refluxed for 20 h with stirring. The solvent is evaporated and the residual oil is purified by column chromatography on alumina using benzene/dichloromethane (1/1) as eluent to give **9**; yield: 204 mg (53%); m.p. 298–302 °C.

Table 1. 1,3-Diaryl-2,4-dithioxo-*N*-methylazacycloalka[2,3-*d*]pyrimidines (**5, 6**)

Product	Reaction time [h]	Yield [%]	m.p. [°C]	Molecular formula[a,b]	I.R. (Nujol) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm] N—CH_3
5a	10	62	260–262°	$C_{19}H_{17}N_3S_2$ (351.5)	1600, 1580, 1520	2.85
5b	10	53	305–309°	$C_{19}H_{15}Cl_2N_3S_2$ (420.4)	1600, 1570, 1540	2.18
5c	10	54	274–276°	$C_{27}H_{21}N_3S_2$[c] (451.6)	1610, 1570, 1540	2.53
6a	20	20	219–223°	$C_{20}H_{19}N_3S_2$ (365.5)	1590, 1575, 1520	2.97
6b	20	41	264–266°	$C_{20}H_{17}Cl_2N_3S_2$[d] (434.4)	1590, 1560, 1520	2.43
6c	20	11	232–234°	$C_{28}H_{23}N_3S_2$ (465.6)	1600, 1570, 1520	2.63

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.22; H, ±0.30; N, ±0.23; except for **5a** (C, −0.43) and for **5c** and **6b** (see footnotes c and d).
[b] The mass spectra of all products showed *m/e:* M^+, $(M - ArNCS)^+$.
[c] The high-resolution mass spectrum of **5c** proved the assigned structure. Exact mass calculated for $C_{27}H_{21}N_3S_2$: 451.1176; found: 451.1166. $2N_3S_2$: 473.0242, 435.0211, 437.0100; found: 433.0254, 435.0266, 437.0025.

Table 2. 1-Methyl-2-methylthio-4,5-dihydropyrrole-3-(*N*-arylcarbothioamides) (**7**) and 1-Methyl-2-methylthio-1,4,5,6-tetrahydropyridine-3-(*N*-arylcarbothioamides) (**8**)

Product	Yield [%]	m.p. [°C]	Molecular formula[a,b]	I.R. (Nujol) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm] S—CH_3	N—CH_3	NH
7a	90	120–122°	$C_{13}H_{16}N_2S_2$ (264.4)	3640, 1600, 1550	2.40	2.93	10.80
7b	63	154–156°	$C_{13}H_{15}ClN_2S_2$ (289.9)	3590, 1600, 1540	2.39	2.97	10.54
7c	63	94–97°	$C_{17}H_{18}N_2S_2$ (314.5)	3590, 1590, 1520	2.47	3.00	10.85
8a	62	131–133°	$C_{14}H_{18}N_2S_2$ (278.4)	3580, 1590, 1560	2.03	2.93	9.33
8b	43	133–135°	$C_{14}H_{17}ClN_2S_2$ (312.5)	3600, 1590, 1560	2.29	2.98	9.37
8c	14	117–122°	$C_{18}H_{20}N_2S_2$ (328.5)	3600, 1600, 1560	2.17	2.91	9.80

[a] The microanalyses were in good agreement with the calculated values: C, ±0.29; H, ±0.16; N, ±0.18; except for **8c** (C, −0.62).
[b] The mass spectra of all products showed *m/e:* M^+.

$C_{19}H_{16}ClN_3S_2$	calc.	C 59.13	H 4.18	N 10.89
(385.9)	found	58.85	4.11	11.12

I.R. (Nujol): ν = 1570, 1540, 1500 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 2.19 ppm (s, 3H).

7-Methyl-1,3-diphenyl-2-oxo-4-thioxo-1,2,3,4,5,6-hexahydro-7*H*-pyrrolo[2,3-*d*]pyrimidine (10):

This compound is prepared from **7a** and phenyl isocyanate in the same manner as **9**; yield of **10**: 302 mg (90%); m.p. 279–281 °C.

$C_{19}H_{17}N_3OS$	calc.	C 67.97	H 5.09	N 12.52
(335.4)	found	68.19	5.36	11.94

I.R. (Nujol): ν = 1690, 1650, 1550 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 2.23 ppm (s, 3H).

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