2,4-Diaminopyrimidines: 6-Substituted 5-Alkylthio (or Arylthio) Derivatives

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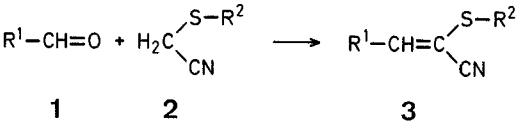
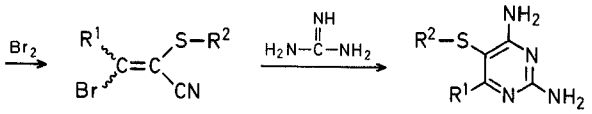
Interest in 2,4-diaminopyrimidine derivatives has been shown recently because of the antimalarial activity of 2,4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine[1,2], which has also promoted the elaboration of convenient or general routes to sulfenylated compounds of type **5**. One method was used for the arylthio derivatives[3] (R^2 = aryl), giving overall yields decreasing rapidly with the number of carbon atoms in R^1: e.g. **5** (R^2 = 4-Cl-C_6H_4): 33% with R^1 = H; 10% for $R^1 = CH_3$; and no trace when $R^1 = C_2H_5$, and, to our knowledge, only one thioalkyl derivative **5** ($R^1 = R^2 = CH_3$), containing, however, dimethylamino groups [$N(CH_3)_2$] has been described[4].

We report here a method of access to arylthio and alkylthio derivatives **5**, using the condensation of guanidine with the bromoacrylonitrile derivative **4** readily obtained from aldehydes[5] **1** and thioalkyl (or aryl)-acetonitrile **2**.



1 **2** **3**



(*Z*/*E*)-**4** **5**

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Table. 6-Substituted 5-Alkylthio-(or Arylthio)-2,4-Diaminopyrimidines **5**

Product No.	R^1	R^2	Yield [%][a]	Ratio sodium methoxide: **4**	Ratio guanidine nitrate: **4**	Reflux time in CH_3OH	m.p. [°C] (solvent)	Molecular formula[b]
5a[c]	CH_3	C_2H_5	81	3	2	8 h	137.5–138° (2:1 $AcOC_2H_5$/PE)	$C_7H_{12}N_4S$ (184.3)
5b	C_2H_5	C_2H_5	85	3	2	8 h	156–156.5° (3:1 $AcOC_2H_5$/PE)	$C_8H_{14}N_4S$ (198.3)
5c	i-C_3H_7	CH_3	76	3	2	8 h	145–145.5° (1:2 C_6H_6/PE)	$C_8H_{14}N_4S$ (198.3)
5d	i-C_3H_7	C_2H_5	86	3	2	8 h	118–119° (1:3 C_6H_6/PE)	$C_9H_{16}N_4S$ (212.3)
5e	n-C_4H_9	C_2H_5	94	3	2	8 h	152.5–153.5° (3:1 $AcOC_2H_5$/PE)	$C_{10}H_{18}N_4S$ (226.3)
5f	C_6H_5	C_2H_5	91	4	3	24 h	193–194° (methanol)	$C_{12}H_{14}N_4S$ (246.3)
5g	2-Cl—C_6H_4	C_2H_5	65	7	6	72 h	164–165° (methanol)	$C_{12}H_{13}ClN_4S$ (280.8)
5h	4-H_3CO—C_6H_4	C_2H_5	91	4	3	48 h	186–187° (methanol)	$C_{13}H_{16}N_4OS$ (276.4)
5i	C_6H_5	C_6H_5	42	4	3	24 h	207–209° (ethanol)	$C_{16}H_{14}N_4S$ (294.4)
5j	4-Cl—C_6H_4	C_6H_5	45	4	3	24 h	172–173 or 184–185° (ethanol)[f]	$C_{16}H_{13}ClN_4S$ (328.8)

[a] Yields were based on the bromo derivative **4**; except for **5i** and **5j** where the crude **4** was used and yield based on **3**.

[b] All products gave satisfactory microanalyses (C ±0.45, H ±0.28, N ±0.32).

[c] ^{13}C-N.M.R. (DMSO-d_6/TMS): δ = 162.00 (C-2); 165.45 (C-4); 94.91 (C-5); 170.06 (C-6); 22.62 (CH_3); 28.25 (CH_2—S); 14.32 ppm [H_3C—CH_2—S].

[d] Exchangeable with CF_3COOD.

[e] In DMSO-d_6.

[f] Two allotropic forms.

The condensation, performed in methanol, provides pyrimidines **5** in good yields (see Table); the reaction is easier with aliphatic groups R^1 (8 h reflux) than with aromatic groups R^1 (24 to 72 h reflux); when $R^2 = C_6H_5$ lower yields were obtained, e.g. **5i, j**, probably due to an unusually difficult bromination step (3.5 h reflux in CCl_4, with the usual amount of bromine) giving slightly impure **4i** and **4j**. [Extraction with dichloromethane of the mother liquor of **5i** and **5j** gives a small amount of the corresponding desulfenylated pyrimidines.] Sodium methoxide in excess with respect to guanidine nitrate was used since the reaction proceeds through the enol ether R^1—$C(OCH_3)$=$C(SR^2)$—CN (Z/E mixture). This intermediate was the only product obtained when equimolar amounts of these two reagents were used according to the procedure described in Ref.[6]. The cyclisation mechanism is then very similar to one of those which were recently reported for the preparation of aminopyrazole derivatives[7].

The structures of compounds **5** were supported by microanalysis and ^{1}H-N.M.R. spectra (see Table). In the I.R. spectra no C≡N absorption band and characteristic bands of aminopyrimidines were observed. Furthermore, the ^{13}C-N.M.R. spectrum of **5a** was in agreement with the data reported for the corresponding desulfenylated derivative[8].

This reaction provides a convenient route for the synthesis of the new 2,4-diaminopyrimidine compounds **5a–j** with potential biological activity.

New starting materials **3** and **4** were prepared by the method described in Ref.[5]: from **2**[9] ($R^2 = CH_3$): **3h**, b.p. 98–103 °C/28 torr; yield: 72%; **4h**, b.p. 86–90 °C/3.2 torr; yield: 78%; from **2**[9] ($R^2 = C_6H_5$): **3i**, b.p. 160–163 °C/0.5, 71%; **3j**, m.p. 121.5–123 °C major isomer + b.p. 183–186 °C/0.8 torr (Z/E mixture); yield: 76%; **4i** and **4j**, oils; not distilled.

6-Alkyl-5-alkylthio-2,4-diaminopyrimidines 5a–e:

To a suspension of guanidine nitrate (0.04 mol) and **4** (0.02 mol) in methanol (20 ml) is added a solution of sodium methoxide (0.06 mol) in methanol (40 ml). The mixture is stirred and heated under reflux for 8 h, then diluted with water (200 ml), and allowed to cool at room temperature with stirring. Products **5a** and **5d** are extracted from the solution with dichloromethane (3 × 60 ml), the organic phase separated, dried with sodium sulfate, then evaporated, and the residue recrystallised (see Table). Products **5b, 5c**, and **5e** precipitate when water is added and are filtered (white pellets); in the case of **5b** and **5c** extraction of the aqueous phase with dichloromethane affords an additional amount of the pyrimidine (about 15%).

6-Aryl-5-alkylthio-(or phenylthio)-2,4-diaminopyrimidines 5f–j:

The procedure is identical to the previous one, except that a greater excess of guanidine is used: guanidine nitrate (0.06 mol) and **4** (0.02 mol) in methanol (20 ml), sodium methoxide (0.08 mol) in methanol (40 ml); with longer reflux times: 24 h for **5f, 5i**, and **5j**; 48 h for **5h**. For **5g** the conditions are more drastic: guanidine nitrate (0.06 mol) and **4** (0.01 mol) in methanol (10 ml), sodium methoxide (0.07 mol) in methanol (20 ml), are heated under reflux for 72 h. Dilution with water gives complete precipitation of the pyrimidine which is collected by filtration and recrystallised (see Table). All these pyrimidines **5f–j**, with R^1 = aryl, tend to retain a mol of solvent (water, methanol) which can be eliminated by heating at about 115 °C under reduced pressure (1 torr) for 2 h.

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	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
	1.20 (t, 3H); 2.45 (s, 3H); 2.59 (q, 2H); 5.37 (b s, 2H)[c]; 5.78 (b s, 2H)[d]
	1.21 (t, 6H); 2.60 (q, 2H); 2.85 (q, 2H); 5.16 (b s, 2H)[c]; 5.67 (b s, 2H)[d]
	1.17 (d, 6H); 2.13 (s, 3H); 3.77 (sept., 1H); 5.23 (b s, 2H)[d]; 5.75 (b s, 2H)[d]
	1.04–1.37 (m, 9H); 2.59 (q, 2H); 3.80 (sept, 1H); 5.32 (b s, 2H)[d]; 5.78 (b s, 2H)[d]
	0.73–1.90 (m, 10H); 2.60 (q, 2H); 2.80 (b t, 2H); 5.28 (b s, 2H)[d]; 5.76 (b s, 2H)[d]
	0.92 (t, 3H); 2.36 (q, 2H); 6.20 (b s, 2H)[d]; 6.66 (b s, 2H)[d]; 7.25–7.70 (m, 5H)[e]
	1.02 (t, 3H); 2.40 (q, 2H); 5.72 (b s, 2H)[d]; 6.03 (b s, 2H)[d]; 7.35 (m, 4H)
	1.00 (t, 3H); 2.40 (q, 2H); 3.86 (s, 3H); 5.33 (b s, 2H)[d]; 5.79 (b s, 2H)[d]; 6.96, 7.67 (arom. quartet, 4H)
	6.45 (b s, 2H)[d]; 6.65 (b s, 2H)[d]; 6.86–7.70 (m, 10H)[e]
	6.48 (b s, 2H)[d]; 6.64 (b s, 2H)[d]; 6.88–7.66 (m, 9H)[e]

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