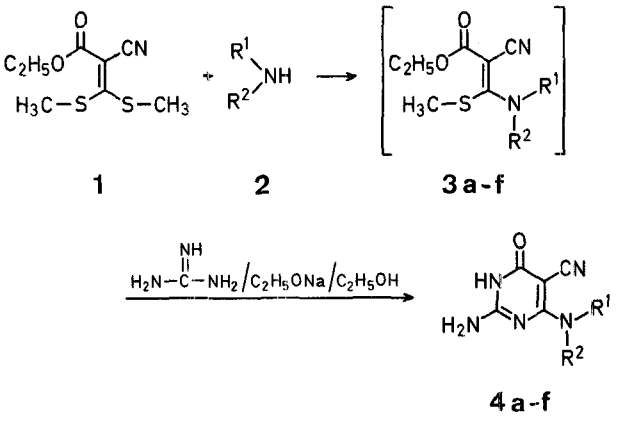
## A Novel and Convenient Synthesis of 2-Amino-4-(*N*-alkyl-*N*-arylamino)-pyrimidines using Polarized Ketene *S,S*- and *S,N*-Acetals[1]

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

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

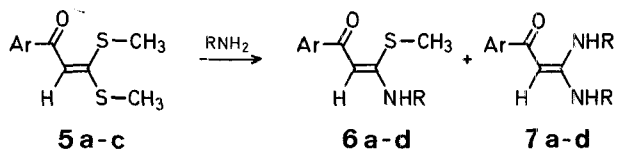
While 2,4-diaminopyrimidines have been synthesized by reacting guanidine with cyano-substituted 3-carbon fragments, the corresponding 4-(*N*-alkyl-*N*-arylamino)- and 4-(*N,N*-dialkylamino)-pyrimidines are usually obtained by displacement of chlorine from chloropyrimidines by amines[2]. The required chloropyrimidines are usually prepared in poor yields by treating the oxopyrimidines with phosphorus halides, using *N,N*-dimethylaniline as catalyst. In the latter transformation, experimental difficulties have been reported, when the $pK_b$ of the chloropyrimidines are close to that of *N,N*-dimethylaniline[2]. Recently, direct formation of aminopyrimidines has been reported by heating the corresponding oxopyrimidines with phosphorus triamide[3] or phosphorus pentoxide/amine mixture[4]. A method for direct synthesis of the *N*-substituted aminopyrimidines is desirable. We now report a novel procedure for 4-*N*-mono- and -disubstituted pyrimidines by reaction of guanidine with ketene *S,N*-acetals, generated *in situ* from the ketene *S,S*-acetals or from ketones and aryl or alkyl isothiocyanates.

When ketene *S,S*-acetal **1** was reacted with aniline (**2a**) in boiling ethanol, the corresponding *S,N*-acetal (**3a**) was obtained in nearly quantitative yield (characterized by spectral and analytical data). Treatment of **3a** (generated *in situ*) with guanidine nitrate in the presence of sodium ethoxide followed by refluxing in ethanol, yielded 2-amino-4-anilino-5-cyano-1,6-dihydro-6-oxopyrimidine (**4a**) in 57% yield. The pyrimidines **4b-f** (Table 1) were similarly prepared in 47–57% overall yields (Scheme **A**).




Scheme **A**

The reaction was next extended to ketene *S,S*-acetals **5** derived from ketones, which are generally less reactive than **1**. Thus the reaction of **5a** and aniline in refluxing ethanol, always yielded a mixture of unreacted **5a**, *S,N*-acetal **6a**, and *N,N*-acetal **7a** even after prolonged heating. However, when **5a** was heated at 160 °C for 15 h, with a slight excess of aniline (1.2 equiv), **5a** completely disappeared, though the mixture of **6a** and **7a** was always formed (4:1 ratio) (Scheme **B**).




Scheme **B**

When this mixture was reacted with guanidine nitrate in the presence of sodium ethoxide, the pyrimidine **8a** was formed in 18% yield and the corresponding *N,N*-acetal **7a** remained unreacted. Attempts to prepare *S,N*-acetals ex-

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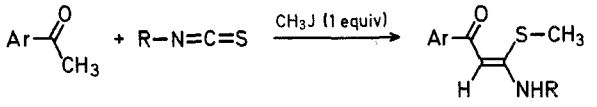
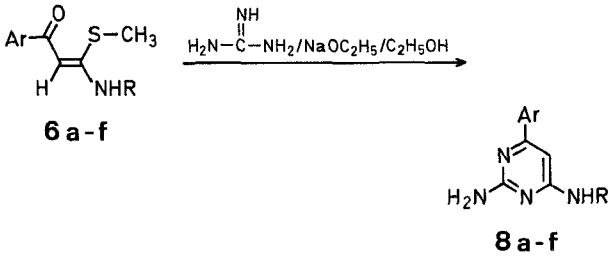
clusively from **5a** and amines failed, and the *N,N*-acetal **7a** was always formed as impurity, which could only be separated by column chromatography. Thus, the direct preparation of ketene *S,N*-acetals **6a–e** from ketones was developed by extending the earlier reported method[5,6] (Method B) (Scheme C). The ketene *S,N*-acetals **6a–e** were prepared in 75–85% yield (Table 2).



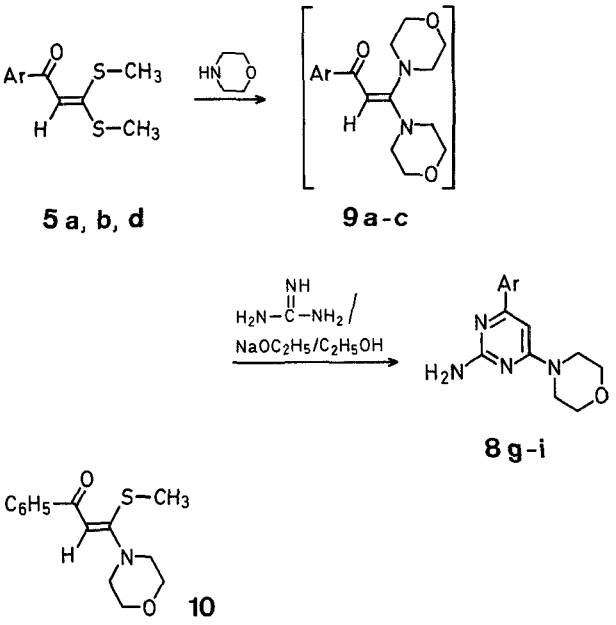

Scheme C

The reaction of pure *S,N*-acetal **6a** with guanidine under identical conditions yielded pyrimidine **8a** in 35% yield. The pyrimidines **8b–e** were similarly prepared in 34–50% yield (Scheme D and Table 3). Reaction of *S,N*-acetal **6f**, reported earlier[7], gave the aminopyrimidine **8f** in 30% yield.




Scheme D

Reaction of ketene *S,S*-acetal **5a** with morpholine yielded *N,N*-acetal **9a** exclusively under varying conditions and attempts to prepare *S,N*-acetal **10** were unsuccessful. However, when **9a** (generated either *in situ*, or after isolation) was reacted with guanidine nitrate and sodium ethoxide in refluxing ethanol, 4-morpholinopyrimidine **8g** was obtained in 28% yield. Pyrimidines **8h–i** were similarly prepared in 30% yields (Scheme E and Table 3).




Scheme E

**2-Amino-4-arylamino (or -morpholino)-5-cyano-6-oxo-1,6-dihydropyrimidines 4; General Procedure:**

A solution of **1** (4.34 g, 0.01 mol) and amine (0.01 mol) in absolute ethanol (35 ml) is heated under reflux for 4 h (checked by T.L.C.), the mixture is then added to a solution of guanidine nitrate (0.01 mol) and sodium ethoxide [prepared by dissolving sodium (0.02 mol) in refluxing ethanol (35 ml)] in absolute ethanol (35 ml) and the combined reaction mixture heated under reflux for 12 h. The ethanol is removed under reduced pressure, the residue diluted with ice-cold water (40 ml), and acidified with 4 normal hydrochloric acid (15 ml). The crude, white oxopyrimidines **4** are filtered and purified by crystallization from acetic acid (Table 1).

**1-Aryl-3-arylamino-3-methylthio-1-oxo-2-propenes 6:**

Method A: A mixture of ketene *S,S*-acetal **5** (0.02 mol) and amine (0.022 mol) is heated at 160 °C for 15 h in an oil bath (monitored by T.L.C.). The mixture of *S,N*-(**6**) and *N,N*-(**7**) acetals is separated by column chromatography on silica gel using benzene/hexane (1:1) as eluent; *S,N*-acetals **6a–d** were prepared by this procedure (Table 2).

**Table 1.** 2-Amino-4-arylamino-(or -morpholino)-5-cyano-6-oxo-1,6-dihydropyrimidines **4a–f**

| Product No. | $R^1$ | $R^2$ | Yield [%] | m.p. [°C] | Molecular formula[a] | I.R. (KBr) $\nu$ [cm$^{-1}$] | $^1$H-N.M.R. ($CF_3COOH$) $\delta$ [ppm] |
|---|---|---|---|---|---|---|---|
| **4a** | $C_6H_5$ | H | 57 | 340° | $C_{11}H_9N_5O$ (227.2) | 3420, 3270, 3155, 2200, 1660, 1635, 1585 | 6.8–7.3 (m, 5 $H_{arom}$); 8.6 (br. s, 1 H, NH) |
| **4b** | 4-$H_3C$—$C_6H_4$ | H | 51 | 360° (dec.) | $C_{12}H_{11}N_5O$ (241.3) | 3280, 3220, 3140, 2215, 1650, 1600, 1540 | insoluble |
| **4c** | 4-$H_3CO$—$C_6H_4$ | H | 54 | 326–328° | $C_{12}H_{11}N_5O_2$ (257.3) | 3425, 3265, 3150, 2215, 1662, 1600, 1560 | 3.51 (s, 3 H, $OCH_3$); 6.80 ($A_2B_2$ q, 4 $H_{arom}$); 8.56 (br. s, 1 H, NH) |
| **4d** | 4-Cl—$C_6H_4$ | H | 57 | 364–366° | $C_{11}H_8ClN_5O$ (261.7) | 3480, 3310, 3280, 3200, 3130, 2200, 1668, 1640, 1600 | insoluble |
| **4e** | 4-F—$C_6H_4$ | H | 53 | 368–370° | $C_{11}H_8FN_5O$ (245.2) | 3475, 3292, 3200, 3123, 2204, 1670, 1624, 1600 | 6.6–7.1 (m, 4 $H_{arom}$); 8.43 (br. s, 1 H, NH) |
| **4f** | $(CH_2)_2$—O—$(CH_2)_2$ | | 47 | 327° (dec) | $C_9H_{11}N_5O_2$ (221.2) | 3280, 3175, 3100, 2180, 1670, 1655, 1580 | 3.66 (s, 8 H, morpholine $CH_2$) |

[a] The microanalyses were in satisfactory agreement with the calculated values (C ±0.38, H ±0.33, N ±0.39); exceptions: **4b** H, −0.47, N, −0.44; **4c**, N +0.57; **3e**, **3f**, C −0.49.

**Table 2.** 1-Aryl-3-aryl-(or alkyl)-amino-3-methylthio-1-oxo-2-propenes **6** and 1-Aryl-3,3-bis[arylamino]-1-oxo-2-propenes **7**

| Product No. | Ar | R | Yield [%] by Method A | B | m.p. [°C] | Molecular formula[a] | I.R. (KBr) [cm$^{-1}$] $\nu_{NH}$ | $\nu_{C=O}$ | $^1$H-N.M.R. ($CDCl_3$) $\delta$ [ppm] |
|---|---|---|---|---|---|---|---|---|---|
| **6a** | H | $C_6H_5$ | 40 | 82 | 56–57° | $C_{16}H_{15}NOS$ (269.3) | 3230 | 1575 | 2.50 (s, 3H, $SCH_3$); 6.11 (s, 1H, H-2); 7.4–7.8 (m, 8$H_{arom}$); 8.0–8.3 (m, 2$H_{arom}$) |
| **6b** | 4-$H_3CO$—$C_6H_4$ | $C_6H_5$ | 32 | 74 | 66–67° | $C_{17}H_{17}NO_2S$ (299.3) | 3230 | 1595 | 2.53 (s, 3H, $SCH_3$); 4.03 (s, 3H, $OCH_3$); 6.23 (s, 1H, H-2); 7.2–7.7 (m, 3$H_{arom}$); 7.8 (m, 4$H_{arom}$); 8.33 (dd, 2$H_{arom}$) |
| **6c** | 4-Br—$C_6H_4$ | $C_6H_5$ | 41 | 84 | 85–86° | $C_{16}H_{14}BrNOS$ (348.3) | 3330 | 1570 | 2.48 (s, 3H, $SCH_3$); 6.01 (s, 1H, H-2); 7.3–7.7 (m, 7$H_{arom}$); 7.8–8.2 (m, 2$H_{arom}$) |
| **6d** | $C_6H_5$ | 4-Cl—$C_6H_4$ | 31 | 76 | 116–117° | $C_{16}H_{14}ClNOS$ (303.8) | 3400 | 1608 | 2.51 (s, 3H, $SCH_3$); 6.18 (s, 1H, H-2); 7.6–7.9 (m, 7$H_{arom}$); 8.2–8.4 (m, 2$H_{arom}$) |
| **6e** | $C_6H_5$ | $C_2H_5$ | — | 70 | oil | $C_{12}H_{15}NOS$ (221.3) | 3350 | 1540 | 1.33 (t, 3H, $CH_2CH_3$); 2.48 (s, 3H, $SCH_3$); 3.48 (q, 2H, $CH_2CH_3$); 5.66 (s, 1H, H-2); 7.3–7.6 (m, 3$H_{arom}$); 7.7–8.0 (m, 2$H_{arom}$); 11.7–12.1 (br, 1H, NH) |
| **7a** | $C_6H_5$ | $C_6H_5$ | 10 | — | 132–133° | $C_{21}H_{18}N_2O$ (314.4) | 3335, 3258, 3200, 1608 | | 5.65 (s, 1H, H-2); 6.5 (br, 1H, NH); 6.7 (br, 1H, NH); 7.0–7.6 (m, 13$H_{arom}$); 7.6–7.9 (m, 2$H_{arom}$) |
| **7b** | 4-$H_3CO$—$C_6H_4$ | $C_6H_5$ | 12 | — | 126–127° | $C_{22}H_{20}N_2O_2$ (344.4) | 3385, 3190, 3100, 1590 | | 3.83 (s, 3H, $OCH_3$); 5.66 (s, 1H, H-2); 6.43 (s, 1H, NH); 6.95 (dd, 2$H_{arom}$); 7.36 (s, 5$H_{arom}$); 7.41 (s, 5$H_{arom}$); 7.80 (dd, 2$H_{arom}$) |
| **7c** | 4-Br—$C_6H_4$ | $C_6H_5$ | 12 | — | 109–110° | $C_{21}H_{17}BrN_2O$ (393.3) | 3270, 3210, 3100, 1618 | | 5.56 (s, 1H, H-2); 6.5 (br. s, 1H, NH); 6.6–7.0 (br, 1H, NH); 7.0–7.5 (m, 10$H_{arom}$); 7.5–8.1 (m, 4$H_{arom}$) |
| **7d** | $C_6H_5$ | 4-Cl—$C_6H_4$ | 11 | — | 194° | $C_{21}H_{16}Cl_2N_2O$ (383.3) | 3300, 3250, 3175, 1590 | | 5.66 (s, 1H, H-2); 6.5 (br. s, 1H, NH); 7.2–7.7 (m, 11$H_{arom}$); 7.8–8.0 (m, 2$H_{arom}$); 13.7 (br, 1H, NH) |

[a] The microanalyses were in satisfactory agreement with the calculated values (C ±0.26, H ±0.41, N ±0.37); exception **6c**, C −0.53.

**Table 3.** 2-Amino-6-aryl-4-aryl-(or -alkyl)-amino- **(8a–f)** or -4-morpholinopyrimidines **(8g–i)**

| Product No. | Ar | R | Yield [%] | m.p. [°C] | Molecular formula[a] | I.R. (KBr) $\nu$ [cm$^{-1}$] | $^1$H-N.M.R. ($CDCl_3$) $\delta$ [ppm] |
|---|---|---|---|---|---|---|---|
| **8a** | $C_6H_5$ | $C_6H_5$ | 35 (18)[b] | 159°[c] | $C_{16}H_{14}N_4$ (262.3) | 3400, 3270, 3130, 1620, 1590 | 5.22 (s, 2H, $NH_2$); 6.61 (s, 1H, H-5); 7.0–7.7 (m, 8$H_{arom}$); 7.7–8.0 (m, 2$H_{arom}$) |
| **8b** | 4-$H_3CO$—$C_6H_4$ | $C_6H_5$ | 34 | 167° | $C_{17}H_{16}N_4O$ (292.3) | 3450, 3380, 3170, 1628, 1600 | 3.71 (s, 3H, $OCH_3$); 5.1 (br. s, 2H, $NH_2$); 6.35 (s, 1H, H-5); 6.7–7.3 (m, 7$H_{arom}$); 7.76 (dd, 2$H_{arom}$) |
| **8c** | 4-Br—$C_6H_5$ | $C_6H_5$ | 45 | 147–148° | $C_{16}H_{13}BrN_4$ (341.2) | 3370, 3320, 3280, 3120, 1618, 1590 | 5.0 (br. s, 2H, $NH_2$); 6.38 (s, 1H, H-5); 7.2–7.8 (m, 9$H_{arom}$) |
| **8d**[d] | $C_6H_5$ | 4-Cl—$C_6H_4$ | 50 | 138° | $C_{16}H_{13}ClN_4$ (296.8) | 3400, 3220, 3150, 1638, 1590 | 5.21 (br. s, 2H, $NH_2$); 6.26 (s, 1H, H-5); 7.1–7.4 (m, 7$H_{arom}$); 7.8–7.9 (m, 2$H_{arom}$) |
| **8e** | $C_6H_5$ | $C_2H_5$ | 40 | 148–149° | $C_{12}H_{14}N_4$ (214.3) | 3320, 3280, 1645, 1590 | 1.30 (t, 3H, $CH_2CH_3$); 3.55 (q, 2H, $CH_2CH_3$); 5.2 (br, 2H, $NH_2$); 6.50 (s, 1H, H-5); 7.7–8.0 (m, 3$H_{arom}$); 8.2–8.5 (m, 2$H_{arom}$) |

**Table 3.** (Continued)

| Product No. | Ar | R | Yield [%] | m.p. [°C] | Molecular formula[a] | I.R. (KBr) $\nu$ [cm$^{-1}$] | $^1$H-N.M.R. ($CDCl_3$) $\delta$ [ppm] |
|---|---|---|---|---|---|---|---|
| **8f** | 4-Cl—$C_6H_4$ | $CH_2CH(OC_2H_5)_2$ | 30 | 118–119° | $C_{16}H_{21}ClN_4O_2$ (336.8) | 3300, 3180, 3090, 1640, 1610 | 1.18 (t, 6H, $OCH_2CH_3$); 3.4–3.9 (m, 6H, $NCH_2$ + $OCH_2CH_3$); 4.63 (t, 1H, —CH—); 5.0 (br, 2H, $NH_2$); 5.2 (br. t, 1H, NH); 6.11 (s, 1H, H-5); 7.36 (dd, 2$H_{arom}$); 7.83 (dd, 2$H_{arom}$) |
| **8g** | $C_6H_5$ | — | 28 | 170° | $C_{14}H_{16}N_4O$ (256.3) | 3470, 3275, 3135, 1620, 1575 | 3.5–3.9 (m, 8H, morpholine $CH_2$); 4.9 (br. s, 2H, $NH_2$); 6.26 (s, 1H, H-5); 7.3–7.5 (m, 3$H_{arom}$); 7.8–8.0 (m, 2$H_{arom}$) |
| **8h** | 4-$H_3CO$—$C_6H_4$ | — | 31 | 214–215° | $C_{15}H_{18}N_4O_2$ (286.3) | 3328, 3170, 1630, 1580 | 3.5–3.8 (m, 8H, morpholine $CH_2$); 3.81 (s, 3H, $H_3CO$); 5.0 (br. s, 2H, $NH_2$); 6.20 (s, 1H, H-5); 6.90 (dd, 2$H_{arom}$); 7.83 (dd, 2$H_{arom}$) |
| **8i** | 4-Cl—$C_6H_4$ | — | 30 | 184–185° | $C_{14}H_{15}ClN_4O$ (290.8) | 3405, 3270, 3135, 1622, 1580 | 3.63 (s, 8H, morpholine $CH_2$); 6.11 (s, 1H, H-5); 7.10 (s, 4$H_{arom}$)[e] |

[a] The microanalyses were in satisfactory agreement with the calculated values (C ±0.44, H ±0.42, N ±0.39); exceptions: **8b**, C −0.46; **8h**, C −0.49.

[b] From mixture of **6a** and **6b**.

[c] M.S.: $m/e$=262 ($M^+$); Lit.[8] m.p. 305 °C.

[d] M.S.: $m/e$=296 ($M^+$, $^{35}Cl$); Lit.[8] m.p. 304 °C.

[e] In $CF_3COOH$ solution.

Method B: The *S,N*-acetals **6a–e** are prepared from the corresponding ketones, aryl or alkyl isothiocyanates, and sodium hydride according to Ref.[5,6] (Scheme C, Table 2).

**2-Amino-4-aryl-(or -alkyl)-amino-6-arylpyrimidines 8a–f; General Procedure:**

A solution of ketene *S,N*-acetal **6a–f** (0.01 mol) in absolute ethanol (10 ml) is added to a suspension of guanidine nitrate (1.22 g, 0.01 mol) and sodium ethoxide (from 0.01 mol sodium) in absolute ethanol (50 ml). The reaction mixture is then heated under reflux for 24 h and after removal of solvent under reduced pressure (water bath), the residue is diluted with ice-cold water (50 ml) and extracted with chloroform (2 × 100 ml). The chloroform layer is dried with sodium sulfate, evaporated, and the crude pyrimidines **8a–e** purified by crystallization (dichloromethane/hexane) (Table 3). The pyrimidine **8f** is obtained by column chromatography on silica gel with benzene/ethyl acetate (7:3) as eluent of the residue obtained after evaporation of chloroform.

**2-Amino-6-aryl-4-morpholinopyrimidines 8g–i; General Procedure:**

*N,N*-Morpholinoacetals **9a–c** are generated *in situ* by refluxing a solution of ketene *S,S*-acetal **5** (0.01 mol) and morpholine (0.022 mol) for 4 h in absolute ethanol (35 ml). The reaction mixture is then added to a suspension of guanidine nitrate (0.01 mol) and sodium ethoxide (from 0.01 mol sodium) in absolute ethanol (35 ml). The reaction mixture, after being refluxed for 24 h, is worked up as for **8a–f**. The crude pyrimidines are crystallized from ethanol (Table 3).

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