

CHEMISTRY OF METALLO-KETENE-*S,N*-ACETALS.NEW SYNTHESIS OF AZACYCLOALKA[2,3-*d*]PYRIMIDINES

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Abstract—— Bis-lithio-ketene-*S,N*-acetals, generated from thiolactams by treatment with *n*-BuLi, react with aryl isothiocyanates to give dithioamides. Bismethylation of the dithioamides followed by condensation with benzamidine affords the azacycloalka[2,3-*d*]pyrimidines.

The thioamide group plays an important role in synthetic methodology due to its versatility^{1,2} and has been utilized in the synthesis of many natural products.³ The carbon-carbon bond-forming reactions employing metallo-ketene-*S,N*-acetals derived from the thioamides have recently been demonstrated.⁴ There, however, have been few attempts to use metallo-ketene-*S,N*-acetals in the heterocyclic synthesis.⁵ We here describe a new synthesis of azacycloalka[2,3-*d*]pyrimidines (10a-c and 11a-c) adopting new 1,3-bis-electrophilic reagents (8 and 9) obtained by the reaction of cyclic bis-lithio-ketene-*S,N*-acetals (3 and 4) derived from thiolactams (1 and 2) with aryl isothiocyanates (5) as electrophiles followed by bismethylation.

The bis-lithio-ketene-*S,N*-acetals (3 and 4), generated from thiolactams (1 and 2) by treatment with 2 equiv. of *n*-BuLi (0°C, 1 h, THF), reacted with aryl isothiocyanates (5a-c) to afford the dithioamides (6a-c and 7a-c),⁶ respectively.⁷ Bismethylation of 6a-c and 7a-c with MeI in the presence of K₂CO₃ gave the dithioimidates (8a-c and 9a-c), respectively, which are regarded as 1,3-bis-electrophilic reagents. Compounds 8a-c and 9a-c without purification were allowed to react with benzamidine hydrochloride as bis-nucleophile in the presence of NaH (3 equiv.) [reflux, 15 h, toluene/DMF (20:1)] to provide the azacycloalka[2,3-*d*]pyrimidines (10a-c and 11a-c)⁶ of pharmacological

interest in moderate yields, respectively.

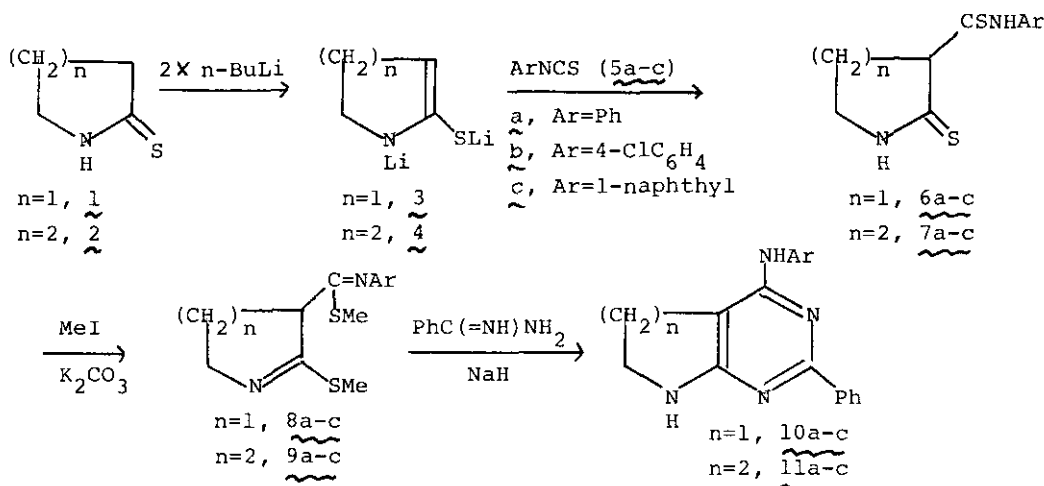


Table 1. The dithioamides (6a-c and 7a-c).

Table 2. The Azacycloalka[2,3-d]

pyrimidines (10a-c and 11a-c).

Compound	mp °C	Yield (%)
<u>6a</u>	144-146	53
<u>6b</u>	159-161	43
<u>6c</u>	138-140	58
<u>7a</u>	161-165	54
<u>7b</u>	173-176	58
<u>7c</u>	165-170	49

Compound	mp °C	Yield (%) ^a
<u>10a</u>	190-193	35
<u>10b</u>	225-229	25
<u>10c</u>	210-215	17
<u>11a</u>	146-148	25
<u>11b</u>	160-165	22
<u>11c</u>	145-150	32

a Overall yields from (6a-c and 7a-c).

Further heterocyclic synthesis employing readily available 3 and 4 is now in progress.

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6. All new compounds were fully characterized spectroscopically (IR, ¹H NMR, and MS spectral) and by combustion.
7. Attempted reaction using lithio-ketene-*S,N*-acetal, generated from cyclic thioimidate (2-methylthio-1-pyrroline) by treatment with LDA, in place of 3 gave an intractable mixture.

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