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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 K_2CO_3 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.

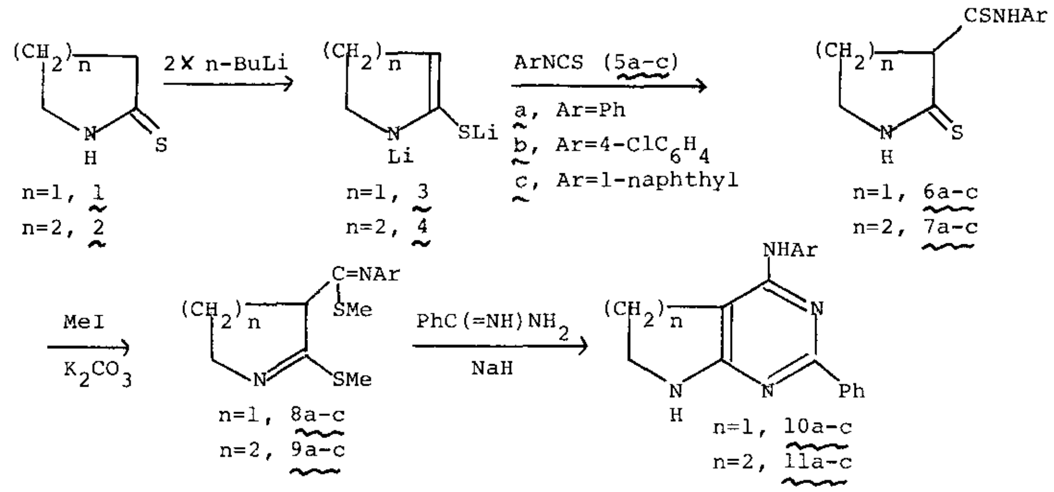

Table 1. The dithioamides (**6a-c** and **7a-c**).

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

Table 2. The Azacycloalka[2,3-*d*] pyrimidines (**10a-c** and **11a-c**).

Compound	mp °C	Yield (%)[a]
10a	190-193	35
10b	225-229	25
10c	210-215	17
11a	146-148	25
11b	160-165	22
11c	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, ^{1}H 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 of **3** gave an intractable mixture.

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