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METALLO-KETENE-S,N-ACETALS.
NEW SYNTHESIS OF AZACYCLOALKA[3,2-c]PYRIDIN-2-ONES

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Abstract - S-Lithio-ketene-S,N-actals (**3** and **4**), generated from N-methylthiolactams (**1** and **2**) with n-buthyllithium (n-BuLi), react with aryl isocyanates (**5**) to give 3-(N-arylcarbamoyl)thiolactams (**6** and **7**), which are transformed into azacycloalka[3,2-c]pyridine-2-ones (**12** and **13**), respectively, using sulfide extrusion of thioiminium salts (**8** and **9**) with malononitrile followed by cyclization.

Because of its versatility, the thioamide group has increasingly been recognized as a useful organic synthon.[1,2] Lithiated thiolactams are regarded as interesting metalated enamines, which react with a variety of electrophiles to form carbon-carbon bonds. We have exploited a new synthesis of heterocycles using lithiated thiolactams.[3,4] In this communication, we describe a new synthesis of azacycloalka[3,2-c]pyridin-2-ones by the reaction of S-lithio-ketene-S,N-acetals with aryl isocyanates as electrophiles followed by sulfide extrusion and cyclization.

S-Lithio-ketene-S,N-acetals (**3** and **4**), generated from N-methylthiolactams (**1** and **2**) with n-BuLi [-78°C, 1 h, tetrahydrofuran (THF)], react with aryl isocyanates (**5a-c**) at -78°C to room temperature to give 3-(N-arylcarbamoyl)thiolactams (**6a-c** and **7a-c**), respectively, in moderate yields. S-Methylation of **6a-c** and **7a-c** with methyl iodide in acetone followed by sulfide extrusion with malononitrile in the presence of triethylbenzylammonium chloride as a catalyst and potassium fluoride as a base in dichloromethane at room temperature for 15 h to yield enaminonitriles (**10a-c** and **11a-c**), respectively. Finally, **10a-c** and **11a-c** are cyclized by treatment with sodium ethoxide in ethanol at room temperature to yield azacycloalka[3,2-*c*]pyridin-2-ones (**12a-c** and **13a-c**) in good yields, respectively. Compounds **12a-c** and **13a-c** prepared possess *o*-aminonitriles, which may be transformed into a variety of condensed heterocycle systems, often in efficient, one step synthesis.[6] This method should be applicable to the synthesis of other pyridin-2-one derivatives by using available tertiary thioamides. The application is now in progress.

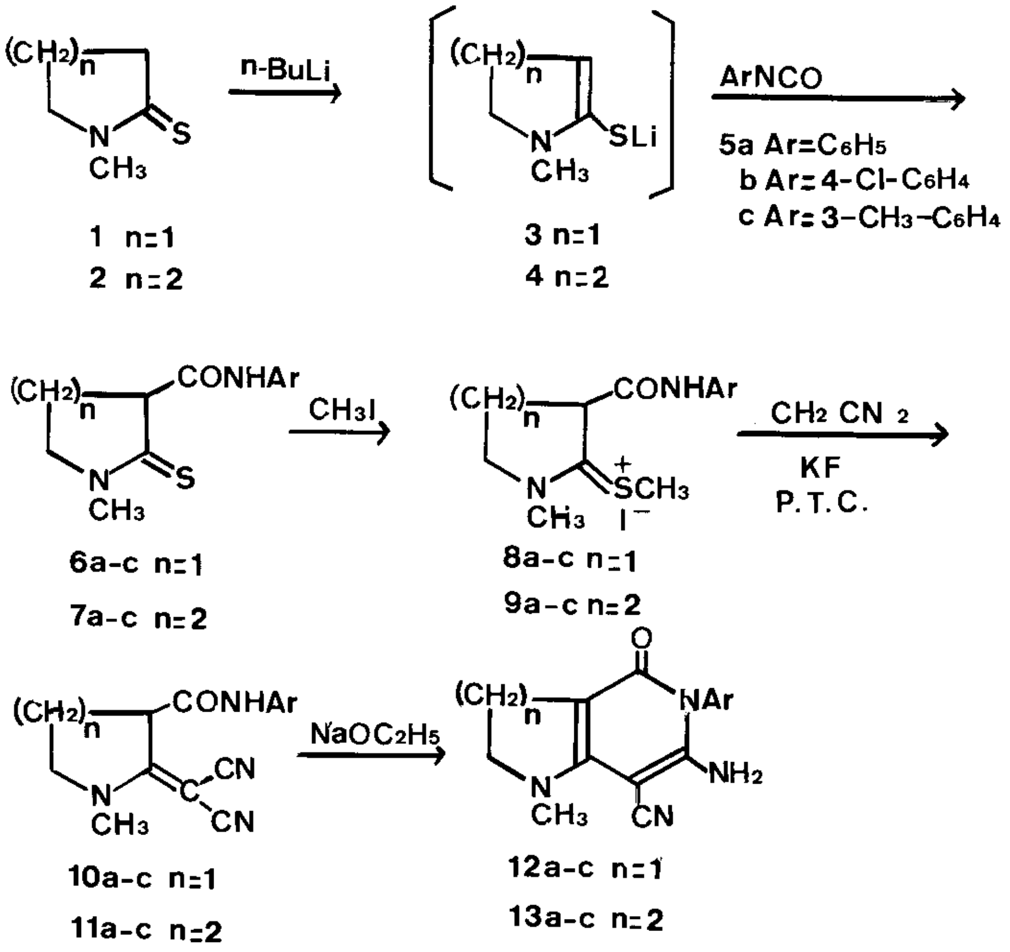

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Table 1. Compounds **6a-c** and **7a-c** prepared[6]

Product	Yield (%)	mp (^{o}C)	^{1}H-NMR ($CDCl_3$) (ppm)
6a	53	151-152	3.30 (s, 3H, N-CH_3), 10.0 (br s, 1H, NH)
6b	70	152-155	3.30 (s, 3H, N-CH_3), 10.0 (br s, 1H, NH)
6c	41	138-139	2.30 (s, 3H, Ar-CH_3), 3.20 (s, 3H, N-CH_3), 9.85 (br s, 1H, NH)
7a	70	90-94	3.50 (s, 3H, N-CH_3), 9.90 (br s, 1H, NH)
7b	96	166-167	3.46 (s, 3H, N-CH_3), 9.95 (br s, 1H, NH)
7c	43	159-160	2.30 (s, 3H, Ar-CH_3), 3.50 (s, 3H, N-CH_3), 9.85 (br s, 1H, NH)

Table 2. Compounds **10a-c** and **11a-c** prepared[6]

Product	Yield[a] (%)	mp (^{o}C)	^{1}H-NMR ($CDCl_3$) (ppm)
10a	62	166-168	3.31 (s, 3H, N-CH_3), 8.85 (br s, 1H, NH)
10b	86	188-190	3.45 (s, 3H, N-CH_3), 8.70 (br s, 1H, NH)
10c	64	154-155	2.26 (s, 3H, Ar-CH_3), 3.40 (s, 3H, N-CH_3), 8.80 (br s, 1H, NH)
11a	80	216-200	3.50 (s, 3H, N-CH_3), 8.80 (br s, 1H, NH)
11b	70	217-221	3.53 (s, 3H, N-CH_3), 8.75 (br s, 1H, NH)
11c	62	160-163	2.20 (s, 3H, Ar-CH_3), 3.50 (s, 3H, N-CH_3), 8.60 (br s, 1H, NH)

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

Table 3. Compounds **12a-c** and **13a-c** prepared[6]

Product	Yield (%)	mp (^{o}C)	^{1}H-NMR ($CDCl_3$) (ppm)
12a	84	293-296	3.20 (s, 3H, N-CH_3), 4.90 (br s, 2H, NH2)
12b	76	300>	3.20 (s, 3H, N-CH_3), 6.05 (br s, 2H, NH2)
12c	99	269-273	2.61 (s, 3H, Ar-CH_3), 3.20 (s, 3H, N-CH_3), 4.90 (br s, 2H, NH2)
13a	95	236-239	3.24 (s, 3H, N-CH_3), 4.95 (br s, 2H, NH2)
13b	98	300>	3.31 (s, 3H, N-CH_3), 4.85 (br s, 2H, NH2)
13c	74	225-227	2.38 (s, 3H, Ar-CH_3), 3.28 (s, 3H, N-CH_3), 4.80 (br s, 2H, NH2)

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6. All new compounds had satisfactory elemental analyses.

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