Communications to the Editor

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KETENE-S,N-ACETALS AS SYNTHETIC INTERMEDIATES FOR HETEROCYCLES. A NOVEL SYNTHESIS OF POLYFUNCTIONALIZED PYRIDINE-2-THIONES[1)]

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A new synthesis of polyfunctionalized pyridine-2-thiones (4a-c) by the carbon-carbon bond formation between β-aminothiocarbonyl-α-methylthioenamines (3a-c) derived from ketene-S,N-acetal (1) and malononitrile as a carbon nucleophile is described. In addition, the reaction of the dianiones (6a-c), prepared from the enaminonitriles (5a-c) and n-BuLi *in situ*, with alkyl halides (7, 8, and 9) was found to give 3-alkylpyridine-2-thiones (10a-c, 11a-c, and 12a-c) in good yields, respectively.

KEYWORDS——— ketene-S,N-acetal; thioamide; enamine; pyridine-2-thione; carbon-carbon bond formation; o-aminonitrile; thioamide dianion

We have been interested in exploring the synthetic utility of ketene-S,N-acetal as the intermediates for hetericyles.[2)] Enamines are important synthetic intermediates and their utility for organic synthesis is well documented.[3)] Ketene-S,N-acetals derived from tertiary thioamides are α-alkylthio substituted enamines. It is known that they react with a variety of electrophiles.[4)] The reaction of ketene-S,N-acetals with aryl isothiocyanates as electrophiles gives 1:1 adducts which are interesting β-aminothiocarbonyl-α-methythioenamines having the character that the α-methylthio substituent is readily replaced by nucleophiles such as amines.[2d)] We wish to report here a novel synthesis of polyfunctionalized pyridine-2-thiones by the carbon-carbon bond formation between β-aminothiocarbonyl-α-methylthioenamines and malononitrile as a carbon nucleophile.

Adding aryl isothiocyanates (2a-c) to ketene-S,N-acetal (1) in ether at room temperature gave the β-aminothiocarbonyl-α-methylthioenamines (3a-c)[5)] in high yields.[6)] The reaction of 3a-c with malononitrile in boiling ethanol

solution in the presence of sodium ethoxide resulted in the formation of pyridine-2-thiones (4a-c)[5] in good yields.

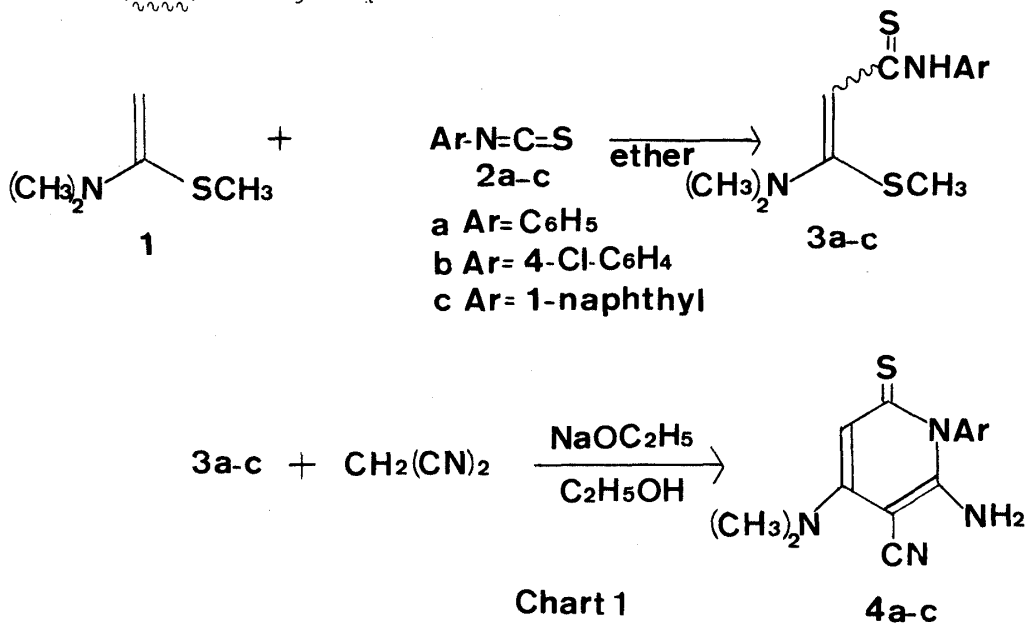

Chart 1

The reaction of 3a-c with malononitrile in acetonitrile without base afforded enaminonitriles (5a-c)[5] in satisfactory yields at room temperature. Subsequently, 5a-c were treated with sodium ethoxide to provide the same pyridine-2-thiones (4a-c) directly obtained from 3a-c. In addition, the alkylation at the carbon atom α to the thiocarbonyl group of dilithio ketene-S,N-acetals (6a-c), generated from 5a-c by treatment with two equivalents of n-BuLi, with one equivalent of alkyl halides (7, 8, and 9) as electrophiles followed by the ring closure produced 3-alkylpyridine-2-thiones (10a-c, 11a-c, and 12a-c)[5] respectively in excellent yields.[7] A general procedure for the synthesis of 10a-c, 11a-c, and 12a-c is as follows: To a solution of 5 (1 mmol) in THF (3 ml) was added n-BuLi (1.47 ml of 1.5 M n-hexane, 2.2 mmol) at -78°C. After stirring the mixture at the same temperature for 0.5 h, alkyl halide (1.1 mmol) was added to this mixture. The reaction mixture was stirred for 1 h, during which time the temperature was elevated to the room temperature, and then the stirring was continued for 1 h. The reaction was quenched with saturated NH_4Cl solution and the usual work-up gave the desired product (10a-c, 11a-c, or 12a-c).

Pyridine-2-thiones (4a-c, 10a-c, 11a-c, and 12a-c) thus prepared possess polyfunctional substituent groups and among them o-aminonitriles especially may be transformed into a variety of the condensed heterocyclic systems,[8] which are of special biological and pharmacological interest as partial components of

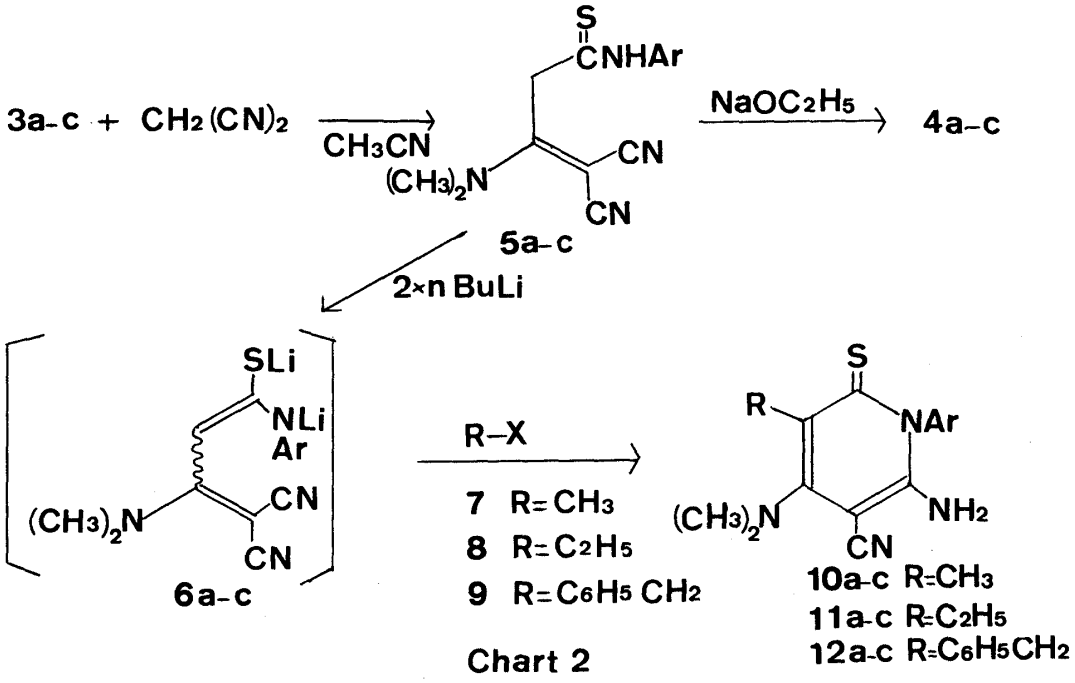

Chart 2

Table

Product	Yield (%)	mp,(°C)	^{1}H-NMR ($CDCl_3$)
4a	82[a] (98)[b]	230-232	6.61 (1H, s, C_3-H)
4b	80[a] (85)[b]	220-221	6.63 (1H, s, C_3-H)
4c	86[a] (84)[b]	329-330	6.88 (1H, s, C_3-H)
5a	82	119-121	4.10 (2H, s, CH_2)
5b	83	138-140	4.07 (2H, s, CH_2)
5c	89	146-148	4.07 (2H, s, CH_2)
10a	84	184-186	2.32 (3H, s, C_3-CH_3)
10b	89	223-225	2.33 (3H, s, C_3-CH_3)
10c	89	194-196	2.33 (3H, s, C_3-CH_3)
11a	85	172-174	1.26 (3H, t, J=7.5Hz, $CH_2\underline{CH_3}$)
			2.76 (2H, q, J=7.5Hz, $\underline{CH_2}CH_3$)
11b	94	167-169	1.30 (3H, t, J=8Hz, $CH_2\underline{CH_3}$)
			2.78 (2H, q, J=8Hz, $\underline{CH_2}CH_3$)
11c	99	213-215	1.18 (3H, t, J=7Hz, $CH_2\underline{CH_3}$)
			2.78 (2H, q, J=7Hz, $\underline{CH_2}CH_3$)
12a	88	212-215	4.07 (2H, s, C_6H_5-$\underline{CH_2}$)
12b	90	118-120	4.02 (2H, s, C_6H_5-$\underline{CH_2}$)
12c	91	133-135	3.90 (2H, s, C_6H_5-$\underline{CH_2}$)

a) Yield from 3 to 4. b) Yield from 5 to 4.

antibiotics and chemotherapeutics. The reaction of 3a-c with another carbon nucleophile is now in progress.

REFERENCES AND NOTES

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2) a) H. Takahata, A. Tomiguchi, M. Nakano, and T. Yamazaki, Synthesis, 1982, 156.
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d) H. Takahata, T. Nakajima, and T. Yamazaki, ibid., 1983, 226.
e) Idem., ibid., in press.

3) Reviews: P. W. Hickmott, Tetrahedron, 38, 1975 and 3363 (1982).

4) a) R. Gompper and W. Elser, Justus Liebigs Ann. Chem., 725, 73 (1969).
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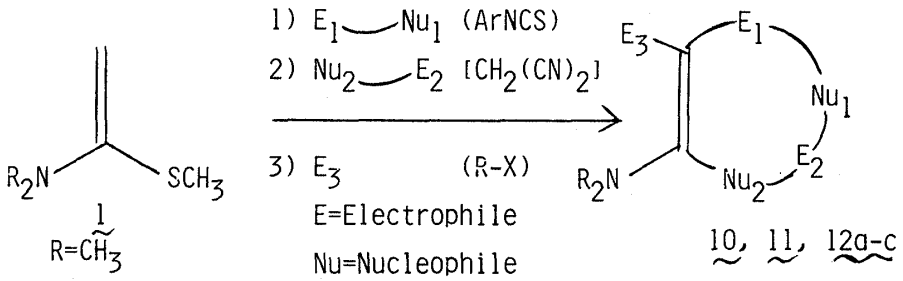
5) All new compounds were fully characterized spectroscopically (IR, ^{1}H-NMR, MS spectral) and by combustion and /or high resolution mass spectral analyses.

6) The details of preparation will be described in full papers.

7) This reaction is formulated as shown below



8) E. C. Taylor and A. McKillop "o-Aminonitriles," in E. C. Taylor (ed.), The Chemistry of Cyclic Enaminonitriles and o-Aminonitriles," Chapter II, in the series "Advances in Organic Chemistry: Methods and Results," 1970, p.79.

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