# Synthesis of Pyridines from Dicyanopyrimidines. A Diels-Alder Approach to the C-Ring of Streptonigrin (1)



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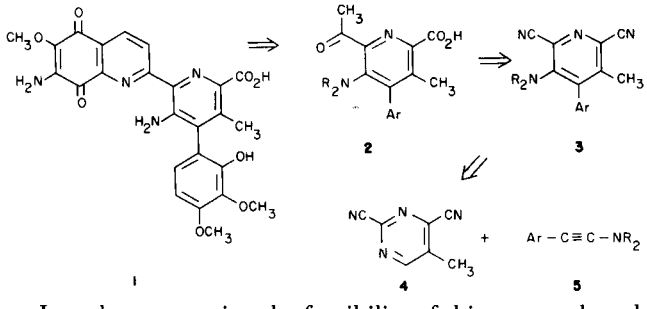
Received February 6, 1980

The reaction of dicyanopyrimidines with yneamines gave pyridines which could potentially serve as precursors to analogs of streptonigrin.

*J. Heterocyclic Chem.*, **17**, 1111 (1980).

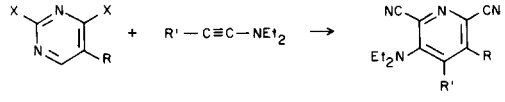
Streptonigrin (**1**), an antitumor antibiotic, has been the focus of considerable synthetic effort (2). However, the total synthesis of this challenging structure has yet to be achieved primarily because of problems associated with the preparation of the penta-substituted pyridine C-ring.

The Diels-Alder reaction of electron deficient pyrimidines with yneamines to give pyridines (3) could serve as a potential regioselective route to the preparation of pyridine C-ring precursors to streptonigrin and analogs thereof. Methodology exists for synthesizing streptonigrin (**1**) from acetyl pyridine **2** (2). Pyridine **2** should be accessible from dicyanopyridine **3**, which in turn would be the expected Diels Alder product of the reaction of pyrimidine **4** and yneamine **5**.



In order to examine the feasibility of this approach and to investigate the Diels-Alder reactivity of dicyanopyrimidines, a model study was initiated. Two dicyanopyrimidines, **4** and **6**, were prepared for use in the model reactions with yneamines. Dichloropyrimidine **7**, which is readily available from thymine (4) gave upon treatment with sodium cyanide and trimethylamine in a mixture of ether and water a 33% yield of 2,4-dicyano-5-methylpyrimidine (**4**). 2,4-Dicyanopyrimidine (**6**) was prepared in 6% yield from dichloropyrimidine **8** by treatment with sodium cyanide in dimethyl sulfoxide (5).

Pyrimidine **6** upon reaction at 22° with l-diethylamino-l-propyne (**9**) and l-diethylamino-2-phenylacetylene (**10**) (6) gave pyridines **11** and **12**, in 97% and 20% yields, respectively. The more hindered pyrimidine **4** reacted with propyne **9** in refluxing tetrahydrofuran to produce pyridine **13** in 36% yield. Presumably because of increased steric interactions, the reaction of pyrimidine **4** with phenylacetylene **10** led only to decomposition of the pyrimidine instead of forming pyridine **14**.



| | | | | | % Yield |
|---|---|---|---|---|---|
| **4**; R=$CH_3$, | X=CN | **9**; R'=$CH_3$ | **11**; R=H, | R'=$CH_3$ | 97 |
| **6**; R=H, | X=CN | **10**; R'=$C_6H_5$ | **12**; R=H, | R'=$C_6H_5$ | 20 |
| **7**; R=$CH_3$, | X=Cl | | **13**; R=$CH_3$, | R'=$CH_3$ | 36 |
| **8**; R=H, | X=Cl | | **14**; R=$CH_3$, | R'=$C_6H_5$ | 0 |

In summary, the dicyanopyrimidines exhibit moderate reactivity toward yneamines and as a result provide a short regioselective pyridine synthesis. Present efforts are being directed toward an examination of methods for differentiating the two cyano groups of pyridines **11**, **12**, and **13**, thereby allowing for the efficient preparation of analogs of streptonigrin. Although pyridines of type **14** could probably be prepared by performing the cycloaddition reaction under ultra high pressure, a more practical approach to the synthesis of stereptonigrin utilizing triazines instead of dicyanopyrimidines is currently being studied. Since triazines are more electron deficient than pyrimidines, they exhibit greater reactivity in Diels-Alder reactions with inverse electron demand. The results of these further investigations will be communicated in due course.

## EXPERIMENTAL

Nuclear magnetic resonance spectra (nmr) were recorded on a Varian A-60 spectrometer, from samples dissolved in deuteriochloroform with tetramethylsilane as an internal standard. Mass spectra (ms) were recorded on an Atlas CH-4 spectrometer operating in the direct inlet mode. Spectroscopic data and elemental analyses were obtained by the Syntex Analytical Research Division. Melting points were determined on a Fisher-Johns apparatus and are uncorrected. 2,4-Dichloropyrimidine and l-diethylamino-l-propyne were purchased from Aldrich and Chemical Samples Co., respectively.

2,4-Dicyano-5-methylpyrimidine (**4**).

A solution of dichloropyrimidine **7** (6.4 g.) in ether (50 ml.) was vigorously stirred for 25 minutes with a solution of sodium cyanide (5.3 g.) in 25% aqueous trimethyl amine (40 ml.). The resulting black solution was extracted with three portions of ether. The combined organic phases were dried over sodium sulfate and concentrated. Column chromatography eluting with 1:5 ethyl acetate/hexane afforded in order of elution 3.6 g. (54%) of dichloropyrimidine **7**, 0.42 g. (7%) of a monosubstitution product, and 1.86 g. (33%) of the dicyanopyrimidine **4**. Pyrimidine **4** was crystallized from ethyl acetate/hexane, m.p. 67-68°;nmr: δ 8.97 (singlet, 1H), 2.68 (singlet, 3H); ms: $M^+$ 144.

*0022-152X/80/051111-02$02.25*

*Anal.* Calcd. for $C_7H_4N_4$: C, 58.33; H, 2.80; N, 38.87. Found: C, 58.35; H, 2.86; N, 38.93.

2,4-Dicyanopyrimidine (**6**).

To a solution of sodium cyanide (0.98 g.) in dimethyl sulfoxide (50 ml.) under argon was added a solution of dichloropyrimidine **8** (3.35 g.) in dimethyl sulfoxide (5 ml.). After 45 minutes, the resulting black solution was taken up in ether, washed with three portions of water then with brine, dried over sodium sulfate and concentrated. Column chromatography eluting with a gradient of 1:9 to 2:8 ethyl acetate/hexane afforded in order of elution 1.38 g. (41%) of dichloropyrimidine **8**, 0.37 g. (12%) of a monosubstitution product, and 0.17 g. (6% of the desired dicyanopyrimidine **6**.Pyrimidine **6** was sublimed at 50°/0.05 torr to give a white solid, m.p. 112-113°;nmr: δ 9.10 (doublet, J = 5 Hz., 1H), 7.84 (doublet, J = 5 Hz., 1H); ms: $M^+$ 130.

*Anal.* Calcd. for $C_6H_2N_4$: C, 55.39; H, 1.55; N, 43.06. Found: C, 55.21; H, 1.40; N, 43.26.

2,6-Dicyano-3-(*N,N*-diethylamino)-4-methylpyridine (**11**).

Dicyanopyrimidine **6** (31.8 mg.) was added with stirring to aminopropyne **9** (0.27 g.). After 30 minutes, the black mixture was taken up in methylene chloride, washed with saturated aqueous sodium bicarbonate, dried over sodium sulfate, and concentrated. Preparative thin-layer chromatography eluting with 3:7 ethyl acetate/hexane afforded 50.7 mg. (97%) of dicyanopyridine **11**. Crystallization was effected from ethyl acetate/hexane, m.p. 133-135°; nmr: δ 7.61 (singlet, 1H), 3.39 (quartet, J = 7 Hz., 4H), 2.38 (singlet, 3H), 1.12 (triplet, J = 7 Hz., 6H); ms: $M^+$ 214.

*Anal.* Calcd. for $C_{12}H_{14}N_4$: C, 67.27; H, 6.59; N, 26.15. Found: C, 67.07; H, 6.71; N, 26.18.

2,6-Dicyano-3-(*N,N*-diethylamino)-4-phenylpyridine (**12**).

Dicyanopyridine **6** (66.4 mg.) was added with stirring to acetylene **10** (0.15 g.) under argon. After 1.5 hours, the black oil was taken up in ether, washed with water, 10% hydrochloric acid, saturated aqueous sodium bicarbonate, and brine, dried over sodium sulfate, and concentrated. Preparative thin-layer chromatography eluting with 2:8 ethyl acetate/hexane afforded 27.6 mg. (20%) of pyridine **12**. Crystallization was effected from ethyl acetate/hexane, m.p. 97-98°; nmr: δ 7.52 (singlet, 1H), 7.43 (singlet, 5H), 3.15 (quartet, J = 7 Hz., 4H), 1.04 (triplet, J = 7 Hz., 6H); ms: $M^+$ 276.

*Anal.* Calcd. for $C_{17}H_{16}N_4$: C, 73.89; H, 5.84; N, 20.27. Found: C, 73.93; H, 5.79; N, 20.38.

2,6-Dicyano-3-(*N,N*-diethylamino)-4,5-dimethylpyridine (**13**).

A solution of dicyanopyrimidine **4** (101 mg.) and propyne **9** (123 mg.) in dry tetrahydrofuran (2 ml.) was heated at reflux under argon for 3 hours. The solution was then diluted with ether, washed with water then brine, dried over sodium sulfate, and concentrated. Preparative thin-layer chromatography afforded 56.9 mg. (36%) of pyridine **13**. Sublimation at 100°/0.05 torr gave a white solid, m.p. 62-63°; nmr: δ 3.38 (quartet, J = 7 Hz., 4H), 2.55 (singlet, 3H), 2.32 (singlet, 3H), 1.09 (triplet, J = 7 Hz., 6H); ms: $M^+$ 228.

*Anal.* Calcd. for $C_{13}H_{16}N_4$: C, 68.39; H, 7.06; N, 24.54. Found: C, 68.00; H, 7.07; N, 24.51.

Acknowledgment.

The author appreciates helpful discussions with Dr. Joseph M. Muchowski and Dr. Ian S. Cloudsdale.

## REFERENCES AND NOTES

(1) Contribution no. 540 from the Institute of Organic Chemistry.

(2a) K. V. Rao and H. S. Kuo, *J. Heterocyclic Chem.*, **16**, 1241 (1979); (b) P. J. Wittlek, T. K. Liao, and C. C. Cheng, *J. Org. Chem.*, **44**, 870 (1979); (c) A. S. Kende and P. C. Naegly, *Tetrahedron Letters*, 4775 (1978); (d) D. Kim and S. M. Weinreb, *J. Org. Chem.*, **43**, 121, 125 (1978); (e) S. Hibino and S. M. Weinreb, *ibid.*, **42**, 232 (1977); (f) and for a review see S. Hibino, *Heterocycles*, **6**, 1485 (1977).

(3) H. Neunhoeffer and G. Werner, *Ann. Chem.*, 1190 (1974).

(4) W. Schmidt-Nickels and T. B. Johnson, *J. Am. Chem. Soc.*, **52**, 4511 (1930).

(5) The reactions of sodium cyanide with dichloropyrimidines **7** and **8** were stopped at low conversion because longer reaction times resulted in decomposition of the products, dicyanopyrimidines **4** and **6**.

(6) H. G. Viehe and M. Reinstein, *Angew. Chem., Int. Ed. Engl.*, **3**, 506 (1964).