Pergamon

Tetrahedron Letters, Vol. 37, No. 7, pp. 1007-1010, 1996

0040-4039/96 $15.00 + 0.00

0040-4039(95)02362-3

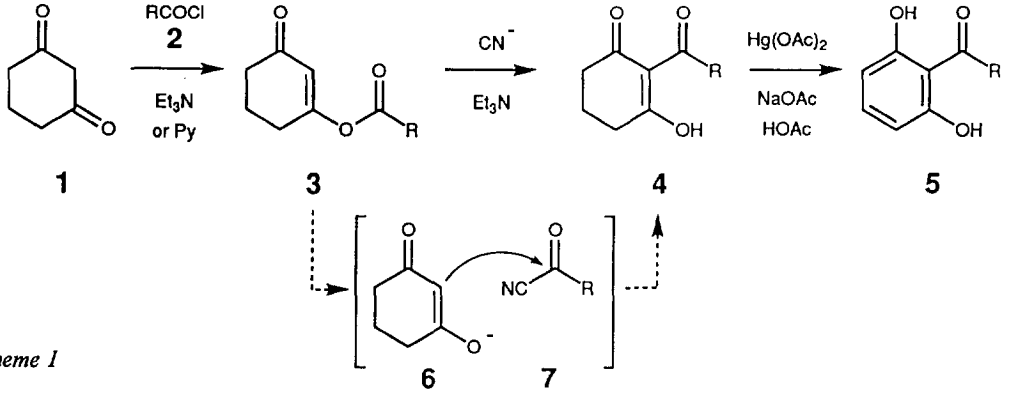
The Cyanide Catalyzed Isomerization of Enol Esters Derived from Cyclic 1,3-Diketones.

By Imber Flores Montes and Ulrich Burger*

Département de Chimie Organique,
Université de Genève
30, quai Ernest Ansermet, CH-1211 Genève 4, Switzerland.

Abstract. Cross-over experiments unveil that the mechanism of the title reaction consists in cleavage of enol esters by cyanide with transient formation of acyl cyanides. These react as 'soft' C-acylating agents with the enolates freed in the initial step. Use is made of the acyl cyanide derived from pyrrole-2-carboxylic acid to set up the triketide type skeleton **12** of the antibiotic pyoluteorin **16**. The aromatization of **12** with mercuric acetate gave the pyrrolo[a]indolone **18**.

The antibiotic pyoluteorin **16**, a secondary metabolite of various species of P*seudomonas*, is a well documented example of the naturally occurring 2-acyl resorcinols.[1] We were interested, in connection with our studies on the suppression of root diseases by *P. fluorescens*,[2] in devising a simple, efficient synthesis of **16**. Nearly all the known preparations of **16** exploit benzoylation of an appropriate pyrrole precursor.[3] However, the methods entail multiple protection/deprotection steps and give modest yields. An alternative approach [4c] for synthesizing **16** would be to exploit the base-catalyzed reaction of an acyl chloride **2** with cyclohexane-1,3-



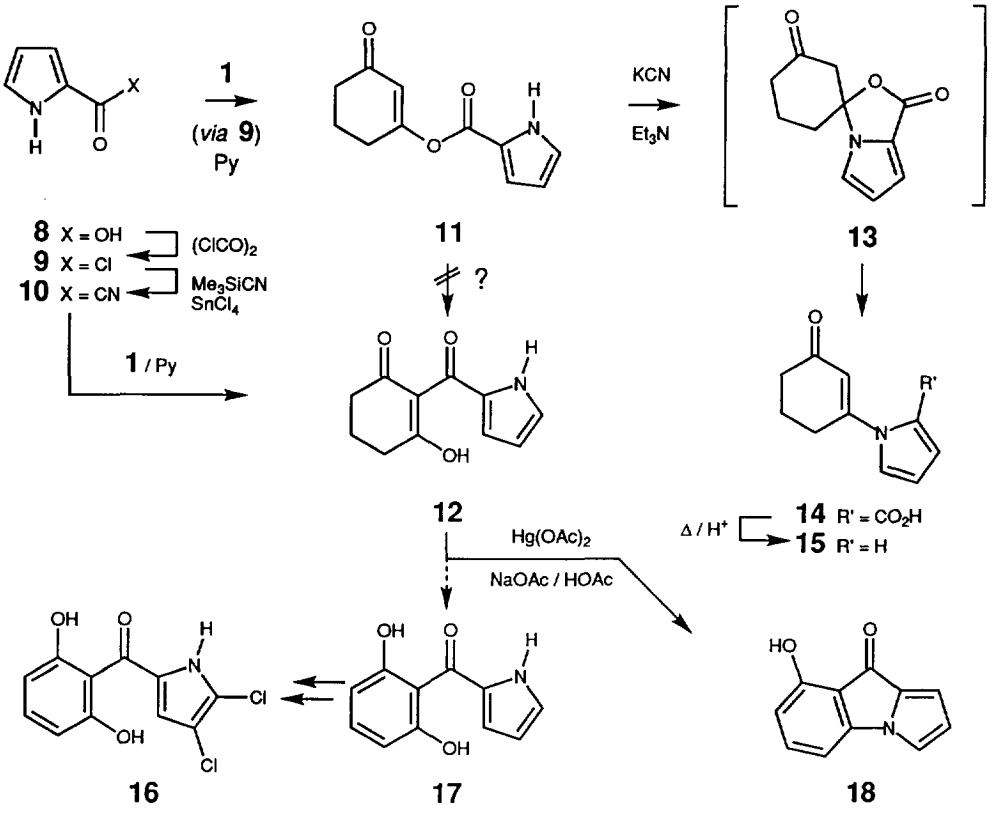
Scheme 1

dione **1** (scheme 1). The first event is O-acylation to give **3**, which on treatment with cyanide ion and base[5] rearranges to the C-acyl isomer **4**.[6] Oxidation of the latter gives **5** the desired 2-substituted resorcinol, which has relevance to polyketide chemistry[7] and of course to various biologically active products such as **16**.

When pyrrole-2-carbonyl chloride (**9**)[8] was used in this sequence the reaction unexpectedly took another course. The acylation of **1** proceeded normally and gave the O-acylated product **11**. However, subsequent

rearrangement with triethylamine and potassium cyanide failed to give the C-acylated product **12**. Instead, the carboxylic acid **14** and its decarboxylation product **15** were obtained.[4c] This result can be interpreted in terms of the intermediate spirocyclic lactone **13** which then opens to **14** (scheme 2).

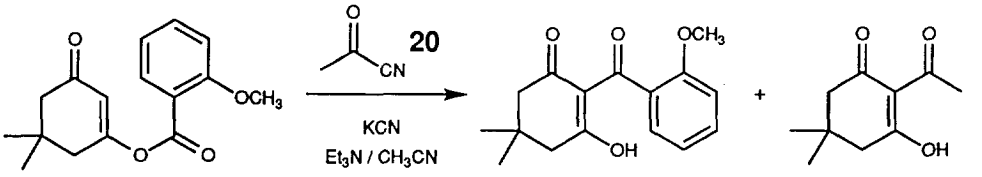
Scheme 2



We tried to modify the above approach in order to circumvent the undesired spirocyclization. The seemingly obvious solution to the problem, *i.e.* N-protection of the intermediate enol ester **11** turned out to be impractical. Nearly all protection protocols of pyrroles[9] involve treatment with base and, under these conditions spirocyclization invariably occurred. We therefore decided to examine the mechanistic details of the cyanide-catalyzed rearrangement **3**→**4**. Of the conceivable pathways, initial attack by cyanide at the carboxylic C-atom of **3** with cleavage of the enol ester and concomitant formation of an acyl cyanide (**7**)[10] seemed the most plausible. Confirmation of this idea was obtained by crossing experiments with an external acyl cyanide. Thus, the enol ester **19** derived from 5,5-dimethylcyclohexane-1,3-dione, [11, 12] when allowed to react in 1M acetonitrile solution with KCN in presence of an equivalent of pyruvonitrile **20**, gave the normal C-acylation product **21**[13] together with the C-acetyl counterpart **22** in a 3:1 ratio. Moreover, when the ester **3** (R = CH_3) was treated in 1M acetonitrile solution with KCN/NEt_3 in the presence of 5,5-dimethylcyclohexane-1,3-dione,

the normal C-acylation product **4** (R = CH_3) and **22** were obtained, again in a 3:1 ratio. Preferred recombination within the primary solvent cage accounts for these proportions. [14]

Scheme 3



19 **21** **22**

These findings provided the key for tackling the assembly of the triketone **12**. To this end, we prepared the acyl cyanide **10** by treating chloride **9** with trimethylsilyl cyanide in the presence of tin(IV) chloride.[15] When **10** was allowed to react with **1** in the presence of NEt_3, the desired C-acylation product **12** was obtained directly in 78 % yield.[16] Much to our surprise, the seemingly trivial aromatization of **12** into the resorcinol **17**, a known precursor to pyoluteorin **16**,[3a] could not be achieved. The use of mercuric acetate, following a standard protocol for synthesizing resocinols, [4a, 4b] gave 7-hydroxy-3a-azacyclopenta[a]inden-8-one (**18**) in 85 % yield.[17] Successive treatment of **12** with isopropenyl acetate and DDQ[18] in a one-pot procedure, was not efficient, affording **17** in only 18% yield. Our studies, although they did not lead to an economical synthesis of pyoluteorin, demonstrate the usefulness of cyanide catalysis and the role of acyl cyanides in the acylation of enolates. Clearly such reactions will prove to be useful in polyketide chemistry.

Acknowledgments. We thank the Swiss National Science Foundation for support of this work (grant no. 20-39'247.93).

References and Notes

1) a) A.J. Birch, P. Hodge, R.W. Richards, R. Takeda, T.R. Watson, *J. Chem. Soc.*, **1964**, 2641-2644; b) D.A. Cuppels, C.R. Howell, R.D. Stipanovic, A. Stoessel, J.B. Stothers, *Z. Naturforsch.* **1986**, *41c*, 532-536.

2) a) C. Keel, P. Wirthner, T. Oberhänsli, C. Voisard, U. Burger, D. Haas, G. Défago, *Symbiosis,* **1990**, *9*, 327-341. b) C. Keel, U. Schnider, M. Maurhofer, C. Voisard, J. Laville, U. Burger, P. Wirthner, D. Haas, G. Défago, *Molecular Plant-Microbe Interactions,* **1992**, *5*, 4-13.

3) a) B.W. Cue, Jr., J.P. Dirlam, L.J. Czuba, W.W. Windisch, *J. Heterocyclic Chem.* **1981**, *18*, 191-192. b) D.M. Bailey, R.E. Johnson, U.J. Salvador, *J. Med. Chem.* **1973**, *16*, 1298-1300.

4) a) J.E. Oliver, W.R. Lusby, *Tetrahedron* **1988**, *44*, 1591-1596; b) J.E. Oliver, K.R. Wilzer, R.M. Waters, *Synthesis* **1990** , 1117-1119; c) J.E. Oliver, W.R. Lusby, *J. Heterocyclic Chem.* **1991**, *28*, 1565-1568.

5) a) C.G. Carter, *Eur. Pat. E.P.* **1986**, 186 118 (C.A. **1986**, *105*, 133519j); b) C . Knudsen, *Eur. Pat. E.P.* **1988**, 249 150 (C.A. **1988**, *109*, 6219); c) In a typical experiment, a solution of 10 mmol of **3** (R = alkyl), 3 ml of triethylamine, 10 mg of potassium cyanide (or 100 ml of acetone cyanohydrin) in 25 ml of acetonitrile was stirred for 12 h at room temperature. The solution was concentrated *in vacuo* and the residue was partitioned between ethyl acetate and 1N hydrochloric acid (hood: HCN!). The triketone **4** was then extracted from the organic layer into aqueous sodium bicarbonate. Neutralization and extraction with ether gave, after drying and concentration, the crude product that was chromatographed.

6) Review: T. H. Black 'Recent Progress in the Control of Carbon versus Oxygen Acylation of Enolate Anions' *Organic Preparations and Procedures* (Newton Highlands, MA) **1989**, *21*, 179-217.

7) D. O'Hagan, 'The Polyketide Metabolites' Ellis Horwood, New York, **1991**.

8) R.J. Boatman, H.W. Whitlock, *J. Org. Chem.* **1976,** *41,* 3050-3051.
9) P.J. Kocienski, 'Protecting Groups', Georg Thieme Verlag, Stuttgart 1994. b) T.W. Greene, P.G.M. Wuts, 'Protective Groups in Organic Synthesis' (second edition), John Wiley, New York, 1991.
10) a) Review: S. Hünig, R. Schaller, *Angew. Chem. Int.Ed.*. **1982,** *21,* 36-49; b) A. Dornow, H. Grabhöfer, *Chem. Ber.* **1958,** *91,* 1824-1929.
11) All new compounds gave correct elemental analyses and mass, IR, ^{1}H-NMR, and ^{13}C-NMR spectra consistent with the structures indicated.
12) compd. **19**: colorless crystals m.p. 55-57°. ^{1}H-NMR ($CDCl_3$, 200 MHz): 1.12 (s, 6H); 2.29 (s, 2H); 2.53 (d, J = 1.3, 2H); 3.90 (s, 3H); 5.98 (t, J = 1.3, 1H); 7.0 (m, 2H); 7.54 (m, 1H); 7.87 (dd, J = 7.9, 1.9, 1H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 28.2 (q); 33.3 (s); 42.3 (t); 50.9 (t); 56.0 (q); 112.2 (d); 116.8 (s); 117.9 (s); 120.2 (d); 132.3 (d); 135.0 (d); 160.2 (s); 162.3 (s); 168.8 (s); 199.4 (s).
13) compd. **21**: ^{1}H-NMR ($CDCl_3$, 200 MHz): 1.12 (s, 6H); 2.30 (s, 2H); 2.58 (s, 2H); 3.73 (s, 3H); 6.85 (d, J = 8.3, 1H); 7.0 (td, J = 7.5, 0.9, 1H); 7.5-7.3 (m, 2H); 17.07 (s, OH). ^{13}C-NMR ($CDCl_3$, 50 MHz): 28.2 (q); 30.9 (s); 45.9 (t); 51.7 (t); 55.4 (q); 110.7 (d); 114.1 (s); 120.6 (d); 128.2 (d); 128.9 (s); 132.0 (d); 156.5 (s); 193.7 (s); 193.8 (s); 196.4 (s).
14) Note: Simple enol esters derived from monoketones do not react in analogous fashion. Normally, they are not cleaved by cyanide.
15) G.A. Olah, M. Arvanaghi, G.K. Surya Prakash, *Synthesis*, **1983**, 636-637.
16) compd. **12**:, colorless crystals m.p. 69-71°.C ^{1}H-NMR ($CDCl_3$, 400 MHz): 2.03 (m, 2H); 2.66 (m, 2H); 2.73 (m, 2H); 6.42 (m, 1H); 7.18 (m, 1H); 7.48 (m, 1H); 13.7 (NH); 19.4 (OH). ^{13}C-NMR ($CDCl_3$, 100 MHz): 19.0 (t); 36.2 (t); 39.7 (t); 110.5 (s); 112.5 (d); 122.1 (d); 126.8 (d); 128.3 (s); 179.3 (s); 197.1 (s); 204.1 (s).
17) compd. **18**: yellow crystals m.p. 103-105 °. ^{1}H-NMR ($CDCl_3$, 400 MHz): 6.29 (m, 1H); 6.61 (m, 2H); 6.75 (m, 1H); 7.08 (m, 1H); 7.28 (t, J = 7.7, 1H); 8.18 (s, OH). ^{13}C-NMR ($CDCl_3$, 100 MHz): 102.4 (d); 114.1 (d); 114.3 (s); 114.6 (d); 115.9 (d); 120.6 (d); 131.5 (s); 136.5 (d); 143.0 (s); 156.9 (s); 182.0 (s).
18) a) A. Bohac, P. Hrnciar, *Synthesis,* **1991,** 881-882; b) Review: D. Walker, J.D. Hiebert, *Chem. Rev.* **1967,** *67,* 153-155.

(*Received in France* 16 *October* 1995; *accepted* 11 *December* 1995)