

"NAKED" CYANIDE-ACETONE CYANOHYDRIN:

A SIMPLE, EFFICIENT AND STEREOSELECTIVE HYDROCYANATING REAGENT.

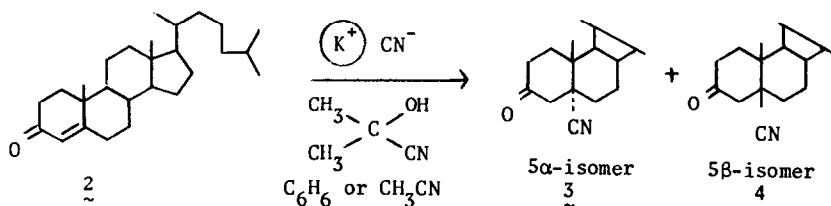
Charles L. Liotta*, A. M. Dabdoub and L. H. Zalkow

School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332

(Received in USA 16 September 1976; received in UK for publication 16 February 1977)

The conjugate hydrocyanation of α,β -unsaturated carbonyl systems has been subject to intensive investigation during the past two decades. The reported methods involving (a) KCN in aqueous alcohol¹, (b) KCN and NH_4Cl in aqueous DMF² and (c) $\text{Ca}(\text{CN})_2$ in N-methylpyrrolidone³, however, suffer from a number of disadvantages. These include undesirable side reactions such as hydrolysis, dimerization and competitive 1,4-addition of protic solvents, poor stereoselectivity and poor efficiency. Nagata and co-workers^{2a,4} have recently described the use of alkyl aluminum cyanide reagents which are not wrought with the aforementioned difficulties. Nevertheless, these reagents are pyrophoric and do require extremely careful handling. It has been recently reported that cyanide ion, solubilized as its potassium salt in non-polar or dipolar aprotic solvents containing 18-crown-6, 1, ("naked" cyanide), is a useful nucleophilic species for introducing a carbon functionality into a wide variety of organic and inorganic substrates by simple addition or displacement processes.⁵ This Communication reports the use of this reagent in conjunction with acetone cyanohydrin as a new stereospecific hydrocyanating reagent for α,β -unsaturated carbonyl systems.

In the presence of acetone cyanohydrin, "naked" cyanide undergoes stereoselective Michael addition to Δ^4 -cholesten-3-one, 2, to give a mixture of α - and β -isomers, 3 and 4, respectively.



The generalized hydrocyanation procedure consists of simply pouring the substrate-crown solution directly over excess, dry KCN. Acetone cyanohydrin is then added and the two phase system is stirred vigorously. The reaction mixture is then filtered, the solvent evaporated and the mixture of cyano products isolated. The isomeric (α - and β -) cyano products are separated from each other using standard column chromatography procedures. The results and the specific details of the experimental procedure are summarized in Table 1. Excellent isolated yields of

TABLE I
Hydrocyanation of Δ^4 -Cholesten-3-one, 2, with "Naked" Cyanide and Acetone Cyanohydrin
in the Presence and Absence of 18-Crown-6

Run	Solvent	[Yield] [a][b]	Ratio 5a/5b	KCN [c]	Concentration [M]		Reaction Temp °C	Reaction Time hrs.	Tend [e] hrs.	Results [f] ^{1,2}
					Crown	Substrate				
1	C ₆ H ₆	-----	-----	stoich.	0.0	0.15	Reflux	32	----	No Reaction
2	C ₆ H ₆	[83.6] 5a-(7.0) 5b-(70.0)	1/10 [g]	2xstoich. [h]	0.19	0.14	Ambient	15	15	Reaction Complete
3	C ₆ H ₆	[82.8] 5a-(13.2) 5b-(62.1)	1/4.7	2xstoich.	0.17	0.16	52°	10	10	Reaction Complete
4	C ₆ H ₆	[84.3] 5a-(18.0) 5b-(56.8)	1/3.16	stoich.	0.19	0.16	Reflux	3	3	Reaction Complete
5	C ₆ H ₆	[85.1] [i] 5a-(15.0) 5b-(60.1)	1/4.0	catalytic	0.10	0.16	Reflux	5	5	Reaction Complete
6	CH ₃ CN	-----	-----	stoich.	0.0	0.16	Reflux	80	----	No [j] Reaction
7	CH ₃ CN	[84.4] 5a-(15.4) 5b-(60.6)	1/3.9	stoich.	0.19	0.14	Reflux	5	5	Reaction Complete
8	CH ₃ CN	[86.12] 5a-(14.7) 5b-(61.4)	1/4.2	stoich.	0.21	0.15	Reflux	10	5	Reaction was complete in 5 hrs but allowed to proceed further
9	CH ₃ CN	[48.8] 5a-(6.1) 5b-(32.1)	1/5.3	2xstoich.	0.20	0.13	52	20	----	Rxn allowed to proceed only to ~60% com- pletion. [k] Rxn allowed to proceed only to ~50% com- pletion. [l] No Reaction
10	CH ₃ CN	[41.2] 5a-(6.9) 5b-(29.7)	1/4.3	catalytic	0.19	0.14	Reflux	7	----	
11	C ₆ H ₆	-----	-----	----- [m]	0.20	0.15	Reflux	35	----	No Reaction
12	C ₆ H ₆	-----	-----	stoich. [n]	0.19	0.16	Reflux	31	----	No Reaction

Notes on Table I

(a) Numbers in squared-brackets refer to percent isolated yield as collected from column chromatography. (b) Numbers in parantheses refer to percent isolated yield of each isomer (separately) after crystallization. (c) Catalytic KCN is ~10% KCN while stoichiometric KCN is 1.0 equivalent KCN to 1.0 equivalent of substrate to 1.2 equivalent acetone cyanohydrin except in cases when 2xstoich. KCN was used in which case 1.2 (2xstoich.) acetone cyanohydrin was used. (d) For those runs with reaction time > 5 hrs, an aliquot sample was analyzed by n.m.r. techniques every 2 hrs. for the first 10 hrs. and every 5-10 hrs. later on. (e) Estimated. (f)¹ In all cases progress of reaction was followed by n.m.r. techniques following the disappearance of vinyl protons in the 4-6 δ region. (f)² Attempts to follow progress of reaction by g.l.c. analysis using 2% SE30 on chrom ϕ , 60/80 mesh, column T 212°C were unsuccessful because at such high temperatures the cyano-products lose HCN easily to product starting material. (g) This is the best ratio of trans/cis products ever reported. (h) When using 1xstoichiometric KCN the reaction was ~80% complete after stirring at ambient temperature for 30 hrs. (i) IR's, nmr's, ORD's, m.p.'s and elemental analysis for the 5-cyano ketones isolated from all runs are consistent with the reported structures. (j) In the absence of crown ether no reaction occurs even after refluxing for prolonged times (runs 1 and 6). (k) In run 9, ~35% of the starting material was recovered. (l) In run 10, ~40% of the starting material was recovered. (m) This run was carried out in the presence of crown ether and acetone cyanohydrin but in the absence of KCN. The reaction was refluxed for 35 hrs, but no reaction occurred. (n) This run was carried out in the presence of crown ether and KCN but in the absence of acetone cyanohydrin. The reaction was refluxed for 31 hrs. but no reaction occurred.

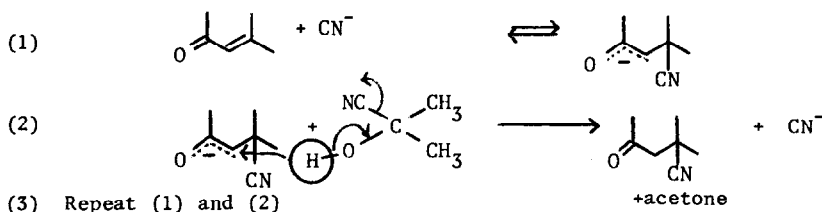
Table II. Hydrocyanation of $\Delta^4(10)$ -Octalin-3-one (5) and 9-Methyl- $\Delta^4(10)$ -Octalin-3-one (6) with "Naked" Cyanide and Acetone Cyanohydrin in the Presence of 18-Crown-6.

Run	Substrate	Solvent	Yield (%)	(a) Ratio (cis/trans)	(a) KCN	[Crown] / [Substrate]	Reaction Temp. (°C)	Reaction Time (hr.)	
1	5	C ₆ H ₆	84.8 (b)	1/3.4	stoich.	0.13	0.67	Ambient	3
2	5	CH ₃ CN	64.1 (c)	1/2.6	stoich.	0.13	0.67	Reflux	1.5
3	5	CH ₃ CN	50.2 (d) (e)	1/2.74	stoich.	0.13	0.67	Ambient	10
4	6	C ₆ H ₆	85	4/1	stoich.	0.15	0.61	Ambient	15

Notes on Table II

(a) The products were analyzed by means of glc using a 20% Carbowax on Chromosorb-W column. (b) A 15.2% yield of dinitrile product was also obtained. (c) A 35.9% yield of dinitrile product was also obtained. (d) A 49.8% yield of dinitrile product was also obtained. (e) Reaction only 70% complete.

hydrocyanation products are obtained in benzene and acetonitrile, (83-86%) and no cyanide hydrolysis products (amides or lactams) or dimers could be detected. The isolated yields of the individual isomers are also excellent and are indicated in Table 1. No reaction is found to take place in the absence of crown (Runs 1 and 6), in the absence of acetone cyanohydrin (Run 12) and in the absence of potassium cyanide (Run 11) and the reaction appears to proceed more rapidly in benzene than in acetonitrile (Runs 3 and 9, Runs 4 and 7). This last observation is attributed to the greater solubility of cholestenone in benzene as compared to acetonitrile. Although potassium cyanide is needed in only catalytic quantities, operationally, the presence of a stoichiometric amount (or greater) allows the reaction to be completed within a much shorter period of time (Runs 4 and 5, Runs 7 and 10). As the reaction temperature decreases the $5\alpha/5\beta$ ratio decreases (Runs 2,3 and 4, Runs 7 and 9) and this trend appears to be independent of the solvent system. Indeed, at ambient temperatures an α/β ratio of 1/10 is obtained in benzene (Run 2). The data indicate that under the conditions described the more thermodynamically stable product is always produced in this enone system. These stereochemical results appear to be equal to or superior to the reported results obtained with other more complex hydrocyanating reagents.¹⁻⁴ It was found that no equilibration of α - and β -isomer products occurs under the reaction conditions described (Run 8). The following mechanistic sequence, consistent with the above observation, may be invoked to rationalize the function of the reagent components:



The results of the reaction of the "naked" cyanide-acetone cyanohydrin reagent with $\Delta^{4(10)}$ -octalin-3-one (5) and with 9-methyl- $\Delta^{4(10)}$ -octalin-3-one (6) are summarized in Table II. As was the case with Δ^4 -cholesten-3-one, the thermodynamic product predominates in each case and the best stereochemical results are obtained in benzene at ambient temperatures.

In conclusion, a simple hydrocyanation procedure has been described which supplements and complements existing methods and which should prove to be valuable to the synthetic organic chemist.

References

- (a) W. Meyer and N. Schnautz, J. Org. Chem., **27**, 2011 (1962); (b) A. Bowers, ibid., **26**, 2043 (1961).
- (a) W. Nagata, M. Yoshioka and S. Hirai, J. Am. Chem. Soc., **94**, 4635 (1972); W. Nagata, K. Kikkawa and M. Fujimoto, Chem. Pharm. Bull., **11**, 226 (1963); (c) W. Nagata, T. Sugawara, M. Narisada, T. Wakabayoshi, and U. Hayase, J. Am. Chem. Soc., **85**, 2342 (1963); (d) ibid., **89**, 1483 (1967).
- H. B. Henbest and W. R. Jackson, J. Chem. Soc. (c), 2465 (1967).
- (a) W. Nagata, N. Yoshioka and M. Murakawa, J. Am. Chem. Soc., **94**, 4654 (1972); (b) W. Nagata, M. Yoshioka and T. Terasawa, ibid., **94**, 4672 (1972).
- (a) F. L. Cook, C. W. Bowers and C. L. Liotta, J. Org. Chem., **39**, 3416 (1974); (b) J. W. Zubrick, B. I. Dunbar and H. D. Durst, Tetrahedron Lett., **71** (1975).