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STEREOCHEMISTRY OF THE DEALKOXYCARBONYLATION OF METHYL α-CYANOCINNAMATE AND OF THE DECARBOXYLATION OF THE CORRESPONDING CYANOACID A FACILE STEREOSELECTIVE ROUTE TO Z-CINNAMONITRILE

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Summary Decarboxylation of E-3-phenyl-2-cyanopropenoic acid (1) in dimethyl sulfoxide containing sodium bicarbonate, lithium chloride, and water in molar excess afforded, with high stereospecificity, Z-cinnamonitrile (6) The dealkoxycarbonylation of the corresponding methyl ester (2) under similar reaction conditions was much less selective and resulted in a 1 1 mixture of E- and Z- stereoisomeric nitriles (6 and 7).

A research project that we were about to initiate required efficient access to large quantities of Z-cinnamonitrile (6) and its ortho- substituted derivatives (e g., 8) Although several stereoselective routes to such compounds have been reported,[1] none seemed suitable for the task at hand

Conceptually, the most direct approach to the desired nitriles appeared to be one involving dealkoxycarbonylation (e g , 2 → 6) of readily available[2] and stereochemically homogeneous[3] esters of E-3-aryl-2-cyanopropenoic acids Unfortunately, however, much conflicting data has been published concerning efforts to achieve a kinetically-controlled decarboxylation of the parent carboxylic acid (1), and results to date would seem to preclude the viability of such an approach Especially ominous are the findings reported by Corey and Fraenkel,[4] who obtained an equilibrium mixture[5] of 35% cis- and 65% trans-cinnamonitrile after heating a stereochemically homogeneous sample of cyanoacid 1 in pyridine at 111°C When the same decarboxylation was conducted in quinoline at higher temperature (140-155°C), Klein and Meyer[6] were able to obtain more cis-cinnamonitrile, however, their results were erratic[7] and yields were generally low Although a kinetically-controlled process to effect this decarboxylation (i e , 1 → 6) was subsequently reported,[1c] yields were moderate and the cis-nitrile had to be removed once formed since it was not stable under the experimental conditions

Despite the fact that a large-scale synthesis of cis- cinnamonitrile (6) via decarboxylation of unsaturated cyanoacid 1 seemed fraught with problems, we decided to investigate the dealkoxycarbonylation of the corresponding esters (2 and 3) using the experimental conditions developed by Krapcho and co-workers.[8] Although extensive work[9] has been done during the past decade on dealkoxycarbonylation of α-cyanoesters and related compounds, few publications have

detailed the stereochemical outcome of such processes [10] Indeed the only study directly related to the reaction we planned to investigate reported[11] that treatment of ethyl benzylidenecyanoacetate (3)[12] with water and sodium chloride in dimethyl sulfoxide (DMSO) at 160°C afforded cinnamonitrile as an unspecified mixture of cis trans stereoisomers When we repeated this reaction using similar conditions (Table I, entry 12), we were disappointed by the stereochemical results (Z E ratio -- 1 3), as well as by the formation of a significant amount of benzaldehyde.[13]

In a previous study[14] designed to assess the diastereoselectivity of protonation in dealkoxycarbonylation of cyclic geminal diesters, lithium chloride and water in DMSO were the reagents of choice since the resulting mixture is homogeneous Although similar conditions applied to cyanoester 3 (Table I, entry 11) increased the amount of cis-cinnamonitrile (6), the stereochemical outcome was still disappointing and a retro-Knoevenagel reaction continued to plague the system Use of the corresponding methyl ester (2)[15] led to equally frustrating results (Table I, entry 10) However, much to our surprise, especially in view of the previous studies[4,6] on the decarboxylation of cyanoacid 1, treatment of α-cyanocinnamic acid (1)[16] under identical conditions (Table I, entry 2) afforded cinnamonitrile in 89% yield as a 7 1 mixture of Z E stereoisomers uncontaminated by any benzaldehyde!

In order to rationalize the disparate stereochemical results cited above, we conducted several additional experiments involving acid 1 and ester 2 as substrates Perhaps most informative of these were the ones (Table I, entries 8 and 9) that indicated an initial rapid formation of trans-cinnamonitrile during the decarbalkoxylation of cyanoester 2, with both a steady increase in the amount of cis-stereoisomer and a leveling off in the formation of benzaldehyde as the reaction proceeded

Such results can be explained by considering two probable reaction pathways available to cyanoester 2 under the conditions selected for decarbalkoxylation

(a) a rapid Michael addition of water to cyanoester 2 affording 10 (equation 1) The latter (10) is capable of undergoing either a facile retro-Knoevenagel reaction to yield benzaldehyde or hydrolysis to afford 11 A subsequent decarboxylative-elimination involving 11 should proceed via a thermodynamically controlled process, affording predominantly trans-cinnamonitrile (7) Results of an earlier study[4] involving decarboxylation of cyanoacid 1 in pyridine also suggested formation of trans-cinnamonitrile (7) via an addition-elimination pathway

(b) hydrolysis (via either $B_{AC}2$ or $B_{AL}2$ cleavage) to afford, in the presence of sodium bicarbonate, benzylidenecyanoacetate (9). Michael addition to the latter should be suppressed, thereby minimizing formation of benzaldehyde and enabling a kinetically-controlled decarboxylation to occur to afford stereospecifically the cis-nitrile (6)

As further evidence for the proposed mechanism, decarboxylation of cyanoacid 1 at 145°C (Table I, entry 7) would be expected to proceed more slowly than at 165°C, enabling the undesired Michael reaction (9 → 11) with water to become more competitive. The latter transformation can be followed by a facile decarboxylative elimination to afford mainly trans-nitrile (7) It would also explain the formation of benzaldehyde as a minor product under these con-

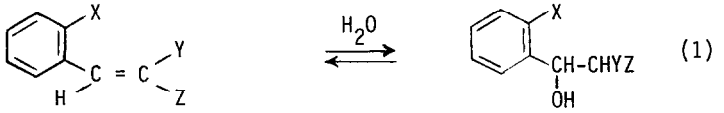
Table I - - Preparation of Cinnamonitrile

Entry No	Starting Material[a]	Additional Reagents[b] (mmol)	Reaction Temperature[c] (°C)	Reaction Time (min.)	Yield[d] of 6 and 7 (%)	cis. trans ratio[e]	Yield[f] of Benzaldehyde (%)
1	1	4 LiCl, 4 H_2O	165°	30	35	8 1	<1
2	1	4 LiCl, 4 H_2O	165°	180	89	7.1	<1
3	1	4 LiCl, 4 H_2O	(-)[g]	120	87[h]	1 3[1]	<1
4	1	2 LiCl, 2 H_2O	165°	180	95	5 1	<1
5	1	2 NaCl, 2 H_2O	165°	180	90	63 37	<1
6	1	6 LiCl, 6 H_2O	165°	180	72	5 1	3
7	1	4 LiCl, 4 H_2O	145°	180	38	3 1	7
8	2	4 LiCl, 4 H_2O	165°	5	25	1 4	11[J]
9	2	4 LiCl, 4 H_2O	165°	30	56	45·55	16[k]
10	2	4 LiCl, 4 H_2O	165°	180	75	1 1	18
11	3	4 LiCl, 4 H_2O	165°	180	63	40 60	21
12	3	4 NaCl, 4 H_2O	165°	180	51	1 3	27

[a]All experiments were conducted under a nitrogen atmosphere using 1 0 mmole of substrate in 2.0 mL of DMSO. Cyanoesters 2 and 3 were prepared from benzaldehyde and methyl or ethyl cyanoacetate respectively using a procedure analogous to that described by F S Prout and co-workers in Org. Syn , Coll Vol. 4, 93 (1963). NMR analysis (vinyl H absorption) showed both of these cyanoesters (2 and 3) to be stereochemically homogeneous. The corresponding cyano-acid (1) was prepared as outlined in footnote 16 in this communication. [b]Sodium bicarbonate (2 0 mmoles) and DMSO (2 0 mL) were also added to each reaction mixture. [c]Temperature of the pre-heated oil bath, unless specified otherwise. [d]Based on starting material. The product was isolated by extraction with ether and subsequent washing of the extracts with 1 1 (v/v) 1M aqueous NaOH saturated brine and 5% aqueous NaCl to remove acidic impurities and DMSO Removal of any undecarboxylated cyanoacid (1) during the base washes in the reaction workup can explain the low material balance in certain of these experiments [e]This ratio was determined by NMR analysis (vinyl H absorption).[19] [f]This yield is based on starting material and was determined by NMR analysis of the reaction product. [g]The reaction mixture in this experiment was heated at reflux [h]This represents the crude yield. NMR analysis indicated the presence of small amounts of unidentified material - - not observed in any of the other experiments. [1]A subsequent experiment demonstrated that Z-cinnamonitrile (6) was not stable under the conditions used in this reaction. After 50 min in DMSO at reflux (in the presence of 4 LiCl - 4 H_2O - 2 $NaHCO_3$) a 7 1 mixture of Z E stereoisomeric nitriles (6 and 7) was slowly isomerized to a 2 1 mixture of 6 7 respectively [J]A 19% recovery of starting material (2) was also obtained in this experiment [k]3% starting material (2) was recovered in this experiment

ditions, in sharp contrast to other experiments involving cyanoacid 1.

In order to determine what effect substituents on the aromatic ring would have on the stereochemical outcome of this decarboxylation, E-3-(o-chlorophenyl)-2-cyanopropenoic acid (5) was prepared by saponification[16] of the corresponding cyanoester (4).[17] Decarboxylation of 5 (DMSO, 2 $NaHCO_3$, 4 LiCl, 4 H_2O, 165°C, 90 min) afforded 3-(2'-chlorophenyl)-2-propenenitrile (8)[18] as a 10·1 mixture of Z E stereoisomers in 92% yield It appears, therefore, that the route outlined in this communication is the most convenient method available for stereoselective preparation of cis-cinnamonitriles.



(1)

1, X = H, Y = CN, Z = COOH
2, X = H, Y = CN, Z = CO_2CH_3
3, X = H, Y = CN, Z = $CO_2CH_2CH_3$
4, X = Cl, Y = CN, Z = $CO_2CH_2CH_3$
5, X = Cl, Y = CN, Z = COOH
6, X = Z = H, Y = CN
7, X = Y = H, Z = CN
8, X = Cl, Z = H, Y = CN
9, X = H, Y = CN, Z = COO^-
10, X = H, Y = CN, Z = CO_2CH_3
11, X = H, Y = CN, Z = COO^-

REFERENCES AND NOTES

1 A stereospecific cyanation process involving cis-β-bromostyrene has been reported to afford cis-cinnamonitrile. See (a) R Lapouyade, M. Daney, M. Lapenue, and H Bousa-Laurent, Bull Soc. Chim. Fr , 720 (1973), (b) T. Funabiki, S Yoshida, and K Tarama, J Chem. Soc , Chem Commun , 1059 (1978) Thermal decarboxylation of cyanoacid 1 using Cu_2O as a catalyst has been reported to afford cinnamonitrile (Z E ratio -- 87 13) in 46% yield See (c) J Fairhurst, D. C. Horwell, and G H. Timms, Tetrahedron Lett , 3843 (1975)

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3. J. Zabicky, J. Chem. Soc , 683 (1961)

4. E. J. Corey and G Fraenkel, J Am. Chem Soc , 75, 1168 (1953)

5. G B. Kistiakowsky and W. R Smith, ibid , 58, 2428 (1936)

6 J Klein and A. Y. Meyer, J. Org Chem , 29 1038 (1964)

7. After heating cyanoacid 1 for 2 hours in quinoline, cinnamonitrile could be isolated in 13% yield as a 96 4 mixture of Z E stereoisomers However, a longer reaction time (5 hours at 140°C) to improve the yield to 45% led to the recovery of a 1 1 mixture of 6 7.

8 A P. Krapcho, J. F. Weimaster, J M Eldridge, E. G. E Jahgen, Jr , and W. P. Stephens, J. Org. Chem , 43, 138 (1978) and references cited therein.

9. For review see A. P. Krapcho, Synthesis, 805-822, 893-914 (1982)

10. See reference 9, pp 817-821.

11 R. V Venkateswaran, A. Ghosh, and A Sarkar, Tetrahedron Lett., 553 (1979)

12 W Baker and W G. Leeds, J. Chem. Soc , 974 (1948)

13 A previous study[11] had reported that a retro-Knoevenagel reaction was quite favorable when alkylidene cyanoesters were subjected to such decarbalkoxylation conditions

14. A P. Krapcho and J F Weimaster, J. Org. Chem., 45, 4105 (1980)

15 Beilstein, Part I, Vol 9, pp 893-4

16 Cyanoacid 1 was obtained in 77% yield by saponification of the corresponding ester (either 2 or 3) in 4 1 (v/v) CH_3OH H_2O containing a molar equivalent of K_2CO_3 (0 4 M solution, 30 min at reflux) Prior to acidification of the mixture and isolation of the desired acid (1), it was diluted with water and extracted with ether to remove any benzaldehyde produced via a retro-Knoevenagel reaction during the course of this saponification

17 F D. Popp, J. Org. Chem , 25, 646 (1960)

18 For a previous synthesis of cis-nitrile 8 see reference 1c

19 The cis stereoisomer (6) exhibited a doublet (J = 12 Hz) at 5 44δ(CHCN), whereas the corresponding absorption for the trans isomer (7) was a doublet at 5 87δ (J = 17 Hz) For additional NMR data on cinnamonitrile, see reference 1b

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