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A FACILE ROUTE TO A VERSATILE SYNTHON FOR PREPARATION OF CIS-PYRETHROIDS[1]

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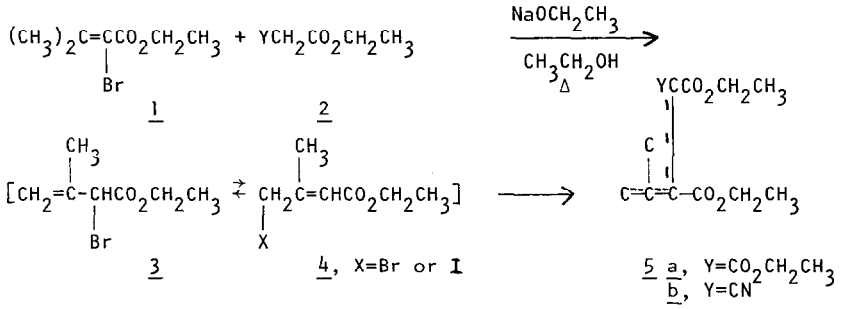
Summary: cis-2-Cyano-3,3-dimethylcyclopropanecarboxylic acid was obtained in >50% overall yield starting with ethyl 3,3-dimethylacrylate. The key step involved a tandem Michael reaction - intramolecular displacement to afford stereoselectively a cyclopropanoid precursor of cis-pyrethroids.

In the past decade numerous routes have been developed for total synthesis of trans-chrysanthemic acid and its analogs, many ester derivatives of which possess potent insecticidal activity.[2] Among the simplest of these methods are those which involve Michael-type reactions of α,β-unsaturated esters with phosphorus[3] and sulfur[4] ylides. Since α-halo-α,β-unsaturated esters have been shown[5] to be useful Michael acceptors, we decided to investigate the base-promoted reaction between malonic ester and bromoester 1,[6] a route which we felt might be more convenient for large-scale preparation of synthons for obtaining pyrethroids.

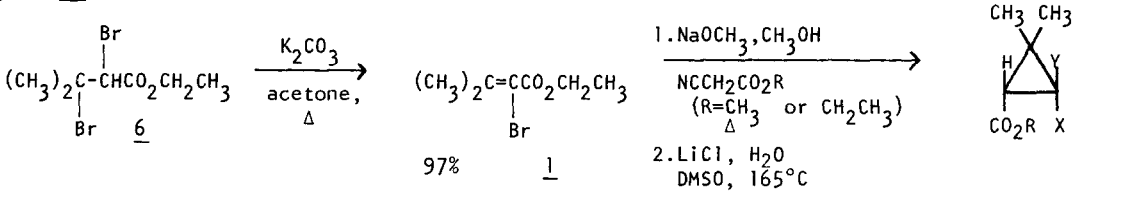


Martin and coworkers had previously studied[5] a Michael-type reaction between bromoester 1 and catechol and reported obtaining none of the expected product. Instead, they isolated an isomeric product presumably derived from allylic halide 3 or 4, formed via the base-catalyzed isomerization of the initial α-haloester (1). Consistent with these observations, we found that treatment of the latter compound (1) with diethyl sodiomalonate in refluxing ethanol afforded no cyclopropanoid products (e.g., 11). Chromatography on silica gel, followed by NMR analysis, indicated the product to be almost exclusively a mixture of unsaturated esters of

general structure 5a.

Much to our amazement, treatment of bromoester 1 with ethyl cyanoacetate[7] and sodium methoxide in refluxing methanol[8] gave only trace amounts of acyclic material corresponding to structure 5b and afforded the desired cyclopropanoid 7[9,10] in 70% yield as an apparent single stereoisomer[11] based on VPC[8] and NMR analysis. Decarbalkoxylation[12] of 7 was effected in 89% yield by use of 2 molar equivalents each of lithium chloride, water, and sodium bicarbonate[13] in dimethyl sulfoxide (2 mL per mmole of 7) at 165° (bath temp.)[14] for 30 minutes. The resultant product was shown by both NMR and VPC analysis[15] to be a 2:1 mixture of cis and trans stereoisomers (8[10] and 9[10]) respectively.

In order to increase the stereospecificity of the decarbalkoxylation step (i.e., 7→8), small amounts (1-2 equivalents) of weak acids such as boric acid, adipic acid, and KH_2PO_4 were added to the reaction mixture. In all cases such experiments led to variable (and substantial) amounts of cyclopropane ring opening. However, the use of a large excess of lithium chloride and water did result in a remarkable enhancement in the stereospecificity of the reaction, although the rate at which the decarboxylation occurred was diminished. For example, treatment of 7 with 7 equivalents each of lithium chloride and water plus 2 equivalents of sodium bicarbonate[13] in dimethyl sulfoxide (2 mL per mmole of 7) at 165° (bath temp.)[14] for 30 minutes resulted in a 64% isolated yield[16] of a 5:1 mixture of cis-trans stereoisomers (8 and 9) respectively, as shown by both NMR and VPC analysis.[15] The stereochemical assignments were confirmed by saponification under mild conditions [0.50M solution of K_2CO_3 (4 equiv) in 4:1 (v/v) CH_3OH: H_2O, room temp., 5 hours] of the ester moiety in 8 and 9. The NMR spectra of these cyanoacids (10 and 15) were identical to those previously reported[17] for these same stereoisomers.



7, R=CH_3; Y=CO_2CH_3; X=CN
8, R=CH_3; Y=H; X=CN
9, R=CH_3; Y=CN; X=H
10, R=Y=H; X=CN
11, R=CH_2CH_3; X=Y=$CO_2CH_2CH_3$
12, R=Y=H; X=CH=CBr_2
13, R=CH_3,CH_2CH_3(Mixture) X=CN; Y=CO_2R
14, R=CH_3; Y=COOH; X=CN
15, R=X=H; Y=CN

In view of the ease with which these reactions can be accomplished and the high stereospecificity possible in the decarbalkoxylation step, cyclopropanoids 8 and 10 represent versatile synthons for synthesis of cis pyrethroids[18] such as the highly active insecticide NRDC 161,[19] the acid component of which is represented by structure 12. The transformations required to effect such syntheses would be similar to those recently reported[17] for the corresponding

trans synthon (15). Furthermore, since we have recently discovered conditions[20] for the decarbalkoxylation step that convert 7 directly to the trans cyanoacid 15 in >80% yield, the route described in this communication takes on added versatility.

REFERENCES

1. The method reported in this communication is the subject of a U.S. Patent Application filed in March, 1981, by Loyola University of Chicago.

2. For a review of some of the methods used to prepare trans-chrysanthemic acid and the related synthetic pyrethroids, see "Synthetic Pyrethroids," ACS Symposium Series 42, M. Elliott, Ed., American Chemical Society, Washington, D.C., 1977, pp. 45-54, 116-136; "The Total Synthesis of Natural Products," Vol. 2, J. ApSimon, Ed., Wiley, New York, NY, 1973, pp. 49-58; M. Elliott and N.F. Janes, Chem. Soc. Rev., 7, 473-505 (1978).

3. M.J. DeVos and A. Krief, Tetrahedron Lett., 1511, 1515 (1979).

4. G.B. Payne, J. Org. Chem., 32, 3351 (1967).

5. A.R. Martin, S.K. Mallick, and J.F. Caputo, J. Org. Chem., 39, 1808 (1974).

6. Prepared in >95% yield by addition of bromine to a solution of ethyl 3,3-dimethylacrylate (Aldrich Chemical Co.) in CH_2Cl_2, followed by treatment of the resultant dibromide (6) with K_2CO_3 (3 equiv.) in refluxing acetone (0.4M solution). Use of 2,6-lutidine for the latter transformation led to a substantial amount of debromination. For a previous synthesis of 1, see reference 5.

7. The success of this Michael reaction may be due to the enhanced acidity of ethyl cyanoacetate (pK_a=9) in comparison with diethyl malonate (pK_a=13). The attempted addition with the latter reagent was of necessity conducted in a more basic medium in which the isomerization of bromoester 1 to the isomeric allylic halide 3 would be expected to occur more rapidly. Furthermore, the Michael reaction with 1 would be subject to less steric hindrance if diethyl malonate is replaced by ethyl cyanoacetate.

8. Although ethanol could be used satisfactorily in this reaction, use of methanol resulted in substantial transesterification and thereby greatly simplified NMR analysis of the product mixture in the subsequent decarbalkoxylation step. The best yield of cyclopropanoid 7 was obtained by refluxing a mixture of bromoester 1 (10 mmoles), 5.0 mL of ethyl cyanoacetate, and 15 mL of a 1M $NaOCH_3$ (from Na) - methanol solution for 3.5 hours. The product was isolated by diluting the mixture with 20 mL of 2M aqueous HCl and 150 mL of brine and extraction with ether, followed by removal of excess ethyl cyanoacetate with 1M aqueous NaOH washes. In addition to a minor amount (10-15%) of starting material, VPC analysis (6' x 1/8" SE-30 column, T: 195°C, flow: 15 mL/min) indicated the product to be a 4:1 mixture respectively of the desired dimethyl ester 7 (t_R = 4.5 min) and the corresponding diester 13 (t_R = 5.2 min) resulting from incomplete transesterification. Chromatography on silica gel (elution with hexane-16% ether) afforded the cyanodiester (7, accompanied by variable amounts of 13) in approx. 70% yield. The initial portion of cyanodiester eluted from the column contained a substantial amount of the slightly less polar component (13) as shown by NMR and VPC analysis. However, the last third of the diester material eluted contained the desired dimethyl ester (7) in >98% purity and was used for the subsequent decarbalkoxylation studies. Cyanodiester 7, virtually uncontaminated with diester 13, was also obtained (>70% yield) more directly by replacement of the ethyl cyanoacetate (5 mL, 47 mmoles) in the Michael reaction mixture with an equivalent amount of methyl cyanoacetate (4 mL, 45 mmoles).

9. bp 50-60°C (bath temp, 0.06mm); ν_{max} (film) 2240 (C≡N), 1745 (C=O), 1300, 1240, 1205, 1155, 1105, 1030, 900,850, 795 cm^{-1}; δMe_4Si (CCl_4) 3.87 (s, CO_2CH_3), 3.78 (s, CO_2CH_3), 2.68 (s, 1 cyclopropyl H), 1.55 (s, CH_3), 1.34 ppm (s, CH_3).

10. Satisfactory elemental analysis was obtained for this novel compound.

11. The presence of a single sharp peak (δ 2.68) for the cyclopropyl H in the crude Michael reaction product suggested the presence of only one stereoisomer (the two ester moieties being trans, as shown by the decarbalkoxylation results).

12. A.P. Krapcho, J.F. Weimaster, J.M. Eldridge, E.G.E. Jahngen, Jr., A.J. Lovey, and W.P. Stephens, J. Org. Chem., 43, 138 (1978).

13. Although sodium bicarbonate is not essential for the success of this reaction, it is desirable since in its presence the reaction proceeds more rapidly and affords slightly higher yields of the desired cyanoester (8 and 9).

14. In order to minimize the reaction time, the oil bath was heated to 165°C prior to submersion of the reaction flask. The product was isolated by dilution of the reaction mixture with saturated brine and extraction with ether.

15. A 6' x 1/8" SE-30 column (T: 178°C, flow: 15 mL/min) was used for this analysis; retention times: 8, 3.1 min.; 9, 2.2 min. These two stereoisomers were readily separable by chromatography on silica gel, the trans stereoisomer (9) being less polar (elution with hexane: 8% ether). The cis stereoisomer (8) had an NMR spectrum which was characterized by a 3H singlet at 3.73 δ (CO_2CH_3) and absorption by the 2 cyclopropyl H's between 1.60 and 1.96 δ (dd, J = 8.5 Hz). The corresponding absorptions for the trans isomer (9) were 3.70 (s, CO_2CH_3) and 1.83-2.03 δ (dd, J = 5 Hz, 2 cyclopropyl H's) respectively.

16. Also recovered from the reaction mixture was the undecarboxylated cyanoacid 14 (20% yield). Surprisingly, only trace amounts of 10 and 15 were detected under these reaction conditions.

17. M.J. DeVos and A. Krief, Tetrahedron Lett., 1891 (1979).

18. For many of these synthetic pyrethroids, the cis isomer is more active than the trans. See M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham, and D.A. Pulman, Pestic. Sci., 6, 537 (1975).

19. M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham, and D.A. Pulman, Nature, 248, 710 (1974).

20. Treatment of 7 with 3 equiv. of $NaHCO_3$ and water in refluxing 1,3-propanediol (2 mL per mmole of 7) resulted in a highly stereoselective transformation to the trans cyanoacid 15. At a reaction temperature of 165°C, under similar conditions (30 min.), the decarboxylation fails to occur.

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