Tetrahedron Letters,Vol.26,No.16,pp 1923-1926,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

A TANDEM MICHAEL REACTION-CYCLOALKYLATION UTILIZING 2-NITROPROPANE: A FACILE ROUTE TO THE ACID COMPONENT OF INSECTICIDAL PYRETHROIDS

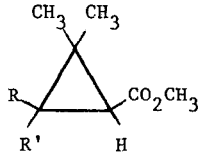
James H. Babler* and Kenneth P. Spina
Department of Chemistry, Loyola University of Chicago
Chicago, Illinois 60626 USA

ABSTRACT: Treatment of three representative β-substituted-α-cyanoacrylates (2) with 2-nitropropane and potassium carbonate in refluxing ethanol afforded stereoselectively cyclopropanoid precursors (4) to 3-substituted-2,2-dimethylcyclopropanecarboxylic acids (7).

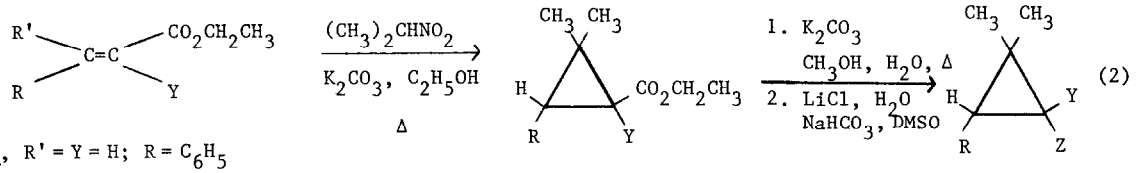
During the past decade a major research effort in agricultural chemistry culminated in the development of a new class of insecticides known as pyrethroids[1], which are synthetic analogues of certain naturally occurring esters obtained from some chrysanthemum species (pyrethrum). Although the latter have been used as insecticides since the early nineteenth century, lack of stability to atmospheric influences precluded their use in agriculture. This limitation was removed with the discovery that certain ester derivatives of specific cyclopropanecarboxylic acids [e.g., permethrinic acid (7, R = $CH{=}CCl_2$)] were far superior in activity to the natural prototypes or the hitherto known insecticides of other structural types. Although the most important insecticidal pyrethroids are derived at present from permethrinic acid and chrysanthemic acid [7, R = $CH{=}C(CH_3)_2$], recent patent literature indicates insecticidal activity for specific ester derivatives of a variety of other cyclopropanecarboxylic acids, including ones lacking a vinyl substituent at C-3 [e.g., 7, R = $CH_2CH(CH_3)_2$].[2] Also noteworthy is the potent acaricidal activity reported[3] for derivatives of 3-aryl-2,2-dimethylcyclopropanecarboxylic acids (e.g., 7, R = C_6H_5).

Although a host of methods have been developed[4] for the synthesis of pyrethroid acids of general structure 7, many of these are limited to the preparation of a specific compound. A route (equation 1) developed by Krief and coworkers,[5] although quite useful for small-scale synthesis of such compounds (7), suffers from the sensitivity of phosphoranes to air and traces of protic solvents. With this in mind, we decided to investigate a novel and more convenient route (equation 2) for synthesis of large quantities of a variety of pyrethroid acids of general structure 7.

$$RR'C{=}CHCO_2CH_3 + (CH_3)_2C{=}PPh_3 \longrightarrow \text{(1)}$$



Due to its appreciable acidity and low cost, 2-nitropropane was selected as the reagent of choice for effecting the cyclopropanation reaction. Although this reagent has been used successfully by others[6] in Michael-type additions, to our knowledge no report of a subsequent displacement of the nitro group to afford a cyclopropanoid has been reported.[7] Indeed, in general, the aliphatic nitro group fails to serve as a leaving group in substitution and elimination reactions that proceed by an ionic process. However, it is well known[8] that β-elimination of nitrite takes place readily to afford olefins if an electron-withdrawing group exists at a position β to the nitro functionality.



(2)

1, R' = Y = H; R = C_6H_5

2, R' = H; Y = CN

3, R' = R = CH_3; Y = CN

4, Y = CN

5, Y = H; Z = CN

6, Y = CN; Z = H

7, Y = CO_2H; Z = H

a, R = C_6H_5; b, R = $CH_2CH(CH_3)_2$; c, R = 3-pyridyl

Our initial efforts to obtain a cyclopropanoid using ethyl cinnamate (1a) and 2-nitropropane in the presence of one equivalent of base met with failure. To our amazement, however, treatment of the Knoevenagel adduct (2a)[9] derived from benzaldehyde and ethyl cyanoacetate with equimolar amounts of 2-nitropropane and anhydrous potassium carbonate in absolute ethanol (0.8 mL/mmol of substrate, 4 hours at reflux) afforded cyclopropanoid 4a[10] as a single diastereomer[11] in 81% yield after product isolation and subsequent distillation.[12] To verify that this methodology could be applied to the total synthesis of pyrethroid acids of general structure 7, the latter product (4a) was saponified[13]; and the corresponding cyanoacid was subjected to decarboxylation[14] [4 LiCl, 4 H_2O, 1.5 $NaHCO_3$, DMSO (2 mL/mmol of substrate), 165°C (temperature of pre-heated oil bath), 4.5 hours] to afford cyclopropanoid nitriles 5a[10] and 6a[10] as a 55:45 mixture[15] respectively in > 60% yield (based on 4a). Subsequent saponification of this stereoisomeric mixture of nitriles (5a and 6a) under conditions [3 equiv KOH, ethylene glycol (2 mL/mmol of substrate), 18 hours at reflux] known[16] to epimerize a related cis cyclopropanoid nitrile afforded, in quantitative yield, trans-3-phenyl-2,2-dimethylcyclopropanecarboxylic acid (7a).[17]

To illustrate further the utility of this cyclization methodology, the Knoevenagel adduct (2b)[18] derived from isovaleraldehyde and ethyl cyanoacetate was treated with 2-nitropropane using the conditions described above for 2a, affording cyclopropanoid cyanoester 4b[10,19] in 95% yield. Although we have been unable to obtain any cyclization product from the β,β-disubstituted cyanoester 3,[20] presumably for steric reasons, this tandem Michael reaction-cycloalkylation methodology afforded the novel[10] cyclopropanoid 4c[21] in > 80% yield when applied to the Knoevenagel adduct (2c)[22] derived from 3-pyridinecarboxaldehyde.

In view of the facility with which the transformations reported in this communication can be effected, the methodology which we report offers great potential for the synthesis of both known and novel pyrethroid acids, including the less accessible cis-stereoisomeric acids.[23] A more detailed study of the tandem Michael reaction-cycloalkylation[24] step, as well as efforts to improve the stereospecificity of the decarbalkoxylation process (4→5), is presently being initiated and results will be reported in a future article.

REFERENCES AND NOTES

1. "Synthetic Pyrethroids," ACS Symposium Series 42, M. Elliott, Ed., American Chemical Society, Washington, D.C. 1977.

2. J.Drabek, S. Faroog, L. Gsell, O. Kristiansen, and W. Meyer, German patent 2,731,033 (1978).

3. K. Ozawa, S. Ishii, M. Hayashi, M. Hirose, and K. Hirata, German patent 2,935,575 (1980).

4. For a review of some of the methods used to prepare trans-chrysanthemic acid and the related acid component of synthetic pyrethroids, see: D. Arlt, M. Jautelat, and R. Lantzsch, Angew. Chem. Internat. Ed. Engl., 20, 703-722 (1981); M. Elliott and N.F. Janes, Chem. Soc. Rev., 7, 473-505 (1978).

5. M.J. Devos, L. Hevesi, P. Bayet, and A. Krief, Tetrahedron Lett., 3911 (1976).

6. For two specific examples, see: R.B. Moffett, "Organic Syntheses," Collective Vol. IV, Wiley: New York, 1963, p. 652; N. Ono, A. Kamimura, and A. Kaji, Synthesis, 226 (1984).

7. An analogous tandem Michael reaction-cycloalkylation involving unsaturated cyanoesters (2) and a large excess of nitromethane under forcing reaction conditions (excess base, 100°C, pressure) has been reported to afford the sterically less-congested cyclopropanoids lacking the geminal dimethyl substituents. Moreover, this process generally proceeded in low to moderate yields except when applied to complex steroidal systems. See: K. Annen, H. Hofmeister, H. Laurent, A. Seeger, and R. Weichert, Chem. Ber., 111, 3094 (1978).

8. For specific examples, see: N. Ono, R. Tamura, H. Eto, I. Hamamoto, T. Nakatsuka, J. Hayami, and A. Kaji, J. Org. Chem., 48, 3678 (1983) and references in footnotes 3 and 8 in that paper.

9. W. Baker and W.G. Leeds, J. Chem. Soc., 974 (1948). For a review of the Knoevenagel condensation, see: G. Jones, Org. Reactions, 15, 204-599 (1967).

10. Satisfactory elemental analysis (C,H,N) was obtained for this novel compound.

11. The presence of a single sharp peak (δ 3.25) for the cyclopropyl H in the crude cyclization product suggested the presence of only one stereoisomer (the phenyl and ester groups being trans, as shown by subsequent decarbalkoxylation results). In addition, cyclopropanoid 4a ($CDCl_3$ solution) exhibited the following ^{1}H NMR properties: δ 7.23 (s, C_6H_5), 4.26 (quartet, J = 7 Hz, OCH_2CH_3), 1.44 (s, CH_3), 1.33 (t, J = 7 Hz, OCH_2CH_3), 1.30 (s, CH_3).

12. The product was isolated by dilution of the reaction mixture with 7 volumes of 15% (w/v) aqueous NaCl and extraction with methylene chloride. Evaporative (Kugelrohr) distillation afforded 4a: bp 94-118°C (bath temperature, 0.10 mm).

13. This saponification was effected by treatment of ester 4a [0.4 M solution in 4:1 (v/v) $CH_3OH:H_2O$, 60 min. at reflux] with one molar equivalent of potassium carbonate.

14. For a review of decarbalkoxylation reactions, see: A.P. Krapcho, Synthesis, 805-822, 893-914 (1982).

15. This ratio was determined by ^{1}H NMR analysis (cyclopropyl CH_3's). Both diastereomers were fully characterized after separation by chromatography on silica gel, the trans stereoisomer (6a) being less polar (elution with hexane: 2% ether). The cis stereoisomer (5a) had an NMR spectrum which was characterized by the following absorption bands: δ 7.39 (s, C_6H_5), 2.41 (d, J = 9 Hz, 1H), 1.67 (d, J = 9 Hz, 1H), 1.36 (s, CH_3), and 1.16 (s, CH_3). The corresponding absorptions for the trans isomer (6a) were: δ 7.35 (m, C_6H_5), 2.55 (d, J = 5.8 Hz, 1H), 1.65 (d, J = 5.8 Hz, 1H), 1.51 (s, CH_3), and 0.92 (s, CH_3). The coupling constants observed for the vicinal cyclopropyl hydrogens in nitriles 5a and 6a were consistent with those previously reported for the corresponding cis- and trans- stereoisomeric acids. See: D.J. Patel, M.E.H. Howden, and J.D. Roberts, J. Am. Chem. Soc., 85, 3218 (1963); J. Farkas, P. Kourim, and F. Sorm, Chem. Listy, 52, 695 (1958).

16. S. Julia, M. Julia, and G. Linstrumelle, Bull. Soc. Chim. Fr., 3499 (1966).

17. The ^{1}H NMR spectral properties of this known compound (7a) were fully consistent with those reported in the literature.[15]

18. For a previous synthesis of 2b, see: F.D. Popp and A. Catala, J. Org. Chem., 26, 2738 (1961).

19. Cyclopropanoid 4b exhibited the following ^{1}H NMR spectral properties: δ 4.21 (quartet, J = 7 Hz, OCH_2CH_3), 1.33 (s, CH_3), 1.31 (t, J = 7 Hz, OCH_2CH_3), 1.28 (s, CH_3), 0.95 [br d, J = 6 Hz, $CH(CH_3)_2$] .

20. S.F. Birch and G.A.R. Kon, J. Chem. Soc., 123, 2440 (1923).

21. bp 128-152°C (bath temp., 0.10 mm); δ$Me_4Si(CDCl_3)$ 8.60 (m, aryl ring H-2 and H-6), 7.75 (doublet of triplets, J = 8 Hz, 1.8 Hz, aryl ring H-4), 7.35 (dd, J = 8 Hz, 5 Hz, aryl ring H-5), 4.35 (quartet, J = 7 Hz, OCH_2CH_3), 3.27 (s, cyclopropyl H), 1.53 (s, CH_3), 1.38 (t, J = 7 Hz, OCH_2CH_3), 1.37 (s, CH_3).

22. B.C. McKusick, R.E. Heckert, T.L. Cairns, D.D. Coffman, and H.F. Mower, J. Am. Chem. Soc., 80, 2806 (1958).

23. The cis- stereoisomeric pyrethroid acids sometimes exhibit greater activity than the corresponding trans- stereoisomer. See: M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham, and D.A. Pulman, Pesticide Sci., 6, 537 (1975).

24. For some recent examples of Michael-initiated cyclizations, see: M.T. Crimmins and J.A. DeLoach, J. Org. Chem., 49, 2076 (1984); P.R. Hamann, J.E. Toth, and P.L. Fuchs, J. Org. Chem., 49, 3865 (1984); S. Danishefsky, S. Chackalamannil, M. Silvestri, and J. Springer, J. Org. Chem., 48, 3615 (1983); P. Prempree, S. Radviroongit, and Y. Thebtaranonth, J. Org. Chem., 48, 3553 (1983) and references in footnote 1 in that paper; R.D. Little and J.R. Dawson, Tetrahedron Lett., 21, 2609 (1980). The latter authors have termed these types of reactions MIRC (Michael-initiated ring closures).

(Received in USA 15 January 1985)