(14) H. C. Brown and M. Ravindranathan, *J. Am. Chem. Soc.*, **99**, 299 (1977).
(15) It appears from the rate data that the temperature range could be extended to at least 50 °C without difficulty, thereby substantially reducing the error probability.
(16) Unfortunately, quotation of the ρ values to within ±0.2% has implied an accuracy greater than that which is evident. Thus, for example, the ρ factor for solvolysis of *exo*-2-aryl-2-benzonorbornenyl *p*-ntrobenzoate is quoted as −4.50, and a value of −4.51 for the corresponding *endo* compound is quoted,[16] yet the rate spread is *greater* for the former compounds.
(17) H. C. Brown, "The Non-Classical Carbonium Ion Problem", Plenum Press, New York, 1977, p 168.
(18) C. Eaborn and P. M. Jackson, *J. Chem. Soc. B*, 21, (1969), F. P. Bailey and R. Taylor, *ibid.*, 1446 (1971).
(19) E. Glyde and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1977, 678.
(20) R. Taylor and G. G. Smith, *Tetrahedron*, **19**, 937 (1963).
(21) Reference 17, p 277.
(22) Reference 17, pp 16–17.
(23) Reference 17, p 75.
(24) The ρ factors were estimated from the rate data for the *p*-CF_3 and unsubstituted *p*-nitrobenzoates *only*, in order to overcome the objections noted above; it follows that the error in ρ may be of the order of ±0.5. The log *k* values are for the phenyl derivatives, since these were derived by minimal extrapolation of rate data; rate coefficients for solvolysis of the 7-phenyl-7-norbornyl and 7-phenyl-7-norbornenyl *p*-nitrobenzoates obtained in 70% aqueous dioxane[25] were multiplied by 0.206[14] in order to obtain the approximate values for 80% aqueous acetone.
(25) P. G. Gassman and A. G. Fentiman, *J. Am. Chem. Soc.*, **92**, 2549 (1970).
(26) H. C. Brown, S. Ikegami, K.-T. Liu, and G. L. Tritle, *J. Am. Chem. Soc.*, **98**, 2531 (1976); H. C. Brown and K.-T. Liu, *ibid.*, **91**, 5909 (1969); J. P. Dirlam and S. Winstein, *ibid.*, **91**, 5907 (1969).
(27) The reactivities cover 14 orders of magnitude and range from the least reactive 7-norbornyl cation (which is sterically precluded from stabilization by either C–H or C–C hyperconjugation) to the 2,2-dimethylcyclopropylcarbinyl cation.
(28) W. L. Jorgensen, *J. Am. Chem. Soc.*, **99**, 280 (1977).

Synthesis and Properties of *trans*-3-(1,4-Cyclohexadienyl)acrylic Acid[1]

Charlotte Ressler,* Francis J. Goodman, Ryoki Tsutsui,[2] and Masakazu Tsutsumi[2]

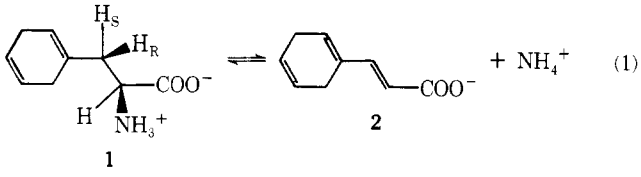
Department of Pharmacology, University of Connecticut Health Center, Farmington, Connecticut 06032

Kenneth R. Hanson

Department of Biochemistry, Connecticut Agricultural Experiment Station, New Haven, Connecticut 06504

Received November 7, 1978

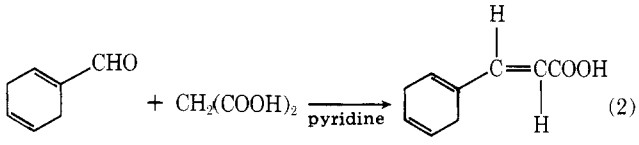
A recent study[3] examined the phenylalanine analogue 3-(1,4-cyclohexadienyl)-L-alanine (**1**)[4] as a substrate for L-phenylalanine ammonia-lyase (EC 4.3.1.5) (eq 1) in order to investigate electronic effects of β substituents on the elimination reaction with L-phenylalanine (**3**). The enzymic reaction with L-phenylalanine had been established to be an anti elimination of the (pro-3S)-H and NH_3 to give *trans*-cinnamate (**4**).[5] The new enzyme product accordingly was assigned the structure *trans*-3-(1,4-cyclohexadienyl)acrylic acid (2,5-dihydrophenylacrylic acid, **2**). Elemental analysis and the ^{1}H NMR spectrum were fully consistent with this structure.



1 2 (1)

To confirm the structure and to make this previously unknown dihydrocinnamate more readily available, synthesis of **2** was undertaken and is described herein.

An initial attempted route to **2** was analogous to a stereospecific synthesis of ethyl *trans*-cinnamate.[6] Ethyl 2-diazo-3-(2,5-dihydrophenyl)propionate, derived from ethyl 3-(2,5-dihydrophenyl)alaninate, was decomposed with sodium alkoxide. After treatment with an equivalent of base in MeOH, the tarry product afforded less than 1% of solid material with the ^{1}H NMR spectrum and melting point of **2**. In another attempt, a Wittig-type condensation[7] of 2,5-dihydrobenzaldehyde[8] and triethyl phosphonoacetate appeared to form an ethyl ester of **2**. However, it was complicated by a strong tendency toward aromatization and difficulty in isolation of the product after the subsequent hydrolysis step. Presumably the strongly alkaline conditions in both experiments were disadvantageous. The Doebner modification of the Knoevenagel reaction was expected to give almost exclusively an α,β-unsaturated compound with the desired substituted *trans*-acrylate structure[9,10] and to yield the free acid directly. This route in which 2,5-dihydrobenzaldehyde (**6**) and malonic acid are condensed in pyridine (eq 2) proved to be reasonably satisfactory, although some aromatization again took place.



6 2 (2)

The condensation reaction was examined under a variety of conditions of temperature, time, and molar ratios of reactants and base as well as with several different catalysts. A maximal yield of about 40% was attained after 3 h at 100 °C with a threefold excess of malonic acid and 1.4 equiv of pyridine on a 37-mmol scale. The crude product was an almost colorless crystalline solid. As determined by ^{1}H NMR, it consisted of a mixture of the desired 3-(1,4-cyclohexadienyl)-acrylic acid and cinnamic acid in a ratio of 75:25.

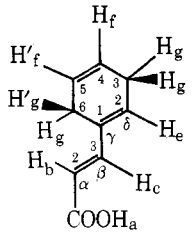
The dehydrogenation side reaction producing cinnamic acid was not investigated in detail. However, it was noted that when 2,5-dihydrobenzaldehyde only was heated with pyridine for the customary reaction time and temperature, the ratio of 2,5-dihydrobenzaldehyde/benzaldehyde was similar to the ratio of **2**/**4** in reaction 2. At least part of the dehydrogenation, therefore, can take place at the aldehyde stage and appears to be pyridine catalyzed. Decreasing the amount of pyridine to 0.2 equiv increased dehydrogenation and decreased the yield, possibly as a result of a decrease in condensation rate. It is likely that the formyl group of dihydrobenzaldehyde and the acrylate side chain of **2** could each promote base-catalyzed C-3 proton ionization that would favor dehydrogenation. In keeping with this, addition to the reaction mixture of cyclohexadiene lacking these groups did not lead to a product with significantly improved composition.

Preliminary attempts to purify **2** by a variety of techniques were unpromising. These included fractional crystallization of the mixture of **2** and **4** both as free acids and as dicyclohexylamine salts, sublimation, and thin-layer chromatography on silica gel sheets in ten solvent systems. Zone electrophoresis on paper was useful for analytical purposes. Partition chromatography with benzene on buffered silica gel columns also separated **2** and **4** but was unwieldy for preparative work.[3] High pressure liquid chromatography (LC) with μ Bondapak reverse-phase support proved to be highly satisfactory for analytical and semipreparative separations. The product was purified in this way and then recrystallized.

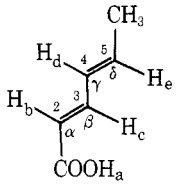
Assignment of the ^{1}H NMR signals of **3** was aided by comparison with reported spectra for *trans,trans*-sorbic acid, *trans*-cinnamic acid, and various 3-(2,5-dihydrophenyl)alanine (**1**) derivatives. The trans configuration of the substituted acrylate double bond of **2** was confirmed by the magnitude of the $J_{b,c}$ coupling constant. Synthetic **2** and the enzyme product agreed closely in ^{1}H NMR and infrared spectra and melting points.

0022-3263/79/1944-2027$01.00/0

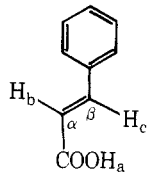
Table I. Chemical Shifts for the ^1H NMR Spectra of *trans*-3-(1,4-Cyclohexadienyl)acrylic Acid (2) and Reference Compounds in $CDCl_3$



2 [*trans*-3-(1,4-cyclohexadienyl)acrylic acid]



5 (*trans,trans*-sorbic acid)[a]



4 (*trans*-cinnamic acid)[b]

proton	chemical shifts, δ		
H_b	5.78 (d)	5.77 (d) (5.77)	6.48 (d) (6.46)
H_c	7.47 (d)	7.40 (d)	7.84 (d)
H_d		6.2 (6.20)	
H_e	6.26	6.2 (6.20)	
$H_f + H'_f$	5.82		
$H_g + H'_g$	2.84		

[a] Literature values (spectrum 6112, ref 13) are given in parentheses. [b] Literature value (spectrum 230, ref 14) is given in parentheses.

Since 2,5-dihydrophenylacrylic acid was noted to be a close structural analogue of sorbic acid, the widely used fungistat for food and cosmetics, it was examined for antimicrobial activity. When tested by the agar plate–filter paper disc method, **2** inhibited the growth of the following bacteria and fungi: *Bacillus subtilis, Shigella flexneri, Mycobacterium smegmatis, Salmonella typhimurium, Penicillium, Staphylococcus aureus, S. epidermis, Streptococcus mutans 10449, Candida albicans, Aspergillus clavatus,* and *Trichoderma viride.* It appeared to be uniformly 2–3 times more effective than sorbic acid. Further details of the inhibition experiments are to be reported elsewhere.

Experimental Section

^1H NMR spectra of most products were obtained on a Varian EM-360 spectrometer; that of purified **2** was obtained on a Jeol JNM-PS-100 NMR spectrometer. The signal of $CHCl_3$ at δ 7.27 or of tetramethylsilane served as an internal reference. Coupling constants of **2** were obtained from direct spacing measurements. Infrared spectra were taken on a Perkin-Elmer Model 137 spectrophotometer on KBr discs for solids and neat for liquids. Elemental analyses were determined by Microtech Laboratories, Skokie, Ill. Propargyl alcohol (95%) and triethyl phosphonoacetate were purchased from Aldrich Chemical Co., Milwaukee, Wis. 1,3-Butadiene (CP) was purchased from Union Carbide Corp., Linde Division. Chromium trioxide and malonic acid were from Fisher Scientific Co., Maywood, N.J.

2,5-Dihydrobenzaldehyde (1-Formyl-1,4-cyclohexadiene, 6). Propiolaldehyde[11] (8.1 g) and 1,3-butadiene (9.35 g) were condensed by a Diels–Alder reaction according to Petrov.[8] The product was distilled once to give 11.5 g (71%): bp 85 °C (20 mm); n^{25}_D 1.5178; lit.[8] bp 80 °C (20 mm); n^{20}_D 1.5182; IR 1542 (CHO), 1528 (C=C), 1430, 1180, 968, 768 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.90 (4 H, CH_2), 5.78 (2 H, HC=CH), 6.84 (1 H, OHCC=CH), 9.5 (1 H, CHO). After storage under N_2 at −35 °C for 1 month, it contained 8% benzaldehyde (^1H NMR signal at δ 7.5).

***trans*-3-(1,4-Cyclohexadienyl)acrylic Acid (2).** To a mixture of malonic acid (12 g, 115 mmol) and pyridine (4 g, 50.6 mmol) in a 50-mL conical flask fitted with a water-cooled condenser was added 2,5-dihydrobenzaldehyde (4 g, 37 mmol). The mixture was heated for 3 h with magnetic stirring in an oil bath held at 100 °C. A moderate effervescence developed in the reaction mixture that continued throughout the reaction period. The clear mixture was then cooled in ice water and adjusted to pH 1–2 with 30% sulfuric acid. The precipitate that formed was separated by decantation, and it was washed in the same way once with cold water. It was then taken up in ether, and the organic layer was extracted three times with saturated sodium bicarbonate. The aqueous extract was adjusted to pH 1–2 with 3 N HCl. The light yellow precipitate was collected by filtration, after which it was washed with cold water until chloride-free and then dried over P_2O_5: wt 2.3 g (41%); mp 131–136 °C.

To calculate the ratio of **2/4** in the product it was convenient to measure for **2** the four-proton allyl H_e singlet at δ 2.84 and for **4** the one-proton vinyl H_b doublet at δ 6.48, respectively, since these overlapped other signals the least. The combined signals at δ 5.5–6–6.75 for H_b for **4** plus H_e, H_f, and H_b for **2** and the combined signals at δ 7.2–8.2 for H_c and five aromatic H for **4** plus H_c for **2** could also be used in simultaneous equations.

Under the following reaction conditions, the percentage of total product and the percentage of **2** in the product were as follows: unmodified, malonic acid, 3 equiv, 41 and 75%; malonic acid, 1 equiv, 18 and 70%; pyridine, 0.2 equiv, 17 and 20%; piperidine, 1 drop added, 17 and 45%; cyclohexadiene, 1.3 equiv added, 30 and 60%; quinoline (pK_a 4.9; cf. pK_a 5.25 of pyridine in aqueous solution[12]), 2 equiv, replacing pyridine, 28 and 5%; H_2SO_4, 1 drop, or triethylamine replacing pyridine, 0%; 25 °C for 9 days, 29 and 40%.

Purification of Compound 2. LC was carried out on a Micromeritics Model 7000B liquid chromatograph with a μ Bondapak C_{18} (10 μm) column (3.6 mm × 30 cm) supplied by Waters Associates. Compounds were detected by absorption at 215 nm. The solvent system was 28:72 acetonitrile/water. The flow rate was 1 mL/min at ambient temperature. Under these conditions 2,5-dihydrophenylacrylic acid had a color constant of 0.27 compared to 1.0 for cinnamic acid. The latter eluted at 10.8 mL followed by **2** at 15.5 mL. When a 2-mg sample was chromatographed, **2** eluted at 16–19.3 mL and was well-separated from **4** at 8–15 mL as well as from a small unidentified peak at 21–25 mL. Rechromatography confirmed the homogeneity of each peak. Evaporation left a crystalline residue that was recrystallized twice from EtOH. From 75 mg of crude product multiple runs furnished 18.5 mg of **2**: mp 155–157 °C; IR 3100–2870 (COOH), 1695 (=CHCO), 1620 (COO^-, C=CC=C), 1425, 1335, 1225, 980, 877, 697 cm^{-1}.

Anal. Calcd for $C_9H_{10}O_2$: C, 72.0; H, 6.71. Found: C, 72.0; H, 6.80.

^1H NMR assignments in $CDCl_3$ are given in Table I along with those for reference compounds. Consistent with the conjugation of H_e to an α,β-unsaturated system in **2** is the pronounced downfield shift of this signal in going from **1**[4,15] to **2**. The signals for H_b and H_c in **2** are further upfield than those in cinnamic acid, reflecting increased deshielding by the aromatic ring relative to the isolated double-bond system.[16] The $J_{b,c}$ spin coupling constant was 15.8 ± 0.3 Hz, within the range characteristic of olefinic protons in a trans orientation.[3,17] Corresponding constants for *trans*- and *cis*-cinnamic acids are 15.8 and 12.3 Hz, respectively.[18] Chemical shifts for the relevant protons H_b, H_c, and H_e correspond closely between **2** and *trans,trans*-sorbic acid and support the trans orientation in **2**.

Acknowledgments. This work was aided by a General Research Support Grant (F.J.G.), the Muscular Dystrophy

Association (C.R.), and Grant BG-42247-X from the National Science Foundation (K.R.H.). We would like to thank Dr. H. Bleich for the Jeol ^1H NMR spectrum.

Registry No.—**2,** 6911-23-0; **4,** 140-10-3; **6,** 58836-15-0; propiolaldehyde, 624-67-9; 1,3-butadiene, 106-99-0; malonic acid, 141-82-2.

References and Notes

(1) Abbreviations and nomenclature: (*E,E*)-hexa-2,4-dienoic acid, sorbic acid, **5**; (*E*)-3-(1,4-cyclohexadienyl)-2-propenoic acid, *trans*-3-(1,4-cyclohexadienyl)acrylic acid, or 2,5-dihydrophenylacrylic acid, **2**; *trans*-3-phenylacrylic acid, *trans*-cinnamic acid, **4**.
(2) Visiting investigator.
(3) K. R. Hanson, E. A. Havir, and C. Ressler, *Biochemistry*, **18**, 1431 (1979).
(4) M. L. Snow, C. Lauinger, and C. Ressler, *J. Org. Chem.*, **33**, 1774 (1968).
(5) K. R. Hanson and E. A. Havir, *Enzymes, 3rd Ed., 1972*, **7**, 75 (1972).
(6) N. Takamura, T. Mizoguchi, and S. Yamada, *Tetrahedron Lett.*, 4267 (1973).
(7) W. S. Wadsworth, Jr., and W. D. Emmons, *J. Am. Chem. Soc.*, **83**, 1737 (1961).
(8) A. A. Petrov, *Zh. Obshch. Khim.*, **24**, 2136 (1955); *Chem. Abstr.*, **50**, 233b (1956).
(9) J. R. Johnson, *Org. React.*, **1**, 226 (1942).
(10) As based on observations with all of a large number of aromatic aldehydes and a limited number of aliphatic aldehydes; see G. Jones, *Org. React.*, **15**, 203 (1967).
(11) Prepared by chromic acid oxidation of propargyl alcohol: J. C. Sauer, "Organic Synthesis", Collect Vol. IV, Wiley, New York, 1963, p 813. The product, which still retained 6 mol % water (^1H NMR), was used in the following step.
(12) R. C. Weast, "Handbook of Chemistry and Physics", 51st ed., The Chemical Rubber Publishing Co., Cleveland, Ohio, 1970–1971, p D-117.
(13) Stadtler Laboratories, "Stadtler Standard NMR Spectra", Vol. 2, Stadtler Research Laboratories, Philadelphia, Pa., 1973.
(14) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "Varian NMR Spectra Catalogue," Vol. 1, Varian Associates, Palo Alto, Calif., 1962.
(15) G. R. Nagarajan, L. Diamond, and C. Ressler, *J. Org. Chem.*, **38**, 621 (1973).
(16) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, New York, 1959, pp 57, 134.
(17) D. H. Williams and I. Fleming, "Spectroscopic Methods in Organic Chemistry", McGraw-Hill, New York, 1966, p 128.
(18) H. P. Baden, M. A. Pathak, and D. Butler, *Nature (London)*, **210**, 732 (1966).

Impregnated Cyanide Reagents. Convenient Synthesis of Nitriles[1]

Steven L. Regen,* Silvio Quici, and Shang-Jiin Liaw

Department of Chemistry, Marquette University, Milwaukee, Wisconsin 53233

Received October 2, 1978

We wish to report a convenient method for carrying out cyanide displacement on organic halides. Our approach is based on an impregnation technique and requires only two steps for product isolation, filtration and solvent evaporation.[2]

Attempted reaction of sodium cyanide with 1-bromooctane in toluene at 130 °C (sealed tube) produced a negligible yield of the corresponding displacement product.[3,5] In contrast, similar reactions carried out in which the salt was first impregnated onto certain inorganic solids resulted in considerable substitution. Empirical testing of 15 supports revealed that neutral alumina was most effective in activating cyanide (Table I).

An optimal procedure for impregnating NaCN onto alumina (reagent 1) is presented in the Experimental Section. Reaction of 1 with a series of organic halides gave yields of nitrile product which are summarized in Table II. The convenience afforded with the use of 1 is exemplified by the conversion of 1-bromododecane to 1-cyanododecane. After a toluene solution of 1-bromododecane was stirred at 90 °C for 45 h in the presence of 1, the spent and unused insoluble reagent were removed under reduced pressure, leaving a 100% yield of 1-cyanododecane which was spectroscopically identical with an authentic sample.

Table I. Impregnated Cyanide Reagents[a]

support	reactive cyanide, mmol/g
LMS 3A ($1/16$-in. pellets)	0.1
LMS 4A ($1/16$-in. pellets)	trace
LMS 5A ($1/16$-in. pellets)	trace
LMS 13X ($1/16$-in. pellets)	1.0
LMS 4A (powder)	0.1
LMS 5A (powder)	trace
LMS 13X (powder)	1.4
LMS 4A (8–12 mesh)	0.2
K-10 Montmorillonite clay (powder)	trace
K-306 Montmorillonite clay (powder)	0.4
K-306 Montmorillonite clay (spheres)	0.1
graphite	trace
Celite	0.1
silica gel (100–200 mesh)	trace
neutral alumina	1.8
none	trace

[a] All impregnated reagents were prepared using the following standard procedure. A 2.0-g amount of support was added to 20 mL of an aqueous solution containing 0.5 g of sodium cyanide. Water was removed by rotary evaporation (bath temperature was kept below 65 °C), and the resulting reagent was dried under reduced pressure [4 h, 110 °C (0.05 mm)]. No effort was made to physically separate nonadsorbed cyanide. The quantity of reactive cyanide was determined by reaction of 0.5 g of impregnated reagent with 2.5 mmol of 1-bromooctane in 3 mL of toluene at 130 °C for 24 h. Reaction mixtures were unstirred and analyzed by GLC using internal standard techniques. Material balance and reproducibility were excellent. Values reported above are in millimoles of 1-cyanooctane per gram of reagent.

Table II. Nitrile Synthesis Using Sodium Cyanide Coated Alumina[a]

reactant	product	time, h	yield, %[b]
1-bromobutane	1-cyanobutane	24	93
1-chlorobutane	1-cyanobutane	40	42
1-iodooctane[7]	1-cyanooctane	40	37
1-bromooctane	1-cyanooctane	24	97[c]
1-chlorooctane	1-cyanooctane	40	52
1-bromododecane	1-cyanododecane	24	100[c]
1-chlorododecane	1-cyanododecane	40	33
2-bromooctane	2-cyanooctane	40	27

[a] Unless noted otherwise, displacement on 1.0 mmol of the indicated organic halide was carried out in 4.0 mL of toluene using 1.49 g of 1 at 90 °C. Reaction mixtures were stirred with a Teflon-coated magnetic stirring bar. [b] Yields were determined by GLC using internal standard techniques. Material balance was >95% in all cases. Control experiments carried out under identical conditions using nonimpregnated sodium cyanide showed no reaction. [c] Isolated yield from a preparative reaction (45 h) using procedures described in the Experimental Section.

The advantage of this procedure for the preparation of nitriles lies in its simplicity, its avoidance of aqueous workup and extraction steps,[4] and also its avoidance of highly toxic solvents (e.g., hexamethylphosphoramide) required in procedures currently used;[6] its principal disadvantage is the relatively slow rate of reaction. Nonetheless, this method serves as a useful synthetic alternative for small-scale conversions.

Experimental Section

General Methods. Unless stated otherwise, all reagents and chemicals were obtained commercially and were used without further

0022-3263/79/1944-2029$01.00/0