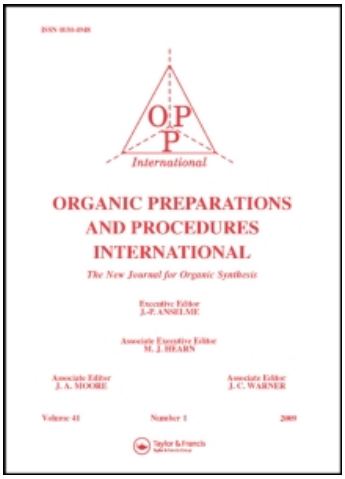

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SYNTHESIS OF METHYL trans-2-PHENYLCYCLOPROPANE CARBOXYLATES

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SYNTHESIS OF METHYL

trans-2-PHENYLCYCLOPROPANE CARBOXYLATES

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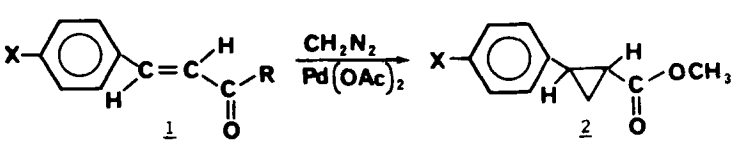
As part of our ongoing synthetic program in designing new adrenergic agents, a series of substituted trans-2-phenylcyclopropane carboxylates was desired. Although the cyclopropanation of ethyl cinnamate using a palladium acetate catalyst has been reported as a preliminary communication,[1] there is no systematic study of the influence of aromatic substituents on the success of the reaction. We have now confirmed that palladium(II) acetate is suitable for the cyclopropanation of a variety of cinnamic acids or their esters with diazomethane under very mild conditions.

The nature of the substituents studied has little effect on the



reaction (see Table). Prior esterification of the cinnamic acid is unnecessary since the use of excess diazomethane results in esterification and cyclopropanation. Although alkyl 2-phenylcyclopropane carboxylates can also be obtained by the addition of methyl or ethyl diazoacetate to substituted styrenes,[2,3] the present method has several distinct advantages. A wide variety of pure trans-cinnamic acids are either commercially available or are readily accessible.[4] The geometry of the cyclopropanes is governed by the geometry of the starting material; therefore separation of cis/trans mixtures which are produced in the

TABLE. Cyclopropanation of Cinnamic Acid Derivatives[a]

	X	R	Ratio of CH_2N_2/cinnamate[b]	%Conversion[c]	% Yield[d]
1a	H	OCH_3	2.8	>90	82
1b	CH_3	OH	4.0	>95	84
1c	OCH_3	OCH_3	3.0	>95	81
1d	Cl	OH	4.0	55[e]	93
	Cl	OCH_3	2.8	>90	76
1e	F	OCH_3	2.8	>90	82
	F	OH	2.8	>80	76
1f	CF_3	OH	4.0	80	82

a) The cinnamate/catalyst mole ratio was 200/1 in every case except with the p-fluorocinnamic acid, where it was 230/1. The use of lower ratios gave poorer conversion. b) Mole ratio of reactants. c) Measured by comparing the intensity of the ^{1}H-NMR residual vinylic signals with the product cyclopropane signals or by comparing the intensities of the OCH_3 singlets from product and starting materials. d) Isolated yield after vacuum distillation. e) The poor conversion may be due to the poor solubility of p-chlorocinnamic acid in ether.

styrene addition reactions is avoided; thus higher yields of pure geometric isomers are obtained.

EXPERIMENTAL SECTION

All of the cinnamic acids used were commercially available. Esterification was accomplished with methanol and sulfuric acid.[5] The esters were

purified by fractional distillation and their identities were verified spectroscopically. The ^{1}H-NMR data of compounds 2b,c,d were identical to those reported in the literature.[2] NMR spectra were recorded on a Perkin-Elmer R 20-B instrument, using TMS as the internal standard; IR spectra were recorded on a Perkin-Elmer 137 spectrophotometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. The cyclopropanation reaction is illustrated by the following detailed procedures. CAUTION: All reactions using diazomethane should be performed in a good hood with adequate safety shields. Also all glassware should be of the smooth joint variety (available from Aldrich Chemical Company). To ensure complete dissipation of residual diazomethane, it is absolutely essential that the reaction mixtures be allowed to stand for the specified 20 hrs period prior to vacuum distillation.

Methyl trans-2-(p-Methoxyphenyl)cyclopropane Carboxylate (2c). From Ester.- A solution of 21.4 g (0.100 mol) of diazald in 200 mL of ether was added slowly to a solution of 5 g of KOH in 8 mL of H_2O and 25 mL of ethanol heated to 60-65°. Ethereal diazomethane was rapidly distilled into a separatory funnel and then slowly added (40 min.) to a stirred solution of 4.49 g (0.023 mol) of methyl trans-p-methoxycinnamate and 26 mg (0.115 mmol) of $Pd(OAc)_2$ in 200 mL of ether at 0-5°C under nitrogen. The solution remained yellow throughout the addition process and became cloudy after about one half of the diazomethane had been added. Stirring was continued for 20 hrs. [SEE CAUTION] A pale yellow precipitate was removed by filtration prior to evaporation of ether on a Rotovap. The viscous yellow liquid which remained, yielded 3.87 g (81%) of yellow solid after 5 hrs. in a vacuum desiccator. Recrystallization from ethanol gave a white crystalline solid, mp. 56-57°. ^{1}H-NMR ($CDCl_3$): δ 6.85 (dd, 4H, ArH), 3.65 (s, 3H, $COOCH_3$), 3.70 (s, 3H, aromatic CH_3O-), 2.5 (m, 1H) and 1.9-1.1 (m, 3H, cyclopropyl). IR (neat): 1725 cm^{-1} (C=O).

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.88; H, 7.00

Methyl trans-2-(p-Methylphenyl)cyclopropane Carboxylate (2b). From Acid.- Ethereal diazomethane prepared as above from 30.6 g (0.143 mol) of diazald was slowly added (1 hr.) to a stirred solution of 4.00 g (0.025 mol) of trans-p-methylcinnamic acid and 28 mg (.125 mmol) of $Pd(OAc)_2$ in 200 mL of ether cooled to 0-5° under nitrogen. Initially, the acid was only

partially soluble, but as the addition proceeded complete solution occurred. Stirring was continued for 20 hrs. [SEE CAUTION] A pale yellow solid was filtered from solution. The ether was removed on a Rotovap leaving a yellow oil which upon vacuum distillation yielded 4.00 g (84%) of a colorless liquid product, bp. 130°/2.2 torr; n_D^{20} = 1.5261. ^{1}H-NMR (CCl_4): δ 6.85 (s, 4H, ArH), 3.5 (s, 3H, $COOCH_3$), 2.2 (s, 3H, aromatic CH_3), 2.4 (m, 1H) and 1.0-0.9 (m, 3H, cyclopropyl). IR (neat): 1725 cm^{-1} (C=O).

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.54; H, 7.52

Methyl trans-2-(p-Chlorophenyl)cyclopropane Carboxylate (2d) bp. 138°/2.3 torr. ^{1}H-NMR (CCl_4): δ 7.03 (dd, 4H, aromatic H), 3.60 (s, 3H, $COOCH_3$), 2.4 (m, 1H) and 1.9-1.0 (m, 3H, cyclopropyl). IR (neat): 1700 cm^{-1} (C=O).

Anal. Calcd. for $C_{11}H_{11}O_2Cl$: C, 62.72; H, 5.26. Found: C, 62.87; H, 5.59

Methyl trans-2-Phenylcyclopropane Carboxylate (2a) bp 108°/1.2 torr. ^{1}H-NMR (CCl_4): δ 7.05 (m, 5H, ArH), 3.55 (s, 3H, $COOCH_3$), 2.4 (m, 1H) and 2.0-1.0 (m, 3H, cyclopropyl). IR (neat): 1725 (C=O).

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.97; H, 6.87. Found: C, 74.95; H, 6.93

Methyl trans-2(p-Fluorophenyl)cyclopropane Carboxylate (2e) bp 107°/1.5 torr. ^{1}H-NMR (CCl_4): δ 6.90 (m, 4H, ArH), 3.60 (s, 3H, $COOCH_3$), 3.4 (m, 1H) and 1.9-1.0 (m, 3H, cyclopropyl). IR (neat) 1725 (C=O).

Anal. Calcd. for $C_{11}H_{11}O_2F$: C, 68.03; H, 5.71. Found: C, 68.02; H, 6.02

Methyl trans-2(p-Trifluoromethylphenyl)cyclopropane Carboxylate (2f) bp 97°/0.5 torr. ^{1}H-NMR (CCl_4): δ 7.3 (dd, 4H, ArH), 3.65 (s, 3H, $COOCH_3$), 2.45 (m, 1H) and 2.0-1.1 (m, 3H, cyclopropyl). IR (neat): 1730 (C=O).

Anal. Calcd. for $C_{12}H_{11}O_2F_3$: C, 59.02; H, 4.54. Found: C, 59.06; H, 4.52

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AN IMPROVED SYNTHESIS OF 1,2-DEHYDRO-N-ACETYLDOPAMINE

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The well-established[1,2] participation of catecholamines and their derivatives in the hardening and tanning of insect cuticle (sclerotization) is essential for the survival of most insects. Cuticular phenoloxidase is known to play a crucial role in this process by oxidizing the catecholamine derivatives which may then crosslink with structural protomers in cuticle to generate protein-protein as well as protein-chitin crosslinks.[1-4] Three major reactive species have been characterized so far as reaction products of phenoloxidases on catecholamine derivatives.