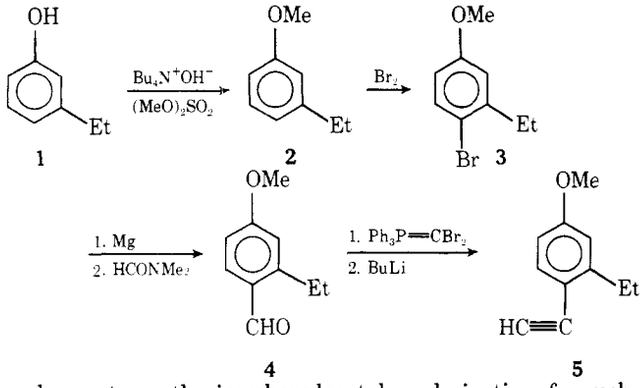
Scheme I



endeavor to synthesize phenylacetylene derivatives for such application has been documented. The synthesis of 2-ethyl-4-methoxyphenylacetylene (**5**) is reported. It is a precursor for a series of alkynes to be synthesized for study of structure–estrogenic activity relationships in such compounds.

Synthetic Approach

Scheme I summarizes the synthesis of the title compound **5**. Two convenient starting materials, 3-ethylphenol (**1**) and 3-methoxyacetophenone, are readily available. Phase-transfer-catalyzed methylation of **1** provided quantitatively 3-methoxyethylbenzene (**2**). Similar high yields of **2** are obtained by Clemmenson reduction of the acetophenone. Attempts to obtain **2** from 3-methoxybenzaldehyde via Wittig reaction with triphenylmethylenephosphorane and subsequent hydrogenation of 3-methoxystyrene are unsatisfactory.

Two methods for carbonylation were studied. Bromination of **2** yielded exclusively 4-bromo-3-ethylanisole (**3**), underscoring the applicability of partial rate factors to this electrophilic aromatic substitution.[3] (The position of bromination was confirmed by conversion to the known 2-ethyl-4-methoxybenzoic acid.[4]) Grignard reaction with *N,N*-dimethylformamide yields 2-ethyl-4-methoxybenzaldehyde (**4**). Friedel–Crafts reaction (Cl_2CHOCH_3 and $TiCl_4$)[5] of **2** is unsatisfactory, as an isomeric mixture of aldehydes results.

Ethinylation, the final conversion, was first attempted using the method of Oliver and Walton.[6] In this procedure an arylcopper reagent couples with iodoethinyl(trimethyl)silane to give an arylethinyl(trimethyl)silane, which may be quantitatively desilylated by treatment with alkali. In our hands this conversion failed, and 3-ethyl-4-iodoanisole was isolated. Steric factors often hinder organocopper reactions,[7] and in this case the *o*-ethyl group probably facilitated exchange over ethinylation. Ethinylation was achieved using the two-step method of Corey and Fuchs (Wittig reaction followed by alkyllithium-promoted rearrangement).[8]

Experimental Section

All reagents were suitably purified before use. Anhydrous $MgSO_4$ served as the drying agent. Boiling points are uncorrected. Infrared spectra of thin films were recorded on the Beckman IR-10 and calibrated using the 6.24-μm band of polystyrene. NMR spectra of dilute solutions in Silanor-C were recorded on the Varian T60 spectrometer. Standard spectral notations apply. X-ray data were obtained using the Picker x-ray fluorescence spectrometer.

3-Ethylanisole (2). To a slurry of NaOH (20 g, 0.5 mol) and tetrabutylammonium hydroxide (10 mol %) in 100 mL of H_2O was added dropwise a solution of 3-ethylphenol (**1**, Aldrich Chemical Co., 30.5 g, 0.25 mol) in 50 mL of H_2O. To the resulting solution was added dropwise 30 mL of dimethyl sulfate (0.3 mol). Rapid, exothermic reaction ensued. After stirring 2 h, separation of the organic layer, extraction of the aqueous layer with CH_2Cl_2, drying and concentration, distillation afforded 31.2 g (95%) of **2** as a colorless oil: bp 70–71 °C (9 Torr); lit.[9] bp 74 °C (10 Torr); IR (film) 1600, 1480, 1260, 1150, 1030, 865, 770, and 680 cm^{-1}; NMR ($CDCl_3$) δ 6.9 (m, 4, phenyl), 3.8 (s, 3, OCH_3), 2.55 (quartet, 2, J = 8 Hz, $-CH_2CH_3$), 1.2 (t, 3, J = 8 Hz, $-CH_2CH_3$).

2-Ethyl-4-methoxybromobenzene (3). A slurry of **2** (6.8 g, 0.05 mol) and 0.1 g of iron filings in 50 mL of CCl_4 was stirred and cooled in an ice–salt bath as a solution of bromine (2.9 mL, 0.055 mol) in 20 mL of CCl_4 was added dropwise over 3 h. After stirring 3 h, the mixture was poured into water and worked up. Drying and concentration gave 9.6 g (90%) of **3** as a colorless oil: bp 79–80 °C (0.5 Torr); IR (film) 1590, 1570, 1470, 1235, 1135, 1005, 860, 840, and 790 cm^{-1}; NMR ($CDCl_3$) δ 7.25 (doubled doublets, 1, J = 1 and 2 Hz, phenyl), 6.7 (m, 2, phenyl), 3.7 (s, 3, OCH_3), 2.75 (quartet, 2, J = 8 Hz, $-CH_2CH_3$), 1.2 (t, 3, J = 8 Hz, $-CH_2CH_3$); x-ray fluorescence K α-Br 29.96°, K β-Br 26.79°.

Anal. Calcd for $C_9H_{11}BrO$: C, 50.26; H, 5.16; Br, 37.15. Found: C, 50.49; H, 5.25; Br, 37.09.

2-Ethyl-4-methoxybenzaldehyde (4). To magnesium turnings (1.6 g, 0.065 g-atom) in 30 mL of anhydrous ether was added a solution of 4.3 g of ethyl bromide (0.04 mol) and 4.3 g of **3** (0.02 mol) in 50 mL of anhydrous ether. After refluxing for 1 h an ethereal solution of 4.3 mL (0.06 mol) of *N,N*-dimethylformamide was added with external cooling. After 1 h it was decomposed with aqueous NH_4Cl. After separation the aqueous layer was extracted twice with ether. Combined ethereal extracts were washed and dried. Concentration and distillation gave 3.1 g (94%) of colorless liquid: bp 107–108 °C (2.5 Torr); IR (film) 2720, 1690, 1610, 1240, 900, and 810 cm^{-1}; NMR ($CDCl_3$) δ 10.3 (s, –CHO), 7.7 (d, 1, J = 7 Hz, phenyl), 6.7 (m, 2, phenyl), 3.8 (s, 3, $-OCH_3$), 2.6 (quartet, 2, J = 8 Hz, $-CH_2CH_3$) and 1.1 (t, 3, J = 8 Hz, $-CH_2CH_3$).

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.12; H, 7.39.

2-Ethyl-4-methoxyphenylacetylene (5). A mixture of Zn powder (2.62 g, 0.04 g atom), 10.5 g of triphenylphosphine (0.04 mol), 13.3 g of CBr_4 (0.04 mol), and 300 mL of CH_2Cl_2 was stirred under Ar for 24 h. After the dropwise addition of 3.3 g of **4** (0.02 mol) the mixture was stirred an additional 2 h. Addition of 1.2 L of pentane, filtration, and evaporation of solvents gave dibromo-2-(2′-ethyl-4′-methoxyphenyl)ethene. Insoluble material was reworked by additional cycles of CH_2Cl_2 extraction–pentane precipitation to maximize yield of dibromoolefin to 5.5 g (86%). This yellow liquid was used without further purification.

A solution of 5.5 g of dibromoolefin in 60 mL of THF was cooled to −78 °C (dry ice–acetone) and *n*-butyllithium (44 mL, 0.8934 M) was added dropwise. After 1 h at −78 °C, the reaction was warmed to room temperature and poured into 200 mL of water. The alkyne was extracted with pentane. Distillation afforded 2.5 g (80%) of clear colorless liquid: bp 112–113 °C (7.5 Torr); IR (film) 3300, 2100, 1605, 1490, 1235, 1030, and 640 cm^{-1}; NMR ($CDCl_3$) δ 6.8 (m, 3, phenyl), 3.7 (s, 3, OCH_3), 2.95 (s, 1, C≡CH), 2.7 (quartet, 2, J = 8 Hz, $-CH_2CH_3$), 1.2 (t, 3, J = 8 Hz, $-CH_2CH_3$).

Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.62; H, 7.64.

Registry No.—**1**, 620-17-7; **2**, 10568-38-4; **3**, 34881-44-2; **4**, 6161-69-9; **5**, 62929-98-0; dibromo-2-(2′-ethyl-4′-methoxyphenyl)ethene, 62929-99-1.

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Synthesis of Olefins via Reduction–Decyanation of β,γ-Unsaturated Nitriles

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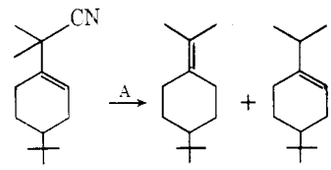
As part of a program aimed at developing methodology for the synthesis of natural products, we are examining dual uses of the cyano function as an activating and leaving group. We

Table I. Variations in Olefin Isomer Ratio with Changing Reaction Conditions

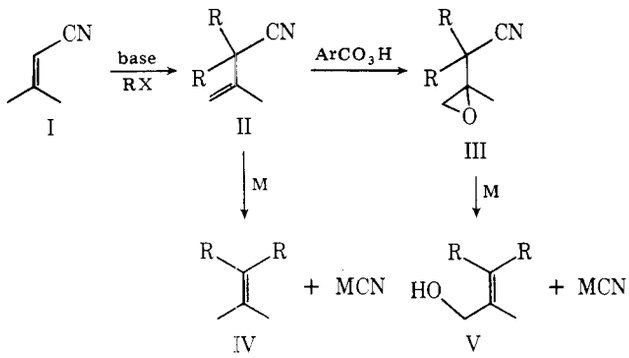


2b 3b 4b

A	3b (rel %)[a]	4b (rel %)[a]	% yield[b]
Na, NH_3, −33 °C	20	80	95
Li, NH_3, −33 °C	20	80	85
Ca, NH_3, −33 °C	20	80	94
Li, NH_3, EtOH, −33 °C	35	65	
Li, NH_3, *t*-BuOH, −33 °C	40	60	
Li, NH_3, *t*-BuOH, −78 °C	30	70	95
Na, NH_3, *t*-BuOH, −33 °C	50	50	99
K, C_6H_6, 80 °C	20	80	99
Na, naphthalene, −78 °C	15	85	
Li, THF, HMPA, 25 °C	20	80	90

[a] Analyzed by gas chromatography. [b] Crude product.

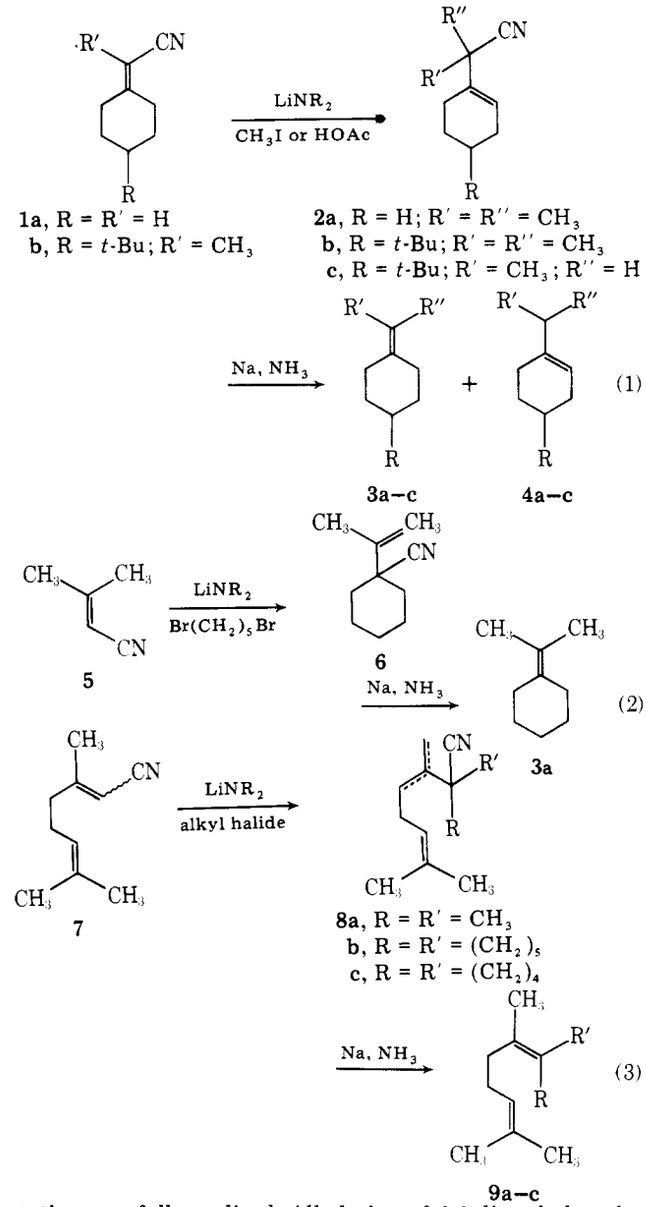
Scheme I



have previously shown that β,γ-epoxy nitriles (III), obtained according to Scheme I, undergo smooth reduction–elimination to allylic alcohols (V) upon treatment with dissolving metals.[1] In this report we describe related work involving the reduction–decyanation of β,γ-unsaturated nitriles (II) to give olefins (IV).

We first explored the synthesis of isopropylidenecyclohexanes **3a** and **3b** from the cyclohexylideneacetonitriles **1a** and **1b** (eq 1). Methylation using lithium diisopropylamide and methyl iodide in THF–HMPA gave the requisite β,γ-unsaturated nitriles **1a** and **2b**.[1] Nitrile **2a** underwent reduction with sodium in ammonia to a 1:2 mixture of the exocyclic and endocyclic olefin isomers **3a** and **4a**.[2] When reduction was carried out in the presence of *tert*-butyl alcohol, a 1:1 mixture of these olefins was obtained. The 4-*tert*-butyl derivative **2b** behaved analogously. Reduction using sodium in ammonia afforded a 1:4 mixture of olefins **3b**[3] and **4b** without added alcohol and a 1:1 mixture in the presence of *tert*-butyl alcohol. Attempts to increase the proportion of isopropylidene isomer **3** by changes in reducing metal, proton source, solvent, and temperature were unpromising. Some representative trials are shown in Table I.

Interestingly, reduction of the monomethylated cyclohexenylacetonitrile **2c** yielded cyclohexene **4c**[4] exclusively. These findings suggested to us that the reduction–decyanation of allylic cyano compounds tends toward thermodynamic control,[5] especially in the absence of an added proton source. Therefore, an alternative approach to isopropylidenecycloalkanes and related olefins starting from isopropenyl-substituted nitriles such as **6** seemed worth pursuing. Here, we would expect the isopropylidene isomer **3a** to be the more stable of the two possible olefin products. In fact, this expectation was fully realized. Alkylation of β,β-dimethylacrylonitrile (**5**)[6] with 1,5-dibromopentane followed by reduction of the resulting nitrile **6** with sodium in ammonia afforded isopropylidenecyclohexane (**3a**) containing 5% of the isopropenyl isomer (eq 2).



The readily available mixture of gerano- and neronitriles (**7**)[7] could be similarly alkylated to the dimethyl- (**8a**), cyclohexyl- (**8b**), and cyclopentyl-substituted (**8c**) unsaturated nitriles (eq 3). These intermediates were obtained as mixtures of double bond isomers judged by NMR analysis to contain principally the *E* isomers. Reduction with sodium in ammonia then yielded the isomerically pure tetrasubstituted olefins **9a, 9b,** and **9c** in high yield.

The foregoing results show that allylic cyano compounds, conveniently prepared by alkylation of conjugated nitriles, serve as useful precursors to olefins. The regiochemistry of the reduction process appears to favor the more highly substituted and/or more stable double bond isomer, although additional studies are needed to establish the controlling factors. Finally, synthetic applications based on the use of α,ω-dihalides as the alkylating agents leading to cycloalkylidene olefins such as **3a, 9b,** and **9c** may find use in connection with bisabolenes[8] and related natural products.

Experimental Section[9]

2-(4-*tert*-Butylcyclohexylidene)propanenitrile (1b). To a

Table II. Unsaturated Nitriles

Nitrile[a]	Registry no.	% yield	NMR, ppm CH_3	NMR, ppm Vinylic H(s)
1b	63089-63-4	97	1.85 (s) 0.85 (s)	
2b	63089-64-5	98	1.45 (s) 0.88 (s)	5.8–6.0
2c	63089-65-6	98	1.26 (d, J = 6 Hz) 0.88 (s)	5.6–5.9
6	63089-66-7	82	1.90 (s)	5.26 (s) 5.00 (m)
8a		98	1.49 (s) 1.62 (s) 1.70 (s)	4.9 5.23 5.05–5.35

[a] Satisfactory analytical data (C, H, N) for all compounds were submitted for review.

Table III. Olefins

Olefin(s)[c]	Registry no.	% yield	NMR CH_3	NMR Vinylic H
4c	15822-49-8	92	0.88 (s) 0.90 (t, J = 8 Hz)	5.3–5.6
3a	5749-72-4	91	1.68 (s)	
4b[a]	63089-67-8	93	0.90 (s) 1.0 (d, J = 14 Hz)	5.3–5.5
9a	63089-68-9	94	1.62 (s)	5.0–5.3
9b	63089-69-0	78[b]	1.65 (s)	4.9–5.3
9c	63089-70-3	88[b]	1.61 (s)	4.9–5.3

[a] Obtained from acid treatment of **3b, 4b** mixture. [b] Overall yield from conjugated nitrile **7**. [c] Satisfactory analytical data for all compounds except **4c** and **3a** were submitted for review.

stirred suspension of 0.83 g (20 mmol) of sodium hydride in 15 mL of 1,2-dimethoxyethane (DME) was added 3.5 mL (20 mmol) of 2-(diethylphosphono)propanenitrile in 5 mL of DME.[10] The mixture was stirred at reflux until cessation of hydrogen evolution, whereupon 1.25 g (9.9 mmol) of 4-*tert*-butylcyclohexanone in 10 mL of DME was added and reflux was continued for 20 h. The cooled mixture was poured into water and the product was isolated by ether extraction and chromatographed on alumina to give 1.58 g (97%) of nitrile **1b**, mp 66–67 °C (Table II).

General Alkylation Procedure. To a solution of lithium diisopropylamide (prepared from 1.25 mL of diisopropylamine in 150 mL of tetrahydrofuran, 3.6 mL of 2.2 M *n*-butyllithium, and 1.8 mL of hexamethylphosphoramide) at −78 °C was added 3.4 mmol of conjugated nitrile in 20 mL of tetrahydrofuran.[1,11] After 15 min, 8 mmol of methyl iodide or 4 mmol of α,ω-dibromide was added and the stirred mixture was allowed to reach room temperature over a 2-h period. Water was added and the alkylated unsaturated nitriles (**2b, 6,** and **8a**) were isolated by ether extraction and purified by short-path distillation. These results are shown in Table II. Nitriles **8b** and **8c** were reduced directly without purification.

2-(4-*tert*-Butyl-1-cyclohexenyl)propanenitrile (2c). To a solution of lithium diisopropylamide (prepared from 0.8 mL of diisopropylamine in 10 mL of tetrahydrofuran, 2.3 mL of 2.2 M *n*-butyllithium, and 1.0 mL of hexamethylphosphoric triamide) at −78 °C was added 0.64 g of nitrile **1c**. After 15 min, 0.6 mL of glacial acetic acid was added.[11] The solution was allowed to reach room temperature, water was added, and the product was isolated by ether extraction to give 0.63 g (98%) of deconjugated nitrile **2c**, bp 70°C at 0.05 Torr (Table II).

General Reduction Procedures. To a stirred solution of 10 mg-atoms of sodium in 25 mL of refluxing ammonia contained in a three-neck flask equipped with a cold finger condenser charged with dry ice–acetone slurry was added a solution of 1 mmol of nitrile in 2–3 mL of tetrahydrofuran. After sitrring for 1 h, the mixture was treated with solid ammonium chloride to discharge the blue color. The ammonia was allowed to evaporate, 25 mL of water was added, and the olefin products (**4c, 3a, 9a, 9b,** and **9c**) were isolated by hexane extraction and purified by short-path distillation. The results are shown in Table III.

Equilibration of Olefins 3b and 4b.[12] A solution of 0.18 g of a 55:45 mixture of olefins **3b** and **4b** in 10 mL of 5% sulfuric acid in acetic acid was stirred at room temperature for 1 h. The acid was neutralized with 10% sodium hydroxide and the product was isolated by hexane extraction, affording 0.17 g (93%) of a 95:5 mixture of **4b** and **3b**, bp 70 °C (bath temperature) at 15 mm.

Acknowledgments. We are indebted to the National Science Foundation for support of this work through a research grant (CHE75-07777). We also thank the Dow Chemical Co. for a fellowship award to R.B. A generous sample of gerano- and neronitriles was provided by Robert Dahill, Givaudan Corp., Clifton, N.J.

Registry No.—3b, 14033-75-1; **8a** isomer I, 63089-71-4; **8a** isomer II, 63089-72-5; **8b** isomer I, 63122-45-2; **8b** isomer II, 63089-73-6; **8c** isomer I, 63089-74-7; **8c** isomer II, 63089-75-8; 2-(diethylphosphono)propanenitrile, 29668-61-9; 4-*tert*-butylcyclohexanone, 98-53-3.

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(9) The apparatus described by W. S. Johnson and W. P. Schneider ["Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 132] was used to maintain an argon atmosphere. The isolation procedure consisted of thorough extractions with the specified solvent, washing the combined extracts with water, saturated brine solution, and drying the extracts over anhydrous sodium sulfate. The solvent was removed from the filtered extracts under reduced pressure on a rotary evaporator. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. Nuclear magnetic resonance spectra were recorded with Varian T-60 or Perkin Elmer R20B spectrometers. Signals are reported as the chemical shift downfield from tetramethylsilane (Me_4Si) in parts per million (ppm) of the applied field. Coupling constants are reported in hertz (Hz).
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Coordinative Role of Alkali Cations in Organic Synthesis. 2. The Chalcone–Flavanone System

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Coordination of alkali cations (M) with neutral organic nucleophiles is now well known,[1–3] and the effect of such interactions on the methylation of kojic acid with dimethyl sulfate has been reported.[4] Significantly, the mechanism of organic reactions involving caustic alkalies and alkali salts is always discussed by considering only the anionic part of the inorganic species.[5] It is demonstrated in this paper that a full mechanism of such reactions cannot be written until the interactive behavior of the cationic counterpart is also discussed, for there is no reason why a cation should be inert when negatively charged or polarized species are involved in the reaction. To illustrate this point, we describe the condensation of 2-hydroxyacetophenone (HAP) with benzaldehyde (BLD) to produce chalcone and cyclization of the latter to produce flavanone as a function of the nature and concentration of the caustic alkalies. In the following, notations such as E, E_4, and