from the dichloride), boiled at 200–203 °C (0.2 torr) and melted at 48.5–51 °C (lit.[18] mp 50 °C).

12,30-Dioxa-3,21-dioxo[5.1.5.1]paracyclophane, 2,16-Dioxapentacyclo[24.2.2.2^{3,6}.2^{12,15}.2^{17,20}]tetraconta-3,5,12,14,17,19,26,28,29,31,33,35-dodecaene-9,23-dione (4). As described above for the synthesis of **3**, **2** (17.12 g, 0.05 mol) was used to prepare the crude mixture of ketones. The material that was insoluble in acetone (3.72 g) melted at 194–203 °C. This impure product was recrystallized from 2-butanone to give 2.18 g of diketone, mp 201–205 °C. Final purification by bulb-to-bulb distillation gave pure **4** (2.05 g, 16.2%): mp 205–206.8 °C; ^{1}H NMR ($CDCl_3$) δ 6.97–6.77 (m, 16 H, Ar H), 2.80 (t, J = 6 Hz, 8 H, $ArCH_2$), 2.51 (t, J = 6 Hz, 8 H, CH_2CO); IR (CCl_4) 1713 cm^{-1} (C=O).

Anal. Calcd for $C_{34}H_{32}O_4$: C, 80.93; H, 6.39; mol wt, 504.63. Found: C, 81.16; H, 6.51; mol wt (Rast), 512.

4,17-Dioxo[7.7]paracyclophane. With a retained sample,[19] spectra were recorded: ^{1}H NMR ($CDCl_3$) δ 6.97 (s, 8 H, Ar H), 2.59 (t, J = 6 Hz, 8 H, $ArCH_2$), 2.02 (t, J = 6 Hz, 8 H, CH_2CO), 1.80 (quintet, J = 6 Hz, 8 H, $CH_2CH_2CH_2$); IR (CCl_4) 1715 cm^{-1} (C=O).

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Registry No. 1, 76358-39-9; 2, 32808-31-4; 3, 76358-40-2; 4, 76358-41-3; 4,17-dioxo[7.7]paracyclophane, 76358-42-4; 4,4′-oxybis[benzenebutanoic acid], 36189-36-3; 4,4′-oxybis[γ-oxobenzenebutanoic acid], 4378-33-0; 4,4′-oxydibenzyl chloride, 2362-18-7.

(18) Tortai, J. -P.; Maréchal, E. *Bull. Soc. Chim. Fr.* **1971**, 1000.
(19) Schimelpfenig, C. W.; Lin, Y. -T.; Waller, J. F. *J. Org. Chem.* **1963**, *28*, 805.

Intramolecular Anionic Cycloaddition of 1-(3-Phenyl-2-propenyl)-4-piperidinecarbonitrile. Synthesis of the 2,4a-Ethanobenz[*g*]isoquinolin-5(1*H*)-one Ring System[1]

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Received November 19, 1980

Although the addition of organometallic compounds to 1,3-dienes and styrenes is well documented,[2] very few examples of the addition of stabilized carbanions to such olefins are known which do not require transition-metal catalysis. Takabe et al.[3] reported the addition of the sodium salt of *N*-(3-methylbutylidene)-*tert*-butylamine to isoprene. More recently, Fujita and co-workers[4] reported the addition of carboxylic acid dianions to styrene, isoprene, and myrcene in the presence of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA). In this paper we describe the intramolecular addition of an α-lithionitrile to a cinnamyl double bond which leads to substituted quinuclidine derivatives.

(1) A preliminary account of this work was presented at the 11th Central Regional Meeting of the American Chemical Society, Columbus, OH, May 7–9, 1979.
(2) For a review of the addition of alkyllithium compounds to conjugated olefins, see: Schöllkopf, U. In "Methoden der Organischen Chemie (Houben-Weyl)"; Georg Thieme Verlag: Stuttgart, 1970; Vol 13/1, p 1.
(3) Takabe, K.; Fujiwara, H; Katagiri, J.; Tanaka, J. *Synth. Commun.* **1975**, *5*, 227.
(4) Fujita, J.; Watanabe, S.; Suga, K.; Nakayama, H. *Synthesis* **1979**, 310.

Scheme I

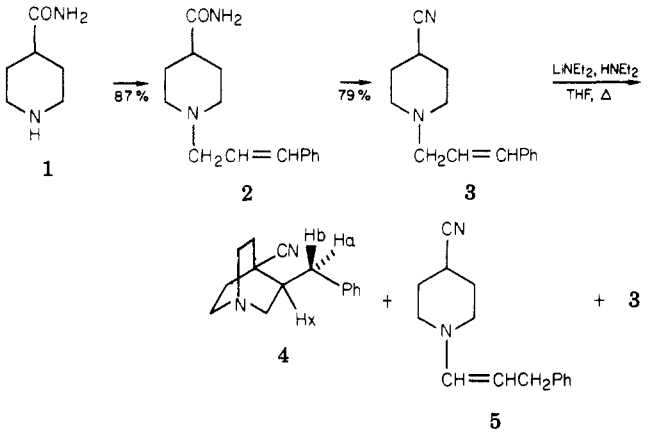
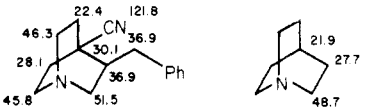


Chart I. Carbon-13 Chemical Shifts[a]



quinuclidine[7]

[a] All shifts are in parts per million downfield from $Si(CH_3)_4$.

Results

In connection with the synthesis of 1-cinnamyl-4,4-disubstituted-piperidine central nervous system agents, cinnamyl nitrile **3** was prepared as a key synthetic intermediate. N-Alkylation of isonipecotamide (**1**) with cinnamyl chloride followed by dehydration of the resulting amide **2** with $POCl_3$ afforded the oily nitrile **3** in excellent overall yield[5] (Scheme I). When cinnamyl nitrile **3** is metalated at 0 °C with 1.03 equiv of lithium diethylamide (LDEA) in the presence of a 1–3 molar excess of diethylamine in tetrahydrofuran (THF) and the resulting solution rapidly warmed[6] to 51–54 °C for 20 min, a 56–60% yield of crystalline 3-(phenylmethyl)-1-azabicyclo[2.2.2]-octane-4-carbonitrile (**4**), a 13% yield of enamine **5**, and a 9–15% yield of recovered cinnamyl nitrile **3** are obtained after quenching with water. Prolonged heating results in the further transformation of products to nonvolatile, intractable materials. The structures of **4** and **5** were assigned on the basis of spectral data and subsequent chemical modifications.

The mass spectrum of **4** showed characteristic peaks at *m/e* 135 and 91 resulting from benzylic cleavage. The UV spectrum [λ_{max} 258 nm (ϵ 190)] indicated the absence of a chromophoric substituted benzene. The 80-MHz ^{1}H NMR spectrum showed no olefinic protons and a doublet of doublets at δ 3.25 assigned to H_a (geminal coupling of 13 Hz and vicinal coupling of 3 Hz), which collapsed to a doublet (J = 13 Hz) upon irradiation at 159 Hz. The ^{13}C NMR spectrum of **4** was in complete accord with the quinuclidine structure. The assignments were made on the basis of chemical shifts and the single-frequency, off-resonance, proton-decoupled spectrum. The ^{13}C chemical shifts for quinuclidine are given in Chart I for comparison.[7] Most notably, there is a characteristic upfield shift for C-5 (δ 22.4) which arises from a γ-gauche interaction with the benzylic carbon atom.[8] A downfield

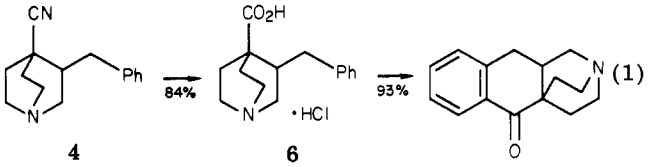
(5) Surrey, A. R. In "Organic Syntheses"; Wiley: New York, 1955; Collect Vol. III, p 535.
(6) House, H. O.; Bare, T. M. *J. Org. Chem.* **1968**, *33*, 943.
(7) Morishima, I.; Okada, K.; Yonezawa, J.; Goto, K. *J. Am. Chem. Soc.* **1971**, *93*, 3922.

0022-3263/81/1946-1212$01.25/0

shift is observed for C-2 (δ 51.5) typical of additional α substitution.[8]

In the crude reaction mixture, the presence of a strong band at 1650 cm^{-1} in the IR spectrum and a multiplet centered at δ 4.57 and a doublet at δ 5.85 (J = 14 Hz) in the ^1H NMR spectrum mixture suggested the presence of an enamine. Hydrolysis with aqueous acid gave dihydrocinnamaldehyde, the IR and ^1H NMR spectra of which were identical with those obtained from an authentic sample [semicarbazone, mp 125.7–127.7 °C (lit.[9] mp 125.5–127.5 °C)].

The chemistry of quinuclidine **4** provided additional evidence in support of our structural assignment. Hydrolysis with 6 N HCl (reflux, 24 h) gave the corresponding amino acid hydrochloride **6** in 84% yield. Cyclodehydration of **6** with polyphosphoric acid (PPA) at 125 °C for 2–3 h or with $H_2SO_4/CHCl_3$ at 25 °C for 1 h gave 3,4,10,10a-tetrahydro-2,4a-ethanobenz[*g*]isoquinolin-5-(1*H*)-one (**7**) in high yield (eq 1). The IR of **7** showed a

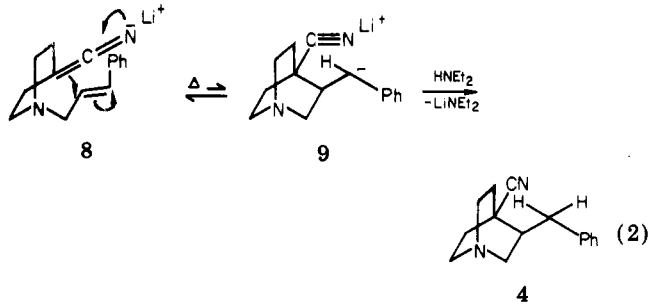


4 6 7 (1)

C=O stretching band at 1680 cm^{-1}, in excellent agreement with that expected for a six-membered ring aromatic ketone.[10] A strong molecular ion at m/e 227 clearly indicated an intramolecular cyclization had occurred.

Discussion

A mechanism which would account for the formation of quinuclidine **4** involves the intramolecular addition of α-lithionitrile **8** to the cinnamyl double bond to generate benzylic carbanion **9** (eq 2). This transformation would

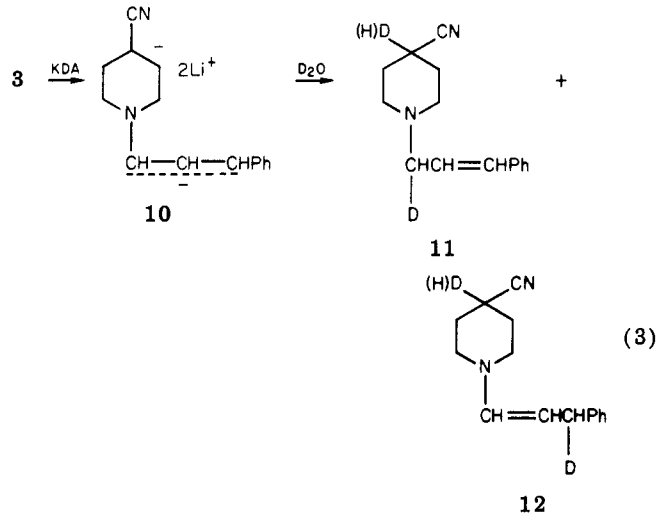


8 9 4 (2)

require that **8** adopt a boat conformation prior to cyclization. Once formed, **9** must be rapidly protonated by the excess diethylamine, as the carbanion cannot be trapped with either CH_3I or D_2O. When lithium diisopropylamide (LDA) is used as the base, only recovered cinnamyl nitrile **3** is isolated. Examination of molecular models suggests that the more hindered diisopropylamine may be sterically unable to protonate the small equilibrium concentration of benzylic carbanion **9** which then merely fragments back to α-lithionitrile **8**. It is important to note that cyclization to **4** occurs only on warming. α-Lithionitrile **8** can be generated at 0 °C with LDEA or LDA and alkylated uneventfully in high yield.

The recovered cinnamyl nitrile **3** and the enamine **5** which are the other major products of this reaction arise from protonation of dianion **10** (vide infra) formed by the excess base generated upon cyclization to the quinuclidine. The dianion is generated only upon heating, as use of 2.2 equiv of LDEA at 0 °C gives only monoanion; warming results in cyclization to the quinuclidine. In fact, comparable yields of quinuclidine **4** are obtained by using 1 or 2 equiv of LDEA.

Two crucial pieces of experimental evidence which lend support to this proposed mechanism are the reversibility of the anionic cyclization (i.e., **9** → **8**) and the formation and protonation of dianion **10**. Benzylic carbanion **9**, generated from **4** with potassium diethylamide–lithium *tert*-butoxide (KDEA), partially fragments on warming (−78 to 0 °C) to give a 92% yield of a 53:47 mixture of **4** and cinnamyl nitrile **3**, along with a trace of enamine **5**. Quantitative formation of dianion **10** with 2.5 equiv of potassium diisopropylamide–lithium *tert*-butoxide (KDA)[11] at −78 °C followed by quenching with D_2O resulted in complete incorporation of deuterium into the side chain as determined by mass spectral analysis and ^1H NMR to give a 9:5 mixture of deuterated starting material **11** and deuterated enamine **12** (eq 3). The ^1H NMR of



11 showed a one-proton doublet of doublets (J = 6 and 1.5 Hz) at δ 3.00 (NCH(D)CH=CH). The multiplet at δ 4.32–4.82 ($NCH=CHCH_2$) in enamine **5** collapsed to a doublet of doublets (J = 14 and 7 Hz) at δ 4.45 in deuterated enamine **12**.

The intramolecular addition of a stabilized carbanion to a conjugated olefin herein reported and the intermolecular examples previously cited[3,4] suggest that this type of reaction is a synthetically useful method of forming carbon–carbon bonds. In each case, it should be pointed out, moderate heating (40–65 °C) of the carbanion was essential to the success of the addition reaction.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer spectrophotometer, Model 521, and UV spectra were recorded on a Cary 17 spectrophotometer. ^1H NMR were recorded on a Varian A-60 or FT-80A instrument; ^{13}C NMR were recorded on the Varian FT-80A. Gas chromatographic/mass spectral data were obtained on a Finnigan mass spectrometer, Model 1015, with a Model 3300 electronics package.

1-(3-Phenyl-2-propenyl)-4-piperidinecarboxamide (2). A mixture of isonipecotamide (**1**; 60.0 g, 0.468 mol), (3-chloropropenyl)benzene (75.0 g, 0.491 mol), and $KHCO_3$ (72 g, 0.72 mol) in 700 mL of toluene was heated at reflux with mechanical stirring

(8) Grant, D. M.; Paul, E. G. *J. Am. Chem. Soc.* **1964**, *86*, 2984.
(9) Goldberg, E. P.; Nace, H. R. *J. Am. Chem. Soc.* **1955**, *77*, 359.
(10) The C=O stretching band for α-tetralone is 1672 cm^{-1}; in contrast, the C=O stretch for 1-indanone is 1709 cm^{-1}, and that for benzosuberone is 1663 cm^{-1}.
(11) Raucher, S.; Koolpe, G. A. *J. Org. Chem.* **1978**, *43*, 3794.

for 4 h. After the mixture cooled, water was added and the mixture filtered. The crude product was washed with water and ether and recrystallized from 5:1 ethanol–water to give 99.4 g (86.9%) of light beige needles: mp 189.5–191.5 °C; IR (KBr) 3335, 3180, 1667, 1618, 975 cm^{-1}; UV (methanol) 251 nm (ϵ 19700). Anal. Calcd for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.46. Found: C, 73.53; H, 8.10; N, 11.30.

1-(3-Phenyl-2-propenyl)-4-piperidinecarbonitrile (3). Amide **2** was dehydrated according to the procedure of Surrey.[5] A mixture of amide **2** (99.4 g, 0.407 mol), phosphorus oxychloride (25 mL, 0.27 mol), and 30 g of NaCl in 750 mL of 1,2-dichloroethane was heated at reflux with vigorous stirring for 2 h. The amide dissolved on heating to give a clear solution from which a white precipitate separated after several minutes at reflux. After the mixture cooled, 10% NaOH was added, and the mixture was decanted into a separatory funnel and extracted with ether. The extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residual oil was fractionally distilled under reduced pressure to give 72.9 g (79.2%) of a viscous colorless oil: bp 169–176 °C (0.35–0.70 mm); IR (neat) 2945, 2800, 2240, 1440, 965, 736, 688 cm^{-1}; NMR ($CDCl_3$) δ 1.61–1.98 (m, 4 H), 2.03–2.86 (complex multiplet, 5 H), 3.07 (d, 2 H), 5.90–6.70 (m, 2 H), 7.13–7.50 (m, 5 H); mass spectrum, *m/e* (relative intensity) 226 (M^+, 5), 135 (100), 117 (69), 115 (42), 91 (20); UV (methanol) 252 nm (ϵ 19000). Anal. Calcd for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02; N, 12.38. Found: C, 79.69; H, 7.91; N, 12.12.

3-(Phenylmethyl)-1-azabicyclo[2.2.2]octane-4-carbonitrile (4). The cyclization conditions were adapted from the nitrile methylation procedure of House and Bare.[6] *n*-Butyllithium (2.45 M in *n*-hexane, 18.6 mL, 45.6 mmol) was added via syringe to a solution of 20 mL (190 mmol) of diethylamine (distilled from CaH_2 and stored over 3A molecular sieves) in 150 mL of tetrahydrofuran (freshly distilled from calcium hydride) at 0 °C under argon. After 15 min a solution of 10.00 g (44.19 mmol) of nitrile **3** in 50 mL of dry tetrahydrofuran was added dropwise over 20 min. After the addition was complete, the solution was stirred at 0 °C for 10 min and then heated to 51–54 °C for 20 min. The optimum reaction time was determined by using *N,N*-dibenzylaniline, which is stable under the reaction conditions, as a GC internal standard. The reaction mixture was briefly cooled in an ice bath before being quenched by addition of water. The mixture was poured into water and extracted twice with ether. The combined extracts were washed with water and then extracted twice with dilute hydrochloric acid.

The ether layer was dried ($MgSO_4$) and concentrated. Kugelrohr distillation of the residue gave 0.75 g (13%) of dihydrocinnamaldehyde [bp 100 °C (0.1 mm)] which was converted to the semicarbazone and recrystallized from ethanol–water to give colorless needles, mp 125.7–127.7 °C (lit.[9] mp 125.5–127.5 °C).

The acidic extracts were washed with ether, made basic with cold aqueous sodium hydroxide, and extracted with ether. The ethereal extract was dried ($MgSO_4$) and concentrated to give 8.7 g of orange oil. Filtration through a short alumina column with methylene chloride gave 7.1 g (71%) of yellow crystals. Recrystallization from cyclohexane (filtering through filter aid) gave 3.67 g of **4** as colorless crystals. Chromatography of the mother liquor on 55 g of silica gel gave 0.89 g (8.9%) of recovered cinnamyl nitrile **3** on elution with 2% methanol/methylene chloride and 2.26 g of **4** as white crystals on elution with 8% methanol/methylene chloride. The total yield of 3-(phenylmethyl)-1-azabicyclo[2.2.2]octane-4-carbonitrile (**4**) was thus 5.93 g (59.3%, 65.1% based on recovered starting material).

A previously characterized sample of **4** was recrystallized from cyclohexane to give white needles: mp 82.5–84 °C; IR (KBr) 2940, 2228, 1452, 738, 705, 678 cm^{-1}; NMR ($CDCl_3$) δ 1.53–3.08 (complex m, 12 H), 3.25 (dd, 1 H, J = 13, 3 Hz), 7.24 (s, 5 H); mass spectrum, *m/e* (relative intensity) 226 (M^+, 8), 135 (85), 117 (26), 107 (27), 91 (25), 43 (34), 42 (100); UV (methanol) 258 nm (ϵ 190). Anal. Calcd for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02; N, 12.38. Found: C, 79.57; H, 8.11; N, 12.33.

The IR of the crude product mixture from a similar cyclization reaction which did not involve an acid workup showed an enamine band at 1650 cm^{-1}. The NMR showed olefinic protons at δ 4.32–4.82 (m, NCH=C**H**CH_2) and 5.85 (d, J = 14 Hz, NC**H**=CH) of approximately equal intensities. Gas chromatographic/mass spectroscopic (GC/MS) analysis of the crude mixture showed a third component [order of elution **4**, **3**, **5**]: *m/e* (relative intensity) 226 (M^+, 7), 135 (100), 117 (16), 115 (18), 91 (19), 41 (28).

3-(Phenylmethyl)-1-azabicyclo[2.2.2]octane-4-carboxylic Acid Hydrochloride (6). Nitrile **4** (35.0 g, 155 mmol) was dissolved in 120 mL of 6 N HCl and heated at reflux for 24 h. The solution was cooled in an ice bath and filtered. The fine white crystals were washed with ice-cold, dilute HCl and ether. Drying in vacuo gave 36.5 g (83.6%) of hydrochloride **6**. Recrystallization from butanone–methanol gave colorless needles: mp 341–344 °C dec; IR (KBr) 3408, 2892, 2586, 1720, 1214, 728, 700 cm^{-1}; NMR (D_2O) δ 2.00–3.63 (complex m, 13 H), 7.35 (s, 5 H); UV (methanol) 258 nm (ϵ 187). Anal. Calcd for $C_{15}H_{19}NO_2$·HCl: C, 63.94; H, 7.15; N, 4.97. Found: C, 63.82; H, 7.18; N, 4.89.

3,4,10,10a-Tetrahydro-2,4a-ethanobenz[*g*]isoquinolin-5-(1*H*)-one (7). Acid **6** (25.4 g, 90.1 mmol) was added in portions to 300 g of polyphosphoric acid at 80 °C. The solution was heated at 125 °C for 3 h and then allowed to cool overnight. The reaction mixture was diluted with ice, made strongly basic with aqueous NaOH, and extracted with ether–benzene. The extract was dried ($MgSO_4$) and concentrated to give 19.1 g (93.2%) of off-white flakes. Recrystallization from cyclohexane gave 15.9 g of white platelets: mp 118.3–120.3 °C; IR (KBr) 2945, 2875, 1680, 1605, 1295, 1275, 796, 779, 742, 630 cm^{-1}; mass spectrum, *m/e* (relative intensity) 227 (M^+, 48), 170 (39), 108 (89), 96 (89), 41 (34), 42 (100). A second crop of 1.5 g of ketone **7** was obtained.

Ketone **7** was converted to the hydrochloride salt and recrystallized from butanone–methanol to give fine white needles: mp >350 °C; IR (KBr) 3435, 2906, 2428, 1678, 1600, 1285, 743 cm^{-1}; NMR (D_2O) δ 1.62–3.91 (complex m, 13 H), 7.22–8.04 (complex m, 5 H); UV (methanol) 248 nm (ϵ 12400). Anal. Calcd for $C_{15}H_{17}NO$·HCl: C, 68.30; H, 6.88; N, 5.31. Found: C, 68.00; H, 6.95; N, 5.19.

Metalation of Quinuclidine 4 with KDEA. A modification of the procedure of Raucher and Koolpe[11] was employed. *n*-Butyllithium/hexane (2.45 mL of 2.35 M solution, 5.8 mmol) was added dropwise to a stirred solution of 0.65 g (5.8 mmol) of potassium *tert*-butoxide and 0.603 mL (5.83 mmol) of $HNEt_2$ (distilled from CaH_2) in 30 mL of THF (freshly distilled from sodium benzophenone ketyl) at −78 °C under argon. After 5 min, a solution of 1.25 g (5.52 mmol) of **4** in 20 mL of THF was added rapidly. The solution turned a reddish orange. The reaction mixture was allowed to warm to 0 °C over 1.5 h, during which time the solution became blood red. The reaction mixture was maintained at 0 °C for 1.5 h before being quenched by addition of water. The mixture was poured into water and extracted twice with ether. The combined extracts were washed with water and brine and dried ($MgSO_4$). Concentration in vacuo gave 1.15 g (92%) of a 53:47 mixture of **4** and **3** as determined by NMR and GC. A trace of enamine **5** was also detected. An experiment in which the reaction mixture was allowed to warm from −78 to 0 °C over 2.5 h before being quenched afforded a similar ratio of 4/3.

Synthesis of Deuterated Cinnamyl Nitrile 11 and Enamine 12. A solution of 25 mmol of KDA in 33 mL of dry THF at −78 °C under argon was prepared as in the previous experiment. To this stirred solution was added dropwise over 10 min a solution of 2.26 g (10.0 mmol) of nitrile **3** in 11 mL of dry THF. After 10 min at −78 °C, the dark red solution was quenched by rapid addition of 4.5 mL of D_2O. The mixture was poured into water and extracted twice with ether. The combined extracts were washed with water and brine and dried ($MgSO_4$). Concentration in vacuo gave 2.0 g (88%) of pale yellow oil which was shown by NMR to contain a 9:5 mixture of **11** and **12**. Gas chromatography/mass spectroscopy of the mixture gave the following: for **11**, *m/e* (relative intensity) 228 (8), 227 (7), 226 (2), 137 (98), 136 (50), 118 (100), 117 (47), 116 (56), 92 (23), 91 (21); for **12**, *m/e* (relative intensity) 228 (17), 227 (6), 226 (3), 137 (64), 136 (100), 92 (93), 91 (29).

The oil was partitioned between dilute HCl and ether. The acid layer was washed with ether. The combined ether layers were washed with water and dried ($MgSO_4$). Concentration in vacuo gave 3-deuterio-3-phenylpropionaldehyde: NMR ($CDCl_3$) δ 2.58–3.08 (m, 3 H), 7.27 (s, 5 H), 9.82 (t, $J \simeq 1.7$ Hz, 1 H).

The acid layer was made basic with aqueous NaOH and extracted with ether. The extract was dried ($MgSO_4$) and concentrated in vacuo to give 1.3 g of **11**: NMR ($CDCl_3$) δ 1.75 (br

t, J = 5 Hz, 3 H), 1.75–2.87 (m, 5 H), 3.00 (dd, J = 6, 1.5 Hz, 1 H), 5.65–6.65 (m, 2 H), 7.08–7.52 (m, 5 H).

Acknowledgment. We are grateful to Dr. David Gustafson for ^{13}C NMR spectra and Dr. Arthur Sill for gas chromatography/mass spectroscopy studies. We are indebted to Drs. Gary Flynn, Boyd Harrison, and Philip Weintraub for helpful suggestions and to Mrs. Brenda Harry for skilled technical assistance.

Registry No. 1, 39546-32-2; 2, 76447-96-6; 3, 76447-97-7; 4, 76447-98-8; 5, 76447-99-9; 6, 76448-00-5; 7, 76448-01-6; 7·HCl, 76448-02-7; 11, 76448-03-8; 12, 76448-04-9; (3-chloropropenyl)-benzene, 102-92-1; dihydrocinnamaldehyde, 104-53-0; dihydrocinnamaldehyde semicarbazone, 27843-08-9; 3-deuterio-3-phenylpropionaldehyde, 76448-05-0.

N-Phenylselenophthalimide. A Useful Reagent for the Facile Transformation of (1) Carboxylic Acids into either Selenol Esters or Amides and (2) Alcohols into Alkyl Phenyl Selenides

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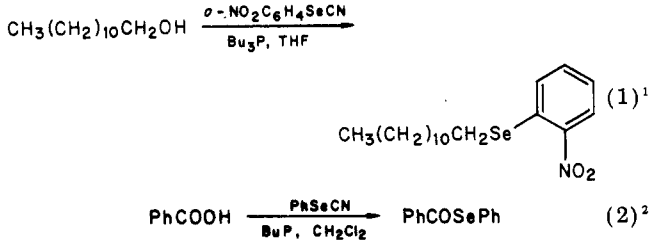
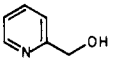
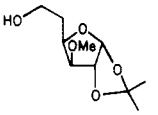
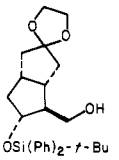
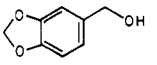
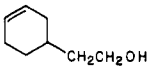
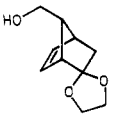
It has previously been reported that aryl selenocyanates react with alcohols (eq 1) and carboxylic acids (eq 2) in



the presence of tri-*n*-butylphosphine, giving rise to alkyl aryl selenides[1] and selenol esters, respectively.[2] The reactions depicted in eq 1 and 2 are general and can be applied to a variety of alcohols and acids. In contrast to *o*-nitrophenyl selenocyanate which is an easy to handle, yellow crystalline substance, phenyl selenocyanate is an extremely sensitive, unpleasant smelling liquid which slowly decomposes on storage after a few days.

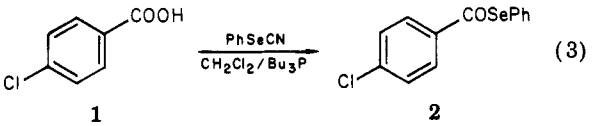
We report herein the reactions of carboxylic acids and alcohols with *N*-phenylselenophthalimide (*N*-PSP),[3] a stable, crystalline, relatively odorless substance. The use of *N*-PSP as detailed below obviates the necessity of working with the difficult to handle phenyl selenocyanate. Treatment of a variety of alcohols with *N*-PSP in tetrahydrofuran at 0 °C (method A) or in methylene chloride (method B) in the presence of tri-*n*-butylphosphine gives rise to high yields of alkyl phenyl selenides (Table I).[4] The major advantage of this new one-step process is the ready availability of *N*-PSP[3] as compared to PhSeCN which is a nuisance to prepare and difficult to work with. As illustrated in Table I, *N*-PSP is compatable with acetals, ketals, silyl ethers, olefins, acetylenes, and aromatic residues.

Table I. Conversion of Alcohols to Alkyl Phenyl Selenides

starting alcohol	method[a]	time, min	temp, °C	% yield of[b,c] selenide
geraniol	A	40	0	82
$CH_3(CH_2)_5CH_2OH$	A	35	0	84
$CH_3CH_2C{\equiv}CCH_2CH_2OH$	A	60	0	75
$C_6H_5CH_2OH$	A	60	0	95
	B	60	−20–0	70
	B	120	−20–25	90
	B	180	−20–25	73
	A	30	0	95
	A	90	25	87
	A	30	0	72

[a] Method A: reactions were carried out in tetrahydrofuran employing 2.0 equiv of *N*-PSP and 2.0 equiv of tri-*n*-butylphosphine. Method B: reactions were carried out in dry, oxygen-free CH_2Cl_2 (0.4 M) with 1.5–2.0 equiv of *N*-PSP and 2.0 equiv of tri-*n*-butylphosphine. [b] All compounds were fully characterized by spectral methods. [c] Yields reported are for isolated, chromatographically pure substances.

We have also observed that carboxylic acids dissolved in either tetrahydrofuran or methylene chloride react with *N*-PSP in the presence of tri-*n*-butylphosphine, providing selenol esters in good to excellent yield (Table II). As illustrated in the table, a variety of aryl- and alkylcarboxylic acids have been examined. In contrast to the reaction of phenyl selenocyanate with *p*-chlorobenzoic acid (eq 3) which gave us only 32% yield of selenol ester **2**, use



1 **2**

of *N*-PSP provided **2** in 91% isolated yield. Reaction of β,β-dimethylacrylic acid at 0 °C with 1.2 equiv of *N*-PSP

(1) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.
(2) Grieco, P. A.; Yokoyama, Y.; Williams, E. *J. Org. Chem.* **1978**, *43*, 1283.
(3) (a) Nicolaou, K. C.; Claremon, D. A.; Barnett, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704. (b) Also see: Frejd, T.; Sharpless, K. B. *Tetrahedron Lett.* **1978**, 2239; Hori, T.; Sharpless, K. B. *J. Org. Chem.* **1979**, *44*, 4208.
(4) The corresponding sulfur reagent has been reported to transform alcohols into phenyl sulfides in a similar manner: Walker, K. A. M. *Tetrahedron Lett.* **1977**, 4475.
(5) Lown, W. J.; Akhtar, M. H.; Dadson, W. M. *J. Org. Chem.* **1975**, *40*, 3363.

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