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(10) Melting points were determined on a Mel-Temp apparatus and are uncorrected.
(11) J. R. Beck, *J. Org. Chem.*, **37**, 3224 (1972).
(12) For the preparation of **1e** and **1f**, 30 mmol was used.

Reaction of Aryllithium Reagents with Nitriles. Synthesis of 1-Substituted 3,4-Dihydroisoquinolines[1,2]

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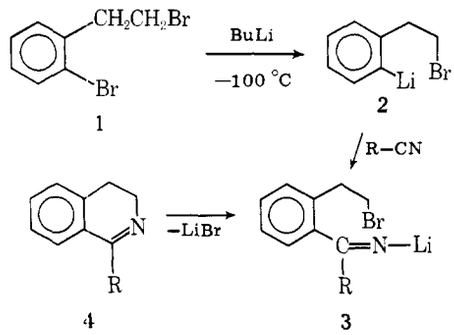
Parham and his students have shown that formation of functionalized organolithium reagents at low temperature (−100 °C), followed by reaction with either an internal or external electrophile, provides an excellent route to various cyclization products, many of which were heretofore difficult to obtain.[3]

A previously unexplored possibility was that *o*-lithiophenethyl bromide (**2**), obtained by selective lithiation of *o*-bromophenethyl bromide (**1**),[3c] might react with nitriles to



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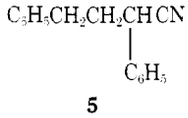
a, R = C_6H_5
b, R = *p*-$CH_3OC_6H_4$
c, R = CH_3OCH_2
d, R = cyclohexyl



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form imine salts which could undergo intramolecular alkylation, affording a new route to 3,4-dihydroisoquinolines. It seemed likely that the cyclization step would occur since it is known[4] that intermolecular alkylation of the lithio salts of imines can be accomplished.

Predictably the best success was had with aryl nitriles. Using *tert*-butyllithium as the reagent for transmetalation, yields of 63 and 43% of the 1-aryl-3,4-dehydroisoquinoline (**4a,b**) were obtained from benzonitrile and 4-methoxybenzonitrile, respectively. For nitriles having an α hydrogen the yields ranged from 18% for methoxyacetonitrile to essentially zero for phenylacetonitrile (Table I). In the latter case the anion formed was alkylated by the phenethyl bromide present in the reaction mixture to provide a 35% yield of 1,3-diphenylbutyronitrile (**5**).

1-Adamantylnitrile which has no α hydrogens and has been shown[5] to react normally with organolithium reagents likewise failed, probably because the rate of attack on the sterically hindered nitrile was slower than the competing cyclization of **2** to afford benzocyclobutene.[3c]

Table I. Reaction of β-(*o*-Lithiophenyl)ethyl Bromide (2) with Nitriles to Afford 3,4-Dihydroisoquinolines (4)

RCN	Registry no.	Yield 4, %[a]	RLi	Picrate, mp, °C
C_6H_5	100-47-0	63	*t*-C_4H_9	177–178[b]
p-$CH_3OC_6H_4$	874-90-8	43	*t*-C_4H_9	162[c]
CH_3OCH_2	1738-36-9	18	*n*-C_4H_9	206–207
Cyclohexyl	766-05-2	16	*t*-C_4H_9	167–168[d]
Adamantyl	23074-42-2	0	*t*-C_4H_9	
C_6H_5–CH_2	140-29-4	0	*n*-C_4H_9	

[a] Determined by GLC analysis. [b] Lit.[11] mp 175 °C. [c] Lit.[12] mp 155–156 °C. [d] Lit.[13] mp 169–170 °C.

The new isoquinoline synthesis would appear inferior to the classical Bischler–Napieralski[6] synthesis unless possibly one were interested in the synthesis of a 1-arylisoquinoline having acid-sensitive groups.

Experimental Section

All reactions involving organolithium reagents were carried out under an atmosphere of nitrogen. Tetrahydrofuran was distilled from lithium aluminum hydride prior to use. Reaction temperatures of −100 °C were obtained via a diethyl ether–liquid nitrogen bath. All organic residues were dried with anhydrous magnesium sulfate. NMR data were obtained from a JEOL Model JNM-MH-100 100-MHz spectrometer using 1–2% tetramethylsilane as an internal standard; IR data were obtained from either a Perkin-Elmer Model 127 or Model 297 spectrometer; and GLC analyses were performed with a Varian Model 920 gas chromatograph (thermal conductivity detector). Microanalyses were performed by MHW Laboratories, Garden City, Mich. All melting points were determined on a Mel-Temp heating block apparatus and are uncorrected.

General Procedure for Halogen–Metal Exchange. β-(*o*-Bromophenyl)ethyl bromide (**1**, 5.28 g, 0.02 mol, bp 67–68 °C (0.2 Torr) [lit.[7] bp 65–66 °C (0.15 Torr)]) and tetrahydrofuran (125 mL)–hexane[3c] (30 mL) were introduced, under nitrogen, into a 250-mL three-neck flask equipped with a low-temperature thermometer, pressure-equalizing addition funnel, nitrogen inlet, and mechanical stirrer. The reaction mixture was cooled to −100 °C and either *n*-butyllithium (1.0 equiv) or *tert*-butyllithium (2.0 equiv)[8] was added at such a rate that the temperature did not exceed −95 °C. Ten minutes after the addition of *n*-butyllithium was completed, a solution of the nitrile (0.02 mol) in tetrahydrofuran (25 mL) was added at a rate such that the temperature did not exceed −95 °C. After an additional 45 min at −100 °C,[9] the reaction mixture was allowed to warm to room temperature (2 h) and was poured into 250 mL of 5% hydrochloric acid. If butyllithium was used, upon reaching room temperature, the reaction mixture was then refluxed under nitrogen (1 h), at which time the mixture was allowed to cool to room temperature and was quenched in 250 mL of 5% hydrochloric acid. The neutral organics were separated from the acidic solution and the organics were then extracted with 5% hydrochloric acid. The acid wash was then combined with the original acidic aqueous solution, which was then made basic with 20% sodium hydroxide solution. The basic aqueous solution was extracted with benzene (3 × 100 mL), and after drying ($MgSO_4$) and concentration (rotary evaporation), the crude product was purified by preparative GLC.[10]

1-Phenyl-3,4-dihydroisoquinoline (4a) (63% yield) was obtained as a light yellow oil: IR (neat) 1613 cm^{-1}; NMR ($CDCl_3$) δ 2.80 (t, 2, CH_2), 3.92 (t, 2, benzylic CH_2), 7.20–7.80 (m, 9, ArH). Anal. Calcd for $C_{15}H_{13}N$: C, 86.96; H, 6.28; N, 6.76. Found: C, 86.84; H, 6.33; N, 6.52.

1-(*p*-Methoxyphenyl)-3,4-dihydroisoquinoline (4b) (43% yield) was obtained as a light yellow oil: IR (neat) 1620, 1590 cm^{-1}; NMR ($CDCl_3$) δ 2.70 (t, 2, CH_2) 3.79–3.82 (singlet overlapping triplet, 5, OCH_3, benzylic CH_2), 6.74–7.90 (m, 8, ArH). Anal. Calcd (picrate) for $C_{22}H_{18}N_4O_8$: C, 56.65; H, 3.89; N, 12.01. Found: C, 56.48; H, 3.88; N, 12.12.

1-Methoxymethyl-3,4-dihydroisoquinoline (4c) (18% yield) was obtained as a light yellow oil: IR (neat) 1600, 1070 cm^{-1}; NMR ($CDCl_3$) δ 2.68 (t, 2, CH_2), 3.40 (s, 3, OCH_3), 3.74 (t, 2, benzylic CH_2), 4.45 (s, 2, $\mathbf{CH_2}OCH_3$), 7.05–7.62 (m, 4, ArH). Anal. Calcd for $C_{11}H_{13}NO$: C, 75.43; H, 7.43; N, 8.00. Found: C, 75.23; H, 7.70; N, 7.84.

1-Cyclohexyl-3,4-dihydroisoquinoline (4d) (16% yield) was

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obtained as a light yellow oil: IR (neat) 1610 cm^{-1}; NMR ($CDCl_3$) δ 0.90–2.08 (m, 10, cyclohexyl CH_2), 2.58 (t, 2, CH_2), 2.80 (m, 1, cyclohexyl CH), 3.60 (t, 2, benzylic CH_2), 6.95–7.65 (m, 4, ArH). Anal. Calcd for $C_{15}H_{19}N$: C, 84.51; H, 8.92; N, 6.57. Found: C, 84.58; H, 9.03; N, 6.36.

Reaction of (2) with Phenylacetonitrile. The general procedure was followed except that an excess (0.6 mol) of phenylacetonitrile was added to 0.2 mol of **2.** The basic fraction was negligible but the neutral fraction on vacuum distillation yielded phenylacetonitrile (88% recovery) and 1,3-diphenylbutyronitrile (**5**) (1.55 g, 35% yield based on **1**, bp 126–128 °C (0.10 Torr)): IR (neat) 2230 cm^{-1}; NMR ($CDCl_3$) δ 2.12 (m, 2, CH_2CH), 2.80 (t, 2, benzylic CH_2), 3.64 (t, 1, CH), 7.00–7.68 (m, 10, ArH). Anal. Calcd for $C_{16}H_{15}N$: C, 86.88; H, 6.79; N, 6.33. Found: C, 86.63; H, 7.00; N, 6.35.

Acknowledgment. The authors wish to thank Dr. Y. Sayed for helpful discussion and suggestions.

Registry No.—**1**, 1074-15-3; **2**, 57918-65-7; **4a**, 52250-50-7; **4b**, 59224-73-; **4b** picrate, 65071-49-0; **4c**, 65071-50-3; **4c** picrate, 65071-51-4; **4d**, 65071-52-5; **5**, 5558-42-9.

References and Notes

(1) This paper is dedicated to the memory of Dr. W. E. Parham, deceased May 21, 1976.
(2) Supported by the U.S. Army Research Office through Grant DAHC04 74 GD128.
(3) (a) W. E. Parham and Y. A. Sayed, *J. Org. Chem.*, **39**, 2051 (1974); (b) W. E. Parham, L. D. Jones, and Y. A. Sayed, *ibid.*, **40**, 2394 (1975); (c) *ibid.*, **41**, 1184 (1976); (d) W. E. Parham and L. D. Jones, *ibid.*, **41**, 1187 (1976); (e) W. E. Parham and R. M. Piccirilli, *ibid.*, **41**, 1268 (1976); (f) W. E. Parham, D. C. Egberg, Y. A. Sayed, R. W. Thraikill, G. E. Keyser, M. Neil, W. C. Montgomery, and L. D. Jones, *ibid.*, **41**, 2628 (1976); (g) W. E. Parham and L. D. Jones, *ibid.*, **41**, 2704 (1976); (h) W. E. Parham and R. M. Piccirilli, *ibid.*, **42**, 257 (1977).
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(8) D. Seebach and H. Neumann, *Chem. Ber.*, **107**, 847 (1974), have shown that unless the extra mole of *tert*-butyllithium is present, greater loss of the aryllithium reagent occurs as a result of the easy dehydrohalogenation of the *tert*-butyl bromide formed in the exchange.
(9) The low temperature was employed to make halogen–metal exchange more selective and to hold at a minimum the formation of benzocyclobutene (ref 3c).
(10) GLC analyses were carried out on a column of 20% SE-30 on 60/80 Chromosorb W [4 ft × 0.25 in., 250 °C, 30 mL/min He]. Preparative GLC appeared preferable to distillation in dealing with small volumes of product. Positive identification of the products was effected by NMR as well as by elemental analysis on either the picrate or the free base.
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Selenium in Synthesis. Conjugated Vinylic Ethers, Esters, and Halides from α-Hetero-Substituted Selenides

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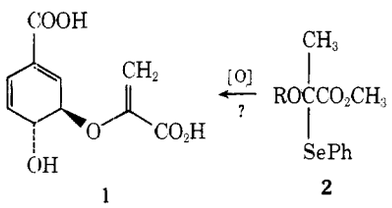
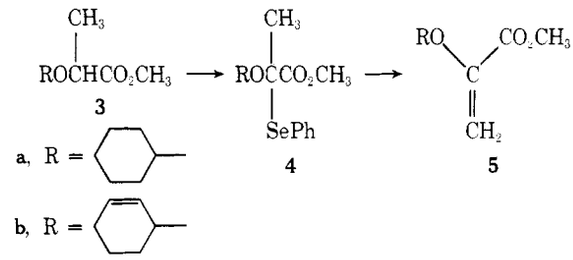
Recent work in our laboratory aimed at the total synthesis of chorismic acid **1**[1] has led us to investigate the oxidative fragmentation of α-oxygenated α-phenylseleno carboxyl derivatives **2** as an approach to the sensitive enol pyruvyl functionality in **1**.[2] Although there have been numerous reports of arylseleno carbonyl compounds serving as precursors for α,β-unsaturated ketones and esters,[3] the effect of an additional heteroatom on such selenoxide eliminations appears not to have been studied. In this note we disclose that α-alkoxy as well as α-acyloxy and α-chloro-unsaturated esters can be prepared from appropriately substituted selenides at neutral pH and below room temperature.



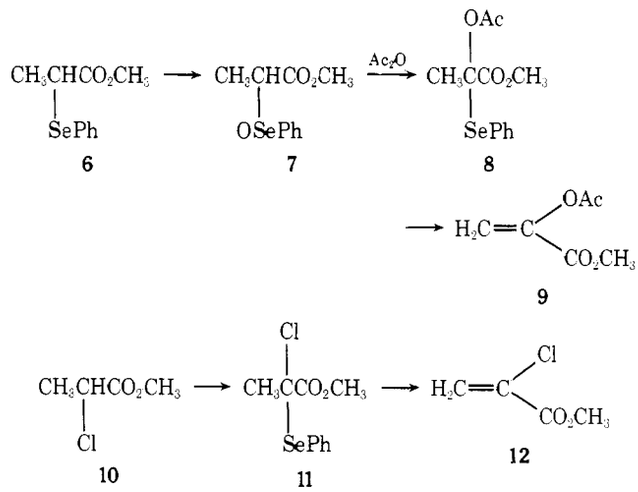
1 2

Cyclohexanol and 2-cyclohexen-1-ol were converted to α-alkoxypropionates **3a** and **3b** by the classical Williamson ether synthesis. Selenation of the corresponding ester enolates



(LDA, THF–HMPA, −70 °C) using phenylselenenyl bromide or diphenyl diselenide afforded **4a** and **4b** without complication. When solutions of these arylseleno esters in ethyl acetate were treated with 30% H_2O_2 (4–6 equiv) at 0 °C for 2 h, the enol pyruvates **5a** and **5b** were produced in 30 and 36% yields, respectively, after column chromatography.

In related experiments we had occasion to prepare two other hetero-substituted selenides. Acyloxyseleno ester **8** arose from the low-temperature Pummerer reaction of selenoxide **7**.[4]



Chloroseleno ester **11** was synthesized by metalation and selenation of methyl α-chloropropionate. Both **8** and **11** underwent smooth oxidation and rapid elimination at 0 °C to produce the known α-acetoxy and α-chloroacrylic esters **9**[5] and **12**.[6]

Unsaturated carbonyl compounds bearing α-oxygen or α-halogen substituents are relatively unstable substances. The very gentle reaction conditions we have delineated constitute a convenient access to these structures.[7,8]

Experimental Section[9]

Selenation of Methyl 2-Cyclohexyloxypropionate. Preparation of 4a and Oxidation to 5a. A solution of LDA (1.2 mmol) was prepared in THF (5 mL) from diisopropylamine (0.168 mL) and *n*-BuLi (0.83 mL of a 1.45 M solution in hexane), then cooled to −70 °C under N_2. To it was added a solution of **3a** (0.186 g, 1.0 mmol) and HMPA (0.358 g, 2 mmol) in THF (1 mL) and the reaction mixture was stirred for 1 h. Meanwhile a solution of PhSeBr was prepared from PhSeSePh (0.47 g, 1.5 mmol) and Br_2 (0.24 g, 1.5 mmol) in THF (3.5 mL). A portion of this solution (1.4 mL, ca. 1.2 mmol of PhSeBr) was added by syringe to the enolate anion at −60 to −70 °C and the dark

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