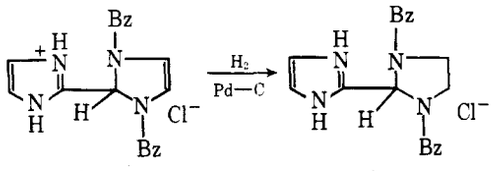
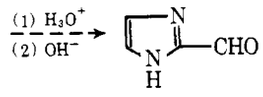
present in 1 was thought to be exploitable toward providing some key 2-substituted imidazoles, thus prompting us to examine some of its properties.

Efforts at bringing about total hydrolysis under the usual aqueous acidic or basic conditions were unrewarding or unpromising. On the other hand, refluxing 1 in methanol containing ca. 20% 2-propanolic hydrochloride readily afforded 2-aminomethylimidazole dihydrochloride (2) in 63% yield. The mechanism almost certainly involves a 1,5-hydrogen shift.

By the same token, 1 may be viewed as a derivatized aminal stemming from imidazole-2-carboxaldehyde (5). It was therefore hydrolyzed to dibenzoyl derivative 3.[3] Subsequent hydrogenation afforded 4, which, in refluxing aqueous HCl gave, besides benzoic acid and ethylenediamine dihydrochloride, aldehyde 5 cleanly and in consistently better than 85% yield.



3 4



5

Compound 5 has previously been obtained by MnO_2 oxidation of the appropriate carbinol[4] or via a multistep procedure centering on treatment of N-substituted 2-imidazolelithium reagents with dimethylformamide,[5] or by acid-promoted cyclization–deacetalization of *N*-(2,2-diethoxyethyl)-2,2-diethoxyacetamidine.[6] The amine (2) has been shown to be derivable from 5 through an oximation–reduction sequence.[7] Considering, however, both the yields and the ease of operation, the approach offered herein may well constitute the method of choice for synthesizing the title compounds.

Experimental Section

General. Melting points were measured with a Fisher-Johns apparatus and are uncorrected. The NMR spectra were recorded in a Varian EM 360A apparatus using Me_4Si as internal standard (δ 0.00). The analytical data furnished by Messrs. P. van den Bosch and H. Eding and the technical assistance of Miss Wilma Oomens are gratefully acknowledged.

2-Aminomethylimidazole Dihydrochloride (2). A solution of 8.96 g (0.02 mol) of 1[3] in 100 mL of methanol containing 20 mL of 2-propanol previously saturated with HCl gas was refluxed for 22 h. Solvents were then removed and the semicrystalline residue was triturated with acetone to give 2.16 g (63.5%) of 2, mp 240–242 °C, and spectrally identical to material reported earlier.[7] An analytical sample was prepared from methanol/isopropyl ether. Anal. Calcd for $C_4H_7N_3 \cdot 2HCl$: C, 28.25; H, 5.33; N, 24.71. Found: C, 28.15; H, 5.38; N, 24.72.

2-(1,3-Dibenzoyl-4-imidazolin-2-yl)imidazole Hydrochloride (3). This compound, previously prepared as the base by Regel[3] by aminolyzing 1, was obtained by us as follows.

Compound 1, 4.48 g (0.01 mol), in 25 mL of methanol containing 2.5 mL of 2-propanol saturated with HCl gas gave a green solution. After 18 h at room temperature the mixture had turned colorless; it was poured onto 200 mL of ethyl ether to give 3.54 g (93%) of 3, mp 240–242 °C; analytical material (methanol/isopropyl ether) gave mp 241–243 °C. Anal. Calcd for $C_{20}H_{16}N_4O_2 \cdot HCl$: C, 63.07; H, 4.56; N, 14.71. Found: C, 63.02; H, 4.60; N, 14.79.

2-(1,3-Dibenzoylimidazolidin-2-yl)imidazole Hydrochloride (4). A solution of 4.5 g (0.0118 mol) of 3 in 50 mL of methanol was hydrogenated in the presence of 0.1 g of Pd–C at room temperature and at atmospheric pressure till 1 equiv of H_2 was taken up. Catalyst and solvent were then successively removed to leave a solid residue. Recrystallization from ethanol–isopropyl ether gave 3.9 g of material: mp 215–217 °C; ^{1}NMR (CD_3OD) AA'BB' system centered around δ 4.17 (4, CH_2CH_2). Anal. Calcd for $C_{20}H_{18}N_4O_2 \cdot HCl$: C, 62.74; H, 5.00; N, 14.64. Found: C, 62.96; H, 4.98; N, 14.42.

Imidazole-2-carboxaldehyde (5). Two grams (0.0052 mol) of 4 in 30 mL of concentrated HCl was refluxed for 22 h. The resulting benzoic acid was removed on chilling and filtration; the filtrate was then evaporated. Addition of a minimum of ethanol to the residue gave 0.63 g (91%) of ethylenediamine dihydrochloride which was removed by filtration. Aqueous dilution of the filtrate, basification (NaOH), extraction with methylene dichloride, drying of the organic phase, and solvent removal left 0.44 g (88%) of 5, melting at 200–202 °C and spectrally identical to material reported earlier.[4,5]

Registry No.—1, 62457-77-6; 2, 22600-77-7; 3, 65276-00-8; 4, 65276-01-9; 5, 10111-08-7.

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Synthesis of 2-Cyanophenyl Thiocyanates and Related Disulfides by Nitro Displacement. A Novel Synthesis of 3-Chloro-1,2-benzisothiazole

J. R. Beck* and J. A. Yahner

Lilly Research Laboratories, Division of Eli Lilly & Company, Box 708, Greenfield, Indiana 46140

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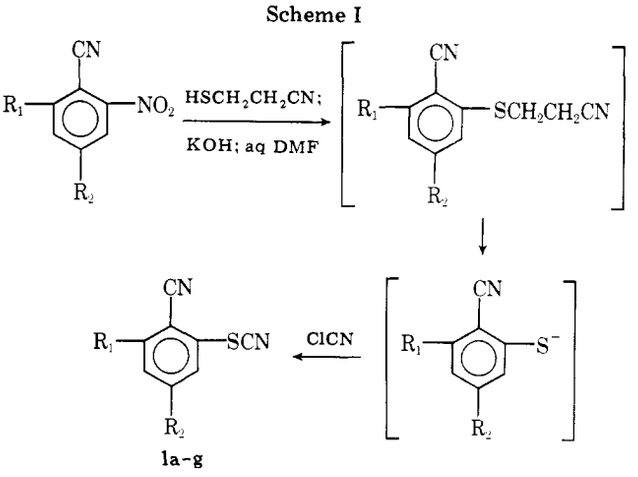
The conversion of a nitro group to a thiocyanate function ordinarily involves reduction, diazotization, and displacement with thiocyanate ion. In the case of a nitro group activated by an *o*-cyano function, a direct displacement by thiocyanate ion should be possible. However, in a previous report[1] we were unable to find conditions for this process, apparently because of the weak nucleophilicity of thiocyanate ion. We wish to report an alternate approach, which involves an initial displacement by 3-mercaptopropionitrile[2] anion to give a cyano ethyl thioether[3] (Scheme I). This intermediate is rapidly converted to the thiol anion by loss of acrylonitrile under the basic reaction conditions or, less likely, through direct displacement by hydroxide ion. Addition of cyanogen chloride then yields the thiocyanic acid ester 1.

Scheme I



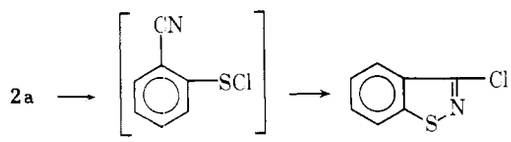
1a-g

Table I. 2-Cyanophenyl Thiocyanates

Compd[a]	Registry no.	R_1	R_2	Mp, °C	Yield, %	Crystn solvent[b]
1a	34263-66-6	H	H	79–81[c]	72	A
1b	65275-70-9	Cl	H	127–128[d]	65	B
1c	65275-71-0	OMe	H	162.5–164	77	C
1d	65275-72-1	OMe	CF_3	54–55	53	C
1e	65275-73-2	NO_2	CF_3	101–102	54	C
1f	65275-74-3	NO_2	H	91–92	67	C
1g	65275-75-4	H	Cl	149–151	70	C

[a] Satisfactory analytical data (±0.3% for C, H, and N) were reported for all compounds in the table. [b] A = alcohol–water; B = benzene–hexane; C = alcohol. [c] Lit.[4] mp 83 °C. [d] Lit.[5] mp 125–126 °C.

Scheme II



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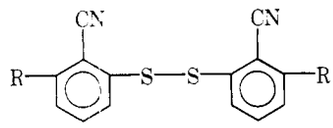
For example, *o*-nitrobenzonitrile was allowed to react with 3-mercaptopropionitrile anion in aqueous DMF for 15 min at ice bath temperature. Cyanogen chloride was added, and after an additional 30 min the reaction was quenched. The product isolated (72% yield) was shown to be 2-cyanophenyl thiocyanate (**1a**).[4] Similarly prepared were **1b–g** (Table I), and the yields were in the range of 50–75%. An attempt was made to isolate the intermediate thiophenol. The reaction mixture containing *o*-nitrobenzonitrile and 3-mercaptopropionitrile anion was stirred at room temperature for 1.5 h and then carefully acidified. The product isolated was not the thiophenol but rather the disulfide **2a** (61%).[6] Similar treatment of 2-chloro-6-nitrobenzonitrile yielded the disulfide **2b** (87%).

When **2a** was allowed to react with chlorine in DMF, the product obtained was 3-chloro-1,2-benzisothiazole (**3**, 36%),[7] apparently formed through the intermediacy of the sulfenyl chloride (Scheme II). Sulfenyl halides are known to undergo addition reactions with nitriles.[8] Two reported examples[9] proceeded by intramolecular cyclization, although neither involved an aromatic nitrile function.



2a, R = H
b, R = Cl

Experimental Section[10]

Materials. 6-Nitro-*o*-anisonitrile,[1] α,α,α-trifluoro-2,6-dinitro-*p*-tolunitrile,[11] α,α,α-trifluoro-2-methoxy-6-nitro-*p*-tolunitrile,[1] and 3-mercaptopropionitrile[2] were prepared by procedures described in the literature. All other chemicals were commercially available.

2-Cyanophenyl Thiocyanate 1a. To a cold solution (ice bath) containing 13.3 g of 2-nitrobenzonitrile (90 mmol) and 9.3 g of 3-mercaptopropionitrile (107 mmol) in 120 mL of DMF was added dropwise a solution containing 15 g of potassium hydroxide in 30 mL of water. The mixture was stirred in the cold for 15 min, and then cyanogen chloride was bubbled into the solution for 10 min. After the mixture had been stirred for a further 30 min, the mixture was poured into ice water. The solid was collected and crystallized from alcohol–water to yield 10.35 g (72%) of product, mp 78–81 °C. An analytical sample, mp 79–81 °C (lit.[4] mp 83 °C), was recrystallized. Anal. Calcd for $C_8H_4N_2S$: C, 59.98; H, 2.52; N, 17.49. Found: C, 59.69; H, 2.77; N, 17.19.

General Procedure for Preparation of Esters 1b–g. To a cold solution (ice bath) of 30 mmol of the appropriate *o*-nitrobenzonitriles and 36 mmol[12] of 3-mercaptopropionitrile in 60 mL of DMF was added dropwise a solution of 5 g of potassium hydroxide in 15 mL of water. The mixture was stirred in the cold for 15 min, and then cyanogen chloride was bubbled in for 5 min. After an additional 1 h, the mixture was poured into ice water. The crude solid was collected and crystallized from the appropriate solvent (Table I). Melting points and yields are summarized in Table I.

2,2′-Dithiobis(benzonitrile) (2a). A solution containing 10 g of potassium hydroxide in 25 mL of water was added dropwise to a cold solution (ice bath) containing 8.9 g of 2-nitrobenzonitrile (60.1 mmol) and 6.2 g of 3-mercaptopropionitrile (71.2 mmol) in 100 mL of DMF. The ice bath was removed and the mixture was stirred for 1.5 h and then carefully acidified with 30 mL of concentrated hydrochloric acid. After 5 min the mixture was poured into ice water. The solid was collected and crystallized from alcohol to yield 4.9 g (61%) of product, mp 105–106 °C (lit.[6] 103–104 °C). Anal. Calcd for $C_{14}H_8N_2S_2$: C, 62.66; H, 3.00; N, 10.44. Found: C, 62.42; H, 2.77; N, 10.38.

2,2′-Dithiobis(6-chlorobenzonitrile) (2b). To a cold solution (ice bath) of 5.5 g of 2-chloro-6-nitrobenzonitrile (30.1 mmol) and 3.1 g of 3-mercaptopropionitrile (35.6 mmol) in 60 mL of DMF was added dropwise a solution of 5 g of potassium hydroxide in 20 mL of water. The mixture was stirred in the cold for 1.5 h and then 15 mL of concentrated hydrochloric acid was added dropwise. The solution was stirred for an additional 5 min and then poured into ice water. The solid was collected and crystallized from DMF–water to yield 4.4 g (87%) of product, mp 183–185 °C. Anal. Calcd for $C_{14}H_6Cl_2N_2S_2$: C, 49.86; H, 1.79; N, 8.31. Found: C, 49.65; H, 1.50; N, 8.12.

3-Chloro-1,2-benzisothiazole (3). Chlorine was bubbled into 50 mL of DMF for several minutes. To this solution was added portionwise 5.6 g of **2a** (20.9 mmol) and the resulting mixture was stirred for 17 h. Chlorine was again bubbled in for several minutes, and the solution was stirred for an additional 4 h. The mixture was poured into ice water, which was then extracted twice with ether. The combined ether extract was washed three times with water and dried. Removal of the solvent and crystallization from alcohol–water yielded 1.5 g of product, mp 40–41 °C (lit.[7] 40 °C). Concentration of the mother liquor yielded 1.05 g of product, mp 39–40 °C. The combined yield was 2.55 g (36%). A mixture melting point with an authentic sample showed no depression. Anal. Calcd for C_7H_4ClNS: C, 49.56; H, 2.38; Cl, 20.90; N, 8.26; S, 18.90. Found: C, 49.27; H, 2.40; Cl, 21.20; N, 7.98; S, 19.20.

Acknowledgments. The authors thank Mr. Paul Unger and associates for spectral measurements and Mr. George Maciak and associates for microanalytical data.

Registry No.—2a, 33174-74-2; **2b,** 65275-76-5; **3,** 7716-66-7; 2-nitrobenzonitrile, 612-24-8; 6-chloro-2-nitrobenzonitrile, 6575-07-1; 6-methoxy-2-nitrobenzonitrile, 38469-85-1; 6-methoxy-4-trifluoromethyl-2-nitrobenzonitrile, 51271-38-6; 4-trifluoromethyl-2,6-dinitrobenzonitrile, 35213-02-6; 2,6-dinitrobenzonitrile, 35213-00-4; 4-chloro-2-nitrobenzonitrile, 34662-32-3; 3-mercaptopropionitrile, 1001-58-7; cyanogen chloride, 506-77-4.

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

William E. Parham, Charles K. Bradsher,* and David A. Hunt

Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706

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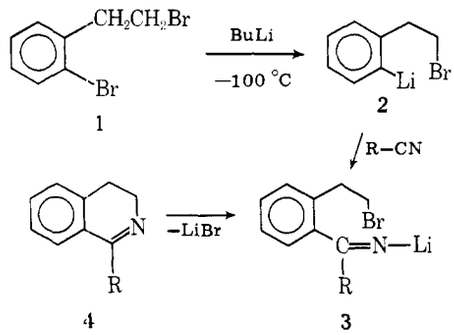
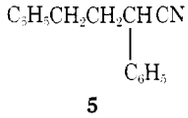
Parham and his students have shown that formation of functionalized organolithium reagents at low temperature (−100 °C), followed by reaction with either an internal or external electrophile, provides an excellent route to various cyclization products, many of which were heretofore difficult to obtain.[3]

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



1 2 4 3

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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