A New Synthesis of Arylmalononitriles

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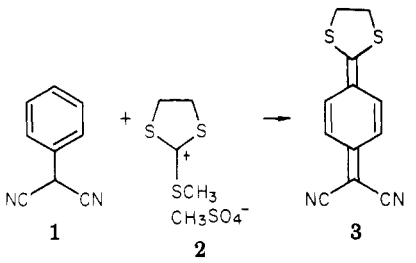
Stable dipolar *p*-quinodimethanes containing electron-donating and electron-withdrawing groups at opposite ends of the π system have been the subject of considerable interest in view of their unusual electronic properties.[1-3] Those which have been the most studied contain two cyano groups at one terminus of the dipole, while the opposite end bears various combinations of oxygen, nitrogen, and sulfur substituents. The most frequently used synthesis of these compounds consists of the reaction of an arylmalononitrile anion with a heteroatom-stabilized carbocation.[1,2] In a typical example, phenylmalononitrile (1) was coupled with 2-(methylthio)-1,3-dithiolium methyl sulfate (2) to give the quinodimethane 3[2] (eq 1).



1 2 3 (1)

Recently, we required a number of arylmalononitriles for the synthesis of some push–pull-stabilized quinodimethanes of this type. An extensive literature search revealed three procedures which have been used for the synthesis of arylmalononitriles.

The simplest compound of this type, phenylmalononitrile (1), was originally synthesized from benzyl cyanide (4) by a three step sequence of methoxycarbonylation, ammonia treatment, and final phosphorus pentachloride dehydration[4] (eq 2).

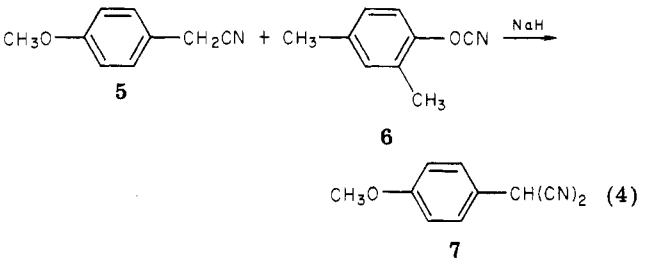
$$\underset{4}{PhCH_2CN} \xrightarrow[2.\ NH_3\quad 3.\ PCl_5]{1.\ NaOCH_3,\ CO(OCH_3)_2} \underset{1}{PhCH(CN)_2} \qquad (2)$$

In an improved procedure, benzyl cyanide (4) was methoxycarbonylated by treatment with sodium methoxide and dimethyl carbonate and then cyanated by cyanogen chloride[5] (eq 3). Hydrolysis of the resulting dicyano ester

$$\underset{4}{PhCH_2CN} \xrightarrow[2.\ ClCN\quad 3.\ OH^-,\ H^+]{1.\ NaOCH_3,\ CO(OCH_3)_2} \underset{1}{PhCH(CN)_2} \qquad (3)$$

and subsequent decarboxylation gave phenylmalononitrile (1). This method has the disadvantage of requiring the use of the toxic and noxious cyanogen chloride and involves a sequence of several steps.

Eicher and his co-workers have employed 2,4-dimethylphenyl cyanate (6) as a cyanating agent in the synthesis of phenylmalononitriles. For example, treatment of 4-methoxybenzyl cyanide (5) with sodium hydride and cyanate 6 gave 4-methoxyphenylmalononitrile (7) (eq 4).



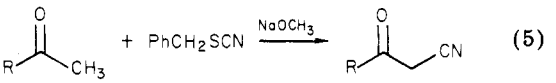
5 6 7 (4)

Although this is a one-step synthesis from benzyl cyanide, yields were modest or low, and the cyanate reagent 6 must itself be synthesized with the use of cyanogen chloride.[6]

We now report the conversion of a number of benzylic cyanides to arylmalononitriles by a convenient one-step method which also avoids the use of a cyanogen halide.

Results and Discussion

In view of the fact the anions of benzylic nitriles can be directly cyanated by attack on an aryl cyanate, it seemed plausible that a similar anionic attack on the cyano moiety of a thiocyanate ester should be possible. Such a reaction would be especially useful if a readily prepared alkyl thiocyanate could be used as the reagent. The literature indicates that the carbanions can attack either the sulfur or the cyano center of thiocyanate. Thus, α-cyano ketones have been prepared in modest yields by the reaction of ketone enolates with benzyl thiocyanate as shown in eq. 5. No attack on the sulfur atom was observed.[7] In



(5)

contrast, treatment of benzyl cyanide with ethyl thiocyanate and sodium hydroxide in the presence of a phase-transfer catalyst (eq 6) led to carbanion attack on

$$PhCH_2CN + C_2H_5SCN \xrightarrow[TEBA]{NaOH} PhCH(CN)SC_2H_5 \qquad (6)$$

sulfur with the formation of an α-cyano sulfide; no phenylmalononitrile was reported as a reaction product.[8]

Despite the latter report, we decided to investigate the reaction of the benzyl cyanide anion with a thiocyanate under various conditions. We chose 2-chlorobenzyl thiocyanate[9] (8) as our reagent for several reasons: (a) it was readily prepared from the inexpensive 2-chlorobenzyl chloride; (b) it is a stable liquid which can be measured out volumetrically as needed.

It was found that the anion of benzyl cyanide was cyanated in a nonpolar solvent. Excellent results were obtained when benzyl cyanide was converted to its lithio derivative by 1 equiv of lithium diisopropylamide (LDA) in benzene, and 1 equiv of thiocyanate 8 was added. However, about half of the original nitrile was recovered from this reaction, a result which is not surprising in view of the much greater acidity of malononitriles as compared with acetonitriles.

The benzyl cyanide was completely consumed when it was treated with 2 equiv of LDA, followed by reaction with 2 equiv of 2-chlorobenzyl thiocyanate; phenylmalononitrile (1) was isolated in excellent yield (94%) by extraction with

(1) Eicher, T.; Eiglmer, K. *Chem. Ber.* **1971**, *104*, 605.
(2) Gompper, R.; Wagner, H.; Kutter, E. *Chem. Ber.* **1968**, *101*, 4123.
(3) Gompper, R.; Wagner, H. *Tetrahedron Lett.* **1967**, 165.
(4) Hessler, J. C. *J. Am. Chem. Soc.* **1904**, *32*, 119.
(5) Williams, J. K.; Martin, E. L.; Sheppard, W. A. *J. Org. Chem.* **1966**, *31*, 919.
(6) Grigt, E.; Putter, P. *Chem. Ber.* **1964**, *97*, 3012.
(7) Rodriques, C.; Lamazouere, A. M.; Sotiropoulas, J. *Hebd. Seances Acad. Sci., Ser. C* **1980**, *291*, 179.
(8) Makosza, M.; Fedorynski, M. *Synthesis* **1974**, 274.
(9) Schlesinger, A. H.; Mowry, D. T. *J. Am. Chem. Soc.* **1954**, *76*, 585.

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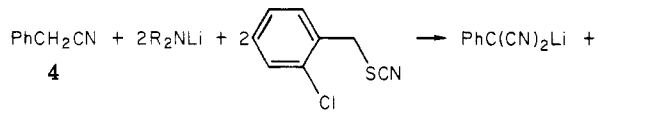
Table I. Synthesis of Arylmalononitriles from Aromatic Acetonitriles

arylacetonitrile	aryl-malono-nitrile	yield, %	mp, °C
phenyl	1	94	67–68
4-methoxyphenyl	7	77	71–72
4-bromophenyl	9	91	86–87.5
3,4-(methylenedioxy)phenyl	10	92	131–133
3-pyridyl	11	56	250 dec
1-naphthyl	12	100	165–166
2-methylphenyl	13	95	49–50
2-chlorophenyl	14	92	62–63

aqueous base, followed by acidification. The overall reaction is shown in eq. 7. Seven additional arylmalononitriles were synthesized in excellent yield by the same general procedure. The results are summarized in Table I.



(7)

2-Chlorobenzyl thiocyanate (8), unlike cyanogen chloride, is a selective cyanating agent and does not react with highly stabilized anions. Thus, the anion of phenylmalononitrile does not react with thiocyanate 8, although it can be further cyanated to phenyltricyanomethane by cyanogen chloride[10] (eq 8).

$$PhCH(CN)_2 \xrightarrow[ClCN]{NaH} PhC(CN)_3 \quad (8)$$

Similarly, thiocyanate 8 did not react with the anion of ethyl α-cyanophenylacetate, whereas the reaction of anions of this type with cyanogen chloride proceeds readily.

Experimental Section

General Methods. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Mass and infrared (KBr) spectra were recorded with a Hitachi Perkin-Elmer RMH-2 and a Perkin-Elmer Model 137 spectrometer, respectively. NMR spectra were recorded on a Bruker 250 FT machine with $CDCl_3$ solution containing Me_4Si as an internal standard unless otherwise noted and are reported in δ units (J values are in hertz). Elemental analyses were carried out by Galbraith Laboratories.

General Procedure for the Cyanation of Arylacetonitriles. To a solution of LDA (11.0 mmol) in benzene (75 mL) at 5 °C under nitrogen was added a solution of the arylacetonitrile (5.00 mmol) in benzene (25 mL), and the reaction mixture was stirred for 15 min. A solution of 2-chlorobenzyl thiocyanate (11.0 mmol) in benzene (50 mL) was added over 15 min, and the reaction mixture was stirred for an additional hour. The reaction was worked up by washing the benzene solution with water and 10% aqueous sodium hydroxide. The combined aqueous solution was cooled in an ice bath and acidified to pH 1 with concentrated hydrochloric acid. The product was extracted into methylene chloride, and the solution was dried over $MgSO_4$ and evaporated to give the arylmalononitrile. Arylmalononitriles **7**, **9–12**, and **14** were crystallized from ethanol, and **1** and **13** were distilled at reduced pressure.

Phenylmalononitrile (1): mp 67–68 °C (lit.[1,4] mp 68–69 °C); IR (KBr) 2900, 1480, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) 5.08 (s, 1 H), 7.50 (s, 5 H); *m/e* (relative intensity) 142 (M^+, 58), 115 (100).

(2-Methylphenyl)malononitrile (13): mp 49–50 °C; IR (KBr) 2900, 1480, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) 2.48 (s, 3 H), 5.05 (s, 1 H), 7.38–7.60 (m, 2 H); MS, *m/e* (relative intensity) 156 (M^+, 35), 141 (15), 129 (100), 91 (23). Anal. Calcd for $C_{10}H_8N_2$: C, 76.92; H, 5.13; N, 17.95. Found: C, 76.75; H, 5.28; N, 17.76.

(2-Chlorophenyl)malononitrile (14): mp 62–63 °C (lit.[1] mp 60–62 °C) IR (KBr) 2900, 1475, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) 5.38 (s, 1 H), 7.40–7.75 (m, 4 H); MS, *m/e* (relative intensity) 176 (M^+, 41) 141 (100), 114 (19).

1-Naphthylmalononitrile (12): mp 165–166 °C (lit.[5] mp 166–167 °C); IR (KBr) 2900, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) 5.58 (s, 1 H), 7.54–8.05 (m, 7 H); MS *m/e* (relative intensity) 192 (M^+, 100), 191 (31), 165 (47).

(4-Bromophenyl)malononitrile (9): mp 86–87.5 °C; IR (KBr) 2900, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) 5.05 (s, 1 H), 7.39 (d, J = 8.5 Hz, 2 H), 7.65 (d, J = 8.5 Hz, 2 H); MS, *m/e* (relative intensity) 222 (18), 220 (M^+, 19), 141 (100); high-resolution mass spectrum, calcd for $C_9H_5BrN_2$ *m/e* 219.9636 and 221.9616, found 219.9664 and 221.9626.

(4-Methoxyphenyl)malononitrile (7): mp 71–72 °C (lit.[1] mp 67–69 °C; IR (KBr) 2850, 1600, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) 3.84 (s, 3 H), 5.01 (s, 1 H), 7.41 (d, J = 8.5 Hz, 2 H), 7.98 (d, J = 8 Hz, 2 H); MS, *m/e* (relative intensity) 172 (M^+, 100), 161 (30), 157 (39), 102 (34).

3-Pyridylmalononitrile (11): decomposes at 250 °C (lit.[10] mp 246–248 °C); IR (KBr) 3100, 2175, 2125 cm^{-1}; ^1H NMR (Me_2So-d_6) 7.60 (s, 2 H), 7.91 (s, 2 H), 13.0 (br s, 1 H); MS, *m/e* (relative intensity) 143 (M^+, 100), 116 (80); high-resolution mass spectrum, calcd for $C_8H_5N_3$, *m/e* 143.0483, found 143,0483.

[3,4-(Methylenedioxy)phenyl]malononitrile (10): mp 131–133 °C; IR (KBr) 2950, 1500, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) 4.96 (s, 1 H), 6.06 (s, 2 H), 6.84–6.98 (m, 3 H); MS, *m/e* (relative intensity) 186 (M^+, 100), 185 (96), 156 (40), 128 (99). Anal. Calcd for $C_{10}H_6N_2O_2$: C, 64.52; H, 3.23; N, 15.05. Found: C, 64.73; H, 3.43; N, 15.04.

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Registry No. **1**, 3041-40-5; **4**, 140-29-4; **5**, 104-47-2; **7**, 33534-87-1; **9**, 86239-14-7; **10**, 86239-15-8; **11**, 25230-06-2; **12**, 5518-09-2; **13**, 86239-16-9; **14**, 32122-65-9; 4-bromophenylacetonitrile, 16532-79-9; 3,4-(methylenedioxy)phenylacetonitrile, 4439-02-5; 3-pyridylacetonitrile, 6443-85-2; 1-naphthylacetonitrile, 132-75-2; 2-methylphenylacetonitrile, 22364-68-7; 2-chlorophenylacetonitrile, 2856-63-5; 2-chlorobenzyl thiocyanate, 2082-66-8.

(10) Wagner, H.,; Gompper, R. *Angew Chem., Int. Ed. Engl.* **1969**, *8*, 986.

A Simple Synthesis of Rhodinose from (*S*)-Ethyl Lactate

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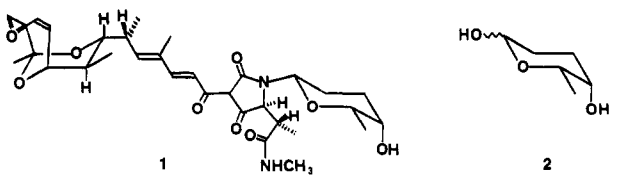
In conjunction with a program directed toward the synthesis of the antibiotic streptolydigin (**1**),[1] we sought a convenient supply of the trideoxyhexose subunit rhodinose (**2**).[2] Two syntheses of rhodinose, both from car-



(1) Rinehart, K. L., Jr.; Borders, D. B. *J. Am. Chem. Soc.* **85**, 4083 (1963).

(2) (a) Stevens, C. L.; Blumbergs, P.; Wood, D. L. *J. Am. Chem. Soc.* **86**, 3592 (1964). (b) Rhodinose is also a component of the oligosaccharides present in the rhodomycin family of anthracycline antibiotics: Brockmann, H.; Greve, H. *Tetrahedron Lett.*, 831 (1975) and references therein.

0022-3263/83/1948-2775$01.50/0