One-Step Synthesis of 2- and 4-Nitrobenzyl Cyanides

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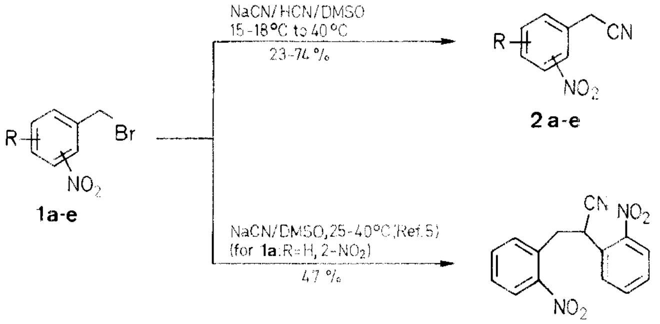
2-Nitrobenzyl cyanide (**2**) and analogs were obtained in fair to good yields by reacting the corresponding bromides with sodium cyanide and hydrogen cyanide in dimethyl sulfoxide. Hydrogen cyanide could be generated *in situ* from an excess of sodium cyanide and trifluoroacetic acid.

2-Nitrobenzyl cyanides serve as useful starting materials for a variety of compounds and particularly their reductive cyclization offers a facile route to substituted indoles.[1-4] The synthesis of these simple compounds is quite difficult, and the direct *ortho*-nitration of a substituted benzyl cyanide[4] is rarely applicable. 2-Nitrobenzyl cyanide (**2a**) was prepared from 2-nitrobenzyl chloride and potassium cyanide in aqueous alcohol, but side-products were also present that may prevail over the desired product.[5] Alternative routes developed require starting materials that are neither inexpensive nor readily available.[6-9]

Friedman and Shechter described a general route to organic cyanides from halides and sodium cyanide in DMSO.[10] They reported that with 4-nitrobenzyl chloride only 4,4'-dinitrostilbene was obtained. This result was explained by assuming the formation of an intermediate carbanion or carbene.[11,12]

2-Nitrobenzyl bromide **1** when reacted with NaCN in DMSO gave only the known 2,3-bis-(2-nitrophenyl)propanenitrile (**3**),[5] and not the desired **2a** or, by analogy with the 4-nitro-isomer, 2,2'-dinitrostilbene. Product **3** was undoubtedly formed from **2** by further alkylation in a basic medium.



We anticipated that the yield of **2a** would be favorably affected by a higher concentration of cyanide and lower pH of the reaction medium. In order to create these conditions hydrogen cyanide was added to the reaction mixture (3 moles per mole of **1a**), and indeed **2a** was then obtained in 70–75% yield. This procedure was simplified by directly adding a strong acid (such as trifluoroacetic acid or sulfuric acid) to an excess of sodium cyanide, thus avoiding the handling of the toxic, gaseous hydrogen cyanide. By this method 4-nitrobenzyl cyanide,[14] 2-chloro-6-nitrobenzyl cyanide[15] and the previously unreported 4-fluoro-2-nitrobenzyl, and 3-methyl-2-nitrobenzyl cyanides were prepared from the corresponding bromides. 4-Nitrobenzyl chloride gave the known 2,3-bis(4-nitrophenyl)-2-(4-nitrophenylmethyl)propanenitrile.[16] The different behavior of 4-nitrobenzyl halides under identical conditions has been reported.[17-19] It may be noted that with acetic acid, only 2-nitrobenzyl acetate, m.p. 32–34 °C,[13] was obtained.

Reactions of 2-Nitrobenzyl Bromide (1a) With Sodium Cyanide; Typical Procedures:

Method A: *Without Hydrogen Cyanide*. 2-Nitrobenzyl bromide[20] (**1a**; 21.6 g, 0.1 mol) is added to a stirred suspension of sodium cyanide (4.9 g, 0.1 mol) in freshly distilled dimethyl sulfoxide. The mixture is

Table. Preparation of Substituted Nitrobenzyl Cyanides **2b**–**e**

Product	R	NO_2	Yield (%)	m.p.[a] (°C)	Molecular Formula[b] or Lit. m.p. (°C)	IR ($CHCl_3$)[c] ν (cm^{-1})	^1H-NMR[d] ($CDCl_3$/TMS) δ (ppm)
2b[e,f]	2-F	6-	23	60–61	$C_8H_5FN_2O_2$ (180.1)	2260	3.98 (s, 2H); 7.6 (m, 3H)
2c[f,g]	2-Cl	6-	49	65–67	67–68[15]	2250	4.04 (s, 2H); 7.6 (m, 3H)
2d[g,h]	3-CH_3	2-	35	73–74	$C_9H_8N_2O_2$ (176.2)	2250	2.34 (s, 3H); 3.76 (s, 2H); 7.35 (m, 3H)
2e[f]	H	4-	40	115–117	116–117[14]		

[a] Uncorrected, measured with a Fisher-Johns apparatus.
[b] Satisfactory microanalyses obtained: C ±0.2, H ±0.2, N ±0.3.
[c] Recorded on a Perkin-Elmer 297 Infrared spectrophotometer.
[d] Obtained on a Jeol 60-MHz spectrometer.
[e] Yield based on the substituted 2-nitrotoluene brominated according to Ref. 20.
[f] Hydrogen cyanide/sodium cyanide.
[g] Trifluoroacetic acid/sodium cyanide.
[h] Hydrolysis with 75% aqeous acetic acid/sulfuric acid gave 3-methyl-2-nitrophenylacetic acid, m.p. 154–155 °C.[22]

stirred for 2 hr at 25 °C and 2 hr at 40 °C and poured into water (250 ml). The solid precipitate is collected and recrystallized from ethanol, it gives *2,3-bis(2-nitrophenyl)propanenitrile* (**3**)[5]; yield: 7 g (47 %): m.p. 110 °C (Lit.[5] m.p. 110.5 °C).

Method B: *With Hydrogen Cyanide*. Powdered sodium cyanide (9.8 g, 0.2 mol) is added in portions to a stirred mixture of **1a** (43.2 g, 0.2 mol) and anhydrous hydrogen cyanide (6.2 g, 0.6 mol) in dimethyl sulfoxide (200 ml). The addition is exothermic, and the temperature is kept at 15–18 °C by external cooling. A blue color appears and quickly turns deep red. After 2 hr at 25 °C, and 2 hr at 40 °C, the mixture is worked up as described above to give cyanide **2a**; yield: 24 g (74 %): m.p. 84 °C (ethanol (Lit.[6] 84 °C).

^{1}H-NMR (DMSO-d_6/TMS): $\delta = 4.30$ (s, 2H, $-CH_2-$); 7.60–8.24 (m, 4H).

Mass spectrum of **2a** has the most abundant ion at *m/e* 135 due to the 1,1-elimination of hydrogen cyanide.[21]

Method C: With Sodium Cyanide and a Strong Acid. A stirred and cooled suspension of sodium cyanide (14.7 g, 0.3 mol) in dimethyl sulfoxide (125 ml) is treated with trifluoroacetic acid (22.8 g, 0.2 mol) at 12 °C, followed by **1a** (21.6 g, 0.1 mol). After work up as above, the crude cyanide **2a** is obtaianed; yield: 3.1 g (81 %); m.p. 78–82 °C (not purified).

When sulfuric acid (9.8 g) is added instead of trifluoroacetic, crude **2a** is isolated in 90 % yield.

Several related compounds have been prepared analogously. The results are summarized in Table.

2,3-Bis(4-nitrophenyl)-2-(4-nitrophenylmethyl)propanenitrile:
4-Nitrobenzyl chloride (34.2 g, 0.2 mol) is added to sodium cyanide (9.8 g, 0.2 mol) and hydrogen cyanide (16.2 g, 0.6 mol) in dimethyl sulfoxide (200 ml) as described under Method B. A solid, m.p. 190–195 °C, is isolated from the reaction and identified as the isobutyronitrile derivative. Recrystallization from acetic acid gives the product; yield: 20 g (69 %); m.p. 200–202 °C (lit.[16] m.p. 204 °C.

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