Facile Preparation of 3-Arylpropanenitriles by the Reaction of Benzylic Halides with Haloacetonitriles Mediated by Metallic Nickel

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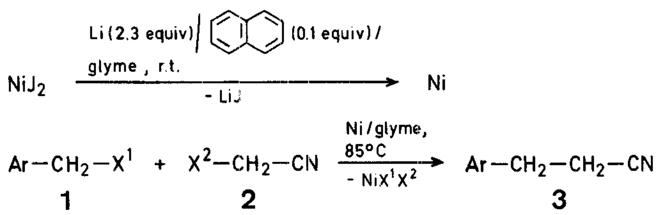
The alkylation of α-cyano anions[1,2] and metal cyanides[1] with organic halides has been one of the well known methods for the preparation of nitriles. Some years ago, Brown et al.[3,4] showed that the reaction of trialkylboranes with chloroacetonitrile gave the corresponding nitriles in good yields. Their results suggest that the alkylation of haloacetonitriles with organometallic compounds would provide an alternative route for the preparation of nitriles by carbon-carbon bond formation, however, no related examples have been reported.

Recently, we found that oxidative addition of aryl, benzyl, and allyl halides to metallic nickel proceeded smoothly to generate the corresponding organonickel intermediates under mild conditions, which afforded homo-coupled products[5,6,7], and ketones by the reaction with acid chlorides[8] or alkyl oxalyl chlorides[9]. We describe here a simple method for the preparation of 3-arylpropanenitriles (**3**) by the reaction of benzylic halides (**1**) with haloacetonitriles (**2**) mediated by metallic nickel.



Metallic nickel was easily prepared by stirring a mixture of nickel iodide and lithium metal with a catalytic amount of naphthalene as an electron carrier at room temperature for 12 h in 1,2-dimethoxyethane (glyme). The reaction of benzylic halides with haloacetonitriles was carried out by adding a mixture of these reagents to the metallic nickel in glyme.

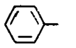
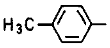
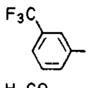
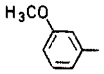
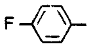
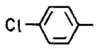
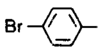
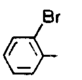
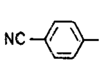
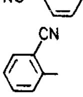
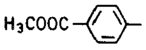
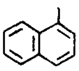
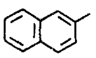
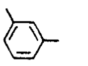
The coupling reaction of benzyl chloride with bromoacetonitrile in the presence of nickel proceeded at 65 °C to give 3-phenylpropanenitrile (**3a**) in 21 % yield, and improved results (57 %) were obtained under refluxing glyme (85 °C). The use of iodo- and chloroacetonitriles as substrates also worked well at 85 °C in the present system and **3a** was formed in 57 % and 52 % yields, respectively. The preparation of a variety of 3-arylpropanenitriles (**3**) was carried out at 85 °C using bromoacetonitrile; the results are summarized in the Table.

Compounds **3** could be generally prepared by the benzylation of sodioacetonitrile[10,11], by the condensation of carbonyl compounds with α-cyano-anions[12,13] followed by a catalytic hydrogenation of 3-arylcinnamonitriles formed[14], or by the cyanoethylation of aromatic substrates with 3-chloropropanenitrile or acrylonitrile/hydrogen chloride[15,16]. However, the first method afforded a mixture of mono- and dibenzylated products. The second method required two reaction steps although the catalytic hydrogenation occurred quantitatively. The last method proceeded with poor regioselectivity when substituted aromatic compounds were employed as substrates.

Our method overcomes these difficulties and the yields are in general compatible with those reported. Furthermore, the preparation of metallic nickel and the following reaction involves a very simple one-pot procedure, and the reaction conditions employed are compatible with a variety of substituents including halogen, cyano, an alkoxycarbonyl groups.

Preparation of Metallic Nickel:
A 50 ml two-necked flask is equipped with a magnetic stirrer, a rubber septum, and a reflux condenser topped with argon inlet and outlet to oil pump. Lithium metal is cut under mineral oil. One piece of lithium with shining metal surface is rinsed in hexane and transfered into glass tube with a stopcock and a rubber septum which has been filled with argon. The glass tube is evacuated to evaporate the hexane, filled with argon, and weighed. Nickel iodide (3.84 g, 12.3 mmol), lithium (0.196 g, 28.2 mmol), and naphthalene (0.157 g, 1.23 mmol) are placed in the flask through the side neck. The flask is evacuated and filled with argon two or three times. The use of a glove box or bag is not required if contact of the lithium with air is kept to a

Table. 3-Arylpropanenitriles (3) Prepared by the Reaction of Benzyl Halides (1) with Bromoacetonitrile (2; X^2 = Br) Mediated by Metallic Nickel[a]

Benzyl Ar	Halide 1 X^1	Product	Yield[b] [%]	m.p. [°C] or b.p. [°C]/torr	Molecular Formula[c] or Lit. Data	I.R.[d] $\nu_{C\equiv N}$ [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
	Cl	**3a**	57	129°/16	125–126°/15[15]	2240	2.52 (t, 2H); 2.87 (t, 2H); 7.02–7.48 (m, 5H)
	Cl	**3b**	60	141°/16	137–141°/15[15]	2240	2.29 (s, 3H); 2.49 (t, 2H); 2.83 (t, 2H); 7.09 (s, 4H)
	Cl	**3c**	58	86°/0.42	$C_{10}H_8F_3N$ (199.2)	2250	2.62 (t, 2H); 2.97 (t, 2H); 7.20–7.73 (m, 4H)
	Cl	**3d**	60	104°/0.43	110–120°/0.5[14]	2240	2.52 (t, 2H); 2.84 (t, 2H); 3.74 (s, 3H); 6.67–6.87 (m, 3H); 7.07–7.33 (m, 1H)
	Cl	**3e**	46	79°/0.65	73–76°/0.05[17]	2240	2.56 (t, 2H); 2.87 (t, 2H); 6.77–7.40 (m, 4H)
	Cl	**3f**	61	163°/18	153–156°/15[15]	2240	2.56 (t, 2H); 2.87 (t, 2H); 7.15 (d, 2H); 7.30 (d, 2H)
	Br	**3g**	52	114°/0.32	116°/0.05[18]	2240	2.54 (t, 2H); 2.84 (t, 2H); 7.08 (d, 2H); 7.42 (d, 2H)
	Br	**3h**	43	98°/0.42	C_9H_8BrN (210.1)	2240	2.63 (t, 2H); 3.04 (t, 2H); 6.93–7.73 (m, 4H)
	Br	**3i**	43	76.5–77°[e]	85–87°[19]	2235, 2220	2.67 (t, 2H); 3.10 (t, 2H); 7.38 (d, 2H); 7.63 (d, 2H)
	Br	**3j**	44	123°/0.49	110°/0.2[20]	2240, 2220	2.76 (t, 2H); 3.18 (t, 2H); 7.27–7.83 (m, 4H)
	Cl	**3k**	55	60.5–61°	$C_{11}H_{11}NO_2$ (189.2)	2235	2.62 (t, 2H); 2.98 (t, 2H); 3.89 (s, 3H); 7.32 (d, 2H); 8.00 (d, 2H)
	Cl	**3l**	20	139°/0.20	$C_{13}H_{11}N$ (181.2)	2240	2.56 (t, 2H); 3.25 (t, 2H); 7.07–7.97 (m, 7H)
	Br	**3m**	53	78–78.5°	$C_{13}H_{11}N$ (181.2)	2240	2.53 (t, 2H); 3.01 (t, 2H); 7.10–8.00 (m, 7H)
	2 Br	**3n**	36[f]	164°/0.34	165–169°/0.1[21]	2240	2.60 (t, 4H); 2.92 (t, 4H); 6.90–7.49 (m, 4H)

[a] Reactions were carried out in glyme under argon at 85°C using the reagents in the ratio of benzylic halide/bromoacetonitrile/metallic nickel = 0.8/0.8/1.0 unless otherwise noted.
[b] Isolated by silica gel chromatography upon elution with chloroform.
[c] Microanalyses were in good agreement with the calculated values: C ±0.23; H ±0.24; N ±0.18.
[d] Measured as film (liquids) or in KBr (solids).
[e] $C_{10}H_8N_2$ (156.2) calc. C 76.90 H 5.16 N 17.94; found 76.62 5.17 17.76
[f] Two equivalents of bromoacetonitrile used; product is 1,3-bis[2-cyanoethyl]benzene.

minimum. Then, glyme (25 ml; distilled prior to use from sodium-potassium alloy) is added through the septum with syringe and the mixture is stirred for 12 h. During the reduction, the surface of lithium is observed to be pink-colored. After the lithium metal has been consumed completely, the stirring is stopped; metallic nickel which has adhered to the walls of the flask is scraped off with the stirrer and a magnet. The nickel is precipitated as bulky black powders in a clear colorless solution after standing. The septum on side neck was replaced with an addition funnel and a mixture of reagents in glyme is added to the nickel.

3-Phenylpropanenitrile (3a); Typical Procedure:

A mixture of benzyl chloride (1.24 g, 9.82 mmol) and bromoacetonitrile (1.18 g, 9.80 mmol) in glyme (10 ml) is added dropwise to the nickel (12.3 mmol) in refluxing glyme for 30 min. After additional heating is continued for 15 min, the mixture is cooled and poured into a separatory funnel containing 3% hydrochloric acid (100 ml), and is extracted with chloroform (2 × 100 ml). The aqueous phase is extracted with chloroform (1 × 150 ml) and the combined extracts are washed with water (200 ml), dried with anhydrous sodium sulfate, and concentrated. The residual oil is chromatographed on silica gel eluting with chloroform to give **3a**: yield: 0.732 g (57%) (Table).

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