Nickel-Catalyzed Synthesis of Arylacetonitriles from Arylzinc Chlorides and Bromoacetonitrile

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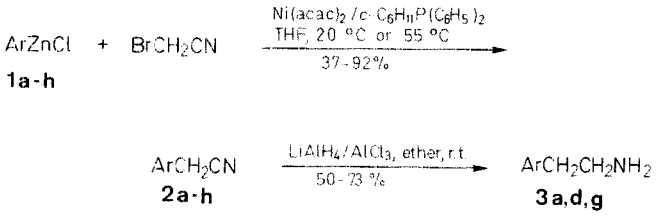
Arylacetonitriles are synthesised by coupling arylzinc chlorides with bromoacetonitrile using $Ni(acac)_2/P(c\text{-}C_6H_{11})(C_6H_5)_2$ as catalyst. The arylacetonitriles are reduced *in situ* with $LiAlH_4/AlCl_3$ to give the corresponding 2-aryl-1-aminoethanes

Arylacetonitriles are frequently used as intermediates in organic synthesis. They are usually prepared by the reaction of arylmethyl halides with alkali metal cyanides[1] or by dehydration of arylacetamides or arylacetaldoximes.[2] In the past few years, several new methods have been published. Thus, a two-step synthesis of arylacetonitriles involving Friedel-Crafts alkylation of arenes by α-chloro-α-methylthioacetonitrile, followed by zinc-mediated desulfurisation has been reported.[3] Another two step-procedure[4] consists of the reaction of alkyl cyanoacetate anion with an aryl halide in the presence of copper(I) iodide in HMPT; the alkyl arylcyanoacetate formed loses the ester group when heated with aqueous sodium hydroxide. Further, aryl bromides react with (cyanomethyl)-tributyltin at 120°C under palladium catalysis to give arylacetonitriles.[5] The photocemical SR_N1 reaction of potassium cyanomethyl anion with naphthalenes and biphenyls in liquid ammonia has in some cases given good results; however, this reaction seems to be of limited utility since bromobenzene gave only a low yield.[6]

We now present a mild and convenient alternative method for the synthesis of arylacetonitriles **(2)** which consists of the reaction of bromoacetonitrile with arylzinc chlorides **(1)** in tetrahydrofuran in the presence of catalytic amounts of $Ni(acac)_2$ and cyclohexyldiphenylphosphine.



The method is compatible with arylzinc halides having functional groups such as methoxy groups and with heteroarylzinc halides. However, the yields of isolated furyl- and thienylacetonitriles are only moderate, due to their insufficient stability and to their difficult isolation. In particular, the isolation of 2-furylacetonitrile **(2f)** is accompanied by losses of material during evaporation of the solvent and by tar formation during distillation at reduced pressure. In all reactions, the major by-product is the corresponding biaryl (up to 10%).

We have previously shown that ethyl bromoacetate reacts with arylzinc chlorides under the catalysis by nickel-phosphine complexes to give ethyl arylacetates.[7] It turned out that ethyl bromoacetate is more reactive than bromoacetonitrile. The former reacts with arylzinc chlorides at −5°C in the presence of only 1% of the catalyst while bromoacetonitrile requires +20°C and 5% of catalyst for comparable rate and yield. In both cases, the heteroarylzinc chlorides are less reactive, requiring more catalyst and higher temperature.

The yield and the selectivity (ratio of aryl acetonitrile to biaryl) depends on the reaction temperature and on the amount of catalyst used. Lower yields and lower selectivity are obtained with lower temperatures and smaller amounts of catalyst. The ratio $Ni(acac)_2$/phosphine was 1:1 in all cases and no advantage was noted by increasing the amount of phosphine. We have earlier observed that cyclohexyldiphenylphosphine is a better ligand than triphenylphosphine.[7] This observation was confirmed by the present work and cyclohexyldiphenylphosphine was therefore used in all preparations.

The arylzinc chlorides **(1)** were prepared from the aryl bromides or the parent heterocycles by lithiation with butyllithium and reaction of the aryllithium derivatives which anhydrous zinc chloride.[7] In the case of 1-bromo-4-methoxybenzene we used the more reactive *t*-butyllithium at −78°C in tetrahydrofuran[8] in order to avoid *ortho*-lithiation, which is reported to take place with the less reactive butyllithium which requires higher reaction temperatures.[9] In the reaction between 3,4-dimethoxyphenyllithium and zinc chloride, a gumlike precipitate was formed, probably due to complex formation between the zinc salt and the aromatic compound possessing vicinal methoxy groups. By adding another equivalent of zinc chloride, the gum-like precipitate could be converted into a granular precipitate which was easier to handle (the arylzinc chloride reagents were added to the solution of bromoacetonitrile).

Catalytic hydrogenation of arylacetonitriles is known to produce the corresponding phenethylamines.[10] Attempts to reduce the nitriles **2** in a one-pot procedure by using the metal complex already present in the reaction mixture as a catalyst, failed. This may be due to the deactivating effect of the phosphine ligand in catalytic hydrogenations alone or in combination with the nitrile, which also may act as a catalyst poison.[11] The addition of

Table 1. Arylacetonitriles **2a–e** and Heteroarylacetonitriles **2f, g, h** Prepared

1, 2	Ar	Amount of Catalyst (mol %)	Reaction Conditions	Yield %		m.p. (°C) or b.p. (°C)/torr	
				GLC[a]	Isolated Product	found	reported
a	C_6H_5	5	20°C, 1 h	88	68[b]	98–100/9	107/12[13]
b	2-$CH_3C_6H_4$	5	20°C, 1 h	99	92[b]	107–109/9	125.5/14[14]
c	4-$CH_3C_6H_4$	5	20°C, 1 h	95	79[b]	107–109/9	115/10[15]
d	4-$CH_3OCH_6H_4$	5	20°C, 1 h	77	58[b]	74–76/0.2	148/15[16]
e	2,4-di(CH_3O)-C_6H_3	5	20°C, 1 h	66	59[c]	46–49	48–51 (61–62[e])[17]
f	2-furyl	10	55°C, 30 min	66	37[d]	64–65/9	78–80/20[18]
g	2-thienyl	10	55°C, 30 min	70	46[b]	98–100/9	115–118/22[19]
h	2-selenophenyl	10	55°C, 30 min	80	61[b]	114–115/9	110–112/7[20]

[a] Yields determined using heptadecane as internal standard.
[b] Isolated by column chromatography on silica gel using petroleum ether/ethyl acetate (85 : 15) as eluent.
[c] Isolated by column chromatography on silica gel using petroleum ether/chloroform/acetone (55 : 37 : 8) as eluent.
[d] Isolated by column chromatography on silica gel using petroleum ether/ethyl acetate (65 : 35) as eluent.
[e] Dimorphism suggested in Lit.[17]

Table 2. 2-Arylethanamines **3a, d** and 2-(2-Aminoethyl)-thiophene **3g** Prepared

3	Yield[a] (%)	b.p. (°C)/torr	
		found	reported
a	73	71–72/9	90–93/15[21]
d	50	50–52/0.03	138–140/20[22]
g	56	75–76/9	56/2[23]

[a] Yield of isolated product.

palladium on charcoal did not improve the situation. Conversion of the nitriles was at best a few percent in these cases. However, reduction of the arylacetonitriles **2** *in situ* with lithium aluminum hydride/aluminum chloride[12] was successful. For best results, the reaction mixture is treated with aqueous ammonia during work-up in order to displace the product amine from its aluminum complex.

Analyses, reagent preparations, and handling were performed as described in Lit.[7]

Arylacetonitriles (2); General Procedure:

Method A (for Arylacetonitriles **2a–e**): In a dried, nitrogen-filled round-bottomed flask fitted with stirrer and addition funnel, bis(acetylacetonato)nickel(II) (218 mg, 0.85 mmol) and cyclohexyldiphenylphosphine (228 mg, 0.85 mmol, 0.05 equiv) are dissolved in tetrahydrofuran (10 ml). A solution of bromoacetontrile (2.05 g, 17.1 mmol) in tetrahydrofuran (15 ml) is added all at once, followed by a cold (0°C) solution of the arylzinc chloride[7] (**1a–e**; 20.5 mmol, 1.2 equiv) in tetrahydrofuran at a moderate rate. The solution is stirred at room temperature for 1 h, then quenched with ice-cold 1 normal hydrochloric acid (25 ml). Ether (25 ml) is then added and the organic phase is separated, washed with water (25 ml), and dried with magnesium sulfate. The solvent is evaporated and the crude product **2** is chromatographed on a silica gel column (20 cm × 4 cm; 230–400 mesh) using the eluents given in Table 1.

Method B (for Heteroarylacetonitriles **2f, g, h**): In a dried, nitrogen-filled round-bottom flask fitted with stirrer and addition funnel, bis(acetylacetonato)nickel(II) (436 mg, 1.7 mmol) and cyclohexyldiphenylphosphine (456 mg, 1.7 mmol, 0.1 equiv) are dissolved in tetrahydrofuran (20 ml). A solution of bromoacetonitrile (2.05 g, 17.1 mmol) in tetrahydrofuran (15 ml) is added all at once followed by a solution (room temperature) of the 2-furylzinc, 2-thienylzinc, or 2-selenophenylzinc chloride (**1f, g, h**; 17.1 mmol, 1.0 equiv) in tetrahydrofuran at a moderate rate. The mixture is stirred at 55°C for 30 min. In the case of 2-furylacetonitrile (**2f**), the mixture is then poured into ice water (25 ml); in the other cases (**2g, h**), the reaction is quenched by the addition of ice-cold 1 normal hydrochloric acid (25 ml). In all cases, ether (25 ml) is then added and the organic phase is separated, washed with water (25 ml), and dried with magnesium sulfate. The solvent is evaporated and the crude product **2** is chromatographed on a silica gel column (20 × 4 cm; 230–400 mesh) using the eluents given in Table 1.

2-Arylethanamines (3a, d, g); General Procedure:

The reducing agent is prepared by adding a solution of aluminum chloride (5.70 g, 42.7 mmol) in ether (55 ml) to a stirred suspension of lithium aluminum hydride (1.62 g, 42.7 mmol) in ether (40 ml) and stirring the mixture for 5 min. To this is added the reaction mixture from Methods A or B at the point at which it would otherwise be quenched hydrolytically, and stirring is continued for 1 h. The mixture is then cooled to 0°C and carefully hydrolyzed by the addition of water (30 ml). The ether phase is separated and the aqueous phase is extracted with ether (2 × 50 ml). To the aqueous phase, ether (50 ml) and conc. aqueous ammonia (50 ml) are added and this mixture is stirred for 20 min. The precipitate is filtered off and the phases are separated. This treatment of the combined precipitate and aqueous phase is repeated twice. All organic phases are combined and extracted with 5 normal hydrochloric acid (100 ml) to completely trap the free amine. The aqueous extract is made alkaline with aqueous 5 normal sodium hydroxide, and extracted with ether (3 × 50 ml). The ether extract is dried with sodium sulfate and evaporated to give the amine **3** which is pure according to GLC and ^{1}H-NMR analysis.

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