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A SIMPLE ONE-POT CONVERSION OF ARYL HALIDES INTO ARYLACETONITRILES

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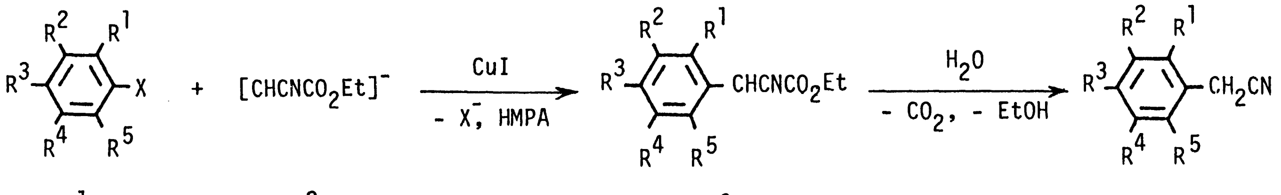
When heated in hexamethylphosphoric triamide in the presence of copper(I) iodide, aryl iodides and bromides react with cyanoacetate anion to form arylcyanoacetates, which lose the ester group on hydrolysis, giving the corresponding arylacetonitriles in good to moderate yields.

Arylacetonitriles are versatile intermediates in organic synthesis. They are normally prepared by the reaction of arylmethyl halides with alkali cyanide, or by the dehydration of arylacetamides and arylacetaldoximes. However, these methods are sometimes limited by the availability of starting materials. We have now elaborated a simple one-pot alternative which can convert aryl halides into arylacetonitriles under relatively mild conditions.



A solution of ethyl cyanoacetate in hexamethylphosphoric triamide (HMPA) is treated with sodium hydride to form anion 2, which reacts smoothly with aryl halide 1 in the presence of copper(I) iodide to afford arylcyanoacetate 3. Without copper(I) catalyst, the arylation of ester anion 2 does not proceed even at higher temperatures. On subsequent treatment with dilute aqueous sodium hydroxide at 80-90°C, ester 3 readily undergoes decarboxylative hydrolysis, giving arylacetonitrile 4 in good to moderate yields. The overall process can usually be carried out within several hours. Table 1 shows the yields of nitriles obtained and conditions required for each of the reactions. No special attempts were made to optimize the results.

Our method proved to be successful with aryl iodides and bromides, the former giving more satisfactory results, but it fails with aryl chlorides. In contrast to the palladium(0) and nickel(0) catalyzed substitution reactions of aryl halides,

Table 1 Conversion of aryl halides into arylacetonitriles

Aryl halide 1						Arylacetonitrile 4		Reaction conditions (time/temperature)	
R^1	R^2	R^3	R^4	R^5	X	Mp (°C)	Yield (%)[a]	Arylation	Hydrolysis
H	H	Me	H	H	I	17-18[2]	69	3 h/90-95°C	2 h/80-90°C
H	H	Bu^i	H	H	I	oil[3]	61	3 h/90-95°C	3 h/80-90°C
Me	Me	H	Me	Me	I	86-87[4]	60	2 h/95-100°C	2 h/80-90°C
H	MeO	MeO	H	H	I	oil[5]	76	2 h/90-95°C	2 h/80-90°C
H	$-OCH_2O-$		H	H	I	42-43[6]	77	2 h/90-95°C	2 h/80-90°c
H	CF_3	H	H	H	Br	oil[7]	50	5 h/150-160°C	3 h/80-90°C[b]

a. Yields are for isolated and characterized products.
b. Hydrolysis was carried out in acetic acid/water containing sulfuric acid.

steric congestion apparently provides no serious problem in the present case.

Aryl halides have been converted into arylacetonitriles by allowing the former to react with cyanomethyl anion in liquid ammonia under irradiation.[1] However, the synthetic utility of this reaction is somewhat limited by the concomitant formation of undesired side products. Our method has the advantages of simple performance and work-up, use of easily available substrate and reagent, short reaction time, and relatively mild reaction conditions.

A typical experimental procedure is as follows: a commercial 60% sodium hydride dispersion (0.160 g, 4 mmol) is placed in 20 ml flask and paraffin oil is removed by washing with dry hexane (3 x 2 ml). The remaining solid is covered with HMPA (1 ml) and a solution of ethyl cyanoacetate (93% purity; 0.486 g, 4 mmol) in the same solvent (2.5 ml) is added with stirring. After several minutes, 4-iodo-1,2-methylenedioxybenzene (0.498 g, 2 mmol) is added, followed by copper(I) iodide (0.762 g, 4 mmol), and the mixture is heated to 90-95°C. The color turns from grey to black as the temperature rises. The progress of the reaction is monitored by TLC. After 2 h a solution of sodium hydroxide (0.144 g, 3.6 mmol) in water (3 ml) is introduced and heating is continued at 80-90°C for additional 2 h. After cooling the solution is made neutral with dilute hydrochloric acid, extracted with ether (3 x 20 ml), and dried over sodium sulfate. Evaporation of the solvent gives 3,4-methylenedioxyphenylacetonitrile as colorless oil, which is further purified by bulb-to-bulb distillation. Yield, 0.249 g (77%). Mp 42-43°C (lit.,[6] 44-45°C).

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