CHEMISTRY LETTERS, pp. 1779-1780, 1985.

COPPER(I) IODIDE-MEDIATED ARYLATION OF DIALKYL CYANOMETHANEPHOSPHONATES. A NOVEL ROUTE TO α-ARYLATED ALKANENITRILES

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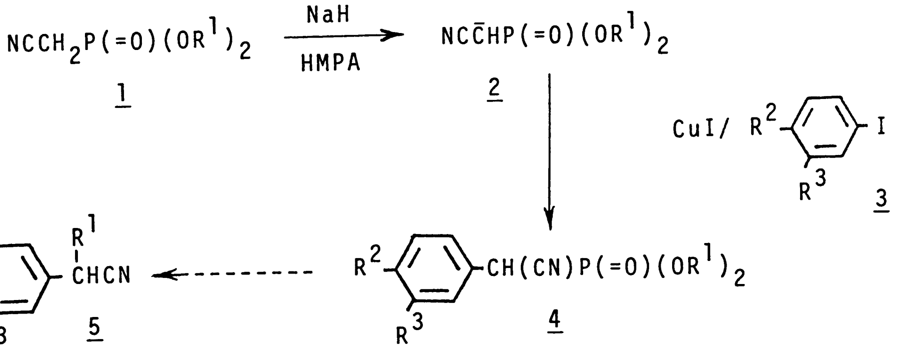
Copper(I)-catalyzed arylation of dialkyl cyanomethanephosphonate anions in hot hexamethylphosphoric triamide affords α-arylalkanenitriles in moderate to good yields.

α-Arylalkanenitriles are valuable starting materials for a variety of compounds of pharmacological interest. Although the literature contains a number of synthetic methods, they sometimes present disadvantages such as tedious processing, limited adaptability, and poor availability of starting materials.1) We now wish to report a novel one-pot alternative, which is based on the copper(I)-mediated arylation of dialkyl cyanomethanephosphonates (1).



A solution of phosphonate 1 in hexamethylphosphoric triamide (HMPA) was treated with sodium hydride to form carbanion (2), which reacted with aryl iodide (3) in the presence of copper(I) iodide to afford α-arylalkanenitrile (5) in moderate to good yields (Table 1). The expected arylcyanomethanephosphonate (4) could not be isolated, but its role as an intermediate was substantiated by the independent synthesis and subsequent transformation of 4 into nitrile 5 under similar conditions. The reaction was clean and no tarry materials were formed.

Use of an equivalent amount of copper(I) iodide was necessary to obtain satisfactory results, although it could be recovered quantitatively. The reaction did not take place at low temperatures (≃100 °C) or in the absence of copper(I) salt.

The reaction was subject to a considerable steric effect. Thus, when *ortho* positions of 3 were occupied by substituent groups, formation of arylacetonitriles

Table 1. α-Arylalkanenitriles 5 obtained from the arylation of dialkyl cyanomethanephosphonates 1

Cyanomethane-phosphonate 1	Aryl iodide 3		Reaction condition[a)]	Arylalkane-nitrile 5
R^1	R^2	R^3		Yield/% [b)]
CH_3	H	H	A	39
CH_3	H	H	B	59
C_2H_5	H	H	A	53
C_2H_5	H	H	B	73
i-C_3H_7	H	H	B	73
C_4H_9	H	H	B	78
C_2H_5	CH_3	H	A	25
C_2H_5	CH_3	H	B	70
C_2H_5	$CO_2C_2H_5$	H	B	73
C_2H_5	CH_3O	CH_3O	A	33

a) Conditions: A, 170 °C/72 h; B, 170 °C/5 h, then 200 °C/overnight.

b) Yields do not represent optimized values.

was the main reaction that took place and the expected nitrile 5 could not be obtained. This is in marked contrast to the similar arylation of ethyl cyanoacetate, where no serious steric problem is observed.2)

Although the scope of the reaction is not extensively studied yet, the present method seems to be an attractive alternative for the preparation of some α-arylalkanenitriles which are otherwise difficult to obtain.

A typical procedure is as follows: To a stirred suspension of sodium hydride (0.13 g, 5.4 mmol; 60% dispersion was washed with hexane prior to use) in dry HMPA (5 ml) under nitrogen was added dropwise diethyl cyanomethanephosphonate (0.885 g, 5.0 mmol). A yellow solution of phosphonate anion was stirred at room temperature for 0.5 h and then copper(I) iodide (0.955 g, 5.0 mmol) followed by iodobenzene (0.408 g, 2.0 mmol) was added. The resulting black mixture was kept at 170 °C for 5 h, then at 200 °C overnight. Dilute hydrochloric acid was added to the mixture and the organic phase was extracted with ether, washed with dilute hydrochloric acid and aqueous sodium hydrogensulfite, dried over sodium sulfate, and evaporated. The residual oil was chromatographed over a short silica gel column to afford α-phenylbutanenitrile. Bp 90-94 °C/3 mmHg (Kugelrohr).3) Yield, 0.212 g (73%).

References

1) For a recent review, see A.J. Fatiadi, "Preparation and Synthetic Applications of Cyano Compounds," in "The Chemistry of Functional Groups, Supplement C," ed by S. Patai and Z. Rappoport, John Wiley, New York (1983), Chap. 26.

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(Received September 2, 1985)