

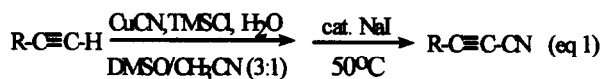
A Novel Synthesis of Cyanoalkynes via Iodide-Catalyzed Cyanation of Terminal Acetylenes with Cuprous Cyanide

Fen-Tair Luo* and Ren-Tzong Wang

Institute of Chemistry, Academia Sinica, Nankang, Taipei, Taiwan, ROC

Abstract: Cyanoalkynes were synthesized in fair to good yields from terminal acetylenes and cuprous cyanide in the presence of trimethylsilyl chloride, water, catalytic amount of sodium iodide, and CH₃CN in DMSO at 50°C.

Cyanoalkynes are important in both synthetic and mechanistic studies.¹ Several methods have already been developed such as the reaction of metallated acetylides with toxic cyanogen chloride,² pyrolysis of β-ketoalkylidenephosphoranes,³ dehydration of acetylenic carboxamides,⁴ or the reaction of acetylenic bromide with cuprous cyanide.⁵ The drawback of the last three reactions is that they need to prepare the precursors β-ketoalkylidenephosphoranes, acetylenic carboxamides, and acetylenic bromides, respectively. Recently, the reaction of phenylacetylene with CuCN/bis(trimethylsilyl)peroxide to give cyanoalkynes has been described by Ricci et al.⁶ However, the formation of acetylenic dimer in 30% yield severely limits its applicability to the preparation of other cyanoalkynes. Herein, we report the cyanation of terminal acetylenes with cuprous cyanide in the presence of trimethylsilyl chloride, water, and catalytic amount of sodium iodide in DMSO/CH₃CN to provide a general procedure for preparing cyanoalkynes in fair to good yields (eq 1). In addition, some aspects of the reaction mechanism have been tested.



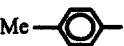
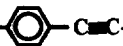


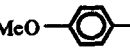

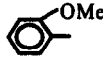

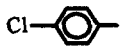
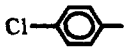
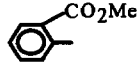
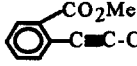
The following procedure for the preparation of methyl 2-cyanoethynylbenzoate is representative. Sodium iodide (150 mg, 1 mmol) and cuprous cyanide (2.69 g, 30 mmol) were placed in a dry flask under nitrogen atmosphere. The flask was then sequentially added DMSO (15 mL), CH₃CN (5 mL), water (0.27 mL, 15 mmol), and freshly distilled trimethylsilyl chloride (3.79 mL, 30 mmol) at room temperature. After the reaction mixture was stirred at room temperature for 10 min, it was added methyl 2-ethynylbenzoate (1.60 g, 10 mmol). The reaction mixture was stirred at 50°C for another 60 h. The reaction mixture was quenched with aqueous ammonium chloride. The organic layer was extracted with dichloromethane, dried over magnesium sulfate, concentrated, and chromatographed (silica gel, hexane/dichloromethane = 4/1) to give

1.37 g (74% yield) of the desired product: $^1\text{H-NMR}$ (CDCl_3 , TMS) δ 3.90 (s, 3H), 7.50-7.58 (m, 2H), 7.63-7.70 (m, 1H), 7.99-8.04 (m, 1H) ppm. $^{13}\text{C-NMR}$ (CDCl_3 , TMS) δ 52.31, 66.62, 80.90, 105.21, 118.04, 130.80, 131.15, 132.10, 133.52, 135.98, 164.67 ppm. IR (CHCl_3) ν ($\text{C}\equiv\text{N}$) 2271 cm^{-1} . MS m/z 185 (M^+), 154, 126.

The experimental results are summarized in Table I. It demonstrated that a wide range of terminal acetylenes bearing various kinds of functional groups can undergo this cyanation reaction. Several features are noteworthy. The use of DMSO with CH_3CN as the co-solvent is critically important in this cyanation process as shown in Table II. Our results showed that the dimerization can be minimized to less than 4% when the volume ratio of DMSO and CH_3CN was 3 to 1. While the increasing of the amount of CH_3CN in the reaction can further minimize the dimerization, but it sacrificed the yield of the desired product. Using DMSO as the solvent alone, the reaction gave the desired and dimerized products in 11% and 22% yields, respectively. Under the same conditions, the use of other solvent system such as CH_3CN , THF, THF + HMPA (10%), and benzene led to recovering the starting material after 72 h at 50°C.

The addition of catalytic amount of NaI can indeed facilitate and accelerate the cyanation process.⁷ On the other hand, the addition of stoichiometric amount of NaI in the reaction gave low yield of the desired

Table I. Cyanoalkynes via Iodide-Catalyzed Cyanation of Terminal Acetylenes with Cuprous Cyanide in the Presence of TMSI and H_2O in DMSO/ CH_3CN

Entry	R in $\text{RC}\equiv\text{CH}$	Time (h)	Product ^a	Isolated Yield (%)
1	Ph-	72	Ph-C \equiv C-CN	72
2	Me- 	72	Me-  -C \equiv C-CN	76
3		72	 -C \equiv C-CN	72
4	MeO- 	60	MeO-  -C \equiv C-CN	84
5		60	 -C \equiv C-CN	78
6	Cl- 	60	Cl-  -C \equiv C-CN	51
7		60	 -C \equiv C-CN	74
8	n-C ₅ -	72	n-C ₅ -C \equiv C-CN	56
9	n-C ₆ -	72	n-C ₆ -C \equiv C-CN	53

^a All new compounds have been fully characterized by ^1H - and ^{13}C -NMR, IR or MS spectroscopy.

product along with one unidentified product. In the absence of iodide salt in our cyanation process desired products were formed in only low yields indicating that the nucleophilic and good leaving properties of iodide ion play an essential role in this reaction. For comparison of halide ion as the catalyst used in the reaction, various kinds of salts were used in the reaction (Table III). Most iodide salts may be employed as the catalyst in the cyanation reaction to give comparable results, but only low yields of the desired product was obtained when used chloride or bromide salt in the reaction. Since HCl can be generated from TMSCl and H₂O,⁸ we attempted to replace TMSCl and H₂O with conc. HCl (37%) in the cyanation of phenylacetylene. However, only 28% yield of 3-phenyl-2-propynenitrile was obtained indicating that the reaction preferred to run in anhydrous conditions. Although the mechanistic details of the cyanation procedure are still unclear. Other experiments carried out in order to elucidate the mechanism of this reaction included the following: (a) Attempts to use 3 equiv of TMSCN or (TMS)₂O to replace TMSCl and H₂O or running the reaction in the absence of TMSCl and H₂O,⁹ only starting material and trace amount of dimer were observed in the GC analyses. (b) The deep brown color solution obtained from mixing 5 equiv of CuCl₂ and 5 equiv of NaCN in DMSO/CH₃CN (3:1) at room temperature reacted with phenylacetylene in the presence of 10 mole % of NaI gave 55% yield of 3-phenyl-2-propynenitrile after 96h at 50°C. (c) The electron donating group at *o*- or *p*-position in the phenyl ring accelerated the cyanation process, while the electron withdrawing group required longer time to complete the reaction. (d) No reaction occurred in 96 h when NaCN instead of CuCN was used in the reaction. In conclusion, this iodide-catalyzed cyanation of terminal acetylenes with cuprous cyanide allows a very easy preparation of cyanoalkynes. Further studies about the reaction mechanism are in progress.

Table II. Effect of Varying the Solvent on the Cyanation of Phenylacetylene after 72 h^a

Entry	Solvent System	Yield of Ph-C≡C-CN (%) ^b	Yield of (Ph-C≡C) ₂ (%) ^b
1	DMSO	11	22
2	DMSO/CH ₃ CN (3/1)	59	3
3	DMSO/CH ₃ CN (1/1)	53	3
4	DMSO/CH ₃ CN (1/3)	47	2
5	CH ₃ CN	<1	<1
6	THF	<1	<1
7	THF + HMPA (10%)	<1	<1
8	C ₆ H ₆	<1	<1

^a 3 equiv of TMSCl and CuCN, 1.5 equiv of H₂O, 0.1 equiv of NaI, and 1 equiv of phenylacetylene were used in the reaction. ^b GC yields.

Table III. Effect of Varying the Salt on the Cyanation of Phenylacetylene after 72 h

Entry	MX	Amount (mol %)	Yield of Ph-C≡C-CN (%)
1	NaCl	10	7
2	NaBr	10	26
3	NaI	10	73
4	LiI	10	77
5	KI	10	82
6	CuI	10	76
7	ZnI ₂	5	72

Acknowledgment

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