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19.5.12 Introduction of the Cyano Group by Addition to Alkynes

J. Podlech

General Introduction

Previously published information regarding this topic can be found in *Houben-Weyl*, Vol. 8, pp 265–268; Vol. E 5/2, pp 1410–1413; Vol. E 18/2, pp 812–816; and Vol. E 21, pp 2594–2595.

The hydrocyanation of alkynes is a significantly useful process since it generates highly versatile α,β -unsaturated nitriles (Michael systems) from easily accessible starting materials.^[1–4] Before suitable catalyst systems for the addition of hydrogen cyanide to alkynes were found, the uncatalyzed reactions needed high temperatures and yields were low. But despite this, thorough optimization of reaction conditions allowed the commercial synthesis of propenenitrile (acrylonitrile)^[5] to operate on a 10 000-ton scale as early as 1944.^[6–8] Since 1970, however, the importance of this process has declined in favor of alternatives that start from propene.^[9]

SAFETY: All the experiments described in the following account are highly hazardous. In particular, hydrogen cyanide is a highly toxic, volatile liquid (bp 27 °C) that is also susceptible to explosive polymerization in the presence of base catalysts. It should be handled only in a well-ventilated fume hood or drybox. Sensible precautions include not working alone and having available proper first aid equipment, hydrogen cyanide monitors, and Scott Air Packs. Hydrogen cyanide should be handled by teams of at least two technically qualified individuals who have received appropriate medical training for treating hydrogen cyanide poisoning [for details see *Prudent Practices for Handling Hazardous Chemicals in Laboratories*, National Academic Press: Washington, DC, (1981); pp 45–47]. Commercial hydrogen cyanide is stabilized with small amounts of strong acids such as sulfuric acid. Small amounts of uninhibited hydrogen cyanide may be obtained by vacuum transfer through Drierite. Uninhibited hydrogen cyanide should be stored cold. Excess hydrogen cyanide may be disposed of by burning or in the case of small amounts of hydrogen cyanide by adding to aqueous sodium hypochlorite (which converts it into the cyanate).^[10]

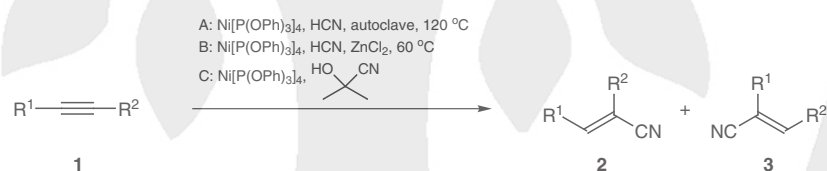
**19.5.12.1 Method 1:
Hydrocyanation of Alkynes**

Tetrakis(triphenyl phosphite)nickel(II) ($\text{Ni}[\text{P}(\text{OPh})_3]_4$), in the presence of excess triphenyl phosphite, is a catalyst that was developed for the hydrocyanation of alkenes {see Section 19.5.13 and *Science of Synthesis*, Vol. 1 [Compounds with Transition Metal–Carbon π -Bonds and Compounds of Groups 10–8 (Ni, Pd, Pt, Co, Rh, Ir, Fe, Ru, Os)] (Section 1.1.3.9)}; however, it also works well for similar reactions with alkynes **1** often giving isomeric unsaturated nitriles **2** and **3** (Scheme 1) with greater efficiency than either rhodium or palladium catalysts, for example.^[11] The catalyst is easy to prepare,^[12] and it can be kept for long periods if stored in the dark under dry nitrogen; it can even be weighed on an open balance immediately prior to use.^[2] The direct hydrocyanation of alkynes is carried out either in an autoclave (Method A),^[11,13–16] or at atmospheric pressure using the same catalyst in the presence of the Lewis acid zinc(II) chloride (Method B). In the latter case, hydrocyanation occurs at 60 °C with the slow addition of a solution of hydrogen cyanide to a solution of

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the catalyst, additional triphenyl phosphite, the alkyne, and the Lewis acid.^[11,13,17] For safety reasons hydrogen cyanide can be replaced by acetone cyanohydrin (2-hydroxy-2-methylpropanenitrile; Method C), and now the reaction can be carried out either at high pressure in benzene at 120 °C in an autoclave,^[11,13] or with rather more catalyst in toluene at reflux.^[16] The latter modification works satisfactorily when silylated alkynes are the substrates using a molar amount of the catalyst tetrakis(triphenyl phosphite)nickel(II), triphenyl phosphite, the silylalkyne, and acetone cyanohydrin in a ratio of 1:12:45:90.^[11,13,16,18–20] In most reactions a highly selective *syn* addition of hydrogen cyanide is observed,^[11,13] but there are exceptions and, for example, dimethyl acetylenedicarboxylate is hydrocyanated by Method C in an *anti* fashion.^[2,11] A low ratio of catalyst to substrate (ca. 1:90) is sufficient for reactions at 120 °C (Method A), but with increased amounts of catalyst the reactions occur at room temperature in moderate to good yields. For example, the hydrocyanation of hex-1-yne at 120 °C (catalyst/substrate 1:90) gives an 88% yield of products, whereas an identical yield is obtained in benzene at 25 °C with a catalyst to substrate ratio of 1:22.^[2] Although the high-pressure procedure (Method A) usually gives slightly better yields, selectivity control is improved by the presence of zinc(II) chloride (Method B). Regioselectivity is partly dependent on steric factors and moderate to high selectivity is observed with terminal alkynes (cyanide is introduced at the terminal carbon), whereas poor selectivity is exhibited by internal alkynes. Method A also allows compounds bearing both double and triple bonds to be selectively hydrocyanated at the alkyne bond; thus, for the alkyne **1** ($R^1 = \text{CH}_2\text{CH}=\text{CH}_2$; $R^2 = \text{Et}$) attack may occur at either alkynic carbon atom,^[14] but the clear 9:1 preference for the nitrile **3** ($R^1 = \text{CH}_2\text{CH}=\text{CH}_2$; $R^2 = \text{Et}$) is not understood. Indeed, steric effects may have low importance as a more bulky α,α' -bis(diphenylphosphino)-*o*-xylenenickel(0) catalyst still gives a product ratio of 3:1 in favor of **3** ($R^1 = \text{CH}_2\text{CH}=\text{CH}_2$; $R^2 = \text{Et}$). Other substrates, which have been hydrocyanated by Method A, include alkynol ethers,^[18,19] alkynols,^[17] and alkynamines;^[21,22] the products obtained from alkynamines have been used for the synthesis of unnatural amino acid derivatives.^[22,23]

Scheme 1 Hydrocyanation of Alkynes Using Tetrakis(triphenyl phosphite)nickel(II) and Hydrogen Cyanide or Acetone Cyanohydrin^[11,13–16]



R ¹	R ²	Method ^a	Ratio (2/3)	Yield (%) of 2 and 3	Ref
Ph	Ph	A	–	93 ^b	[11,13]
		B	–	82 ^b	[11,13]
		C	–	57 ^b	[11,13]
CO ₂ Me	CO ₂ Me	A	–	27 ^{b,c}	[11,13]
		B	–	5 ^{c,d}	[11,13]
Pr	H	A	3:22	60	[11,13]
		B	1:19	40	[11,13]
Bu	H	A	7:43	73	[11,13]
		B	1:24	33	[11,13]
(CH ₂) ₅ Me	H	A	7:43	60	[11,13]
		B	2:23	45	[11,13]

R ¹	R ²	Method ^a	Ratio (2/3)	Yield (%) of 2 and 3	Ref
Ph	H	A	49:1	48	[11,13]
		B	17:3	35	[11,13]
		C	–	16 ^b	[11,13]
t-Bu	H	A	22:3	15	[11,13]
		B	4:1	45	[11,13]
t-Bu	Me	B	9:1	78	[11,13]
CH ₂ CH=CH ₂	Et	A	1:9 ^c	41	[14]
TBDMS	H	A	7:13 ^f	57	[15,16]
TBDMS	Me	A	49:1 ^f	88	[15,16]
TBDMS	Ph	A	9:1 ^f	74	[15,16]
TMS	H	A	1:3 ^f	74	[15,16]
		C	1:3 ^g	75	[15,16]
TMS	Me	A	4:1 ^h	90	[15,16]
		C	4:1 ^g	87	[15,16]
TMS	Bu	A	18:7 ^h	94	[15,16]
		C	18:7 ^g	90	[15,16]
TMS	Ph	A	0:100 ^h	80	[15,16]
		C	0:100 ^g	81	[15,16]

^a Method A: 0.5 mol% Ni[P(OPh)₃]₄, autoclave, 120 °C; B: atmospheric pressure at 60 °C, slow addition of a solution of HCN to a solution of Ni[P(OPh)₃]₄ (2.5 mol%), additional ligand, the alkyne, and ZnCl₂; C: 0.5 mol% Ni[P(OPh)₃]₄, autoclave, 120 °C in benzene.

^b Only product 3 formed.

^c The *syn*-product is formed.

^d Slow addition of the alkyne and HCN to the catalyst system.

^e 1.8 mol% Ni[P(OPh)₃]₄.

^f 2.2 mol% Ni[P(OPh)₃]₄.

^g 2.2 mol% Ni[P(OPh)₃]₄, reflux in toluene.

^h 1.1 mol% Ni[P(OPh)₃]₄.

(E)-2,3-Diphenylprop-2-enitrile (3, R¹ = R² = Ph); Typical Procedure:^[11]

CAUTION: Hydrogen cyanide can be absorbed through the skin and is extremely toxic.

CAUTION: Triphenyl phosphite is a skin irritant and sensitizer, with experimental neurotoxic properties.

Method A: Ni[P(OPh)₃]₄ (0.24 g, 0.2 mmol), P(OPh)₃ (0.8 g, 2.5 mmol), diphenylacetylene (1, R¹ = R² = Ph; 7 g, 39 mmol), HCN (1.25 mL, 32 mmol), and benzene (25 mL) (**CAUTION:** *carcinogen*) were placed in a stainless steel autoclave (75 mL). The vessel was heated at 120 °C for 18 h, then cooled, and the benzene was distilled off. Column chromatography (basic alumina, activity grade II, Et₂O/petroleum ether 1:9), followed by distillation, gave the title compound as colorless crystals; yield: 6.12 g (93%); mp 48–49 °C; bp 130 °C/0.01 Torr.

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**(tert-Butyldimethylsilyl)propenenitriles 2 (R¹ = TBDMS) and 3 (R¹ = TBDMS);
General Procedure for Method A:^[16]**

CAUTION: Hydrogen cyanide can be absorbed through the skin and is extremely toxic.

CAUTION: Triphenyl phosphite is a skin irritant and sensitizer, with experimental neurotoxic properties.

Benzene (25 mL) (**CAUTION:** carcinogen), Ni[P(OPh)₃]₄ (0.24 g, 0.2 mmol), P(OPh)₃ (0.74 g, 2.4 mmol), the alkyne **1** (R¹ = TBDMS; 9.0 mmol), and HCN (0.21 g, 7.8 mmol) were placed in a stainless steel Koke-type autoclave and protected under a N₂ atmosphere. The vessel was heated to 120 °C for 18 h. It was then cooled, and most of the catalyst was removed by filtration, after the addition of pentane (15 mL). Removal of the solvents followed by distillation gave the title compounds.

(E)-2,4,4-Trimethylpent-2-enenitrile (2, R¹ = t-Bu; R² = Me) and (E)-2-tert-Butylbut-2-enenitrile (3, R¹ = t-Bu; R² = Me); Typical Procedure:^[11]

CAUTION: Hydrogen cyanide can be absorbed through the skin and is extremely toxic.

CAUTION: Triphenyl phosphite is a skin irritant and sensitizer, with experimental neurotoxic properties.

Method B: A soln of HCN (1.25 mL, 32 mmol) in toluene (5 mL) was slowly added by means of a syringe pump to a mixture of Ni[P(OPh)₃]₄ (0.7 g, 0.54 mmol), P(OPh)₃ (0.75 g, 2.4 mmol), anhyd ZnCl₂ (0.14 g, 1 mmol), 4,4-dimethylpent-2-yne (**1**, R¹ = t-Bu; R² = Me; 2 g, 21 mmol), and toluene (25 mL) over 10 h at 60 °C. The toluene was removed by distillation, and bulb-to-bulb distillation gave the unsaturated nitriles (9:1 as determined by GLC) as a clear liquid; yield: 2.0 g (78%); bp 100 °C/25 Torr. The isomers could be separated by preparative GLC.

Hydrocyanation of Alkynes 1 Using Tetrakis(triphenyl phosphite)nickel(II)/Acetone Cyanohydrin; General Procedure for Method C:^[16]

CAUTION: Triphenyl phosphite is a skin irritant and sensitizer, with experimental neurotoxic properties.

Toluene (50 mL), Ni[P(OPh)₃]₄ (0.24 g, 0.2 mmol), P(OPh)₃, a silylalkyne **1**, and acetone cyanohydrin in a molar ratio of 1:12:45:90 were placed in a predried 100-mL round-bottomed flask and protected under a N₂ atmosphere. The mixture was refluxed under a positive pressure of N₂ for 18 h. After cooling, most of the catalyst was removed by filtration after precipitation with pentane (15 mL). Removal of the solvents at reduced pressure gave a residue that was purified by distillation.

19.5.12.2

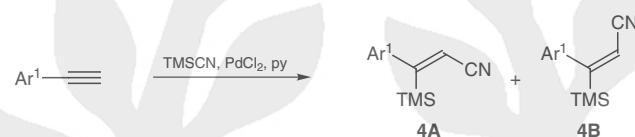
**Method 2:
Addition of Trimethylsilyl Cyanide or
Tributylstannanecarbonitrile to Alkynes**

Silylated or stannylated alkenes are very useful intermediates in organic synthesis since they can be used in the most powerful Stille-type cross-coupling protocols. Consequently, methods for the concomitant introduction of a cyano and a stannyl or silyl group are of great interest.

19.5.12.2.1 Variation 1: Addition to Terminal Arylalkynes

The addition of trimethylsilyl cyanide to a terminal arylalkyne is possible using catalytic amounts of palladium(II) in the presence of a basic additive. The best results are obtained with palladium(II) chloride and pyridine.^[24] The cyano function is introduced vicinally to the aryl group in all cases (Scheme 2), but sterically undemanding arenes form *Z*-alkenes **4A** exclusively, while bulky arenes give a mixture of isomers **4A** and **4B** (although the *Z*-product is still favored). Yields range from 17–90%, and there is no advantage in using electron-rich over electron-poor alkynes.

Scheme 2 Addition of Trimethylsilyl Cyanide to Terminal Arylalkynes^[24]



Ar ¹	Ratio (4A / 4B) ^a	Yield ^b (%) of 4A	Ref
Ph	95:5	90	[24]
4-MeOC ₆ H ₄	95:5	90	[24]
4-FC ₆ H ₄	>95:5 ^c	38	[24]
4-ClC ₆ H ₄	94:6	47	[24]
4-BrC ₆ H ₄	>95:5 ^c	17 ^d	[24]
2-MeOC ₆ H ₄	83:17	85 ^e	[24]
2-ClC ₆ H ₄	81:29	23 ^e	[24]
1-naphthyl	71:29	68 ^e	[24]
2-naphthyl	93:7	54	[24]
2-thienyl	>95:5 ^c	39	[24]

^a Determined by gas chromatography.

^b Isolated yields.

^c Determined by ¹H NMR spectroscopy.

^d (*Z*)-2-(4-Cyanophenyl)-3-(trimethylsilyl)propenenitrile is also isolated in 19% yield.

^e A mixture of the isomeric products **4A**/**4B** is isolated.

(*Z*)-3-Phenyl-3-(trimethylsilyl)propenenitrile (**4A**, Ar¹ = Ph); Typical Procedure:^[24]

PdCl₂ (36 mg, 0.2 mmol) and pyridine (32 μL, 0.4 mmol) were added to a soln of phenylacetylene (0.55 mL, 5 mmol) and TMSCN (1.34 mL, 10 mmol) in toluene (10 mL). The mixture was refluxed with stirring for 20 h under N₂, the solvents were removed at reduced pressure, and the residue was purified by chromatography (silica gel, hexane/EtOAc 9:1), followed by bulb-to-bulb distillation; yield: 0.90 g (90%); bp 130–140 °C/25 Torr.

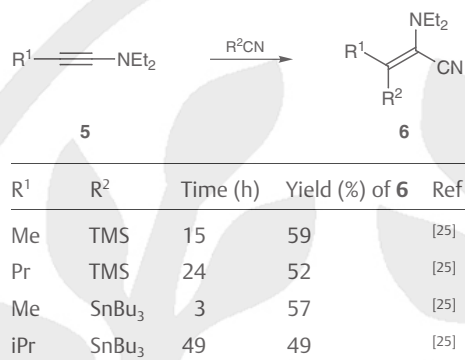
19.5.12.2.2 Variation 2: Addition to Ynamines

Palladium catalysis is unsuitable for the addition of trimethylsilyl cyanide to dialkylaminoalkynes; however, the reaction times for the process are accelerated from 1–2 weeks to a matter of hours by a catalytic amount of iodotrimethylsilane. The stereo- and regio-chemistries of the addition reactions of both trimethylsilyl cyanide and tributylstannane-

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carbonitrile to diethylaminoalkynes **5** are the same, giving the corresponding *E*-alkenes **6** bearing the cyano group geminal to the amino function as the only products (Scheme 3). Yields are usually about 50%.^[25]

Scheme 3 Addition of Trimethylsilyl Cyanide or Tributylstannanecarbonitrile to Ynamines^[25]



(2*E*)-2-(Diethylamino)-3-(trimethylsilyl)propenenitriles **6 (R² = TMS) or (2*E*)-2-(Diethylamino)-3-(tributylstannyl)propenenitriles **6** (R² = SnBu₃); General Procedure:**^[25]

A soln of either TMSCN or Bu₃SnCN (1.2 mmol) was added dropwise at rt to the ynamine (**5**; 1 mmol) in dry CH₂Cl₂ (2 mL). In the case of TMSCN addition, a catalytic amount of TMSI (ca. 5 mol%) is favorable. After the reaction was complete (monitoring by IR spectroscopy), the solvent was removed at reduced pressure and the residue was distilled or chromatographed (silica gel).

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