Cobalt-Mediated Synthesis of Propargyl Nitriles and α-Alkoxy Propargyl Nitriles

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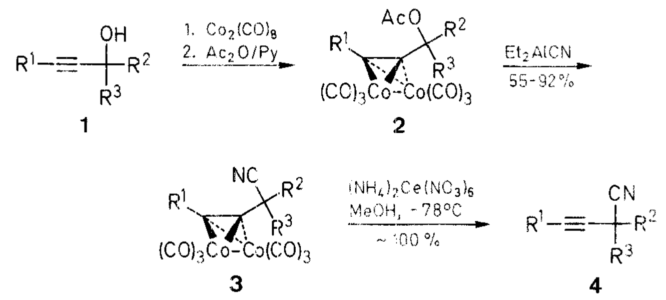
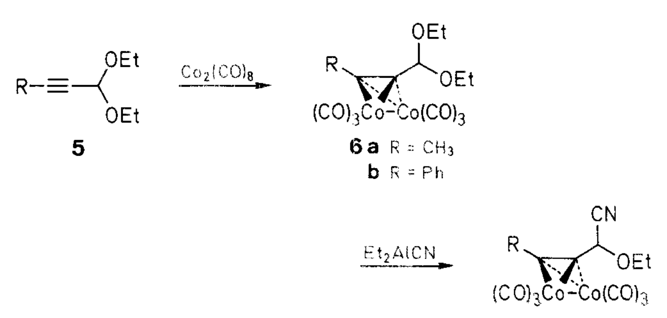
Dicobalt hexacarbonyl complexes of propargyl acetates and acetylenic acetals couple efficiently with diethylaluminum cyanide to produce the corresponding complexed propargyl nitriles and cyanohydrin derivatives, respectively. A convenient procedure for preparing propargyl nitriles and α-alkoxy propargyl nitriles from propargyl alcohols and acetylenic acetals using this methodology is described.

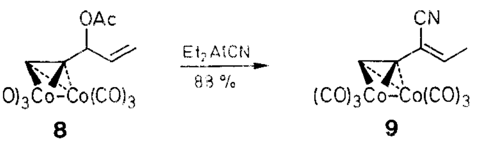
The preparation of propargyl nitriles[1] by simple nucleophilic substitution, as with many propargyl derivatives,[2] is complicated by formation of the isomeric allenic products and often proceeds in modest yield. In earlier studies, we have demonstrated that (propargylium)$Co_2(CO)_6^+Z^-$ complexes couple regiospecifically with a variety of nucleophiles to afford propargyl isomers exclusively,[3] thus potentially providing a potentially general solution to the propargyl/allenyl problem. Having need for an efficient route to propargyl nitriles in another context, we examined the reactions of dicobalt hexacarbonyl complexes of propargyl acetates with diethylaluminum cyanide. We report here that this reaction, in combination with the convenient introduction and removal of the cobalt carbonyl unit, is a convenient method for the regiospecific preparation of a variety of propargyl nitriles and cyanohydrin ethers.



1-4	R^1	R^2	R^3
a	H	H	H
b	CH_3	H	H
c	n-C_5H_{11}	H	H
d	Ph	H	H
e	H	CH_3	H
f	Ph	Et	H
g	H	CH_3	CH_3



Propargyl acetate complexes **2a–g** and acetylenic acetals **6a, b** when added to a dichloromethane solution containing 1.1 equivalents of diethylaluminum cyanide at 0 °C are rapidly converted (0.5–1 h) to the corresponding cyano derivatives **4a–g** and **7a, b**, respectively, which can be isolated in good to excellent yield following aqueous work-up and chromatography (Table). It is apparent that the reaction proceeds efficiently for a variety of substrates (including those having 1°, 2°, and 3° centers) and the acetal derivatives **6a, b**. The yields and reaction rates were somewhat higher for the latter, consistent with a mechanism involving significant positive charge buildup promoted by the powerful electron-releasing effect of the adjacent (alkynyl)$Co_2(CO)_6$ unit. No allenic derivatives or elimination products were observed. Unexpectedly, reaction of the complex of 3-acetoxy-1-penten-4-yne (**8**) with diethylaluminum cyanide gave in good yield the conjugated nitrile complex **9** arising from α-attack and double bond isomerization, apparently as a single stereoisomer (of undetermined stereochemistry).



Since the complexes **2a–g** were prepared from commercially available propargyl alcohols, it was of interest for synthetic convenience to demonstrate that the free propargyl nitriles could be prepared from the latter without isolation/purification of the synthetic intermediates. Accordingly, 1-phenyl-1-pentyn-3-ol (**1f**) was complexed with dicobalt octacarbonyl, then treated with diethylaluminum cyanide as above to form the nitrile complex **3f**. The latter without purification was demetalated with ceric ammonium nitrate (−78 °C, 3 h). Aqueous work-up afforded 2-ethyl-4-phenyl-3-butynenitrile (**4f**), which

Table. Propargyl Nitriles **3a**–**g**, **7a**, **b**, and **9** Prepared

Product	Yield[a] (%)	mp (°C)[b]	Molecular Formula[c]	^{1}H-NMR (CDCl$_3$) δ, *J*(Hz)	MS (12 eV) *m*/*z* (%)
3a	56	41–42	$C_{10}H_3Co_2NO_6$ (350.8)	3.90 (s, 2H); 6.05 (s, 1H)	350.9 (M$^+$, 6); 322.8 (100)
3b	68	70 (dec)	$C_{11}H_5Co_2NO_6$ (364.8)	2.73 (s, 3H); 3.88 (s, 2H)	364.9 (M$^+$, 8); 280.8 (100)
3c	55	oil	$C_{15}H_{13}Co_2NO_6$ (420.9)	0.95 (t, 3H, *J* = 12); 1.45 (m, 4H); 1.70 (m, 2H); 2.9 (t, 2H, *J* = 12); 3.90 (s, 2H)	420.9 (M$^+$, 3); 308.9 (100)
3d	69	44–45	$C_{16}H_7Co_2NO_6$ (426.9)	4.10 (s, 2H); 7.35 (m, 3H); 7.49 (m, 2H)	426.9 (M$^+$, 6); 314.9 (100)
3e	85	49–50	$C_{11}H_5Co_2NO_6$ (364.8)	1.68 (d, 3H, *J* = 6.5); 4.05 (q, 1H, *J* = 6.5); 6.10 (s, 1H)	364.9 (M$^+$, 6); 336.9 (100)
3f	70	oil	$C_{18}H_{11}Co_2NO_6$ (454.9)	0.79 (t, 3H, *J* = 7.3); 1.55 (m, 2H); 3.47 (dd, 1H, *J* = 5.4); 7.0 (m, 3H); 7.49 (d, 2H, *J* = 8)	454.9 (M$^+$, 1); 169 (100)
3g	92	74–75	$C_{12}H_7Co_2NO_6$ (378.8)	1.72 (s, 6H); 6.15 (s, 1H)	378.8 (M$^+$, 2); 350.8 (100)
7a	90	38–39	$C_{13}H_9Co_2HO_7$ (408.9)	1.30 (t, 3H, *J* = 6); 2.65 (s, 3H); 3.70 (m, 1H); 3.96 (m, 1H); 5.26 (s, 1H)	408.9 (M$^+$, 6); 268.9 (100)
7b	85	68–69	$C_{18}H_{11}Co_2HO_7$ (470.9)	1.35 (t, 3H, *J* = 6); 3.80 (m, 1H); 4.15 (m, 1H); 5.64 (m, 1H); 7.35 (m, 2H); 7.6 (m, 3H)	470.9 (M$^+$, 5); 268.9 (100)
9	88	82–83	$C_{12}H_5Co_2NO_6$ (376.8)	2.1 (d, 3H, *J* = 7.3); 6.2 (s, 1H); 6.8 (q, 1H, *J* = 7.3)	376.8 (M$^+$, 4); 237 (100)

[a] Yield following chromatography, based on **2**.
[b] Uncorrected.
[c] Satisfactory microanalyses obtained: C ±0.4, H ±0.38, N ±0.1. Exceptions: Compounds **2c** and **2d** contained trapped solvent molecules and gave unsatisfactory values. Compounds **2a**, C −0.67; **2e**, N −0.83; **2f**, N −0.51.

was obtained pure following chromatography. The overall yield from the free alcohol for the convenient four reaction sequence was 68%.

The method described herein for the preparation of propargyl nitriles and acetylenic cyanohydrins constitutes an attractive alternative to other ostensibly more direct routes, which typically proceed in modest yields with accompanying allene formation. Stereochemical aspects of these reactions are presently under investigation.

The propargyl alcohols, acetals, Et_2AlCN, and $Co_2(CO)_8$ were obtained commercially. Propargyl acetate complexes **3a–g**, **8** were prepared by acetylation of the corresponding complexed alcohols,[4] and the acetal complexes **6a, b** by direct reaction of $Co_2(CO)_8$ with the free acetylenic acetals.[5] CH_2Cl_2 was distilled from CaH_2. All reactions were carried out under an atmosphere of dry N_2. ^{1}H-NMR spectra were recorded on a Varian XL 300 (MHz) spectrometer.

Dicobalt Hexacarbonyl Complexed Propargyl Cyanides 3a–g, 7a, b, and 9; General Procedure:

A solution of the appropriate propargyl acetate or acetal complex **2a–g**, **6a, b** or **8**, respectively (2 mmol) in CH_2Cl_2 (50 mL) is added to a stirred solution (3.0 mL) of Et_2AlCN (3.0 mmol) in CH_2Cl_2 (3 mL) at 0°C. After the addition is complete, the mixture is allowed to warm to room temperature and stirred for 30 min. In an efficient fume hood, ice water (200 mL) is then added to the mixture followed by extraction with ether (2 × 100 mL). The combined ether extract is dried ($MgSO_4$), filtered through a small bed of celite/alumina, concentrated by evaporation, and then chromatographed over silica gel using 1:1 ether/*n*-hexane. The products are obtained as dark red oils or solids upon solvent evaporation; solids are obtained analytically pure following low temperature recrystallization from *n*-pentane (Table).

The decomplexation to corresponding propargyl nitriles is carried out by treating with ceric ammonium nitrate as described below in the typical multistep procedure for the preparation of 2-ethyl-4-phenyl-3-butynenitrile (**4f**).

Multistep Procedure for the Preparation of 2-Ethyl-4-phenyl-3-butynenitrile (4f):

To a solution of 1-phenyl-1-pentyn-3-ol (**1f**; 6 g, 37.5 mmol) dissolved in CH_2Cl_2 (100 mL) is added $Co_2(CO)_8$ (13.5 g, 39.0 mmol). The mixture is stirred under N_2 for 4 h (CO evolution!) after which, acetic anhydride (100 mL), pyridine (8 mL), and dimethylaminopyridine (0.5 g) is added. After stirring for an additional 5 h, cold sat. $NaHCO_3$ (300 mL) is added and the mixture extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extract is dried ($MgSO_4$), concentrated to ca. 50 mL, and then added dropwise to a stirred solution of Et_2AlCN (50 mmol) in CH_2Cl_2 (50 mL) at 0°C. After 40 min the reaction is complete as judged by TLC (silica gel, 1:1 pentane/ether). This solution is then added dropwise to a mixture of silica gel (20 g) and $(NH_4)_2Ce(NO_3)_6$ (42 g) in MeOH (350 mL) at −78°C (CO evolution!). After gas evolution is complete, the mixture is allowed to warm to 20°C and stirred for an additional 3 h. Water (200 mL) is added and then the mixture is extracted with CH_2Cl_2 (2 × 100 mL). The combined extract is dried ($MgSO_4$) and concentrated to provide 4.36 g (68%) of **4f** as a yellow oil, which is purified by chromatography over silica gel (eluent: pentane/ether, 2:1).

^{1}H-NMR ($CDCl_3$): δ = 1.2 (t, 3 H, *J* = 7.4 Hz); 2.0 (m, 2 H); 3.75 (t, 1 H, *J* = 7 Hz); 7.32–7.54 (m, 5 H).

MS (70 eV): *m*/*z* = 169 (M$^+$, 64); 140 (100).

HRMS (70 eV): *m*/*z* calc. for $C_{12}H_{11}N$ 169.0891; found 169.0888.

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(1) For examples, see:
Reddy, G.S., Mandell, L., Goldstein, J.H. *J. Am. Chem. Soc.* **1961**, *83*, 4729.
Haruki, E., Hirai, Y., Imoto, E. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 267.
Trost, B.M., Matsuda, K. *J. Am. Chem. Soc.* **1988**, *110*, 5233.
Brandsma, L., Verkruijsse, H.D. *Synthesis of Acetylenes and Allenes*, Elsevier, Amsterdam, 1981, pp. 225, 226.
(2) Review: Wotiz, J., in: *Chemistry of Acetylenes*, Viehe, H.G. (ed.), Marcel Dekker, N.Y., 1969, pp. 365–424.
(3) Nicholas, K.M. *Acc. Chem. Res.* **1987**, *20*, 207.
(4) Padmanabhan, S., Nicholas, K.M. *J. Organomet. Chem.* **1981**, *212*, 107.
(5) Montana, A.M., Nicholas, K.M., Khan, M. *J. Org. Chem.* **1988**, *53*, 5193.

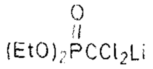
1988

- Chen, Q.-Y., He, Y.-B. *Synthesis* **1988**, 896. On page 897 the amount of $Pd(PPh_3)_2Cl_2$ in the general procedure for *Arenes* **3** should be 0.075 mmol.

1989

- Bhaha, S.K., Hajdu, J. *Synthesis* **1989**, 16. Throughout the paper thioacetyl should be replaced by acetylthio. Hence **7** is named 2-*S*-acetyl-1-*O*-hexadecyl-L-2-thioglycerol.

- Burger, A., Hetru, C., Luu, B. *Synthesis* **1989**, 93. On page 94 the formulae of the Horner–Emmons reagent used is:



$$(EtO)_2\overset{\overset{\displaystyle O}{\|}}{P}CCl_2Li$$

and the correct name *in the experimental section p.* 96 is: diethyl dichloromethylphosphonate.

- Schinzer, D. *Synthesis* **1989**, 179. On page 180 compound **14b** is (2*R*,3*RS*,4*SR*)-3-hydroxy-2,4,6-trimethyl-5-heptenoyltriethylsilane.

- Cristau, H.J., Fonte, M., Torreilles, E. *Synthesis* **1989**, 301. *On page* 301 compound **7** is 2-(2-benzylaminoethoxy)-1-[(2-methyl-1,3-dioxolan-2-yl)methyl]ethyltriphenylphosphonium iodide.

- Zhou, W.-S., Zhou, Y.-P., Jiang, B. *Synthesis* **1989**, 426. On page *427 compound* ***8*** is (22*E*,24*R*)-3α,5-cyclo-5α-ergosta-7,22-dien-6-one and **9** is (22*E*,24*R*)-3α5-cyclo-5α-ergost-22-en-6-one.

- Stuart, J.G., Nicholas, K.M. *Synthesis* **1989**, 454. In the title abstract and text propargyl nitriles should read propargyl *cyanides*.

- Schick, H., Eichhorn, I., *Synthesis* **1989**, 477. On page 481 the final entry to Table 4 should read:
$CH_2CH{=}CH-(CH_2)_3CO_2Me$