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Direct conversion of α , β -unsaturated nitriles into cyanohydrins using Mn(dpm)₃ catalyst, dioxygen and phenylsilane

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Abstract—Treatment of α , β -unsaturated nitriles with Mn(dpm)₃ (3 mol%), PhSiH₃ in isopropyl alcohol in the presence of oxygen resulted in reduction and α - and β -hydroxylation. © 2001 Elsevier Science Ltd. All rights reserved.

The use of cyanohydrins in synthesis has a long history starting with the Lapworth benzoin reaction.¹ Cyanohydrin O-ethers have also been used to implement reversed-polarization reactions of aldehydes (umpolung), and also serve as a protecting group for the carbonyl function.² While the oxidative conversion of nitriles to carbonyl functionality is known, there are no reports of the direct transformation of an α , β -unsaturated nitrile into a cyanohydrin.³ We recently reported the conversion of α,β -unsaturated ketones into α hydroxy ketones using tris(dipivaloylmethanato) manganese(III) [abbreviated to Mn(dpm)₃],⁴ phenylsilane and oxygen. The application of this system to other functional groups has provided a new synthetic route to cyanohydrins (Scheme 1) from α,β -unsaturated nitriles. Examples are shown in Table 1.

The substrates 1a-1g (listed in Table 1) were prepared from the corresponding aldehydes and cyanomethylphosphonate, and where applicable, were approximately 1:1 mixtures of the *E*- and *Z*-isomers. Treatment of 1a-1g with Mn(dpm)₃ (3 mol%) in isopropyl alcohol and phenylsilane under an oxygen atmosphere resulted in complete conversion of the starting materials (the volatility of some products may have diminished the isolated yields). Small amounts of the conjugate reduction products were observed (¹H NMR) in the cases of entries **b**, **c**, and **e**. The substituents at the β -position affected the product distribution. A single aliphatic group resulted in only α -hydroxylation. Cinnamonitrile (**1e**) gave a 2:1 mixture of β -hydroxy and α -hydroxy nitriles. Mukaiyama obtained a 6:1 mixture of β -: α -hydroxy esters upon treatment of ethyl cinnamate with Mn(dpm)₃, phenylsilane and oxygen.⁵ Similarly, as we had observed for the corresponding unsaturated ester,⁴ treatment of unsaturated nitrile **1f** gave a mixture of products, although **3f** was not isolated. For the cyclooctyl substrate **1g**, the ratio of β -: α -hydroxylation was again around 2:1.

We had previously found that treatment of β -ionone with Mn(dpm)₃, phenylsilane and O₂ resulted in 1,6 reduction and hydroxylation at the γ -position.⁴ Similar results were obtained for the analogous nitriles (Scheme 2). Compound 4, with an extended conjugated system, gave 5 (24%), but since this initial product is also a substrate for the reaction, 6 (21%, 1:1 diastereomers) was also obtained. Similarly, 7 gave 8 (11%), but also 9 (15%, 1:1 diastereomers).

In the absence of oxygen, no reaction was observed for compound 1a, whereas the conjugate reduction of unsaturated ketones proceeds well in the absence of air.⁴

ОН

Scheme 1.

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Entry	Substrate	Yield (%), 2	Yield (%), 3	Conditions		
a	CN	54	-	1hr, 0.75mmol		
b	CN	44	-	45mins, 1.25mmol		
с	CN CN	27	-	1hr, 0.76mmol		
d	CN	29	-	20hrs, 1.01mmol		
e	CN CN	16	33	2hrs, 1.61mmol		
f	СМ	53	~10 (NMR)	16hrs, 0.70mmol		
g	CN	13	27	20hrs, 1.09mmol		
$4 \xrightarrow{CN} \frac{3 \mod \% \operatorname{Mn}(\operatorname{dpm})_3}{O_2/\operatorname{PhSiH}_3/i\operatorname{-PrOH}} \xrightarrow{OH} \xrightarrow{CN} + OH \xrightarrow{OH} $						
$\begin{array}{c cccc} & & & & & & & & & & & & & & & & & $						

Scheme 2.

The reaction was studied with a variety of more activated substrates (Scheme 3), including dinitrile **10a**, nitrile ester **10b** and diester **10c**. In each case the product of conjugate reduction was the major one, although the proportion of α -hydroxylation varied depending upon the substituents. No β -hydroxylation was observed in this series. Results are shown in Table 2.

Evidently, protonation of the intermediate to give 12 occurs more rapidly than reaction with oxygen for these substrates. No conversion was observed for 10d under catalytic conditions. Incomplete conversion was

observed for entries **a**–**c** when 3 mol% of catalyst was used. Changing the ligand from dipivaloylmethane to hexafluoroacetylacetone (acac-F₆) gave complete conversion, but resulted only in conjugate reduction (**12b**, 77%) when the Mn(acac-F₆)₃, O₂, PhSiH₃ system was applied to **10b**.

Typical procedure: To a solution of unsaturated nitrile **1a** (105 mg, 0.776 mmol) and $Mn(dpm)_3$ (14 mg, 3 mol%) in *i*-PrOH (1 ml) under an oxygen atmosphere (balloon) at 0°C was added PhSiH₃ (124 µL, 1.3 equiv., 1.01 mmol). After 10 min the ice bath was removed, and the reaction was allowed to stir for a further 1 h, at

Table 2.

Entry	Substrate	Yield (%), 11	Yield (%), 12	Conditions
a	X, $Y = CN$	10 (NMR)	56 (5% SM)	16 h, 2.00 mmol
b	X=CN, $Y = CO_2Me$	18	42 (30% SM)	16 h, 2.00 mmol
c	X, $Y = CO_2Me$	42	44 (10% SM)	5 h, 2.00 mmol
d	X = NO ₂ , Y = H		20	1 equiv. Mn(dpm) ₃ , 4 h, 0.30 mmol
e	$X = CN, Y = CONC_5H_{10}$	24	71	1 h, 1.00 mmol

which point it was filtered through a silica plug (eluted with ethyl acetate) and the residue purified by flash chromatography (hexane:ethyl acetate, 9:1) to yield 64 mg (54%) of cyanohydrin 2a as a clear oil.

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