

A Convenient and Improved Method for the Preparation of Cyanohydrin Esters from Acyl Cyanides and Aldehydes

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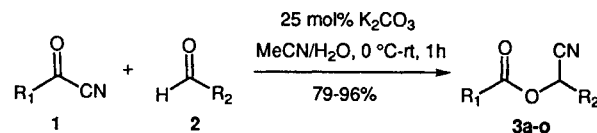
Various kinds of cyanohydrin esters can be obtained in good to excellent yields from aldehydes by treatment with acyl cyanides in a heterogeneous mixture of aqueous potassium carbonate and acetonitrile.

Cyanohydrin esters serve as important precursors to many useful organic compounds, and they are usually prepared from cyanohydrins by acylation with the appropriate acyl halide or acid anhydride.¹ However, alternative methods by treatment of aldehydes with acyl halides in aqueous cyanide solution,² or with acyl cyanides in aqueous alkaline solution³ appear to be attractive for the direct preparation of cyanohydrin esters from aldehydes. Since such acylating reagents are susceptible to hydrolysis and, particularly aliphatic aldehydes having an α -hydrogen atom, readily undergo aldol condensation under alkaline conditions, the reaction in aqueous media has been believed to be less preferable in order to effectively obtain the desired products. Consequently, several modified methods have been proposed, for example, employing a phase-transfer catalyst.^{4,5} More recently, it has also been reported that Bu_3SnCN is an efficient catalyst for the addition of acyl cyanides to aldehydes.⁶

We report the simple procedure for the preparation of cyanohydrin esters **3** by the reaction of aldehydes **2** with acyl cyanides **1** without using special reagents. The addition reaction was performed by adding a solution having a slight excess of acyl cyanide in acetonitrile into a heterogeneous mixture consisting of the aldehyde, acetonitrile, and aqueous potassium carbonate with vigorous stirring at an ice bath temperature. The corresponding cyanohydrin esters were isolated from the organic layer in good to excellent yields by distillation or recrystallization (Table).

The present reaction is quite general and successful for preparing a wide variety of cyanohydrin esters **3**. The required amount of potassium carbonate was approximately 25 mol% for the aldehyde. The use of a stronger base, such as sodium hydroxide, instead of potassium carbonate gave lower yields of **3**, due to the hydrolysis of acyl cyanides and aldol condensation in the case of aliphatic aldehydes. As the reaction medium, a mixture of acetonitrile and water resulted in the optimum conversion into **3**. The replacement of acetonitrile with another aprotic solvent, such as propionitrile, benzene, chloroform or DMF drastically decreased the yield. Also, the presence of water was essential for the formation of **3**. For example, when the same reaction between benzaldehyde and benzoyl cyanide was run without adding water, the yield of **3** was only about 15%. Also, during the reaction in aqueous potassium carbonate without using acetonitrile, the yield did not exceed 50%.

Although the reason for the remarkable effect of the mixed solvent of acetonitrile–water for the formation of



3	R₁	R₂	3	R₁	R₂
a	Me	<i>n</i> -Pr	i	C ₆ H ₅	C ₆ H ₅
b	Me	<i>cyclo</i> -C ₆ H ₁₁	j	C ₆ H ₅	4-MeO-C ₆ H ₄
c	Me	C ₆ H ₅	k	C ₆ H ₅	4-Cl-C ₆ H ₄
d	MeO	<i>n</i> -Pr	l	C ₆ H ₅	furyl
e	MeO	<i>cyclo</i> -C ₆ H ₁₁	m	C ₆ H ₅	C ₆ H ₅ CH=CH
f	MeO	C ₆ H ₅	n	4-MeO-C ₆ H ₄	C ₆ H ₅
g	C ₆ H ₅	<i>n</i> -Pr	o	4-Cl-C ₆ H ₄	C ₆ H ₅
h	C ₆ H ₅	<i>cyclo</i> -C ₆ H ₁₁			

3 is not yet clear, the high yields of **3** observed here indicates that both the alkaline sensitive substrates **1** and **2** are protected from water in the organic phase, and that the key steps during the reaction take place at the hydrophobic interfacial layer.

The present reaction most likely involves the formation of the cyanohydrin anion as has already been reported by Thesing and Photis.^{1,5} A catalytic amount of cyanide ion that is generated by hydrolysis of acyl cyanide adds to the aldehyde affording the cyanohydrin anion, which is very rapidly trapped by acyl cyanide. The regenerated cyanide ions act as the catalyst again. Indeed, the reaction was essentially completed within 10 minutes in most cases.

Attempts to extend this reaction to ketones were unsuccessful. With acetone and cyclohexanone, the yield of the corresponding **3** was less than 10% each even if the reaction was continued for a long time.

The aldehydes used were purchased and distilled before use. Acetyl cyanide,⁷ methyl cyanoformate,⁸ and benzoyl cyanides⁹ were prepared by methods published in the literature. K_2CO_3 and MeCN were commercial products and were used without further purification.

Cyanohydrin Esters **3a-o**; General Procedure:

To a heterogeneous mixture consisting of MeCN (10 mL) and K_2CO_3 (5 mmol) in H_2O (6 mL) was added a solution of aldehyde (20 mmol) in MeCN (10 mL) with vigorous stirring in an ice-water bath. A solution of acyl cyanide (22 mmol) in MeCN (10 mL) was then added dropwise over a period of 10 min, and the stirring was continued for 1 h at r.t. For the preparation of **3b** and **3j**, acyl cyanides (2 equiv) and K_2CO_3 (10 mmol) were used, and the stirring

Table. Cyanohydrin Esters **3** Prepared

Prod- uct	Yield ^a (%)	mp (°C) or bp (°C)/Torr ^b (solvent)	Molecular Formula ^c or Lit. mp (°C)	IR (KBr) (cm ⁻¹) ^d ν _{CN} , ν _{CO}	¹ H NMR (CDCl ₃ , TMS) ^e δ, J (Hz)	¹³ C NMR (CDCl ₃ , TMS) ^e δ	MS (70 eV) ^f m/z (%)
3a	95	84–85/13	C ₇ H ₁₁ NO ₂	2249 (vw) 1755	0.99 (t, J = 7, 3 H), 1.3–1.7 (m, 2 H), 1.7–2.1 (m, 2 H), 2.13 (s, 3 H), 5.32 (t, J = 7, 1 H)	13.3 (CH ₃), 18.0 (CH ₂), 20.4 (CH ₃), 61.0 (CH), 117.0 (CN), 169.2 (CO)	– ^g
3b^h	79	103–105/5		2249 (vw) 1755	0.9–1.5 (br m, 5 H), 1.5–2.1 (br m, 6 H), 2.14 (s, 3 H), 5.16 (d, J = 6, 1 H)	20.3 (CH ₃), 25.4 (CH ₂), 25.9 (CH ₂), 28.0 (CH ₂), 28.2 (CH ₂), 40.1 (CH), 65.7 (CH), 116.3 (CN), 169.4 (CO)	181 (M ⁺ , 1), 83 (100)
3c^{h,i}	90	105–107/2		2249 (vw) 1755	2.12 (s, 3 H), 6.38 (s, 1 H), 7.3–7.7 (m, 5 H)	20.4 (CH ₃), 62.9 (CH), 116.2 (CN), 127.9 (CH), 129.2 (CH), 130.4 (CH), 131.8 (C), 169.0 (CO)	175 (M ⁺ , 30), 133 (100)
3d	92	97–98/13	C ₇ H ₁₁ NO ₃	–	1.00 (t, J = 7, 3 H), 1.3–1.8 (m, 2 H), 1.8–2.1 (m, 2 H), 3.86 (s, 3 H), 5.22 (t, J = 6, 1 H)	13.3 (CH ₃), 17.9 (CH ₂), 34.3 (CH ₂), 55.7 (CH ₃), 64.9 (CH), 116.7 (CN), 154.4 (CO)	– ^g
3e^h	96	121–122/5		2247 (vw) 1761	0.9–1.5 (br m, 5 H), 1.5–2.2 (br m, 6 H), 3.85 (s, 3 H), 5.06 (d, J = 6, 1 H)	25.3 (CH ₂), 25.8 (CH ₂), 27.8 (CH ₂), 28.0 (CH ₂), 40.2 (CH), 55.7 (CH ₃), 69.6 (CH), 115.9 (CN), 154.5 (CO)	197 (M ⁺ , 2), 83 (100)
3f^h	95	125–127/4		2251 (vw) 1761	3.80 (s, 3 H), 6.26 (s, 1 H), 7.3–7.7 (m, 5 H)	55.9 (CH ₃), 66.7 (CH), 115.9 (CN), 127.9 (CH), 129.3 (CH), 130.7 (CH), 131.4 (C), 154.1 (CO)	191 (M ⁺ , 35), 116 (100)
3gⁱ	94	50–51 (EtOH)		2243 (vw) 1720	1.01 (t, J = 7, 3 H), 1.4–1.8 (m, 2 H), 1.8–2.2 (m, 2 H), 5.57 (t, J = 6, 1 H), 7.3–7.7 (m, 3 H), 7.9–8.2 (m, 2 H)	13.4 (CH ₃), 18.1 (CH ₂), 34.4 (CH ₂), 61.5 (CH), 117.1 (CN), 128.4 (C), 128.7 (CH), 129.9 (CH), 134.0 (CH), 164.8 (CO)	203 (M ⁺ , 2), 105 (100)
3h	96	106–107 (EtOH)	C ₁₅ H ₁₇ NO ₂	2243 (vw) 1720	0.9–2.3 (m, 11 H), 5.43 (d, J = 6, 1 H), 7.3–7.8 (m, 3 H), 7.9–8.2 (m, 2 H)	25.4 (CH ₂), 25.8 (CH ₂), 28.1 (CH ₂), 28.2 (CH ₂), 40.3 (CH), 66.0 (CH), 116.2 (CN), 128.5 (C), 128.6 (CH), 129.9 (CH), 133.9 (CH), 164.8 (CO)	243 (M ⁺ , trace), 105 (100)
3iⁱ	94	60–61 (EtOH)	63–64 ² 59 ³	2249 (vw) 1732	6.67 (s, 1 H), 7.3–7.8 (m, 8 H), 8.0– 8.2 (m, 2 H)	63.4 (CH), 116.2 (CN), 127.8 (CH), 128.2 (C), 128.6 (CH), 129.3 (CH), 130.1 (CH), 130.4 (CH), 132.0 (C), 134.1 (CH), 164.6 (CO)	237 (M ⁺ , 36), 105 (100)
3j	89	64–65 (EtOH)	64–65 ³	1732	3.82 (s, 3 H), 6.62 (s, 1 H), 6.96 (d, J = 9, 2 H), 7.4–7.7 (m, 5 H), 8.0–8.2 (m, 2 H)	55.4 (CH ₃), 63.2 (CH), 114.7 (CH), 116.4 (CN), 124.0 (C), 128.4 (C), 128.6 (CH), 129.7 (CH), 130.1 (CH), 134.0 (CH), 161.2 (C), 164.7 (CO)	267 (M ⁺ , 36), 146 (100), 105 (63)
3kⁱ	81	51–53 (EtOH)	57–58 ²	2243 (vw) 1724	6.64 (s, 1 H), 7.2–7.7 (m, 7 H), 7.9– 8.2 (m, 2 H)	62.6 (CH), 115.9 (CN), 127.9 (C), 128.6 (CH), 129.2 (CH), 129.5 (CH), 130.0 (CH), 130.5 (C), 134.1 (CH), 136.6 (C), 164.4 (CO)	271 (M ⁺ , 21), 105 (100)
3l	88	49–50 (EtOH)	C ₁₃ H ₉ NO ₃	– 1719	6.46 (dd, J = 2, 3, 1 H), 6.74 (s, 1 H), 6.78 (m, 1 H), 7.2–7.7 (m, 4 H), 7.9– 8.2 (m, 2 H)	56.3 (CH), 111.2 (CH), 112.7 (CH), 114.3 (CN), 127.9 (C), 128.7 (CH), 130.1 (CH), 134.2 (CH), 144.3 (C), 145.1 (CH), 164.5 (CO)	227 (M ⁺ , 25), 105 (100)
3m	86	68–69 (EtOH)	72–73 ²	2259 (vw) 1728	6.1–6.5 (m, 2 H), 6.9–7.1 (m, 1 H), 7.2–7.8 (m, 8 H), 8.0–8.2 (m, 2 H)	62.1 (CH), 115.6 (CN), 118.5 (CH), 127.3 (CH), 128.3 (C), 128.7 (CH), 128.9 (CH), 129.5 (CH), 130.1 (CH), 134.1 (CH), 134.5 (C), 138.0 (CH), 164.6 (CO)	263 (M ⁺ , 5), 105 (100)
3nⁱ	95	54–55 (EtOH)	58–59 ²	– 1720	3.80 (s, 3 H), 6.64 (s, 1 H), 6.89 (d, J = 9, 2 H), 7.3–7.8 (m, 5 H), 8.00 (d, J = 9, 2 H)	55.5 (CH ₃), 63.1 (CH), 114.0 (CH), 116.4 (CN), 120.4 (C), 127.8 (CH), 129.2 (CH), 130.3 (CH), 132.3 (CH), 159.6 (C), 164.3 (CO)	267 (M ⁺ , 12), 135 (100)
3o	90	69–70 (EtOH)	C ₁₅ H ₁₉ NO ₂ Cl	2241 (vw) 1722	6.65 (s, 1 H), 7.2–7.7 (m, 7 H), 7.9– 8.1 (m, 2 H)	63.6 (CH), 116.1 (CN), 126.6 (C), 127.9 (CH), 129.0 (CH), 129.3 (CH), 130.5 (CH), 131.4 (CH), 131.7 (C), 140.6 (C), 163.7 (CO)	271 (M ⁺ , 27), 139 (100)

^a Yield of isolated, purified products.^b Uncorrected.^c Satisfactory analyses obtained: C ± 0.25, H ± 0.22, N ± 0.10, Cl ± 0.12 %.^d Recorded on a Shimadzu FT-IR 8200 spectrophotometer.^e IR spectra of **3** showed no or very weak absorptions in CN stretching region 2240–2250 cm⁻¹.^f Recorded on a JEOL JNM-EX 90A spectrometer.^g Obtained on a JEOL JMS-SX 102A spectrometer.^h No parent peak was observed in the EI-MS, but M⁺ + 1ⁱ peak was observed in the CI-MS.^j The ¹H and ¹³C NMR spectra were agreement with those reported in the literature.⁶^k The IR, ¹H and ¹³C NMR spectra were agreement with those reported in the literature.⁴

was continued for 3 h. After the reaction was complete, the aqueous layer was removed, and the organic layer was washed with brine (2×50 mL), dried (MgSO_4), and evaporated. The residue was recrystallized from EtOH or distilled in vacuo. The isolated yields are shown in the Table.

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