Organic Process Research & Development **1997**, *1*, 250–252

A Novel and Practical Method for Hydrocyanation of Chalcones

James E. Ellis,* Edward M. Davis, and Phillip L. Brower

Parke-Davis Pharmaceutical Research Division, Warner Lambert Co., Chemical Development Department, 188 Howard Avenue, Holland, Michigan 49424

Abstract:

A novel and practical method for the hydrocyanation of chalcones is described. The chalcone hydrocyanation reaction proceeds very efficiently using only 125 mol % of acetone cyanohydrin and 5 mol % of tetramethylammonium hydroxide. This reaction stoichiometry provides high-quality product in good yield on pilot scale. In addition, the reduced amounts of acetone cyanohydrin improve the workup, in which the excess cyanide is destroyed with sodium hypochlorite.

A series of novel hydroxybutenolide compounds (**3**) with activity as endothelin antagonists was discovered recently in our endothelin program.[1] These compounds are nonpeptides and have selective activity at nanomolar concentrations with endothelin A receptors. As part of this endothelin antagonist program, we required a practical method for hydrocyanation of chalcones (**1**) which would allow preparation of kilogram quantities of β-keto nitriles (**2**) as intermediates to hydroxybutenolides. In this paper we describe our work developing a scalable hydrocyanation procedure.

There are a number of potentially useful methods available in the literature for hydrocyanation of α,β-enones.[2,3] Some of the methods, such as using hydrogen cyanide or trialkylaluminum cyanides, have significant associated safety issues on scale. We evaluated the two methods which appeared to be the most practical for scale-up: (1) the Lapworth procedure using potassium cyanide and acetic acid[4] and (2) the Nazarov base catalyzed hydrocyanation using acetone cyanohydrin as the cyanide source.[5] The Lapworth hydrocyanation reaction was run in ethoxyethanol because it was an excellent solvent for chalcones. The reaction proceeded to completion in approximately 1 h at reflux using 2 mol of potassium cyanide and 1.5 mol of acetic acid per mole of substrate. A significant problem with this method from a scale-up perspective was that large amounts of hydrogen cyanide are generated by the process since it involved partial neutralization of the potassium cyanide. This process would have required special equipment to prevent release of hydrogen cyanide.

In addition to the safety concerns, the reaction mixture became highly colored on reaching reflux. This was also the case when other alcoholic solvents, acetonitrile, THF, and acetone were used. Since we found that the color carried through the remainder of our synthesis to the bulk pharmaceutical compound, the keto nitrile required recrystallization and carbon treatment to remove the colored impurities. Attempts to directly isolate keto nitrile that was not colored were unsuccessful. Consequently, we began to look for a suitable alternative method.

We next evaluated the sodium carbonate catalyzed hydrocyanation with acetone cyanohydrin. In the literature, this reaction is typically run in alcoholic solvents. Therefore, several different solvents were evaluated: methanol, ethanol, ethoxyethanol, and also acetone. In all of the solvents, except acetone, the reaction mixture darkened considerably at reflux. Consequently, acetone was chosen for further studies.

We initially used a reaction stoichiometry of 2 mol of acetone cyanohydrin and 0.25 mol of a 10% aqueous solution of base per mole of chalcone substrate, which Betts and Davey had described as optimal.[5b] Under these conditions the sodium carbonate catalyzed hydrocyanation with acetone as solvent proceeded smoothly to the desired product with good purity. Colored products were not obtained. However, the reaction rate was slow with the sodium carbonate catalyzed method, requiring more than 40 h to complete the reaction on scale. This problem is partly due to the reaction in acetone starting out as a slurry, since the chalcones (**1**) and sodium carbonate have low solubility in acetone. But it also is a function of the substituents on the chalcone. This was very pronounced when chalcones with several electron-donating substituents were used. The electron-donating substituents decrease the electrophilicity of the chalcone double bond, resulting in a decreased rate of Michael addition by the cyanide anion.

We thought the slow reaction rate using sodium carbonate catalyst was related, in part, to the low solubility of the base in the reaction solvent. Consequently, several other bases which would have better solubility were evaluated. Catalytic triethylamine did not give complete reaction even after 40 h of reaction time. Aqueous potassium hydroxide gave no improvement in rate and also gave an oily product. Catalytic aqueous potassium cyanide also did not significantly improve the reaction rate. Aqueous potassium carbonate did improve the reaction rate, with complete reaction at 20−24 h.

At this point, we tried 25% tetrabutylammonium hydroxide in water as a soluble form of hydroxide. This could also function as a phase transfer catalyst to assist in the delivery of the cyanide in the Michael reaction. The reaction proceeded very well, reaching completion after about 4 h.

(1) Doherty, A. M.; Patt, W. C.; Edmunds, J. J.; Berryman, K. A.; Reisdorph, B. R.; Plummer, M. S.; Shahripour, A.; Lee, C.; Cheng, X.; Walker, D. M.; Haleen, S. J.; Keiser, J. A.; Flynn, M. A.; Welch, K. M.; Hallak, H.; Taylor, D. G.; Reynolds, E. E. *J. Med. Chem.* **1995**, *38*, 1259.

(2) For a review: Nagata, W.; Yoshioka, M. In *Organic Reactions*; Dauben, W. O., Ed.; John Wiley and Sons Inc.: New York, 1977; Vol. 25, 255.

(3) Liotta, C. L.; Dabdoub, A. M.; Zalkow, L. H. *Tetrahedron Lett.* **1977**, 1117.

(4) Ishii, H.; Chen, I.; Ishikawa, T. *J. Chem. Soc., Perkin Trans. 1* **1987**, 671. Davey, W.; Tivey, D. J. *J. Chem. Soc.* **1958**, 1230. Lapworth, A.; Wechsler, E. *J. Chem. Soc.* **1910**, 97, 38.

(5) (a) Nazarov, I. N.; Zav'yalov *J. Gen. Chem. USSR (Engl. Transl.)* **1954**, *24*, 475 (*Chem. Abstr.* **1955**, *49*, 6139f). (b) Betts, B. E.; Davey, W. *J. Chem. Soc.* **1958**, 4193.

 S1083-6160(96)00048-5 CCC: $14.00

However, the presence of water in the reaction system appears to adversely affect the reaction by reducing the solubility of the chalcone in acetone. With this in mind, we next evaluated 25% tetramethylammonium hydroxide in water and achieved the same result. Further studies used this reagent, since it is nearly twice the molar concentration of the 25% tetrabutylammonium hydroxide solution and the reaction could be run at the same stoichiometry but with only half the amount of water.

As the reaction conditions were optimized, we found that the amounts of both cyanohydrin and base could be reduced substantially. However, as the amounts of cyanohydrin and base were reduced, the reaction times increased. We chose a maximum desirable reaction time of 10 h, which was obtained using 1.25 mol of cyanohydrin/mol of substrate with 5 mol % of tetramethylammonium hydroxide. The reduction in the amount of cyanohydrin used in the reaction was a very significant improvement from a development perspective since it facilitated the waste treatment by reducing the amount of excess cyanide to be destroyed. In addition, the increase in concentration gave an increase in throughput.

An additional benefit in using acetone as the reaction solvent is that it simplified the waste treatment. The use of acetone avoided mixed organic solvents in the waste stream since acetone is released in the reaction of acetone cyanohydrin. More importantly, the acetone could be separated from the water phase easily by atmospheric distillation, since it does not form an azeotrope with water. This allowed the treatment of the water phase with sodium hypochlorite to destroy the residual cyanide.[6] This distillation separation was used successfully on pilot scale using a still connected to an atmospheric scrubber containing sodium hypochlorite to remove any HCN vapors. The acetone distillate that was obtained contained less than 10 ppm of hydrogen cyanide. Then the residual cyanide in the water was treated with sodium hypochlorite without any problems. By avoiding alcoholic solvents, we eliminated the possibility of the water layer containing residual alcohol, which would have been dangerous to treat with sodium hypochlorite since alcohols form alkyl hypochlorites.[7]

The hydrocyanation reaction was studied with a variety of substituted chalcones. A summary of the reaction data is given in Table 1. The reaction rate is strongly affected by the substituents on the chalcone.

Chalcones with electron-withdrawing substituents are very reactive but also are sensitive to base. Nitrochalcones gave only decomposition. The reaction ran fairly well with other electron-withdrawing substituents (**2c**−**f**), with good reaction times and acceptable purities. With unsubstituted chalcones and chalcones having electron-donating substituents, the reaction works very well with acceptable reaction times and excellent product purities. As expected, the reaction rate decreased with an increasing number of electron-donating substituents.

In conclusion, we have developed a scalable hydrocyanation method which gives high-purity products in excellent yields. This was achieved with mild reaction conditions that gave acceptable reaction rates even with chalcones with several electron-donating substituents. The process we developed also allowed facile waste disposal with easy destruction of excess cyanide in the waste stream.

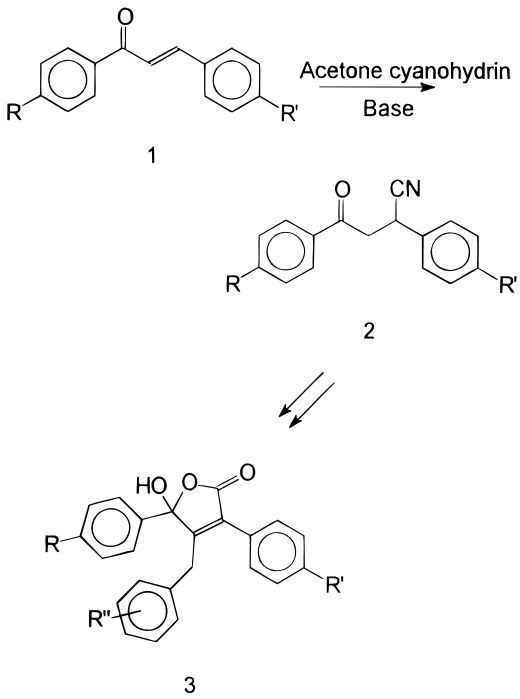
(6) Jenks, W. R. In *Encyclopedia of Chemical Technology*; Grayson, M., Ed.; Wiley: New York, 1979; Vol. 7, p 320.
(7) Brethereck, L. *Handbook of Reactive Chemical Hazards*, 2nd ed.; Butterworths: London, 1979; p 805.

Table 1. **Hydrocyanation of substituted chalcones**

	R	R′	t^a (h)	yield^b (%)	purity^c (%)
2a	NO_2	H		decomposition	
2b	H	NO_2		decomposition	
2c	H	CN	0.5	56	90.9
2d	H	CO_2Me	0.75	90	99.4
2e	F	H	2	95	98.2
2f	H	F	1.5	94	93.6
2g	H	H	1	93	99.7
2h	MeO	H	3	97	100
2i	H	MeO	2.75	98	100
2j	H	Me	2.5	95	100
2k	Me	H	3.5	97	100
2l	H	$N(Me)_2$	5	85	93
2m	MeO	OCH_2O^d	9	90	97.5
2n	MeO	$(OMe)_3{}^e$	9	87	98.1

^{a} Reaction time at reflux. ^{b} Isolated yields. ^{c} Purities are HPLC % area normalization. ^{d} 3,4-Methylenedioxy. ^{e} 3,4,5-Trimethoxy.

Scheme 1



Experimental Section

All of the reagents used in this study were purchased from the Aldrich Chemical Company. Acetone was purchased from commercial bulk sources. All of the reactions were run under a nitrogen atmosphere. The ^1H spectra were obtained on a Varian 200 MHz spectrometer, and chemical shifts are expressed in ppm from tetramethylsilane as an internal standard. The melting points were determined on a Buchi melting point apparatus and are uncorrected. HPLC for the in-process assay and final product assay were performed on a Perkex 5μ C-18 column with a mobile phase of 45% acetonitrile and 55% 0.1 M sodium acetate buffer adjusted to pH 6 with the detector at 254 nm. The analyses

by HPLC are expressed by % area normalization for individual components.

The nitro- and cyanochalcones were prepared via the acid-catalyzed Claisen−Schmidt reaction of the corresponding acetophenone and the appropriately substituted benzaldehyde according to the procedure of Lyle and Paradis.[8] All of the other chalcones were prepared via a modification of the base-catalyzed Claisen−Schmidt reaction of Kohler and Chadwell.[9]

General Hydrocyanation Procedure. The chalcone (0.05 mol) was slurried into 50 mL of acetone. Acetone cyanohydrin (5.32 g, 0.0625 mol) was added all at once, followed by a tetramethylammonium hydroxide 25% aqueous solution (1.12 g, 0.003 12 mol). The mixture was heated at reflux until the reaction was complete by HPLC. After cooling of the mixture to room temperature, 25 mL of water was added to induce crystallization. The slurry was cooled below 10 °C and filtered to collect product. The product was washed with water and vacuum dried at 45 °C. The reaction times and yields are summarized in Table 1. The products were recrystallized from ethanol, if necessary, for analytical testing. The analytical data for the keto nitrile products are listed below.

2-(4-Cyanophenyl)-4-phenyl-4-oxobutyronitrile (2c): mp 136.8−137.3 °C; ^{1}H NMR (200 MHz, DMSO-d_6) 3.8 (1H, dd, CHCH_aHCO), 4.1 (1H, dd, CHCH_bHCO), 4.8 (1H, dd, ArCHCH$_2$), 7.1−8.1 (9H, m, ArH). Anal. Calcd for $C_{17}H_{12}N_2O$: C, 78.44; H, 4.65; N, 10.76. Found: C, 78.43; H, 4.65; N, 10.48.

2-(4-(Methoxycarbonyl)phenyl)-4-phenyl-4-oxobutyronitrile (2d): mp 113.9−114.5 °C; ^{1}H NMR (200 MHz, $CDCl_3$) 3.5 (1H, dd, CHCH_aHCO), 3.7 (1H, dd, CHCH_bHCO), 3.9 (3H, s, OMe), 4.65 (1H, dd, ArCHCH$_2$), 7.4−7.65 (5H, m, ArH), 7.9 (2H, d, ArH), 8.05 (2H, d, ArH). Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.45; H, 5.19; N, 4.68.

2-Phenyl-4-(4-fluorophenyl)-4-oxobutyronitrile (2e): mp 134.0−134.5 °C; ^{1}H NMR (200 MHz, DMSO-d_6) 3.75 (1H, dd, CHCH_aHCO), 4.0 (1H, dd, CHCH_bHCO), 4.6 (1H, t, ArCHCH$_2$), 7.2−7.7 (7H, m, ArH), 8.15 (2H, m, ArH). Anal. Calcd for $C_{16}H_{12}FNO$: C, 75.88; H, 4.78; N, 5.53. Found: C, 75.81; H, 4.75; N, 5.40.

2-(4-Fluorophenyl)-4-phenyl-4-oxobutyronitrile (2f): mp 101.9−102.5 °C; ^{1}H NMR (200 MHz, DMSO-d_6) 3.7 (1H, dd, CHCH_aHCO), 4.0 (1H, dd, CHCH_bHCO), 4.65 (1H, m, ArCHCH$_2$), 7.3 (2H, t, ArH), 7.4−7.7 (5H, m, ArH), 8.0 (2H, d, ArH). Anal. Calcd for $C_{16}H_{12}FNO$: C, 75.88; H, 4.78; N, 5.53. Found: C, 75.65; H, 4.69; N, 5.41.

2-Phenyl-4-phenyl-4-oxobutyronitrile (2g): mp 124.9−125.4 °C (lit.[5b] mp 127 °C); ^{1}H NMR (200 MHz, DMSO-d_6) 3.75 (1H, dd, CHCH_aHCO), 4.0 (1H, dd, CHCH_bHCO), 4.6 (1H, dd, ArCHCH$_2$), 7.3−7.7 (8H, m, ArH), 8.0 (2H, m, ArH).

2-Phenyl-4-(4-methoxyphenyl)-4-oxobutyronitrile (2h): mp 56.3−58.1 °C (lit.[5b] mp 65 °C); ^{1}H NMR (200 MHz, $CDCl_3$) 3.5 (1H, dd, CHCH_aHCO), 3.7 (1H, dd, CHCH_bHCO), 3.9 (3H, s, OMe), 4.6 (1H, t, ArCHCH$_2$), 6.9 (2H, m, ArH), 7.4 (5H, m, ArH), 7.9 (2H, m, ArH). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.78; H, 5.63; N, 5.17.

2-(4-Methoxyphenyl)-4-phenyl-4-oxobutyronitrile (2i): mp 116.6−117.2 °C (lit.[5b] mp 119 °C); ^{1}H NMR (200 MHz, DMSO-d_6) 3.7 (1H, dd, CHCH_aHCO), 3.95 (1H, dd, CHCH_bHCO), 3.75 (3H, s, OMe), 4.1 (1H, m, ArCHCH$_2$), 6.95 (2H, d, ArH), 7.5−7.7 (5H, m, ArH), 8.0 (2H, d, ArH).

2-(4-Methylphenyl)-4-phenyl-4-oxobutyronitrile (2j): mp 135.1−135.7 °C (lit.[5b] mp 137 °C); ^{1}H NMR (200 MHz, DMSO-d_6) 2.3 (3H, s, Me), 3.7 (1H, dd, CHCH_aHCO), 4.0 (1H, dd, CHCH_bHCO), 4.6 (1H, t, ArCHCH$_2$), 7.2 (2H, m, ArH), 7.5 (5H, m, ArH), 8.0 (2H, m, ArH).

2-Phenyl-4-(4-methylphenyl)-4-oxobutyronitrile (2k): mp 75.4−77.5 °C; ^{1}H NMR (200 MHz, DMSO-d_6) 2.4 (3H, s, Me), 3.7 (1H, dd, CHCH_aHCO), 3.95 (1H, dd, CHCH_bHCO), 4.6 (1H, m, ArCHCH$_2$), 7.3−7.6 (7H, m, ArH), 7.9 (2H, d, ArH). Anal. Calcd for $C_{17}H_{15}NO$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.78; H, 5.63; N, 5.17.

2-(4-(Dimethylamino)phenyl)-4-phenyl-4-oxobutyronitrile (2l): mp 102.5−103.6 °C (lit.[5b] mp 103 °C); ^{1}H NMR (200 MHz, DMSO-d_6) 2.85 (6H, s, Me), 3.65 (1H, dd, CHCH_aHCO), 3.9 (1H, dd, CHCH_bHCO), 4.5 (1H, dd, ArCHCH$_2$), 6.7 (2H, d, ArH), 7.3 (2H, d, ArH), 7.4−7.8 (5H, m, ArH), 8.1 (2H, dd, ArH).

2-(Benzo[1,3]dioxol-5-yl)-4-(4-methoxyphenyl)-4-oxobutyronitrile (2m): mp 93.9−94.9 °C; ^{1}H NMR (200 MHz, DMSO-d_6) 3.4 (1H, dd, CHCH_aHCO), 3.6 (1H, dd, CHCH_bHCO), 3.9 (3H, s, OMe), 4.5 (1H, t, ArCHCH$_2$), 5.95 (2H, s, OCH$_2$O), 7.3 (1H, d, ArH), 7.35−7.5 (4H, m, ArH), 7.9 (2H, d, ArH). Anal. Calcd for $C_{18}H_{15}NO_6$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.89; H, 4.70; N, 4.38.

2-(3,4,5-Trimethoxyphenyl)-4-(4-methoxyphenyl)-4-oxobutyronitrile (2n): mp 126.8−127.4 °C; ^{1}H NMR (200 MHz, DMSO-d_6) 3.6 (1H, dd, CHCH_aHCO), 3.7 (3H, s, OMe), 3.83 (6H, s, OMe), 3.9 (3H, s, OMe), 4.0 (1H, dd, CHCH_bHCO), 4.5 (1H, m, ArCHCH$_2$), 6.9 (2H, s, ArH), 7.1 (2H, d, ArH), 8.0 (2H, d, ArH). Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.69; H, 5.97; N, 3.88.

Preparation of 2-(Benzo[1,3]dioxol-5-yl)-4-(4-methoxyphenyl)-4-oxobutyronitrile (2m) on Scale. 3-(Benzo[1,3]dioxol-5-yl)-1-(4-methoxyphenyl)prop-2-en-1-one (9.3 kg, 32.9 mol) was slurried into 32 L of acetone at room temperature. Acetone cyanohydrin (3.5 kg, 41.1 mol) and a 25% aqueous solution of tetramethylammonium hydroxide (0.75 L, 2.08 mol) were added to the slurry. The reaction mixture was heated at reflux for 10 h. The mixture was cooled and 18 L of water added to crystallize the product. The resulting slurry was then cooled to 0−10 °C for at least 3 h. The product was collected by centrifugation and dried at 40−50 °C. The desired product (8.6 kg, 85% theory) was obtained with a purity of 99% by HPLC.

Received for review November 29, 1996.[⊗]

OP960048Q

(8) Lyle, R. E.; Paradis, L. P. *J. Am. Chem. Soc.* **1955**, *77*, 6667.
(9) Kohler, E. P.; Chadwell, H. M. *Organic Syntheses*; Wiley: New York, 1941; Collect. Vol. I, 2nd ed., p 78.

[⊗] Abstract published in *Advance ACS Abstracts*, April 1, 1997.