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Reaction of Carboxylic Acids with Diethyl Phosphorocyanidate; A Novel Synthesis of Homologated α-Hydroxycarboxylic Acids from Carboxylic Acids

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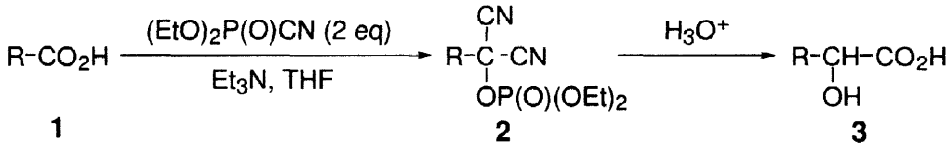
Abstract: Carboxylic acids react with 2 equivalents of diethyl phosphorocyanidate in the presence of triethylamine to give dicyanophosphates in good yields; these dicyanophosphates can be hydrolyzed easily to give homologated α-hydroxycarboxylic acids.
Keywords: carboxylic acids, homologation, hydroxy acids, cyano compounds

We have already demonstrated that diethyl phosphorocyanidate (DEPC, $(EtO)_2P(O)CN$) is a versatile reagent for organic synthesis.[1] In a continuation of our work on the synthetic utility of DEPC, this paper will present a novel method for the synthesis of α-hydroxycarboxylic acids **3**, which are important both in themselves and as synthetic intermediates, *via* dicyanophosphates **2** produced by the reaction of carboxylic acids **1** with 2 equivalents of DEPC in the presence of triethylamine. The overall route presents a conversion of carboxylic acids **1** to α-hydroxycarboxylic acids **3** with one carbon homologation.



1 **2** **3**

We have already reported that, depending on the substrate, the reaction of carboxylic acids with 1 equivalent of DEPC in the presence of triethylamine affords an acyl cyanide dimer, its elimination product, or an acyl phosphate.[2] Except the formation of the acyl phosphates, the obvious intermediates are acyl cyanides. Surprisingly, however, when we extended this reaction and used 2 equivalents of DEPC, the reaction took a different course to give dicyanophosphates **2** in good yields. Representative results are summarized in Table. Although sterically hindered carboxylic acids such as pivalic acid **1c** and 2-substituted benzoic acids **1i**, **1k**, and **1m** require longer reaction times or higher reaction temperature, various aliphatic and aromatic carboxylic acids **1** are effectively converted into dicyanophosphates **2**. The mechanism of this novel reaction is under investigation, but it seems reasonable to suggest initial formation of an acyl cyanide, followed by addition of another molecule of DEPC to the carbonyl group. Obviously, the addition reactivity of DEPC will be much higher than that of acyl cyanides.[3]

In order to study the synthetic utility of dicyanophosphates **2**, we focused on the hydrolysis of **2** to α-hydroxycarboxylic acids **3**. As illustrated in Table, most of the dicyanophosphates **2** can be smoothly hydrolyzed to the corresponding α-hydroxycarboxylic acids **3** upon treatment with concentrated hydrochloric acid at reflux. In the cases of **2e**, **2f**, **2k**, and **2o**, they were very labile under acidic conditions and yielded a complex mixture. Thus, the present method provides a useful synthetic method for conversion of carboxylic acids to one carbon-homologated α-hydroxycarboxylic acids. One well-known and important method for the preparation of α-hydroxycarboxylic acids from compounds with one less carbon is the addition

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of hydrogen cyanide or its equivalents to aldehydes followed by hydrolysis of the resulting cyanohydrins. Our method may be complementary to the cyanohydrin route, but since the starting aldehydes will in general be prepared from carboxylic acids or their derivatives, our method will take fewer steps and be much superior.

Table. Preparation of homologated α-hydroxycarboxylic acids from carboxylic acids

Carboxylic acid		Reaction[a]		Dicyanophosphate		Reaction[c]	α-Hydroxy-carboxylic acid[d]	
No.	R	time (h)	temp (°C)	No.	Yield (%)[b]	time (h)	No.	Yield (%)[b]
1a	*n*-Bu	3	-20	**2a**	72	12	**3a**	96
1b	*i*-Pr	3	0	**2b**	84	14	**3b**	95
1c	*t*-Bu	2	20	**2c**	79	24	**3c**	93
1d	cyclohexyl	3	0	**2d**	77	14	**3d**	96
1e	$PhOCH_2$	4	-40	**2e**	60	2	**3e**	-
1f	(S)-$PhCH_2CHNHFmoc$	3	-20	**2f**	77	6	**3f**	-
1g	$MeSCH_2CH_2$	6	-40	**2g**	73	5	**3g**	85
1h	Ph	3	-20	**2h**	70	12	**3h**	63
1i	2-MeC_6H_4	18	-20	**2i**	68	4	**3i**	25
1j	4-MeC_6H_4	5	-20	**2j**	76	3	**3j**	90
1k	2-$MeOC_6H_4$	21	0	**2k**	80	2	**3k**	-
1l	3-$MeOC_6H_4$	2	-20	**2l**	69	5	**3l**	41
1m	2-ClC_6H_4	12	-20	**2m**	61	35	**3m**	89
1n	4-ClC_6H_4	1	-20	**2n**	65	10	**3n**	92
1o	2-naphthyl	2	-20	**2o**	66	5	**3o**	-

a) Dicyanophosphorylations were carried out by adding DEPC (2.1 eq) and Et_3N (1.05 eq) to a solution of the carboxylic acids in THF. b) Isolated yield after chromatographic purification. c) Hydrolyses of the dicyanophosphates were performed by heating to reflux with c. HCl. d) All α-hydroxycarboxylic acids were identified by mp, IR, and ^1H NMR spectra.

A representative experimental procedure is as follows: To a stirred solution of *n*-valeric acid **1a** (218 μL, 2.0 mmol) and DEPC (93%, 685 μL, 4.2 mmol) in THF (4 mL) was added triethylamine (293 μL, 2.1 mmol) at -20 ℃. After being stirred at -20 ℃ for 3 h, the mixture was diluted with ether (30 mL) and washed with water (2 x 20 mL). Drying over $MgSO_4$, evaporation of the solvents, followed by purification by silica gel column chromatography with ethyl acetate/hexane (1:3) as eluant afforded dicyanophosphate **2a** (395 mg, 72%).[4] A mixture of dicyanophosphate **2a** (395 mg, 1.4 mmol) and HCl (35%, 5.8 mL) was heated at reflux for 12 h. The reaction mixture was cooled, then extracted with ether (3 x 20 mL), and the extracts were dried over $MgSO_4$. Evaporation of the solvents and then purification by silica gel column chromatography with THF/hexane (1:2) as eluant gave 2-hydroxycaproic acid **3a** (183 mg, 96%).

In conclusion, our method using dicyanophosphates as intermediates offers a simple and convenient preparation of α-hydroxycarboxylic acids from carboxylic acids with one less carbon. An investigation of more favorable conditions of hydrolysis as well as the reaction's scope and limitation is in progress.

References and Notes

1. (a) Shioiri, T. *J. Synth. Org. Chem.* Japan **1979**, *37*, 856. (b) Patel, H. H. in *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A. Ed.; John Wiley & Sons, Chichester, **1995**, Vol. 3, 1851-1854.
2. Shioiri, Y.; Yokoyama, Y.; Kasai, Y.; Yamada, S. *Tetrahedron* **1976**, *32*, 2211 and 2854 (corrigendum).
3. For a review on acyl cyanides, see Hünig, S.; Schaller, R. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 36.
4. Data for **2a**: IR (neat) 2965, 2250, 1284, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.99 (3H, t, *J* = 7.6 Hz), 1.42 (6H, td, *J* = 7.2, 0.8 Hz), 1.47 (2H, ddq, *J* = 7.6, 7.6, 7.6 Hz), 1.64-1.71 (2H, m), 2.31-2.35 (2H, m), 4.21-4.34 (4H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.3, 15.7, 21.4, 25.3, 40.2, 64.8, 65.5, 112.2; HRMS (EI) calcd for $C_{11}H_{18}N_2O_4P$ [$(M-H)^+$] 273.1004, found 273.0998.