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Cyanide Ion Promoted Addition of Acyl Phosphonates to Ethyl Cyanoformate: Synthesis of Tertiary Carbinols via Tandem Carbon−Carbon Bond Formations

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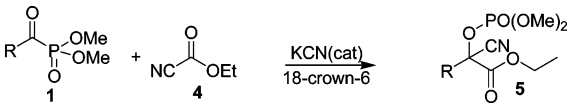

New cyanation/phosphonate−phosphate rearrangement/*C*-acylation reactions of cyanophosphate anion with cyanoformate esters are described. Phase-transfer cocatalysts facilitate cyanide-catalyzed reactions between acyl phosphonates and cyanoformates to afford protected tertiary carbinol products in good to excellent yields (74−95%). Ethyl cyanoformate is used as a cyanide source and electrophile. The scope of the reaction was investigated by using a number of benzoyl and acyl phosphonates along with ethyl cyanoformate. Representative chemoselective reduction of the product **5a** afforded ethyl 3-amino-2-hydroxy-2-phenylpropanoate (**13**) in good yield.

The synthesis of cyanohydrins has gained much attention due to the importance of cyanohydrins as a synthetic building block for a variety of pharmaceutically desirable compounds.[1] In fact, these compounds have a dense functionality, the transformations of which provide easy access to many other valuable functional groups. Therefore, a plethora of methods has been devised for the synthesis of these targets in a racemic and an enantioselective manner. The typical method for their synthesis is the addition of a cyanide source, in various forms, to the corresponding carbonyl compounds in a single C−C bond-forming event

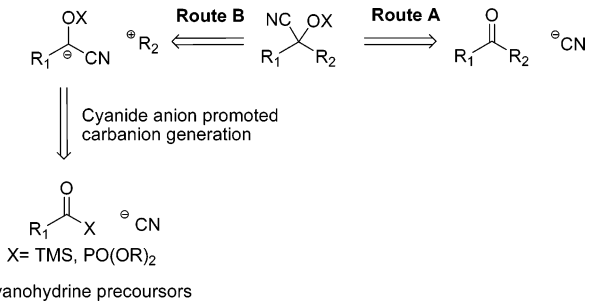

FIGURE 1. Synthesis of cyanohydrine with quaternary carbon center.

(Figure 1, route A). The source of cyanide, furthermore, determines the type of protecting group on the hydroxyl functionality, which is, most of the time, crucial for the sake of subsequent transformations. Although this approach has been widely investigated,[1] other promising methods include a three-component domino reaction that utilizes a cyanide source,[2] carbanion precursors, and an electrophile (Figure 1, route B). It is in this way that two sequential C−C bond formations take place via a cyanide ion promoted carbanion generation from a carbanion precursor and its subsequent reaction with the electrophilic carbon center. This sequence of reactions has an obvious advantage over the traditional approach for the synthesis of cyanohydrins with quaternary carbon centers.

The viability of an approach based on the use of acyl anions obviously depends on the availability of these valuable entities. Acyl anions are available though polarity reversal (umpolung) of the carbonyl compounds and adds a dimension of flexibility to a synthetic design.[3] Although acyl anion equivalents were traditionally obtained by functional group manipulation and the stoichiometric strong base deprotonation of the corresponding carbonyl compounds, recently impressive progress has been made in the catalytic methods for the generation of these useful entities.[4] From this end, the nucleophile-promoted Brook rearrangement of acylsilanes has been introduced as a powerful and useful way of generating acyl anion equivalents in a variety of C−C bond-forming reactions.[2c−f,5] Recently, Johnson's group and then our group introduced acyl phosphonates **1** as acyl anion precursors based on a nucleophile-promoted phosphonate−phosphate rearrangement in the regioselective synthesis of cross-benzoin products **3**.[6] In this transformation, the addition of cyanide anion to acyl phosphonates **1** forms the intermediate alkoxide **2a** that rearranges to the critical acyl anion intermediate

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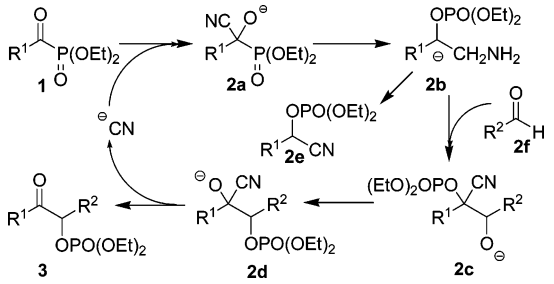
SCHEME 1



SCHEME 2

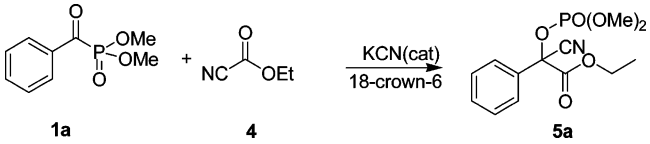
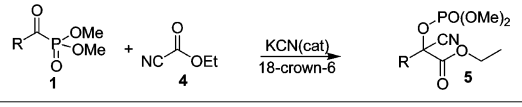


TABLE 1. Addition of 1a to Ethyl Cyanoformate in Various Solvents

entry	solvent	yield (%) (KCN)	yield (%) (KCN−18-crown-6)
1	Et_2O	<5	75
2	THF	<5	91
3	toluene		88
4	DMF	56	82
6	$CHCl_3$		68
7	CH_3CN	<5	79

2b, which in turn reacts with the electrophile **2f** to provide the product **3** in a similar fashion as the well-known benzoin reaction. Therefore, the critical acyl anion equivalents are available from acyl phosphonates **1**. Unlike the similar reagent acylsilanes, acyl phosphonates are readily available on a multigram scale from acyl chlorides and trialkyl phosphites via an Arbuzov reaction without needing any special condition or apparatus. This apparently makes them more advantageous in terms of practical issues. Furthermore, it is a highly intriguing question as to whether acyl phosphonates can be utilized in a sequence of reactions as depicted in Scheme 1 for the generation of carbanion and their consequent reactions with carbon electrophiles as a generalized strategy for the synthesis of quaternary cyanohydrins. Similar work on acylsilanes was performed by Johnson et al.[2d−f,m] We report our initial results herein toward the investigation of this goal by utilizing alkyl cyanoformates as a cyanide source and electrophile.

TABLE 2. Addition of Acyl Phosphonates 1 to Ethyl Cyanofomate



Entry	Acyl phosphonate 1	Product 5	Yield (%)
1	**a**	**a**[a]	91
2	**b**	**b**[a]	86
3	**c**	**c**[a]	88
4	**d**	**d**[a]	95
5	**e**	**e**[a]	90
6	**f**	**f**	90
7	**g**	**g**[a]	90
8	**h**	**h**	90
9	**i**	**i**	87
10	**j**	**j**	75
11	**k**	**k**	74
12	**l**	**l**	90

[a] The compounds are nearly pure after workup. No further purification is needed.

For the investigation of the reaction of the ethyl cyanoformate **4** with acyl phosphonates **1**, we planned to gain direct and uncatalyzed access to ethoxycarbonylcyanophosphate **5** by using ethyl cyanoformate **4** as a cyanide source and an electro-

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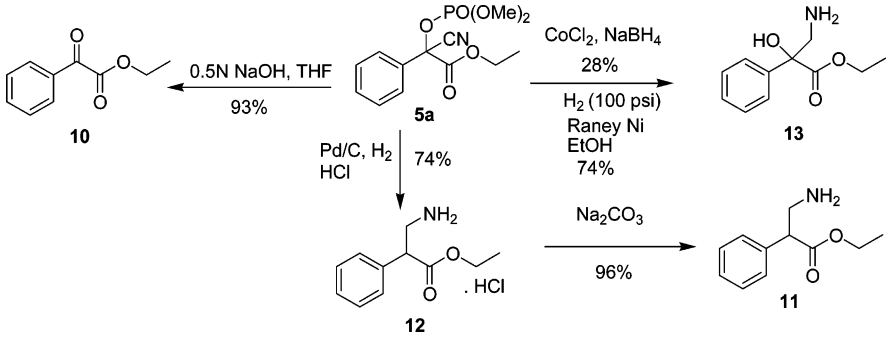
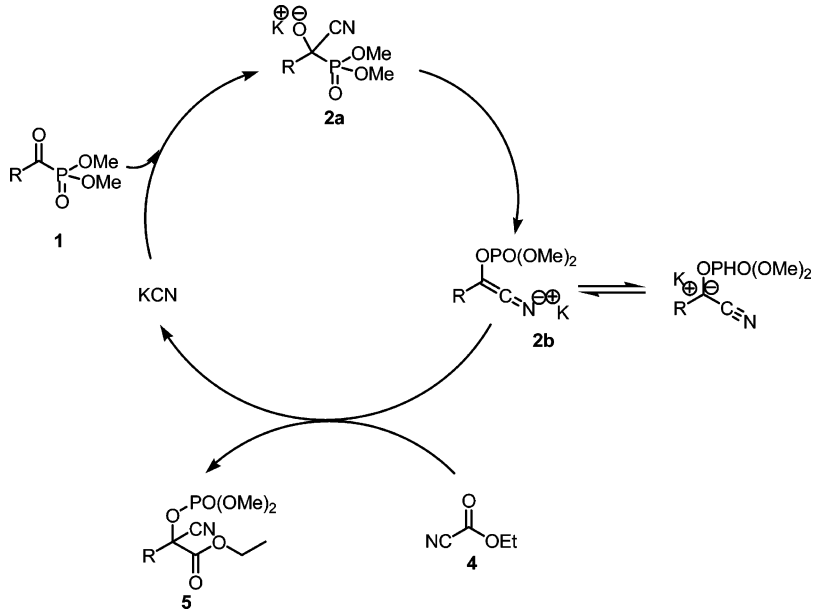
SCHEME 3



SCHEME 4



phile.[2] Moreover, we hoped that the **4** could supply a catalytic amount of cyanide ion by decomposition in order to provide cyanohydrine, which can subsequently start the reaction. The formation of cyanohydrine, via phosphonate-phosphate rearrangement, and followed by C-acylation should in turn form tertiary carbinol.

In an initial reaction, which is shown in Scheme 2, benzoylphosphonate **1a** was reacted with ethyl cyanoformate **4** at ambient temperature in ether and monitored by TLC, in which no product formation was observed. However, in the presence of catalytic quantities of KCN, benzoylphosphonate **1a** reacted slowly with ethyl cyanoformate in Et_2O to afford the desired acylation product **5a** in a very low yield. The reaction was repeated with various solvents, and as shown in Table 1, only DMF gave a satisfactory yield. The limited solubility of the KCN in the medium could have hindered the reactivity.

According to Johnson's work,[2d−f] the phase-transfer catalysts were employed in order to increase the concentration of cyanide ion in solution. The 18-crown-6 proved to be optimal for attaining a better solubility of KCN.[7]

As shown in Scheme 2, the reaction of **1a** with a catalytic amount of KCN/18-crown-6 in ether at ambient temperature was studied. The highest yield (75%) was obtained in a short reaction period (20 min monitoring of the reaction by TLC).

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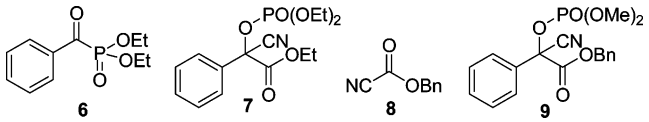
Different solvents are employed for the addition reaction, and as shown in Table 1, the highest yield is obtained by using THF (91%). The substrate scope was further investigated in the context of cyanoformate and phosphonate ester structures. For this, ethyl phosphonate **6** was used and the product **7** was obtained in 90% yield. The use of benzyl cyanoformate **8** in place of ethyl cyanoformate with **1a** furnished **9** in comparable yield (88%).



With the efficient catalyst system 18-crown-6 and KCN in THF, the reaction scope was studied using a variety of acyl phosphonates. In general, benzoyl and acyl phosphonates gave good to excellent yields (74−95%, Table 2). In all cases, the reaction takes 15−20 min. The change of the color of the reaction mixture to red is a good indicator for stopping the reaction as a prolonged reaction time causes the decomposition of the product. In many cases the crude product is so pure that further purification is not essential.

Under the given conditions, the competing proton abstraction product,[6c] the cyanohydrin *O*-phosphate **2e**, was also formed

(**5i**, **5j**, **5k**; 3−4%), which was separable from the desired product by chromatography.[6d]

Benzoylphosphonates with the electron-withdrawing and electron-donating groups attached to the phenyl ring affected the yield slightly as shown in Table 2.

As shown in Scheme 3, **5a** is converted into α-keto ester **10** by using 0.5 N NaOH in THF.[8] Interesting conversion of **5a** is carried out to the corresponding amino ester **11** either by using Pd/C, H_2, HCl, then Na_2CO_3 in good yield,[9] or $CoCl_2$, $NaBH_4$ in moderate yield.[2d−f]

By using ethyl cyanoformates as a cyanide source and electrophile, a new cyanide ion promoted cyanation/phosphate−phosphonate rearrangement/C-acylation sequence was developed that results in the efficient formation of polyfunctionalized unsymmetrical malonic acid derivatives.

In this transformation, the addition of cyanide anion to acyl phosphonates **1** forms the intermediate alkoxide **2a**, which rearranges to the carbanion **2b** that in turn reacts with the ethyl cyanoformate **4** in order to provide the product **5**. The proposed catalytic cycle is outlined in Scheme 4.

In conclusion, we developed a convenient, one-pot procedure for preparing various polyfunctionalized tertiary carbinol with the concomitant formation of two new carbon−carbon bonds starting from readily available acyl phosphonates and ethyl cyanoformate under very mild conditions in good to excellent yields (74−95%). Phase-transfer cocatalysts and cyanide ions have been used successfully in the formation of cyanohydrine. The general applicability of the reaction with a range of acyl phosphonate and ethyl cyanoformate has been demonstrated. Representative chemoselective reduction of the product **5a** afforded ethyl 3-amino-2-hydroxy-2-phenylpropanoate (**13**) in good yield.

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Experimental Section

General Procedure. An oven-dried Schlenk flask with a magnetic stir bar was charged with 0.5 mmol of acyl phosphonate. Subsequently, 1 mL of dry THF, 0.6 mmol of ethyl cyanoformate, 0.025 mmol of 18-crown-6, and 2 mg of KCN was added under argon. The reaction was monitored by TLC (completed within 15−20 min). After the completion of the reaction, the reaction was extracted with ether, and the organic layer was washed with brine three times. The organic phases were combined and concentrated under reduced vacuum. If needed, the crude product was purified with automatic flash column chromatography using ether−petroleum ether as eluent.

(Ethoxycarbonyl)(cyano)(phenyl)methyl dimethyl phosphate (5a): yield 142 mg (91%); yellow liquid; IR (neat) $\nu = 2963, 1769, 1255, 1042$ cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.21 (3H, t, $J = 7.3$ Hz), 3.79 (3H, d, $J = 11.5$ Hz), 3.88 (3H, d, $J = 11.5$ Hz), 4.20−4.30 (2H, m), 7.37−7.41 (3H, m), 7.62−7.64 (2H,m); ^{13}C NMR ($CDCl_3$) δ 12.6, 54.0 (d, $J = 5.5$ Hz), 54.3 (d, $J = 5.5$ Hz), 63.3, 76.7 (d, $J = 6.3$ Hz), 115.3, 124.6, 128.0, 129.6, 131.6 (d, $J = 9.6$ Hz), 163.3 (d, $J = 2.3$ Hz); ^{31}P NMR ($CDCl_3$) δ −1.64. Anal. Calcd for $C_{13}H_{16}NO_6P$: C, 49.85; H, 5.15; N, 4.47. Found: C, 49.66; H, 5.35; N, 4.78.

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Supporting Information Available: Experimental procedures and characterization data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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