Cyanide-Catalyzed Additions of Acyl Phosphonates to Aldehydes: A New Acyl Donor for Benzoin-Type Reactions

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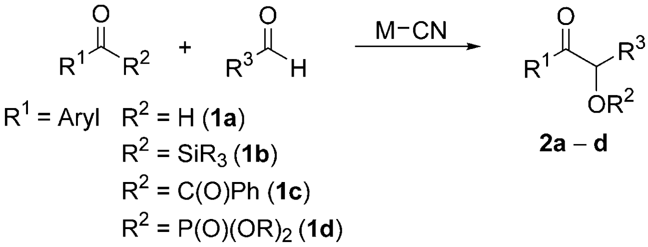
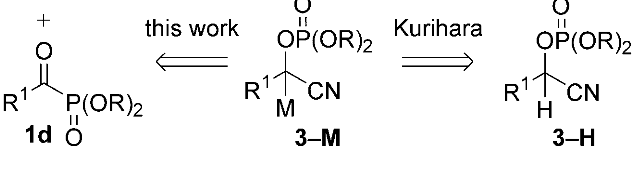
Abstract: Acyl phosphonates have been utilized as new acyl donors for cyanide-catalyzed benzoin-type reactions. Cyanation of acyl phosphonates, followed by a [1,2]-phosphoryl migration generates the active acyl anion intermediate. The presumed (cyano)phosphate anion reacts with a variety of aryl aldehydes to yield phosphate ester-protected, unsymmetrical benzoins in good to excellent yields. The unsymmetrical benzoin product can be obtained after deprotection of the phosphate ester with an aqueous amine solution.

Keywords: benzoin condensation; cyanide catalysis; ketones; phosphate ester; rearrangement; umpolung

The cyanide-catalyzed benzoin reaction is an expeditious route to α-hydroxy ketones [Eq. (1), $R^2 = H$]. The reaction proceeds *via* a catalytically-generated (hydroxy)nitrile anion that functions as an acyl anion equivalent.[1] Regioselectivity issues in the catalytic process have been addressed through the application of stoichiometrically-generated acyl anion equivalents. Metalated dithioacetals,[2] (silyloxy)nitriles[3] and (cyano)-phosphates[4] are representative stoichiometrically-generated acyl anion equivalents employed to synthesize unsymmetrical benzoin products. While effective, these routes are not without attendant efficiency considerations: added steps in making the starting materials, stoichiometric reagents, and in the case of the dithiane chemistry, deprotection with Hg(II). As part of a continuing effort to uncover new strategies for polarity reversal catalysis, this communication documents our progress in the development of acyl phosphonates (**1d**) as acyl donors for a new cyanide-catalyzed benzoin-type reaction with aldehydes [Eq. (1)].



(1)



Scheme 1. Access to (cyano)phosphate anions.

Our ongoing interest in acyl anion catalysis led us to consider the viability of alternative acyl donors in conjunction with nucleophilic catalysts.[5,6] A seminal report by Schowen demonstrated that benzil [**1c**, Eq. (1)] could be utilized as an acyl donor in benzoin-type reactions.[7] Later work from Demir and Reis expanded upon that initial report, showing the application of the reaction to a broader range of aromatic diketone and aldehyde reaction partners.[8] Considering the [1,2]-acyl migration implicit in these reactions, we viewed with some interest a report by Kurihara and co-workers describing cyanophosphate anions as effective nucleophilic partners with aldehyde electrophiles (**3-M**, Scheme 1).[4] It occurred to us that **3-M** could be generated from an acyl phosphonate (**1d**) *via* [1,2]-phosphoryl migration.[9,10] Pending carbonyl addition, phosphoryl transfer, and retrocyanation, a complete catalytic cycle could be envisioned.

The projected application was not without practical merit. Acyl phosphonates are easily synthesized and purified in one step *via* the Michaelis–Arbuzov reaction of acyl chlorides and trialkyl phosphites.[11] The phosphate ester-protected benzoin products that would result from a phospha-benzoin reaction also have documented utility as benign instruments of inorganic phosphate photorelease.[12,13]

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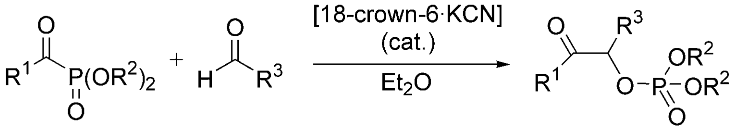
Preliminary results revealed that cyanide successfully catalyzed acyl phosphonate addition to aldehydes (Table 1). The conditions for the cross-silyl benzoin and the benzil addition were attempted and modified, with the [18-crown-6/KCN] complex[14] in diethyl ether providing the optimal catalyst/solvent combination. Reaction times ranged from 20–60 min at 0–25 °C. The use of KCN in DMF was successful, but led to concurrent regioisomerization of the unsymmetrical benzoin product. Reactivity decreased with alternative phase-transfer catalysts such as Bu_4NBr and Bu_4PBr; poorer conversion was also observed in THF and toluene. The conditions were further simplified with the use of undried, unpurified diethyl ether, without the need of an inert atmosphere.

With the optimum catalytic conditions identified, the scope of the reaction was explored (Table 1). The reaction works well with benzoyl diethylphosphonate and a variety of aryl aldehydes (entries 1–5). Reactivity was diminished considerably when an electron-poor acyl phosphonate was employed (entry 6). The catalyst loading was increased to 15 mol % at ambient temperature, but slight regioisomerization occurs before complete consumption of the starting material. (Cyano)-phosphate **3-H** is also observed. Electron-rich acyl phosphonates give good yields with 10 mol % catalyst at ambient temperatures. Heteroaromatic aldehydes can be utilized, giving moderate yields with 15 mol % catalyst loading at 0 °C.

Table 1. Cyanide-catalyzed phospha-benzoin reactions.[a]



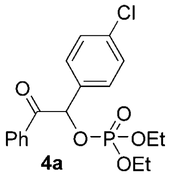
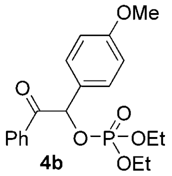
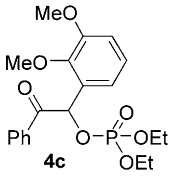
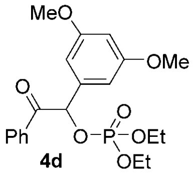
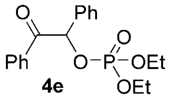
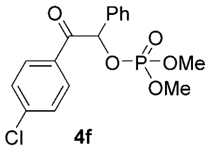
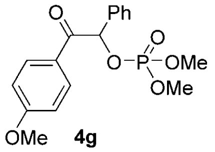
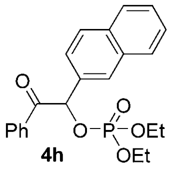
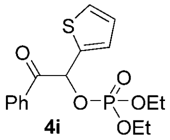
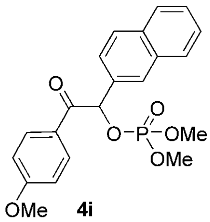
Entry	R^1/R^2	R^3	Product	Yield [%][b]
1	Ph/Et	4-ClC_6H_4	 **4a**	80
2	Ph/Et	4-$MeOC_6H_4$	 **4b**	85
3	Ph/Et	2,3-$(MeO)_2C_6H_3$	 **4c**	88
4	Ph/Et	3,5-$(MeO)_2C_6H_3$	 **4d**	93
5	Ph/Et	Ph	 **4e**	88
6	4-ClC_6H_4/Me	Ph	 **4f**	54

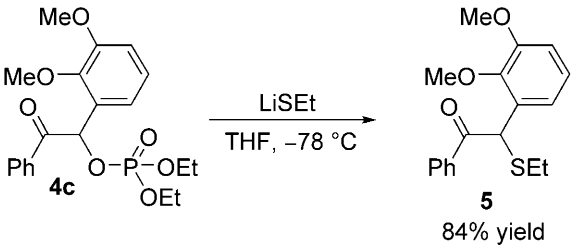
Table 1 (cont.)

Entry	R^1/R^2	R^3	Product	Yield [%][b]
7	$4\text{-}MeOC_6H_4/Me$	Ph	 **4g**	88
8	Ph/Et	2-napthyl	 **4h**	75
9	Ph/Et	2-thienyl	 **4i**	56
10	$4\text{-}MeOC_6H_4/Me$	$4\text{-}MeC_6H_4$	 **4i**	90

[a] $R^1C(O)PO(OR^2)_2$ (1.0 equiv.), R^3CHO (1.1 equivs.), KCN/18-crown-6 (0.10–0.15 equivs.) in Et_2O at 0 to 23 °C.
[b] Yield of isolated, analytically pure material.

The main obstacle encountered with this reaction is the propensity for regioisomerization if the product is left in the presence of KCN long past consumption of the acyl phosphonate. For most combinations of aryl acyl phosphonates and aryl aldehdyes, the standard conditions of 10 mol % catalyst at ambient temperature are sufficient, but in some cases the temperature needs to be decreased or the catalyst loading increased. The reaction is not tolerant of alkyl acyl phosphonates, as only undefined decomposition is observed. Aryl acyl phosphonates do give desired products with aliphatic aldehydes, but only minimal reactivity is achieved, even with electron-rich acyl phosphonates. Advantages of using acyl phosphonates are the ease of starting material synthesis, the ability to use unpurified, undried solvent, and the fact that an inert atmosphere is not required. The only by-product is **3-H**, which presumably occurs from protonation of **3-M**; however, it is formed in minimal quantities and can be easily separated by flash chromatography. In cases where slight regioisomerization occurs, the isomers are separable by flash chromatography, which allows for isolation of the desired product.

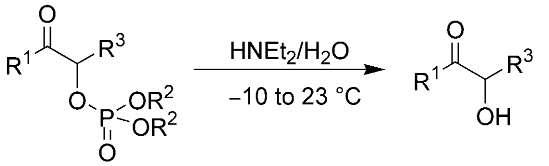
Preliminary observations indicate that the phosphate-protected benzoin can directly participate in S_N reactions. The reaction of phosphate **4c** with lithium ethanethiolate cleanly gives the derived thioether **5** in 84% yield [Eq. (2)].

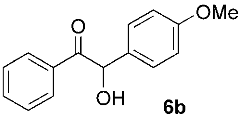
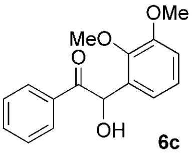
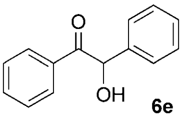


(2)

We evaluated a number of reaction conditions with the intent of developing an efficient deprotection protocol to reveal the α-hydroxy ketone products. The (keto)-phosphates were remarkably stable in aqueous acid: even at elevated temperatures only starting material was recovered. Attempts with simple basic conditions (e.g., K_2CO_3/MeOH or NaOH/MeOH) gave the desired benzoin product, but with competing oxidation to the diketone. The same reactions were attempted with degassed water under an inert atmosphere; these conditions afforded the desired benzoin product and its regioisomer in varying amounts. We ultimately found that an aqueous amine solution will cleave the phos-

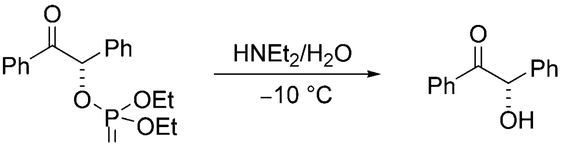
Table 2. Deprotection of (keto)phosphates.



Entry	Product	Yield [%]
1	 **6b**	64
2	 **6c**	56
3	 **6e**	74

phate ester and reveal the desired α-hydroxy ketone.[15] Optimal conditions entail the treatment of the phosphate with distilled diethylamine in degassed water. The results of the deprotection studies are summarized in Table 2.

As a prerequisite for any future asymmetric variant of the title process, it was important to determine whether the deprotection conditions would compromise the stereochemical integrity of an enantioenriched benzoin [Eq. (3)].



4e 82% ee

6e 70% ee 75% yield (3)

To perform the analysis, an enantioenriched benzoin was synthesized using reported methods,[16] yielding (*S*)-**6e** with an enantiomeric excess of 82%. This hydroxy ketone was protected with diethyl chlorophosphate and pyridine, furnishing the phosphate-protected benzoin in 82% ee. Deprotection of the phosphate ester using a 9:1 diethylamine/water solution at −10 °C gives the free benzoin **6e** in 75% yield and 70% ee after 1 h. We therefore conclude that it is possible to largely retain the stereochemical integrity of the α-stereocenter under these conditions. Efforts are ongoing to reduce the stereochemical loss in this reaction to zero.

A new benzoin-type reaction has been discovered using acyl phosphonates as the acyl anion precursor. The reaction gives moderate to excellent yields for aryl-aryl′ couplings of acyl phosphonates and aldehydes. These products can be deprotected using an aqueous amine solution to give the free unsymmetrical benzoins.

Experimental Section

General Procedure for the Preparation of Acyl Phosphonates

Acyl phosphonates were prepared by the literature method.[11] A flame-dried, 25-mL round-bottomed flask with a magnetic stir bar and addition funnel was charged with 51.7 mmol of acyl chloride under argon. The addition funnel was charged with 51.7 mmol of trialkyl phosphite which was added dropwise at a rate such that the temperature did not exceed 40 °C. After 30 min, the product was purified by vacuum distillation.

2-Diethylphosphoryloxy-2-(4-methoxyphenyl)-1-phenylethanone (4b); Representative Procedure for the Addition of Acyl Phosphonates to Aldehydes

A 25-mL, round-bottomed flask with a magnetic stir bar was charged with benzoyl diethylphosphonate (0.41 mmol, 1.0 equiv.) and 4-methoxybenzaldehyde (0.45 mmol, 1.1 equivs.). Et_2O (2 mL) was added to make a 0.2 M solution, followed by [18-crown-6-KCN] (0.041 mmol).[14] After 30 min at 23 °C, Et_2O (10 mL) was added and the organic layer was washed twice with H_2O (10 mL). The organic extracts were dried ($MgSO_4$), filtered, and the solvent was removed with a rotary evaporator. The product was purified by flash chromatography with 40% EtOAc/hexanes to afford the product as a cloudy oil; yield: 132.8 mg (85%). Spectral data correspond to those previously reported.[4] Analytical data for the title compound: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.91$ (d, 2H, $J = 8.0$ Hz), 7.49 (t, 1H, $J = 7.6$ Hz), 6.87 (d, 2H, $J = 8.8$ Hz), 6.63 (d, 1H, $J = 8$ Hz), 4.24–4.14 (m, 2H), 3.96–3.86 (m, 2H), 3.77 (s, 3H), 1.33 (t, 3H, $J = 7.6$ Hz), 1.16 (t, 3H, $J = 7.2$ Hz).

Acknowledgements

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