JOC Note

Catalytic Intermolecular Aldehyde−Ketone Coupling via Acyl Phosphonates

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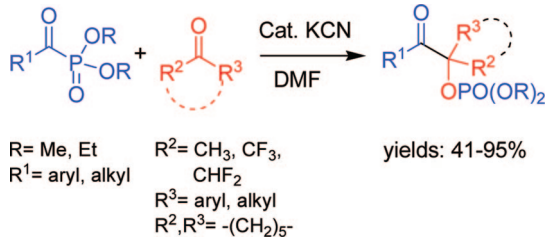
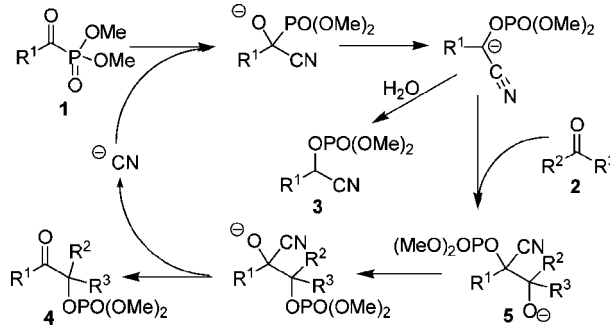
Received December 4, 2008



The first catalytic intermolecular aldehyde−ketone coupling via acyl phosphonate is reported. Acyl phosphonates are potent acyl anion precursors, which generate acyl anion equivalents under the influence of cyanide anion via phosphonate−phosphate rearrangement. These anions readily react with activated ketones to form acyloin type coupling in 41−95% yields.

Polarity reversal (umpolung) of the carbonyl group (acyl anion equivalents) provides a powerful alternative to traditional carbon−carbon bond construction methods and adds new dimensions of flexibility to the design of synthetic targets.[1] Recently, impressive progress has been made in the catalytic generation of acyl anion equivalents, especially in benzoin[2] and Stetter[3] reactions. As far as the cross-benzoin and intramolecular Stetter reactions are concerned, the use of acylsilanes[4,5] as acyl anion precursors based on the nucleophile-promoted Brook rearrangement[6] were the most practical and selective methods available. Acyl phosphonates are comparably useful entities as acyl anion equivalents within a cross-benzoin reaction with certain advantages, including ease of preparation from carboxylic acids or aldehydes, as well as their stability and reactivity under a variety of conditions.[7] These aspects make acyl phosphonates highly promising reagents as acyl anion equivalents. The mode of acyl anion generation from acyl phosphonates is similar to that of acylsilanes[4a] (Scheme 1). Therefore, acylphosphonates **1** react with cyanide anion to generate an acyl anion equivalent, which reacts with the electrophile **2** ($R^3 = H$) to afford the corresponding acyloin **4**.

SCHEME 1. Mechanism of Cross-Acyloin Formation via Cyanide Ion Promoted Generation of Acyl Anions from Acylphosphonates



Reactions of acylanion equivalents with ketone as an acceptor to perform aldehyde−ketone acyloin are relatively underdeveloped compared to aldehyde−aldehyde reactions due to the lower reactivity of ketones and their enolizable nature. Although successful intramolecular coupling of aldehydes and ketones under nucleophilic carbene catalysis has been reported,[8] corresponding intermolecular catalytic couplings are still in their infancy.

We proposed the idea of using acyl phosphonates in the cross coupling of aldehyde with activated ketone in the presence of a catalytic amount of cyanide ion. The mechanism of a proposed catalytic cycle has common steps with cross-benzoin reactions that are mediated with acylsilanes,[4a] benzils,[3g] and acyl phosphonates.[7] The generated acyl anion is promoted by the rearrangement of acyl phosphonates **1** in the presence of cyanide ion and in turn reacts with ketones **2** to afford intermediate **5**. The intermediate undergoes a 1,4-phosphate migration producing the protected acyloins **4**.

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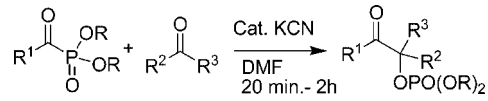
10.1021/jo8026627 CCC: $40.75 © 2009 American Chemical Society
Published on Web 02/04/2009

TABLE 1. Synthesis of Acyloins from Acyl Phosphonates and Ketones



Ent	Phosphonate	Ketone	Product	Yield[a] (%)	Ent	Phosphonate	Ketone	Product	Yield[a] (%)
1	**1a**	**2a**	**4a**	87	10	**1a**	**2d**	**4j**	95
2	**1b**	**2a**	**4b**	95	11[c]	**1j**	**2e**	**4k**	41
3	**1c**	**2a**	**4c**	79	12[d]	**1i**	**2f**	**4l**	54
4	**1d**	**2a**	**4d**	87	13[e]	**1k**	**2d**	**4m**	82
5	**1e**	**2a**	**4e**	83	14[e]	**1k**	**2a**	**4n**	78
6	**1f**	**2a**	**4f**	59	15[e]	**1k**	**2b**	**4o**	72
7	**1g**	**2a**	**4g**	61	16[c]	**1l**	**2b**	**4p**	63
8	**1h**	**2b**	**4h**	83	17[c]	**1m**	**2b**	**4q**	60
9[b]	**1i**	**2c**	**4i**	78					

[a] Isolated yields. [b] THF was used as a solvent. [c] 10% mol of $Cu(OTf)_2$ was used and the reaction was performed at 50 °C. [d] THF was used as a solvent, and 20 mol % of (3,5-bistrifluoromethylphenyl)thiourea was used as an additive. [e] The reaction was performed in toluene at 80 °C.

To investigate the feasibility of the method, we chose benzoylphosphonate (**1a**) and 2,2,2-trifluoroacetophenone (**2a**) as model substrates. The mixture of **1a** and **2a** was treated with (20%) KCN in various dry solvents (dichloromethane (DCM), hexane, toluene, THF, DMF) at room temperature and monitored with TLC. The reaction proceeded in DMF smoothly to form protected acyloin **4a** in 30 min. By using other solvents (hexane, toluene, THF, and DCM), the reaction furnished no product, only starting materials were obtained.

As shown in Table 1, various benzoylphosphonates were reacted with **2a** in DMF and the products are obtained in high yield (Table 1, entries 1−6). Reactions with sterically hindered ortho-substituted acyl phosphonates did not react to form the desired product, in which only the unchanged starting materials were isolated (*o*-BrC_6H_4, *o*-$CH_3C_6H_4$, *o*-$MeOC_6H_4$). The reaction was repeated under various conditions without success. The product formation was only observed with the less sterically hindered *o*-fluoro derivative. The acyl phosphonate **1f** furnished the desired product **4f** in 59% yield (entry 6). The change of ester functionality from ethyl to methyl does not change the yield of the reaction (entries 6 and 7).

We observed that the increase of nucleophilicity of acyl anion that was generated from acyl phosphonates furnished the products in shorter reaction time (in 20−30 min) and higher yields. For example, the reaction of 4-F-benzoylphosphanate (**1c**), benzoylphosponate (**1a**), and 4-MeO-benzoylphosphanate (**1b**) with **2a** in turn provided the products in 79%, 82%, and 95% yields, respectively (entries 1, 2, and 3).

Activation of acetophenone from the phenyl ring by introducing the trifluoromethyl group in turn provided the corresponding acyloin in good yield. For example, taking 3-trifluoromethylacetophenone (**2c**) as an acceptor ketone with acyl phosphonate **1i** under the standard conditions furnished the product **4i** in 78% yield (entry 9). This method can also be used for the coupling of heteroaromatic phosphonates such as **1e** with ketone **2a** (entry 5). In all of the cases, increasing the catalyst load resulted in a slightly higher reaction rate.

For proving the effect of the electropositive nature of the ketones, 3′-fluoro-2,2,2-trifluoroacetophenone **2d** and **2a** are reacted with **1a**. The reaction with **2d** in DMF works faster and in higher yield (95%) with respect to the reactions with **2a** (85%) (entries 1 and 10).

The coupling of enolizable aldehydes and ketones in acyloin reactions is always problematic. This is obvious from a few reactions that utilize aliphatic aldehydes in acyl anion chemistry. In our initial investigation we chose **1a** and commercially available 1,1,1-trifluorobutan-2-one (**2e**) as model substrates for aldehyde/ketone cross-acyloin coupling. To perform the coupling reaction, **1j** and **2e** were reacted in various solvents (hexane, diethylether, DCM, THF, and DMF) at room temperature. The addition of a phase transfer catalyst such as 18-crown-6, Bu_4NBr, and the application of the TMS + CsF system[7a] did not give the coupling reaction. Finally, when **1j** in DMF was treated with **2e** in the presence of $Cu(OTf)_2$, the desired product **4k** was isolated in 7% yield. Carrying out the same reaction in DMF and increasing the reaction temperature to 50 °C gave the product **4k** in 41% yield (entry 11).

We tried acetophenone as a substrate without and with additives (Lewis and Bronsted acids) without success. Next, we chose cyclohexanone as an acceptor. Our initial attempt to activate cyclohexanone was executed by using Lewis acid-like $LiClO_4$ and metal triflates. Lewis acid activation in different solvents (hexane, THF, DCM, toluene, DMF) did not furnish the product, only unreacted starting materials were isolated. The use of thiourea derivative (3,5-bistrifluoromethylphenyl)thiourea to activate cyclohexanone in dry THF in the presence of 18-crown-6 as a catalyst at ambient temperature furnished acyloin **4*l*** in 54% yield (entry 12).

Fortunately, we can obtain aliphatic acyl phosphonates with **2a** and **2b** in tolune in the presence of 18-crown-6 at 80 °C (entries 13−17). Enolizable phosphonates **1*l*** and **1m** each provided with **2a** two nonseparable products that are identified as accepted trifluoromethyl (data not shown) and difluoromethyl acyloins **4p** and **4q** (entries 16 and 17). For the formation of these compounds, we suggest that during the reaction, 2,2-difluoroacetophenone (**2b**) is formed first and then reacted with acyl anion to form the products **4p** and **4q** (the proposed mechanism is depicted in the Supporting Information).

The *O*-protected acyloins can be easily deproctected to acyloins according to the procedures described in the literature.[7b]

In summary, the first catalytic intermolecular aldehyde−ketone coupling via acyl phosphonate is described. The cyanide ion-catalyzed formation of acyl anion from acyl phosphonates and the reaction of this anion with activated ketones furnished aldehyde−ketone coupling products in 41−95% yields. The cross-acyloin reaction is dependent on the electropositive nature of the acceptor molecule and electronegative nature of an acyl anion. A more detailed study concerning the activation of ketones for an acyloin reaction is currently under investigation.

Experimental Section

General Procedure for Aromatic−Aromatic Acyl Phosphonate/Ketone Coupling. To a solution of 1 mmol of acyl phosphonate in 2 mL of dry DMF were added 1.1 mmol of ketone (2,2,2-trifluoroacetophenone) and 10 mol % of KCN. The reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was diluted by 10 mL of ether and water. The organic phase was separated and the aqueous phase was extracted with 10 mL of ether three times. The combined organic phase was extracted with a brine solution, separated, and dried over $MgSO_4$. The organic phase was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel by using ether or ether/petroleum ether as an eluent.

Diethyl 3,3,3-trifluoro-1-oxo-1,2-diphenylpropan-2-yl phosphate (4a):[7a] white solid; ^{1}H NMR ($CDCl_3$) δ 1.07 (3H, dt, J_1 = 1.0 Hz, J_2 = 7.1 Hz), 1.20 (3H, dt, J_1 = 1.0, J_2 = 7.1 Hz), 3.61−3.78 (2H, m), 3.93−4.09 (2H, m), 7.15−7.21 (2H, m), 7.32−7.37 (4H, m), 7.45−7.55 (2H, m), 7.60−7.63 (2H, m); ^{13}C NMR ($CDCl_3$) δ 15.7 (d, J = 3.7 Hz), 15.8 (d, J = 3.8 Hz), 64.2 (d, J = 6.1 Hz), 64.7 (d, J = 6.1 Hz), 86.3 (d, J = 28 Hz), 125 (q, J = 287 Hz), 126.4, 128.0, 128.9, 130.0, 130.3, 132.1(d, J = 10.4 Hz), 133.0, 134.0, 189.6; ^{31}P NMR ($CDCl_3$) δ −6.38. Anal. Calcd for $C_{19}H_{20}F_3O_5P$: C, 54.81; H, 4.84. Found: C, 54.66; H, 4.75.

Procedure for the Coupling of Aromatic Acyl Phosphonates with Cyclohexanone. KCN (20 mol %), 18-crown-6 (20 mol %), and catalyst (3,5-bistrifluoromethylphenyl)thiourea (25 mol %) were placed in a round-bottomed flask, and then 2 mL of freshly dried THF was added via a syringe. One millimole of aromatic acyl phosphonate and 2 mmol of cyclohexanone were added to the reaction mixture under an inert atmosphere at ambient temperature. After completion, the reaction (1 h) mixture was diluted with 15 mL of ether and worked up as aromatic−aromatic reactions. This procedure is only valid for the coupling of dimethyl(4-methoxyphenyl)oxomethyl phosphonate and cyclohexanone.

(1-*p*-Methoxybenzoylcyclohexyl)dimethyl phosphate (4*l*): white solid; ^{1}H NMR ($CDCl_3$) δ 1.24−1.33 (2H, m), 1.55−1.60 (3H, m), 1.67−1.77 (2H, m), 1.95−2.01 (2H, m), 2.17−2.25 (2H, m), 3.54 (6H, d, J = 11.3 Hz), 3.79 (3H, s), 6.84 (2H, d, J = 9.0 Hz), 8.07 (2H, d, J = 8.9 Hz); ^{13}C NMR ($CDCl_3$) δ 20.6, 23.9, 33.5, 33.6, 53.3 (d, J = 5.5 Hz), 54.4, 88.0 (d, J = 6.9 Hz), 112,4, 126.4, 131.3, 162,0, 196.1; ^{31}P NMR ($CDCl_3$) δ −1.67. Anal. Calcd for $C_{16}H_{23}O_6P$: C, 56.14; H, 6.77. Found: C, 56.36; H, 6.71.

General Procedure for Aliphatic−Aromatic Acyl Phosphonate/Ketone Coupling. KCN (20 mol %) and 18-crown-6 were (20 mol %) were placed in a round-bottomed flask, and then 5 mL of dried toluene was added via a syringe. One millimole of aliphatic acylphoshonate and 2 mmol of 2,2,2-trifluoroacetophenone were added to the reaction mixture under an inert atmosphere. The reaction mixture was heated to 80 °C, in which the reaction was monitored by TLC or NMR (40−50 min). After completion, the reaction mixture was diluted with 15 mL of ether and water. The organic phase was separated and the aqueous phase was extracted with 10 mL of ether three times. The combined organic phase was extracted with a brine solution, separated, and dried over $MgSO_4$. The organic phase was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel, using ether or ether/petroleum ether as an eluent.

Diethyl 1,1,1-trifluoro-2-(3-fluorophenyl)-4,4-dimethyl-3-oxopentan-2-yl phosphate (4m): yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.10 (9H, s), 1.26−1.32 (6H, m), 4.12−4.19 (4H, m), 7.06−7.10 (1H, m), 7.19−7.25 (2H, m), 7.29−7.36 (1H, m); ^{13}C NMR ($CDCl_3$) δ 14.8, 14.9, 15.0, 27.9, 45.0, 63.8 (d, J = 6.0 Hz), 64.0 (d, J = 6.0 Hz), 113.7 (d, J = 24.5 Hz), 116.1 (d, J = 21.3 Hz), 119.6, 122.1, 128.9 (d, J = 7.9 Hz), 132.5, 162.8 (d, J = 254 Hz), 203.6; ^{31}P NMR ($CDCl_3$) δ −7.60. Anal. Calcd for $C_{17}H_{23}F_4O_5P$: C, 49.28; H, 5.60. Found: C, 49.11; H, 5.55.

Acknowledgment. Financial support from the Scientific and Technological Research Council of Turkey (TÜBITAK), the Turkish Academy of Science (TÜBA), the Turkish State Planning Organization, and the Middle East Technical University (METU) are all gratefully acknowledged.

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

JO8026627