# Copper Triflate as a Useful Catalyst for the High-Yielding Preparation of α-Acetyloxyphosphonates under Solvent-Free Conditions

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**Abstract:** A high-yielding and convenient procedure for the efficient conversion of α-hydroxyphosphonates to α-acetyloxyphosphonates using acetic anhydride in the presence of catalytic amounts of copper triflate is described.

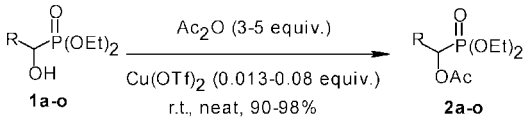
**Key words:** hydroxyphosphonates, solvent-free, copper triflate, acetic anhydride, acetyloxyphosphonates

α-Acetyloxyphosphonates are considered as important and valuable phosphorus compounds for the synthesis of optically active α-hydroxyphosphonates. Enzymatic systems have been introduced for the enantioselective hydrolysis of racemic α-acetyloxyphosphonates.[1] Chiral and nonracemic α-hydroxyphosphonates are useful precursors for a variety of α-substituted phosphonates especially for α-aminophosphonic acids which have received considerable attention in medical, bioorganic and organic chemistry owing to their potential activities as analogues of α-amino acids.[1a,2]

Literature survey indicates that a practical and high yielding method for the synthesis of pure α-acetyloxyphosphonates is rare. The reactions of aldehydes and ketones with acyl phosphites is reported for the preparation of α-acetyloxyphosphonates at 120 °C to produce the desired products in low yields.[3] The other reported procedures for this purpose include direct acetylation of α-hydroxyphosphonates[4] with ketene catalyzed by $BF_3{\cdot}Et_2O$[5] or $H_2SO_4$.[6] These protocols suffer from usually low yields[5], requiring rather high temperatures (70–80 °C) and long reaction times (10–15 h).[6] Acetylation of α-hydroxyphosphonates with $Ac_2O$ or AcCl in the presence of $Et_3N$ or pyridine has been conducted at room temperature in 1–18 hours resulting in low to excellent yields.[1b,1c,7] In the other reported procedure, AcCl has been used for direct acetylation of α-trimethylsilyloxyphosphonates at a rather high temperature (120 °C) to produce α-acetyloxyphosphonates in moderate yields (55–70%).[8]

In this article we present a new procedure in which a mild Lewis acid, copper triflate [$Cu(OTf)_2$][9] has been used for the first time for direct acetylation of α-hydroxyphosphonates with $Ac_2O$ at room temperature in the absence of solvent in excellent yields with short reaction times.

Reactions of diethyl α-hydroxyphosphonates have been under investigation in our laboratory in recent years.[10] Along this line, recently we have introduced [$Cu(OTf)_2$] as a mild and efficient catalyst for the silylation of α-hydroxyphosphonates with HMDS.[10d] A recent report on the acetylation of traditional hydroxy functional groups with $Ac_2O$ catalyzed by $Cu(OTf)_2$[11] prompted us to apply this Lewis acid catalyst for direct acetylation of diethyl α-hydroxyphosphonates. We have studied the reactions of various diethyl α-hydroxyphosphonates **1a**–**o** in the presence of $Ac_2O$ catalyzed by 0.013–0.08 equivalents of $Cu(OTf)_2$ in the absence of solvent at room temperature (Scheme 1 and Table 1).




**Scheme 1**

As shown in Table 1, various types of diethyl α-hydroxy(arylmethyl)phosphonates **1a**–**k** were cleanly converted into their corresponding diethyl α-acetyloxyphosphonates **2a**–**k** in excellent yields (92–98%). Diethyl α-hydroxy-2-naphthyl-, 3-pyridyl-, alkyl- and aryl-β,γ-unsaturated phosphonates **1l**–**o** were also acetylated efficiently giving the corresponding diethyl α-acetyloxyphosphonates **2l**–**o** in 90–96% yields.

In all the reactions we have reported in this paper cleavage of C–P bond of the phosphonates were not detected and the conversion of the substrates to their corresponding acetyloxy compounds was clean and quantitative. Work-up of the reaction mixture is very easy and gives highly pure liquid products, which do not need further purification (detected by TLC and their spectral data).

Consequently, in this paper, we have described a simple procedure for the high yielding synthesis of a variety of diethyl α-acetyloxyphosphonates by direct acetylation of diethyl α-hydroxyphosphonates with $Ac_2O$ catalyzed by $Cu(OTf)_2$ as a mild Lewis acid. This method is superior with respect to the other reported methods, which use corrosive $BF_3{\cdot}Et_2O$, $H_2SO_4$ and AcCl and also purification of the acetyloxy products from pyridine and $Et_3N$ is a tedious and a time consuming process. Solvent-free and mild reaction conditions, short reaction times and easy workup

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**Table 1** Acetylation of Diethyl α-Hydroxyphosphonates **1a–o** to Diethyl α-Acetyloxyphosphonates **2a–o** with $Ac_2O$ in the Presence of $Cu(OTf)_2$ under Solvent-Free Conditions at Room Temperature

| Product **2** | R | **1**/$Ac_2O$/$Cu(OTf)_2$ Ratio | Time (min) | Yield[a] (%) |
|---|---|---|---|---|
| **a** | Ph | 1:5:0.013 | 30 | 98 |
| **b** | 4-$MeC_6H_4$ | 1:5:0.027 | 30 | 97 |
| **c** | 4-$MeOC_6H_4$ | 1:5:0.013 | 30 | 92 |
| **d** | 2,4,6-$Me_3C_6H_2$ | 1:5:0.027 | 30 | 97 |
| **e** | 2-$ClC_6H_4$ | 1:5:0.08 | 240 | 96 |
| **f** | 3-$ClC_6H_4$ | 1:5:0.08 | 60 | 94 |
| **g** | 4-$ClC_6H_4$ | 1:5:0.08 | 60 | 94 |
| **h** | 2,6-$Cl_2C_6H_3$ | 1:5:0.013 | 70 | 92 |
| **i** | 2-$O_2NC_6H_4$ | 1:5:0.053 | 70 | 92 |
| **j** | 3-$O_2NC_6H_4$ | 1:5:0.027 | 60 | 92 |
| **k** | 4-$O_2NC_6H_4$ | 1:5:0.027 | 30 | 96 |
| **l** | 2-naphthyl | 1:5:0.013 | 30 | 94 |
| **m** | 3-pyridyl | 1:3:0.013 | 30 | 96 |
| **n** | PhCH=CH | 1:5:0.013 | 60 | 92 |
| **o** | MeCH=CH | 1:5:0.027 | 90 | 90 |

[a] Yields refer to isolated products.

make this protocol a useful addition to the available methods for this purpose.

Chemicals were purchased from Merck and Fluka Chemical Companies. The products were characterized by comparison of their physical data with those of known samples or by their spectral data. IR spectra were run on a Shimadzu model 8300 FT-IR spectrophotometer. NMR spectra were recorded on a Bruker Avance DPX-250. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX. The test for the purity of the products and the progress of the reactions were accomplished by TLC on silica gel polygram SILG/$UV_{254}$ plates.

**Diethyl α-Acetyloxyphosphonates 2; General Procedure**

$Cu(OTf)_2$ (0.005–0.029 g, 0.013–0.08 mmol) was added to a mixture of **1** (0.218–0.342 g, 1 mmol) and $Ac_2O$ (0.342–0.57 g, 3–5 mmol) at r.t. The progress of the reaction was monitored by TLC. After complete conversion of the starting material, $Et_2O$ (10 mL) was added to the reaction mixture and the $Et_2O$ phase was washed with aq sat. $NaHCO_3$ (3 × 10 mL) and then $H_2O$ (3 × 10 mL). The organic layer was separated, dried ($Na_2SO_4$), and filtered. Evaporation of the filtrate resulted in highly pure **2** in 90–98% yields (Table 1). Spectral data for selected compounds are given below.

**2a**

IR (neat): 1745 $cm^{-1}$ (C=O).

$^1H$ NMR ($CDCl_3$/TMS): δ = 1.17–1.29 (m, 6 H, $OCH_2CH_3$), 2.16 [s, 3 H, $OC(O)CH_3$], 3.86–4.13 (m, 4 H, $OCH_2CH_3$), 6.14 (d, 1 H, $^1J_{PH}$ = 13.6 Hz, CH), 7.35 (d, $J_{HH}$ = 7.1 Hz, 3 H, $C_6H_5$), 7.50 (d, $J_{HH}$ = 7.3 Hz, 2 H, $C_6H_5$).

$^{13}C$ NMR ($CDCl_3$/TMS): δ = 16.68 (d, $^3J_{CP}$ = 5.85 Hz, $OCH_2CH_3$), 16.80 (d, $^3J_{CP}$ = 5.7 Hz, $OCH_2CH_3$), 21.26 [$OC(O)CH_3$], 63.74 (d, $^2J_{CP}$ = 6.5 Hz, 2-$OCH_2CH_3$), 70.84 (d, $^1J_{CP}$ = 170.1 Hz, CH), 128.25–129.15, 133.8 ($C_6H_5$), 169.66 (d, $^3J_{CP}$ = 8.9 Hz, $OC(O)CH_3$).

MS (70 eV): *m*/*z* = 286 ($M^+$).

Anal. Calcd for $C_{13}H_{19}O_5P$: C, 54.54; H, 6.64. Found: C, 54.50; H, 6.60.

**2c**

IR (neat): 1750 $cm^{-1}$ (C=O).

$^1H$ NMR ($CDCl_3$/TMS): δ = 1.22–1.40 (m, 6 H, $OCH_2CH_3$), 2.19 [s, 3 H, $OC(O)CH_3$], 3.84 (s, 3 H, 4-$OCH_3$), 3.96–4.28 (m, 4 H, $OCH_2CH_3$), 6.13 (d, 1 H, $^1J_{PH}$ = 13.08 Hz, CH), 6.94 (d, 2 H, $J_{HH}$ = 8.0 Hz, $C_6H_4$), 7.48 (d, $J_{HH}$ = 8.0 Hz, 2 H, $C_6H_4$).

$^{13}C$ NMR ($CDCl_3$/TMS): δ = 16.39 (d, $^3J_{CP}$ = 5.85 Hz, $OCH_2CH_3$), 16.41 (d, $^3J_{CP}$ = 5.7 Hz, $OCH_2CH_3$), 20.91 [$OC(O)CH_3$], 55.26 (4-$OCH_3$), 63.38 (d, $^2J_{CP}$ = 6.5 Hz, $OCH_2CH_3$), 70.09 (d, $^1J_{CP}$ = 173 Hz, CH), 113.96–113.99, 128.86–130.96 ($C_6H_4$), 169.41 [d, $^3J_{CP}$ = 8.99 Hz, $OC(O)CH_3$].

MS (70 eV): *m*/*z* = 316 ($M^+$).

Anal. Calcd for $C_{14}H_{21}O_6P$: C, 53.16; H, 6.64. Found: C, 53.15; H, 6.62.

**2e**

IR (neat): 1743 $cm^{-1}$ (C=O).

$^1H$ NMR ($CDCl_3$/TMS): δ = 1.16–1.35 (m, 6 H, $OCH_2CH_3$), 2.19 [s, 3 H, $OC(O)CH_3$], 4.02–4.16 (m, 4 H, $OCH_2CH_3$), 6.12 (d, 1 H, $^1J_{PH}$ = 13.9 Hz, CH), 7.29–7.69 (m, 4 H, $C_6H_4$).

$^{13}C$ NMR ($CDCl_3$/TMS): δ = 16.28 (d, $^3J_{CP}$ = 5.85 Hz, $OCH_2CH_3$), 16.37 (d, $^3J_{CP}$ = 5.7 Hz, $OCH_2CH_3$), 20.72 [$OC(O)CH_3$], 63.74 (d, $^2J_{CP}$ = 6.4 Hz, $OCH_2CH_3$), 69.78 (d, $^1J_{CP}$ = 170.5 Hz, CH), 126.12–131.09, 134.38–135.72 ($C_6H_4$), 169.17 [d, $^3J_{CP}$ = 8.9 Hz, $OC(O)CH_3$].

MS (70 eV): *m*/*z* = 320 ($M^+$), 322 (M + 2).

Anal. Calcd for $C_{13}H_{18}ClO_5P$: C, 48.67; H, 5.62. Found: C, 48.70; H, 5.65.

**2h**

IR (neat): 1749 $cm^{-1}$ (C=O).

$^1H$ NMR ($CDCl_3$/TMS): δ = 1.22–1.35 (m, 6 H, $OCH_2CH_3$), 2.17 [s, 3 H, $OC(O)CH_3$], 4.01–4.26 (m, 4 H, $OCH_2CH_3$), 6.85 (d, 1 H, $^1J_{PH}$ = 17.9 Hz, CH), 7.17–7.23 (m, 1 H, $C_6H_3$), 7.32–7.35 (m, 2 H, $C_6H_3$).

$^{13}C$ NMR ($CDCl_3$/TMS): δ = 16.43 (d, $^3J_{CP}$ = 5.8 Hz, $OCH_2CH_3$), 16.57 (d, $^3J_{CP}$ = 5.8 Hz, $OCH_2CH_3$), 22.24 [$OC(O)CH_3$], 63.66 (d, $^2J_{CP}$ = 6.8 Hz, $OCH_2CH_3$), 69.45 (d, $^1J_{CP}$ = 174.1 Hz, CH), 128.96, 129.67, 129.69, 130.32, 130.36, 135.94 ($C_6H_3$), 169.51 [d, $^3J_{CP}$ = 10.4 Hz, $OC(O)CH_3$].

MS (70 eV): *m*/*z* = 355 ($M^+$ ), 357 (M + 2,), 359 (M + 4).

Anal. Calcd for $C_{13}H_{17}Cl_2O_5P$: C, 43.9; H, 4.8. Found: C, 43.92; H, 4.83.

**2i**

IR (neat): 1748 $cm^{-1}$ (C=O).

$^1H$ NMR ($CDCl_3$/TMS): δ = 1.19–1.38 (m, 6 H, $OCH_2CH_3$), 2.24 [s, 3 H, $OC(O)CH_3$], 4.05–4.25 (m, 4 H, $OCH_2CH_3$), 6.25 (d, 1 H, $^1J_{PH}$ = 14.2 Hz, CH), 7.59 (t, 1 H, $J_{HH}$ = 7.9 Hz, $C_6H_4$), 7.85 (d,

$J_{HH}$ = 7.5 Hz, 1 H, $C_6H_4$), 8.20 (d, $J_{HH}$ = 8.1 Hz, 1 H, $C_6H_4$), 8.34 (s, 1 H, $C_6H_4$).

$^{13}$C NMR ($CDCl_3$/TMS): δ = 16.18 (d, $^3J_{CP}$ = 5.85 Hz, $OCH_2CH_3$), 16.24 (d, $^3J_{CP}$ = 5.7 Hz, $OCH_2CH_3$), 20.55 [OC(O)$CH_3$], 63.67 (d, $^2J_{CP}$ = 6.5 Hz, $OCH_2CH_3$), 69.30 (d, $^1J_{CP}$ = 169.8 Hz, CH), 122.34–123.42, 128.67, 135.79 ($C_6H_4$), 168.99 [d, $^3J_{CP}$ = 8.68 Hz, O$C$(O)$CH_3$].

MS (70 eV): *m*/*z* = 331 ($M^+$).

Anal. Calcd for $C_{13}H_{18}NO_7P$: C, 47.13; H, 5.44. Found: C, 47.11; H, 5.43.

**2l**

IR (neat): 1749 $cm^{-1}$ (C=O).

$^1$H NMR ($CDCl_3$/TMS): δ = 1.16–1.34 (m, 6 H, $OCH_2CH_3$), 2.19 [s, 3 H, OC(O)$CH_3$], 3.89–4.14 (m, 4 H, $OCH_2CH_3$), 6.32 (d, 1 H, $^1J_{PH}$ = 13.7 Hz, CH), 7.44–7.48 (m, 2 H, $C_{10}H_7$), 7.61 (d, 1 H, $J_{HH}$ = 8.5 Hz, $C_{10}H_7$), 7.78–7.86 (m, 3 H, $C_{10}H_7$), 7.96 (s, 1 H, $C_{10}H_7$).

$^{13}$C NMR ($CDCl_3$/TMS): δ = 16.29 (d, $^3J_{CP}$ = 5.85 Hz, $OCH_2CH_3$), 16.42 (d, $^3J_{CP}$ = 5.7 Hz, $OCH_2CH_3$), 20.88 [OC(O)$CH_3$], 63.42 (d, $^2J_{CP}$ = 6.5 Hz, $OCH_2CH_3$), 70.63 (d, $^1J_{CP}$ = 170.3 Hz, CH), 125.33–128.27, 130.88, 130.92–133.31 ($C_{10}H_7$), 169.31 [d, $^3J_{CP}$ = 9.2 Hz, O$C$(O)$CH_3$].

MS (70 eV): *m*/*z* = 336 ($M^+$).

Anal. Calcd for $C_{13}H_{19}O_5P$: C, 60.71; H, 6.25. Found: C, 60.70; H, 6.25.

**2m**

IR (neat): 1759 $cm^{-1}$ (C=O).

$^1$H NMR ($CDCl_3$/TMS): δ = 1.03–1.32 (m, 6 H, $OCH_2CH_3$), 2.20 [s, 3 H, OC(O)$CH_3$], 3.99–4.20 (m, 4 H, $OCH_2CH_3$), 6.19 (d, 1 H, $^1J_{PH}$ = 14.1 Hz, CH), 7.36–7.41 (m, 1 H, $C_5H_4N$), 7.91 (d, 1 H, $J_{HH}$ = 7.7 Hz, $C_5H_4N$), 8.61–8.71 (m, 2 H, $C_5H_4N$).

$^{13}$C NMR ($CDCl_3$/TMS): δ = 16.54 (d, $^3J_{CP}$ = 5.5 Hz, $OCH_2CH_3$), 16.63 (d, $^3J_{CP}$ = 5.5 Hz, $OCH_2CH_3$), 20.94 [OC(O)$CH_3$], 63.99–64.16 ($OCH_2CH_3$), 68.46 (d, $^1J_{CP}$ = 171.4 Hz, CH), 124.05, 136.67, 148.32–149.28 ($C_5H_4N$), 169.36 [d, $^3J_{CP}$ = 8.9 Hz, O$C$(O)$CH_3$].

MS (70 eV): *m*/*z* = 287 ($M^+$).

Anal. Calcd for $C_{12}H_{18}NO_5P$: requires C, 50.2; H, 6.3. Found: C, 50.0; H, 6.0.

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