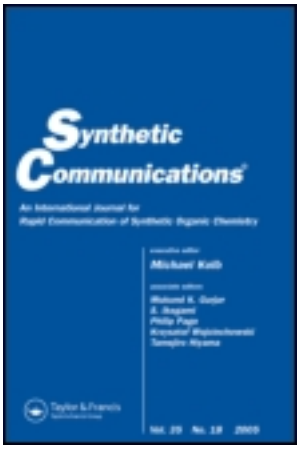

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Bismuth(III) Chloride-Catalyzed Three-Component Coupling: Synthesis of α-Amino Phosphonates

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Abstract: A simple and efficient method has been developed for the one-pot synthesis of α-amino phosphonates from the reaction of a carbonyl compound, amine, and dialkyl phosphite. The highly catalytic nature of bismuth(III) chloride and the fact that it is relatively nontoxic, low cost, easy to handle, and insensitive to small amounts of air and moisture make this method especially attractive for large-scale synthesis.

Keywords: Amine, α-amino phosphonate, bismuth trichloride, carbonyl compound, dialkyl phosphite

α-Amino phosphonates are key compounds as analogues of α-amino acids in medicinal chemistry and pharmaceutical sciences.[1] The potential of α-amino phosphonates as haptens of catalytic antibodies,[2] enzyme inhibitors,[3] and antibiotic and pharmacologic agents[4] has been established. Thus, how to efficiently synthesize α-amino phosphonates has been explored. Of the methods available, the nucleophilic addition of phosphites to imines is most convenient. These reactions are usually promoted by a base or an acid.[5]

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Lewis acids such as $SnCl_2$, $SnCl_4$, $BF_3 \cdot OEt_2$, $ZnCl_2$, and $MgBr_2$ have been found to be effective.[6] However, these reactions cannot be carried out in a one-pot operation with carbonyl compound, amine, and phosphite, because amine and water produced during imine formation can decompose or deactivate these Lewis acids. Recently, it has been reported that using lanthanide triflate,[7] samarium diiodide,[8] scandium tris(dodecyl sulfate),[9] indium(III) chloride,[10] and $TaCl_5$-SiO_2[11] as catalysts, one-pot reactions can proceed smoothly. However, some of these catalysts are either expensive or somewhat difficult to prepare.

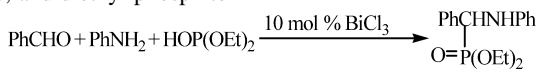
Of late, bismuth(III) compounds have received attention because of their low toxicity, low cost, and relative insensitivity to air and small amounts of moisture. As Lewis acids, bismuth(III) compounds have been used in many chemical transformations.[12] Herein, we report that bismuth(III) chloride is a highly efficient catalyst for the one-pot synthesis of α-amino phosphonates from a carbonyl compound, amine, and dialkyl phosphite.

First, the reaction of benzaldehyde with aniline and diethyl phosphite was carried out using 10 mol% $BiCl_3$ as a catalyst. Several solvents and reaction conditions were investigated. The results are summarized in Table 1.

The reaction in acetonitrile worked best at reflux. Compared with the result obtained at room temperature, the yield of α-amino phosphonates increased prominently at reflux condition (entries 1, 3). Effects of solvents on the yields of α-amino phosphonates were tested at reflux conditions (entries 3, 5, 6). Acetonitrile (92%) was a much better solvent in terms of yields than THF (51%) and dichloromethane (27%). Although $MgSO_4$ or 4 Å mol. sieves as additives were needed when using $Yb(OTf)_3$ or SmI_2 to catalyze this conversion,[7a,8] in our method, such additives can be dispensed with. The reaction proceeded smoothly both with and without molecular sieves, giving the product in similar yields (entries 1–4).

A typical experimental procedure is as follows: a mixture of a carbonyl compound (3 mmol), an amine (3 mmol), and a dialkyl phosphite (3 mmol)

Table 1. Effect of reaction conditions on the $BiCl_3$-catalyzed reaction of benzaldehyde, aniline, and diethyl phosphite

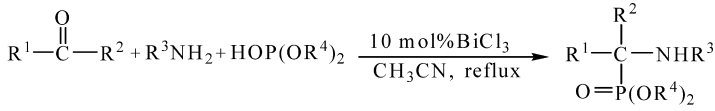


Entry	Solvent	Reaction temp.	Time (h)	Additive	Isolated yield (%)
1	CH_3CN	rt	6	—	23
2	CH_3CN	rt	6	4 Å mol. sieves	26
3	CH_3CN	Reflux	6	—	92
4	CH_3CN	Reflux	6	4 Å mol. sieves	91
5	CH_2Cl_2	Reflux	6	—	27
6	THF	Reflux	6	—	51

was added to a solution of $BiCl_3$ (10 mol%) in acetonitrile (15 mL) and the mixture was stirred at reflux for the period of time required to complete the reaction (TLC). Unlike indium(III) chloride, where inert ambience is required, the use of an inert atmosphere is not required for our reactions. A wide range of structurally varied carbonyl compounds were used as substrates and converted to the corresponding α-amino phosphonates in good to excellent yields. The results are reported in Table 2.

Considering that when using $TaCl_5 \cdot SiO_2$ as a catalyst, aliphatic amines gave uncharacterizable products, and when carbonyl compounds were ketones many catalysts such as lanthanide triflate, samarium diiodide, and scandium tris(dodecyl sulfate) proved to be less effective, $BiCl_3$ performed highly efficient catalytic activity for three-component coupling reactions. Not only benzaldehydes but also electron-rich aromatic aldehydes, electron-deficient aromatic aldehydes, and aliphatic aldehydes react with aromatic as well as

Table 2. Synthesis of α-amino phosphonates from aldehydes, ketones, and amines catalyzed by $BiCl_3$



1 **2** **3** **4**

Entry	R^1	R^2	R^3	R^4	Time (h)	4/%[a]
1	Ph	H	Ph	Et	6	4a/92
2	Ph	H	Ph	Me	5	4b/92
3	Ph	H	Ph	*i*-Pr	6	4c/95
4	*p*-MeO-Ph	H	Ph	Et	8	4d/95
5	*o*-MeO-Ph	H	Ph	Et	10	4e/93
6	2,4-Dichloro-C_6H_4	H	Ph	Et	12	4f/90
7	*p*-MeO-Ph	H	*n*-Pr	Et	13	4g/85[b]
8	*o*-HO-Ph	H	Ph	Et	8	4h/82
9	*p*-NO_2-Ph	H	Ph	Me	7	4i/83
10	Cyclohexyl	H	Ph	Et	6	4j/90
11	Ph	H	$PhCH_2$	Et	14	4k/91
12	Ph	H	$PhCH_2$	Me	12	4l/82
13	PhCH=CH (trans)	H	$PhCH_2$	Et	9	4m/81
14	Cyclohexanone	—	$PhCH_2$	Et	15	4n/80
15	Cyclohexanone	—	*n*-Pr	Et	7	4o/87[b]
16	CH_3	CH_3	$PhCH_2$	Et	9	4p/86[c]
17	Cyclopentanone	—	*n*-Pr	Et	15	4q/83[b]
18	CH_3	Isobutyl	$PhCH_2$	Et	28	4r/70

[a]Isolated yields after column chromatography.
[b]The reaction was carried out at 45°C.
[c]The reaction was carried out at 53°C.

aliphatic amines to give the α-amino phosphonates in high yields. This procedure is equally effective for conversion of ketone to the respective dialkyl phosphonates. Several sensitive functionalities such as NO_2, OMe, OH, Cl, and the C-C double bond are unaffected in the reaction. The advantages of this method are operational simplicity, no requirement for an inert atmosphere for the reaction, and no requirement of an additive. The highly catalytic nature of bismuth(III) chloride and the fact that it is relatively nontoxic, low cost, easy to handle, and insensitive to small amounts of air and moisture make this procedure especially attractive for large-scale synthesis.

EXPERIMENTAL

Infrared spectra were measured with a Nicolet Avatar 360 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Unity +500 spectrometer with tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Mass spectra were recorded by Bruker Dalton Esquire 3000 Plus and Finnigan Mat-LCQ (ESI direct injection). Elemental analysis were performed using a Vario RL analyzer.

General Procedure for the Preparation of 4a–4r

A mixture of carbonyl compound (3 mmol), amine (3 mmol), dialkyl phosphite (3 mmol), and bismuth trichloride (10 mol%) in acetonitrile (15 mL) was stirred under reflux for 5–28 h. The acetonitrile was removed at reduced pressure. Water was added to the residue and the mixture extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by chromatography on silica gel to afford pure α-amino phosphonates.

The ^{1}H NMR, MS, and IR spectral data of those known compounds are given. The ^{1}H NMR, ^{13}C NMR, MS, and IR spectra data and CHN analysis result of the new compounds are also given.

Product of 4a: IR (film): 3294, 1603, 1498, 1234, 1024, 969 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48–7.08 (10H, m), 4.76 (1H, d, $^2J_{PH} = 24.0$ Hz), 4.18–4.05 (2H, m), 3.98–3.89 (1H, m), 3.72–3.63 (1H, m), 1.28 (3H, t, $J = 7.0$ Hz), 1.11 (3H, t, $J = 7.0$ Hz); ESI-MS: m/z (%) = 320 (68) $[M + H^+]$, 342 (100) $[M + Na^+]$.

Product of 4b: IR (film): 3415, 1602, 1499, 1238, 1056, 1030 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42–6.52 (10H, m), 4.78–4.70 (2H, m), 3.70 (3H, d, $^3J_{PH} = 11.0$ Hz), 3.41 (3H, d, $^3J_{PH} = 11.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.98, 145.86, 135.43, 129.03, 128.57, 127.91, 127.66, 127.63, 118.35, 113.70, 56.06, 54.86, 53.68; ESI-MS: m/z (%) = 292 (39) $[M + H^+]$,

314 (100) [M + Na^+]; Analysis calculated for $C_{15}H_{18}NO_3P$: C, 61.85; H, 6.23; N, 4.81. Found: C, 61.70; H, 6.57; N, 4.63.

Product of 4c: IR (film): 3416, 1603, 1499, 1453, 1233, 999 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.51–6.59 (10H, m), 4.83–4.79 (1H, m), 4.74–4.66 (2H, m), 4.50–4.43 (1H, m), 1.33 (3H, d, $J = 6.0$ Hz), 1.28 (3H, d, $J = 6.0$ Hz), 1.23 (3H, d, $J = 6.0$ Hz), 0.93 (3H, d, $J = 6.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.54, 146.42, 136.16, 129.08, 128.38, 128.36, 127.97, 127.92, 127.69, 118.15, 113.72, 72.04, 71.98, 71.89, 71.84, 57.00, 55.79, 24.21, 24.16, 23.70, 23.13; ESI-MS: m/z (%) = 370 (100) [M + Na^+]; Analysis calculated for $C_{19}H_{26}NO_3P$: C, 65.69; H, 7.54; N, 4.03. Found: C, 65.62; H, 7.47; N, 4.10.

Product of 4d: IR (film): 3301, 1603, 1510, 1245, 1025, 971 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.40–6.58 (9H, m), 4.72 (1H, d, $^2J_{PH} = 24.0$ Hz), 4.17–4.06 (2H, m), 3.98–3.92 (1H, m), 3.77 (3H, s), 3.73–3.66 (1H, m), 1.28 (3H, t, $J = 7.0$ Hz), 1.14 (3H, t, $J = 7.0$ Hz); ESI-MS: m/z (%) = 350 (66) [M + H^+], 372 (100) [M + Na^+].

Product of 4e: IR (film): 3416, 1603, 1499, 1233, 1056, 971 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.40–6.50, (9H, m), 5.32 (1H, dd, $J_1 = 16.0$ Hz, $J_2 = 8.0$ Hz), 4.80–4.76, (1H, m), 4.12–4.08 (2H, m), 3.85 (3H, s), 3.83–3.78 (1H, m), 3.56–3.52 (1H, m), 1.23 (3H, t, $J = 7.0$ Hz), 0.96 (3H, t, $J = 7.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.22, 157.17, 146.26, 146.16, 129.09, 128.97, 128.14, 124.45, 120.99, 120.90, 118.01, 113.48, 113.44, 110.34, 62.99, 62.93, 55.68, 48.52, 47.29, 16.29, 16.06, 15.83, 15.78; ESI-MS: m/z (%) = 350 (100) [M + H^+], 372 (86) [M + Na^+]; Analysis calculated for $C_{18}H_{24}NO_3P$: C, 61.88; H, 6.92; N, 4.01. Found: C, 61.82; H, 7.00; N, 4.00.

Product of 4f: IR (film): 3415, 1603, 1499, 1233, 1056, 1025 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.54–6.56 (8H, m), 5.32 (1H, d, $^2J_{PH} =$ 24.0 Hz), 4.27–4.20 (2H, m), 4.00–3.93 (1H, m), 3.79–3.71 (1H, m), 1.36 (3H, t, $J = 7.0$ Hz), 1.14 (3H, t, $J = 7.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.41, 145.29, 134.69, 134.63, 134.15, 134.12, 132.89, 129.75, 129.72, 129.26, 129.13, 127.70, 118.69, 113.42, 63.59, 63.54, 63.46, 63.40, 51.80, 50.58, 16.42, 16.37, 16.14, 16.09; ESI-MS: m/z (%) = 388 (90) [M + H^+], 410 (100) [M + Na^+]; Analysis calculated for $C_{17}H_{20}Cl_2NO_3P$: C, 52.59; H, 5.19; N, 3.61. Found: C, 52.74; H, 5.20; N, 3.68.

Product of 4g: IR (film): 3439, 1610, 1512, 1249, 1029, 966 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.21 (2H, d, J = 7.5 Hz), 6.75 (2H, d, J = 7.5 Hz), 4.05–3.96 (2H, m), 3.90–3.85 (2H, m), 3.77–3.73 (1H, m), 3.71 (3H, s), 2.42–2.28 (2H, m), 1.41–1.33 (2H, m), 1.19 (3H, t, $J = 7.0$ Hz), 1.07 (3H, t, $J = 7.0$ Hz), 0.77 (3H, t, $J = 7.0$ Hz); ESI-MS: m/z (%) = 316 (100) [M + H^+], 338 (24) [M + Na^+].

Product of entry 4h: IR (film): 3407, 1603, 1503, 1458, 1207, 1051, 1024 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.28–6.67 (9H, m), 4.92 (1H, d, $^2J_{PH} = 23.0$ Hz), 4.19–3.97 (4H, m), 1.28–1.17 (6H, m); ESI-MS: m/z (%) = 336 (39) [M + H^+], 358 (100) [M + Na^+].

Product of 4i: IR (film): 3418, 1632, 1520, 1347, 1206, 1052 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.20 (2H, d, $J = 8.5$ Hz), 7.68 (2H, dd, $J = 8.5$ Hz, $^4J_{PH} = 2.0$ Hz), 7.13–7.09 (2H, m), 6.75–6.71 (1H, m), 6.57–6.55 (2H, m), 5.00–4.91 (1H, m), 3.81 (3H, d, $^3J_{PH} = 5.3$ Hz), 3.63 (3H, d, $^3J_{PH} = 5.3$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.43, 145.35, 145.24, 143.59, 129.15, 128.51, 128.48, 123.67, 118.92, 113.61, 55.80, 54.62, 54.08, 54.03, 53.71, 53.66; ESI-MS: m/z (%) = 337 (41) $[M + H^+]$, 375 (100) $[M + K^+]$; Analysis calculated for $C_{15}H_{17}N_2O_5P$: C, 53.57; H, 5.10; N, 8.33. Found: C, 53.54; H, 5.17; N, 8.12.

Product of 4j: IR (film): 3423, 1602, 1499, 1230, 1054, 1026 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.09–7.05 (2H, m), 6.62–6.65 (3H, m), 4.04–3.96 (3H, m), 3.94–3.86 (1H, m), 3.83–3.77 (1H, m), 3.59–3.51 (1H, m), 1.90–1.54 (7H, m); 1.25–1.01 (10H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.65, 147.62, 129.13, 117.62, 113.04, 62.55, 62.50, 61.73, 61.67, 56.49, 55.29, 39.77, 39.73, 30.89, 28.19, 26.19, 25.90, 16.37, 16.32, 16.27; ESI-MS: m/z (%) = 326 (100) $[M + H^+]$, 348 (54) $[M + Na^+]$; Analysis calculated for $C_{17}H_{28}NO_3P$: C, 62.75; H, 8.67; N, 4.30. Found: C, 63.15; H, 8.63; N, 4.33.

Product of 4k: IR (film): 3444, 1633, 1494, 1453, 1242, 1027, 966 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.38–7.16, (10H, m), 4.07–3.85 (4H, m), 3.78–3.70 (2H, m), 3.47 (1H, d, $^2J_{PH} = 13.0$ Hz), 2.40 (1H, s), 1.20 (3H, t, $J = 7.0$ Hz), 1.05 (3H, t, $J = 7.0$ Hz). ESI-MS: m/z (%) = 334 (100) $[M + H^+]$.

Product of 4l: IR (film): 3439, 1633, 1494, 1453, 1241, 1029 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.46–7.25 (10H, m), 4.07 (1H, d, $^2J_{PH} = 20.5$ Hz), 3.82 (1H, d, $J = 15.0$ Hz), 3.75 (3H, d, $^3J_{PH} = 10.5$ Hz), 3.57–3.53 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.03, 135.31, 135.28, 128.49, 128.44, 128.27, 128.21, 127.95, 127.93, 127.04, 59.72, 58.49, 53.66, 53.61, 53.34, 53.29, 51.06, 50.92; ESI-MS: m/z (%) = 306 (100) $[M + H^+]$, 328 (98) $[M + Na^+]$; Analysis calculated for $C_{16}H_{20}NO_3P$: C, 62.94; H, 6.60; N, 4.59. Found: C, 63.08; H, 6.97; N, 4.81.

Product of 4m: IR (film): 3424, 1639, 1453, 1277, 1052, 1026, 969 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.42–7.16 (10H, m), 6.28 (1H, dd, $J = 16.0$ Hz, $^4J_{PH} = 4.0$ Hz), 6.08–6.03 (1H, m), 4.10–3.45 (7H, m), 1.28 (3H, t, $J = 7.0$ Hz), 1.18 (3H, t, $J = 7.0$ Hz); ESI-MS: m/z (%) = 360 (100) $[M + H^+]$, 382 (53) $[M + Na^+]$.

Product of 4n: IR (film): 3439, 1633, 1453, 1234, 1061, 1026, 969 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.43–7.23 (5H, m), 4.20–4.14 (4H, m), 3.92 (2H, d, $^4J_{PH} = 3.0$ Hz), 1.89–1.85 (2H, m); 1.78–1.68 (6H, m), 1.52–1.49 (2H, m), 1.35 (6H, t, $J = 7.0$ Hz); ESI-MS: m/z (%) = 326 (100) $[M + H^+]$, 348 (49) $[M + Na^+]$.

Product of 4o: IR (film): 3441, 1632, 1444, 1234, 1026, 954 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.14–4.07 (4H, m), 2.68 (2H, dt, $^4J_{PH} = 2.5$ Hz, $J = 10.0$ Hz), 1.80–1.42 (12H, m), 1.31 (6H, t, $J = 7.0$ Hz), 0.94 (3H, t, $J = 7.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 60.82, 60.76,

55.58, 54.45, 43.74, 29.03, 25.01, 23.60, 19.30, 19.21, 15.96, 15.92, 11.16; ESI-MS: m/z (%) = 278 (100) $[M + H^+]$, 300 (20) $[M + Na^+]$; Analysis calculated for $C_{13}H_{28}NO_3P$: C, 56.30; H, 10.18; N, 5.05. Found: C, 56.37; H, 10.31; N, 5.15.

Product of 4p: IR (film): 3439, 1634, 1454, 1229, 1050, 958 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.37–7.22 (5H, m), 4.22–4.13 (4H, m), 3.92 (2H, s), 1.39–1.33 (12H, m), ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.98, 128.28, 128.10, 127.88, 63.13, 62.04, 54.09, 47.49, 46.98, 23.63, 22.60, 17.06, 16.08; ESI-MS: m/z (%) = 286 (100) $[M + H^+]$; Analysis calculated for $C_{14}H_{24}NO_3P$: C, 58.93; H, 8.48; N, 4.91. Found: C, 58.85; H, 8.89; N, 4.49.

Product of 4q: IR (film): 3425, 1633, 1444, 1227, 1026, 955 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.14–4.07 (4H, m), 2.68 (2H, dt, $^4J_{PH} = 3.0$ Hz, $J = 10.0$ Hz), 1.80–1.58 (10H, m), 1.31 (6H, t, $J = 7.0$ Hz), 0.94 (3H, t, $J = 7.0$ Hz), ^{13}C NMR (125 MHz, $CDCl_3$): δ 64.06, 62.90, 61.68, 61.62, 45.70, 34.23, 34.17, 24.59, 24.51, 24.22, 16.57, 16.54, 11.70; ESI-MS: m/z (%) = 264 (100) $[M + H^+]$; Analysis calculated for $C_{12}H_{26}NO_3P$: C, 54.74; H, 9.95; N, 5.32. Found: C, 54.51; H, 10.20; N, 5.57.

Product of 4r: IR (film): 3423, 1632, 1453, 1224, 1026, 956 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.40–7.23 (5H, m), 4.22–4.15 (4H, m), 3.96, 3.91 (AB-system, 2H, $J = 12.0$ Hz), 2.07–2.01 (1H, m), 1.76–1.71 (1H, m), 1.63–1.57 (1H, m), 1.39–1.33 (9H, m), 1.04 (3H, d, $J = 6.5$ Hz), 1.00 (3H, d, $J = 6.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.17, 128.24, 128.04, 126.72, 61.95, 61.89, 61.68, 61.62, 57.67, 56.57, 47.70, 42.10, 25.30, 24.97, 22.92, 22.84, 20.74, 16.61; ESI-MS: m/z (%) = 328 (100) $[M + H^+]$, 350 (29) $[M + Na^+]$; Analysis calculated for $C_{17}H_{30}NO_3P$: C, 62.36; H, 9.24; N, 4.28. Found: C, 62.56; H, 9.34; N, 4.61.

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