Remarkable effect of phosphine on the reactivity of $O,P$-acetal

–Efficient substitution reaction of $O,P$-acetal

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General
The $^1$H, $^{13}$C, $^{19}$F and $^{31}$P NMR spectra were measured by JEOL JNM-ECS 400 or JEOL JNM-AL 300 spectrometers with tetramethylsilane as an internal standard at 20-25 ºC. IR spectra were recorded by SHIMADZU FTIR-8400 using a diffuse reflectance measurement of samples dispersed in KBr powder. HRMS spectra were recorded by JEOL LMS-D 300 spectrometers. Merck silica gel 60 (230-400 mesh) was used for column chromatography.

Materials
Acetals 1a, 1b and 1d were synthesized from commercially available corresponding aldehydes and alcohols. $(o$-$CF_3Ph)_3P$ was prepared according to the literature. Other reagents were commercially available and used without further purification.

General procedure for the preparation of acetals 1a, 1b and 1d. A solution of aldehyde (1 equiv.), 10-camphorsulfonic acid (0.15 equiv.) and alcohol (100 equiv.) in dry CH$_2$Cl$_2$ (0.1 M) was stirred at room temperature. After checking for the disappearance of the aldehyde on TLC, sat. NaHCO$_3$ aq. was added to the reaction mixture and the solution was extracted with CH$_2$Cl$_2$. The organic layer was washed with brine, dried over Na$_2$SO$_4$ and filtered, then evaporated under vacuum. The residue was purified by flash column chromatography on SiO$_2$ to give the acetal.
**n-Dodecanal dimethyl acetal (1a)**: colorless oil; $^1$H NMR (CDCl$_3$): $\delta$ 0.88 (3H, t, $J = 6.7$ Hz), 1.26 (18H, brm), 1.56-1.61 (2H, m), 3.31 (6H, s), 4.36 (1H, t, $J = 5.7$ Hz).

**3-Phenylpropionaldehyde dimethyl acetal (1b)**: colorless oil; $^1$H NMR (CDCl$_3$): $\delta$ 1.89-1.96 (2H, m), 2.68 (2H, $J = 8.0$ Hz), 3.33 (6H, s), 4.37 (1H, t, $J = 5.8$ Hz), 7.16-7.31 (5H, m).

**n-Dodecanal diisopropyl acetal (1d)**: colorless oil; IR (KBr, cm$^{-1}$): 2972, 2926, 2855, 1266, 1381, 1111, 1015; $^1$H NMR (CDCl$_3$): $\delta$ 0.88 (3H, t, $J = 6.7$ Hz), 1.14 (6H, d, $J = 6.2$ Hz), 1.19 (6H, d, $J = 6.0$ Hz), 1.26-1.39 (18H, brm), 1.53-1.58 (2H, m), 3.86 (2H, sept, $J = 6.2$ Hz), 4.54 (1H, t, $J = 5.5$ Hz); $^{13}$C NMR (CDCl$_3$): $\delta$ 14.1, 22.6, 22.7, 23.5, 24.9, 29.3, 29.5, 29.6 (3C), 31.9, 35.4, 67.4, 100.4; HRFABMS calcd for C$_{18}$H$_{38}$O$_2$ (M+Na$^+$): 309.2770, found: 309.2780.

**General procedure for the substitution reaction of O,P-acetal with nucleophiles (Table 2)**

In a flame-dried two-necked Schenck tube with nitrogen, TESOTf (2 equiv.) was added slowly to a stirred solution of acetal 1 (1 equiv.) and (o-tol)$_3$P (3 equiv.) in dry CH$_2$Cl$_2$ (0.1 M) at -5 °C and the resulting solution was stirred for 0.5 h at the same temperature. After checking for the disappearance of 1 and the formation of O,P-acetal on TLC, H$_2$O (10 ml/mmol) or nucleophile (1.2 or 3.0 equiv.) was added to the mixture, and the solution was then stirred at rt. After checking for the disappearance of O,P-acetal on TLC, sat. NaHCO$_3$ aq. was added to the reaction mixture. The resulting solution was extracted with CH$_2$Cl$_2$ and dried over anhydrous Na$_2$SO$_4$. After removal of the solvent, the residue was subjected to silica-gel column chromatography to give the products 2-6. Compounds 2a-2c are commercially available and 3b$^3$, 3c$^6$, 4b$^4$, 4c$^4$, 5b$^5$, 5c$^7$ are known compounds.

**1-Methoxydodecylphenylsulfide (3a) (entry 2)**: colorless oil; IR (KBr, cm$^{-1}$): 2926, 2855, 2253, 1468, 1379, 1098; $^1$H NMR (CDCl$_3$): $\delta$ 0.88 (3H, t, $J = 6.7$ Hz), 1.24 (16H, brm), 1.44 (2H, brm), 1.69-1.78 (2H, m), 3.47 (3H, s), 4.62 (1H, t, $J = 6.6$ Hz), 7.26-7.33 (3H, m), 7.46-7.49 (2H, m); $^{13}$C NMR (CDCl$_3$): $\delta$ 14.1, 22.7, 26.2, 29.1, 29.3, 29.5 (2C), 29.6 (2C), 31.9, 35.6, 55.3, 91.0, 127.4, 128.7, 133.4, 133.5; HREIMS calcd
for C_{19}H_{32}O: 308.2174, found: 308.2193.

2-Methoxytridecanonitrile (4a) (entry 3): colorless oil; IR (KBr, cm\(^{-1}\)): 2928, 2855, 2255, 1462, 1109; \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 0.88 (3H, t, \(J = 6.7\) Hz), 1.26-1.29 (16H, brm), 1.43-1.50 (2H,m), 1.79-1.87 (2H, m), 3.49 (3H, s), 4.04 (1H, t, \(J = 6.6\) Hz); \(^1\)C NMR (CDCl\(_3\)): \(\delta\) 14.1, 22.7, 24.7, 29.0, 29.3 (2C), 29.4, 29.6 (2C), 31.9, 33.3, 57.9, 70.7, 118.2; HRFABMS calcd for C\(_{14}\)H\(_{27}\)NO (M+Na\(^+\)): 248.1990, found: 248.1968.

1-Methoxydodecylbenzene (5a) (entry 4): colorless oil; IR (KBr, cm\(^{-1}\)): 2926, 2853, 1454, 1263, 1099; \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 0.87 (3H, t, \(J = 6.8\) Hz), 1.24-1.38 (18H, brm), 1.60-1.65 (1H, m), 1.75-1.81 (1H, m), 3.20 (3H, s), 4.07 (1H, t, \(J = 6.6\) Hz), 7.24-7.37 (5H, m); \(^1\)C NMR (CDCl\(_3\)): \(\delta\) 14.1, 22.7, 25.8, 29.3, 29.5, 29.6 (4C), 31.9, 38.2, 56.6, 84.2, 126.7, 127.4, 128.3, 142.5; HREIMS calcd for C\(_{19}\)H\(_{32}\)O: 276.2445, found: 276.2453.

2-Methoxytridecane (6a) (entry 5): colorless oil; IR (KBr, cm\(^{-1}\)): 2959, 2855, 2820, 1464, 1373, 1261, 1142, 1123, 1092; \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 0.88 (3H, t, \(J = 6.6\) Hz), 1.12 (3H, d, \(J = 6.0\) Hz), 1.26-1.38 (20H, brm), 3.25-3.31 (1H, m), 3.31 (3H, s); \(^1\)C NMR (CDCl\(_3\)): \(\delta\) 14.1, 19.0, 22.7, 25.4, 29.3, 29.6 (2C), 29.7, 29.8, 29.9, 31.9, 36.3, 55.9, 76.9;

(1-Methoxy-3-phenylpropyl)phenylsulfide (3b)\(^3\) (entry 7): colorless oil; \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.98-2.12 (2H, m), 2.76 (2H, t, \(J = 7.6\) Hz), 3.48 (3H, s), 4.54 (1H, t, \(J = 6.6\) Hz), 7.13-7.31 (8H, m), 7.45-7.48 (2H, m).

2-Methoxy-4-phenylbutyronitrile (4b)\(^4\) (entry 8): colorless oil; \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 2.05-2.25 (2H, m), 2.82 (2H, t, \(J = 7.6\) Hz), 3.48 (3H, s), 3.96 (1H, t, \(J = 6.7\) Hz), 7.17-7.26 (3H, m), 7.29-7.34 (2H, m).

1,3-Diphenyl-1-methoxypropane (5b)\(^5\) (entry 9): colorless oil; \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.92-2.14 (2H, m), 2.63-2.73 (2H, m), 3.21 (3H, s), 4.08 (1H, t, \(J = 6.6\) Hz), 7.16-7.34 (10H, m).

[Methoxy(4-methoxyphenyl)methyl]phenylsulfide (3c)\(^6\) (entry 11): colorless oil; \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 3.48 (3H, s), 3.78 (3H, s), 5.69 (1H, s), 6.78-6.83 (2H, m), 7.20-7.26 (5H, m), 7.31-7.36 (2H, m).
2-Methoxy-2-(4-methoxyphenyl)acetonitrile (4c) (entry 12); colorless oil; $^1$H NMR (CDCl$_3$): $\delta$ 3.42 (3H, s), 3.75 (3H, s), 5.06 (1H, s), 6.86 (2H, d, $J = 8.6$ Hz), 7.33 (2H, d, $J = 8.4$ Hz).

1-Methoxy-4-[methoxy(phenyl)methyl]benzene (5c) (entry 13); colorless oil; $^1$H NMR (CDCl$_3$): $\delta$ 3.28 (3H, s), 3.69 (3H, s), 5.12 (1H, s), 6.77 (2H, d, $J = 8.6$ Hz), 7.16-7.25 (7H, m).

Isolation and characterization of the stable $O,P$-acetal generated from 1a and (p-tol)$_3$P

In a flame-dried two-necked Schrenk tube with nitrogen, TESOTf (2 equiv.) was added slowly to a stirred solution of acetal 1a (1 equiv.) and (p-tol)$_3$P (3 equiv.) in dry CH$_2$Cl$_2$ (0.1 M) at 0 ºC and the reaction mixture was stirred for 0.5 h at the same temperature. After checking for the disappearance of 1 and the formation of $O,P$-acetal on TLC, sat. NaHCO$_3$ aq. was added to the reaction mixture. The resulting solution was extracted with CH$_2$Cl$_2$ and dried over anhydrous Na$_2$SO$_4$. After removal of the solvent, the residue was subjected to silica-gel column chromatography to give the stable $O,P$-acetal.

(1-Methoxydodecyl)tris(p-tolyl)phosphonium trifluoromethanesulfonate; colorless gummy oil; IR (KBr, cm$^{-1}$): 3061, 3032, 2926, 2853, 2249, 1599, 1503, 1454, 1435, 1402, 1379, 1316, 1261, 1225, 1194, 1157, 1111, 1032; $^1$H NMR (CDCl$_3$): $\delta$ 0.87 (3H, t, $J = 6.9$ Hz), 1.22-1.30 (16H, brm), 1.61-1.62 (2H, brm), 1.70-1.88 (2H, m), 2.49 (9H, s), 3.49 (3H, s), 5.45 (1H, dt, $J = 9.9, 2.9$ Hz), 7.49 (6H, dd, $J =8.0, 3.0$ Hz), 7.67 (6H, dd, $J =11.9, 8.2$ Hz); $^{13}$C NMR (CDCl$_3$): $\delta$ 14.0, 21.7, 22.5, 26.0, 26.2, 29.2, 29.3, 29.4 (2C), 31.7, 32.1 (2C), 62.9 (d, $J_{C,P} = 6.7$ Hz), 78.4 (d, $J_{C,P} = 61.3$ Hz), 113.5 (d, $J_{C,P} = 84.3$ Hz), 120.8 (d, $J_{C,F} = 321.1$ Hz), 130.9 (d, $J_{C,P} = 12.5$ Hz), 134.1 (d, $J_{C,P} = 10.5$ Hz), 146.2 (d, $J_{C,P} = 2.9$ Hz); $^{19}$F NMR (CDCl$_3$): $\delta$ -78.1; $^{31}$P NMR (CDCl$_3$): $\delta$ 21.1; HRFABMS (positive) calcd for C$_{34}$H$_{48}$OP ($M^+$): 503.3437, found: 503.3423; HRFABMS (negative) calcd for CO$_3$F$_3$S ($M^-$): 148.9520, found: 148.9521.
$^1$H and $^{13}$C NMR of 1d
$^1$H and $^{13}$C NMR of $3a$
$^1$H and $^{13}$C NMR of 4a
$^1$H and $^{13}$C NMR of 5a

![NMR Spectra](image)

**1H NMR Spectra:**
- Chemical Shifts
- Integration
- Multiplicities
- Coupling Constants

**13C NMR Spectra:**
- Chemical Shifts
- Integration
- Assignments

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**Supplementary Material (ESI) for Chemical Communications**

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$^1$H and $^{13}$C NMR of 6a
$^{1}H$, $^{13}C$, $^{19}F$ and $^{31}P$ NMR of $O$, $P$-acetal generated from \textbf{1a} and (\textit{p}-tol)$_{3}$P
References