A Facile Synthesis of Benzo[*b*]thiophene Derivatives

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Lithiation of *S*-(2-methylphenyl) *N,N,N',N'*-tetramethylphosphorodiamidothioate with *sec*-BuLi at -105° gave the corresponding benzylic anion which was acylated with various aromatic esters to give various deoxybenzoin derivatives in moderate to high yields. Acidic treatment of these products in refluxing formic acid gave 2-arylbenzo[*b*]thiophene derivatives. 2-Methylbenzo[*b*]thiophene and benzo[*b*]thiophen-2(3*H*)-one were also prepared using the similar procedure.

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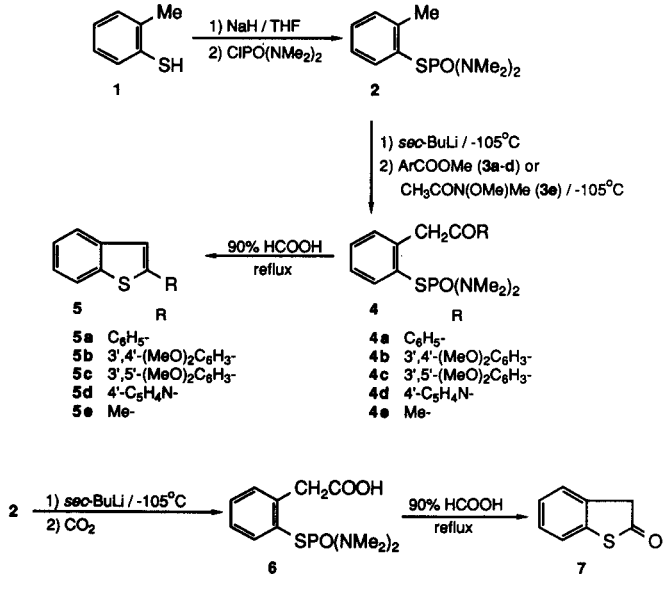
There are many synthetic methods for the preparation of benzo[*b*]thiophene derivatives [1]. Although the cyclodehydration of phenylthiomethyl ketones under strong acidic conditions were widely used for their construction, the presence of acid labile groups on the molecule may present difficulties [1,2].

Recently, we developed a convenient method for the synthesis of 2-arylbenzo[*b*]furan derivatives using regioselective lithiation of *ortho*-cresol derivatives bearing *O*-bis(dimethylamino)phosphoryl group as a directing group followed by condensation with aromatic esters and subsequent acidic treatment [3]. To extend the directed lithiation for the synthesis of heterocyclic compounds using bis(dimethylamino)phosphoryl group [4], we report here an efficient synthesis of benzo[*b*]thiophene derivatives starting from *ortho*-thiocresol. Although the directed lithiations of aromatic thiols [5] and thioethers [6] have recently been reported, lithiation of 2-(alkylthio)-toluenes could not generate the corresponding benzylic anions in regioselective manner and subsequent reaction with electrophiles gave a mixture of regioisomers [6].

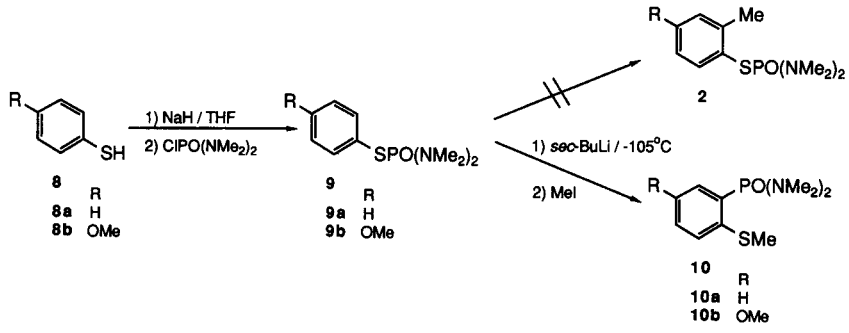
The required *S*-(2-methylphenyl) *N,N,N',N'*-tetramethylphosphorodiamidothioate (**2**) [7] were easily prepared in high yield by the reaction of *ortho*-thiocresol (**1**) with bis(dimethylamino)phosphoryl chloride in the presence of sodium hydride in tetrahydrofuran (THF). Lithiation of **2** with 1.2 equivalents of *sec*-BuLi in THF at -105° for 1 hour resulted in the formation of the corresponding benzylic anion, which upon treatment with methyl benzoate (**3a**) and quenching with saturated ammonium chloride at -90° gave deoxybenzoin derivative **4a** in 59% yield (Chart 1). When methyl 3,4-dimethoxybenzoate (**3b**), 3,5-dimethoxybenzoate (**3c**) or isonicotinate (**3d**) were employed, the corresponding condensation products **4b,c,d** were obtained in 64, 50 or 80% yields. Phenylacetone derivative **4e** was obtained in 74% yield by the reaction of **2** with *N*-methoxy *N*-methylacetamide (**3e**) under the similar conditions described above. Acidic treatment of **4a** in refluxing 90% formic acid for 1 hour [3] gave 2-phenylbenzo[*b*]thiophene (**5a**) [8] in 63% yield. Similarly, 2-(3',4'-dimethoxyphenyl)benzo[*b*]thiophene (**5b**), 2-(3',5'-dimethoxyphenyl)benzo[*b*]thiophene (**5c**), and 2-(4'-pyridyl)benzo[*b*]thiophene (**5d**) were obtained in 70, 90, and 90% yields starting from **4b**, **4c**, and **4d**, respectively, Similar treatment of **4e** gave 2-methylbenzo[*b*]thiophene (**5e**) [9] in 54% yield. When the benzylic anion of **2a** was quenched with carbon dioxide, phenylacetic acid derivative **6** was obtained in 96% yield. Acidic treatment of **6** gave benzo[*b*]thiophen-2(3*H*)-one (**7**) [10] in high yield (Chart 1).

Chart 1



An attempt for the synthesis of *S*-(2-methylphenyl) *N,N,N',N'*-tetramethylphosphorodiamidothioate derivatives **2** *via ortho*-lithiation of the corresponding *S*-phenyl

Chart 2



phosphorodiamidothioates **9a,b** with methyl iodide unfortunately failed. Namely, *S*-phenyl or *S*-(4-methoxyphenyl) *N,N,N',N'*-tetramethylphosphorodiamidothioates **9a,b**, prepared starting from **8a,b**, were lithiated by the action of *sec*-BuLi at -105° and the reaction mixture was immediately reacted with methyl iodide at the same temperature to give exclusively *S*→*C* 1,3-tetramethylphosphoryl migration products **10** [4], and none of the desired **2** was detected (Chart 2). However, the preparations of *ortho*-thiocresol derivatives have been well established [11], the above method provided a new and efficient synthesis of various benzo[*b*]thiophene derivatives.

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were obtained in KBr disk using a JASCO 810 spectrophotometer. The UV spectra were recorded in 95% ethanol on a Hitachi 323 spectrophotometer. The ^{1}H-nmr spectra were obtained with JEOL JNM-PMX 60 and Hitachi R-600 spectrometer using deuteriochloroform as a solvent and tetramethylsilane as an internal reference. The ms were determined on a JEOL JMX-DX 303 mass spectrometer. Elemental analyses were performed at the Microanalytical Laboratory of the Center for Instrumental Analysis in Nagasaki University. All solvents used for lithiation reaction were freshly distilled from benzophenone ketyl before use. Conventional column or flash column chromatography was carried out on Merck Kieselgel 60 (230-400 mesh).

General Procedure for the Syntheses of *S*-Aryl Tetramethylphosphorodiamidothioates **2** and **9a,b**.

The following procedure for the synthesis of *S*-(2-methylphenyl) *N,N,N',N'*-tetramethylphosphorodiamidothioate (**2**) is representative; the other amidothioates **9a,b** were obtained similarly.

S-(2-Methylphenyl) *N,N,N',N'*-Tetramethylphosphorodiamidothioate (**2**).

ortho-Thiocresol (**1**, 12.4 g, 100 mmoles) in THF (100 ml) was added to a stirred suspension of sodium hydride (60% NaH, 5.2 g, 130 mmoles) in THF (50 ml) at 0°. The reaction mixture was stirred at room temperature for 30 minutes and was then cooled in an ice bath and bis(dimethylamino)phosphoryl chloride (25.6 g, 150 mmoles) in THF (50 ml) was added dropwise. The reaction mixture was stirred at room temperature for 12 hours. After the solvent was removed, saturated ammonium chloride solution and methylene chloride were added to the residue. The organic layer was separated, dried over sodium sulfate and then the solvent was removed to yield crude **2** as an oil. Purification by distillation gave pure **2** (21.4 g, 83%), bp 136°/0.5 mm Hg; ms: m/z: 258 (M^+); ir (neat): 3460, 2930, 2900, 1475, 1300, 1210, 995 cm^{-1}; uv: nm (log ϵ) 270 (sh) (3.52), 277.5 (sh) (3.42). ^{1}H-nmr: δ 2.51 (3H, s), 2.65 (12H, d, J = 10.8), 7.05-7.28 (3H, m), 7.51-7.73 (1H, m).

Anal. Calcd. for $C_{11}H_{19}N_2OPS$: C, 51.11; H, 7.41; N, 10.89. Found: C, 50.83; H, 7.39; N, 10.97.

S-Phenyl *N,N,N',N'*-Tetramethylphosphorodiamidothioate (**9a**).

This compound was obtained in 88% yield, bp 140°/1 mm Hg; ms: m/z 244 (M^+); ir (neat): 3500, 3450, 2920, 2870, 1570, 1470, 1290, 1200, 980 cm^{-1}; uv: nm (log ϵ) 218 (s) (3.92), 240 (s) (3.66), 272 (s) (2.64); ^{1}H-nmr: δ 2.62 (12H, d, J = 12), 7.20-7.51 (5H, m).

Anal. Calcd. for $C_{10}H_{17}N_2OPS$: C, 49.16; H, 7.01; N, 11.47. Found: C, 48.89; H, 6.93; N, 11.57.

S-(4-Methoxyphenyl) *N,N,N',N'*-Tetramethylphosphorodiamidothioate (**9b**).

This compound was obtained in 85% yield, bp 160°/0.8 mm Hg; ms: m/z: 274 (M^+); ir (neat): 3450, 2930, 2900, 1590, 1495, 1460, 1290, 1250, 1210, 1180, 1100, 1060, 1020, 980 cm^{-1}; uv: nm (log ϵ) 229 (s) (4.01), 244 (4.10), 279 (s) (3.14), 285.5 (s) (3.05); ^{1}H-nmr: δ 2.65 (12H, d, J = 11.3), 3.77 (3H, s), 6.84 (2H, d, J = 8.8), 7.51 (2H, dd, J = 8.8, 1.5).

Anal. Calcd. for $C_{11}H_{19}N_2O_2PS$: C, 48.16; H, 6.98; N, 10.21. Found: C, 48.18; H, 6.86; N, 10.27.

General Procedure for the Synthesis of Deoxybenzoin Derivatives **4**.

The following procedure for the synthesis of *S*-2-(phenacyl)-phenyl *N,N,N',N'*-tetramethylphosphorodiamidothioate (**4a**) is representative; the other deoxybenzoins **4b-d** were obtained similarly.

S-2-(Phenacyl)phenyl *N,N,N',N'*-Tetramethylphosphorodiamidothioate (**4a**).

A solution of *sec*-BuLi (1.00 *M* in cyclohexane, 7.20 ml, 7.20 mmoles) was injected into a stirred solution of *S*-(2-methylphenyl) *N,N,N',N'*-tetramethylphosphorodiamidothioate (**2**, 1.55 g, 6.00 mmoles) in THF (50 ml) at -105° (liquid nitrogen-ethanol bath) under a nitrogen atmosphere. After stirring at -105° for 1 hour, a solution of methyl benzoate (**3a**, 1.22 g, 9.00 mmoles) in THF (10 ml) was injected into the lithiated solution at -105°. The stirring

was continued for additional 1 hour at -105°. The reaction mixture was quenched with saturated ammonium chloride solution at -90° and the solution was allowed to warm to room temperature. THF was removed under reduced pressure. The residue was extracted with dichloromethane and the organic layer was separated, dried over sodium sulfate, and then evaporated to give crude **4a**. Chromatographic purification using dichloromethane as an eluent gave pure **4a** (1.23 g, 59%), mp 97° (recrystallization from ether/dichloromethane); ms: m/z 362 (M^+); ir (potassium bromide): 2940, 2900, 2850, 2810, 1695, 1595, 1580, 1480, 1460, 1445, 1345, 1290, 1220, 1180, 1165, 990, 975, 670, 560 cm^{-1}; uv: nm (log ϵ) 243 (3.78); ^{1}H-nmr: δ 2.64 (12H, d, J = 11.4), 4.76 (2H, s), 7.22-7.33 (3H, m), 7.47 (1H, d, J = 7.3), 7.49 (1H, d, J = 7.7), 7.57 (2H, td, J = 7.3, 1.8), 7.63 (2H, dd, J = 7.7, 1.8), 8.11 (2H, dd, J = 7.7, 2.2).

Anal. Calcd. for $C_{18}H_{23}N_2O_2PS$: C, 59.62; H, 6.39; N, 7.77. Found: C, 59.39; H, 6.36; N, 7.70.

S-2-(3',4'-Dimethoxyphenacyl)phenyl *N,N,N',N'*-Tetramethylphosphorodiamidothioate (**4b**).

This compound was obtained in 64% yield, mp 92° (ether/dichloromethane); ms: m/z 422 (M^+); ir (potassium bromide): 2975, 2850, 1675, 1585, 1520, 1470, 1420, 1270, 1205, 1160, 1150, 1030, 995, 970, 670, 550 cm^{-1}; uv: nm (log ϵ) 229 (4.43), 276 (4.08), 306.5 (3.82); ^{1}H-nmr: δ 2.62 (12H, d, J = 12.0), 3.89 (6H, s), 4.68 (2H, s), 6.88 (1H, d, J = 8.2), 7.18-7.30 (3H, m), 7.51-7.66 (2H, m), 7.77 (1H, dd, J = 8.2, 2.0).

Anal. Calcd. for $C_{20}H_{27}N_2O_4PS$: C, 56.84; H, 6.44; N, 6.66. Found: C, 56.90; H, 6.69; N, 6.60.

S-2-(3',5'-Dimethoxyphenacyl)phenyl *N,N,N',N'*-Tetramethylphosphorodiamidothioate (**4c**).

This compound was obtained in 50% yield, mp 115-116° (ether/dichloromethane); ms: m/z 422 (M^+); ir (potassium bromide): 3000, 2940, 2900, 2850, 1680, 1600, 1460, 1420, 1340, 1300, 1295, 1210, 1200, 1160, 1050, 980 cm^{-1}; uv: nm (log ϵ) 265 (3.93), 321 (3.63); ^{1}H-nmr: δ 2.61 (12H, d, J = 10.8), 3.80 (6H, s), 4.66 (2H, s), 6.63 (1H, t, J = 2.4), 7.20-7.72 (6H, m).

Anal. Calcd. for $C_{20}H_{27}N_2O_4PS$: C, 56.86; H, 6.44; N, 6.63. Found: C, 56.72; H, 6.32; N, 6.69.

S-2-(Isonicotinoylmethyl)phenyl *N,N,N',N'*-Tetramethylphosphorodiamidothioate (**4d**).

This compound was obtained in 80% yield, mp 128° (ether/dichloromethane); ms: m/z 363 (M^+), ir (potassium bromide): 2920, 2850, 1700, 1460, 1410, 1380, 1355, 1300, 1280, 1225, 1220, 1205, 1180, 1060, 1015, 995, 965, 810, 775, 740, 675, 590, 560 cm^{-1}; uv: nm (log ϵ) 268 (s) (3.54). ^{1}H-nmr: δ 2.60 (12H, d, J = 12.0), 4.76 (2H, s), 7.20-7.36 (3H, m), 7.47-7.71 (1H, m), 7.89 (2H, dd, J = 6.0, 2.0), 8.83 (2H, dd, J = 6.0, 2.0).

Anal. Calcd. for $C_{17}H_{22}N_3O_2PS$: C, 56.15; H, 6.10; N, 11.62. Found: C, 56.09; H, 6.02; N, 11.47.

Synthesis of *S*-2-(Acetylmethyl)phenyl *N,N,N',N'*-Tetramethylphosphorodiamidothioate (**4e**).

A solution of *N*-methoxy *N*-methylacetamide (**3e**, 0.52 g, 5 mmoles) in THF (10 ml) was injected into a solution of the benzylic anion of **2**, which was prepared from *sec*-BuLi (0.66 *M* in cyclohexane, 7.6 ml, 5 mmoles) and **2** (0.98 g, 4 mmoles), at -105° under a nitrogen atmosphere. Standard workup and chromatographic purification (dichloromethane/acetone = 9/1 as an eluent) gave **4e** (bp 145°/0.2 mm Hg, 0.89 g, 74%); ms: m/z 300 (M^+); ir (neat): 3450, 2930, 2900, 1720, 1470, 1460, 1360, 1290, 1210, 1160, 1060, 980 cm^{-1}; uv: nm (log ϵ) 230.5 (s) (3.91), 249.5 (s) (3.58); ^{1}H-nmr: δ 2.17 (3H, s), 2.63 (12H, d, J = 10.8), 4.09 (2H, s), 7.26-7.70 (4H, m).

Anal. Calcd. for $C_{13}H_{21}N_2O_2PS$: C, 51.98; H, 7.05; N, 9.33. Found: C, 51.72; H, 6.99; N, 9.32.

General Procedure for the Synthesis of 2-Arylbenzo[*b*]thiophenes (**5**).

The following procedure for the synthesis of 2-phenylbenzo[*b*]thiophene (**5a**) is representative; the other benzo[b]thiophenes **5b-d** were obtained similarly.

2-Phenylbenzo[*b*]thiophene (**5a**).

A solution of **4a** (0.41 g, 1.13 mmoles) in 90% formic acid (3 ml) was refluxed for 1 hour. After removal of formic acid under reduced pressure, 5% sodium bicarbonate solution was added to the residue and the mixture was extracted with dichloromethane. The organic layer was separated, dried over sodium sulfate, evaporated to give a residue, which was chromatographed using benzene as an eluent to give 2-phenylbenzo[*b*]thiophene (**5a**). Further purification by recrystallization from ether/*n*-hexane gave pure **5a** (mp 171°, 0.15 g, 63%) (lit [8] mp 175.5-176°); ms: m/z 210 (M^+); dichloromethane 2960, 2930, 2860, 1445, 825, 755 cm^{-1}; uv: nm (log ϵ) 232 (4.28), 256 (4.04), 265 (s) (3.98), 298 (4.33), 305 (s) (4.31), 319 (s) (4.06); ^{1}H nmr: δ 6.92-7.83 (10H, m).

Anal. Calcd. for $C_{14}H_{10}S$: C, 79.96; H, 4.79; S, 15.25. Found: C, 79.69; H, 5.09; S, 15.16.

2-(3',4'-Dimethoxyphenyl)benzo[*b*]thiophene (**5b**).

This compound was obtained 70% yield, mp 109° (ether/*n*-pentane); ms: m/z 270 (M^+); ir (potassium bromide): 2960, 2920, 2850, 1585, 1520, 1480, 1450, 1380, 1260, 1150, 1030, 850, 810, 750 cm^{-1}; uv: nm (log ϵ) 239 (s) (4.12), 278.5 (s) (3.76); ^{1}H-nmr: δ 3.67 (3H, s), 3.80 (3H, s), 6.53-7.28 (8H, m).

Anal. Calcd. for $C_{16}H_{14}O_2S$: C, 71.08; H, 5.22; S, 11.86. Found: C, 70.90; H, 5.43; S, 11.78.

2-(3',5'-Dimethoxyphenyl)benzo[*b*]thiophene (**5c**).

This compound was obtained in 90% yield, mp 35-38° (ether/n-hexane); ms: m/z 270 (M^+); ir (potassium bromide): 2950, 2830, 1595, 1520, 1460, 1460, 1430, 1340, 1320, 1300, 1200, 1160, 1080, 980, 940 cm^{-1}; uv: nm (log ϵ) 232.6 (4.51), 251 (3.99), 301.8 (4.39), 325.8 (s) (4.00); ^{1}H-nmr: δ 3.86 (6H, s), 6.47 (1H, t, J = 1.8), 6.87 (2H, d, J = 1.8), 7.26-7.91 (5H, m).

Anal. Calcd. for $C_{16}H_{14}O_2S$: C, 71.08; H, 5.22; S, 11.86. Found: C, 70.96; H, 5.50; S, 11.60.

2-(4'-Pyridyl)benzo[*b*]thiophene (**5c**).

This compound was obtained in 90% yield, mp 193° (methanol); ms: m/z 211 (M^+); ir (potassium bromide): 2960, 2930, 2850, 1590, 1460, 1380, 815, 745, 730, 720 cm^{-1}; uv: nm (log ϵ) 230 (4.28), 255.5 (3.99), 310 (4.34). ^{1}H-nmr: δ 7.25-7.61 (4H, m), 7.73-7.92 (3H, m), 8.59-8.70 (2H, m).

Anal. Calcd. for $C_{13}H_9NS$: C, 73.87; H, 4.29; N, 6.66; S, 15.17. Found: C, 74.10; H, 4.39; N, 6.47; S, 15.12.

Synthesis of 2-Methylbenzo[*b*]thiophene (**5e**).

A solution of **4e** (0.6 g, 2 mmoles) in 90% formic acid (5 ml) was refluxed for 1 hour. Standard workup and chromatographic purification (dichloromethane as an eluent) gave **5e** (0.16 g, 54%), mp 46° (ether) (lit [9] mp 51-52°); ms: m/z 148 (M^+); ^{1}H-nmr:

2.58 (3H, d, J = 1.0), 6.95 (1H, t, J = 1.0), 7.23-7.30 (2H, m), 7.68-7.78 (2H, m).

Synthesis of 2-[*S*-(*N*,*N*,*N'*,*N'*-Tetramethylphosphoryl)thio]phenylacetic Acid (**6**).

Carbon dioxide gas was passed through into the solution of the benzylic anion of **2** (1 g, 3.88 mmoles) generated with *sec*-BuLi (1.00 *M* in cyclohexane, 4.2 ml, 4.2 mmoles) at -105°. Standard workup and chromatographic purification (dichloromethane/acetone = 7/3 as an eluent) gave **6** (1.14 g, 97%), mp 120-121° (*n*-hexane/dichloromethane); ms: m/z 302 $(M+1)^+$; ir (potassium bromide): 2950, 2690, 1755, 1440, 1380, 1300, 1180, 1160, 1060, 980; uv: nm (log ε) 227 (s) (3.93), 250 (s), (3.61); ^{1}H-nmr: δ 2.65 (12H, d, J = 10.9), 4.07 (2H, s), 7.17-7.67 (4H, m).

Anal. Calcd. for $C_{12}H_{19}N_2O_3PS$: C, 47.67; H, 6.33; N, 9.27. Found: C, 47.70; H, 6.14; N, 9.19.

Synthesis of Benzo[*b*]thiophen-2(3*H*)-one (**7**).

A solution of **6** (0.78 g, 2.58 mmoles) in 90% formic acid (5 ml) was refluxed for 1 hour. Standard workup and chromatographic purification (dichloromethane as an eluent) gave **7** (0.37 g, 95%), mp 30-32° (petroleum ether) (lit [10a] mp 32-34°, lit [10b]. mp 44-45°); ms: m/z 150 (M^+); ^{1}H-nmr: δ 3.89 (2H, s), 7.24 (4H, s).

Lithiation of **9a** and **b**. Synthesis of Arylphosphonic Tetramethyldiamidates **10a,b**.

The following procedure for the synthesis of 2-(methylthio)-phenylphosphonic *N*,*N*,*N'*,*N'*-tetramethyldiamidate (**10a**) is representative; the other diamidate **10b** was obtained similarly.

2-(Methylthio)phenylphosphonic *N*,*N*,*N'*,*N'*-Tetramethyldiamidate (**10a**).

A solution of *sec*-BuLi (0.66 *M* in cyclohexane, 7.6 ml, 5 mmoles) was injected into a stirred solution of **9a** (0.91 g, 4 mmoles) in THF (50 ml) at -105° under a nitrogen atmosphere. After stirring at -105° for 5 minutes a solution of methyl iodide (0.85 g, 6 mmoles) in THF (10 ml) was injected into the lithiated solution at -105°. The stirring was continued for additional 30 minutes at -105°. The reaction mixture was quenched with saturated ammonium chloride solution at -80° and the solution was allowed to warm to room temperature. Standard workup and chromatographic purification (dichloromethane/acetone = 9/1) gave **10a** (0.73 g, 76%), bp 130°/0.3 mm Hg; ms: m/z 259 (M^+); ir (neat): 3400, 2900, 1630, 1570, 1480, 1440, 1420, 1290, 1190, 1100, 1050, 980 cm^{-1}; uv: nm (log ε) 262 (3.90), 304 (3.39); ^{1}H-nmr: δ 2.42 (3H, s), 2.66 (12H, d, J = 9.6), 7.15-7.78 (4H, m).

Anal. Calcd. for $C_{11}H_{20}N_2OPS$: C, 50.96; H, 7.78; N, 10.80. Found: C, 50.56; H, 7.55; N, 10.56.

5-Methoxy-2-(methylthio)phenylphosphonic *N*,*N*,*N'*,*N'*-Tetramethyldiamidate (**10b**).

This compound was obtained in 56% yield, bp 130°/0.2 mm Hg; ms: m/z: 288 (M^+); ir (neat): 3450, 2920, 2850, 1590, 1560, 1460, 1430, 1390, 1280, 1260, 1220, 1200, 1100, 1020, 990 cm^{-1}; uv: nm (log ε) 270 (3.98), 321 (3.45); ^{1}H-nmr: δ 2.44 (3H, s), 2.68 (12H, d, J = 9.6), 3.80 (3H, s), 7.03-7.38 (3H, m).

Anal. Calcd. for $C_{21}H_{21}N_2O_2PS$: C, 49.98; H, 7.34; N, 9.72. Found: C, 49.73; H, 7.25; N, 9.68.

REFERENCES AND NOTES

[1] A. Katritzky and C. W. Rees, *Comprehensive Heterocyclic Chemistry*, Vol **4**, Pergamon Press 1984, p 863.

[2] N. Durani, R. Jain, A. Saeed, D. K. Dikshit, S. Durani and R. S. Kapil, *J. Med. Chem.*, **32**, 1700 (1989).

[3] M. Date, K. Kawanishi, T. Hori, M. Watanabe and S. Furukawa, *Chem. Pharm. Bull.*, **37**, 2884 (1989).

[4] M. Watanabe, M. Date, K. Kawanishi, M. Tsukazaki and S. Furukawa, *Chem. Pharm. Bull.*, **37**, 2564 (1989).

[5] G. D. Figuly, C. K. Loop and J. C. Martin, *J. Am. Chem. Soc.*, **111**, 654 (1989); E. Block, V. Eswarakrishnan, M. Gernon, G. Ofori-Okai, C. Saha, K. Tang and J. Zubieta, *ibid*, **111**, 658 (1989); K. Smith, C. M. Lindsay and G. J. Pritchard, *ibid.*, **11**, 665 (1989).

[6] S. Cabiddu, C. Floris and S. Melis, *Tetrahedron Letters*, **27** 4625 (1986); S. Cabiddu, C. Fattuoni, C. Floris, G. Gelli, S. Melis and F. Sotgiu, *Tetrahedron*, **46**, 861 (1990).

[7] The related esters, *O*,*O*-diethyl *S*-phenyl phosphorothiolates, were known: A. Zwierzak, *Synthesis*, 507 (1975); S. Torii, N. Sayo, and H. Tanaka, *Chem. Letters*, 695 (1980).

[8a] A. W. Horton, *J. Org. Chem.*, **14**, 761 (1949); [b] R. Leardini, G. F. Pedulli, A. Tundo and G. Zandardi, *J. Chem. Soc., Chem. Commun.*, 1390 (1985).

[9] C. Hansch and W. A. Blondon, *J. Am. Chem. Soc.*, **70**, 1561 (1948).

[10a] G. W. Stacy, F. W. Villaescusa and T. E. Wollener, *J. Org. Chem.*, **30**, 4074 (1965); [b] W. C. Lumma, Jr., G. A. Dutra, and C. A. Voeker, *ibid.*, **35**, 3442 (1970).

[11] S. R. Sandler and W. Karo, Organic Functional Group Preparation, Vol **1**, Academic Press, New York, 1968, p 478.