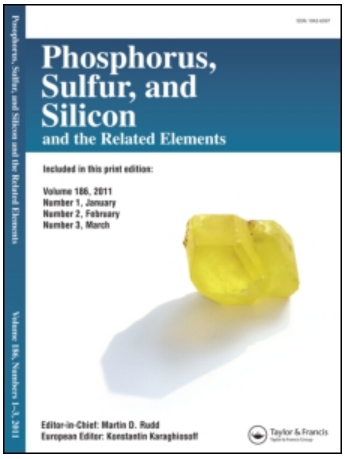

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SYNTHESIS OF N-ALKYL-*N*-{[(TRIPHENYLPHOSPHORANYLIDENE)-AMINO]SULFONYL}THIOUREAS FROM ETHYL *N*-ALKYL-*N'*-{[(TRIPHENYL-PHOSPHORANYLIDENE)AMINO] SULFONYL}CARBAMIMIDOTHIOATES

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N-(Triphenylphosphoranylidene)sulfamoyl chloride was reacted with the ethyl ester monohydrobromide of a series of *N*-alkylcarbamimidothioic acids (alkylpseudothiuronium salts) to give ethyl *N*-alkyl-*N'*-{[(triphenylphosphoranylidene)amino]sulfonyl}carbamimidothioates which were converted to the corresponding *N*-alkyl-*N'*-{[(triphenylphosphoranylide)amino]sulfonyl}thioureas by *S*-dealkylation with $NaHS/H_2S$ in DMF.

Keywords: *N*-(Triphenylphosphoranylidene)sulfamoyl chloride; *N*-alkylcarbamimidothioic acids, ethyl ester monohydrobromides; ethyl *N*-alkyl-*N'*-{[(triphenylphosphoranylidene)amino]sulfonyl}carbamimidothioates; *N*-alkyl-*N'*-{[(triphenylphosphoranylidene)amino]sulfonyl}thioureas; *S*-dealkylation; sodium hydrogen sulfide

INTRODUCTION

Sulfonylthioureas have been found to be useful in a number of applications. Members of this class of compounds have found use as complexing agents;[1–3] stabilizers and color developers for thermal recording sheets;[4,5] antibacterial agents;[6] and intermediates in the synthesis of herbicides[7] and heterocycles.[8] As part of a study of the chemistry of *N*-(triphenylphosphoranylidene)sulfamoyl chloride, Ph_3PNSO_2Cl (**1**), we have prepared a series of ethyl

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N-alkyl-*N'*-{[(triphenylphosphoranylidene)amino]sulfonyl}carbamimidothioates (alkylpseudothioureas) and have successfully *S*-dealkylated these to the corresponding sulfonylthioureas.

RESULTS AND DISCUSSION

As a guide to possible synthetic routes, the extensive chemistry of the sulfonyl chlorides was examined. The chemistry of the more formally analogous sulfamoyl chlorides, $R_1R_2NSO_2Cl$ (R_1, R_2 = alkyl), is of limited extent and an examination of the known chemistry of this class of compounds did not uncover any routes that proved fruitful.

Synthetic routes to sulfonylthioureas have been reviewed by Kurzer[9] and a general preparative route to sulfonylthioureas by the reaction of sulfonyl isothiocyanates with amines has appeared subsequent to his review.[10,11] Of the various methods surveyed, the one that proved successful was the reaction of **1** with an alkylpseudothiuronium salt (**2**; equation 1), followed by *S*-dealkylation of the product (**3**) with sodium hydrogen sulfide to give the sulfonylthiourea (**4**; equation 2):

(**1**) + $[R_1NHC(SR_2)NH_2]^+X^-$ → $Ph_3PNSO_2N{=}C(SR_2)NHR_1$ (1)

(**2**) **3**a, R_1 = H, R_2 = C_2H_5 or CH_3 d, R_1 = *n*-C_3H_7, R_2 = C_2H_5
b, R_1 = CH_3, R_2 = C_2H_5 e, R_1 = *n*-C_4H_9, R_2 = C_2H_5
c, R_1 = C_2H_5, R_2 = C_2H_5 f, R_1 = C_6H_5, R_2 = C_2H_5

(**3**) + NaHS → $Ph_3PNSO_2NHC(S)NHR_1$ (2)

4a, R_1 = H d, R_1 = *n*-C_3H_7
b, R_1 = CH_3 e, R_1 = *n*-C_4H_9
c, R_1 = C_2H_5

In the case of **3f**, dealkylation did not produce the expected thiourea; instead, the sulfamide, Ph_3PNSO_2NHPh, was obtained in 93% yield. Attempts to produce the desired thioureas by the condensation of *N*-(triphenylphosphoranylidene)sulfamide, $Ph_3PNSO_2NH_2$, with alkylisothiocyanates or dialkylthiocarbamoyl chlorides under a variety of conditions were unsuccessful. We attribute this to the substantially reduced nucleophilic character of the sulfamido nitrogen atom over that found in amines or sulfonamides.

The sulfamoyl chloride **1** reacts with alkylpseudothiuronium salts **2** (alkylpseudothioureas) in methylene chloride in the presence of triethylamine as HCl acceptor to give the corresponding sulfamoyl pseudothioureas (alkyl esters of *N*-alkyl-*N'*-{[(triphenylphosphoranylidene)amino]sulfonyl} carbamimidothioic acid) in moderate yields. Initially, we had sought to use the *N*-alkyl-*S*-methylp-

seudothiuronium iodides (**2**; $R_2 = CH_3$, X = I) throughout this study, but reasonable yields of **3** were obtained only in the case of the unsubstituted (at nitrogen) iodide **2** ($R_1 = H$, $R_2 = CH_3$).

Numerous experiments were run in which the solvent, base, temperature, order of addition, etc., were varied in an effort to maximize yields, but improvements were minimal. In all cases some decomposition of the product, or the sulfamoyl chloride itself, occurred, resulting in varying yields of triphenylphosphiniminium iodide, $(C_6H_5)_3PNH_2^+I^-$. Decomposition was more extensive when alkylpseudothiuronium iodides were used. In an attempted preparation of **3** ($R_1 = R_2 = CH_3$) in acetone using a vigorously stirred suspension of K_2CO_3 as the base, a 50% yield of triphenylphosphiniminium iodide was obtained. When methylene chloride and, to a lesser extent, acetonitrile were used as solvents, a deep red discoloration developed and purification of the products obtained from such solutions was very difficult. This discoloration did not occur when pseudothiuronium bromides were used and yields were significantly higher. Therefore, the bromides were employed in all subsequent reactions which, nevertheless, were still accompanied by some decomposition to the triphenylphosphiniminium halide.

Several methods were examined for the dealkylation of **3a-f**: the use of hydrogen sulfide in mixtures of pyridine and triethylamine;[12] sodium hydrogen sulfide and hydrogen sulfide in boiling alcohol;[13] and ethanolic NaHS at elevated temperatures in closed vessels.[14] In trial experiments with **3a** and **3b**, the use of H_2S in pyridine/triethylamine or refluxing ethanolic NaHS/H_2S at atmospheric pressure failed to dealkylate the pseudothiourea, which was recovered unchanged. Heating the compounds with ethanolic NaHS in a pressure reactor, however, did produce **4a** and **4b** but in low yields (< 10%). Better yields, and at a greater convenience, were obtained when the dealkylation was carried out in dry dimethylformamide at 95–110°C. The pseudothioureas **3a-d** were dealkylated to the corresponding thioureas in crude yields up to 90%.

EXPERIMENTAL

Unless noted otherwise, starting materials were obtained from commercial suppliers and used as received. Solvents and Et_3N were dried when required by standard techniques. Melting points were obtained using a Fisher-Johns melting-point apparatus and are uncorrected. Infrared spectra were recorded with a BIO RAD FTS 40 FT-IR spectrometer and NMR spectra ($CDCl_3$, TMS internal standard) with a Brucker or General Electric QE Plus instrument at 300 MHz. Microanalyses were by Galbraith Laboratories, Knoxville, TN.

Ethyl, *n*-propyl, and *n*-butyl isothiocyanates were prepared by the procedure of Schmidt et al[15,16] and converted into the thioureas by reaction with aqueous ammonia following a procedure similar to that described for the preparation of methylthiourea.[17] The thioureas were subsequently converted to the ethyl ester monohydrobromide of the corresponding *N*-alkylcarbamimidothioic acid (alkylpseudothiuronium salt) by reaction with ethyl bromide in dry alcohol.[18] The methyl, ethyl, and phenylpseudothiuronium salts were isolated as crystalline solids, but the *n*-propyl and *n*-butyl derivatives were obtained as syrups and used as such; however, a large quantity of the *n*-butylpseudothiuronium bromide had mostly crystallized after standing for five years in a refrigerator at 4 °C.

Sodium hydrogen sulfide was prepared as described in Brauer.[19] All reactions were run in a hood.

Ethyl N-alkyl-N'- {[(triphenylphosphoranylidene)amino]sulfonyl} carbamimidothioates (3a-f)

A one-liter, three-necked flask equipped with a mechanical stirrer, dropping funnel and a thermometer/gas-inlet adapter was charged with 37.6 g (0.100 mol) of **1**, 0.130 mol of the ethyl ester monohydrobromide of the appropriate N-alkylcarbamimidothioic acid (alkylpseudothiuronium salt) and approximately 500 mL of CH_2Cl_2; a drying tube ($CaSO_4$) was connected to the gas-inlet adapter. The slightly yellow mixture was stirred, cooled to 5 °C in an ice bath and a solution of Et_3N (23.3 g, 0.230 mol, ≈32 mL) in an equal volume of CH_2Cl_2 was added during 30–45 minutes. The cooling bath was then removed and, with continued stirring, the solution was warmed spontaneously to room temperature and allowed to stand overnight. If a tlc (silica gel) examination of the reaction mixture indicated the presence of **1**, then additional portions of the alkylpseudothiuronium salt and Et_3N were added until **1** was no longer detected.

Solvent was removed on a rotovap and the residue (a solid or yellow oil) was treated with 100 mL of cold acetone and suction filtered. The acetone filtrate was placed in a refrigerator and the solid on the frit was washed with cold water and dried. The solid which crystallized from the chilled acetone filtrate was filtered, washed with a little cold acetone, then cold water, and dried. An additional crop of crystals could sometimes be obtained by reducing the volume of the acetone filtrate from the first crop of crystals and cooling again, but a fair amount of a yellow oil, which could not be induced to crystallize, was obtained in all of the reactions as well as variable quantities of $Ph_3PNH_2^+$salts (identified by adding KI to the aqueous extracts and precipitating Ph_3PNH_2I).

The solids remaining from the cold water washings were combined and recrystallized from suitable solvents to give white, crystalline products.

3a: 83% yield; rx from CH_3CN, mp 169.5–170.0 °C; ^1H NMR (δ; coupling constants, *J*, in Hz): 1.03 (t, *J* = 7.3, 3H), 2.48 (q, *J* = 7.3, 2H), 6.43 (br s, 2H, NH_2), 7.45–7.81 (m, 15H, 3Ph); IR (KBr): 3371, 3265, 1624, 1605, 1437, 1333, 1238, 1153, 1114, 829, 759, 722, 695, 591, 520 cm^{-1}. Anal. Calcd (found) for $C_{21}H_{22}N_3O_2PS_2$: C, 56.87 (56.80); H, 5.00 (4.97); N, 9.47 (9.40).

3b: 63% yield; mp 174–176 °C (CH_3CN) ; ^1H NMR: 1.04 (t, *J* = 7.6, 3H, ethylthio CH_3), 2.46 (q, *J* = 7.6, 2H, ethylthio CH_2), 2.77 (d, *J* = 5.3, 3H, methylamino CH_3), 7.45–7.81 (m, 15H, 3Ph). IR (KBr): 3332, 1583, 1438, 1394, 1326, 1260, 1178, 1115, 1033, 848, 781, 750, 724, 693, 688, 598, 568, 528, 520 cm^{-1}. Anal. Calcd (found) for $C_{22}H_{24}N_3O_2PS_2$: C, 57.75 (57.87); H, 5.29 (5.26); N, 9.18 (9.27).

3c: 67% yield; mp 164–165 °C (CH_3CN/Et_2O) ; ^1H NMR: 1.04 (t, *J* = 7.6, 3H, ethylthio CH_3), 3.17 (m, 2H, ethylamino CH_2), 7.45–7.81 (m, 15H, 3Ph). IR (KBr): 3289, 1598, 1438, 1322, 1242, 1150, 1089, 846, 725, 694, 528 cm^{-1}. Anal. Calcd (found) for $C_{23}H_{26}N_3O_2PS_2$: C, 58.58 (58.74); H, 5.56 (5.58); N, 8.91 (8.62).

3d: 52% yield; mp 147–149 °C (CH_3CN/Et_2O); ^1H NMR: 0.90 (t, *J* = 7.6, 3H, propylamino CH_3), 1.04 (t, *J* = 7.6, 3H, ethylthio CH_3), 1.53 (m, 2H, propylamino β-CH_2), 2.47 (q, *J* = 7.6, 2H, ethylthio CH_2), 3.08 (m, 2H, propylamino α-CH_2), 7.45–7.81 (m, 15H, 3Ph). IR (KBr): 3307, 2966, 1599, 1538, 1320, 1237, 1169, 1152, 1113, 1089, 844, 725, 694, 601, 527 cm^{-1}. Anal. Calcd (found) for $C_{24}H_{28}N_3O_2PS_2$: C, 59.36 (59.30); H, 5.81 (5.77); N, 8.65 (8.69). Exact mass (MH^+): Calcd (found), 486.1439 (486.1439).

3e: 24% yield; mp 120–121.5 °C (CH_3CN/Et_2O) ; ^1H NMR: 0.88 (t, *J* = 7.6, 3H, butylamino CH_3), 1.04 (t, *J* = 7.6, 3H, ethylthio CH_3), 1.32 (m, 2H), 3.13 (m, 2H, NCH_2), 7.45–7.81 (m, 15H, 3Ph). IR (KBr): 3315, 2961, 1585, 1438, 1261, 1138, 1113, 831, 786, 759, 723, 696, 584, 519 cm^{-1}. Anal. Calcd (found) for $C_{25}H_{30}N_3O_2PS_2$: C, 60.10 (59.99); H, 6.05 (6.09); N, 8.41 (8.18). Exact mass (MH^+): Calcd (found), 500.1595 (500.1596).

3f: 67% yield; mp 166.5–167.5 °C (CH_3CN) ; ^1H NMR: 1.18 (t, *J* = 7.6, 3H, ethylthio CH_3), 2.83 (q, *J* = 7.6, 2H, ethylthio CH_2), 7.00–7.26 (m, 5H, C_6H_5N), 7.45–7.75 (m, 15H, 3Ph). IR (KBr): 3293, 1578, 1487, 1437, 1316, 1282, 1249, 1194, 1180, 1154, 1137, 1115, 1079, 938, 725, 695, 591, 517 cm^{-1}. Anal. Calcd (found) for $C_{27}H_{26}N_3O_2PS_2$: C, 61.41 (62.68); H, 5.04 (5.12); N, 8.09 (8.00).

N-alkyl-N′-{[(triphenylphosphoranylidene)amino]sulfonyl}thioureas (4a-e)

The synthesis of 4b is typical. A 500-mL, three-necked flask equipped with a mechanical stirrer, reflux condenser, and a thermometer/gas-inlet adapter was charged with 64.2 g (0.140 mol) of **3b**, 15.7 g (0.280 mol) of freshly prepared

NaHS, and 250 mL of dry DMF. The top of the reflux condenser was connected via a drying tube to a bottle of either NaOH(aq) or Clorox contained in an ice bath. The contents of the flask were stirred and heated in an oil bath to an internal temperature of 95–110 °C while a slow stream of H_2S was passed through the mixture. This temperature range was maintained for 30–60 minutes during which time the solids dissolved and the color of the reaction mixture changed from a striking aquamarine to deep green; the characteristic odor of ethyl mercaptan was noted. After ca. 60 min of heating, the oil bath was removed, the flow of H_2S stoped and the flask contents allowed to cool spontaneously to room temperature with continued stirring. If a tlc (silica gel) examination of the reaction mixture indicated the presence of unreacted **3b**, additional NaHS was added and the entire process repeated; otherwise, the flask contents were poured into 1800 mL of ice water containing 22 mL of conc. $HC_2H_3O_2$. The solid that precipitated was filtered, washed with cold water and dried thoroughly in air. The pale green, crude product was dissolved in hot CH_3CN, treated with 1–2 g of activated carbon, filtered and the filtrate chilled overnight to give 50.5 g (85%) of colorless, crystalline product, mp 167–168 °C. ^{1}H NMR: 3.04 (d, J= 4.7, 3H), 7.48–7.79 (m, 15H), 8.08 (s, 1H, methylamino NH). The doublet at δ 3.04 collapses to a singlet upon decoupling of the methylamino N nucleus. IR (KBr): 3320, 3093, 1554, 1479, 1438, 1413, 1360, 1273, 1196, 1175, 1114, 1056, 848, 725, 694, 563, 517 cm^{-1}. Anal. Calcd (found) for $C_{20}H_{20}N_3O_2PS_2$: C, 55.93 (55.91) ; H, 4.69 (4.73); N, 9.78 (9.64).

4a: 81% yield; mp 172–173 °C (DMF/CH_3CN) ; ^{1}H NMR: 7.53–7.80 (m, 15H). IR (KBr): 3376, 3272, 3182, 3114, 1615, 1439, 1330, 1198, 1140, 1115, 1040, 826, 725, 693, 596, 573, 524 cm^{-1}. Anal. Calcd (found) for $C_{19}H_{18}N_3O_2PS_2$: C, 54.93 (54.68); H, 4.37 (4.50); N, 10.11 (10.13). Exact mass (MH^+): Calcd (found), 416.0656 (416.0656). The methyl ester was also used to prepare **4a**.

4c: 87% yield; mp 165.0–166.8 °C (CH_3CN) ; ^{1}H NMR: 1.19 (t, 3H, J = 7.2, CH_3), 3.59 (m, 2H, CH_2), 7.5–7.8 (m, 15H), 8.09 (s, 1H, ethylamino NH). The multiplet at δ 3.59 collapses to a quartet upon decoupling of the ethylamino N nucleus. IR (KBr): 3345, 3097, 1547, 1482, 1466, 1438, 1388, 1327, 1194, 1176, 1151, 1101. 848, 723, 695, 604, 573, 532, 515 cm^{-1}. Anal. Calcd (found) for $C_{21}H_{22}N_3O_2PS_2$: C, 56.87 (56.82); H, 5.00 (5.36); N, 9.47 (9.09).

4d: 88% yield; mp 160–161.5 °C (CH_3CN). An analytical sample was obtained by column chromatography on silica gel with $CHCl_3$ as eluent, followed by rx from CH_3CN. ^{1}H NMR: 0.95 (t, 3H, CH_3), 1.63 (m, 2H, CH_2), 3.55 (m, 2H, CH_2), 7.45–7.82 (m, 15H), 8.18 (br s, 1H, propylamino NH). Shaking with D_2O caused the peak at δ 8.18 to disappear and the multiplet at δ 3.55 to collapse to a triplet. IR (KBr): 3356, 3076, 1547, 1481, 1438, 1391, 1191, 1174,

1157, 1120, 1100, 843, 723, 694, 605, 569, 532, 515 cm^{-1}. Anal. Calcd (found) for $C_{22}H_{24}N_3O_2PS_2$: C, 57.75 (58.30); H, 5.29 (5.42); N, 9.18 (9.32). Exact mass (MH^+): Calcd (found), 458.1126 (458.1126).

4e: 85% yield; mp 162–163.5 °C (CH_3CN). An analytical sample was obtained as described for **4d**. ^1H NMR: 0.91 (t, 3H, CH_3), 1.36 (m, 2H), 1.56 (m, 2H), 3.56 (m, 2H), 7.48–7.80 (m, 15H), 8.15 (br s, 1H). Shaking with D_2O caused the singlet at δ 8.15 to disappear and the multiplet at δ 3.56 to collapse to a triplet. IR (KBr): 3370, 3076, 2954, 1555, 1485, 1437, 1396, 1353, 1168, 1155, 1119, 847, 724, 694, 612, 555, 518 cm^{-1}. Anal. Calcd (found) for $C_{24}H_{28}N_3O_2PS_2$: C, 58.58 (59.73); H, 5.56 (5.59); N, 8.91 (9.10). Exact mass (MH^+): Calcd (found), 472.1282 (472.1283).

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