Studies on Organophosphorus Compounds. XXXIV.* Syntheses of 2,3-Dihydro-1,3,4,2-Thiadiazaphospholes and Thiohydrazides

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N'-Substituted hydrazides, 2, react with 2,4-bis-(4-methoxyphenyl) - 1,3,2,4 - dithiadiphosphetane - 2,4-disulfide, I, in refluxing benzene to give 2,3-dihydro-1,3,4,2-thiadiazaphospholes, 3; in one case also the thiohydrazide, 4e, was isolated. Benzohydrazone, 10, N',N'-disubstituted hydrazides, 6, and 4,5-dihydro-6-phenyl-3(2H)pyridazinone, 8, gave the corresponding thioanalogues after reaction with I at 80 °C. 4-Butyl-1,2-diphenyl-3,5-pyrazolidinedione (phenylbutazone), 14, reacts with I under formation of the unexpected 3,3'-dithio-bis(4-butyl-1,2-diphenyl-5-thiozo-3-pyrazolone), 15. A mechanism for the formation of 3 is suggested.

Various methods for the preparation of thiohydrazides are known, e.g. the reactions of dithioacids, 1 dithioesters, 2 or sodium dithioformate 3,4 with hydrazines and reactions of N'-thiobenzoylimidazoles with hydrazines. 5 The preparation of thiohydrazides from hydrazides and P4S10 has been reported in a few cases 6,7 but the yields are poor (see also a review 8 on thiohydrazides). As 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide, I, has been shown to be a very efficient thiation reagent for ketones, 9 carboxamides, 10-14 esters and S-substituted thioesters, 15,16 lactones, 17 lactams and imides 18 and enamines, 19 the reactions of I with hydrazides have been studied and the results are reported in this paper.

\[
\begin{align*}
\text{CH}_3\text{O} & \quad \text{O} \\
\text{O} & \quad \text{S}\quad \text{S}\quad \text{P}\quad \text{S}\quad \text{S} \\
\text{O} & \quad \text{OCH}_3
\end{align*}
\]

RESULTS AND DISCUSSION

N'-Phenyl substituted hydrazides 2a-e (Scheme 1) were reacted with I in refluxing benzene but only in one case (2e, R = Ph) was the corresponding thiohydrazide, 4e, isolated. In all cases a 2,3-

![Scheme 1](https://example.com/scheme1.png)

\[
\begin{align*}
\text{a} : R & = \text{H} \\
\text{b} : R & = \text{Me} \\
\text{c} : R & = \text{Me}_2\text{CH} \\
\text{d} : R & = \text{Me}_2\text{C} \\
\text{e} : R & = \text{Ph}
\end{align*}
\]

Scheme 1. Syntheses of 2,3-dihydro-1,3,4,2-thiadiazaphospholes from hydrazides and I.

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dihydro-1,3,4,2-thiadiazaphosphole, 3, was produced in a reasonable yield. Reaction times, yields, m.p.'s and analytical data are given in Experimental.

The phosphorus heterocyclic system, 3, has been reported once but no spectroscopic data were given. The structures, 3a–e, were confirmed by $^1$H NMR, $^{13}$C NMR, $^{31}$P NMR, mass spectroscopy and elemental analyses. The $^{31}$P NMR, chemical shifts of 3a–e were found in the region δ 86.9–97.4 which is in accordance with other compounds containing the structure 3f.

$$
\text{S} \overset{<}{\longrightarrow} \text{R} \overset{<}{\longrightarrow} \text{P} \overset{<}{\longrightarrow} \text{N} \overset{<}{\longrightarrow} \text{S} \rightarrow \text{3f}
$$

In the $^1$H NMR spectrum of 3a (R=H) H-5 absorbs at δ 7.6 and $J_{PC}$ is 5.6 Hz. The $^{13}$C NMR data of 3a–c are given in Table 1. The assignments of the chemical shifts can be made with the help of comparison compounds (Anisole derivatives and phenylhydrazine) and are supported by the magnitude of the C,P coupling constants. In an undecoupled spectrum of 3a, C(5) is distinguished from C(10) by its large C,H coupling constant.

Comparing the carbon atoms C(5) in 3a–c the same conclusion can be reached as the chemical shift value of C(5) increases with substitution whereas C(10) is unaffected. It is noted that $^4J_{PC(115)}$ =2 Hz in 3c but no $^3J_{PC(115)}$ is observed.

Concerning the mechanism for the formation of 3, different possibilities exist: As a thiohydrazide was isolated in one case and as treatment of 4e with 1 gave 3e quantitatively, reaction path A in Scheme 2 is suggested. Possibly the thiohydrazide reacts through the thiol form as has been proposed recently.

The last step is supported by the fact that salts of the type R - P(S)(NHR')S⁻ NH₃R' lose H₂S upon heating to 140 °C yielding the corresponding diamides. An alternative mechanism (B in Scheme 2) is an attack of the nucleophilic N' of 2 on 1 which gives 5. Subsequent ring closure and elimination of water gives 3.

4-Methoxy-N'-methyl-N'-phenylbenzohydrazide, 6, unable to give a phosphorus heterocycle, was reacted with 1 to give 7 in a quantitative yield and similarly 8 was transformed into 9.

**Table 1.** $^{13}$C NMR data of 2,3-dihydro-1,3,4,2-thiadiazaphospholes (CDCl₃).

|          | δ    | $|J_{PC}|$ (Hz) |
|----------|------|---------------|
|          | 3a   | 3b | 3c | 3a | 3b | 3c |
| 5        | 131.0 | 141.4 | 151.6 | 4.1 | 4.8 | 5.0 |
| 6        | 125.0 | 125.7 | 125.9 | 113.7 | 112.4 | 111.4 |
| 7        | 134.6 | 134.6 | 134.5 | 15.6 | 15.7 | 15.6 |
| 8        | 114.1 | 114.1 | 114.1 | 16.9 | 16.5 | 16.8 |
| 9        | 163.3 | 163.4 | 163.4 | 3.4 | 3.4 | 3.4 |
| 10       | 139.7 | 140.3 | 140.6 | 7.4 | 8.2 | 7.4 |
| 11       | 120.0 | 120.1 | 119.6 | 3.2 | 3.4 | 2.5 |
| 12       | 128.6 | 128.7 | 128.7 | 0 | 0 | 0 |
| 13       | 124.5 | 124.1 | 123.9 | 0 | 0 | 0 |
| 14       | 55.3  | 55.5  | 55.5  | 0 | 0 | 0 |
| 15       | –     | 19.9  | 34.0  | – | 0 | 0 |
| 16       | –     | –     | 21.2  | – | – | 2.0 |

Scheme 2. Reaction paths for the formation of 2,3-dihydro-1,3,4,2-thiadiazaphospholes, 3.

The NMR spectra of 7 show signals for two isomers in a ratio of 5.5:1, presumably the Z and E isomer with respect to the C–N bond. 24 From the spectral data no conclusion could be reached as to the preferred conformation around the N–N bond. The protons of the N–CH₃ group appear as two singlets at 2.86 (minor) and 3.18 ppm, and the corresponding signals in the $^{13}$C spectrum are at 40.3 and 38.7 ppm. The reaction between 10 and 1 leads to 11 in 20% yield and also to 2,5-diphenyl-1,3,4-thiadiazole, 12, in a 9% yield (Scheme 3).

The formation of 12 from 10 would imply an acylation or thioacylation on N' of 10 or 11; it is noted that 1,2-dibenzoylehydrazine, 13, gives 12 after reaction with $\text{P}_4\text{S}_{10}$ 25,26 or 1. When 4-butyl-1,2-diphenyl-3,5-pyrazolidinedione (phenylbutazone), 14, was allowed to react with 1 at 80 °C

Scheme 3. Thiation of benzohydrazide and 1,2-dibenzoylehydrazine.

for 3 h, 3,3′-dithio-bis(4-butyl-1,2-diphenyl-5-thioxo-3-pyrazoline), 15, was isolated in 85% yield.

The structure of 15 was determined from an X-ray crystallographic investigation. The mass spectrum obtained with an inlet temperature of 160 °C showed m/e 340, which corresponds to \( \frac{3}{2} \) M + 1. With a probe temperature of 250 °C, M (m/e 678, < 1%) is detected. The noise decoupled \(^{13}\)C spectrum of 15 shows 15 peaks of which 8 can be assigned to two nonequivalent phenyl groups. C(5) is found at \( \delta 175.3 \) which is anomalous for a thiocarbonyl carbon. C(3) and C(4) absorb at \( \delta 142.1 \) and 133.3, respectively. Acylation of 15 gives \( C_2H_2N_2O_2S \), 16, which will be dealt with in coming publications.

CONCLUSION

The method described for obtaining 2,3-dihydro-1,3,4,2-thiadiazaphospholes is advantageous as the only other method for preparing compounds of this type gives mixtures of products and low yields.

EXPERIMENTAL

\(^{1}\)H, \(^{13}\)C and \(^{31}\)P NMR spectra, IR, UV and mass spectra were obtained as described earlier. Elemental analyses were carried out by Novo Microanalytical Laboratory, Novo Industri A/S, Novo Allé, DK-2880 Bagsvaerd, supervised by Dr. R. E. Amsler. Silica gel 60 (Merck) was used for column chromatography. The b.p. of the light petroleum used was below 45 °C; m.p.s. are uncorrected.

Starting materials were prepared by known methods as follows: \(^1\)H, \(^2\)H, \(^2\)C, \(^2\)D, \(^2\)O, \(^15\)N, \(^13\)C. \(^3\)H was kindly placed at our disposal by Ciba-Geigy AG, Basel, Switzerland.

General procedure for the reaction of 2a–e, 6, 8, and 10 with I. Starting compound (10.0 mmol) and 4.04 g (10.0 mmol) of I were heated in 10 ml of anhydrous benzene with stirring until no more of the starting material could be detected (TLC). After cooling to room temperature the excess of I was filtered off. Then the reaction mixture was evaporated on silica gel under reduced pressure and applied to a silica gel column using ether/light petroleum as eluent. The reaction conditions (temperature/°C for a period of h), and the physical and analytical data are given below.

Compound 3a. 25 °C, 12 h. Yield 1.15 g (36%). m.p. 89 °C. Mass Anal. C\(_{14}\)H\(_7\)N\(_2\)O\(_2\)PS; C, H, N, P, S, MS [m/e (% rel. int.)]: 320 (100, M), 232 (86), 171 (72). \(^1\)H NMR (CDCl\(_3\)) \( \delta 3.9 \) (3 H, d), 6.5 – 7.6 (10 H, m), 7.5 (2 H, d, J\(_{PH} \) 5.6 Hz). \(^3\)P NMR (CDCl\(_3\)) \( \delta 86.9 \).

Compound 3b. 80 °C, 10 h. Yield 3.24 g (97%). m.p. 133 °C. Mass Anal. C\(_{14}\)H\(_7\)N\(_2\)O\(_2\)PS; C, H, N, P, S, MS [m/e (% rel. int.)]: 334 (100, M), 284 (61), 256 (100), 132 (81), 129 (100). \(^1\)H NMR (CDCl\(_3\)) \( \delta 2.41 \) (3 H, d, J\(_{PH} \) 2 Hz), 3.88 (3 H, s), 6.9 – 7.4 (7 H, m), 8.08 (2 H, dd, J\(_{PH} \) 15 Hz, J\(_{IH} \) 9 Hz). \(^3\)P NMR (CDCl\(_3\)) \( \delta 97.4 \).

Compound 3c. 80 °C, 12 h. Yield 2.35 g (65%). m.p. 80 °C. Mass Anal. C\(_{17}\)H\(_{19}\)N\(_2\)O\(_2\)PS; C, H, N, P, S, MS [m/e (% rel. int.)]: 362 (100, M), 160 (74). \(^1\)H NMR (CDCl\(_3\)) \( \delta 1.33 \) (6 H, d, J\(_{HH} \) 7 Hz), 2.95 (1 H, br. q, J\(_{HH} \) 7 Hz), 3.82 (3 H, s), 6.8 – 7.3 (7 H, m), 8.05 (2 H, dd, J\(_{PH} \) 15 Hz, J\(_{IH} \) 9 Hz). \(^3\)P NMR (CDCl\(_3\)) \( \delta 91.4 \).

Compound 3d. 80 °C, 12 h. Yield 3.76 g (100%). m.p. 104 °C. Mass Anal. C\(_{18}\)H\(_{21}\)N\(_2\)O\(_2\)PS; C, H, N, P, S, MS [m/e (% rel. int.)]: 376 (55, M), 248 (18), 233 (100), 174 (47). \(^1\)H NMR (CDCl\(_3\)) \( \delta 1.4 \) (9 H, s), 3.8 (3 H, s), 6.8 – 7.4 (7 H, m), 8.01 (2 H, dd, J\(_{PH} \) 15 Hz, J\(_{IH} \) 9 Hz). \(^3\)P NMR (CDCl\(_3\)) \( \delta 92.7 \).

Compound 3e. 80 °C, 1.5 h. Yield 1.58 g (40%). m.p. 114 °C. Mass Anal. C\(_{19}\)H\(_{23}\)N\(_2\)O\(_2\)PS; C, H, N, P, S, MS [m/e (% rel. int.)]: 396 (100, M), 194 (86). \(^1\)H NMR (CDCl\(_3\)) \( \delta 3.8 \) (3 H, s), 6.8 – 8.2 (14 H, m). \(^3\)P NMR (CDCl\(_3\)) \( \delta 92.5 \).

Compound 4e. 80 °C, 1.5 h. Yield 0.68 g (24%). m.p. 83 °C.

Compound 7. 80 °C, 0.75 h. Yield 2.70 g (100%). m.p. 116 °C. Mass Anal. C\(_{18}\)H\(_{20}\)N\(_2\)O\(_2\)S; C, H, N, S, MS [m/e (% rel. int.)]: 272 (27, M), 167 (54), 151 (100). \(^1\)H NMR (CDCl\(_3\)) \( \delta 2.86 \) and 3.18 (3 H, two s, N – CH\(_3\) of two formamides), 3.80 (3 H, s), 6.5 – 7.9 (9 H, m), 9.08 (1 H, br. s).

Compound 9. 80 °C, 1.75 h. Yield 1.87 g (100%). m.p. 160 °C. Mass Anal. C\(_{19}\)H\(_{18}\)N\(_2\)S; C, H, N, S, MS [m/e (% rel. int.)]: 190 (100, M), 130 (12), 103 (18), 77 (21). \(^1\)H NMR (DMSO-d\(_6\)) \( \delta 2.78 \) – 3.10 (4 H, m), 7.1 – 7.9 (5 H, m), 10.57 (1 H, br. s).

Compound 11. Solvent: toluene 110 °C, 3 h. Yield 0.30 g (20%), m.p. 71 °C.  

Compound 12. Solvent: toluene, 110 °C, 3 h. Yield 0.22 g (9 %), m.p. 140 °C.\textsuperscript{36}

Reaction of 4e with 1. 0.11 g (0.5 mmol) of 4e and 0.20 g (0.5 mmol) of 1 were refluxed with stirring in 10 ml of anhydrous benzene for 6 h. Working up as above. Yield: 0.1 g (85 %) of 3e. M.p. and mixed m.p. with an authentic sample 114 °C.

Reaction of 13 with 1. The general procedure was followed with the following exceptions: 8.08 g (20.0 mmol) of 1 was used instead of 4.04 g (10.0 mmol). 80 °C, 8 h. Yield 2.15 g 12 (91 %).

Reaction of 14 with 1. As above. 80 °C, 3 h. Yield 2.89 g (85 %), 15, m.p. 139 – 141 °C. Anal. C\textsubscript{39}H\textsubscript{38}N\textsubscript{4}S\textsubscript{2}: C, H, N, S.

Compound 15. MS [m/e (% rel. int.): 340 (70, M), 307 (100), 86 (100), 84 (95). \textsuperscript{1}H NMR (360 MHz, CDCl\textsubscript{3}): δ 0.98 (3 H, t, J\textsubscript{HH} 7.0 Hz), 1.43 (2 H, m), 1.72 (2 H, m), 2.75 (2 H, t, J\textsubscript{HH} 7.5 Hz), 6.84 (2 H, aromatic ortho protons), 7.24 – 7.37 (8 H, m, aromatic). IR (film): 3060 (m), 2940 (m), 2880 (m), 2220 (w), 1600 (s) cm\textsuperscript{-1}. UV (EtOH) [nm (log ε)]: 222 (4.01), 307 (3.91).

Acetylation of 15. 0.68 g (2.0 mmol) of 15 and 0.21 g (2.1 mmol) of triethylamine were dissolved in 4 ml of CH\textsubscript{3}Cl\textsubscript{2}. 0.16 (2.0 mmol) of acetyl chloride was added drop by drop to the stirred reaction mixture. After reflux for 30 min the reaction mixture was evaporated on silica gel and applied to a column using 75 % ether – light petroleum (v/v) as eluent. Yield 0.38 g (50 %) of compound 16. 0.28 g (41 %) of the starting material was regenerated.

Compound 16. M.p. 141 °C (ether). MS [m/e (% rel. int.): 382 (58, M), 339 (100), 307 (72). \textsuperscript{1}H NMR (CDCl\textsubscript{3}): δ 0.93 (3 H, t, J\textsubscript{HH} 6.9 Hz), 1.12 – 2.00 (4 H, m), 2.28 (3 H, s), 2.70 (2 H, t, J\textsubscript{HH} 7.3 Hz), 6.83 – 7.50 (10 H, m). IR (CHCl\textsubscript{3}): 2940 (s), 1740 (s), 1600 (m). UV (EtOH) [nm (log ε)]: 228 (5.64), 350 (5.46). Anal. C\textsubscript{21}H\textsubscript{22}N\textsubscript{2}O\textsubscript{5}: C, H, N, S.

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