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Reactions of 3,5-Diethoxycarbonyl 1,2,4-Diazaphospholes and Arsoles with Alkyl Vinyl Ethers, Sulfur Ylides, and Diazocompounds

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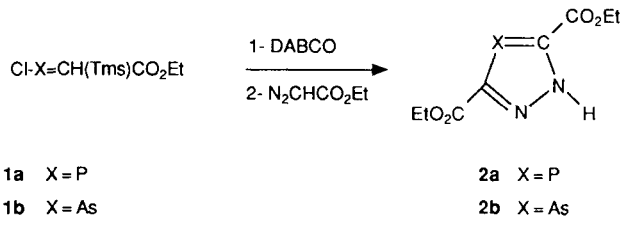
ABSTRACT

3,5-Diethoxycarbonyl 1,2,4-diazaphospholes and arsoles undergo N-alkylation by reaction with alkyl vinyl ether, sulfur ylides, and diazocompounds, owing to the acidity of the NH group. © 1995 John Wiley & Sons, Inc.

We have previously reported a synthesis of functionalized NH diazaphospholes [1] and arsoles [2] by 1,3 dipolar cycloaddition of ethyl diazoacetate with phospha and arsaalkenes according to Scheme 1. As previously described by Schmidpeter [3], for analogous compounds, the hydrogen exchanges between the two N atoms so rapidly that **2** appears to be symmetrical.



1a X = P
1b X = As

2a X = P
2b X = As

SCHEME 1

RESULTS AND DISCUSSION

We now report our studies related to the potential reactivity of these heterocycles as heterodienes or heteroalkenes.

First, we studied their reactions toward alkenes to see whether they could lead to a Diels Alder or 2 + 2 cycloaddition. With methyl acetylenedicarboxylate or ethyl acrylate, there was no reaction even after 24 hours at reflux in chloroform. Interestingly, with electron-rich alkenes, such as alkyl vinyl ethers **3**, we observed a nearly quantitative *N*-alkylation at room temperature in $CHCl_3$ for **2a** and at reflux in $CHCl_3$ for **2b** with formation of heterocycles **4** (Scheme 2).

When X = As, **4ba** and **4bb** are stable, but when X = P, the stability is highly dependent on the substituents R^1 and R^2 (**4ac** remains unchanged for a few minutes, **4aa** and **4ab** for a few hours), and the heterocycles are hydrolyzed back to **2a** [4].

The structures of all these compounds were assigned on the basis of ^1H, ^{13}C, and ^{31}P NMR and mass spectrometry. In particular, ^{31}P NMR data are consistent with the presence of a divalent phosphorus in such heterocycles, the absence of $^2J_{P-H}$ allowing us to exclude the structure with *a* > P–CH(OR^1)Me, which could have arisen from a 2 + 2 cycloaddition on –C=P– to give a bicyclic intermediate, followed by ring opening and H migration leading to an aromatic P-substituted five-membered ring. A 4 + 2 cycloaddition to give a bicyclic intermediate, followed by ring opening and H migration, according to Scheme 3, may account for the formation of **4**.

The lack of reaction between *N*-methyl diazaarsole **2c** and ethyl vinyl ether may be due to the reversibility of the 4 + 2 cycloaddition, the cycloadduct being unable to aromatize by H migration.

A more straightforward mechanism could re-

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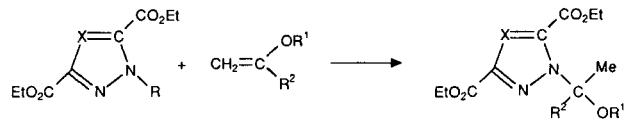
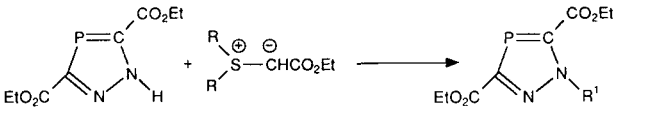


2a X = P, R = H
2b X = As, R = H
2c X = As, R = Me

3a R^1 = Et, R^2 = H
3b R^1 = nBu, R^2 = H
3c R^1 = R^2 = Me

4 aa, ab, ac
4 ba, bb

SCHEME 2



2a R = Me or Ph

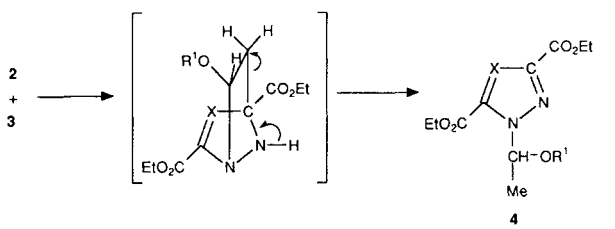
7ac, R^1 = CH_2CO_2Et
9 R^1 = Me

SCHEME 5

sult from the protonation of the vinyl ether by the acidic NH followed by nucleophic attack of the resulting aromatic anion.

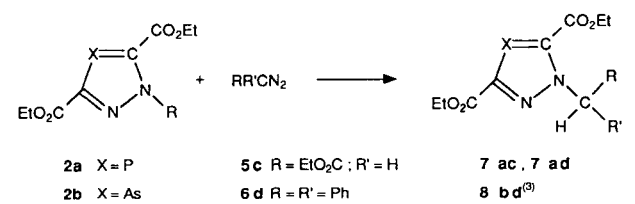
This acidic character is also shown by the reactivity of these heteropyrazoles toward diazocompounds, such as ethyl diazoacetate or diphenyl diazomethane [5]. Initially, these reactions were studied in an attempt to prepare bicyclic phosphiranes or arsiranes after nitrogen extrusion from the expected primary 1-pyrazoline. However, the only reaction observed was again *N*-alkylation (Scheme 4).

Though these reactions are not carried out under carbene-forming conditions (**5c** was added in C_6H_6 at reflux and **6d** at room temperature in chloroform), they proceed because of the acidity of the NH proton. In fact, it is known that amines and alcohols react with diazocompounds to give alkylation products, but it is necessary to use a catalyst (BF_3 or copper (I) cyanide) [6]. With our heteropyrazoles, the corresponding amide being aromatic, this catalysis is not necessary. Also, in this case, a (3 + 2) cycloaddition of the diazocompounds to the C=N bond, followed by ring opening and N_2 elimination, could reasonably account for **7** or **8** formation.



4

SCHEME 3



2a X = P
2b X = As

5c R = EtO_2C; R' = H
6d R = R' = Ph

7ac, **7ad**
8 **bd**[3]

SCHEME 4

This acidic strength was also exhibited when we tried to prepare bicyclic phosphiranes by reaction of **2a** with sulfur ylides, as we have already reported for diazaarsole **2c** [5]. Again, only the *N*-alkylated compounds were formed (Scheme 5).

When the ylide (with R = Me) was used, a mixture of **7ac** and **9** (66/34) arose. In this case, the ylide acted as a base to remove the NH proton of **2a**, and the resulting anion underwent nucleophilic substitution on the corresponding sulfonium salt, either on the methyl group with MeS CH_2CO_2Et elimination or on CH_2 with Me_2 S elimination. When R = Ph, only **7ac** was formed after Ph_2S elimination. Compound **9** may be obtained alone in 81% yield by reacting **2a** with dimethylsulfoxonium methylide in DMF at 50° during 24 hours.

All of the results which point up the acidic character of the NH proton lead to *N*-alkylation products, which are much more readily prepared at room temperature by standard alkylation processes (NaH, DMF, room temperature, $BrCH_2CO_2Et$, or Me I for **7ac** and **9**, 85 and 88% yield, respectively) in agreement with previously reported reactions of azoles and azaphospholes [7].

EXPERIMENTAL

NMR spectra were run on a Bruker AM 300 (121,49 MHz) instrument for phosphorus 31, 300 MHz for proton, and 75,47 MHz for carbon 13. High resolution mass spectra were obtained on a Varian-Mat 311 instrument located at the "Centre Regional de Mesures Physiques de l'Quest."

SYNTHESIS OF **4aa, ab, ac**

To a solution of diazaphosphole **2a** ($6.5 \cdot 10^{-4}$ mole, 0.15 g) in 0.5 mL of $CDCl_3$, there was added under nitrogen the vinyl ether ($6.5 \cdot 10^{-4}$ mole). The *N*-alkylated compound was readily formed and characterized by NMR spectroscopy.

4aa. ^{31}P NMR: δ = 137.38; ^1H NMR: δ = 1.15 (t, 3H $OCH_2\underline{CH_3}$); 1.42 and 1.43 (2t, 6H, $CO_2CH_2-\underline{CH_3}$); 1.80 (d, 3H, $\underline{CH_3}$); 3.30–3.51 (ABX_3, 2H, $^2J_{AB}$ = 9.24 Hz, $^3J_{AX}$ = 7.04 Hz, $^3J_{BX}$ = 7 Hz, $O\underline{CH_2}-CH_3$); 4.42 and 4.44 (2q, 4H, $2CO_2\underline{CH_2}CH_3$); 6.76 (q, 1H, $\underline{CH}$); ^{13}C NMR: 14.15 (qt, $^1J_{CH}$ = 127 Hz); 14.35 (qt, $^1J_{CH}$ = 127 Hz); 14.77 (qt, $^1J_{CH}$ = 126 Hz); 21.59 (qd,

$^1J_{CH}$ = 129 Hz, $^2J_{CH}$ = 131 Hz); 61.54 (tq, $^1J_{CH}$ = 148 Hz); 62.23 (tq, $^1J_{CH}$ = 148 Hz); 64.63 (tq, $^1J_{CH}$ = 142 Hz); 89.26 (dm, $^3J_{PC}$ = 2.4 Hz); 161.44 (dt, $^2J_{PC}$ = 19.6 Hz); 162.6 (d, $^1J_{PC}$ = 55.5 Hz); 163.1 (dt, $^2J_{PC}$ = 23.9 Hz); 168.47 (d, $^1J_{PC}$ = 56.1 Hz); MS calcd for $C_{12}H_{19}N_2O_5P$ (M^+): 302.1031; found: 302.1034.

4ab. ^{31}P NMR: δ = 137.8; ^{1}H NMR: δ = 0.85 (t, 3H, O(CH_2)$_3$–$\underline{CH_3}$); 1.2–1.7 (m, 4H, $OCH_2(\underline{CH_2})_2$–$CH_3$); 1.41 and 1.42 (2t, 6H, CO_2CH_2–$\underline{CH_3}$); 1.79 (d, 3H, $CH\underline{CH_3}$); 3.23–3.43 (ABX_2, 2H, $^2J_{AB}$ = 9.2 Hz, J_{AX} = 6.4 Hz, J_{BX} = 6.5 Hz, $O\underline{CH_2}(CH_2)_2CH_3$); 4.41 and 4.44 (2q, 4H, $CO_2\underline{CH_2}CH_3$); 6.73 (q, 1H, $C\underline{H}$); ^{13}C NMR: δ = 13.72 (qt, $^1J_{CH}$ = 124.7 Hz); 14.15 (qt, $^1J_{CH}$ = 127.4 Hz); 14.35 (qt, $^1J_{CH}$ = 127.1 Hz); 19.08 (tm); 21.49 (qd, $^1J_{CH}$ = 129.2 Hz, $^2J_{CH}$ = 1.2 Hz); 31.26 (tm); 61.54 (tq, $^1J_{CH}$ = 148 Hz); 62.21 (tq, $^1J_{CH}$ = 148.4 Hz); 68.86 (tq, $^1J_{CH}$ = 141.1 Hz); 89.57 (dm, $^3J_{PC}$ = 2.4 Hz); 161.45 (dt, $^2J_{PC}$ = 19.6 Hz); 162.6 (d, $^1J_{PC}$ = 55.6 Hz); 163.2 (dt, $^2J_{PC}$ = 23.9 Hz); 168.4 (d, $^1J_{PC}$ = 56.0 Hz); MS $C_8H_{11}N_2O_5P^+$ (M^+–CHMe O Bu + H)$^+$ calcd: 230.0456; found: 230.0456.

4ac. ^{31}P NMR: δ = 122; ^{1}H NMR: δ = 1.22 and 1.23 (2t, 6H, CO_2CH_2–$\underline{CH_3}$); 1.73 (s, 6H, $C(\underline{CH_3})_2$); 2.97 (s, 3H, $O\underline{CH_3}$); 4.2 and 4.27 (2q, 4H, $CO_2\underline{CH_2}CH_3$); ^{13}C NMR: δ = 13.95 (qt, $^1J_{CH}$ = 127.3 Hz); 14.24 (qt, $^1J_{CH}$ = 127.2 Hz); 27.0 (qm, $^1J_{CH}$ = 129.3 Hz); 51.8 (q, $^1J_{CH}$ = 143.8 Hz); 61.57 (tq, $^1J_{CH}$ = 148.1 Hz); 62.47 (tq, $^1J_{CH}$ = 148.4 Hz); 98.6 (dm, $^3J_{PC}$ = 1.8 Hz); 163.34 (dt, $^2J_{PC}$ = 24.07 Hz); 163.48 (dt, $^2J_{PC}$ = 20.7 Hz); 164.29 (d, $^2J_{PC}$ = 54.9 Hz); 166.16 (d, $^1J_{PC}$ = 58.03 Hz).

Synthesis of **4ba** *and* **4bb**

To a solution of **2b** (0.5 g, $1.8 \cdot 10^{-3}$ mole), there was added an excess of **3a** (0.8 g, $1 \cdot 10^{-2}$ mole) in 8 mL of chloroform. The mixture was refluxed for 24 hours at 40°C. After evaporation, **4ba** was obtained in 53% yield after chromatography (SiO_2 petroleum ether:ether, 50/50).

4ba. ^{1}H NMR: δ = 1.12 (t, 3H $OCH_2\underline{CH_3}$); 1.40 (t, 6H, CO_2CH_2–$\underline{CH_3}$); 1.75 (d, 3H, $\underline{CH_3}CH$); 3.37 (m, 2H, $O\underline{CH_2}CH_3$); 4.37 and 4.42 (2q, 4H, $CO_2\underline{CH_2}CH_3$); 6.70 (q, 1H, $C\underline{H}CH_3$); ^{13}C NMR: δ = 14.17, 14.24, 14.33 (q); 21.67 (q); 61.6 and 62.2 (2t); 64.65 (t); 89.87 (d); 162.85 and 164.35 (2s); 176.46 and 178.83 (2s); MS calcd for $C_{12}H_{19}N_2O_5As$: 346.0509; found: 346.0523.

A solution of **2b** (0.48 g, $1.75 \cdot 10^{-3}$ mole) and butyl vinyl ether (0.175 g, $1.75 \cdot 10^{-3}$ mole) in 6 mL of chloroform was refluxed during 24 hours. After evaporation and column chromatography (SiO_2, petroleum ether/ether 50/50), **4bb** was obtained in 60% yield.

4bb. ^{1}H NMR: δ = 0.96 (t, 3H $O(CH_2)_3\underline{CH_3}$); 1.42 (m, 10H, $2CO_2CH_2$–$\underline{CH_3}$ and O–CH_2–$(\underline{CH_2})_2CH_3$); 1.77 (d, 3H, $\underline{CH_3}CH$); 3.32 (m, 2H, $O\underline{CH_2}(CH_2)_2CH_3$); 4.35 and 4.38 (2q, 4H, $CO_2\underline{CH_2}CH_3$); 6.70 (q, 1H, $CH_3C\underline{H}$); ^{13}C NMR: 13.70, 14.17, 14.33 (3q); 19.05 (t); 21.55 (q); 31.22 (t); 61.50, 62.16 (2t); 68.78 (t); 90.0 (d); 162.74 and 164.26 (2s); 176.4 and 178.7 (2s); MS calcd for $C_{14}H_{23}N_2O_5As$: 374.0822; found: 374.0817.

Synthesis of **7ac, ad**

An equimolecular amount of **2a** ($1.3 \cdot 10^{-3}$ mole, 0.3 g) and ethyl diazoacetate (0.15 g, 0.14 mL) was refluxed in 5 mL of C_6H_6 during 6 hours. ^{31}P NMR spectroscopy showed that **7ac** was formed in 50% yield. (Spectroscopic data are given for the isolated compound; see end of the Experimental section.)

To 0.02 mole of **2a** (0.5 g) in 2 mL of chloroform, there was added 0.02 mole of diphenyldiazomethane **6d** (0.42 g) in 1 mL of chloroform. After 5 hours at room temperature, **7ad** was obtained in a quantitative yield (mp = 112°C).

7ad. ^{31}P NMR: δ = 137.45; ^{1}H NMR: 8.20 (s, $\underline{CH}Ph_2$); ^{13}C NMR: 70.1 (d, $^1J_{CH}$ = 142.82 Hz $\underline{C}HPh_2$); MS calcd for $(C_{21}H_{21}N_2O_4\ P)^+$: 396.1239; found: 396.1266.

Synthesis of **8bd**

To a solution of **2b** ($1.8 \cdot 10^{-3}$ mole, 0.5 g) in 5 mL of CH_2Cl_2, there was added ($2 \cdot 10^{-3}$ mole, 0.39 g) diphenyldiazomethane in 5 mL of CH_2Cl_2. Stirring at room temperature for 48 hours afforded a quantitative yield of crude **8bd**. Recrystallization from petroleum ether/ether gave 57% of pure **8bd**, mp = 94°C.

8bd. ^{1}H NMR: 1.31 (t, 6H, $CO_2CH_2\underline{CH_3}$); 4.32 and 4.28 (2q, 4H, $CO_2\underline{CH_2}CH_3$); 7.22 (10H, ArH); 8.21 (s, 1H, $C\underline{H}Ph_2$); ^{13}C NMR: 14.15, 14.25 (2q); 61.37, 62.11 (2t); 70,46 (d, $^1J_{CH}$ = 150 Hz, $\underline{C}HPh_2$); 127.97, 128.39, 128.92, 139.29 (m); 162.84, 164.10 (2t); 176.14 and 178.26 (2s); MS calcd for $(C_{21}H_{21}N_2O_4\ As)^+$; 440.0717; found: 440.0707.

Reactions of **2a** *with Sulfur Ylides*

To a solution of **2a** ($1.3 \cdot 10^{-3}$ mole, 0.3 g) in anhydrous chloroform (5 mL) there was added ethyoxycarbonyl methyl diphenyl sulfonium ylide ($1.3 \cdot 10^{-3}$ mole, 0.35 g) in chloroform (5 mL). After 48 hours, ^{31}P NMR spectroscopy showed that 50% of **7ac** had been formed.

9 was obtained by reacting **2a** ($2.17 \cdot 10^{-3}$ mole, 0.5 g) with a small excess of dimethylsulfoxonium methylide (1.2 equivalent, $2.6 \cdot 10^{-3}$ mole) in DMF (3 mL). After 24 hours at 50°C, the reaction mixture was poured into 20 mL of ice water and extracted three times with 20 mL of ether. After drying, evaporation, and distillation, **9** crystallized (mp 68°C, 81% yield).

9. ^{31}P NMR: 138; ^{1}H NMR: 1.37 and 1.38 (2t, 6H, $2CO_2CH_2$–$\underline{CH_3}$); 4.36 and 4.40 (2q, 4H, $CO_2\underline{CH_2}CH_3$); 4.42 (s, 3H, N–$\underline{CH_3}$); ^{13}C NMR: 14.17 (qt, $^1J_{CH}$ = 127.4 Hz), 14.32 (qt, $^1J_{CH}$ = 127.2 Hz);

43.78 (dq, $^3J_{PC}$ = 2.0 Hz, $^1J_{CH}$ = 143.6 Hz); 61.68 (tq, $^1J_{CH}$ = 148.1 Hz); 62.02 (tq, $^1J_{CH}$ = 148.3 Hz), 161.31 (dt, $^2J_{PC}$ = 18.2 Hz, $^3J_{CH}$ = 2.9 Hz); 161.55 (dt, $^1J_{PC}$ = 55.6 Hz); 163.16 (dt, $^2J_{PC}$ = 23.7 Hz, $^3J_{CH}$ = 3.48 Hz); 167.74 (d, $^1J_{PC}$ = 55.8 Hz).

Alkylation with NaH

1.1 equivalents of sodium hydride, washed with pentane, was covered with freshly distilled DMF and 1 equivalent of **2a** in DMF was added. After 30 minutes at room temperature, 1 equivalent of ethyl bromoacetate or methyl iodide was added. After 12 hours, the reaction mixture was poured into ice water and extracted with ether. Drying, evaporation, and short path distillation afford **7ac** (mp: 55°C) in 85% yield and **9** in 88% yield.

7ac. ^{31}P NMR: 138.5; ^{1}H NMR 1.27, 1.38, 1.41 (3t, $3CO_2CH_2-\underline{CH_3}$); 4.23, 4.37, 4.44 (3q, 6H, $3CO_2\underline{CH_2}CH_3$); 5.60 (s, 2H, $N-\underline{CH_2}-CO_2Et$); MS calcd for $(C_{12}H_{17}N_2O_6\ P)^+$: 316.0824; found: 316.0808.

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