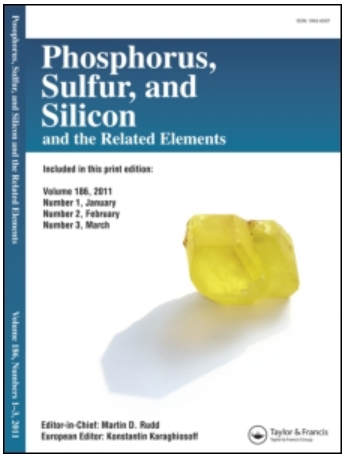

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TANDEM REACTIONS OF CYCLIC AZA-YLIDES WITH ALKYLATING AGENTS AND CARBONYL COMPOUNDS

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Reactions of 2-aminophosphonium salts with methyliodide in the presence of sodium hexamethyldisilazide(NaHMDS) gave N-methylated phosphonium salts which reacted benzaldehyde and isocyanates in the presence of NaHMDS to give ω-N-methyl-aminoalkenes and ω-N-phosphinoylamide.

Keywords: cyclic aza-ylide; Wittig reaction; alkylation; acylation

INTRODUCTION

Cyclic phosphonium salts have two nucleophilic carbons on α-positions of phosphorus atom. Recently, we reported tandem Wittig[1] and tandem Michael-Wittig reactions[2] of five and six membered phosphonium salts using these two nucleophilic points. On the other hand, iminophosphoranes are versatile reagents for synthesis of imines and nitrogen containing heterocycles[3]. Furthermore, cyclic 2-azaphosphonium salts have different kinds of nucleophilic atoms, carbon and nitrogen as shown in Figure 1.

Previously, we showed a synthesis and some applications of 2-azaphosphonium salts for preparations of heterocycles using the different kinds of theses nucleophilic centers[4]. In our continuing studies on the utilities of

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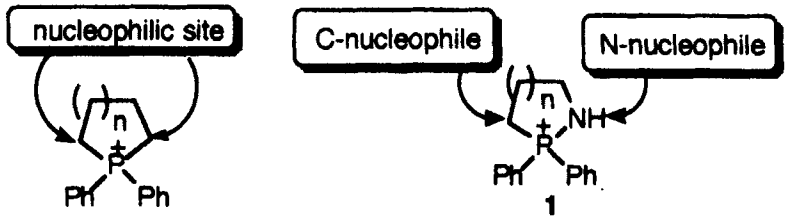


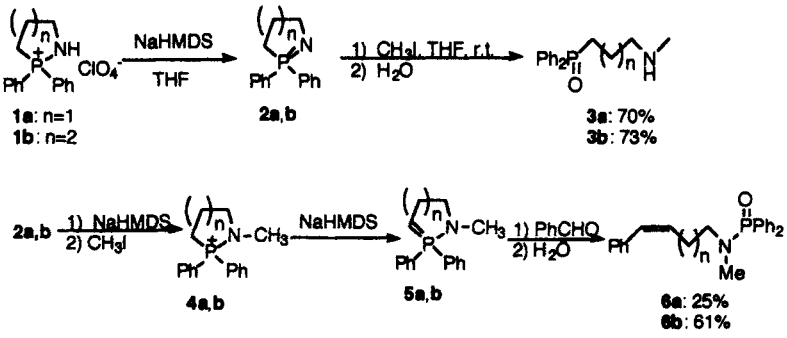
FIGURE 1

cyclic phosphonium salts to organic synthesis, we wish to report tandem reactions of 2-amino phosphonium salts.

RESULTS AND DISCUSSION

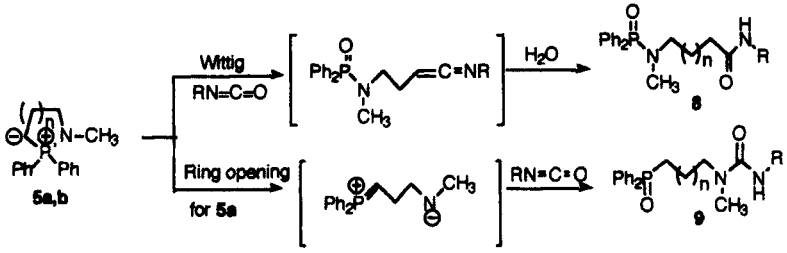
A reaction of five membered cyclic aza-yilde **2a,** generated from aminophosphonium salt **1a** in the presence of sodium hexamethyldisilazide (NaHMDS), with methyliodide gave ω-N-methylaminophosphine oxide **3a** in 70 % yield. An attempt to isolate N-methylated aminophosphonium salts **4a,b** failed. Similarly, a reaction of six membered aza-ylide **2b** gave **3b** in 73% yield. When one more equivalent of NaHMDS and benzaldehyde were added to the reaction mixture in the same reaction vessel, N-phosphinoylaminoalkenes **6a,b** were isolated in 25% and 61% yields, respectively. The geometry of olefin position in **6a,b** were determined by their nmr spectra. The coupling constant of the olefin protons was 10.7Hz for **6a,** and 12Hz for **6b** which suggests a cis configuration.

Similarly, reactions of six membered **5b** with isocyanates gave Wittig products **8,** ω-N-phosphinoylamino-amides, as major products, whereas when using the five membered **5a,** ω-phosphinoylureas **9** were the only isolated products (Scheme 2). The compound **8** would come from a Wittig reaction of ylide with isocyanate followed by hydrolysis of ketenimine. On the other hand, the product **9** would come from the ring opening of ylide **5a** to form the intermediate **A** which would react with isocyanate. The structures of **8** and **9** were determined by spectral data. Especially, in the ^{13}C nmr spectra of amides **8**, the carbonyl group appeared at 172–173 ppm. On the other hand, the chemical shifts of urea carbonyls were



SCHEME 1

observed at 156–159 ppm. These results are consistent with the observations that the carbonyl resonance of amides, N-methylacetamide, and N,N-dibutylacetamide, appear at 171.6 and 169.1 ppm, and that those of ureas such as urea and dimethylurea, appear at 161.2 and 160.3 ppm, respectively[5].

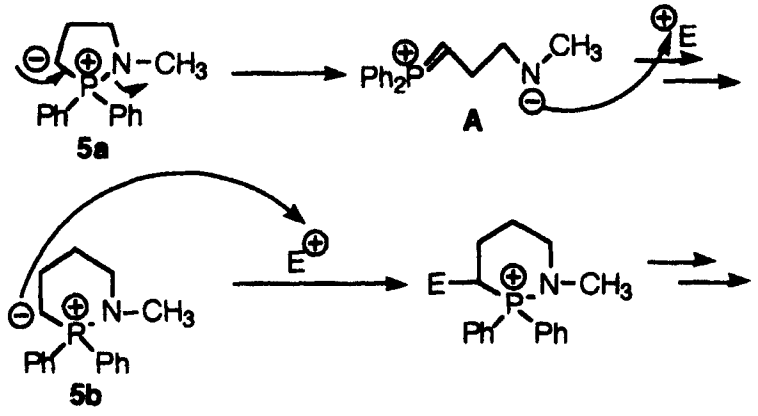


n	R	Yield(%) Amide 8	Yield(%) Urea 9
1	Ph	---	31(9aa)
	n-Pr	---	25(9ab)
2	Ph	32(8ba)	18(9ba)
	n-Pr	40(8bb)	---
	allyl	54(8bc)	---

SCHEME 2

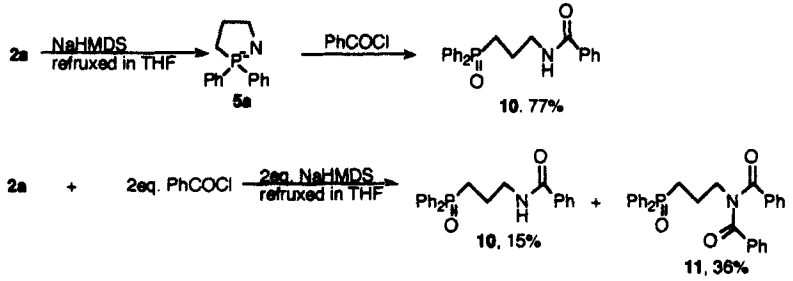
These results clearly support the intermediate formation of ylides **5a,b.** The difference of the reactivities between five and six membered ylides, **5a** and **5b,** would be due to the stabilities of the rings. Because the ring

strain of five-membered-**5a** would be much larger than that of six-membered-**5b**, the ylide **5a** would be decomposed immediately to form the intermediate **A** which reacts with electrophiles as shown in Scheme 3. The more stable six-membered ylide **5b** would react with electrophiles to form the Wittig products.



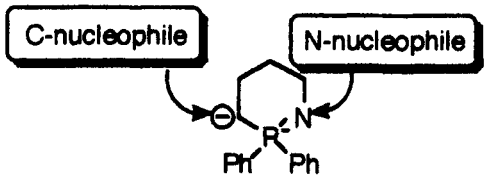
SCHEME 3

Furthermore, a reaction of **2a** with benzoylchloride in the presence of an equimolar amount of NaHMDS gave amide **10** in 77% yield. Using two equimolar amounts of benzoylchloride and NaHMDS, however, amide **10** and N,N-disubstituted amide **11** were obtained in 15% and 36% yields, respectively. The product **11** would be formed by the reaction of the intermediate **A** with benzoyl chloride.



SCHEME 4

In summary, cyclic 2-azaphosphonium salts have different kinds of nucleophilic atoms, carbon and nitrogen, and we showed that the two kinds of nucleophilic sites on the six-membered salt could be used efficiently for the formation of carbon-nitrogen and carbon-carbon bond. In the case of five membered salt, because of the lability of the phosphorus ylide formed in the second step, the ring opening reaction has occurred.



Experimental Section

3-N-methylaminopropyl-diphenylphosphine oxide 3a

To a suspension of 2-aminophospholanium perchlorate **1a**(0.68g, 2mmol) in dry THF(10ml) was added a 1M solution of NaHMDS in THF(2.2ml, 2.2mmol) at room temperature with stirring. After 15 min., a solution of methyliodide(0.28g, 2mmol) in THF(10ml) was added to the mixture and stirred for 1 hr. Then 10ml of water was added and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, and concentrated in vacuo to give **3a**(0.38g, 70%) as a white syrup; IR (neat) ν (cm^{-1}) 3400, 2980, 1590, 1480, 1420, 1310, 1260, 1210, 1180, 1120, 1100, 1070, 1030, 1000, 750, 700, 660; ^{1}H-NMR (90MHz, $CDCl_3$) δ 1.68–2.01 (m, 3H), 2.03 (s, 1H), 2.15–2.75 (m, 4H), 3.07 (s, 2H), 7.27–7.75 (m, 10H); ^{13}C-NMR (22.49MHz, $CDCl_3$) δ 18.8(d, $^{2}J_{PC}$=3.41Hz), 26.3(d, $^{1}J_{PC}$=72.8Hz), 41.6 (d, $^{3}J_{PC}$=13.7Hz), 44.2; Ms (m/z) 272 (M^+); HRMS calcd for $C_{16}H_{20}ONP$, M: 273.1283. Found, M^+: m/z 273.1277.

Compound **3b**(73% yield): white syrup; IR (neat) ν (cm^{-1}) 3400, 3050, 2950, 2875, 1590, 1480, 1440, 1400, 1310, 1290, 1210, 1100, 1010, 950, 910, 880, 840, 800, 720 ; 1H-NMR (90MHz, $CDCl_3$) δ 1.80–2.28 (m, 5H), 2.66–2.85 (m, 5H), 3.34–3.53 (m, 2H), 7.71–7.89 (m, 10H); ^{13}C-NMR (22.49MHz, $CDCl_3$) 20.54 (d, $^{3}J_{PC}$=32.23Hz), 21.8 (d, $^{1}J_{PC}$=105.47Hz), 25.02 (d, $^{2}J_{PC}$=5.37Hz), 38.65, 51.57; Ms (m/z) 287 (M^+).

Preparation of 6a

To a suspension of **1a**(0.68g, 2mmol) in dry THF(10ml) was added a 1M solution of NaHMDS in THF(2.2ml, 2.2mmol) at room temperature with stirring. After 15 min., a solution of methyliodide(0.28g, 2mmol) in THF(10ml) was added to the mixture and stirred for 1 hr. To the reaction mixture was added a 2.2ml of 1M NaHMDS(2.2mmol) in THF dropwise and the this mixture was stirred for 30min(A color of the solution was changed to red). Then a solution of benzaldehyde(0.21g, 2mmol) in THF(10ml) was added and the mixture was refluxed for 20hr. After cooling, 10ml of water was added and the mixture was extracted with dichloromethane. The organic extract was dried over anhydrous Na_2SO_4, and concentrated in vacuo to give crude mixture which was chromatographed on silica gel using ethyl acetate/methanol(9/1) as an eluent to give pure **6a**(0. 18g, 25%) as pale yellow syrup; IR (neat) $\nu(cm^{-1})$ 3040, 2400, 1740, 1440, 1380, 1220, 1120, 1050, 760, 665; ^{1}H-NMR (90MHz, $CDCl_3$) δ 2.35–2.75 (m, 5H), 2.93–3.19 (m, 2H), 5.45–5.70 (m, 1H, Ph-CH=C<u>H</u>-CH_2-), 6.41–6.54 (d, 1H, J= 11.7Hz, Ph-C<u>H</u>=), 7.17–7.69 (m, 10H, P<u>Ph</u>$_2$), 7.72–7.95 (m, 5H, Ph); ^{13}C-NMR (22.49MHz, $CDCl_3$): δ 27.5 (d, $^3J_{PC}$=5.37Hz), 34.0 (d, $^2J_{PC}$=2.93Hz), 49.0 (d, $^2J_{PC}$=2.44Hz); Ms (m/z) 361 (M+); HRMS calcd for $C_{23}H_{24}ONP$, M: 361.1595. Found, M^+: m/z 361.1607. **6b**(61% yield): ^{1}H-NMR (90MHz, $CDCl_3$) δ 1.22–3.06 (m, 9H), 5.43–5.56 (m, 1H), 6.36 (d, 1H, J=12Hz, Ph-C<u>H</u>=), 6.97–7.48 (m, 10H, P<u>Ph</u>$_2$), 7.59–7.94 (m, 5H, Ph); ^{13}C-NMR (22.49MHz, $CDCl_3$) δ 25.9, 28.5 (d, $^3J_{PC}$=4.89Hz), 34.0 (d, $^2J_{PC}$=2.93Hz), 49.0 (d, $^2J_{PC}$=1.95Hz), Ms (m/z) 375 (M^+); HRMS calcd for $C_{24}H_{26}ONP$, M: 375.1750. Found, M^+: m/z 375.1735.

Preparation of 8 and 9

After generation of **2b** from 1M NaHMDS(2.2ml, 2.2mmol) and **1b**(0.71g, 2mmol) in THF(10ml), methyliodide(0.28g, 2mmol) in THF(10ml) was added and the mixture stirred for 1hr. at room temperature. Then an additional solution of 1M NaHMDS(2.2ml, 2.2mmol) and phenylisocyanate(0.2 24g, 2mmol) in THF(10ml) was added and the mixture, refluxed overnight. After cooling to room temperature, 10 ml of water was added and extracted with dichloromethane. The organic layer wad dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was chromato-

graphed on silica gel using ethyl acetate/ethanol(9/1) as an eluent to give pure **8ba**(0.26g, 32%) and **9ba**(0.15g, 18%).

8ba: IR (neat) ν(cm^{-1}) 3240, 3180, 3050, 2940, 2850, 2320, 1670, 1590, 1540, 1480, 1440, 1330, 1250, 1160, 1110, 970, 720, 680; ^{1}H-NMR (90MHz, $CDCl_3$) δ 1.22–2.00 (m, 5H), 2.26–2.62 (m, 5H), 2.95–3.13 (m, 2H), 6.99–7.93 (m, 15H); ^{13}C-NMR (22.49MHz, $CDCl_3$) δ 22.86, 26.95 (d, $^2J_{PC}$=3.67Hz), 34.05 (d, $^2J_{PC}$=3.66Hz), 36.76, 48.05 (d, $^3J_{PC}$=2.44Hz), 171.98; Ms (m/z) 406 (M^+); HRMS(FAB) calcd for $C_{24}H_{28}O_2N_2P$, M+1: 407.1888. Found, M^++1: m/z 407.1871.

9ba: IR (neat) ν(cm^{-1}) 3300, 3060, 2940, 2340, 1650, 1600, 1540, 1490, 1440, 1380, 1310, 1220, 1180, 1120, 750, 720, 690; ^{1}H-NMR (90MHz, $CDCl_3$) δ 0.88–0.91 (m, 1H), 1.19–1.48 (m, 1H), 1.60–1.75 (m, 3H), 2.18–2.37 (m, 2H), 2.88 (s, 3H), 3.27–3.42 (m, 2H), 6.94–7.83 (m, 15H); ^{13}C-NMR (22.49MHz, $CDCl_3$) δ 19.04 (d, $^2J_{PC}$=3.66Hz), 28.33 (d, $^3J_{PC}$=10.99Hz), 29.00 (d, $^1J_{PC}$=71.41Hz), 34.48, 48.08, 155.91; Ms (m/z) 406 (M^+); HRMS(FAB) calcd for $C_{23}H_{26}O_2N_2P$, M+1: 407..1888. Found, M^++1: m/z 407.1893.

8bb(40% yield): IR (neat) ν(cm^{-1}) 3280, 3180, 2970, 2950, 2880, 1650, 1560, 1420, 1380, 1340, 1180, 1120, 1100, 980, 720, 700; ^{1}H-NMR (90MHz, $CDCl_3$) δ 0.82–0.97 (m, 4H), 1.39–1.67(m, 6H), 2.05–2.12 (m, 2H), 2.60 (d, 3H), 2.86–3.28 (m, 4H), 7.32–7.92 (m, 10H); ^{13}C-NMR (22.49MHz, $CDCl_3$) δ 11.35, 23.00(overlapped 2 carbons), 27.44 (d, $^2J_{PC}$=3.66Hz), 34.14 (d, $^2J_{PC}$=3.05Hz), 36.05, 41.34, 48.49 (d, $^3J_{PC}$=2.45Hz), 172.98; Ms (m/z) 372 (M^+); HRMS(FAB) calcd for $C_{21}H_{30}O_2N_2P$, M+1: 373.2045. Found, M^++1: m/z 373.2028.

8bc(54% yield): IR (neat) ν(cm^{-1}) 3280, 3070, 2950, 2860, 1650, 1550, 1440, 1180, 1120, 980, 920, 720, 690; ^{1}H-NMR (90MHz, $CDCl_3$) δ 1.16–1.69 (m, 5H), 2.01–2.24 (m, 2H), 2.60 (d, 3H), 2.80–3.05 (m, 2H), 3.84 (t, 2H), 5.00–5.27 (m, 2H), 5.64–5.89 (m, 1H), 7.30–7.92 (m, 10H); ^{13}C-NMR (22.49MHz, $CDCl_3$) δ 22.97, 27.41 (d, $^2J_{PC}$=3.66Hz), 34.18 (d, $^2J_{PC}$=3.66Hz), 35.94, 42.01, 48.43 (d, $^3J_{PC}$=2.44Hz), 115.91, 134.95, 172.87; Ms m/z 370(M^+); HRMS(FAB) calcd for $C_{21}H_{28}O_2N_2P$, M+1: 371.1888. Found, M^++1: m/z 371.1878.

9aa(31% yield): IR (neat) ν(cm^{-1}) 3300, 3050, 2950, 2330, 1650, 1600, 1540, 1380, 1310, 1220, 1170, 1120, 1070, 1020, 1000, 900, 750, 720, 690; ^{1}H-NMR (90MHz, $CDCl_3$) δ 1.65–2.37 (m, 5H), 3.18–3.60 (m, 5H), 6.82–7.84 (m, 15H); ^{13}C-NMR (22.49MHz, $CDCl_3$) δ 20.63 (d, $^2J_{PC}$=4.27Hz), 25.95 (d, $^1J_{PC}$=72.02Hz), 33.91, 48.70 (d, $^3J_{PC}$=9.77Hz),

156.56 ; Ms (m/z) 392 (M^+); HRMS(FAB) calcd for $C_{23}H_{26}O_2N_2P$, M+1: 393.1732. Found, M^++1: m/z 393.1737.

9ab(25% yield): IR (neat) ν(cm^{-1}) 3350, 2990, 2890, 1640, 1550, 1440, 1380, 1210, 1180, 1120, 1070, 1030, 1000, 910, 760, 700, 660; ^{1}H-NMR (90MHz, $CDCl_3$); 0.72–0.93 (m, 3H), 1.19–2.35 (m, 8H), 2.81 (s, 1H), 3.10–3.69 (m, 5H), 7.4&7.84 (m, 10H); ^{13}C-NMR (22.49MHz, $CDCl_3$) δ 11.35, 20.63 (d, $^2J_{PC}$=4.27Hz), 23.57, 25.95 (d, $^1J_{PC}$=72.02Hz), 33.91, 42.91, 48.70 (d, $^3J_{PC}$=9.77Hz), 159.41; Ms (m/z) 358 (M^+).

Reaction of 2a with benzoylchloride

To a solution of **2a** prepared from **1a**(0.68g, 2mmol) and 1M NaHMDS(2.2ml, 2.2mmol) in THF was added a solution of benzoylchloride(0.28g, 2mmol) in THF(10ml), and the mixture was stirred for 1hr. at room temperature. Then 10 ml of water was added and the mixture was extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4, and concentrated in vacuo to give **10**(0.56g, 77%) as white crystals; m. p. 242–244°C; IR (neat) ν(cm^{-1}) 3260, 3070, 2940, 1645, 1545, 1435, 1300, 1180, 1160, 1120, 690; ^{1}H-NMR (90MHz, $CDCl_3$) δ 1.73–2.29(m, 3H), 2.35–2.57(m, 2H), 3.48–3.68(m, 2H), 7.26–8.13(m, 15H); ^{13}C-NMR (22.49MHz, $CDCl_3$): δ 22. (d, $^2J_{PC}$=4.27Hz), 28.1 (d, $^1J_{PC}$=71.41Hz), 40.2 (d, $^3J_{PC}$=7.94Hz), 167.5; Ms (m/z) 363 (M+); HRMS calcd for $C_{22}H_{22}O_2NP$, M: 363.1388. Found, M^+: m/z 363.1405. When two equimolar amounts of NaHMDS were used, the compound 11 was obtained in 36% yield, along with **10**(15%). **11** has m. p. 181–184°C; IR (neat) ν(cm^{-1}) 3075, 2960, 2340, 1700, 1655, 1440, 1250, 1195, 1100, 1000, 890, 725, 700, 655; ^{1}H-NMR (90MHz, $CDCl_3$) δ 1.92–2.52(m, 4H), 4.05–4.19(m, 2H), 7.00–7.83(m, Ph, 20H); ^{13}C-NMR (22.49MHz, $CDCl_3$) δ 21.66 (d, $^2J_{PC}$=3.05Hz), 27.79 (d, $^1J_{PC}$=72.03Hz), 47.67 (d, $^3J_{PC}$=17.09Hz), 173.98; HRMS(FAB) calcd for $C_{29}H_{27}O_3NP$, M+1: 468.1729. Found, M^++1: m/z 468.1738.

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