SYNTHESES OF SIX- AND SEVEN-MEMBERED NITROGEN HETEROCYCLES FROM CYCLIC AMINO PHOSPHONIUM SALTS

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Abstract: The cyclic aza-ylides, **2a,b**, that are generated from 6- or 5-membered cyclic amino phosphonium salts, **1a,b**, can react with various carbonyl compounds. The acyclic imine derivatives were obtained by the reaction of these cyclic aza-ylides with benzils, and these imine derivatives were treated with LDA to produce the tetrahydropyridine or tetrahydroazepine derivatives.

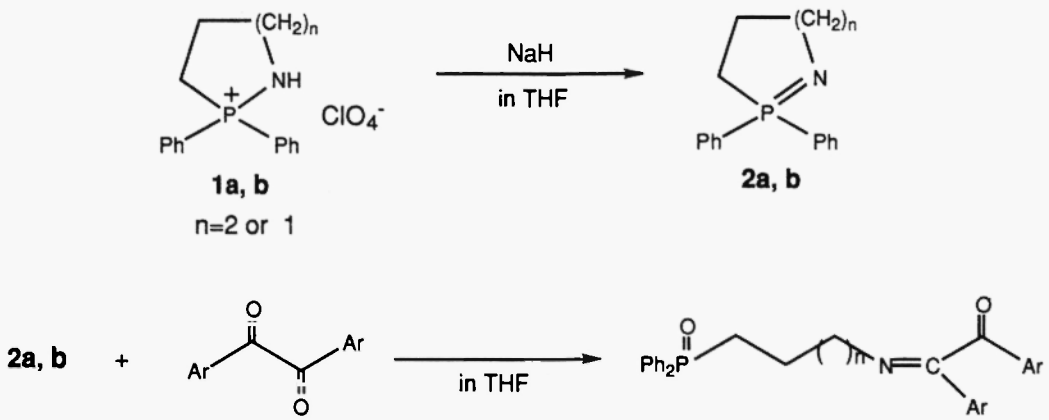
Introduction

Recently, we reported the reaction of 6- or 5-membered cyclic phosphonium ylides with α,β-unsaturated ketone such as methyl vinyl ketone, chalcone and benzalacetone, which did not give simple Wittig products but a cycloheptenyl or cyclooctenyl diphenylphosphine oxide via a Michael addition of the ylide followed by the intramolecular Wittig reaction (1)-(4). We then attempted to synthesize similar 6- or 5-membered cyclic amino phosphonium salts, **1a,b**, and investigated the reaction of aza-ylides, **2a,b**, generated from these amino phosphonium salts, **1a,b**, and carbonyl compounds. We reported the reaction of these aza-ylides, **2a,b**, with aldehydes to afford the corresponding imines in high yield and with isocyanates to afford the corresponding urea derivatives in good yield without isolating the carbodiimide intermediates prior to the hydrolysis (5).

We are interested in the reactivities of these cyclic aza-ylides, **2a,b**. Therefore, we continue to study the utilities of **2a,b** for a versatile reagents to construct nitrogen containing heterocycles. This paper reports the reaction of these aza-ylides, **2a,b**, with benzils.

Results and Discussion

The cyclic aza-ylides, **2a,b**, were generated from 6- or 5-membered cyclic amino phosphonium salts, **1a,b**, which were treated with NaH in THF. The imino phosphine oxide derivatives, **4a-d** and **5a-d**, were obtained in good yields (Table 1) as expected from the reaction of cyclic aza-ylides, **2a,b**, with benzils, **3a-d**, in THF for 2 h at 60 °C.

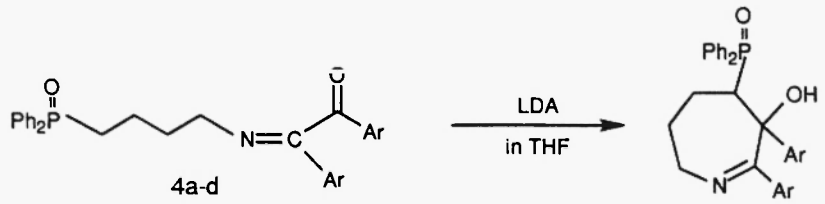


Scheme 1

Table 1 : Yields of the Purified Acyclic Imine Derivatives

Ar	Yield, %	
	n =2	n = 1
Ph	82(**4a**)	76(**5a**)
p-$CH_3C_6H_4$	67(**4b**)	74(**5b**)
p-$CH_3OC_6H_4$	50(**4c**)	64(**5c**)
m-$CH_3OC_6H_4$	64(**4d**)	75(**5d**)

The imino phosphine oxide derivative **4a** were treated with LDA in THF at -78 °C to produce 7-membered cyclic imine derivative **6a** in 23 % yield (Table 2). The structure of **6a** was determined by spectral data. Especially, the ^{31}P-NMR spectrum of **6a** showed a single peak at δ -40.23 ppm. Furthermore, in the ^{13}C-NMR of **6a**, a couple of signals attributed to the three bond coupling between a phosphorus and carbon nuclei at δ 26.60(CH_2, $^3J_{PC}$=12.20Hz) and 172.29(C=N, $^3J_{PC}$=9.15Hz) was observed. These observations suggest the compound **6a** should be a single diastereomer, and has a cyclic framework. Actually, it was confirmed that the configuration of the tetrahydroazepine derivatives, **6d**, is the 3S*,4R* form according to the X-ray crystal structure analysis(Fig. 1).



Scheme 2

Table 2 : Yields of the Purified Tetrahydroazepine Derivatives

Product	Ar	Yield (%)	m.p. (°C)	δ_p(ppm)[a]
6a	Ph	23	186.5	-40.23
6b	p-$CH_3C_6H_4$	32	215-218	-40.27
6c	p-$CH_3OC_6H_4$	46	175-179	-40.38
6d	m-$CH_3OC_6H_4$	49	174-176	-40.45

a) 98% Phosphoric acid was used as an external reference.

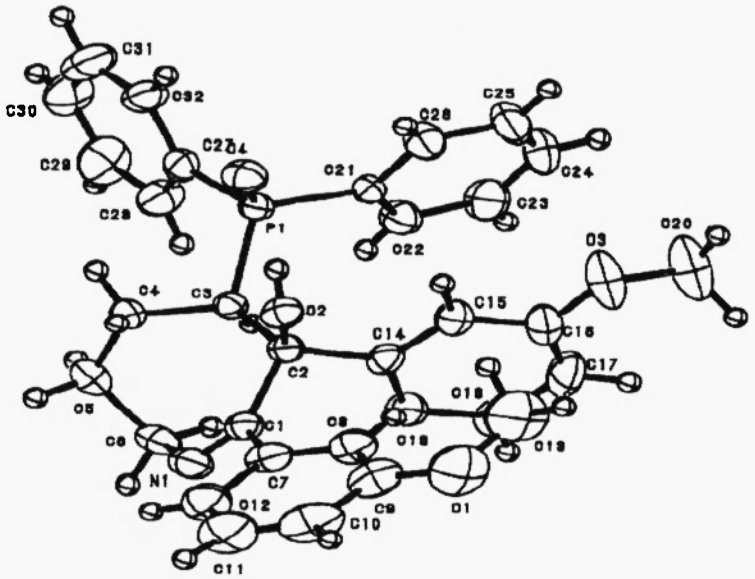
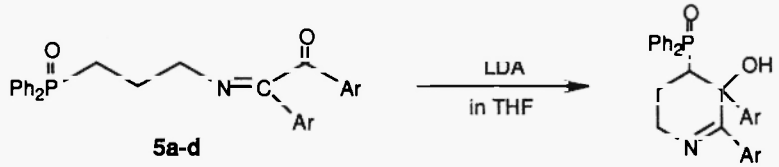


Figure 1. X-ray crystal structure of the Tetrahydroazepine derivative **(6d)**

Similarly, These imino phosphine oxide derivatives, **5a-d**, were then treated with LDA in THF at -78 °C to produce the 6-membered cyclic imine derivatives, **7a-d**, with a yield ranging from 49 % to 64 % (Table 3). Because these compounds, **7a-d**, were assumed to be a diastereomeric mixture from the ^{1}H-NMR results, we measured the existent ratio of these tetrahydropyridine derivatives using ^{31}P-NMR. The ^{31}P-NMR of **7a** showed two signals at δ -39.0 and -37.9 ppm(Table 4). The distance between the oxygen of phosphinyl group and the hydrogen of hydroxyl group was 1.793Å for S*,R*-**7a** which was calculated by Chem 3D plus. The value would be presumed to result from a hydrogen bond or an electrostatic interaction

between these two atoms. Therefore, the signal appeared at lower field, δ -39.0 ppm, should be attributable to S*,R*- form, and the upper one should be assigned to R*,R*-form. Consequently, it was found that the diastereomeric ratios of the 3S*, 4R* form and 3R*, 4R* form were ranging from 70 vs. 30 to 100 vs. 0 (Table 4). On the other hand, when compound **7d** was used, the reaction gave a single diastereomer. The diastereomer mixture of tetrahydropyridine derivative **7a** was treated with NaH in DMF at 60 °C (6) to produce the pyridine derivative **8a** in 69 % yield (Table 5). Generally, a Horner-Wittig reaction proceed in a manner of syn elimination, therefore this value is in good agreement with the ratio of the diastereomer 3S*, 4R* form in the tetrahydropyridine derivative **7a**. It can also be presumed from this result that the major product of tetrahydropyridine derivatives, **7a-d**, is the 3R*, 4S* form..



5a-d **7a-d**

Scheme 3

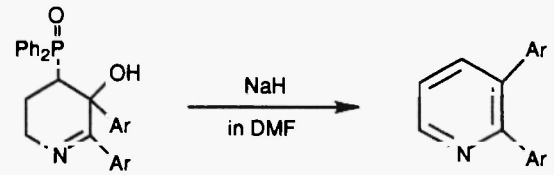
Table 3 : Yields of the Purified Tetrahydropyridine Derivatives

Product	Ar	Yield (%)	m.p. (°C)
7a	Ph	57	240-248
7b	p-$CH_3C_6H_4$	64	262-264
7c	p-$CH_3OC_6H_4$	63	218-222
7d	m-$CH_3OC_6H_4$	49	248-250

Table 4 : Diastereomer ratio of **7a-d**

Compounds	3S*, 4R*	δ_P [a)]	:	3R*, 4R*	δ_P [a)]
7a	70	-39.0	:	30	-37.9
7b	69	-39.0	:	31	-37.0
7c	76	-39.1	:	24	-37.9
7d	> 99	-39.1	:	< 1	----

a) 98% Phosphoric acid was used as an external reference.



7a-d 8a-d

Scheme 4

Table 5 : Yields of the Purified Pyridine Derivatives

Product	Ar	Yield (%)
8a	Ph	69
8b	p-$CH_3C_6H_4$	64
8c	p-$CH_3OC_6H_4$	70
8d	m-$CH_3OC_6H_4$	65

Experimental Section

General Procedures: Diphenyl[3,3-(benzoylphenylmethylideneamino) propyl] phosphine oxide(5a): A mixture of sodium hydride (60% dispersion in mineral oil, 90 mg, 2.25 mmol) and 1,1-diphenyl -2-azaphospholanium perchlorate **1b** (680 mg, 2 mmol) in 10 ml of dry THF was stirred for 30 min at room temperature and 10 min at reflux temperature. After cooling to room temperature, to the mixture was added dropwise benzil **3a** (420 mg, 2 mmol) in 5 ml of dry THF solution at room temperature and stirred for 2 h at reflux temperature. The reaction mixture was allowed to cool to room temperature. Then, water (20 ml) was added dropwise and dichloromethane (50 ml) was poured, and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 × 50 ml). The combined organic extracts were washed with brine (3 × 50 ml), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a yellow syrup (674 mg, 76%) : IR (neat) 3400, 3075, 2980, 1675, 1440, 1180 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.8-2.6 (4H, m), 3.51 (2H, t), 7.26-7.90 (20H, m); ^{13}C-NMR ($CDCl_3$) δ 23.06 (d, $^2J_{PC}$ = 3.06 Hz), 27.23 (d, $^1J_{PC}$ = 72.63 Hz), 53.62 (d, $^3J_{PC}$ = 15.26 Hz), 168.18 (s), 198.55 (s), Ph : 127.20, 127.66, 128.31, 128.61, 128.83, 129.02, 129.26, 130.53, 130.94, 131.54, 131.64, 134.52, 134.70, 135.08, 135.25; MS m/z 452.2 (M^++1); HRMS calcd for $C_{29}H_{26}O_2N_1P_1$ (M^++1) 452.1779, found 452.1790.

2-Phenyl-3-hydroxy-3-phenyl-4-diphenylphosphino-3,4,5,6-tetrahydro azepine(6a): To a LDA solution, freshly prepared from diisopropylamine(0.24g, 2.4 mmol) and n-BuLi(2.4mmol, hexane solution) was added acyclic imine **4a** (2 mmol) in 10 ml of dry THF solution at -78 °C and stirred for 20 h

was allowed to warm to room temperature. Then, water (10 ml) was added dropwise and dichloromethane (50 ml) was poured, and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 × 50 ml). The combined organic extracts were washed with brine (3 × 50 ml), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford a crude product. This crude product was recrystallized from ethyl acetate to give white crystals (214 mg, 23%) : mp 186.5 °C ; IR (neat) 3277, 3054, 2936, 1627, 1438, 1184, 1153, 1116, 989 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.73-4.29 (8H, m), 6.73-7.82 (20H, m); ^{13}C-NMR ($CDCl_3$) δ 22.05 (s), 26.49 (d, $^3J_{PC}$ = 12.20 Hz), 44.11 (d, $^1J_{PC}$ = 66.53 Hz), 47.24 (s), 86.49 (d, $^2J_{PC}$ = 4.88 Hz), 172.98 (d, $^3J_{PC}$ = 8.54 Hz), Ph : 126.28, 127.50, 128.15, 128.56, 128.72, 128.96, 129.50, 130.07, 130.29, 130.48, 131.05, 131.16, 132.08, 132.21, 135.25, 135.54, 141.64, 141.77, 143.13, 143.18; ^{31}P-NMR ($CDCl_3$, H_3PO_4 was used as external reference.) δ -40.23 (3S*, 4R* form only); MS m/z 466 (M^++1); HRMS calcd for $C_{30}H_{28}O_2N_1P_1$ (M^++1) 466.1936, found 466.1908.

2-Phenyl-3-hydroxy-3-phenyl-4-diphenylphosphino-3,4,5,6-tetrahydropyridine(7a): A LDA solution (2.1 ml, 2.2 mmol) was added to a solution of acyclic imine **5a** (2 mmol) in 6.6 ml of dry THF at -78 °C and stirred for 24 h was allowed to warm to room temperature. Then, water (10 ml) was added dropwise and dichloromethane (50 ml) was poured, and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 × 50 ml). The combined organic extracts were washed with brine (3 × 50 ml), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford a crude product. This crude product was recrystallized from ethyl acetate to give white crystal (415 mg, 57%) : mp 240-248 °C ; IR (neat) 3300, 3059, 2934, 1672, 1439, 1156, 1116 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.2-4.4 (6H, m), 6.65-7.90 (20H, m); ^{13}C-NMR ($CDCl_3$) δ 20.29 (s), 44.29 (d, $^1J_{PC}$ = 69.58 Hz), 50.02 (d, $^3J_{PC}$ = 10.38 Hz), 75.90 (d, $^2J_{PC}$ = 4.88 Hz), 168.12 (d, $^3J_{PC}$ = 5.49 Hz), Ph : 126.09, 127.01, 127.26, 127.82, 128.23, 128.37, 128.53, 128.64, 129.04, 129.53, 129.83, 130.24, 130.51, 130.91, 131.02, 131.83, 131.97, 133.89, 134.27, 138.61, 138.69, 143.67, 143.78; ^{31}P-NMR (H_3PO_4) δ -39.00 (3S*,4R* : 70), -37.86 (3R*, 4R* : 30); MS m/z 452 (M^++1); HRMS calcd for $C_{29}H_{26}O_2N_1P_1$ (M^++1) 452.1779, found 452.1737.

2,3-Diphenylpyridine(8a): A mixture of sodium hydride (60% dispersion in mineral oil, 60 mg, 1.8 mmol) and 2-Phenyl-3-hydroxy-3-phenyl-4-diphenylphosphino-3,4,5,6-tetrahydro pyridine (**7a**, 0.68 g, 1.5 mmol) in 40 ml of dry DMF was stirred for 4 h at 60 °C and allowed to cool to room temperature. Then, water (10 ml) was added dropwise and diethyl ether (50 ml) was poured, and the organic layer was separated. The aqueous layer was extracted with diethyl ether (2 × 50 ml). The combined organic extracts were washed with brine (3 × 50 ml), dried over anhydrous sodium sulfate, and concentrated under reduced

pressure. The crude product was purified by column chromatography on 100 g of silica gel using n-hexane/ethanol (8:2) as eluent to give a pale yellow syrup (239 mg, 69%) : IR (neat) 3058, 3039, 1580, 1556, 1496, 1420, 760, 747, 698 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.22-7.65 (11H, m), 7.66-7.75 (1H, m), 8.64-8.72 (1H, m); ^{13}C-NMR ($CDCl_3$) δ 122.00, 127.17, 127.72, 127.82, 128.29, 129.53, 129.88, 136.06, 138.42, 139.96, 140.23, 148.33, 157.21.

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