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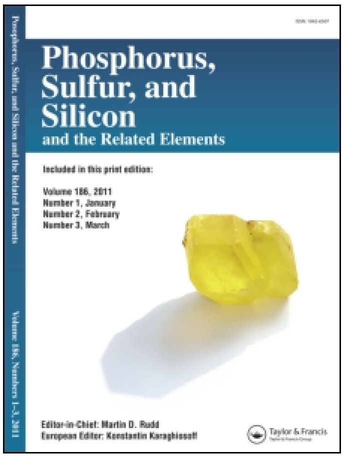

Phosphorus, Sulfur, and Silicon and the Related Elements

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REACTIONS OF CYCLIC AZA-YLIDS WITH THIOESTERS

Tetsuya Uchiyama[a]; Satoshi Katsuyama[a]; Tetsuya Fujimoto[a]; Iwao Yamamoto[a]
[a] Department of Functional Polymer Science, Faculty of Textile Science and Technology, Shinshu University, Nagano, Japan

To cite this Article Uchiyama, Tetsuya , Katsuyama, Satoshi , Fujimoto, Tetsuya and Yamamoto, Iwao(2001) 'REACTIONS OF CYCLIC AZA-YLIDS WITH THIOESTERS', Phosphorus, Sulfur, and Silicon and the Related Elements, 173: 1, 115 — 121

To link to this Article: DOI: 10.1080/10426500108045264

URL: http://dx.doi.org/10.1080/10426500108045264

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Phosphorus, Sulfur and Silicon, 2001, Vol. 173, pp. 115-121
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REACTIONS OF CYCLIC AZA-YLIDS WITH THIOESTERS

TETSUYA UCHIYAMA, SATOSHI KATSUYAMA,
TETSUYA FUJIMOTO and IWAO YAMAMOTO*

Department of Functional Polymer Science, Faculty of Textile Science and Technology, Shinshu University, Ueda, Nagano 386–8567 Japan

(Received October 27, 2000.; In final form December 7, 2000)

Reactions of five and six membered cyclic phosphonium aza-ylids, **2a,b** with phenyl thiobenzoate and aryl thiocinnamate gave acylated products **3** and **4**. On the other hand, the reactions of **2a,b** with phenyl alkenylthioesters gave compounds **5**, **6**, and **7**.

Keywords: cyclic aza-ylid; acylation; thioester

THE Wittig reaction is one of the most important methods in synthetic organic chemistry. Since Wittig and Geissler reported a new olefination technique in 1953[1], Wittig reactions including Horner-Wittig reactions and Horner-Wadsworth-Emons reactions were applied to the synthesis of various alkenes, penem and sephem β-lactams, and natural products[2]. Recently, we reported tandem Wittig and tandem Michael-Wittig reactions[3] using five and six membered cyclic phosphonium ylides. On the other hand, aza-ylids are versatile reagents for the synthesis of imines and nitrogen containing heterocycles[4]. However, no reports about reactions of cyclic aza-ylids appeared in the literatures except our publications[5]. In our continuing studies on the utilities of cyclic aza-ylides to organic synthesis, we wish to report on the reactions of 2-amino cyclic phosphonium ylides with thioesters.

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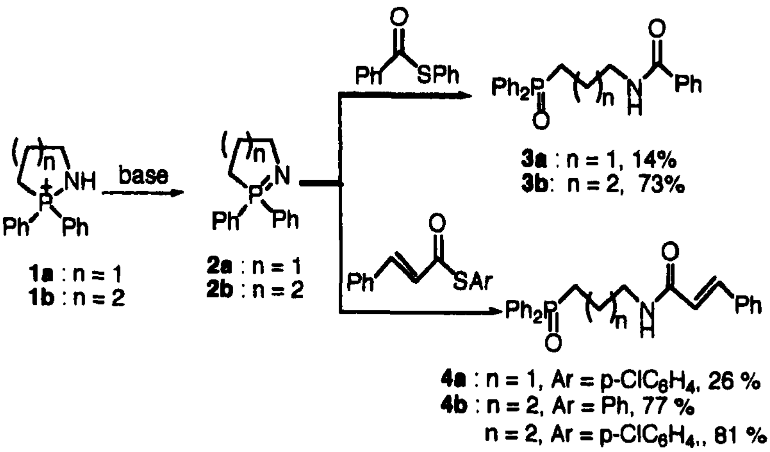
* Corresponding Author.

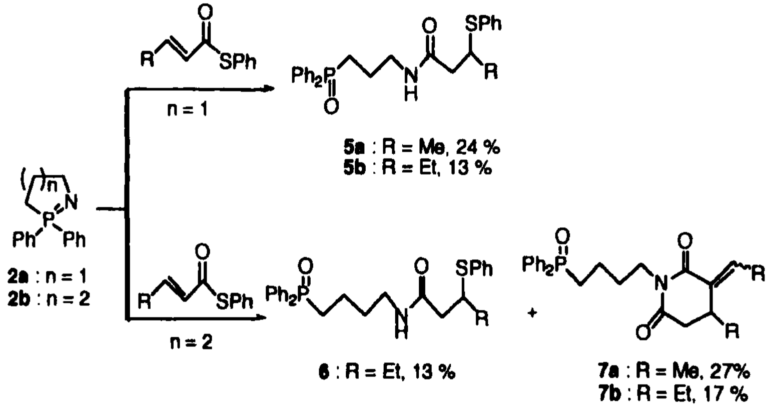
RESULTS AND DISCUSSION

Reactions of the cyclic aza-ylids **2a, b**, prepared from 2-aza-phosphonium perchlorate **1a, b** in the presence of sodium hexamethyldisilazid (NaHMDS), with phenyl thiobenzoate gave N-(ω-diphenyl-phosphinoylalkyl)-benzamide **3a, b** in 14% and 73 % yields, respectively. Similarly a reaction of **2a, b** with aryl thiocinnamate gave simple acylated products **4a, b** in 26% and 77–81% yields, respectively (SCHEME 1).



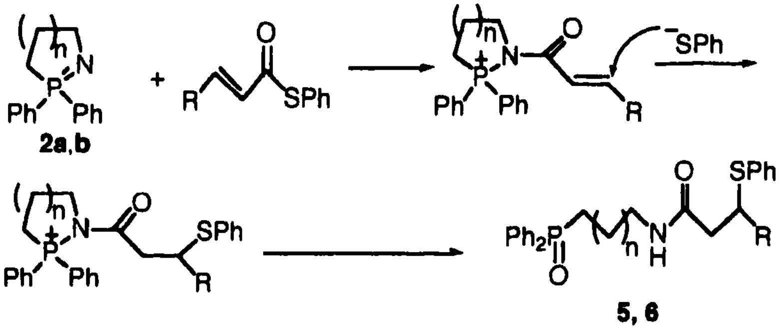
SCHEME 1

On the other hand, reactions of five membered **2a** with phenyl thiocrotonate and phenyl thio-2-pentenoate gave **5a** and **5b** in 24% and 13 % yields, respectively. Furthermore, a reaction of six membered **2b** with phenyl thiocrotonate gave **7a** in 27% yield. In the reaction of phenyl thio-2-pentenoate, **6** and **7b** were obtained in 13% and 17% yields, respectively (SCHEME 2). The structures of **5**, **6**, **7** were determined by spectral methods. In the ir spectra of **5** and **6**, a NH stretching was observed at 3270–3280 cm^{-1}, and typical amide I and II band were observed at 1660 and 1560 cm^{-1}, respectively. Furthermore, amide carbonyl group appeared at 170.84–171.18 ppm in the ^{13}C-nmr spectra of these compounds. These results are consistent with the observations that the carbonyl resonance of amides appear at 169–171 ppm[6]. The ir spectra of **7a,b** showed two carbonyl stretching bands at 1670 and 1640 cm^{-1}, and did not show any NH absorbances.

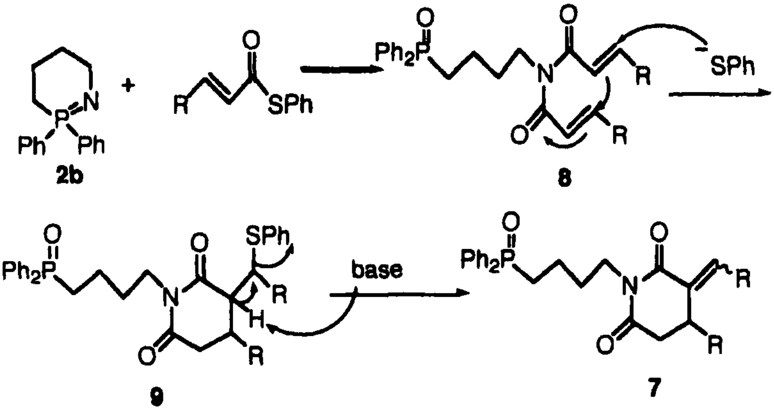


SCHEME 2

The products **5** and **6** would be come from a simple acylation of the aza-ylide followed by a Michael addition of the phenylthiolate anion. The plausible mechanism of the formation of compound **7** is envisaged as shown in SCHEME 4. N,N-bis-acylation is occurred to give an intermediate **8** in the initial step. The bis-acylation reaction was observed in the reaction of **2b** with benzoyl chloride[5c]. The intermediate **8** then reacted with the phenylthiolate anion in a Michael-type followed by an intramolecular Michael reaction to give **9**. An elimination of thiophenol from **9** under basic condition led to formation of product **7**.



SCHEME 3



SCHEME 4

EXPERIMENTAL SECTION

N-(ω-phosphinoylpropyl) benzamide 3a

To a solution of 1-aminophospholanium perchlorate **1a** (0.34 g, 1 mmol) in THF (5 ml) was added a solution of NaHMDS in THF (1.1 ml, 1.1 mmol) at room temperature under a nitrogen atmosphere. After 15 min., a solution of phenyl thiobenzoate (0.24 g, 1 mmol) in THF (5 ml) was added to the mixture and stirred for 16 hr. at room temperature. Then 5 ml of water was added and extracted with diethyl ether. The organic layer was dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a crude mixture which was chromatographed on silica gel using ethyl acetate/methanol (10/1) as eluent to give pure **3a** (0.051 g, 14%) as a colorless syrup; IR (KBr) 3250, 1640, 1540, 1440, 1300 cm^{-1}; ^{1}H-NMR (400.13MHz, $CDCl_3$) δ 1.94–2.01 (m, 2H), 2.39–2.45 (m, 2H), 3.57–3.61 (m, 2H), 7.26–7.94 (m, 15H); ^{13}C-NMR (100.61MHz, $CDCl_3$) δ 22.54 (d, $^{2}J_{pc}$=4.60Hz), 28.57 (d, $^{1}J_{pc}$=70.54Hz), 40.60 (d, $^{3}J_{pc}$=8.43Hz), 127.8–135.00 (m), 168.01 (s); MS (FAB) m/z 364 (M^{+}+1); HRMS (FAB) calcd. for $C_{22}H_{23}NO_2P$ (M+1) 364.1466. Found 364.1534.

Compound **3b** was obtained in 73% yield (0.55 g) from the reaction of **1b** (0.71g 2mmol) with phenyl thiobenzoate (0.43g, 2mmol) at reflux temperature. The crude product was purified by column chromatography on silica gel using ethyl acetate/methanol (9/1) to give pure **3b**. IR (neat) 3270, 3060, 1660, 1620, 1560, 1440, 1180, 980 cm^{-1}; MS (70eV) m/z 377 (M$^+$); HRMS (70eV) calcd for $C_{23}H_{24}NO_2P$ (M) 377.1545. Found 377.1555.

Compound **4a** was obtained in 26% yield (0.101 g) from the reaction of **1b** (0.341g, 1mmol) with *p*-chlorophenyl thiocinnamate (0.291g, 1 mmol) at room temperature. The crude product was purified by column chromatography on silica gel using ethyl acetate/methanol (15/1) to give pure **4a**.: IR (neat) 3210, 3050, 1660, 1620, 1540, 1440, 1160, 970 cm^{-1}; ^{1}H-NMR (400.13MHz, $CDCl_3$) δ 1.78–1.89 (m, 2H), 2.29–2.35 (m, 2H), 3.39–3.56 (m, 2H), 6.47 (d, J=15.72 Hz, 1H), 7.22–7.66 (15H, m), 7.40 (d, J=15.57Hz, 1H); ^{13}C-NMR (100.61MHz, $CDCl_3$) δ22.45 (d, $^2J_{pc}$=3.83Hz), 28.16 (d, $^1J_{pc}$=71.30Hz), 40.33 (d, $^3J_{pc}$=9.97Hz), 121.97 (s), 128.36–135.74 (m), 140.81 (s), 166.90 (s); MS (70eV) m/z 389 (M$^+$); HRMS (70eV) calcd for $C_{24}H_{24}NO_2P$ (M$^+$) 389.1545 found 389.1544; MS (FAB) m/z 390 (M$^+$+1); HRMS (FAB) calcd. for $C_{24}H_{25}NO_2P$ (M+1) 390.1623. Found 390.1667.

Compound **4b** was obtained from the reaction of **1b** (0.356g, 1mmol) with aryl thiocinnamate (1 mmol) at room temperature. The crude product was purified by column chromatography on silica gel using ethyl acetate/methanol (9/1) to give pure **4b** (81% when Ar=p-ClC_6H_4, 77% when Ar=Ph); IR (neat) 3270, 3025, 1660, 1620, 1550, 1440, 1170, 980 cm^{-1}; ^{1}H-NMR (500.13 MHz, $CDCl_3$) δ 1.70 (brs,4H), 2.28–2.35 (m, 2H), 3..36–3.37 (m, 2H), 6.47 (d, J=15.67 Hz, 2H), 6.96 (br, 1H), 7.27–7.74 (m, 15H); ^{13}C-NMR (125.76MHz, $CDCl_3$) δ 18.90 (d, $^2J_{pc}$=3.90Hz), 28.74 (d, $^1J_{pc}$=71.82Hz), 30.01 (d, $^3J_{pc}$=12.45Hz), 38.68 (s), 121.33 (s), 127.74–140.31 (m), 166.20 (s); MS (FAB) m/z 404 (M$^+$+1); HRMS (FAB) calcd. for $C_{25}H_{27}NO_2P$ (M+1) 404.1755. Found 404.1779.

Compound **5a** was obtained from the reaction of **1a** (0.341g, 1mmol) with phenyl thiocrotonate (0.178g, 1mmol) at reflux temperature. The crude product was purified by column chromatography on silica gel using ethyl acetate/methanol (20/1) to give pure **5a** (24% yield as yellow crystals); mp. 97–99 °C; IR (neat) 3280, 1660, 1560, 1440, 700cm^{-1}; ^{1}H-NMR (400.13MHz, $CDCl_3$) δ 1.26 (d, J=5.04 Hz, 3H), 1.82–1.85 (m, 2H), 2.30–2.39 (m, 2H), 2.48–2.53 (m, 2H), 3.32–3.37 (m, 2H), 3.70–3.75 (m, 1H), 7.20–7.72 (m, 16H); ^{13}C-NMR (100.61MHz, $CDCl_3$) δ 21.04 (s), 21.91 (d, $^2J_{pc}$=3.83Hz), 27.50 (d, $^1J_{pc}$=71.31Hz), 39.55 (d, $^3J_{pc}$=10.73Hz), 39.87 (s), 43.78 (s), 126.96–134.54 (m), 170.84 (s); MS (FAB) m/z 438

(M+1); HRMS (FAB) calcd. for $C_{25}H_{28}NO_2PS$ (M+1) 438.1657. Found 438.1744.

Compound **5b** was obtained from the reaction of **2a** (0.341g, 1mmol) with phenyl thio-2-pentenoate (0.184g, 1mmol) at reflux temperature. The crude product was purified by column chromatography on silica gel using ethyl acetate/methanol (20/1) to give pure **5b** (13% yield as a colorless solid); mp. 97.0–99.5°C; IR (neat) 3270, 1660, 1560, 1440, 690 cm^{-1}; ^{1}H-NMR (400.13MHz, $CDCl_3$) δ 0.99 (t, J=7.35 Hz, 3H), 1.54–1.63 (m, 2H), 1.80–0.86 (m, 2H), 2.31–2.40 (m, 2H), 2.44 (d, J=7.18 Hz, 2H), 3.29–3.44 (m, 2H), 3.56–3.59 (m, 1H), 7.16–7.70 (m, 16H); ^{13}C-NMR (100.61MHz, $CDCl_3$) δ 11.22 (s), 21.82 (d, $^2J_{pc}$=3.92Hz), 27.26 (d, $^1J_{pc}$=72.34Hz), 27.74 (s), 37.52 (d, $^3J_{pc}$=11.57Hz), 41.83 (s), 47.01 (s), 126.80–134.84 (m), 171.18 (s); MS (FAB) m/z 452 (M^++1); HRMS (FAB) calcd. for $C_{26}H_{30}NO_2PS$ (M+1) 452.1813. Found 452.1835.

Compound **7a** was obtained from the reaction of **1b** (0.356g, 1mmol) with phenyl thiocrotonate (0.178g, 1mmol) at reflux temperature. The crude product was purified by column chromatography on silica gel using ethyl acetate/methanol (9/1) to give pure **7a** (27% yield); IR (neat) 1670, 1640, 1440 cm^{-1}; ^{1}H-NMR (400.13MHz, $CDCl_3$) δ 1.01 (d, J=7.12 Hz, 3H), 1.60–1.68 (m, 4H), 1.86 (d, J=7.28 Hz, 3H), 2.29–2.36 (m, 2H), 2.56–2.65 (m, 2H), 3.09–3.13 (m, 1H), 3.73–3.88 (m, 2H), 6.98 (q, J=14.64Hz, 1H), 7.27–7.76 (10H, m); ^{13}C-NMR (100.61MHz, $CDCl_3$) δ 13.63 (s), 18.76 (d, $^2J_{pc}$=3.83Hz), 19.61 (s), 5.76 (s), 28.93 (s), 29.37 (d, $^1J_{pc}$=56.73Hz), 38.88 (s), 39.05 (s), 128.54–133.48 (m), 132.68 (s), 165.66 (s), 171.48 (s); MS (FAB) m/z 410 (M^++1); HRMS (FAB) calcd. for $C_{24}H_{28}NO_3P$ (M+1) 410.1885. Found 410.1882.

Compound **6** and **7b** were obtained from the reaction of **1b** (0.356 g, 1 mmol) with phenyl thio-2-pentenoate (0.184 g, 1 mmol) at reflux temperature. The crude product was purified by column chromatography on silica gel using ethyl acetate/methanol (9/1) to give pure **6** and **7b**.

Compound **6** (13% yield); IR (neat) 3280, 1660, 1560, 1440cm^{-1}; ^{1}H-NMR (400.13MHz, $CDCl_3$) δ0.99 (t, J=7.32Hz, 3H), 1.51–1.66 (m, 4H), 2.23–2.35 (m, 2H), 2.39–2.44 (m, 2H), 3.19–3.22 (m, 2H), 3.50–3.57 (m, 1H), 6.85–6.88 (m, 1H), 7.17–7.72 (m, 15H); ^{13}C-NMR (100.61MHz, $CDCl_3$) δ 11.22 (s), 18.77 (d, $^2J_{pc}$=3.07Hz), 27.55 (s), 28.74 (d, $^1J_{pc}$=72.08Hz), 30.11 (d, $^3J_{pc}$=13.03Hz), 38.50 (s), 41.82 (s), 46.90 (s), 126.85–134.70 (m), 170.97, (s); MS (FAB) m/z 466 (M^++1); HRMS (FAB) calcd. for $C_{27}H_{32}NO_2P$ (M+1) 466.1970. Found 466.1996.

Compound **7** (17% yield); IR (neat) 1670, 1640, 1440 cm^{-1}; ^{1}H-NMR (400.13MHz, $CDCl_3$) δ 0.84 (t, J=7.46 Hz, 3H), 1.09 (t, J=7.58 Hz, 3H)1.24–1.44 (m, 2H), 1.60–1.68 (m, 4H), 2.18–2.37 (m, 4H), 2.60–2.73 (m, 2H), 2.81–2.86 (m, 1H), 3.72–3.85 (m, 2H), 6.93 (t, J=7.72 Hz, 1H), 7.32–7.72 (m, 10H); ^{13}C-NMR (100.61MHz, $CDCl_3$) δ 11.71 (s), 13.28 (s), 18.74 (d, $^2J_{pc}$=3.52Hz), 21.70 (s), 27.10 (s), 29.06 (s), 29.24 (d, $^1J_{pc}$=68.25Hz), 32.90 (s), 37.53 (s), 38.80 (s), 128.55–133.33 (m), 130.10 (s), 145.00 (s), 166.22 (s), 171.58 (s); MS (FAB) m/z 438 (M^++1); HRMS (FAB) calcd. for $C_{26}H_{32}NO_3P$ (M+1) 438.2198. Found 438.2165.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture of Japan (No. 11650889). We are grateful to the Ihara Chemical Co., Ltd., for the gift of triphenylphosphine. We thank Welfide Co., Ltd., for the MS and HRMS measurements.

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