SYNTHESIS OF BIS-IMIDAZOLONE CONDENSED RING DERIVATIVES BEARING POTENTIAL FUNGICIDAL ACTIVITIES

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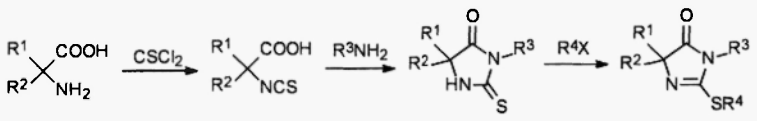
Abstract: Bis-imidazolone condensed ring derivatives **4** were synthesized by S-alkylation of bis-imidazolidinones **3**, which were obtained via tandem aza-Wittig reaction of vinyliminophosphoranes **1**, carbon disulfide and ethylenediamine.

Introduction

4H-Imidazol-4-ones are important heterocycles having biological activities(1-3). Some derivatives of 5-furfurylidene-4H-imidazolin-4-one were found to show good antiinflammatory activity(4). Some of them appear in a variety of biologically active molecules in which a common structural unit is a derivatized 2-alkylthio-4H-imidazol-4-one moiety(5-7). However, most of the 2-alkylthioimidazolones reported are of the 5,5-disubstituted type and were generally synthesized from corresponding α-amino acetic acid(7,8) (Scheme 1). Unfortunately, 5-arylmethylidene-2-alkylthioimidazolones cannot be prepared by this general method for the corresponding starting material needed would be unstable vinyl amino acetic acids. Recently, we are interested in the synthesis of biologically active imidazolones via tandem aza-Wittig reaction(9-15). Here we report the synthesis of bis-imidazolone condensed ring derivatives **4** from the stable vinyliminophosphoranes **1** (Scheme 2).



Scheme 1

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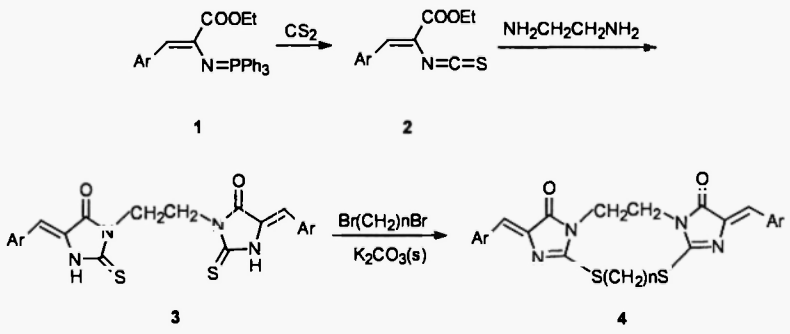
Results and Discussion

The easily accessible vinyliminophosphoranes **1** reacted with carbon disulfide to give vinyl isothiocyanates **2**. The reaction of **2** with ethylenediamine took place smoothly at room temperature to give the yellow crystal bis-imidazolidinones **3** in 79~87% yields (Scheme 2 and Table 1).

S-Alkylation of **3** with dibromohydrocarbons in presence of solid potassium carbonate provided bis-imidazolone condensed ring derivatives **4** in 41~62% yields. The alkylation had to be carried out at 50~60□ (Scheme 2 and Table 1).



Scheme 2

The structure of **3** and **4** has been confirmed by spectral date ^{1}H NMR, IR and MS. For example, the ^{1}H NMR spectrum data in **4b** show the signals of =CH and -NCH_2CH_2N- at 6.98 ppm and 3.87 ppm as single absorption respectively. The chemical shift of aryl hydrogens is 8.15~7.26 ppm with multiple absorption. The other signals appeared at 3.35(t, 4H, SCH_2) and 2.24(m, 2H, $SCH_2\underline{CH_2}CH_2S$). The IR of **4b** showed the strong stretching vibration peak of imidazolone C=O at 1720 cm^{-1} and the peak of C=C at about 1638 cm^{-1}. The MS of **4b** showed M^+ at m/z 474 with 30% abundance.

Table-1: Preparation of bis-imidazolidinones **3** and bis-imidazolone condensed ring derivatives **4**

Entry	Ar	n	Conditoin	Yield(%)[a]	m.p.(°C)
3a	Ph		r.t./3h	87	277~278
3b	Furyl		r.t./4h	79	255~257
4a	Ph	2	60°C/6h	41	161~162
4b	Ph	3	50°C /4h	50	161~163
4c	Ph	4	50°C /3h	57	161~162
4d	Ph	5	60°C /6h	55	152~154
4e	Ph	6	60°C/7h	45	145~147
4f	Furyl	2	60°C/7h	48	133~134
4g	Furyl	3	50°C/4h	56	135~136
4h	Furyl	4	50°C/4h	62	131~132
4i	Furyl	5	60°C/8h	59	138~140
4j	Furyl	6	60°C/8h	53	167~168

[a]A: Isolated yields of **3** based on vinyliminophosphoranes **1**; B: Purified yields of **4** based on bis-imidazolidinones **3**.

Experimental

Melting points were uncorrected. MS were measured on a Finnigan Trace spectrometer. IR were recorded on a PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1}. NMR were taken in $CDCl_3$ or DMSO-d_6 on a Varian Mercury 400 spectrometer and resonances are given in ppm (δ) relative to TMS. Elementary analyses were taken on a Perkin-Elmer 2400 CHN Elementary Analysis Instrument. CS_2 is poisonous and a good hood should be used. Vinyliminophosphoranes **1** was prepared by the literature report(16).

General Preparation of Bis-imidazolidinones **3**-To a solution of vinyliminophosphoranes **1** (5mmol) in dry methylene dichloride (15mL) was added excess carbon disufide (5mL). After the reaction mixture was refluxed for 28h, the solvent was removed under reduced pressure and ether/petroleum ether (1:2, 20mL) was added to precipitate triphenylphosphine sulfide which was removed by filtration. The filtrate was evaporated to give vinyl isothiocyanates **2**, which was used directly without further purification. To the solution of **2** in CH_3CN (15mL) was added ethylenediamine (0.17mL, 2.5mmol). The mixture was allowed to stand for 3~4h at room temperature and the precipitated solid was collected and washed with water and ethanol, recrystallized from methylene dichloride/petroleum ether to give bis-imidazolidinones **3**.

recrystallized from methylene dichloride/petroleum ether to give bis-imidazolidinones **3**.

3a: yellow crystals, ^{1}H NMR(DMSO-d_6, 400MHz) □9.06(s, 2H, N-H), 7.79~7.40 (m, 10H, Ph-H), 6.55(s, 2H, =CH), 4.14(s, 4H, CH_2CH_2); IR(cm^{-1}), 3255(N-H), 1718(C=O), 1646(C=C); MS(m/z, %), 434(M^+, 88), 401(2), 230(49), 204(32), 188(12), 160(39), 144(7), 117(100), 102(13), 89(43); Anal. Calcd. for $C_{22}H_{18}N_4O_2S_2$: C, 60.83; H, 4.15; N, 12.90. Found: C, 61.09; H, 3.98; N, 13.14.

3b: yellow crystals, ^{1}H NMR(DMSO-d_6, 400MHz) □ 9.30(s, 2H, N-H), 7.82~6.41 (m, 6H, Ar-H), 6.23(s, 2H, =CH), 4.08(s, 4H, CH_2CH_2); IR(cm^{-1}), 3324(N-H), 1707(C=O), 1650(C=C); MS(m/z, %), 414(M^+, 10), 373(8), 365(18), 290(5), 220(11), 194(10), 169(19), 107(22), 77(22), 40(100). Anal. Calcd. for $C_{18}H_{14}N_4O_4S_2$: C, 52.17; H, 3.38; N, 13.53. Found: C, 51.95; H, 3.11; N, 13.82.

Preparation of Bis-imidazolone Condensed Ring Derivatives **4**-A mixture of **3** (4mmol), dibromohydrocarbons (4mmol) and solid potassium carbonate (1.11g, 8mmol) in CH_3CN (30mL) was stirred for 3~8h at 50~60□ and filtered, the filtrate was condensed and the residual was recrystallized from methylene dichloride/petroleum ether to give bis-imidazolone condensed ring derivatives **4**

4a: yellow crystals, ^{1}H NMR($CDCl_3$, 400MHz) □8.15~7.26 (m, 10H, Ph-H), 6.98 (s, 2H, =CH), 3.85 (s, 4H, NCH_2CH_2N), 3.38 (s, 4H, SCH_2CH_2S); IR(cm^{-1}), 1718 (C=O), 1637 (C=C); MS (m/z, %), 460 (M^+, 1), 434(2), 314(1), 288(2), 231(5), 203(6), 188(6), 160(25), 144(11), 130(14), 121(31), 116(100), 91(87); Anal. Calcd. for $C_{24}H_{20}N_4O_2S_2$: C, 62.61; H, 4.35; N, 12.17. Found: C, 62.88; H, 4.57; N, 12.44.

4b: yellow crystals, ^{1}H NMR($CDCl_3$, 400MHz) □8.15~7.26 (m, 10H, Ph-H), 6.98 (s, 2H, =CH), 3.87(s, 4H, NCH_2CH_2N), 3.35 (t, 4H, SCH_2), 2.24 (m, 2H, $SCH_2\underline{CH_2}CH_2S$); IR($cm^{-1}$), 1720 (C=O), 1638 (C=C); MS (m/z, %), 474 (M^+, 30), 459(4), 445(5), 414(6), 271(100), 255(15), 244(44), 230(33), 202(22), 129(75), 116(94), 91(87); Anal. Calcd. for $C_{25}H_{22}N_4O_2S_2$: C, 63.29; H, 4.64; N, 11.81. Found: C, 63.52; H, 4.79; N, 12.06.

4c: yellow crystals, ^{1}H NMR($CDCl_3$, 400MHz) □8.15~7.26 (m, 10H, Ph-H), 6.97 (s, 2H, =CH), 3.86(s, 4H, NCH_2CH_2N), 3.20 (t, 4H, SCH_2), 1.82 (m, 4H, $SCH_2\underline{CH_2}\underline{CH_2}CH_2S$); IR($cm^{-1}$), 1722 (C=O), 1640 (C=C); MS (m/z, %), 489 (M^++1, 3), 344(2), 285(6), 243(1), 231(5), 203(5), 160(11), 144(7), 130(26), 116(37), 91(27), 55(100); Anal. Calcd. for $C_{26}H_{24}N_4O_2S_2$: C, 63.93; H, 4.92; N, 11.48. Found: C, 64.19; H, 5.17; N, 11.76.

4d: yellow crystals, ^{1}H NMR($CDCl_3$, 400MHz) □8.14~7.26 (m, 10H, Ph-H), 6.96 (s, 2H, =CH), 3.86(s, 4H, NCH_2CH_2N), 3.20 (t, 4H, SCH_2), 1.67 (m, 4H, $SCH_2\underline{CH_2}CH_2\underline{CH_2}CH_2S$), 1.43 (m, 2H,

$SCH_2CH_2CH_2CH_2CH_2S$); IR(cm^{-1}), 1722 (C=O), 1640 (C=C); MS (m/z, %), 503 (M^++1, 8), 469(3), 434(6), 401(4), 299(5), 231(20), 203(10), 160(32), 144(16), 116(91), 89(32), 69(83), 41(100); Anal. Calcd. for $C_{27}H_{26}N_4O_2S_2$: C, 64.54; H, 5.18; N, 11.16. Found: C, 64.80; H, 5.19; N, 11.21.

4e: yellow crystals, ^{1}H NMR($CDCl_3$, 400MHz) □ 8.15~7.26 (m, 10H, Ph-H), 6.96 (s, 2H, =CH), 3.87(s, 4H, NCH_2CH_2N), 3.24 (t, 4H, SCH_2), 1.67 (m, 4H, $SCH_2CH_2CH_2CH_2CH_2CH_2S$), 1.30 (m, 4H, $SCH_2CH_2CH_2CH_2CH_2CH_2S$); IR($cm^{-1}$), 1721 (C=O), 1640 (C=C); MS (m/z, %), 517 (M^++1, 17), 503(3), 483(2), 434(16), 401(6), 369(9), 313(6), 231(36), 203(14), 160(45), 144(19), 116(65), 55(100); Anal. Calcd. for $C_{28}H_{28}N_4O_2S_2$: C, 65.12; H, 5.43; N, 10.85. Found: C, 64.89; H, 5.68; N, 11.13.

4f: yellow crystals, ^{1}H NMR($CDCl_3$, 400MHz) □ 7.58~6.92 (m, 6H, Ar-H), 6.58 (s, 2H, =CH), 3.84(s, 4H, NCH_2CH_2N), 3.23 (s, 4H, SCH_2); IR(cm^{-1}), 1723 (C=O), 1643 (C=C); MS (m/z, %), 441 (M^++1, 6), 306(5), 248(39), 221(58), 192(18), 178(11), 160(16), 150(21), 134(14), 120(49), 107(100), 92(17); Anal. Calcd. for $C_{20}H_{16}N_4O_4S_2$: C, 54.54; H, 3.64; N, 12.73. Found: C, 54.78; H, 3.81; N, 13.00.

4g: yellow crystals, ^{1}H NMR($CDCl_3$, 400MHz) □ 7.60~6.91 (m, 6H, Ar-H), 6.58 (s, 2H, =CH), 3.85(s, 4H, NCH_2CH_2N), 3.24 (t, 4H, SCH_2), 1.87 (m, 2H, $SCH_2CH_2CH_2S$); IR(cm^{-1}), 1722 (C=O), 1641 (C=C); MS (m/z, %), 455 (M^++1, 4), 429(3), 320(4), 262(47), 235(12), 220(38), 193(13), 178(17), 161(13), 149(25), 134(11), 120(46), 107(49), 92(10), 81(14), 41(100); Anal. Calcd. for $C_{21}H_{18}N_4O_4S_2$: C, 55.51; H, 3.96; N, 12.33. Found: C, 55.77; H, 4.19; N, 12.58.

4h: yellow crystals, ^{1}H NMR($CDCl_3$, 400MHz) □ 7.59~6.92 (m, 6H, Ar-H), 6.58 (s, 2H, =CH), 3.84(s, 4H, NCH_2CH_2N), 3.26 (t, 4H, SCH_2), 1.86 (m, 4H, $SCH_2CH_2CH_2CH_2S$); IR(cm^{-1}), 1716 (C=O), 1634 (C=C); MS (m/z, %), 469 (M^++1, 5), 443(3), 334(3), 275(59), 249(17), 233(4), 221(32), 194(17), 178(12), 162(10), 150(30), 134(17), 120(51), 107(76), 92(13), 81(35), 55(100); Anal. Calcd. for $C_{22}H_{20}N_4O_4S_2$: C, 56.41; H, 4.27; N, 11.97. Found: C, 56.66; H, 4.40; N, 12.21.

4i: yellow crystals, ^{1}H NMR($CDCl_3$, 400MHz) □ 7.58~6.91 (m, 6H, Ar-H), 6.58 (s, 2H, =CH), 3.84(s, 4H, NCH_2CH_2N), 3.25 (t, 4H, SCH_2), 1.72 (m, 4H, $SCH_2CH_2CH_2CH_2CH_2S$), 1.47 (m, 2H, $SCH_2CH_2CH_2CH_2CH_2S$); IR(cm^{-1}), 1717 (C=O), 1635 (C=C); MS (m/z, %), 483 (M^++1, 8), 449(3), 414(7), 381(3), 363(2), 289(7), 263(5), 247(2), 220(33), 194(18), 178(14), 150(40), 134(9), 122(20), 107(67), 69(100), 41(92); Anal. Calcd. for $C_{23}H_{22}N_4O_4S_2$: C, 57.26; H, 4.56; N, 11.62. Found: C, 57.50; H, 4.51; N, 11.89.

4j: yellow crystals, ^{1}H NMR($CDCl_3$, 400MHz) □ 7.58~6.90 (m, 6H, Ar-H), 6.58 (s, 2H, =CH), 3.89(s, 4H,

NCH_2CH_2N), 3.21 (t, 4H, SCH_2), 1.73 (m, 4H, $SCH_2\underline{CH_2}CH_2CH_2\underline{CH_2}CH_2S$), 1.38 (m, 4H, $SCH_2CH_2\underline{CH_2CH_2}CH_2CH_2S$); IR($cm^{-1}$), 1719 (C=O), 1638 (C=C); MS (m/z, %), 497 (M^++1, 5), 414(6), 381(2), 349(3), 236(3), 221(13), 194(10), 180(9), 150(20), 134(6), 122(12), 106(44), 81(19), 67(9), 55(98), 51(15), 41(100); Anal. Calcd. for $C_{24}H_{24}N_4O_4S_2$: C, 58.06; H, 4.84; N, 11.29. Found: C, 57.92; H, 5.11; N, 11.55.

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