AN EFFICIENT SYNTHESIS OF 2-ALKYLTHIO-3-ALKYL-5-FURFURYLIDENE-4H-IMIDAZOL-4-ONES

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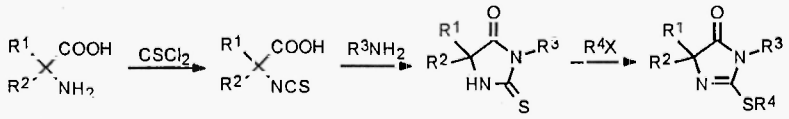
Abstract: 2-Alkylthio-3-alkyl-5-furfurylidene-4H-imidazol-4-ones **4** were synthesized by N-alkylation and S-alkylation of 2-thioxo-5-furfurylidene-4-imidazolidinone **3**, which was obtained via cyclization of vinyl isothiocyanate **2** with excess ammonium hydroxide (28% NH_3 in water).

Introduction

4H-Imidazol-4-ones are important heterocycles having biological and pharmaceutical activities(1-3), and some 2-alkylthioimidazolones show significant fungicidal activities(4-6). Until now, many of the new derivatives of imidazolones have been synthesized to evaluate their biological and pharmaceutical activities. However, most of the 2-alkylthioimidazolones reported are of the 5,5-disubstituted type and were generally synthesized from corresponding α-amino acetic acid(6,7) (Scheme-1). Regrettably, 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 new imidazolone derivatives, especially in 5-arylmethylideneimidazolones, via tandem aza-Wittig reaction, and some of them have been shown potential fungicidal activities(8-19). In the present work we wish to report further a new efficient synthesis of some new 2-alkylthio-3-alkyl-5-furfurylidene-4H-imidazol-4-ones derivatives from the stable vinyliminophosphorane **1**.

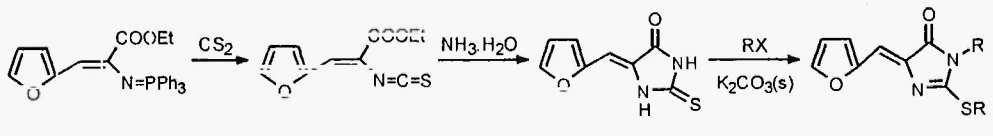


Scheme-1

Results and Discussions

The easily accessible vinyliminophosphorane **1** reacted with carbon disulfide to give vinyl isothiocyanate **2**. The reaction of **2** with excess ammonium hydroxide (28% NH_3 in water) took place smoothly at room temperature to give the yellow crystals 2-thioxo-5-furfurylidene-4-imidazolidinone **3** in 87% yield (Scheme 2).

S-Alkylation and N-alkylation of **3** with excess alkyl halides in presence of solid potassium carbonate provided 2-alkylthio-3-alkyl-5-furfurylidene-4H-imidazol-4-ones **4** in satisfactory yields (Scheme 2). When the active alkylating reagents (RI, $BrCH_2COR$) were used, the alkylation could be carried out at room temperature. When other alkylating reagents were applied, the alkylation should be carried out at 50~60℃ (see Table-1).



1 **2** **3** **4**

Scheme-2

The structure of 3 and 4 has been confirmed by spectral date ^1H NMR, IR and MS. For example, the ^1H NMR spectrum data in 4f show the signals of =CH, NCH_2, and SCH_2 at 6.58 ppm, 4.36 ppm, and 4.10 ppm as single absorption respectively. The chemical shift of furyl hydrogens is 7.58~6.97 ppm with multiple absorption. The other signals appeared at 4.27~4.22(m, 4H, $NCH_2COOCH_2CH_3$ and $SCH_2COOCH_2CH_3$) and 1.31~1.27(m, 6H, $NCH_2COOCH_2CH_3$ and $SCH_2COOCH_2CH_3$). The IR of 4f showed the strong stretching vibration peaks of

imidazolone and carboxylic ester C=O at 1718 cm^{-1}, 1738 cm^{-1} and 1741 cm^{-1} respectively. The peak of C=C appeared at about 1637 cm^{-1}. The MS of 4f showed M^+ at m/z 366 with 100% abundance.

Table-1: Preparation of 2-alkylthio-3-alkyl-5-furfurylidene-4H-imidazol-4-ones 4 by S-alkylation and N-alkylation of 3

Compounds	RX	Conditoin	Yield(%)[a]	m.p.(□)
4a	MeI	r.t./2h	73	148~150
4b	EtBr	50 °C/5h	66	110~112
4c	*n*-PrBr	60 °C/6h	63	87~89
4d	*n*-BuBr	60 °C/8h	59	49~51
4e	$PhCH_2Cl$	50 °C/3h	82	137~139
4f	$ClCH_2COOEt$	50 °C/4h	68	109~111
4g	$BrCH_2COOMe$	r.t./2h	72	124~126
4h	$BrCH_2COPh$	r.t./2 h	83	167~169

[a]A: Purified yields based on 3.

Experimental

Melting points were uncorrected. MS were measured on a Finnigan Trace MS spectrometer. IR were recorded on a PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1}. NMR were taken on a Varian Mercury 400 spectrometer and resonances are given in ppm (δ) relative to TMS. Elementary analyses were taken on a Vario EL III elementary analysis instrument. CS_2 is poisonous and a good hood should be used. Vinyliminophosphorane 1 was prepared by the literature report(20).

General Preparation of 2-Thioxo-5-furfurylidene-4-imidazolidinone 3

To a solution of vinyliminophosphorane 1 (2.20g, 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 isothiocyanate 2, which was used directly without further purification. To a solution of crude 2 prepared previously in CH_3CN (15mL) was added excess ammonium hydroxide (28% NH_3 in water) (2mL, 30mmol). The mixture was allowed to stand for 3h at room temperature and the precipitated solid was collected and washed with water and ethanol, recrystallized from ethanol to give 0.84g(87%, isolated yield based on 1) of 3 as yellow crystals. M.p. 264~265□, ^{1}H NMR(DMSO-d_6, 400MHz) δ12.34 (s, 1H, O=CN-H), 11.80 (s, 1H, C=CN-H), 7.85~6.66 (m, 3H, Furyl-H), 6.41(s, 1H, =CH); IR(cm^{-1}), 3339(O=CN-H), 3224(C=CN-H), 1709(C=O), 1651(C=C); MS(m/z, %), 194(M^+, 100), 135(2), 121(4), 106(93), 96(2), 92(1), 86(16), 77(30), 67(4), 58(32), 51(54); Anal. Calcd. For $C_8H_6N_2O_2S$: C, 49.48; H, 3.09; N, 14.43. Found: C, 49.73; H, 2.96; N, 14.69.

Preparation of 2-Alkylthio-3-alkyl-5-furfurylidene-4H-imidazol-4-ones 4-A mixture of 3 (0.78g, 4mmol), excess alkyl halide (16mmol) and solid potassium carbonate (2.22g, 16mmol) in CH_3CN (30mL) was stirred for 2~8h at room temperature or 50~60□ and filtered, the filtrate was condensed and the residual was recrystallized from methylene dichloride/petroleum ether to give 2-alkylthio-3-alkyl-5-furfurylidene-4H-imidazol-4-ones 4.

4a: Green-yellow crystals, ^{1}H NMR($CDCl_3$, 400 MHz) δ7.56~6.90 (m, 3H, Furyl-H), 6.56 (s, 1H, =CH), 3.15 (s, 3H, NCH_3), 2.73 (s, 3H, SCH_3); IR(cm^{-1}), 1716 (C=O), 1641 (C=C); MS (m/z), 222 (M^+, 98), 207 (1), 193 (4), 189(15), 175(5), 164(1), 160(14), 146(2), 131(4), 121(10), 106(51), 92(3), 89(5), 87(100), 77(17), 72(28), 62(11) , 51(27) , 45(20); Anal. Calcd. for $C_{10}H_{10}N_2O_2S$: C, 54.05; H, 4.50; N, 12.61. Found: C, 53.78; H, 4.29; N, 12.88.

4b: Yellow crystals, ^{1}H NMR($CDCl_3$, 400 MHz) δ7.55~6.88(m, 3H, Furyl-H), 6.56(s, 1H, =CH), 3.62(q, 2H, NCH_2CH_3), 3.36(q, 2H, SCH_2CH_3) , 1.51(t, 3H, NCH_2CH_3), 1.24(t, 2H, SCH_2CH_3); IR(cm^{-1}), 1716(C=O), 1635(C=C); MS(m/z, %), 250(M^+, 92), 235(6), 222(40), 217(59), 207(5), 188(30), 182(4), 177(12), 161(9), 149(16), 133(24), 121(35), 119(18) , 116(24), 106(100), 91(8), 87(54), 77(29), 72(11), 62(14), 59(68), 51(30) , 44(9); Anal.Calcd.for $C_{12}H_{14}N_2O_2S$: C, 57.60; H, 5.60; N, 11.20. Found: C, 57.81; H, 5.36; N, 10.99.

4c: Yellow crystals, ^{1}H NMR($CDCl_3$, 400 MHz) δ7.55~6.88(m, 3H, Furyl-H), 6.56(s, 1H, =CH), 3.54(t, 2H, $NCH_2CH_2CH_3$), 3.32(t, 2H, $SCH_2CH_2CH_3$), 1.91~1.85(m, 2H, $NCH_2\underline{CH_2}CH_3$), 1.76~1.66(m, 2H, $SCH_2\underline{CH_2}CH_3$), 1.10(t, 3H, $NCH_2CH_2\underline{CH_3}$), 0.94(t, 3H, $SCH_2CH_2\underline{CH_3}$); IR(cm^{-1}), 1716(C=O), 1637(C=C); MS(m/z, %), 278(M^+, 84), 263(1), 250(1), 245(48), 236(33), 221(7), 203(22), 191(9), 189(6), 148(11), 134(17), 120(27), 101(7), 106(100), 92(15), 86(9), 76(11), 58(7), 51(23); Anal. Calcd. for $C_{14}H_{18}N_2O_2S$: C, 60.43; H, 6.47; N, 10.07. Found: C, 60.19; H, 6.68; N, 10.30.

4d: Yellow crystals, ^{1}H NMR($CDCl_3$, 400 MHz) δ7.54~6.87(m, 3H, Furyl-H), 6.56(s, 1H, =CH), 3.54(t, 2H, $NCH_2CH_2CH_2CH_3$), 3.31(t, 2H, $SCH_2CH_2CH_2CH_3$), 1.83~1.31(m, 8H, $NCH_2\underline{CH_2}\underline{CH_2}CH_3$ and $SCH_2\underline{CH_2}\underline{CH_2}CH_3$), 1.08~0.89(m, 6H, $NCH_2CH_2CH_2\underline{CH_3}$ and $SCH_2CH_2CH_2\underline{CH_3}$); IR(cm^{-1}), 1717(C=O), 1637(C=C); MS(m/z, %), 306(M^+, 34), 277(3), 273(11), 249(9), 235(3), 217(100), 208(7), 200(6), 193(17), 150(10), 134(12), 120(5), 106(58), 89(31), 67(13), 57(38); Anal. Calcd. for $C_{16}H_{22}N_2O_2S$: C, 62.75; H, 7.19; N, 9.15. Found: C, 63.01; H, 6.95; N, 9.39.

4e: Yellow crystals, ^{1}H NMR($CDCl_3$, 400 MHz) δ7.57~6.97(m, 13H, Ph-H and Furyl-H), 6.56(s, 1H, =CH), 4.73(s, 2H, NCH_2Ph), 4.54(s, 2H, SCH_2Ph); IR(cm^{-1}), 1712(C=O), 1636(C=C); MS(m/z, %), 374(M^+, 57), 341(50), 283(22), 255(3), 250(4), 239(2), 196(2), 178(6), 166(3), 147(7), 120(8) , 115(4), 106(6), 91(100), 65(34); Anal. Calcd. for $C_{22}H_{18}N_2O_2S$: C, 70.59; H, 4.81; N, 7.49. Found: C, 70.81; H, 5.03; N, 7.69.

4f: Yellow crystals, ^{1}H NMR($CDCl_3$, 400 MHz) δ7.58~6.97(m, 3H, Furyl-H), 6.58(s, 1H, =CH), 4.36(s, 211, NCH_2), 4.27~4.22(m, 4H, $NCH_2COOCH_2CH_3$ and $SCH_2COOCH_2CH_3$), 4.10(s, 2H, SCH_2), 1.31~1.27(m, 6H, $NCH_2COOCH_2CH_3$ and $SCH_2COOCH_2CH_3$); IR(cm^{-1}), 1741(COOEt), 1738(COOEt), 1718(C=O), 1637(C=C); MS(m/z, %), 366(M^+, 100), 321(10), 292(50), 263(7), 251(2), 247(8), 235(41), 219(45), 205(6), 190(15), 178(6), 162(4), 149(20), 134(8), 119(49), 105(92), 101(10), 91(16), 85(11), 77(27), 71(95), 58(26), 50(25), 44(30); Anal. Calcd. for $C_{16}H_{18}N_2O_6S$: C, 52.46; H, 4.92; N, 7.65. Found: C, 52.21; H, 5.18; N, 7.89.

4g: Yellow crystals, ^{1}H NMR($CDCl_3$, 400 MHz) δ7.58~6.98(m, 3H, Furyl-H), 6.58(s, 1H, =CH), 4.38(s, 2H, NCH_2), 4.29(s, 3H, $NCH_2COOC\underline{H_3}$), 4.24(s, 3H, SCH_2COOCH_3), 4.11(s, 2H, SCH_2); IR(cm^{-1}), 1742(COOEt), 1739(COOEt), 1719(C=O), 1641(C=C); MS(m/z, %), 338(M^+, 96), 307(15), 279(47), 251(5), 233(25), 221(87), 206(9), 191(23), 148(16), 134(5), 105(100), 91(12), 87(13), 73(7), 59(72), 51(29); Anal. Calcd. for $C_{14}H_{14}N_2O_6S$: C, 49.70; H, 4.14; N, 8.28. Found: C, 49.89; H, 4.38; N, 8.37.

4h: Yellow crystals, ^{1}H NMR($CDCl_3$, 400 MHz) δ7.59~7.00(m, 13H, Ph-H and Furyl-H), 6.59(s, 1H, =CH), 4.67(s, 2H, NCH_2), 4.39(s, 2H, SCH_2); IR(cm^{-1}), 1719(C=O), 1699(COPh), 1692(COPh), 1645(C=C); MS(m/z, %), 430(M^+, 14), 325(11), 311(19), 220(41), 206(48), 192(11), 150(13), 134(12), 120(17), 119(22), 105(100), 89(81). Anal. Calcd. for $C_{24}H_{18}N_2O_4S$: C, 66.98; H, 4.19; N, 6.51. Found: C, 67.23; H, 4.44; N, 6.67.

Acknowledgements

We gratefully acknowledge financial support of this work by the Natural Science Foundation of Hubei Education Commission of China (Project No. D200560003) and the National Natural Science Foundation of China (Project No. 20102001).

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Received on August 05, 2005.