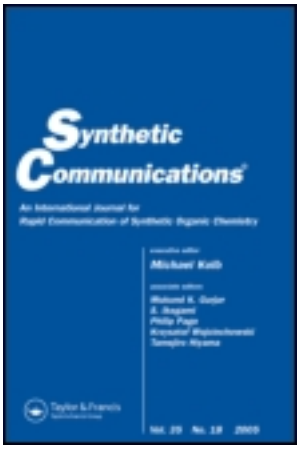

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An Efficient Synthesis of Double 2-Alkylthio-5-phenylmethylidene-4

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An Efficient Synthesis of Double 2-Alkylthio-5-phenylmethylidene-4*H*-imidazol-4-ones

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Abstract: Double 2-alkylthio-5-phenylmethylidene-4*H*-imidazol-4-ones **6** were synthesized by S-alkylation of double 2-thioxo-5-phenylmethylidene-4-imidazolidinone **5**, which was obtained via cyclization of vinyl isothiocyanate **4** with ethylenediamine.

Keywords: 4*H*-Imidazol-4-ones, aza-Wittig reaction, alkylation, synthesis

4H-Imidazol-4-ones are important heterocycles having bactericidal, antiinflammatory, and angiotensin II antagonistical activities.[1–4] Some of them appear in a variety of biologically active molecules in which a common structural unit is a derivatized 2-alkylthio-4*H*-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). Regrettably, 5-arylmethylidene-2-alkylthioimidazolones cannot be prepared by this general method for the corresponding

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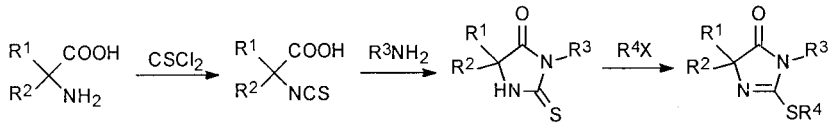
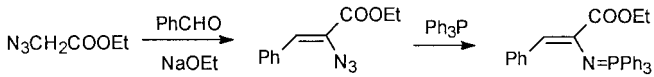


Scheme 1.

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.[9–13,15,16] Here we wish to report a new efficient synthesis of some new double 5-arylmethylidene-2-alkylthioimidazolone derivatives from the stable vinyliminophosphorane **3**.

The vinyliminophosphorane **3** can be easily prepared according to the following procedure: azide **1** was condensed with benzaldehyde in presence of sodium ethoxide to give vinyl azide **2** in 58% yield. Staudinger reaction of **2** with Ph_3P gave vinyliminophosphorane **3** in 82% yield.

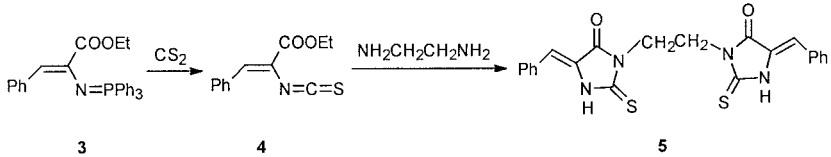


1 **2** **3**

The vinyliminophosphorane **3** reacted with carbon disulfide to give vinyl isothiocyanate **4**. The reaction of **4** with ethylenediamine took place smoothly at room temperature to give the yellow crystal double 2-thioxo-5-phenylmethylidene-4-imidazolidinone **5** in 87% yield (Scheme 2).

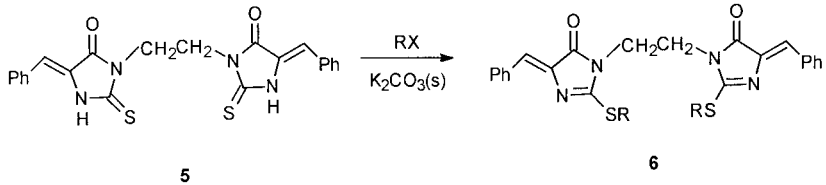
S-Alkylation of **5** with alkyl halides in presence of solid potassium carbonate provided double 2-alkylthio-5-phenylmethylidene-4*H*-imidazol-4-ones **6** in satisfactory yields (Scheme 3). When the active alkylating reagents (RI, $BrCH_2COR$) were used, the alkylation could be carried out at room temperature. When other alkylating reagents were applied, the alkylation should be carried out at $50 \sim 60^{\circ}C$ (see Table 1).

The formation of **5** can be rationalized in terms of an initial nucleophilic addition of ethylenediamine to give the intermediate **7**, which directly cyclized to give **5** (Scheme 4).



3 **4** **5**

Scheme 2.



5 6

Scheme 3.

EXEPERIMENTAL

Melting points were uncorrected. MS were measured on a HP5988A spectrometer. IR were recorded on a PE-983 infrared spectrometer as KBr pellets. NMR were taken on a Varian XL-200 spectrometer and resonances are given relative to TMS. Elementary analysis were taken on a Perkin-Elmer 2400 CHN Elementary Analysis Instrument. CS_2 is poisonous and a good hood should be used.

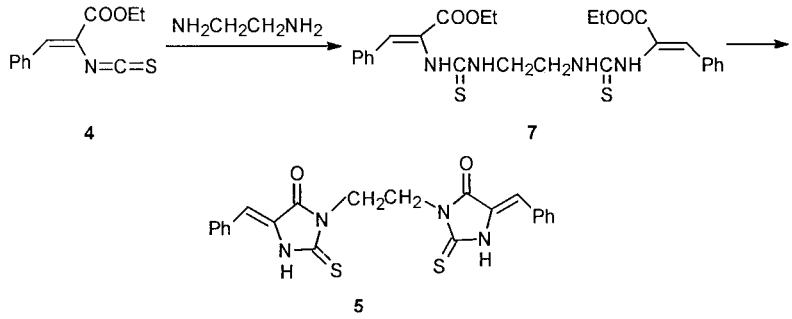
Preparation of Vinyliminophosphorane 3

To a well-stirred solution containing sodium (6.0 g, 260 mmol) in dry ethanol (160 mL), a solution of ethyl azidoacetate **1** (33.5 g, 260 mmol) and benzaldehyde (13.8 g, 130 mmol) in dry ethanol (30 mL) was added dropwise at -10°C under nitrogen. The reaction mixture was stirred at 0°C for 4 h. After this, it was poured into aqueous 30% ammonium chloride (240 mL) and the formed solid was separated by filtration, washed with water (30 mL), and dried to give vinyl azide **2**, yield 16.4 g (58%).

Table 1. Preparation of double 2-alkylthio-4*H*-imidazol-4-ones **6** by alkylation of **5**

Compounds	RX	Condition	Yield (%)[a]
6a	MeI	r.t./3 h	71
6b	EtBr	50°C/5 h	62
6c	*n*-PrBr	60°C/6 h	68
6d	*n*-BuBr	60°C/7 h	73
6e	*s*-BuBr	60°C/10 h	61
6f	*n*-$C_5H_{11}Br$	60°C/8 h	63
6g	$PhCH_2Cl$	50°C/3 h	82
6h	$ClCH_2COOEt$	50°C/2 h	76
6i	$BrCH_2COOMe$	r.t./2 h	67
6j	$BrCH_2COPh$	r.t./2 h	58

[a]Isolated yields based on **5**.



Scheme 4.

To a solution of Ph_3P (19.6 g, 75 mmol) in dry CH_2Cl_2 (60 mL), a solution of the azide **2** (16.3 g, 75 mmol) in dry CH_2Cl_2 (40 mL) was added dropwise at room temperature and stirred for 4 h. The solvent was removed under reduced pressure and the residual was recrystallized from methylene dichloride/petroleum ether (1 : 2) to give vinyliminophosphorane **3**, yield 27.7 g (82%), m.p. 148–150°C (lit., 149°C).[14]

Preparation of Double 2-Thioxo-5-phenylmethylidene-4-imidazolidinone 5

To a solution of vinyliminophosphorane **3** (2.25 g, 5 mmol) in dry methylene dichloride (15 mL) was added excess carbon disufide (5 mL). After the reaction mixture was refluxed for 28 h, the solvent was removed under reduced pressure and ether/petroleum ether (1 : 2, 20 mL) was added to precipitate triphenylphosphine sulfide, which was removed by filtration. The filtrate was evaporated to give vinyl isothiocyanate **4**, which was used directly without further purification. To a solution of crude **4** prepared previously in CH_3CN (15 mL) was added ethylenediamine (0.17 mL, 2.5 mmol). The mixture was allowed to stand for 2 h at room temperature and the precipitated solid was collected and washed with water and ethanol, recrystallized from methylene dichloride/petroleum ether to give **5**.

Double 2-Thioxo-5-phenylmethylidene-4-imidazolidinone **5**: yield 87%, yellow crystals, m.p. 277 ~ 278°C, ^{1}H NMR(DMSO-d_6, 200MHz) δ 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%). Elemental 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.

General Preparation of Double 2-Alkylthio-5-phenylmethylidene-4*H*-imidazol-4-ones 6

A mixture of **5** (1.74 g, 4 mmol), alkyl halide (10 mmol) and solid potassium carbonate (2.22 g, 16 mmol) in CH_3CN (30 mL) was stirred for 2 ~ 10 h at room temperature or 50 ~ 60°C and filtered, the filtrate was condensed and the residual was recrystallized from methylene dichloride/petroleum ether to give double 2-alkylthio-5-phenylmethylidene-4H-imidazol-4-ones **6**.

6a. yellow crystals, m.p. 266 ~ 268°C, ^{1}H NMR($CDCl_3$, 200 MHz) δ 8.15 ~ 7.26(m, 10H, Ph-H), 6.96(s, 2H, =CH), 3.89(s, 4H, NCH_2CH_2N), 2.65(s, 6H, SCH_3); IR(cm^{-1}), 1716(C=O), 1635(C=C); MS(m/z), 462(M^+, 84%), 447(3%), 415(6%), 244(56%), 229(28%), 218(15%), 201(7%), 174(7%), 144(12%), 130(29%), 116(100%), 102(12%), 89(42%); Anal. Calcd. for $C_{24}H_{22}N_4O_2S_2$: C, 62.34; H, 4.76; N, 12.12. Found: C, 62.38; H, 5.02; N, 12.39.

6b. yellow crystals, m.p. 194 ~ 196°C, ^{1}H NMR($CDCl_3$, 200 MHz) δ 8.14 ~ 7.26(m, 10H, Ph-H), 6.96(s, 2H, =CH), 3.86(s, 4H, NCH_2CH_2N), 3.23(q, 4H, SCH_2, J = 7.3Hz), 1.34(t, 6H, CH_3, J = 7.3Hz); IR(cm^{-1}), 1717(C=O), 1633(C=C); MS(m/z), 490(M^+, 57%), 462(9%), 434(4%), 429(6%), 401(6%), 258(59%), 243(18%), 230(50%), 204(22%), 188(19%), 160(52%), 144(38%), 130(68%), 116(100%), 102(29%), 89(80%); Anal. Calcd. for $C_{26}H_{26}N_4O_2S_2$: C, 63.67; H, 5.31; N, 11.43. Found: C, 63.89; H, 5.39; N, 11.68.

6c. yellow crystals, m.p. 154 ~ 155°C, ^{1}H NMR($CDCl_3$, 200 MHz) δ 8.14 ~ 7.26(m, 10H, Ph-H), 6.95(s, 2H, =CH), 3.87(s, 4H, NCH_2CH_2N), 3.20(t, 4H, SCH_2), 1.71(m, 4H, $SCH_2\underline{CH_2}$), 0.91(t, 6H, CH_3); IR(cm^{-1}), 1717(C=O), 1633(C=C); MS(m/z), 518(M^+, 84%), 476(20%), 443(19%), 434(49%), 429(8%), 401(8%), 272(11%), 247(8%), 230(52%), 204(14%), 160(28%), 144(9%), 130(11%), 116(64%), 102(12%), 89(27%), 43(100%); Anal. Calcd. for $C_{28}H_{30}N_4O_2S_2$: C, 64.86; H, 5.79; N, 10.81. Found: C, 65.11; H, 6.04; N, 11.09.

6d. yellow crystals, m.p. 130 ~ 132°C, ^{1}H NMR($CDCl_3$, 200 MHz) δ 8.15 ~ 7.26(m, 10H, Ph-H), 6.95(s, 2H, =CH), 3.86(s, 4H, NCH_2CH_2N), 3.20(t, 4H, SCH_2), 1.64(m, 4H, $SCH_2\underline{CH_2}$), 1.31(m, 4H, $\underline{CH_2}CH_3$), 0.77(t, 6H, CH_3); IR(cm^{-1}), 1720(C=O), 1634(C=C); MS(m/z), 546(M^+, 75%), 513(5%), 499(34%), 490(22%), 457(54%), 443(36%), 434(38%), 415(11%), 397(23%), 230(59%), 204(20%), 160(51%), 116(90%), 89(31%), 41(100%); Anal. Calcd. for $C_{30}H_{34}N_4O_2S_2$: C, 65.93; H, 6.23; N, 10.26. Found: C, 65.72; H, 6.04; N, 10.55.

6e. yellow crystals, m.p. 171 ~ 172°C, ^{1}H NMR($CDCl_3$, 200 MHz) δ 8.13 ~ 7.26(m, 10H, Ph-H), 6.94(s, 2H, =CH), 3.96(m, 2H, SCH) 3.84(s, 4H, NCH_2CH_2N), 1.68(m, 4H, $SCH\underline{CH_2}$), 1.35(d, 6H, $SCH\underline{CH_3}$), 0.90(t, 6H, $CH_2\underline{CH_3}$); IR(cm^{-1}), 1716(C=O), 1634(C=C); MS(m/z), 546(M^+, 69%), 490(33%), 457(33%), 434(80%), 429(18%), 425(10%),

401(13%), 370(14%), 286(10%), 261(14%), 230(93%), 204(70%), 160(91%), 144(41%), 116(100%), 89(36%), 41(85%); Anal. Calcd. for $C_{30}H_{34}N_4O_2S_2$: C, 65.93; H, 6.23; N, 10.26. Found: C, 66.17; H, 5.98; N, 10.49.

6f. yellow crystals, m.p. 151 ~ 153°C, ^{1}H NMR($CDCl_3$, 200 MHz) δ 8.15 ~ 7.26(m, 10H, Ph-H), 6.95(s, 2H, =CH), 3.86(s, 4H, NCH_2CH_2N), 3.19(t, 4H, SCH_2), 1.66(m, 4H, $SCH_2\underline{CH_2}$), 1.30 ~ 1.18(m, 8H, $\underline{CH_2CH_2}CH_3$), 0.78(t, 6H, CH_3); IR(cm^{-1}), 1715(C=O), 1635(C=C); MS(m/z), 574(M^+, 30%), 541(2%), 527(11%), 503(17%), 471(27%), 457(11%), 444(7%), 434(20%), 411(10%), 369(13%), 231(29%), 204(11%), 160(21%), 116(37%), 89(14%), 43(100%); Anal. Calcd. for $C_{32}H_{38}N_4O_2S_2$: C, 66.90; H, 6.62; N, 9.76. Found: C, 67.14; H, 6.89; N, 10.01.

6g. yellow crystals, m.p. 198 ~ 200°C, ^{1}H NMR($CDCl_3$, 200 MHz) δ 8.20 ~ 6.94(m, 22H, Ph-H and =CH), 4.35(s, 4H, SCH_2Ph), 3.83(s, 4H, NCH_2CH_2N); IR(cm^{-1}), 1716(C=O), 1634(C=C); MS(m/z), 614(M^+, 1%), 523(1%), 231(1%), 206(2%), 204(1%), 178(3%), 160(3%), 116(12%), 102(3%), 91(100%), 89(10%); Anal. Calcd. for $C_{36}H_{30}N_4O_2S_2$: C, 70.36; H, 4.89; N, 9.12. Found: C, 70.63; H, 5.18; N, 9.40.

6h. yellow crystals, m.p. 206 ~ 208°C, ^{1}H NMR($CDCl_3$, 200 MHz) δ 8.10 ~ 7.26(m, 10H, Ph-H), 6.97(s, 2H, =CH), 4.16(q, 4H, OCH_2, J = 7.3 Hz), 4.02(s, 4H, SCH_2), 3.91(s, 4H, NCH_2CH_2N), 1.22(t, 6H, CH_3, J = 7.3 Hz); IR(cm^{-1}), 1737(COOEt), 1718(C=O), 1636(C=C); MS(m/z), 606(M^+, 50%), 561(5%), 533(3%), 520(18%), 487(4%), 401(3%), 229(6%), 203(5%), 160(11%), 144(12%), 130(16%), 116(100%), 102(14%), 89(40%); Anal. Calcd. for $C_{30}H_{30}N_4O_6S_2$: C, 59.41; H, 4.95; N, 9.24. Found: C, 59.45; H, 5.07; N, 8.99.

6i. yellow crystals, m.p. 228 ~ 230°C, ^{1}H NMR($CDCl_3$, 200 MHz) δ 8.11 ~ 7.27(m, 10H, Ph-H), 6.96(s, 2H, =CH), 4.15(s, 6H, OCH_3), 4.00(s, 4H, SCH_2), 3.90(s, 4H, NCH_2CH_2N); IR(cm^{-1}), 1736(COOMe), 1719(C=O), 1636(C=C); MS(m/z), 578(M^+, 69%), 547(6%), 519(4%), 506(23%), 373(7%), 230(9%), 204(6%), 160(17%), 144(15%), 130(21%), 116(100%), 102(12%), 89(44%); Anal. Calcd. for $C_{28}H_{26}N_4O_6S_2$: C, 58.13; H, 4.50; N, 9.69. Found: C, 57.96; H, 4.77; N, 9.91.

6j. yellow crystals, m.p. 264 ~ 266°C, ^{1}H NMR($CDCl_3$, 200 MHz) δ 8.17 ~ 7.28(m, 20H, Ph-H), 6.95(s, 2H, =CH), 4.32(s, 4H, SCH_2), 3.87(s, 4H, NCH_2CH_2N); IR(cm^{-1}), 1719(C=O), 1698(COPh), 1637(C=C); MS(m/z), 670(M^+, 3%), 565(6%), 551(4%), 230(7%), 204(11%), 160(16%), 144(12%), 130(13%), 116(19%), 91(100%). Anal. Calcd. for $C_{38}H_{30}N_4O_4S_2$: C, 68.06; H, 4.48; N, 8.36. Found: C, 67.97; H, 4.71; N, 8.60.

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