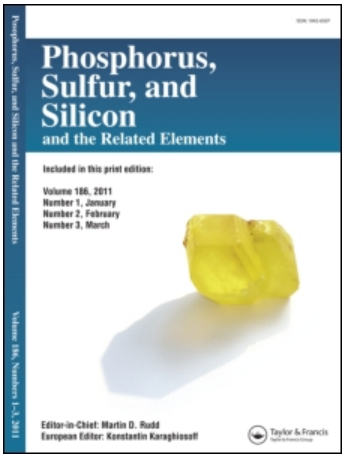

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AN EFFICIENT SYNTHESIS OF SOME BIS-(2-ALKYLTHIO-5-FURFURYLIDENE-4H-IMIDAZOL-4-ONE) DERIVATIVES BEARING POTENTIAL FUNGICIDAL ACTIVITIES

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Some bis-(2-alkylthio-furfurylidene-4H-imidazol-4-one) derivatives ***4*** *were synthesized by S-alkylation of bis-(2-thioxo-5-furfurylidene-4-imidazolidinone)* ***3****, which was obtained via tandem aza-Wittig reaction of vinyliminophosphorane* ***1****, carbon disulfide, and ethylenediamine.*

Keywords: 4H-Imidazol-4-one; S-alkylation; synthesis; tandem aza-Wittig reaction

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-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] (Equation (1)). Unfortunately, 5-arylmethylidene-2-alkylthioimidazolones cannot be prepared by this general method because the corresponding starting material needed would be unstable vinyl amino acetic acids. Presently, we are interested in the synthesis of biologically active imidazolones via tandem aza-Wittig reaction.[9–15] Here we report an efficient synthesis of some new bis-(2-alkylthio-5-furfurylidene-4H-imidazol-4-one) derivatives **4**

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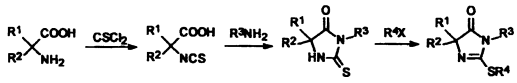
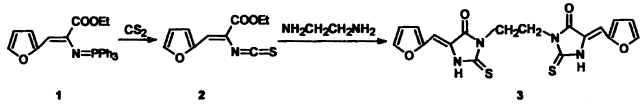
from the stable vinyliminophosphorane **1**.



(1)

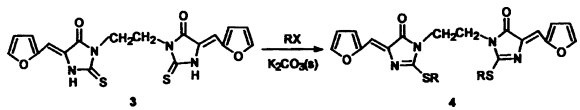
RESULTS AND DISCUSSION

The easily accessible vinyliminophosphorane **1** reacted with carbon disulfide to give vinyl isothiocyanate **2**. The reaction of **2** with ethylenediamine took place smoothly at room temperature to give the yellow crystal bis-(2-thioxo-5-furfurylidene-4-imidazolidinone) **3** in 79% yield (Equation (2) and Table I).



(2)

S-Alkylation of **3** with alkyl halides in presence of solid potassium carbonate provided bis-(2-alkylthio-5-furfurylidene-4H-imidazol-4-one) derivatives **4** in 60–80% yields (Equation (3)). When activated alkylating reagents (RI, $BrCH_2COR$) were used, the alkylation could be carried out at room temperature. When other alkylating reagents were applied, the alkylation had to be carried out at 50–60°C (Table I).



(3)

TABLE I Preparation of Bis-(2-Thioxo-5-furfurylidene-4-imidazolidinone) **3** and Bis-(2-alkylthio-5-furfurylidene -4H-imidazol-4-one) Derivatives **4**

Entry	RX	Condition	Yield (%)[a]	m.p.(°C)
3		r.t./4 h	79	255–257
4a	MeI	r.t./4 h	66	244–246
4b	EtBr	50°C/6 h	60	203–205
4c	*n*-PrBr	60°C/7 h	63	202–204
4d	*n*-BuBr	60°C/8 h	68	177–178
4e	n-$C_5H_{11}Br$	60°C/9 h	68	139–141
4f	$PhCH_2Cl$	50°C/3 h	80	198–199
4g	$ClCH_2COOEt$	50°C/3 h	78	217–218
4h	$BrCH_2COOMe$	r.t./3 h	70	228–229
4i	$BrCH_2COPh$	r.t./2 h	78	241–242

[a]A: Isolated yield of **3** based on vinyliminophosphorane **1**. B: Purified yields of **4a–i** based on bis-(2-thioxo-5-furfurylidene-4-imidazolidinone) **3**.

r.t., room temperature.

The structures of **3** and **4** have been characterized spectroscopically. For example, the ^{1}H NMR spectral data in **4a** show the signals of =CH, $-NCH_2CH_2N-$, and $-SCH_3$ at 6.56 ppm, 3.86 ppm, and 2.63 ppm as single absorption, respectively. The chemical shift of aryl hydrogens is 7.58–6.91 ppm with multiple absorption. In the IR spectral data of **4a**, the strong stretching peak of imidazolone C=O appears at 1714 cm^{-1}. The stretching vibration of C=C shows relatively strong absorbtion at about 1639 cm^{-1} due to a resonance effect. The MS of **4a** shows relatively strong molecule ion peak at m/z 442 with 45% abundance.

EXEPERIMENTAL

Melting points were uncorrected. MS were measured on a HP5988A spectrometer. IR were recorded on a PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1}. NMR were taken on a Varian XL-200 spectrometer and resonances are given in ppm (δ) relative to tetramethylsilane (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. Vinyliminophosphorane **1** was prepared by the literature report.[16]

Preparation of Bis-(2-thioxo-5-furylmethylidene-4-imidazolidinone) 3

To a solution of vinyliminophosphorane **1** (2.20 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 **2**, which was used directly without further purification. To the solution of **2** in CH_3CN (15 ml) was added ethylenediamine (0.17 ml, 2.5 mmol). The mixture was allowed to stand for 4 h at room temperature, and the precipitated solid was collected and washed with water and ethanol, and recrystallized from methylene dichloride/petroleum ether to give **3**.

Bis-(2-Thioxo-5-furfurylidene-4-imidazolidinone) (3)

Yellow crystals, ^{1}H NMR (DMSO-d_6, 200 MHz): δ 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%). Elemental 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-(2-Alkylthio-5-furfurylidene-4H-imidazol-4-one) Derivatives 4

A mixture of **3** (1.66 g, 4 mmol), alkyl halide (10 mmol) and solid potassium carbonate (2.22 g, 16 mmol) in CH_3CN (30 ml) was stirred for 2–9 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 bis-(2-alkylthio-5-furfurylidene-4H-imidazol-4-one) derivatives **4**.

Bis-(2-Methylthio-5-furfurylidene-4H-imidazol-4-one) (4a)

Yellow crystals, ^{1}H NMR ($CDCl_3$, 200 MHz): δ7.58–6.91 (m, 6H, Ar—H), 6.56 (s, 2H, =CH), 3.86 (s, 4H, NCH_2CH_2N), 2.63 (s, 6H, SCH_3). IR (cm^{-1}): 1714 (C=O), 1639 (C=C). MS (m/z): 442 (M^+, 45%), 428 (3%), 395 (3%), 362 (3%), 234 (47%), 219 (24%), 208 (20%), 201 (10%), 191 (7%), 120 (26%), 106 (100%), 92 (10%), 86 (41%). Anal. calcd. for $C_{20}H_{18}N_4O_4S_2$: C, 54.30; H, 4.07; N, 12.67. Found: C, 54.55; H, 3.81; N, 12.93.

Bis-(2-Ethylthio-5-furfurylidene-4H-imidazol-4-one) (4b)

Yellow crystals, ^{1}H NMR ($CDCl_3$, 200 MHz): δ7.56–6.90 (m, 6H, Ar—H), 6.55 (s, 2H, =CH), 3.82 (s, 4H, NCH_2CH_2N), 3.22 (q, 4H, SCH_2, $J = 7.3$ Hz), 1.34 (t, 6H, CH_3, $J = 7.3$ Hz). IR (cm^{-1}): 1717 (C=O), 1634 (C=C). MS (m/z): 470 (M^+, 76%), 442 (11%), 414 (3%), 409 (6%), 381 (7%), 376 (17%), 349 (3%), 248 (74%), 233 (27%), 220 (71%), 215 (31%), 205 (9%), 194 (38%), 178 (19%), 150 (49%), 134 (21%), 122 (43%), 106 (100%), 92 (15%), 86 (82%). Anal. calcd. for $C_{22}H_{22}N_4O_4S_2$: C, 56.17; H, 4.68; N, 11.91. Found: C, 55.94; H, 4.68; N, 12.19.

Bis-[2-(n-Propylthio)-5-furfurylidene-4H-imidazol-4-one] (4c)

Yellow crystals, ^{1}H NMR ($CDCl_3$, 200 MHz): δ7.56–6.90 (m, 6H, Ar—H), 6.56 (s, 2H, =CH), 3.84 (s, 4H, NCH_2CH_2N), 3.20 (t, 4H, SCH_2), 1.72 (m, 4H, $SCH_2\underline{CH_2}$), 0.94 (t, 6H, CH_3). IR (cm^{-1}): 1715 (C=O), 1636 (C=C). MS (m/z): 498 (M^+, 70%), 456 (15%), 423 (12%), 414 (22%), 381 (7%), 363 (6%), 350 (8%), 262 (21%), 247 (9%), 236 (10%), 220 (93%), 194 (52%), 178 (27%), 150 (64%), 134 (16%), 122 (41%), 107 (100%), 86 (45%). Anal. calcd. for $C_{24}H_{26}N_4O_4S_2$: C, 57.83; H, 5.22; N, 11.24. Found: C, 58.10; H, 4.97; N, 11.49.

Bis-[2-(n-Butylthio)-5-furfurylidene-4H-imidazol-4-one] (4d)

Yellow crystals, ^{1}H NMR ($CDCl_3$, 200 MHz): δ7.56–6.90 (m, 6H, Ar—H), 6.56 (s, 2H, =CH), 3.83 (s, 4H, NCH_2CH_2N), 3.21 (t, 4H, SCH_2),

1.64 (m, 4H, $SCH_2\underline{CH_2}$), 1.33 (m, 4H, $\underline{CH_2}CH_3$), 0.81 (t, 6H, CH_3). IR (cm^{-1}): 1716 (C=O), 1638 (C=C). MS (m/z); 526 (M^+, 84%), 479 (11%), 470 (11%), 437 (23%), 423 (10%), 414 (11%), 395 (4%), 377 (5%), 363 (4%), 221 (12%), 194 (10%), 178 (8%), 150 (21%), 122 (15%), 106 (49%), 57 (64%), 41(100%). Anal. calcd. for $C_{26}H_{30}N_4O_4S_2$: C, 59.32; H, 5.70; N, 10.65. Found: C, 59.41; H, 6.00; N, 10.91.

Bis-[2-(n-Amylthio)-5-furfurylidene-4H-imidazol-4-one] (4e)

Yellow crystals, ^1H NMR ($CDCl_3$, 200 MHz): δ7.56–6.90 (m, 6H, Ar—H), 6.56 (s, 2H, =CH), 3.83 (s, 4H, NCH_2CH_2N), 3.19 (t, 4H, $S\underline{CH_2}$), 1.65 (m, 4H, $SCH_2\underline{CH_2}$), 1.31–1.19 (m, 8H, $\underline{CH_2CH_2}CH_3$), 0.81 (t, 6H, CH_3). IR (cm^{-1}): 1718 (C=O), 1638 (C=C). MS (m/z): 554 (M^+, 42%), 507 (5%), 483 (10%), 451 (22%), 437 (7%), 414 (12%), 349 (16%), 291 (9%), 263 (8%), 243 (10%), 220 (62%), 194 (32%), 178 (24%), 150 (58%), 122 (32%), 107 (86%), 86 (24%), 43 (100%). Anal. calcd. for $C_{28}H_{34}N_4O_4S_2$: C, 60.65; H, 6.14; N, 10.11. Found: C, 60.93; H, 5.98; N, 10.39.

Bis-(2-Benzylthio-5-furfurylidene-4H-imidazol-4-one) (4f)

Yellow crystals, ^1H NMR ($CDCl_3$, 200 MHz): δ7.64–6.89 (m, 16H, Ar—H), 6.63 (s, 2H, =CH), 4.37 (s, 4H, $PhCH_2$), 3.80 (s, 4H, NCH_2CH_2N). IR (cm^{-1}): 1710 (C=O), 1637 (C=C). MS (m/z), 594 (M^+, 2%), 504 (2%), 439 (2%), 150 (3%), 122 (3%), 107 (7%), 91 (100%), 86 (2%), 78 (5%), 65 (17%), 51 (10%), 39 (8%). Anal. calcd. for $C_{32}H_{26}N_4O_4S_2$: C, 64.65; H, 4.38; N, 9.43. Found: C, 64.89; H, 4.61; N, 9.72.

Bis-(2-Ethoxycarbonylmethylthio-5-furfurylidene-4H-imidazol-4-one) (4g)

Yellow crystals, ^1H NMR ($CDCl_3$: 200 MHz): δ7.56–6.93 (m, 6H, Ar—H), 6.57 (s, 2H, =CH), 4.16 (q, 4H, $O\underline{CH_2}CH_3$, $J = 6.8$ Hz), 3.98 (s, 4H, SCH_2), 3.88 (s, 4H, NCH_2CH_2N), 1.23 (t, 6H, CH_3, $J = 6.8$ Hz). IR (cm^{-1}): 1740 (COOEt), 1719 (C=O), 1639 (C=C). MS (m/z): 586 (M^+, 40%), 541 (5%), 500 (8%), 467 (8%), 435 (6%), 394 (5%), 362 (3%), 306 (3%), 233 (3%), 219 (4%), 150 (11%), 120 (19%), 106 (100%). Anal. calcd. for $C_{26}H_{26}N_4O_8S_2$: C, 53.24; H, 4.44; N, 9.56. Found: C, 53.27; H, 4.63; N, 9.80.

Bis-(2-Methoxycarbonylmethylthio-5-furfurylidene-4H-imidazol-4-one) (4h)

Yellow crystals, ^1H NMR ($CDCl_3$, 200 MHz): δ7.56–6.92 (m, 6H, Ar—H), 6.58 (s, 2H, =CH), 4.14 (s, 6H, CH_3), 3.99 (s, 4H, SCH_2), 3.87 (s,

4H, NCH_2CH_2N). IR (cm^{-1}): 1738 (COOMe), 1718 (C=O), 1640 (C=C). MS (m/z): 558 (M^+, 46%), 527 (6%), 486 (10%), 453 (12%), 407 (4%), 380 (7%), 348 (4%), 291 (5%), 233 (2%), 219 (3%), 150 (13%), 120 (16%), 106 (100%). Anal. calcd. for $C_{24}H_{22}N_4O_8S_2$: C, 51.61; H, 3.94; N, 10.04. Found: C, 51.40; H, 4.19; N, 10.33.

Bis-(2-Benzoylmethylthio-5-furfurylidene-4H-imidazol-4-one) (4i)

Yellow crystals, ^1H NMR ($CDCl_3$, 200 MHz): δ7.54–6.90 (m, 16H, Ar—H), 6.53 (s, 2H, =CH), 4.40 (s, 4H, SCH_2), 3.85 (s, 4H, NCH_2CH_2N). IR (cm^{-1}): 1721 (C=O), 1693 (COPh), 1644 (C=C). MS (m/z): 650 (M^+, 3%), 545 (7%), 531 (10%), 499 (5%), 487 (1%), 473 (2%), 339 (4%), 325 (3%), 311 (2%), 220 (8%), 150 (4%), 122 (5%), 107 (47%), 91 (100%). Anal. calcd. for $C_{34}H_{26}N_4O_6S_2$: C, 62.77; H, 4.00; N, 8.62. Found: C, 63.01; H, 4.25; N, 8.60.

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